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*REVIEW*

# Prevalence and correlates of aggressive behavior in psychiatric inpatient populations

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**Author contributions:** Gazdag G and Fekete S designed the project; Girasek H and Nagy VA performed the literature search and prepared the first draft of the manuscript; Gazdag G, Fekete S and Ungvari GS critically reviewed and corrected the manuscript; all authors approved the final version of the text.

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## Abstract

Aggressive behavior in patients with psychiatric disorders is attracting increasing research interest. One reason for this is that psychiatric patients are generally considered more likely to be aggressive, which raises a related question of whether diagnoses of psychiatric disorders predict the prevalence of aggressive behavior. Predicting aggression in psychiatric wards is crucial, because aggressive behavior not only endangers the safety of both patients and staff, but it also extends the hospitalization times. Predictions of aggressive behavior also need careful attention to ensure effective treatment planning. This literature review explores the relationship between aggressive behavior and psychiatric disorders and syndromes (dementia, psychoactive substance use, acute psychotic disorder, schizophrenia, bipolar affective disorder, major depressive disorder, obsessive-compulsive disorder, personality disorders and intellectual disability). The prevalence of aggressive behavior and its underlying risk factors, such as sex, age, comorbid psychiatric disorders, socioeconomic status, and history of aggressive behavior are discussed as these are the components that mostly contribute to the increased risk of aggressive behavior. Measurement tools commonly used to predict and detect aggressive behavior and to differentiate between different forms of aggressive behavior in both research and clinical practice are also

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reviewed. Successful aggression prevention programs can be developed based on the current findings of the correlates of aggressive behavior in psychiatric patients.

**Key Words:** Aggression; Mental disorders; Inpatients; Prevalence; Risk factors; Risk assessment

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**Core Tip:** The aim of this paper is to provide an overview of the prevalence of aggressive behavior of patients with various psychiatric disorders focusing mainly on inpatient populations. It also discusses the most commonly used measurement tools for aggressive behavior. As aggressive behavior endangers the safety of both patients and staff, predicting aggression is a key to its prevention. This review also highlights the importance of risk assessment and prevention of aggression in psychiatric patients.

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## INTRODUCTION

The relationship between psychiatric disorders and aggressive behavior has always been a contentious issue, as it is difficult to determine whether psychiatric patients are more likely to be aggressive and whether psychiatric disorders predict aggressive behavior[1].

The authors of most recently published studies agree that there is an increased risk of aggressive behavior in certain psychiatric disorders[2-5]. In a meta-analysis, the proportion of patients classified as aggressive during their acute psychiatric treatment ranged from 8% to 44%[2]. Aggressive behavior and violence pose a serious challenge to psychiatric care providers as they threaten the safety of both the patients and staff[1,2,6]. They also result in longer hospitalization times and the increased stigmatization of psychiatric patients[3]. To predict and prevent violent events in inpatient units, it is crucial to recognize the relationships of the sociodemographic and clinical characteristics of inpatients with the risk of aggression[2].

The aims of this paper are to review the risks of aggressive behavior associated with different psychiatric disorders and assess the commonly used measurement tools to measure various aspects of aggressive behavior.

## DEFINITION OF AGGRESSION

There are several definitions of aggression, a rather broad term used with different emphases in criminology, political and social science, and psychiatry. For the purpose of this review, aggression is defined as a human behavior manifesting as verbal or physical acts that target other human beings, animals, or objects with the aim of causing harm. The aggressors are not always aware of the implications of their actions and the damage caused. If the harm is coincidental or a secondary consequence, the act is not considered as aggressive[7,8].

Instrumental or proactive aggression involves intentionally harming an individual to achieve a desired goal. In contrast, impulsive aggression is often referred to as hostile or reactive aggression that has no identifiable goal. In impulsive aggression, the perpetrator is driven by anger, and the act is an inconsiderate and unplanned response to perceived provocation[7,9,10]. In line with most definitions, in this paper, violence is referred to as an extreme form of aggressive behavior with the purpose of physically harming others, irrespective of the consequences[7].

## METHODS OF THE REVIEW

This narrative review began with a search of the PubMed, PsychINFO, Google Scholar databases using the key words such as (psychiat* or mental*) and (aggress* or violen* or hostil*) and measure*. The publication was chosen if it included any of the following categories of psychiatric disorders and syndromes: dementia, psychoactive substance use, acute psychotic disorder, schizophrenia, bipolar affective disorder, major depressive disorder, obsessive-compulsive disorder, personality disorders (PDs) and intellectual disability. The papers included were peer-reviewed journal articles and books that were published mainly in English. Further articles were reached by following up references. We tried to review the most recent research data to present the current findings of the prevalence and correlates of aggressive behavior in psychiatric inpatient populations.

## AGGRESSION IN DIFFERENT PSYCHIATRIC DISORDERS

### *Dementia*

Alzheimer's disease (AD) and mild cognitive impairment (MCI) increase the risk of agitation and aggressive behavior[11-14]. Aggressive behavior is one of the most common and disturbing complications of cognitive impairment, such as dementia; it contributes to early hospital admission and increases the burdens of caregivers and hospital staff[11], as patients with dementia can harm themselves and other patients [12,13]. The extent of functional deficits and cognitive impairment in dementia is correlated with behavioral and psychiatric symptoms, including apathy, irritability, agitation, aggression, delusions, depressive mood, and anxiety[12].

The main neuropathological finding related to progressive changes in behavior and aggression[15-17] is prefrontal cortical atrophy, which is also associated with dementia [18]. In frontotemporal dementia, anger and other confrontational/critical and emotionally charged ideas and behaviors underpin the development of interpersonal aggression and social isolation[19]. Further brain areas significantly associated with aggression in dementia include the dorsomedial prefrontal and orbitofrontal cortices and the amygdala[20-22].

In a meta-analysis, the prevalence of aggressive behavior in patients with AD and MCI was reported to be 27.8% and 7.4%, respectively[11]. However in another study aggression was found to be the major cause of hospitalization - in 34.2% of all cases - particularly in patients with moderate/severe dementia[23]. Place of residence was also correlated with aggression. For example, agitation and aggressive behavior were observed in 20% of outpatients living in the community, but in 40%–60% of patients living in nursing homes[24]. In a meta-analysis, no significant difference was observed in the risk of physical aggression between patients with different types of dementia with the exception of patients with frontotemporal dementia, among whom the prevalence of criminal behavior was 37%, as opposed to only 8% in patients with AD [11]. In contrast, studies of verbal aggression in AD showed significantly higher rates ranging from 28% to 67%[14]. However, no significant correlation was reported between verbal aggression and the severity of dementia measured by the Mini Mental State Examination, although verbal aggression was found to be related to the presence of delusions[14].

Aggressive behavior in AD is associated with depression, loss of family contact, a poor caregiver–patient relationship, and chronic pain[11,25-27]. Objectively assessing the level of pain in dementia patients can be challenging, although reducing pain could decrease agitation and aggressive behavior[13].

A systematic review confirmed the clinical impression that compared with women, men have higher rates of aggression and other behavioral problems, such as wandering, abuse of others, and social incompetence[28].

### *Psychoactive substance use*

Substance use disorders are among the most prevalent psychiatric disorders, but only a minority of such patients seeks treatment. The relationship between drug use and aggressive behavior is a constantly growing concern[29,30]. It is universally accepted that alcohol and certain drugs significantly increase the incidence of aggressive behavior[2,29-33]. In a forensic psychiatric sample, 28% of patients with previous offences committed crime under the influence of a psychoactive substance[34]. Aggressive behavior occurs at any stage of drug use: in acute intoxication, in connection with drug-seeking behavior, in withdrawal, or in episodes of drug-induced psychosis[31].

Drugs and violence are related directly when the drug pharmacologically induces violence or indirectly when the violence serves as a method of obtaining the drug[32]. Overall, the relationship between drugs and aggression is complex and is driven by a combination of factors related to both transient and permanent physiological, psychological, environmental, and individual differences[30].

**Alcohol:** Alcohol is the substance most commonly associated with aggressive and violent behavior[31]. The link between acute alcohol consumption and aggressive behavior is well-known[35]. Even moderate amounts of alcohol increase the likelihood of aggressive behavior[32]. Alcohol consumption has been associated with increased frequency and severity of physical aggression toward acquaintances and strangers[36, 37], increased verbal aggression[38], domestic and marital violence[39,40], sexual harassment[41-43], and suicide[44]. There is preliminary evidence that alcohol is more closely associated with murder, rape, and abuse than any other substance[31].

Alcohol increases aggression in both men and women, but this effect is stronger in men[35]; men intoxicated with alcohol are prone to physical aggression, whereas women are prone to verbal aggression[45]. However, a recent study[46] found no intersex difference in the effect of alcohol on aggressive behavior. Alcohol consumed by women at home increases their physical aggression toward their male partners, and the amount of alcohol consumed is positively correlated with physical aggression[47-49].

Chronic alcohol dependence can lead to changes in personality structure; the person increasingly blames others for his/her condition, and frequent interpersonal conflicts develop, often leading to physical or verbal aggression. Furthermore, irritability and agitation increase during periods of withdrawal, triggering the onset of aggression[31].

Because of the high individual variability in the effects of alcohol on aggressive behavior, most authors emphasize the interplay between several factors[32]. Alcohol impairs frontal lobe functions, affecting the handling of threatening situations[50-53], reduces inhibitions[51], and influences neurochemical systems that mediate aggressive behavior[54-56]. It is well-established that heavy alcohol consumption affects prefrontal cortex thereby contributing to the development of aggressive behavior[57-59]. Even a small amount of alcohol can reduce the activity of the medial prefrontal cortex[60] resulting in the impairment of prefrontal executive functions, which may lead to careless, inappropriate, or aggressive behavior[61,62]. Alcohol consumption frequently provides false justification for the variety of antisocial behaviors displayed by the intoxicated person[63].

**Heroin:** There is compelling evidence that heroin increases aggressive behavior, including physical aggression against others, impulsivity, and suicidality[30,64-66]. An analysis of the history of 527 heroin users found that almost 43% of them had attempted suicide[67]. The symptoms of opioid withdrawal can be so severe and painful that opioid users may unintentionally become violent when trying to obtain opioid drugs to seek relief from the withdrawal symptoms[31]. Research data support the view that the elevated level of aggression among heroin users is driven by individual differences in aggressive behavior and other risk factors, such as childhood abuse, family history of aggression and psychiatric illness, and living in a poor neighborhood, rather than the direct effect of heroin itself[30,68].

**Cannabis:** Cannabis is commonly regarded as a relatively harmless substance, but there is strong evidence that cannabis withdrawal can cause anger and lead to hostile behavior[30,69,70]. Compared with non-users, regular cannabis users were almost twice as likely to show aggressive behavior towards their partner, were 1.2 times more likely to be victims of aggression by their partners and were 2.4 times more likely to be both perpetrators and victims of aggressive behavior[71]. These findings remained true even after controlling for the effects of alcohol and other drugs[71].

**Stimulants:** Both cocaine[22,59] and methamphetamine use can trigger hostile behavior[31,72-74]. 3,4-methylenedioxy-N-methamphetamine has been found to reduce aggression during its acute use[30,75,76], followed by a flare-up of aggression in the following days and a return to baseline after approximately one week[77]. A meta-analysis found that among illicit drugs, cocaine has the strongest link to physical, sexual, and psychological aggression[78]. Tomlinson *et al*[30] highlighted that the relationship between cocaine use and aggressive behavior may be enhanced by personality traits, such as poor impulse control and antisocial traits.

**Hallucinogens:** The use of most hallucinogens has been negatively correlated with aggression, *i.e.*, positively associated with a lowered risk of aggressive behavior and

elevated mood[30,79]. Both psilocybin[80] and lysergic acid diethylamide[30,31] decrease interpersonal conflicts and subsequent aggressive behavior[81].

### *Acute psychotic disorder*

More than 50% of all violent incidents in the context of psychiatric illness occur during psychiatric care[82-85]. Psychotic symptoms have traditionally been considered as a major contributing factor to aggression[83,86-88].

Several studies have shown that first-episode psychoses carry a high risk of aggressive behavior[89-91]: approximately one-third of patients with first-episode psychosis exhibit hostility and verbal and/or physical aggression during hospitalization, and the severity of their violence frequently poses risk to others[92]. In one study, 16% of patients with first-episode psychosis were reported to be aggressive in the week before admission, 7% were aggressive in the week after admission, and 10% were aggressive in both periods[92]. In another study, aggressive behavior was observed in more than half of the patients with first-episode psychosis, with verbal aggression being the most common aggressive behavior in inpatient wards[88,93]. In a similar study, nearly 70% of participants with first-episode psychosis were reported to have committed at least one act of physical and/or verbal abuse in the year prior to admission, and 43% and 61.5% showed physical and verbal aggression, respectively [85].

A study reported that most of the violent acts by patients with first-episode psychosis targeted themselves or property, whereas only 7% of the violent acts were committed against another person, and only 2.5% of these caused actual injuries, such as bruises and scratches[92]. Furthermore, 46% of patients had conflicts with the law, of whom 42.9% were arrested and 35.1% spent at least one night in prison[85]. Approximately one-fifth of patients reported some form of suicidal ideation and behavior, including suicide attempts, during the first episode of psychosis[88]. A recent meta-analysis found that 18.4% of patients attempted suicide during their first episode of psychosis prior to seeking treatment[94].

Several sociodemographic and illness-related factors can contribute to the development of aggressive behavior[95,96]. Risk factors for aggression during first-episode psychosis include younger age, male sex, lower socioeconomic status, a longer duration of untreated psychosis, a manic state, drug use, antisocial personality traits, childhood emotional/physical/sexual abuse, and impulsivity[85,88,90,97-99].

### *Schizophrenia*

Patients with schizophrenia tend to exhibit hostile behavior, particularly during an acute psychotic episode. These patients face an almost four times greater risk of aggressive behavior than people with no psychiatric problems[82,100,101]. The degree of aggression is significantly related to psychopathology[101-103]. Violent behavior is more commonly displayed by patients who have psychotic symptoms, such as command hallucinations that encourage them to act violently[104]. Impulsivity in schizophrenia is also closely related to aggression and suicidal behavior[3,105-107]; in a study of risk factors for suicide in schizophrenia, 11.6% of the patients attempted suicide right after the violent behavior[108]. Patients with schizophrenia, particularly those in the acute phase, frequently exhibit hostility, anger, and agitation that can lead to verbal or even physical aggression[109-111]. Both hostility and aggressive behavior are associated with longer and more frequent hospitalization[100,112-115]. Aggression also occurs frequently after discharge from hospital: a meta-analysis revealed that 10% of patients with schizophrenia, compared with only 2% of the general population, exhibited aggressive behavior in the community[116].

The prevalence of threatening and aggressive behavior is common in hospitalized schizophrenia patients, ranging from 10% to 45%[1,110,117-121], but a recent meta-analysis found higher rates of 15.3%–53.2%[122]. Although different forms of aggression are common, with verbal aggression occurring in up to 75% of the cases, serious physical injury is rare[1,93,123-125].

The prevalence of auto- and hetero-aggression in schizophrenia has been reported to show considerable intersex differences. For example, in a previous study, 75% of the male patients and 53% of the female patients demonstrated some form of aggressive behavior during their first hospitalization and in the following two years, while 17% of the male patients and 26% of the female patients attempted suicide[100]. Demographic factors that predict aggression include younger age, male sex, and single marital status [1,3].

Co-morbid psychiatric disorders, primarily substance use disorders, significantly contribute to aggressive and violent behavior in patients with schizophrenia[100,116,

126,127]. It is estimated that 20%–65% of patients with schizophrenia use illicit drugs, compared with 16.7% of the general population[101]. In addition to substance use disorders, other common comorbidities, such as antisocial personality disorder, can also increase the risk of aggressive behavior in patients with schizophrenia[2,3].

### *Bipolar affective disorder*

Bipolar disorder is associated with an increased risk of aggressive behavior[128-131]. A high risk of aggressive behavior has also been demonstrated in bipolar patients in remission[110,132-134]. The lifetime prevalence of aggression was 12.2% in a mixed group of bipolar patients[135] and 25.3% in patients with bipolar I disorder[136].

Aggressive or violent behavior in bipolar patients usually appears during acute manic episodes[137-139] and is a common cause of hospitalization in this population [130,140-142]. Involuntary hospitalization for acute mania is significantly associated with higher rates of aggression/violence and lower rates of insight[109,143]. A clear association was found between the presence and severity of aggression during a manic episode and psychotic symptoms[130,144]. Patients with mood-incongruent psychotic symptoms are more prone to agitation or aggression[145-149]. Agitation — a common symptom in acute bipolar mania — is characterized by motor restlessness and increased responsiveness that can lead to physical aggression[110,150]. No association has been found between aggressive and suicidal behaviors in bipolar illness[130] or between male sex and aggressive behavior[141,151].

Serotonergic hypoactivation has been hypothesized to play a role in the neurobiological basis of aggression in bipolar illness[131]. The association between prefrontal cortical dysfunction and aggressive behavior in bipolar patients has been repeatedly confirmed[152-154]. Damage to the prefrontal cortex results in disruption of executive functions, leading to dysfunctional patterns of behavior in the social realms including emotional outbursts, increased risk-taking and aggression as well as disorganized behavior[61,155]. Executive dysfunction is common in bipolar disorder, schizophrenia and acute psychoses[156,157], where impaired impulse control and dysregulated behavior manifest in aggression[158].

A further possible explanatory factor for aggression in mania may be a lack of insight. Aggressiveness during acute manic episodes depends on the severity of the episode and the degree of insight[130,159]. Possible predictors of aggressive or violent behavior in mania include past aggressive or violent behavior, criminal history, childhood sexual abuse, being a victim of previous violence, comorbid PDs, and alcohol and/or drug abuse[110].

### *Major depressive disorder*

Depression is a risk factor for aggressive behavior, mostly in the form of auto-aggression[160]. Factors associated with aggressive behavior in depression include impulsivity[160-163], alcohol use[160,164-168], and the risk of suicidal behavior[169-173]. High impulsivity scores were found in a sample of patients diagnosed with major depressive disorder who had previously attempted suicide[163]. Suicide attempters are more aggressive than non-attempters[174-177].

Associations have also been found between attachment anxiety and suicide attempts[178,179] and between the expression, proneness, and attributions of anger and adult attachment styles[179]. Adults with a preoccupied attachment style, which is characterized by the person having a negative image of him/herself and a positive image of others, are more likely to display high-risk behaviors and even suicidal gestures due to their dysregulated emotional and behavioral control[178]. Insecurity is associated with signs of dysfunctional anger, such as hostility. An anxious-ambivalent attachment style is characterized by inward-directed anger and displaced aggression, whereas a secure attachment style is characterized by the appropriate, functional expression of anger[173,178,179].

Symptoms of depression and anger have been associated with attachment style and auto-aggression in depressed inpatients[173]. It was hypothesized that the aggressive behavior of patients with elevated attachment anxiety is self-directed, resulting in non-suicidal self-harm or suicide attempts. This theory is supported by the fact that depressive symptoms are strongly associated with suicide attempts, suggesting that depression is a partial mediator to the relationship between attachment anxiety and self-directed aggression[173].

Increased alcohol consumption is also a mediator to the relationship between depression and aggression. In one study, the prevalence of alcohol use disorder was estimated at 32.3% in a sample of people who reported a depressive episode in the previous year, as opposed to only 9.5% in the non-depressed sample[180].

It was hypothesized that in the anxiety/aggression-driven subtype of depression, depressive episodes are triggered by increased anxiety and/or unregulated, outwardly directed aggression, such as irritability or outbursts of anger. Consequently, in this subtype of depression, the symptoms of dysregulated aggression and/or anxiety mask the depressive mood[181]. Assessment of depression should include a search for evidence of comorbidity with alcoholism and personality traits such as aggression and impulsivity to better understand the link between depression and suicidal behavior and to identify patients at a higher risk of suicidal behavior[166].

### *Obsessive–compulsive disorder*

The relationship between obsessive–compulsive disorder (OCD) and aggression has been explored in relatively few studies. Increased aggression and hostility in OCD are positively correlated with symptoms of hoarding[182,183], the inhibition of avoidant behavior or rituals[184], and the severity of OCD symptoms[183,185,186].

In OCD, indirect aggression is more common and direct aggression is relatively infrequent[187]. The relationship between latent aggression (hostility/aggression toward other individuals, which is not openly expressed but manifested in fantasies or disguised forms that are not always conscious to the individual) and OCD has been explored[188-190] but not extensively studied. Explanations offered for this association include the psychodynamic theory of OCD[189,190] and the role of anxiety, which may prevent OCD patients from expressing their anger because they are worried about how others will react to an openly aggressive behavior[183,191].

Increased anger[192,193], hostile behavior[183,194], and frequent interpersonal conflicts have been reported in studies on OCD[183,189,190,195]. In one study, more than half of the OCD patients reported interpersonal conflicts, with one in two patients admitting that they were aggressive with their partner[195]. Family members who refuse to participate in the rituals of an OCD patient may be targets of aggressive behavior[190,195]. Another source of interpersonal conflict in OCD is when patients take excessive precautions to maintain the safety of others (*e.g.*, forced control of locks) who do not take these precautions as seriously[196], which induces anger and hostile behavior in OCD patients[197]. Patients find it harder to alleviate their anxiety when experiencing high levels of hostility, which predicts poor treatment outcomes[183,191,198]. Hostility and high levels of anxiety are linked to suicide in OCD patients; in a recent study, 27% of the OCD patients had suicidal ideation during their lifetime and 33% had attempted suicide[198].

### *Personality disorders*

PDs are associated with an increased risk of developing aggressive and violent behavior[199-201]. The relationship between PDs and aggression is complex, because PDs differ in terms of the type, severity of frequency of aggressive behavior[202,203]. Among the 10 PDs described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, aggression is typically associated with Cluster B PDs (antisocial, borderline, histrionic, and narcissistic PDs) and paranoid PD among Cluster A PDs[204-208]. Patients with Cluster B PDs are 10 times more likely to have a criminal conviction and eight times more likely to be in prison than patients with other PDs[209]. Violent crime is most frequently exhibited by individuals with antisocial PD but is also common among criminals with borderline, narcissistic, and paranoid PDs [210].

Patients with antisocial and borderline PDs have the greatest risk of hostile behavior [208], being four times more likely to be hostile in a psychiatric ward than patients with other PDs[121]. Patients with antisocial PD are 12.8 times more likely to commit a violent act, compared with the general population[211]. Up to 73% of patients with borderline PD have been found to behave aggressively during a one-year period[212], 58% participated in "occasional or frequent" fights, and 25% used a gun against others at some point in their lives[213]. Crimes committed by patients with borderline PD are impulsive, explosive episodes of physical violence, whereas those committed by patients with antisocial PD are driven by instrumental aggression[214,215].

**Borderline personality disorder:** The hostile behavior of patients with borderline PD is predicted by several possible factors, including interpersonal dysfunction, negative interpersonal events[216,217], hypersensitivity to social rejection[218], and increased sensitivity to threat[208,219]. One study reported that patients with borderline PD experienced significantly more fear than did healthy controls when presented with neutral faces[220,221]. These results suggest that patients with borderline PD do not properly recognize facial emotional expressions, which increases their feelings of threat or provocation and may ultimately lead to reactive aggression[219]. Factors

underlying hostility in borderline PD include comorbid psychiatric disorders and/or substance use, affective lability, and childhood abuse[222,223]. Affective dysregulation and impulsive aggression in these patients require special attention, as they are risk factors for suicidal behavior, self-harm, and interpersonal aggression and influence the choice of psycho- and pharmacotherapy[223]. Most studies have found no significant intersex difference in the aggressive behavior of patients with borderline PD, but one study reported more self-aggressive behavior among female patients than among their male counterparts[224].

**Antisocial personality disorder:** While the aggressive behavior of patients with borderline PD is generated primarily from intense anger and instability[225], patients with antisocial PD usually perceive their environment as hostile, and therefore, their aggressive behavior stems from their perceived need to fight for their own safety and survival[226]. These patients use hostility to gain personal benefits[227-229]. They are scarcely able to delay gratification and thus use aggressive behavior when their demands are not met[226].

**Narcissistic personality disorder:** Narcissism has been reported to be a significant predictor of violent behavior in clinical and forensic psychiatric samples, with odds ratios ranging from 1.21 to 11.46[230]. A systematic review found that both low self-esteem[231] and unstable self-esteem[230] in patients with narcissistic PD are associated with violent behavior and hostility. Individuals with high but unstable self-esteem are most likely to report anger and hostility, whereas high but stable self-esteem prevents anger and aggression[225].

### *Intellectual disability*

Aggressive behavior by people with intellectual disability is the main reason for their referral to healthcare services[232-235]. A hostile attitude can have serious negative consequences for people with intellectual disabilities, as it can damage their personal development and social relationships and their quality of life[236-238]. In addition, the aggressive behavior of patients with intellectual disabilities often imposes a heavy burden on their relatives and caregivers and thereby negatively impacts their quality of life[235,237].

Patients with intellectual disabilities exhibit different forms of aggression, including physical and verbal aggression, destructive behavior toward the physical environment, self-harm behavior, and sexually aggressive behavior[232,235], and the prevalence of these different forms also differs significantly among patients[239]. The prevalence of physical aggression ranges from 2.1%[240] to 24.4%[232], while that of verbal aggression ranges from 5.9%[241] to 37.6%[232]. Verbal aggression is the most common form of aggressive behavior in this population[232,234,242]. A study reported that the incidence of any form of aggressive behavior in these patients assessed in a one-year period was 51%, whereas that of all forms of hostile behavior was less than 6%[232].

The extent of hostility and its behavioral manifestations are linked with psychosocial and sociodemographic factors, the severity of intellectual disability, and the presence of comorbid psychiatric disorders. For example, aggressive behavior is more common in men with intellectual disability than in women[243]. Sexually aggressive behavior is associated with the severity of intellectual disability[235] and with the frequency of rage and objectionable personal habits[244]. Physical aggression is associated with more severe intellectual disability and younger age[234]. Hostile behavior is more common in cases wherein intellectual disability is associated with autism, psychotic disorder, paranoia, depression, and/or a PD[245]. Self-harm behavior is more common in cases with comorbid autism[232,246].

The incidence of auto-aggression, destructive behavior, and hostility against others is higher in health care facilities than at home[247]. van den Akker *et al*[235] emphasized that hostility is also determined by factors such as the quality of care and the quality and frequency of interpersonal interactions with caregivers. Among patients with intellectual disability, aggressive behavior is frequently used to attract the attention of caregivers thereby increasing the frequency of social interactions[235,248]. Therefore, understanding the background of hostile behavior for each individual is essential to find an effective treatment[235].

## MEASUREMENT TOOLS FOR AGGRESSION

Predicting and preventing aggression and violence are key issues faced by psychiatrists and forensic physicians[249]. Several methods are used to measure aggression, namely interviews, observation, laboratory tests, and projective and self-reported questionnaires[250]. However, all of these methods have limitations, such as social desirability, the effect of cognitive functioning on an individual's self-perception, or the observer's effect on observational methods[250,251]. Interpretation of risk factors should involve the patients and their family members to better understand the triggering factors, such as impulsive behavior and substance use[5]. Self-administered questionnaires correctly predict aggressive acts only if the patients admit to committing violent acts[252]. Patients who deny their symptoms and aggressive behavior, particularly physical aggression, have lower scores in self-administered questionnaires (*e.g.*, in AQ)[252]. Structured, systematic assessment tools for predicting direct aggression are a relatively new addition to clinicians' armamentarium to report, predict, and assess the risk of violence in psychiatric populations[249,253]. In a study by Ogloff *et al*[254], the accuracy of predicting impending aggression was significantly increased by using a dynamic, structured risk assessment tool for nurses in an acute psychiatric hospital. The main limitations of structured risk assessment tools are the time and resources required to administer them and the difficulties in translating the results into clinical practice[255] (Table 1).

### *Measurement tools based on observation*

**Dynamic Appraisal of Situational Aggression–Inpatient Version (DASA-IV[254]):** The DASA-IV is a 7-item (negative attitudes, impulsivity, irritability, verbal threats, sensitive to perceived provocation, easily angered when requests are denied, and unwillingness to follow directions) structured risk assessment tool used to evaluate inpatient aggression. Each of the seven items is evaluated dichotomically, based on its presence or absence in the last 24 h. It takes less than 5 min to complete the scale. Scores of 0, 1 to 3, and 4 or higher indicate very low, medium, and high risks of aggression, respectively, while a score of 6 or 7 indicates a risk of immediate aggression warranting preventive measures[254]. The DASA-IV has moderate or good power for predicting aggressive events[249,253,255].

**Historical, clinical, risk management: 20 factors (HCR-20$^{V3}$[256]):** The HCR-20$^{V3}$ is a 20-item assessment tool that predicts the risk of interpersonal violence. The historical (H) scale consists of 10 items related to violence, and their presence is not expected to decrease with time or treatment even if the relevance of these factors may change over time. The clinical (C) scale consists of five items that are dynamic in nature and can change over time or during treatment. The risk management (R) scale also consists of five items that are dynamic and appraise concerns about the future. The items of the HCR-20$^{V3}$ are similar to those in the second version of the HCR-20, although some have been revised or classified under other items in the third version[257]. Although relatively few validation studies have been performed on the third version[258], good inter-rater reliability was found for both the whole scale and its sub-scales (between 0.90 and 0.93) when scores were based on interviews and clinical documentation. The HCR-20$^{V3}$ has good predictive value for violence occurring over a 6- to 12-mo follow-up period[259].

**Brøset Violence Checklist (BVC[260]):** The BVC is a 6-item violence risk assessment checklist that evaluates six behavioral changes (confusion, irritability, boisterousness, physical threats, verbal threats, and attacks on objects) that often trigger aggression among inpatients[260]. The BVC can be assessed quickly and easily ("1" denotes the presence of the behavior and "0" its absence) and is intended to predict the risk of inpatient violence occurring within 24 h. The total score is derived from the sum of the scores for each item. A score of 1 or 2 indicates a moderate risk of violence that requires preventive action, whereas a score of 3 or higher indicates a high risk of violence that requires immediate preventive action and activation of attack management plans[253,260,261].

**Staff Observation Aggression Scale-Revised (SOAS-R[262]):** The SOAS-R consists of five items measuring different aspects of aggression: observed provocation, means used by patient, aim of aggression, consequences, and immediate measures taken by nurses. The total score is calculated by summing the scores for each item; scores range from 0 (no aggression) to 22 (most severe form of aggression). A score of 9 or higher indicates severe aggression[262]. The good psychometric properties of this scale have been confirmed by validation studies[249,262,263].

**Table 1 Measurement tools for agression**

| Name of the questionnaire | Year of development | Method of rating | Items | Scoring |
|---|---|---|---|---|
| Dynamic Appraisal of Situational Aggression–Inpatient Version[254] | 2006 | Observation | 7 (negative attitudes, impulsivity, irritability, verbal threats, sensitive to perceived provocation, easily angered when requests are denied, and unwillingness to follow directions) | 0-7 |
| Historical, clinical, risk management: 20 factors[256] | 2013 | Observation | 20 (historical (H) scale consists of 10 items; clinical (C) scale consists of 5 items; risk management (R) scale consists of 5 items) | 0-40 |
| Brøset Violence Checklist[260] | 2000 | Observation | 6 (confusion, irritability, boisterousness, physical threats, verbal threats, and attacks on objects) | 0-6 |
| Staff Observation Aggression Scale-Revised[262] | 1999 | Observation | 5 (observed provocation, means used by patient, aim of aggression, consequences, and immediate measures taken by nurses) | 0-22 |
| Modified Overt Aggression Scale[264] | 1989 | Observation | 4 (verbal aggression and aggression against property, self, and others) | 0-40 |
| Buss–Durkee Hostility Inventory[269] | 1957 | Self-rating | 75 (7 subscales: assault or direct physical violence against others; indirect hostility; irritability or explosiveness; negativism; resentment, anger, jealousy; mistrust; and verbal aggression) | 0-66 total hostility score; 0-9 guilt score |
| Aggression Questionnaire[272] | 2000 | Self-rating | 34 (5 subscales: physical aggression; verbal aggression; anger; and hostility; indirect aggression) | 34-170 (5-point Likert scale) |
| State–Trait Anger Expression Inventory 2[274] | 1999 | Self-rating | 57 (contains 6 scales: state anger; trait anger; anger expression-out; anger expression-in; anger control-out; anger control-in and 5 subscales: state anger/feeling, state anger/verbal, state anger/physical, trait anger/temperament, and trait anger/reaction, and an anger expression index) | 57-228 (4-point Likert scale) |

**Modified Overt Aggression Scale (MOAS[264]):** Adapted from the Overt Aggression Scale[265], the MOAS is used to measure aggression. Although the scale was developed to evaluate the hostile behavior of adult psychiatric inpatients, it has also been used in older patients with dementia[250]. The MOAS consists of four subscales (verbal aggression and aggression against property, self, and others). The items are rated on a 5-point Likert scale, and each category is weighted: the severity of verbal aggression is given the lowest weight, whereas that of physical aggression is given the highest weight. The sum of the scores for the four subscales indicates the severity of overall aggressive behavior. The total weighted score ranges from 0 to 40. Psychometric studies of the MOAS have demonstrated good reliability and validity[266-268].

### *Self-report measurement scales*

**Buss–Durkee Hostility Inventory (BDHI[269]):** The BDHI consists of 75 dichotomous (true or false) items and is divided into seven subscales: assault or direct physical violence against others; indirect hostility through gossiping, joking, slamming doors, or breaking things; irritability or explosiveness and annoyance at the smallest stimulus; negativism as either active rebellion or passive obedience to rules and authority; resentment, anger, jealousy, and/or hate of others due to real or supposed maltreatment; mistrust and the belief that others are damaging and diminishing the

patient; and verbal aggression in style or content. Scores are added up to obtain a total hostility score based on 66 of the 75 items, after omitting the guilt items, which form a separate guilt scale to examine the influence of guilt on aggressive behavior. In a meta-analysis, the subscale score reliability for the BDHI was found to be less than desirable, as the Cronbach's alpha coefficients were generally between 0.50 and 0.69[270]. Nevertheless, the BDHI is one of the most widely used aggression measurement questionnaires both in clinical practice and research[271].

**Aggression Questionnaire (AQ[272]):** The AQ was developed to measure aggression [272], following the widespread and most commonly used BDHI[248]. The AQ contains 29 items rated on a 5-point Likert scale and has four subscales: physical aggression (9 items), verbal aggression (5 items), anger (7 items), and hostility (8 items). Buss and Warren[273] revised the AQ and developed a 34-item version in which a fifth subscale—indirect aggression—was added. A higher score indicates an elevated predisposition to aggression. For the 29-item AQ, the Cronbach's alpha scores for the subscales ranged from 0.72 (verbal aggression) to 0.85 (physical aggression), and with a score of 0.89 for the overall scale. The internal consistency of the 34-item AQ is acceptable, with Cronbach's alpha scores for the subscales ranging from 0.71 (indirect aggression) to 0.88 (physical aggression) and an overall reliability score of 0.94[271,273].

**State–Trait Anger Expression Inventory 2 (STAXI-2[274]):** The 57-item STAXI-2 consists of six scales that evaluate the experience, expression, and control of anger [274]. The State Anger subscale assesses the intensity of anger at a particular time, whereas the Trait Anger scale measures the intensity of anger over time. The Anger Expression and Anger Control scales assess four mostly independent traits: expression of anger toward objects or others (Anger Expression-Out), holding in or suppressing angry feelings (Anger Expression-In), controlling angry feelings by preventing their expression toward objects or others (Anger Control-Out), and controlling suppressed anger by calming down or cooling off (Anger Control-In). The psychometric indicators of the STAXI-2 suggest adequate reliability and factorial, criterion, and construct validity[275-278].

## CONCLUSION

The aim of this review was to provide an overview of the aggressive behavior exhibited by patients with various psychiatric disorders. It discussed the manifestations and frequencies of aggression and the most commonly used measurement tools for aggression. Our review reveals that certain psychiatric disorders may carry an increased risk of aggressive behavior, which may be influenced by several other factors in addition to the presence of the psychiatric disorder. Examples of such factors include sex, age, socioeconomic status, comorbid disorders, and pre-existing aggressive behavior. Quantitative measurement tools, of which we have presented the most frequently used options, can help with the appropriate assessment of aggression. Successful aggression prevention programs can be developed based on the results of aggression risk evaluation. Note that the present review does not intend to increase the degree of stigmatization of psychiatric patients. Rather, it aims to draw attention to the risk factors for aggressive behavior, the importance of risk assessment and prevention of aggression, and the different possible interventions to manage aggression.

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*REVIEW*

# Resilience to the effects of social stress on vulnerability to developing drug addiction

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## Abstract

We review the still scarce but growing literature on resilience to the effects of social stress on the rewarding properties of drugs of abuse. We define the concept of resilience and how it is applied to the field of drug addiction research. We also describe the internal and external protective factors associated with resilience, such as individual behavioral traits and social support. We then explain the physiological response to stress and how it is modulated by resilience factors. In the subsequent section, we describe the animal models commonly used in the study of resilience to social stress, and we focus on the effects of chronic social defeat (SD), a kind of stress induced by repeated experience of defeat in an agonistic encounter, on different animal behaviors (depression- and anxiety-like behavior, cognitive impairment and addiction-like symptoms). We then summarize the current knowledge on the neurobiological substrates of resilience derived from studies of resilience to the effects of chronic SD stress on depression- and anxiety-related behaviors in rodents. Finally, we focus on the limited studies carried out to explore resilience to the effects of SD stress on the rewarding properties of drugs of abuse, describing the current state of knowledge and suggesting future research directions.

**Key Words:** Resilience; Stress; Depression; Drug addiction; Animal models; Social defeat

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**Core Tip:** Preclinical research on drug addiction has focused on the factors that enhance vulnerability to develop drug addiction. Recent studies of resilience have determined

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Grade D (Fair): 0
Grade E (Poor): 0

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the neurobehavioral traits that confer protection against developing an addictive disorder after stress exposure. Active coping strategies to face the stressor and the absence of depression-like symptoms are consistently associated with resilience to the stress-induced potentiation of the rewarding effects of cocaine and alcohol. Unravelling the neurobiological substrates of resilience is key to developing pharmacological and psychological interventions to enhance stress resilience in order to prevent the development of addiction and other stress-related disorders.

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## INTRODUCTION

The noun resilience derives from the Latin *resiliens*, the present participle of resilire (re- "back" + salire "to jump"), and was first used by Cicero and Francis Bacon (among others) as a synonym of rebound[1]. From the nineteen century on, material science has also used the word resilience to indicate the flexibility of a material or its ability to resist stress (force being applied) without permanent deformation. In the context of psychology, resilience can be defined as "the process of adapting well in the face of adversity, trauma, or other significant sources of stress"[2,3]. Besides the rebound of the equilibrium, resilience often implies an increase in mental resistance.

Although resilience is sometimes considered an extraordinary capacity of some individuals, research indicates that it is a common trait. The majority of individuals exposed to trauma or stressful events adapt to and overcome stress and maintain normal psychological and physical functioning without developing stress-related disorders[4]. Approximately 50% of people experience trauma in their life, but the prevalence of post-traumatic stress disorder (PTSD) is about 8%[5]. Resilience is an innate capacity, although it is not a stable trait, it is a dynamic process[6,7] that changes through a life span and can be enhanced by different factors.

## RESILIENCE TO STRESS AND DRUG ADDICTION

Most research on resilience has focused on the biological and behavioral profile of individuals who are resilient to developing psychiatric illnesses such as depression and PTSD after exposure to stress. However, studies on resilience to the effects of stress on the initiation, maintenance and relapse to addictive disorders are very limited. In fact, almost all research regarding substance use disorders (SUD) has focused on risk; *i.e.*, the factors that predispose an individual to develop an addictive disorder. Vulnerability to the effects of drugs of abuse depends on multiple factors, including biologic factors such as genetic load, which are modified by life experiences and the environment in which the individual lives. Stressful experiences have a profound impact on the brain[8], for this reason, stress can increase vulnerability to addiction. Exposure to stress, especially in early life and adolescence, induces long-term modifications in the physiological response to stress, emotional reactivity, the brain reward system and cognitive processing, all of which contribute to the increased vulnerability to develop a SUD[9]. However, as commented on before, most people are resilient to stress. Consequently, only a small percentage of individuals that experience a traumatic event or are exposed to chronic stress develop an addictive disorder.

In recent years there has been an important impulse in the study of resilience to develop a SUD or an addictive behavior. In fact, until 2010, literature related to resilience and addiction was scarce, while in the last ten years the number of works on the subject has increased exponentially (Figure 1). Epidemiologic studies indicate a clear association between low resilience (often during adolescence) and the increment of addictive behaviors[10,11]. Resilience is a factor moderating the relationship between stress and alcohol use disorders (AUD)[12] and is strongly associated with a

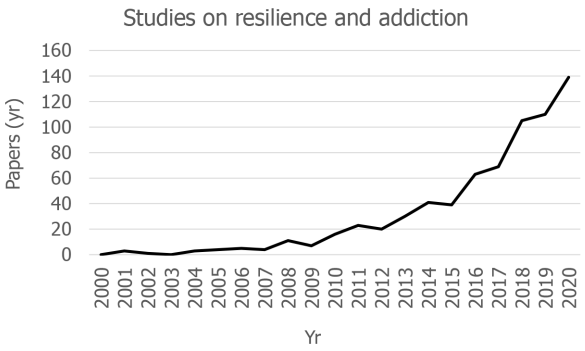


**Figure 1 Results from the search "resilience and addiction" in the PubMed database (https://pubmed.ncbi.nlm.nih.gov, accessed on December 15, 2021).** Number of papers published each year from 2000 until 2020.

reduction in the risk of AUD, though there is not a direct causal relationship but rather an overlapping of genetic and environmental influences[13]. Animal models used to study the impact of stress on drug addiction[14,15] are also being incorporated into research to identify the behavioral and physiological traits that characterize animals' resilience to the effects of stress on the rewarding properties of drugs of abuse, as well as the neurobiological substrates of the resilience process.

Addressing the perspective of resilience in the study of addictive behaviors is promising as a way of enhancing knowledge regarding the neuroscience of addiction. However, as Rudzinski *et al*[16] noted, there are difficulties in the use of the concept of resilience in the field of drug addiction, especially regarding its definition and operationalization as a trait, as a process or, as is more common, as an outcome (for example, the absence of SUD). In addition, it is important to distinguish between resilience (a concept with multiple meanings) and resiliency, which is a personality trait that has been linked to alcohol/drug problems and is defined as "the ability to flexibly adapt impulse control relative to contextual demand"[17]. Some studies define resilience as the capacity to maintain abstinence and not relapse to drug use during a recovery period[18,19]. In this sense, neuroimaging studies have shown that conserved prefrontal cortex (PFC) morphology and heightened neural PFC engagement are linked to abstinence and resilience against relapse in alcohol-dependent patients[19]. Other studies consider drug use as a stressor or risk factor for resilience (for example [20]), while some studies do not evaluate resilience to stress. In the last case, the concept of resilience is used to design a reduced response to the drugs of abuse in rodents that have been exposed to a genetic or pharmacological manipulation[21,22].

In the present review we mainly focus on research that has studied resilience to the effects of stressful experiences on subsequent drug use/abuse in animal models. First, we succinctly comment on the protective factors associated with resilience in studies with humans and explain the relationship between the physiological response to stress and resilience, since most human studies have focused on the neuroendocrine changes that are predictive of resilience. We then discuss the main animal models used to study resilience to social stress and review advances concerning the neurobiological substrates of resilience in said studies. Finally, we discuss research that specifically addresses resilience to the effects of repeated social defeat (SD) on the rewarding properties of drugs of abuse and lay out future research directions and conclusions.

## BEHAVIORAL TRAITS AND PROTECTIVE FACTORS ASSOCIATED WITH RESILIENCE

Different protective factors associated with resilience can be identified on biological, psychological, and social levels. Among the internal factors are stable predispositions (such as genotype or personality traits) and the influence of skills or capacities acquired through interaction with stressors (emotion-regulation abilities, appraisal styles, *etc.*). Resilient people are more prone to experience positive emotions, realistic optimism, cognitive reappraisal (ability to replace negative thoughts with more positive ones), secure attachment, an active coping with stress, high coping self-efficacy, self-esteem, empathy, prosocial behavior and altruism, a healthy lifestyle (for example, physical exercise) and a sense of coherence (moral compass that gives

meaning of life)[4,16,23,24].

There are also external factors related with resilience at three levels[16]: Family (parental supervision, setting boundaries, bonding, support, *etc.*), school (positive environment, good relationships with teachers and peers, school engagement and extra-curricular activities involvement, *etc.*) and community (positive relationships with friends or neighbors, participation in religious practices, community engagement, community support, *etc.*). All these internal strengths and external resources help to prevent maladaptive responses to adversity[9]. Longitudinal studies have indicated several key factors related with resilience and a successful transition from childhood and adolescence to adulthood, such as social support (family, peer relationships, romantic partners, *etc.*), self-discipline, and good cognitive and executive functioning (planification, cognitive flexibility, *etc.*)[25]. Children exposed to war show increased risk of PTSD in adulthood, but some protective factors against the deleterious impact of war have been identified, including a loving and supportive environment (family, peers, teachers, *etc.*), a shared sense of values and religious beliefs, positive thinking and generosity[26]. Similarly, in patients with psychiatric disorders (depression and/or anxiety), factors predictive of low resilience include lack of purpose in life, less frequent physical exercise and low spirituality[27]. A study with fire-workers indicated that the trait of mindfulness (concentration on and moment-to-moment awareness of bodily activities and feelings) contributed to resilience, thus reducing avoidant coping in response to stress. Fire-workers with this trait reported less alcohol problems and reduced physical, depressive and PTSD symptoms[28].

As mentioned before, resilience is a dynamic process that raises individuals up from life's adversities and allows them to successfully overcome stressful events. The phenomenon known as "stress inoculation" occurs when a person exposed to mild or moderate stressors develops an adaptive stress response and shows a higher resilience to the negative effects of a variety of subsequent stressors[5,29]. As demonstrated by the group of McEwen, the behavioral effects of stress follow an inverted U–shape curve; low and high stress levels induced impairing effects, but intermediate levels promote better coping responses[30]. In the same way as a vaccine induces immunity against disease[2], stress inoculation is a form of immunity or protection against later stress that may be a result of neuroplasticity in the PFC[29]. The "Systematic Self-reflection model" proposes that engaging with moderate stressors can have positive consequences on mental health if sca□olded in self-reflection, a meta-cognitive skill (consisting of an honest reflection on the individual's coping and emotion regulatory practices) that leads to a cognitive maturity and on-going adaptation of the capacity of resilience[31]. On the other hand, substance use and other adjustment problems (depression, anxiety, rule-breaking, *etc.*) have been observed in adolescents from affluent families that have not been exposed to identified stressful experiences. These individuals are now considered as a group at risk that needs to build resilience through positive changes in parenting, construction and maintenance of supportive social networks, promotion of coping self-efficacy and self-esteem, *etc*[32].

## PHYSIOLOGICAL RESPONSE TO STRESS AND RESILIENCE

Exposure to a physically or psychologically stressful stimulus immediately activates a physiological response characterized by a cascade of hormones in the hypothalamus-pituitary-adrenal (HPA) axis that prepare the body for fight or flight. The paraventricular nucleus of the hypothalamus releases corticotropin-releasing factor (CRF), which leads to the release of adrenocorticotropic hormone (ACTH) by the adenohypophysis, which in turn stimulates the release of glucocorticoids (cortisol in humans and corticosterone in rodents) by the cortex of adrenal glands. There are negative feedback mechanisms in the HPA axis; for example, glucocorticoids suppress CRF and ACTH production. In addition, stress activates the sympathetic nervous system (SNS), which induces the adrenomedullary release of noradrenaline (NA). Stress also stimulates the brain's noradrenergic system, resulting in the release of NA from the locus coeruleus (LC) to the amygdala, hippocampus, hypothalamus and PFC [33,34]. Dopamine (DA) release is also altered by stress, with an increase in the PFC and a reduction in the nucleus accumbens (NAcc)[35], and acute stress increases serotonin turnover in the amygdala, hippocampus, PFC and NAcc[36-38], although other studies have shown a lack of an effect of acute stress on serotonin turnover in the amygdala, NAcc, striatum[39] and hypothalamic paraventricular nucleus[38].

Glucocorticoid elevation may cause damage and atrophy of neurons in different brain areas involved in memory and emotional behavior, such as the hippocampus

and amygdala, inducing physical and psychological problems. Moreover, chronic stress interferes with the activity of neurotrophic factors that are responsible for the formation and strengthening of new neurons and synaptic connections, especially in the hippocampus, such as brain-derived neural factor (BDNF). The volume of this structure and the levels of BDNF are reduced in subjects exposed to prolonged stress, which could be a risk factor for the development of PTSD[40-42]. Resilience can avoid these negative effects of stress, for example, through the release of substances that block the physiological stress response. Neuropeptide Y (NPY) and dehydroepiandrosterone (DHEA) counteract CRF and cortisol, respectively[43,44]. Higher levels of NPY in response to acute stress predict less psychological distress and fewer symptoms of dissociation[45]. Furthermore, the brain of resilient people produces more BDNF, which also decreases levels of glucocorticoids in the hippocampus, and BDNF-mediated plasticity increases attention and memory and accelerates recovery from adversity. Resilient people have been shown to exhibit an adaptive stress response, rapid stress recovery (levels of cortisol decreasing fast after adversity) and lower susceptibility to stress-related physical and mental pathology[4].

There is an interface between the endocrine stress response and the immune system. Communication between neural, hormonal and immune systems is mediated by cytokines and chemokines, small molecules that mediate inflammatory processes, corticosteroids, pituitary hormones, catecholamines and neuropeptides[46,47]. Feedback between the peripheral immune system and the brain contributes to individual differences in the behavioral response to stress[48,49]. Resilient subjects display reduced neuroinflammation, which facilitates habituation to and recovery from stressful events and explains the lower incidence of medical and psychiatric diseases amongst these individuals[49,50,51]. Resilient people have lower systemic inflammation, and the psychosocial factors associated with resilience mitigate the impact of stress on systemic inflammation[51]. These bidirectional relationships between resilience and immunity are modulated by the gut microbiota[52]. There is an interaction between the gut and the brain that involves neural, endocrine, and immune pathways. It seems that the stress-induced activation of the HPA axis stimulates the immune system and causes changes in microbial diversity[53]. The gut microbiota has been associated with a wide range of physiological processes, including the response to stress[54]. Oral intake of Bifidobacterium was shown to significantly increase the number of mice that were resilient after repeated SD stress with respect to control animals not receiving treatment[55]. Moreover, administration of Lactobacillus was found to decrease anxiety-like behavior induced by repeated SD stress and to improve the immune response[56].

## ANIMAL MODELS AND BEHAVIORAL PARADIGMS TO STUDY RESILIENCE TO SOCIAL STRESS

Animal models are necessary to understand the different aspects of human resilience, such as physiological or behavioral changes. As mentioned before, after exposure to stress, some humans develop a psychopathological disorder, such as depression or anxiety, while others are resilient to such effects. These disorders are complex and multifactorial and affect many aspects of human life; thus, no animal model can mimic the complexity of human disorder. However, animal models are useful for simulating some of the psychiatric symptoms[57] or behavioral dimensions that characterize a disorder[58]. After exposure to chronic stress, some animals develop depression– and anxiety–like symptoms and other behavioral alterations (susceptible or vulnerable animals), while others exhibit clear resistance to at least some of the maladaptive sequelae of stress (resilient animals). In addition, animal models also contribute to our understanding of the mechanisms underlying the development of resilience, such as the therapeutic effects of the inoculation of stress[59].

In this section, we first describe the animal models and behavioral tests used to study resilience to the symptoms of stress-related disorders, such as anxiety, depression, cognitive impairment or drug addiction and then the models used to induce stress in experimental animals. This is not an exhaustive review of these models, but only a brief description of the main paradigms used in preclinical studies of resilience. We focus on the model of SD stress in rodents, and on the behavioral paradigms that have been used to evaluate its short- and long-term consequences.

## ANIMAL MODELS OF STRESS EXPOSURE

There are multiple techniques to induce stress in experimental rodents. Some of them use pharmacological stressors, such as daily administration of corticosterone[60], or physical stressors, such as restraint or immobilization[61]. Another model is based on a combination of physical and psychosocial stressors (chronic unpredictable stress (UCS) or chronic "mild" stress (CMS) paradigm)[62]. In the CMS, most animals (about 70%) show anhedonia–like symptoms (less sucrose consumption), reduction of hippocampal volume and alterations in glutamate metabolism, although there is a subset of resilient animals that do not exhibit these changes[62]. Resilience to stress has also been studied with the model known as "predator odor", in which the stress response is induced by exposing animals to the odor of a predator[63]. Usually, rats are classified into 3 groups according to the number and type of behavioral deficits observed as extremely, partially, or minimally disrupted. Anxiety–like symptoms, increased acoustic startle responses and reductions in NPY are observed in animals that are extremely disrupted, while partially and minimally disrupted animals exhibit mixed deficits within these domains[63].

The paradigm of learned helplessness is an animal model of depression that is also employed to induce stress and study resilience by exposing animals to the stress induced by an inescapable, unpredictable and uncontrollable foot shock[60,64,65]. After such exposure to stress, a subset of susceptible animals develops learned helplessness (coping deficits to deal with the inescapable shocks), while another subset of resilient animals displays escape responses with latencies similar to those of non-stressed animals[64]. Results are in function of the severity, duration and control over cessation of the footshock, the last variable of which promotes resilience[65].

As commented on before, in the present work we focus on the model of chronic SD stress because it is the most used animal model to study resilience to the effects of stress and has more ethological and ecological validity. In fact, the most frequent type of stress faced by humans is the chronic social stress derived from problems with social interaction (family or friend relationships, work-place stress, bullying, *etc.*). In the chronic SD model, brief episodes of aggression from a more aggressive conspecific in the resident-intruder paradigm result in the defeat of the experimental animal (intruder), which usually shows anxiety- and depression-like symptoms[15,66-69]. In the most widely employed SD model, rats or mice are exposed to SD for 10 days. Each day, the experimental animal undergoes 10 min of physical attack by the aggressive opponent, followed by 24 h of sensory contact. The consequences of this kind of stress are also a function of the severity and duration of the defeat episodes but chronic SD exposure induced an escalation of cocaine and alcohol consumption. To study resilience, genetically inbred C57BL6/J male mice are usually employed. Following chronic SD stress, all mice exhibit heightened reactivity of the HPA axis, deficits in exploration (interpreted as increased anxiety) and polydipsia[70]. However, there are differences between susceptible and resilient mice regarding other consequences of chronic SD. Resilient mice do not exhibit social avoidance, hyperthermia elicited by social interactions, anhedonia–like symptoms, or metabolic syndrome, characterized by over–eating, obesity, and leptin resistance[70,71]. Approximately 35% of C57BL6/J mice are resilient, although the relative distribution of resilience differs across strains [72]. Similarly, wild-type Groningen rats have better coping strategies and are more resilient to SD stress than Wistar rats[73].

A variation of the classical 10-day SD paradigm consists of exposing animals to intermittent repeated SD (IRSD); usually, four episodes of defeat separated by intervals of 72 h. The IRSD model is frequently employed in studies on the influence of social stress on vulnerability to developing drug addiction. Exposure to IRSD has also been shown to increase the rewarding effects of drugs of abuse[14,74,75,76]. In our laboratory, mice exposed to IRSD during adolescence or adulthood exhibit a long-term enhanced sensitivity to the rewarding effects of drug of abuse such as cocaine and MDMA[77,78,79].

To study the phenomenon of "stress inoculation" several types of moderate stressors have been used, including exposure to intermittent foot shocks[80] and brief intermittent maternal separations during early periods of life[81] or a combination of maternal separation and UCS[81]. Infant rats exposed to intermittent foot shocks subsequently respond more effectively than non-stressed control rats when confronted with novel situations[80]. The combination of maternal deprivation during early life with UCS during adolescence promotes greater resilience in adulthood than maternal deprivation alone or when combined with UCS[81].

During chronic exposure to stress, behavioral strategies that limit the experience of stress may promote resilience[5]. During chronic SD, animals that engage in less submissive postures when threatened and attacked by the opponent show less social avoidance, suggesting that this behavioral coping strategy reduces the effects of the stress[82]. Behavioral manipulations have also been used to reduce the effects of stress and increase resilience; for example, exposure to physical exercise[83,84] or environmental enrichment[85].

## BEHAVIORAL PARADIGMS TO STUDY STRESS-RELATED PSYCHIATRIC DISORDERS

### *Behavioral tests of anxiety- and depression-like symptoms*

The forced swim test (FST) is a classic behavioral test of depression-like symptomatology in which animals are placed into a cylinder filled with water and forced to swim during a period lasting a few minutes. Initially animals attempt to escape and swim, but afterwards they stop fighting and become passive. Immobility (passive floating with minor movements necessary to keep the head above water) is interpreted as a failure to persist in escape-directed behavior, hopelessness, negative mood and depressive-like behavior. The FST is frequently used to evaluate resilience since SD increases immobility in this test in susceptible but not in resilient animals[60,86,87,88]. Similar to the FST, the tail suspension test (TST) measures immobility, which is considered to represent despair and depressive-like behavior[89]. Rodents are hung in an uncontrollable fashion by their tail for a few minutes[90] and, after initial escape-oriented movements, develop an immobile posture. The effects of SD exposure in the TST are unclear, and it has been suggested that this paradigm models the stress-coping strategy from which depressive-like behavior is inferred[91]. An increase in immobility is observed in animals reared in a limited bedding and nesting environment, which induces erratic maternal care and social stress[92]. Similarly, exposure to chronic mild stress (CMS) has been shown to increase immobility in anhedonia-susceptible animals[87]. However, our group has recently observed a reduction of immobility after IRSD exposure, which could be interpreted as an enhanced reactivity of defeated mice to the situation of moderate inescapable stress that the TST represents [93].

Anhedonia– or depressive-like symptoms are also frequently evaluated by measuring sucrose consumption. During training, after some hours of food and water deprivation, a bottle containing a sucrose solution is made available in the home cage. Sucrose intake is measured at different intervals during stress exposure and is reduced in vulnerable but not resilient stressed animals[70,71,88,94,95]. The splash test consists of spraying a 10% sucrose solution on the dorsal coat of a rodent to stimulate grooming behavior. An increase in the latency of grooming and a decrease in the time and/or frequency of grooming is interpreted as depressive-like behavior[96]. This test has also been used to evaluate resilience to the consequences of SD stress[60,93].

In the social interaction test, animals are placed within an open field in two trials (2.5-10 min), in the absence (no target) and presence (target) of a conspecific animal contained in a perforated Plexiglas cage, in order to allow for social interaction while preventing confrontation. Social avoidance is considered to take place when the experimental animal spends less time in the area immediately surrounding the enclosure containing the opponent (interaction zone) and more time in the corners of the open field. Social avoidance is associated with depressive-like behaviors and is frequently observed after SD exposure in susceptible but not in resilient animals[70,71,93,97,98].

The novelty suppressed feeding test is based on the innate fear of rodents of novelty and the inhibition of feeding behavior when exposed to a novel environment. Animals' access to food is restricted for 12-24 h. Animals are placed in a corner of a box containing a pellet of food and the latency to begin eating is recorded. Immediately after this, animals are placed in its home cage and the amount of food consumed in 5 min is measured. This test detects behaviors related to depression and anxiety, because a conflict appears between the anxiogenic environment and hunger-induced behavior[60,99].

The elevated plus maze (EPM) is one of the most used paradigms to measure anxiety in rodents. This test is based on the natural aversion of rodents to open elevated areas and the exploratory behavior that they exhibit in novel environments. The apparatus, elevated about 50 cm above floor level, consists of two open arms and two enclosed arms, and the junction of the four arms forms a central platform. Subjects

are placed on the central platform and allowed to explore the maze for 5 min. The total time spent in and the number of entries into the open (and closed) arms, and the percentage of time and entries into the open arms are measured. Anxiety levels are considered to be lower when the measurements in the open arms are higher and those in the closed arms are lower, and vice versa[100,101]. Mice exposed to chronic SD exhibit higher anxiety levels in this paradigm[93,97,102]. The EPM is also frequently used in studies of resilience to the effects of social stress on anxiety[60,92,102]. In a recent study in our laboratory, we observed that mice that were resilient to the effects of stress on cocaine reward spent less time in the open arms[93].

In the open field/exploration test, the animal is placed into an open-field arena for several min and its locomotor activity is evaluated by measuring distance travelled and velocity. A reduction of these measures is indicative of anxiety[103]. Sometimes the open field is divided into a center and a surrounding area, with thigmotaxis being indicative of anxiety. Maternal separation decreases the time that mice remain in the center of the open field[104]. SD induces deficits in exploration that are not observed in resilient animals[60,70,71,102].

The hole-board test is used to evaluate anxiety-related and novelty-seeking behavior of rodents. This test is carried out in a square box with equidistant holes in the floor. The animal is placed in a corner of the box and is allowed to freely explore the apparatus for a few minutes. Head-dipping represents exploratory tendencies that are distinct from general locomotor activity; thus, the latency to perform the first head-dip and the frequency of dips is recorded. Stress exposure elevates anxiety-related behavior in the hole-board test in rats and mice[105,106]. In our laboratory, we have observed that mice with low novelty-seeking are resilient to the effects of SD on cocaine reward[93].

### *Behavioral tests to evaluate cognitive impairment*

The novel object recognition test evaluates episodic memory in rodents[107] and has been used to measure cognitive dysfunction according to deficits in object-context identification[108]. The task is performed in an open field box and consists of three phases: habituation (free exploration of the empty box), training (exploration of the box, which contains two small river stones) and test (one of the stones is replaced with a small plastic toy). In the training and test sessions, separated for a memory retention interval (1 min), the exploration of the objects is measured for 3 min. It is assumed that if the animal recognizes the stone, it has spent more time exploring the new object. Exposure to different paradigms of stress induces cognitive deficits in recognition memory[94,104,105,109]. Acute[110] and chronic[97] SD impairs performance of the object recognition task. This task has also been used to study resilience to the impairing effects of social stress on cognition[88,94,97,111,112].

The Morris water maze task measures spatial memory that is dependent on the hippocampus[113]. The apparatus consists of a circular swimming pool, divided into 4 equal quadrants (NW, NE, SE and SW), with an escape platform placed 1 cm below the water surface. Several visual cues surrounding the maze are placed on the walls. During the training phase the animal is placed in the water inside one of the quadrants and allowed to swim freely until it locates and climbs onto the platform. If the animal fails to locate the platform, it is guided to the platform by the experimenter and allowed to stand on it for several seconds. The training is performed over 4-5 consecutive days (3 trials per day), measuring the escape latency (the time taken to locate the platform in each trial). The test is performed 24 h after the last training session (the platform is removed and the time spent in each quadrant is measured). If the animal recalls the placement of the hidden platform it will spend more time in that quadrant. Unpredicted CMS impairs performance of the water maze[114], but chronic SD stress does not affect this task[102]. The water maze has also been used to study resilience to the effects of stress on cognitive processes[114,115]. An interesting study [115] showed that rats that emitted ultrasonic vocalizations during intermittent swim stress later showed resilience in the Morris water maze and an instrumental swim escape test.

The Y-maze is a spatial task that requires intact hippocampal function[116]. The Y-maze apparatus has three identical and symmetrical arms that radiate out from the center. Explicit cues are presented outside the maze (located on the walls around the room). In the first trial, the animal is placed in one arm, designated as the "start" arm, while another arm is blocked so that the animal can only explore the start and the other arm. After 4 h, in the second trial, animals are placed in the start arm and can freely explore all three arms. The number of entries and the time spent in each arm is measured. If the animal recalls the arms previously explored in trial 1, it will spend more time in the "novel" arm in trial 2 (discrimination performance). CMS induces

deficits in the performance of the Y-maze among vulnerable anhedonic-rats[88]. Acute [110] but not chronic[117] SD stress also impairs performance in the Y-maze. However, the combination of chronic SD with a slight peripheral infection (produced by injection of a sub-threshold of LPS) impairs the performance of susceptible mice in the Y-maze [111].

The radial arm maze is a model of hippocampus-dependent memory. Animals are food-restricted (approximately 85.0% of their previous body weight) and pre-trained to associate the maze with a food reward placed at the end of all 8 arms. Subsequently, the animals are trained for several consecutive days. In each trial the animal is placed in the central chamber of the maze for habituation and can then freely explore the arms until it consumes all food reward or until a maximum time. The measurement of memory is the number of errors committed, defined as entries in a previously visited arm[118,119]. Chronic stress induced by visual and olfactory exposure to a predator (Long Evan rat) without direct physical contact impairs performance in the radial maze[118]. Similarly, maternal separation induces an overall impairment in the performance of the radial maze in adulthood; however, this impairment is observed in susceptible, but not in resilient mice[119]. On the other hand, adult rats exposed to maternal deprivation perform better in the radial maze, an effect probably related with the phenomenon of inoculation of stress[120].

The radial arm water maze also evaluates spatial ability in rodents[121,122,123]. In this case, the radial arm maze is filled with cloudy water to conceal a platform placed in one of the eight arms, and there are prominent extra-maze cues on the walls of the room. The animals perform several trials in three days, which consists of placing the animal into an arm (the start arm, which does not contain the platform). When the animal reaches the hidden platform it remains on it for several seconds to visualize the room spatially. If the animal fails to find the hidden platform, it is guided there by the experimenter. The number of entrances is measured in each trial. Two types of errors are considered in each trial; reference memory errors (number of first-time entries into arms that did not contain the platform) and working memory errors (number of repeat entries into an arm that did not contain the platform). Chronic restraint stress impairs radial arm water maze performance[122,123], but this effect recedes with time[124] and is prevented by environmental enrichment[85].

It is important to note that chronic stressors do not affect the performance of females in most of these tests (spatial object recognition, radial arm maze, Morris water maze, Y-maze), while males show stress-induced impairments in all of them[125]. These sex-dependent differences include the use of different strategies by the sexes to solve cognitive tasks and may be related to estradiol levels[87].

### *Animal models of addiction-like symptoms*

The animal models of drug reward and addiction-like symptoms are essential to progress in understanding the biological basis of SUD and for the identification of new therapeutic targets. Drug addiction is a neuropsychiatric disorder characterized by loss of control over drug-seeking and drug-taking, the presence of a negative emotional state and an intense craving for the drug when it is not available, and a high propensity to relapse even after long-term periods of abstinence[126]. Drug addiction represents a profound disruption of different neural circuits, including a deficit of the brain reward system, an over-activation of the stress systems, aberrant associative learning (which confers exaggerated incentive salience to stimuli or contexts associated with the drug), and a dysfunction of the PFC, resulting in the inability to inhibit drug-taking behavior. The transition from an initial recreational and controlled drug use to compulsive consumption is also related with a change from the ventral to the dorsal striatum in the control of drug use behavior, with the consequent development of rigid stimulus-response habits[127,128].

Drug addiction has a multifactorial nature, since environmental and biological factors interact to confer vulnerability or resilience to the development of this disorder. The complexity of addictive behavior cannot be captured by an animal model, but they are useful in modelling some specific aspects of drug addiction. The two main models to study vulnerability or resilience to drug addiction are the self-administration (SA) paradigm, which is based on the primary hedonic effects produced by the consumption of a drug of abuse, and the conditioned place preference (CPP) paradigm, which focuses on the component of reward related to associative or incentive learning.

The intravenous SA paradigm is the most important procedure for assessing the primary intrinsic reinforcing effect of drugs, and is the most commonly used in rodents[129,130]. In this paradigm animals are trained in daily sessions to obtain the drug by performing an operant response; for example, by pressing a lever or performing a nose-poke. This response is reinforced by injection of the drug, usually

according to a fixed response (FR) program in which the animal must perform a fixed number of responses in order to obtain the dose of the drug. Variable or progressive response programs are also used to measure motivation of the animal for the drug. The oral SA paradigm, frequently used for alcohol, is similar regardless of the way in which the substance is ingested by the animal. Pharmacological and methodological factors may influence the results obtained with the SA paradigm, such as the drug, dose and rate of infusion, duration of the SA session, the requirements of response, the sex and age of the animal, *etc.*

The SA paradigm is also used to study extinction and reinstatement of drug-seeking behavior. During the extinction phase, the drug of abuse is not presented after responding, and as a consequence, a progressive decrease in the operant response takes place[131-133]. When extinction has been completed, reinstatement of the operant response by several stimuli is observed. Reinstatement of drug SA is a model of relapse to drug consumption after a period of abstinence. As in humans, administration of the drug of abuse (priming), re-exposure to drug-associated stimuli, or exposure to stress reinstates the initially learned operant response[134]. Indeed, some researchers have adapted the SA paradigm in order to model the main features of addiction in humans based on the DSM-5 criteria: loss of control or persistence in drug seeking (active responses during periods in which the reinforcer is not available), high motivation for the drug (using a progressive reinforcement schedule), and maintenance of consumption despite its negative outcomes (association between reinforcement and a foot shock)[135]. The SA model has excellent predictive and face validity; however, it also has some drawbacks related with the complexity of the technique (surgical implantation of an intravenous catheter or previous familiarization with the drug for intravenous or oral SA, respectively) and the training of the animals until they effectively acquire operant response.

Using the SA paradigm, it has been demonstrated that exposure to social stress increases the reinforcing effects of drugs of abuse[136-139]. Recently, resilience to these effects has also been studied using different types of social stress and drugs of abuse, such as cocaine[140-143], methamphetamine[144] and alcohol[145-147].

The CPP is a paradigm that evaluates the conditioned rewarding effects of a drug of abuse, since some contextual stimuli acquire appetitive properties when associated with the drug[148-151]. This paradigm is characterized by its methodological simplicity and is thus frequently used. Animals are conditioned in a box with two or three compartments that are clearly distinct in terms of the stimuli present in each compartment; for example, they have different colored walls and floor textures. Before conditioning, a pre-conditioning phase takes place to evaluate the time spent by the animal in each compartment without any treatment. During conditioning the animal receives the drug (usually 4 injections in 4 or 8 days) in a specific compartment (without access to the other compartment) and physiological saline in the opposite compartment. Later, in the post-conditioning phase (equal to pre-conditioning) it is evaluated whether the animal has learned to associate the rewarding effects of the drug with the environmental cues present in the drug-paired compartment. If the animal spends more time in this compartment (in comparison to the time spent in pre-conditioning or to the time spent in the saline-paired compartment), it is considered that the animal has acquired CPP. All drugs abused by humans induce CPP in rodents [150].

As described for the SA paradigm, the CPP procedure can also be used to evaluate other processes besides acquisition, such as extinction and reinstatement of motivated behavior[148]. To induce extinction, animals are placed in the CPP box and perform daily or weekly sessions similarly to pre- and post-conditioning (*i.e.*, they are exposed to the previously drug-paired compartment without administration of the drug). Progressively, the association between the reinforcing value and environmental cues weakens, and the CPP is finally extinguished. The period needed for extinction of CPP is influenced by different factors, including exposure to stressful events. For example, exposure to SD before each acquisition session[152], or 3-weeks before the initiation of the CPP procedure[78], slows the extinction of MDMA-induced CPP. After extinction, an injection of the drug of abuse (priming) or exposure to stress induces the reinstatement of CPP. In this paradigm, reinstatement refers to the recovery of the conditioned response and involves renewed memory of the association - learned during conditioning - between the reinforcing effect of the drug and the environmental cues associated with its pleasant effects. In our laboratory we have observed that SD exposure induces reinstatement of the CPP induced by cocaine[153,154].

The CPP has been widely used to evaluate the influence of social stress on the conditioned rewarding effects of different drugs of abuse, including alcohol, cocaine and MDMA[15]. In our laboratory, the animals are exposed to SD three weeks before

initiation of the CPP procedure. We have seen that exposure to SD induces a long-term increase in the rewarding effects of cocaine, since defeated mice acquire CPP with doses that are ineffective in inducing place conditioning in control mice[77]. Furthermore, we have observed how SD induces a long-term enhancement in the vulnerability of mice to priming-induced reinstatement of the CPP induced by cocaine [155] and MDMA[78]. In addition, the CPP model has been used to study resilience to the effects of social stress on the rewarding effects of methamphetamine[156], MDMA [157] and cocaine[93,143,158,159,160-163].

Finally, the effects of social stress on alcohol intake and resilience to these effects have been studied in the two-bottle choice test, a paradigm of voluntary consumption, in which animals can choose freely, during a limited time, to drink from one of the two bottles placed in the home cage: one containing water and the other containing alcohol [92,164].

## ADVANCES CONCERNING THE NEUROBIOLOGICAL SUBSTRATES OF RESILIENCE

The study of the neurobiology of resilience is a relatively young area of scientific investigation[24,35]. Research carried out with animal models in the last decade has identified several behavioral, hormonal, neural and molecular mechanisms underlying the development and enhancement of resilience, mainly in relation with the reduced susceptibility to develop psychiatric disorders, such as depression or PTSD, after stress or trauma (Figure 2). As Russo *et al*[5] noted, resilience is mediated not only by the absence of neurobiological abnormalities that occur in susceptible animals after stress exposure (passive resilience), but also by the presence of neuroadaptations which occur in individuals that are resilient to stress, which help them to maintain normal functioning (active resilience). In this section we review the main results obtained in studies using electrophysiological, optogenetic, pharmacological, and molecular profiling techniques to unravel the neurobiological substrates of resilience to the negative consequences of chronic SD stress, mainly social avoidance and anhedonia. Advances in this field may guide ongoing research regarding the neurobiological substrates of resilience to the effects of SD on addiction disorders.

### *Glutamatergic system*

The glutamatergic system seems to play an important role in resilience to stress[165]. Chronic stress reduces the dendritic spine density of glutamatergic neurons in the PFC and hippocampus, while it increases it in the amygdala and NAcc[166]. In the chronic predator and SD stress paradigms, resilient mice show greater expression of immediate early genes (c–Fos, FosB, or ΔFosB) in glutamatergic neurons of the medial PFC[106,167,168] and in medium spiny neurons (MSN) of the NAcc, inducing expression of the AMPA glutamate receptor subunit GluA2[169]. Optogenetic stimulation of either medial PFC or amygdala glutamate afferents to the NAcc induces resilience[168,170], while attenuation of glutamatergic transmission from the ventral hippocampus to the NAcc is pro-resilient, and reduced activity in the ventral hippocampus is observed in mice that are resilient to the effects of chronic SD[170]. Furthermore, several environmental manipulations that promote resilience to stress–induced depression– and anxiety–like behaviors, such as early intermittent maternal separation and environmental enrichment, increase the volume of ventro-medial PFC[171], the dendritic spine density of hippocampal and PFC neurons[172], and expression of FosB and ΔFosB in medial PFC[167]. All these results suggest that increased neuronal activation of mPFC represent pro–resilience adaptation[5].

NMDA receptors have been implicated in stress resilience[165]. Mice susceptible to chronic SD stress exhibit low activity of hippocampal extrasynaptic NMDA receptors, and enhancement in the function of these receptors prevents social avoidance behavior in defeated mice[173]. The NMDA antagonist ketamine protects against the long-term consequences of different types of stress in animal models[165,174]. For example, administration of ketamine protects mice against SD-induced depressive symptomatology in the FST and against learned helplessness-induced coping deficits when dealing with inescapable shocks, although it did not protect against the anxiety-like phenotype in the EPM[60]. Reducing brain D-serine, an endogenous co-agonist at the glycine site of the NMDA receptors, may also improve stress resilience[175], and NMDA receptor blockade in the right medial PFC facilitates resilience to SDS-induced anxiety in mice[176]. Furthermore, we have observed that the NMDA antagonist memantine increases resilience to the effects of IRSD on the CPP induced by cocaine in

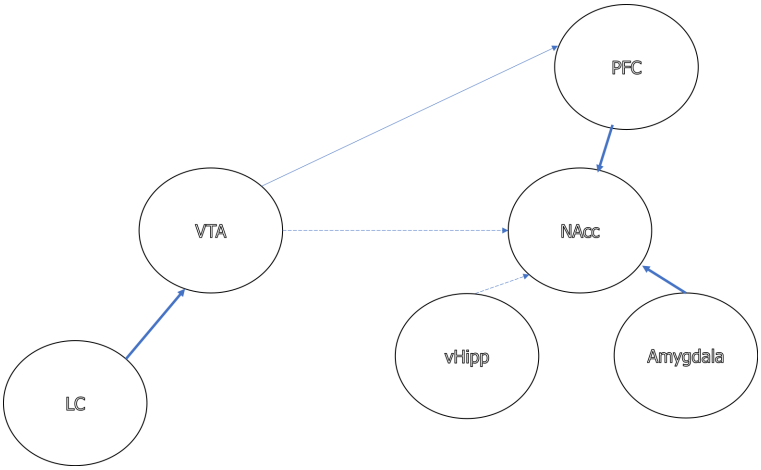


**Figure 2 Simplified diagram of the neurobiological substrates of resilience to the effects of social defeat in rodents.** Resilience is induced by activation of the pathways indicated with gross lines and by inhibition or normalization of the pathways represented with dashed lines. LC: Locus coeruleus; VTA: Ventral tegmental area; PFC: Prefrontal cortex; NAcc: Nucleus accumbens; vHipp: Ventral hippocampus; Amyg: Amygdala.

mice[77].

Some subunits of AMPA receptors might be involved in resilience. For instance, mice resilient to developing social avoidance after chronic SD show increased GluR2 mRNA expression compared to control mice, while susceptible mice display a decrease in GluR2 levels in the NAcc[169]. In addition, AMPA agonists prevent increases in corticosterone and latency to feed in the novelty-suppressed feeding induced by chronic stress[177].

The role of metabotropic glutamate receptors in stress resilience remains uncertain [165]. After 3 days exposure to learned helplessness or SD, mGluR5 KO mice exhibit enhanced susceptibility to stress-induced depression, social avoidance, and anhedonia. In addition, susceptible mice exhibit less mGluR5 in the NAcc than both resilient and control mice[178]. Finally, blockade of mGlu2/3 and deletion of mGlu2, but not mGlu3, promotes stress resilience, including protection against stress-induced depressive-like symptoms[179].

### *GABAergic system*

There are a limited number of studies on the role of GABA in resilience to the effects of chronic SD, and the effects observed to date have been in the function of the brain area containing GABA neurons and the subtype of receptor studied.

Chronic SD defeat activates GABA neurons of the dorsal raphe nucleus (DRN) and strengthens inhibition of 5-HT neurons in susceptible mice, but this effect is not observed in resilient mice without a social interaction deficit; accordingly, optogenetic inhibition of DRN GABA neurons was shown to disinhibit 5-HT neurons and promote resilience[180]. Conversely, SD stress impairs the inhibitory tone in the NAcc. Stress-susceptible mice exhibit reduced levels of inhibitory synaptic markers and protein expression (vesicular GABA transporters (vGAT) and gephyrin) in the NAcc that are not observed in resilient mice[181]. GABA (B) receptors in the habenular nuclei are also down-regulated in susceptible mice, which display elevated c-Fos expression in this structure; furthermore, intra-habenular injection of baclofen and CGP36216 (GABA (B) agonist and antagonist, respectively) reverses social avoidance[182]. Studies with KO mice have also indicated the role of GABA in resilience to the effects of SD. GAT-1-deficient mice demonstrate an increase in resilience to the effects of acute stress on depressive- and anxiety-like symptoms[183,184]. Moreover, GABA(B1a) KO mice are more susceptible, whereas GABA(B1b) KO mice are more resilient to both stress-induced anhedonia and psychosocial stress-induced social avoidance[185].

### *Dopaminergic system*

Adaptations within the brain reward system, and in particular in the mesolimbic DA circuit, are closely associated with resilience to the effects of chronic SD stress. The firing rate of ventral tegmental area (VTA) DA neurons has been shown to be increased in susceptible animals exposed to chronic SD; conversely, resilient mice show an increase in K + channels that normalizes hyperexcitability of VTA DA

neurons and prevents social avoidance and sucrose preference deficit[70,186,187]. A further increase in the hyperactivity of VTA DA neurons in susceptible mice produced by optogenetics or pharmacological treatments induces homeostatic plasticity and reverses depression-related behaviors[187,188]. Such studies bring to light the self-stabilizing capacity of midbrain DA neurons of the brain reward system[187]. A recent study has demonstrated that a baseline level of physical activity (voluntary wheel running), mediated by the tyrosine hydroxylase (TH) neurons in the VTA, affects susceptibility and resilience to chronic SD. Mice with low levels of physical activity showed lower TH expression in the VTA and were susceptible to SD, while mice with high levels of activity showed higher TH expression and were resilient to SD; activation of TH neurons in the VTA of mice with lower levels of activity increased resilience, while inhibition of these neurons increased susceptibility to SD[189].

Different MSN subtypes of the NAcc (D1-MSN and D2-MSN, with predominant expression of DA D1 and D2 receptors, respectively) are also involved in susceptibility and resilience to chronic SD stress. Susceptible mice that develop depression-like behaviors after SD showed decreased frequency of excitatory synaptic input in D1-MSN (but an increase in D2-MSN); in addition, enhancing the activity[190] or the spine density[191] of D1-MSN has been shown to induce resilience. Fosb-targeted histone methylation in D1-MSN or histone acetylation in D2-MSN promote a susceptible, depressive-like phenotype, while histone acetylation in D1-MSN or histone methylation in D2-MSN increase resilience[192]. Resilient animals also display an upregulation of synaptic strength at dendritic spines of D1-MSN and a concomitant downregulation in D2-MSN[193]. In addition, chronic SD selectively reduces NLGN-2, a neuronal postsynaptic cell adhesion protein, in DA D1-MSN of susceptible mice [181]. D1-MSN activity prior to stress is also a predictor of resilience, as mice that will later become resilient display increased baseline D1-MSN activity[194].

Single and repeated SD stress induces D1 receptor-mediated changes in medial PFC neurons. A single SD was shown to increase arborization and the spines of apical dendrites of pyramidal neurons in the medial PFC, whereas repeated SD reduced dendritic lengths of these neurons[195]. Optogenetic inhibition of the DA VTA neurons projecting to the medial PFC promotes susceptibility[188]. DA D1 receptors in medial PFC excitatory neurons plays a role in suppressing susceptibility to stress, since repeated SD reduces the expression of these receptors in susceptible mice, while its genetic deletion facilitates the induction of social avoidance[195].

DA transmission in other brain areas is also involved in susceptibility or resilience to stress, although results are contradictory. Vulnerable mice were reported to display increased expression of DA D2 receptors in the amygdala[102,196] and increased levels of DA in the hippocampus and PFC[197]. However, another study found that hippocampal dopaminergic activity was inversely correlated with the level of social avoidance induced by SD and chronic treatment with hop bitter acids enhanced stress resilience[198]. Similarly, treatment with caffeine (from 14 days before until the end of SD) reverses social avoidance and anhedonia, and this pro-resilience effect of caffeine is reversed by the antagonism of DA D1 (but not D2) receptors[199].

### *Noradrenergic system*

Noradrenergic (NA) neurons in the LC have direct connections within the VTA and regulate vulnerability to SD through inhibitory control of VTA DA neurons[200]. NA LC neurons projecting to the VTA exhibit enhanced firing activity in resilient, but not susceptible, mice, and optogenetic activation of LC neurons in susceptible mice reverses depression-related behaviors[201]. α1- and β3-adrenergic receptors are highly expressed in VTA neurons projecting to the NAcc, and the antagonism of these receptors blocks the effects of the optogenetic and pharmacologic activation of LC neurons; *i.e.*, it reverses hyperactivity and homeostatic plasticity in the VTA-NAcc pathway in susceptible mice[201].

### *Serotonergic system*

Plasticity of the serotonergic system also contributes to susceptibility or resilience to the effects of SD stress, although the role of serotonin depends on the brain area under consideration. As commented on before, inhibition of GABA neurons of DRN disinhibits 5-HT neurons and promotes resilience to social avoidance induced by SD in mice[180]. In fact, the mechanism underlying SD-induced social avoidance is a hyposerotonergic state in the DRN, which results from the activation of p38α mitogen-activated protein kinase (MAPK), the consequent translocation of the SERT to the membrane, and the increase in the rate of serotonin uptake[202]. Down-regulation of the 5-HT1A auto-receptors in 5-HT neurons of DRN (which can result in increased 5HT release), improves behavioral resilience to SD[203]. On the other hand, rats

susceptible to stress-induced anhedonia, but not resilient rats, display an increased number of neurons expressing tryptophan-hydroxylase-2 (TPH2, the enzyme for serotonin synthesis) in the ventral subnucleus of the DRN (DRNv), while activation of the CRF containing neurons of the amygdala induce resilience, suppressing the increase of TPH2 positive neurons in the DRNv and ameliorating anhedonia in susceptible rats[204]. Mice resilient to the effects of chronic SD also display a reduction of serotonin in the hippocampus[197].

### Cholinergic system

ACh signaling in the hippocampus may be related with differential responses to SD stress. Interference with hippocampal AChE activity increases anxiety- and depression-like behaviors and decreases resilience to repeated SD stress[205]. In addition, nicotinic cholinergic (nACh) signaling in the basolateral amygdala seems to play a role in the effects of SD, since β2 nAChR subunit knockdown undermines resilience to SD stress and c-fos immunoreactivity in this structure[206].

### Endogenous opioids

Chronic SD stress increases μ and κ opioid receptors and reduces δ opioid receptors in the PFC of susceptible mice (with social avoidance), while resilient mice show no alteration in the levels of opioid receptors and increased p38 MAPK phosphorylation [207]. Besides the increased mRNA expression of the opioid μ and κ receptors in the frontal cortex, susceptible mice also show a reduction in the expression of μ receptors in the hippocampus and a reduction of κ receptors in the basolateral amygdala[208, 209]. Conversely, mRNA of dynorphin is increased in the shell of NAcc in susceptible rats and in the striatum of resilient animals[208].

Chronic SD also decreases mRNA levels of δ opioid receptors and enkephalins in the basolateral amygdala and in the ventral hippocampus (CA1) of vulnerable mice [209]. Administration of an agonist of δ receptors increases resilience and reduces oxidative stress markers in CA1 neurons, a mechanism that may be involved in the pro-resilient effect of enkephalin signaling[210]. Similarly, susceptible animals display reduced enkephalin levels in the NAcc and enkephalinase inhibitors, while intra-NAcc infusion of a δ receptor agonist induces resilience and increases phosphorylation of extracellular signal-regulated kinase (ERK), which is downregulated by SD stress[211].

μ-opioid receptor G-allele carriers express less submissive behavior and exhibit resilience to SD, demonstrated by a lack of subsequent social avoidance and reductions in anhedonia; moreover, the resilience in question was associated with a greater induction of c-fos in the NAcc and periaqueductal gray[212].

### Neuropeptide Y

Neuropeptide Y (NPY) is a neuropeptide that is widely distributed in the brain and promotes protective responses in the face of stress[213,214] by inducing anxiolytic effects and counteracting the anxiogenic effects of CRF. Multiple studies indicate a positive correlation between NPY levels and resilience to the deleterious effects of stress in humans and animal models. A significant down-regulation of NPY in the amygdala and hippocampus has been observed in animals with PTSD-like symptoms, and administration of NPY reversed the negative behavioral effects of predator-scent stress[63]. Mice susceptible to the effects of chronic SD also show a down-regulation of NPY and NPY2R in the hippocampus[215]. Administration of NPY significantly reduces submissive/defensive behaviors in socially defeated hamsters, although this effect is not mediated by the Y1 receptor[216]. Such results demonstrate that NPY may function as an important factor in resilience against the impairing effects of SD, and a recent study has suggested that deficiency of NPY plays a role in the impairing effects of stress on hippocampal function and the processes mediated by this structure[217].

### Orexins

Orexins (OX) produced in the lateral hypothalamus also play an important role in the response to stress[218,219]. Chronic SD stress-susceptible and -resilient mice (with or without deficits in social interaction) display different levels of prepro-OX in the hypothalamus[220] and basolateral amygdala, with increased OX1 and decreased OX2 observed in susceptible mice[221]. Brain infusion of OX A was found to induce an antidepressant-like effect only in susceptible mice, while co-infusion of OX A and B induced an anxiogenic effect only in resilient mice[220]. In addition, knocking down the OX2 receptors in the basolateral amygdala increases social avoidance and reduces the time spent in the center of an open field[221]. Similarly, after SD stress, resilient (actively coping) rats express lower prepro-OX mRNA levels than passively coping

rats, while inhibition of OX before each SD episode increases social interaction and decreases depressive-like behavior in vulnerable rats[222]. These results suggest that lower levels of OX contribute to resilience to repeated SD, although in this context it is important to consider the different types of OX receptors. A recent study indicated that OX1 and OX2 receptors exert opposite functions and that the agonism of OX2 receptors promotes resilience to the anxiety and depression induced by exposure to SD stress in mice[223,224].

### Neurotrophic factors

Neurotrophic factors and their signaling pathways, such as BDNF or ERK1/2, have been implicated in the neuroadaptations that take place in response to stress.

ERK is reduced after SD stress in both susceptible and resilient mice[207]. SD also decreases phosphorylation of ERK[211] and the pERK/ERK ratio[225]. Overexpression of ERK2 in the VTA increases susceptibility to SD stress in mice, while blockade of VTA ERK2 activity promotes behavioral resilience and decreases the frequency of firing of the VTA DA neurons, an important electrophysiological hallmark of resilience [226]. Phosphorylation of ERK is enhanced by treatments that induce resilience, such as the intra-NAcc infusion of a delta opioid receptor agonist or enkephalinase inhibitors[211].

BDNF is expressed in the amygdala, hippocampus, PFC and basal forebrain, and acts through its two main receptors, TrkB and p75[227]. BDNF has antidepressant-like effects and enhances hippocampal neurogenesis[228,229], which suggests an important role of this factor in the potentiation of resilience. Chronic SD stress decreases BDNF/TrkB in the PFC, the dentate gyrus (DG), and the CA3 region of the hippocampus, but increases BDNF/TrkB in the NAcc[175,225]. A differential expression of BDNF has been observed in susceptible and resilient mice in function of the brain area studied. Susceptible mice have higher levels of BDNF mRNA in the VTA than resilient and control mice, suggesting that this increase is associated with depressive-like behavior induced by SD[230]. An increase of BDNF-4 has been observed in the PFC of susceptible mice exposed to chronic SD, but the same animals also showed a selective reduction of BDNF-6 transcript in the hippocampus[231]. Conversely, in another study with mice exposed to chronic SD stress, levels of BDNF in the medial PFC and hippocampus were lower in susceptible mice than in control and resilient animals[232]. Finally, several studies support the contribution of hippocampal BDNF expression to resilience to chronic stress[233]. In rodents exposed to SD, activation of hippocampal BDNF/TRKB signaling (by means of branched-chain amino acids, exercise and high protein diets) induces resilience to social avoidance [234,235,236]. In addition, enhancement of BDNF and TRKB levels and signaling has been implicated in the nicotine-induced resilience to the social deficit induced by SD [237].

### Hormones of the HPA axis

Stress activates the HPA axis and the release of stress hormones that regulate the individual response to stress. SD stress induces hypercortisolemia and adrenal hypertrophy in susceptible mice, but not in resilient rodents[48,238]. In addition, susceptible mice exhibit reduced glucocorticoid (GR) receptor expression in the hippocampus in comparison to resilient mice, suggesting that up-regulation of GR and enhancement of GR nuclear translocation in the hippocampus play an important role in resilience to chronic SD stress[238]. Susceptible mice show higher plasma corticosterone concentrations 2 h and 48 h after single and chronic SD stress, respectively; and administration of corticosterone *via* drinking water enhances susceptibility while a GR antagonist alleviates the negative consequences of chronic stress[239]. A single dose of ketamine that improved depressive-like behaviors was shown to decrease plasma corticosterone levels and rescue GR expression and nuclear translocation in the hippocampus of susceptible mice[239].

Resilient rats (with proactive behavior in resisting defeat) show decreased efficacy of CRF[82]. Similarly, mice in which CRF is deleted from GABAergic forebrain neurons were found to display a resilient phenotype[240], and PFC mRNA expression of CRF was stronger in susceptible mice than in resilient counterparts[48]. However, another study showed that increasing CRF neuronal activity in a subtype of GABAergic inhibitory interneurons in the medial PFC promoted lasting resilience to SD stress[241,226].

### Epigenetic factors

A wide variety of genetic factors - polymorphisms of genes of NPY, CRFR1, catecholamines (COMT, DAT, DAR1, DAR4), serotonin (SERT, 5-HTR1A, 5-HTR3A, 5-

HTR2C), BDNF, among others - have been implicated in resilience (for a review see[4,242]). Like all aspects of psychological function, resilience results from the interaction between genes and environment. Epigenetic factors are functional modifications to the genome (such as DNA methylation and demethylation, and histone methylation, acetylation, and phosphorylation) that regulate gene expression and phenotype without changing the DNA sequence. Different epigenetic mechanisms have been linked to resilience[243]. For instance, changes in gene expression and chromatin modifications in specific brain regions are associated with resilience to chronic SD stress[70,231,244,245]. In particular, histone methyltransferases are up-regulated in the NAcc of resilient mice, which exhibit low depression-like symptoms after chronic SD [246], while susceptible mice show reduced g9a mRNA levels in the hippocampus, and a reduction of HDAC-5 and DNMT3a mRNA levels in the PFC[231].

HDAC inhibitors may also regulate stress-related behaviors independently of their action on histones, through prevention of glucocorticoid signaling in serotonin pathways. Deletion of HDAC6 in serotonin neurons prevents the electrophysiological and morphological changes induced by chronic SD in these neurons and blocks the expression of social avoidance[247]. In one study, lower acetylated Hsp90 levels, higher GR-Hsp90 association, and enhanced GR translocation were observed in the DRN of vulnerable mice after chronic SD stress, and a HDAC6-selective inhibitor or the serotonin-selective viral overexpression of the acetylation-mimic mutant of Hsp90 in DRN neurons promoted resilience to chronic SD stress[248].

### *Immune system*

Inflammation may underlie individual differences in vulnerability and resilience to chronic SD stress[249,250].

Exposure to SD increases inflammatory markers, but the enhancement of proinflammatory proteins is more pronounced in susceptible rats (with passive coping during defeats and anhedonia) than in active coping rats[236]. In addition, only susceptible rats exhibit elevated levels of inflammatory proteins (IL-1β, TNF-α, GM-CSF) in the LC [251], and higher systemic levels of interleukin-6 (IL-6)[252]. Rats with short-defeat latencies (vulnerable rats) exhibit increased anxiety- and depression-like behaviors, and inflammation in the ventral hippocampus[253]. On the other hand, selective KO of the miR-106b~25 cluster in peripheral leukocytes promotes behavioral resilience to chronic SD stress[254]. Preexisting individual differences in the sensitivity of the peripheral immune system (IL-6) may predict vulnerability or resilience to social stress [250].

Gut microbiota, important activators of inflammatory substances, have emerged as a putative mechanism for promoting stress vulnerability[253]. For example, in one study, mice that were most susceptible to the behavioral effects of chronic SD (reflected by severe social avoidance behaviors) displayed the greatest changes within particular sets of bacteria in the phylum and genus taxonomic ranks[255].

## RESILIENCE TO THE EFFECTS OF SOCIAL DEFEAT ON THE REWARDING PROPERTIES OF DRUGS OF ABUSE

There is a well-known link between stress and the development of AUD/SUD, and preclinical studies have shown that early life stress, social rank stress, and SD stress impact on vulnerability and resilience to alcohol, cocaine and other drugs of abuse[14,15,256]. However, as mentioned previously, there are few works studying resilience to the effects of social stress on the rewarding properties of drugs of abuse. For example, in the search "social defeat, addiction, resilience" in PubMed we identified only 18 papers, and some of these studies did not employ any paradigm of drug reward or addiction. After an exhaustive search and review of the literature we found only 8 papers on resilience to the consequences of repeated or chronic SD for the rewarding effects of cocaine, alcohol or methamphetamine.

In a classic preclinical study of resilience, Krishnan *et al*[70] demonstrated for the first time that, following exposure to chronic SD stress, mice can be classified as susceptible or resilient according to their differential response to stress. Susceptible mice exhibited anhedonia, social avoidance and anxiety-like behavior in the EPM, while resilient mice did not show such symptoms. This study was also pioneering in demonstrating differences between susceptible and resilient mice in sensitivity to the rewarding effects of cocaine. Only susceptible mice showed CPP after conditioning with a low dose of cocaine, while resilient or non-stressed mice did not acquire CPP [70]. Surprisingly, until recently, no other studies have addressed this issue.

In our laboratory, we have studied the influence of IRSD stress on the rewarding properties of cocaine in the CPP paradigm. Exposure to four episodes of SD during late adolescence (on post-natal day (PND) 47-56) subsequently increased the sensitivity of adult mice to a low dose of cocaine. In particular, 1 mg/kg of cocaine induced CPP in defeated mice but not in non-stressed control mice[77]. In a recent study, we evaluated whether some animals were resilient to the effects of IRSD. Overall, exposure to SD decreased all measurements related to the open arms of the EPM, immobility in the TST, social contact in the social interaction test, and grooming in the splash test. IRSD exposure also increased the sensitivity of the mice to the rewarding effects of cocaine, since only defeated animals acquired CPP. However, the potentiation of cocaine CPP was not observed in all the defeated mice, as some of them were resilient to the effects of IRSD on cocaine reward[93]. In the same study we characterized the behavioral profile of vulnerable and resilient mice during defeat episodes and in several behavioral paradigms shortly after SD. Vulnerable mice that showed CPP also exhibited depressive-like behavior, in line with the results of Krishnan *et al*[70]. In comparison with vulnerable mice, resilient mice displayed different behavioral traits, such as less submissive behavior during episodes of defeat, a lower percentage of time in the open arms of an EPM, lower novelty-seeking in the hole board, higher social interaction, greater immobility in the TST, and higher frequency of grooming in the splash test. These results indicate that the behavioral profile of resilient mice is characterized by an active coping response during defeat episodes, a reduced short-term response to SD (lesser reactivity to moderate unavoidable stress, enhanced concern in a potentially dangerous environment and absence of depressive symptoms), and a lack of long-term responses to SD, as evidenced by the absence of cocaine CPP[93].

Two similar studies also showed that control mice do not develop CPP with a low dose of cocaine, while defeated mice did overall develop a preference for the drug-paired compartment[143,162]. Among the defeated animals, two populations could be distinguished - resilient (did not develop preference) and susceptible mice (developed preference) - and they differed in their active or passive behavior during the SD sessions. As the authors stated, "resilient animals showed less flight and submission behaviors than susceptible mice and they presented attack behaviors towards the residents, thereby showing their resistance to being defeated"[162]. Besides passive coping behavior during SD episodes, susceptible mice (which showed cocaine CPP) also displayed social avoidance and higher IL-6 levels in the striatum and hippocampus after the last SD episode[143]. The results of all these studies suggest that an active coping style can protect the individual from the negative consequences of social stress. It is important to note that differences in the responses to cocaine between susceptible and resilient mice were not always observed, since both subgroups of defeated mice showed similar levels of cocaine SA[143].

Rats exposed to repeated SD (five episodes) and social isolation (approximately 12 wk) can also be classified as SD-prone or SD-resilient, based on their affective (depression-like behavior) and cognitive performance. In one study, although SD was shown to increase alcohol SA in both groups, only SD-prone rats displayed heightened motivation for alcohol, persistent alcohol-seeking despite unavailability, resistance to extinction, and increased cue-induced reinstatement of alcohol SA[145]. Similarly, among rats exposed to SD stress, there was a subpopulation in which SD exposure increased anxiety-like behavior and induced escalation of alcohol SA. In comparison with resilient rats, vulnerable rats showed a strong upregulation of vasopressin and oxytocin that correlated positively with the magnitude of the anxiety-like behavior and alcohol SA[146]. These studies suggest that proneness to depression or anxiety enhances vulnerability to AUD, while resilience to mental disorders induced by stress can protect the individual from the development of AUD.

No studies have evaluated resilience to the effects of SD on the rewarding effects of drugs of abuse other than cocaine and alcohol, although one did show that a single SD episode combined with drug priming potentiated the reinstatement of methamphetamine SA (in comparison with priming alone). Interestingly, the defeat latency during the episode of SD correlated with reinstatement values and c-Fos-immunoreactivity in the basolateral amygdala; priming-induced reinstatement and c-Fos were both potentiated in rapidly defeated rats. Conversely, these effects were not observed in rats that were undefeated during the social encounter, but inactivation of the basolateral amygdala induced potentiation of reinstatement, suggesting that this structure mediates resilience against SD stress[144]. The positive correlation between reinstatement and passive coping (high values of reinstatement in animals with lower latency defeat) was reported in another study, although the authors questioned its real meaning, and proposed that active coping behaviors during SD episodes were

associated with the magnitude of reinstatement[257]. In the study in question animals were exposed to SD-predictive cues (discrete environmental stimuli present during the SD stress experience) or not (control group) before reinstatement. Animals exposed to SD-predictive cues exhibited stronger reinstatement of cocaine SA and increased serum corticosterone with respect to the control group. Reinstatement magnitude was positively and significantly correlated with the time spent in a "submissive supine posture", considered a "passive" coping response. However, there was a narrow (though non-significant) correlation between the magnitude of resilience and three behavioral categories indicative of active coping responses; "aggressive allogrooming", "dominant posture", and "retreat". Further studies are needed to determine the real nature of the correlation between the coping strategy of mice during defeat and subsequent vulnerability to reinstatement.

Although scarce, there is research on resilience to the effects of stress on drug reward carried out with other paradigms of social stress. Mice segregated according to whether they are vulnerable or resilient (socially-submissive or socially-dominant mice, respectively) were exposed to CMS for 4 wk; vulnerable, submissive mice displayed a marked increase in cocaine preference after stress, whereas the preference of resilient, dominant mice did not change. In addition, vulnerable mice displayed an increase in the expression of CRF and a reduction in the expression of DA D1 and D2 receptors in the hippocampus[159]. Following exposure to predator odor stress, animals were classified as susceptible or resilient based on EPM behavior and context avoidance; as expected, susceptible animals showed heightened motivation to self-administer cocaine[141]. With the same model, female and male rats were classified according to their stress-reactive behavior (digging and immobility during exposure to the predator odor); no different subgroups could be distinguished in males because all presented the same profile, but female rats were composed of two different populations - high digging/low immobility *vs* low digging/high immobility - and the former showed increased alcohol SA[147].

Early-life adversity consisting of rearing mouse pups in a limited bedding and nesting environment facilitates the escalation of ethanol intake in males at an earlier stage of exposure to alcohol, while females are insensitive to both stress and alcohol. In the study in question, stressed males exposed to alcohol showed reduced open arm exploration in the EPM and increased immobility in the TST compared to alcohol-naïve mice, although they did not differ in grooming response in the splash test, novel object recognition test or corticosterone levels. There were also no differences among control-reared males exposed or not to alcohol. The authors concluded that early stress accelerates the transition from moderate to excessive alcohol drinking and produces anxiety- and depression-like symptoms during alcohol withdrawal[92].

Finally, foot shock stress has been shown to increase two-bottle drinking in some mice, although others show resilience to this effect, displaying higher G-CSF, IL-13, and leptin levels[164]. All these studies suggest that differences in the ability to cope with stressful situations or in the response to stress results in varying tendencies to develop addictive behaviors.

Stress and drug use can lead to common alterations in synaptic plasticity that may contribute to the ability of stress to elicit relapse. For example, disruption of PKC-mediated GluA2 phosphorylation increases vulnerability to both SD-induced enhancement of social avoidance and stress-induced reinstatement of cocaine AA and CPP[258]. Study of resilience to the reinstating effects of SD stress may help to identify therapies that prevent stress-induced relapse. In line with this, Bruchas *et al*[202] demonstrated that SD stress produced reinstatement of cocaine-induced CPP in wild-type mice, but not in mice with a selective deletion of p38α MAPK in DRN serotonergic neurons. The antagonism of DA D3 receptors also prevents the SD-induced reinstatement of cocaine CPP and the increase in corticosterone provoked by SD[259]. Similarly, elimination of Rgs7 (a regulator of G-protein-coupled receptors) in striatal neurons induces a resilient phenotype, since mice do not show SD-induced reinstatement of cocaine CPP and exhibit an anxiolytic- and antidepressant-like profile [163]. Finally, our group has demonstrated that cannabidiol can prevent SD-induced reinstatement of cocaine CPP[154]. Altogether, these studies suggest that resilience to the effects of social stress on relapse to cocaine seeking can be pharmacologically enhanced.

## FUTURE RESEARCH DIRECTIONS

An important variable in the development of resilience is sex. Studies on resilience to

stress in animal models have been performed almost exclusively in males, although the prevalence of stress-related disorders clearly differ between males and females [260]. Some studies have shown sex differences in vulnerability and resilience to stress through a lifetime. Prenatal or early stress affects males more than females, inducing problems in social interaction, attention and cognition; conversely, adolescent stress induces more effects in females, increasing the risk of depression, anxiety and PTSD [261]. Thus, research suggests that hormonal activation during puberty, pregnancy or perimenopause highlights the risk associated with stress in females. Furthermore, in comparison with males, female rodents are more resilient to the effects of stress on cognitive processes (for example, in the object recognition task), but are more susceptible to the effects of stress in emotional domains (for example, in the sucrose preference and the FST)[86,87]. In fact, the effects of stress on cognition depend on both sex and the learning task. For example, stress improves the performance of radial arm maze, Morris water maze, Y-maze, non-associative learning, and object placement tasks in females, but impairs it in males[262-264]. Conversely, stress enhances learning of aversive conditioning in males but impairs it in females[265,266]. These data point to the possibility that males and females use different coping strategies in the face of stress[5]. Females are more resilient than males to the impairing effects of chronic unpredictable intermittent restraint on spatial memory, suggesting that chronic stress negatively impairs hippocampal-dependent function in males, but not in females[125]. Sexual differences in the consequences of stress on corticolimbic areas[267], including the brain reward system and the NAcc[202,250], and on the NA LC system[109] have also been reported. In fact, there are sex differences in the effects of ketamine on resilience to chronic stress, as this drug is only effective in males[268]. Research on sex differences in vulnerability and resilience to stress in general and in the field of drug abuse in particular should be a priority of future research. The knowledge obtained by studies with females is critical to the development of effective treatments customized for each sex, which may improve psychological disorders derived from or related with stress, including drug addiction.

Age is another essential variable to be taken into account in the study of resilience to the effects of stress. Adolescents are particularly sensitive to environmental influences, since DA circuitries in the PFC undergo maturational changes at this age. This can render adolescents more vulnerable to the effects of SD. For example, we have observed how SD exposure during adolescence induces a long-term increase in vulnerability to reinstatement[78,155]. A recent study has compared adolescent and adult mice according to their resilience or susceptibility to social avoidance behavior after SD exposure. Although the majority of adolescent mice were resilient, they exhibited risk-taking behavior, alterations in PFC DA connectivity and deficits in inhibitory control when they reached adulthood. Conversely, the majority of adult mice were susceptible (they exhibited social avoidance), but did not show alterations in anxiety-like traits, PFC connectivity or cognition[269]. Chronic SD stress in adolescent mice has a profound impact on the development and plasticity of reward circuity, inducing alterations in the glutamatergic development of the NAcc and mesolimbic DA system [270]. In our laboratory we are now studying the behavioral traits that characterize resilient mice exposed to IRSD stress during early adolescence, with the objective of comparing the results with those of our previous study in adult mice. As maternal experience promotes resilience to the effects of stress on cognition[271], we believe it could be interesting to evaluate how maternity modifies resilience to the effects of SD on drug reward and other behavioral outcomes. The study of stress resilience in the context of aging is very limited[165] but necessary, because the likelihood of the mood and cognitive disorders frequently associated with drug addiction increases in older adults. Thus, future research on resilience must be extended to cover the whole lifespan, with a special focus on critical periods such as prenatal or early life, adolescence, maternity and old age. In addition, it is essential to determine if resilience is a stable trait or changes with time. In this context, a recent study has analyzed the behavior of stressed mice after chronic SD at early and late stages of their lives and has found very dynamic courses of behavior: there are those that are consistently resilient or susceptible over time; those that are susceptible in the short term after stress, but recover with time; and there are animals that are initially resilient but develop vulnerability at a later date[112].

Another area of future research in the field of resilience to the effects of stress on drug addiction is that which explores the behavioral or pharmacological manipulations that increase or promote resilience to the effects of stress on drug reward. Regarding behavioral manipulations, we have observed that mice allowed to perform voluntary physical exercise before exposure to IRSD become resilient to the effects of stress on cocaine-induced CPP (Calpe-López *et al*[93], in preparation). Positive social

conditions, such as paired housing, also increase stress resilience and reverse the potentiation of cocaine reward induced by IRSD, effects that are mediated by oxytocin [161]. In addition, it is essential to improve our understanding of the phenomenon of stress inoculation in order to define the right type and level of stress and the influence of age and sex variables. In recent studies we have tested the effects of different types of stress inoculation, which can modulate the subsequent response of mice to IRSD. In particular, a brief maternal separation (6 h on PND 9) or exposure during adolescence (PND 27) to immobilization, to a single SD or a vicarious defeat experience all induced resilience, and mice did not show cocaine-induced CPP (Calpe-López *et al*[93], in preparation).

Regarding pharmacological manipulations, preclinical studies have shown the effectiveness of several pharmacological treatments in models of resilience to the effects of stress on depressive- and anxiety-like symptoms and in animal models of drug addiction. These studies have highlighted the potential of several drugs that may increase resilience to some of the effects of social stress, including cannabidiol, NMDA antagonists and NOS inhibitors, NPY, galanin, and OX receptor modulators. Thus, it may be interesting to test whether these compounds are a therapeutic target to increase resilience to the effects of stress on drug addiction. Among these compounds, we would highlight cannabidiol, which is effective in reducing PTSD[272] and the effects of cocaine and other drugs of abuse[273,274,275]. A recent study in our laboratory demonstrated that cannabidiol prevents the stress-induced reinstatement of cocaine CPP[154]. Thus, it would be interesting to test the potential of cannabidiol to promote resilience to the effects of stress on the rewarding properties of drugs of abuse. We consider this drug to be a promising pro-resilience compound. Similarly, several studies have demonstrated that the NMDA antagonist ketamine exerts protective effects against the long-term consequences of different kinds of stress in animal models[165,174]. We believe this drug may prevent the long-term effects of stress on drug addiction, as we have demonstrated that another NMDA antagonist, memantine, induces resilience to the effects of social stress on the CPP induced by cocaine in mice[77]. In the same way, the effects of nitric oxide (NO) modulators need to be evaluated, since exposure to stressful events activates NO synthase (NOS), while pharmacological inhibition of NOS reduces depressive and anxious behaviors in animal models[276]. Furthermore, previous studies have demonstrated that NO is also involved in the rewarding effects of drugs of abuse[79,277], and NOS inhibition has been shown to prevent the effects of social stress on the rewarding properties of MDMA in the CPP paradigm[157].

The role of several neuropeptides in the effects of stress in animal models of drug addiction must also be evaluated. As commented on in the previous section, NPY is involved in the regulation of stress responses and plays an important role in emotional behaviors, mediating PTSD and addictive disorders[213-214]. Thus, NPY, as well as galanin[83,84], could induce resilience and prevent the effects of stress on drug addiction. OX play an important role in the response to stress and drugs of abuse [219]. In particular, OX-A activates the HPA axis and induces ACTH and corticosterone release[218]. Furthermore, the antagonism of OX1 receptor blocks the stress-induced reinstatement of cocaine seeking[224,278], and the genetic manipulation of animals to induce a deficiency of OX has been shown to reduce cocaine-seeking after a withdrawal period and responsivity to cocaine-associated cues[22]. Conversely, agonism of the OX2 receptor promotes resilience to the anxiety- and depression-like symptoms induced by SD[224]. Thus, it would be of interest to test whether OX1 antagonists or OX2 agonists increase resilience to the effects of SD in animal models of drug addiction. Finally, p38 MAPKs are key signaling molecules in response to stress, regulation of pro-inflammatory cytokines and drug addiction. For these reasons, p38 MAPK and HDAC6 inhibitors are promising drugs, because they might increase resilience against stress and addiction relapse induced by adverse experiences[160].

It is vital that future research focus on other drugs of abuse, since, with the exception of one study on methamphetamine, cocaine and alcohol are the only drugs to have been evaluated. It is also important to study the relationship between different aspects of resilience (for example, between resilience to the development of depressive symptomatology and resilience against developing drug addiction after stress exposure). Frequently, resilience to a particular effect of stress does not imply resilience to another effect. For example, inhibition of 5-HT synthesis provides resilience against the effects of CMS in the open field, but not in the EPM[103]. Pre-treatment with ketamine before SD protects mice against depressive-like behavior in the FST but does not prevent anxiety-like behavior in the EPM[60]. A recent study showed that susceptibility to SD-induced social avoidance is unrelated to susceptibility to develop a deficit in appetitive, goal-directed motivation after SD; however,

motivational impairments were related to ventral hippocampus hyperactivity, since successful task completion in resilient animals was associated with suppression of ventral hippocampal neural activity[279]. Similarly, rats displaying high cognitive competence in the Y-maze and radial arm maze are also resilient to the negative effects of the FST[280]. Resilience to the effects of SD on cocaine and alcohol reward frequently correlates with the absence of depressive-like symptoms[70,93,143,145].

Finally, translational studies of potential cognitive treatments to increase resilience are essential. For example, cognitive training in humans reduces vulnerability in the face of environmental stress. Similarly, it has been observed that a brief 9-day cognitive training can promote long-term resilience to the CPP induced by cocaine in mice, thus accelerating the extinction of CPP[158]. Coordination between human and animal studies is also required to understand the neural circuit of resilience, and neuroimaging techniques in humans can be combined with classic or more innovative methods in animals.

## CONCLUSION

In the fields of medicine and psychology, the concept of resilience has implied a change of paradigm, placing the focus on factors that maintain health and promote wellness. The majority of research on drug addiction aims to identify individual and environmental factors that enhance the vulnerability of a subject to drug addiction. From our point of view, the incorporation of the concept of resilience - a complex, multidimensional construct - will allow scientists to unravel the neurobehavioral traits that confer protection against developing an addictive disorder after exposure to stressful or traumatic events, as well as permitting the underlying neurobiological substrates of resilience to be determined.

Overall, our understanding of the neurobiology of resilience is still at an early stage, but research in the last decade has made leaps and bounds by identifying genetic, epigenetic, molecular, neurochemical, psychological and environmental factors that protect individuals from the neuropsychiatric disorders related to stress[9,281-284]. Currently, resilience is considered an active and dynamic process that can be enhanced to allow individuals to adapt positively to a stressful context that, in other cases, could increase the risk of developing a psychiatric disorder. This concept of resilience has fueled the number of studies focused on specific protective factors and how the neurobiological mechanisms of resilience (HPA axis, GABA, serotonin, glutamate, DA, NA, acetylcholine, endocannabinoids, BDNF-TrkB, OX/hypocretin, NPY, galanin, *etc.*) can be manipulated to increase stress resilience in high-risk individuals and thus prevent the development of psychiatric disorders related to stress[165,219,281,284-286]. However, as stated before, most studies to date have focused on resilience to the development of emotional and anxiety disorders, while those on resilience to addictive disorders are few and far between. The members of our research team are pioneers in the study of resilience to stress in the context of drug addiction. Besides identifying behavioral traits that predict resilience in mice[93], we have highlighted behavioral manipulations (papers in preparation) and pharmacological treatments that increase resilience to the effects of stress in preclinical models of drug addiction. In particular, antagonism of glutamate receptors and inhibition of NOS reverses the effects of IRSD on cocaine and MDMA CPP[77,157,287], while cannabidiol reduces the effects of cocaine[154,273,274] and blocks SD-induced reinstatement of cocaine CPP[154].

Although promising, research on resilience to developing drug addiction after stress in animal models is not devoid of limitations; namely, the difficulty of determining the intensity and duration of exposure to adversity, and the definition of a concrete criterion to consider an animal resilient (absence or reduction of substance use; resistance to developing a SUD or to reinstatement of drug seeking, *etc.*). In addition, the incorporation of females and rodents at different developmental ages is crucial if the realities of resilience are to be fully understood.

From a translational point of view, understanding how an individual develops resilience is of paramount relevance to the design of training programs that increase this ability and promote coping mechanisms, especially in subjects with a maladaptive stress response. There is a well-known link between stress and the development of AUD/SUD, anxiety and depression disorders. Comorbidity between these disorders is frequent and associated with more severe symptoms and poor treatment outcomes. Besides reducing addictive behaviors, resilience training may have positive effects on mental health, reducing vulnerability to the development of anxiety, depressive, and cognitive disorders. Advances in the identification of neurobiological substrates of

resilience will help in the development of pharmacological and psychological interventions for enhancing resilience to adversity and stress.

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*REVIEW*

# Depression among caregivers of patients with dementia: Associative factors and management approaches

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## Abstract

As elderly people increasingly come to represent a higher proportion of the world's population, various forms of dementia are becoming a significant chronic disease burden. The World Health Organization emphasizes dementia care as a public health priority and calls for more support for family caregivers who commonly play a significant, central role in dementia care. Taking care of someone with dementia is a long-term responsibility that can be stressful and may lead to depression among family caregivers. Depression and related behavioral and cognitive changes among caregivers could in turn affect the status and prognosis of the dementia patient. This review article explores depression in dementia caregivers and summarizes proposed mechanisms, associated factors, management and research findings, and proposes future research directions.

**Key Words:** Dementia; Depression; Caregiver; Caregiver burden; Activities of daily living; Functional status

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**Core Tip:** The prevalence of depression among caregivers of patients with dementia is higher than that of the general population. The cause of depression in caregivers is complicated and thought to be related to the patients, caregivers and cultural backgrounds. Multifaceted treatment for depression is regarded as the current mainstream clinical intervention. In some areas, supplementation with smart technology for interventions to alleviate the burden and depression of caregivers could be considered. There are also some ideas and directions for future research included in the conclusion section of this review.

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## INTRODUCTION

Depression is a common and serious health condition that is different from usual mood fluctuations and short-lived emotional responses to challenges in everyday life. It can cause the affected person to suffer greatly and function poorly at work, at school and within the family. According to the World Health Organization, over 264 million people globally suffer from major depressive disorder, which is one of the leading causes of disability worldwide[1]. The prevalence of depression among dementia caregivers is even higher than that of the general population[2]. Because patients with dementia suffer from impairment in cognitive functioning and activities of daily living (bathing, eating, *etc.*), the caregiver's quality of care to his or her patient or family member is central, and the caregiver is usually with the patient for several hours per day (or resides in the same house). Many studies have shown that the behavioral and psychological symptoms of dementia (BPSD) mutually affect the caregiver's skills and are also reflexively influenced by the caregiver, so the caregiver's own physical and mental health is extremely important. The topics of depression and the burden of caregivers of dementia patients are popular in clinical research. One of the significant reasons is that interventions for caregiver burden and depression are still a great challenge and an unmet need in clinical practice.

Depression can cause a variety of psychological and physical problems and raise the risk of caregiver suicide[2]. It compromises caregivers' physical health[3], reduces caregivers' quality of life[4], and has been shown to cause caregivers to place patients with dementia in an institutional care facility more rapidly[5,6]. Depression in caregivers can also influence dementia patients' cognitive status and has been associated with more rapid cognitive decline in the dementia patients studied[7].

Caregiver depression is producing a growing impact on existing medical care and insurance systems. Guterman *et al*[8] suggest that caregiver depression shows a significant association with increased emergency department use. They report that medical systems should specifically address patient- and caregiver-centered dementia care and suggest that improved health outcomes and lower costs for this high-risk population could be achieved.

Many studies have investigated the factors associated with dementia caregiver depression and explored various interventions to address it. The work presented in this review falls into several categories, including prevalence, mechanism, associated factors, management, and research trends of depression in caregivers of patients with dementia.

## DEFINITION FOR BURDEN AND DEPRESSION IN CAREGIVERS

The author defined a family caregiver as an adult who directly provides observation, encouragement, assistance, or care that substitutes for a patient's efforts related to the activities of elderly patients with dementia. Such activities may include assisting the dementia patient to complete housework cleaning or maintenance, managing economic affairs, facilitating and supervising activities outside the home, and the broad supervision and management of safety, legal, and medically related matters.

### *Caregiver burden*

The author can summarize 4 characteristics on the formation and the source of caregiver burden: (1) Direct care work, assistance in daily activities for patients and implementation of medical care; (2) The gap between the caregiver's expectations and the reality; (3) Breaking the personal routine of the caregiver; and (4) The feelings of taking on the responsibility of the caregiving role.

The caregiver burden has subjective and objective dimensions. The subjective burden refers to the stress and anxiety that the caregiver feels about his or her own situation and the feeling of being manipulated by the care recipient. Objective distress refers to the interference and change of the caregiver's life habits and household caused by care work[9]. In addition to the above concepts, in clinical outpatient

services, caregivers often ask for help and have distress due to the BPSD[10,11].

### Caregiver depression

Depression (melancholia) is an emotional response to chronic frustration and disappointment. In psychopathology, it is an affective and emotional disorder[12]. The etiologies for melancholia can be divided into reactive or endogenous types. In general, the mildest form of depressive mood is difficult to distinguish from the experience of disappointment and loss. It is a common, recurrent, and impairing condi -tion that can lead to future suicide attempts, interpersonal problems, unemployment, and psychosocial dysfunctions.

Approximately 80% of dementia patients are being cared for by their families in the community. It was found that patients spent an average of 6.5 years being cared for at home before they were sent to a nursing institution[13]. It takes an average of 4 to 8 h a day to care for elderly individuals with dementia. Fuh *et al*[14] reported that 56.6% of dementia caregivers care for patients for more than 8 h a day. In the early stage of dementia, family members assist patients with higher and more complex daily life functions, such as assistance in dealing with money or with medication problems. However, as the patient's disease progresses, part of the caregiver's care gradually changes to assisting with self-care, such as bathing, dressing, and eating. The safety of the patient becomes the focus, and the problem of urine or stool incontinence gradually develops. At the same time, the caregiver must also deal with the patient's behavioral disturbances. In the process of caring, caregivers have to face the gradual disappearance and changes of the personality of his or her loved one, and witness the process of degeneration, suffering, distress and facing death. In addition to the direct distress of caring for patients, caregivers also deal with family conflicts, financial problems, and employment problems and adapt themselves to the role of caregiving. Furthermore, family caregivers also play a role in the medical care process of patients, including providing the patient's illness history, describing symptoms, and assisting in medical care[13].

## EPIDEMIOLOGY OF CAREGIVER DEPRESSION

Many studies have investigated the quality of life of dementia caregivers and found that they experienced high levels of grief, ambivalence, and other psychological ailments[15]. Major depressive symptomatology was most common, reported by more than 50% of caregivers[16,17]. A meta-analysis study revealed that depression occurs in at least 1 in 3 caregivers of persons with dementia[18,19]. Some previous studies have also reported high rates of caregiver depression, approximately 30%–83%[20].

## CLINICAL MECHANISMS OF DEPRESSION IN CAREGIVERS OF DEMENTIA PATIENTS

High prevalence rates of caregiver depression may be explained by several factors. Many mechanisms and models have been developed and tested, and the evolution in understanding depression in those who provide care to family members with dementia is introduced in this section.

### Stress process model

The stress process model[21] proposes that caregiver demographics (such as age, sex, employment status, and relationship to the patient) are associated with and actively affect each part of the stress process and types of stress, including subjective stressors, objective stressors, the perception of those stressors, and outcomes such as caregiver burden and depression.

The stress process model assumes that various factors influence stress and coping reactions. Some factors are naturally protective bodily resources that decrease the negative effects of stress. Other associated factors may increase the effects of stress and render the individual more vulnerable to stress. The model suggests that caregiver outcomes are often influenced by subjective and objective stressors, role strains, and psychological strains and are balanced with mediating influences such as coping strategies and social support resources such as family, friends, and other social groups. Other caregiver distress studies identified similar variables present in the stress process model[22]. Caregivers' mental health outcomes depend not only on objective

factors such as the BPSD and number of caregiving hours worked, but also on the caregivers' subjective appraisals of the individuals with dementia or the accompanying situations[23]. Many caregivers misunderstand that problematic behaviors are under dementia patients' control. Caregivers making this assumption are more likely to be depressed than those who attribute the BPSD to the disease itself and accept them[23]. On the other hand, caregivers with a sense of purpose, more closeness with the patients, and higher competencies may more easily find positive rewards in this challenging situation[24,25]. Previous studies have indicated that caregiver outcomes, including a sense of self-efficacy in controlling upsetting thoughts about the patient, rather than mechanistically dealing with problematic behaviors or obtaining respite, are highly associated with improved caregiver outcomes[26-29].

### *Core stress and coping model*

Previous studies[30] suggest a common core model for explaining the formation of caregiver distress. In this core model, BPSD are seen as basic stressors for informal caregivers, the caregivers' personal perceptions of burden as key mediators are incorporated, and it is suggested that higher levels of caregiver burden are positively associated with worse caregiver outcomes.

### *Sociocultural stress and coping model*

Aranda and Knight[31] suggest that culture and ethnicity play important roles in the stress and coping processes of caregivers to elderly individuals. Cultural and ethnic factors may even be associated with specific health disorders and disabilities and explain variations in caregivers' appraisals of potential stressors. Knight and Sayegh [32] suggest a revised model (Figure 1) that takes cultural values into more robust consideration. They suggest that familism as a cultural value adds multidimensional effects and that values regarding social or familial obligations show more influence than family solidarity. Knight and Sayegh[32] further point out that the effects of cultural values and ethnicity on stress and coping processes are found to relate more to social support and coping styles than to caregiver burden. In summary, cultural values are, at best, indirectly related to the mental health of caregivers, which in turn affects the social and family support of dementia caregivers and further affects the way they respond to dementia patient(s) in their care. The authors suggest that these factors are at least indirectly associated with the mental health of caregivers.

### *Systemic family framework model*

The psychological and dynamic dimensions within a family are thought to affect caregiver stress perceptions and coping processes. Acceptance of aversive experiences and a commitment to personal values by the caregiver are proven to be associated with challenges and experiences, including sadness and grief. Although there is usually one member of the family that assumes most caregiving responsibility, the caregiving process impacts the whole family.

Mitrani *et al*[33] applied structural family theory[34] in studying the role of family functioning in caregiver stress and coping processes. They indicated that family functioning partially mediates the relationship between objective burden and caregiver distress in the stress process model (Figure 2). Mitrani *et al*[33] suggested that caregiver distress appraisal may be mitigated by any intervention that is best targeted at correcting problematic family interactions and preserving protective family patterns. Family interventions may enhance the participation of dementia patients in family activities, resolution of disagreements, and expressions of emotionality and further decrease expressed negative responses to the patient.

### *Activity restriction model*

The Activity Restriction Model[35] suggests that the stresses of caregiving discourage one's ability to engage in social and recreational activities, and this restriction is expected to contribute to depression. Mausbach *et al*[36] examined the activity restriction model in the context of dementia caregiver research. Their results suggest that activity restriction significantly mediated the relationship of the caregiving role and depression. On the other hand, they also found that depression acts as a key mediating factor of the caregiving role and activity restrictions. These findings support the use of social and recreational activities of dementia caregivers as opportunities for useful depression-improving behavioral interventions. Moreover, the caregiver's participation in pleasurable activities (*i.e.*, behavioral activation) could be promoted with behavioral and cognitive-behavioral approaches[37]. These results raise the importance and application of the activity restriction model in explaining and treating

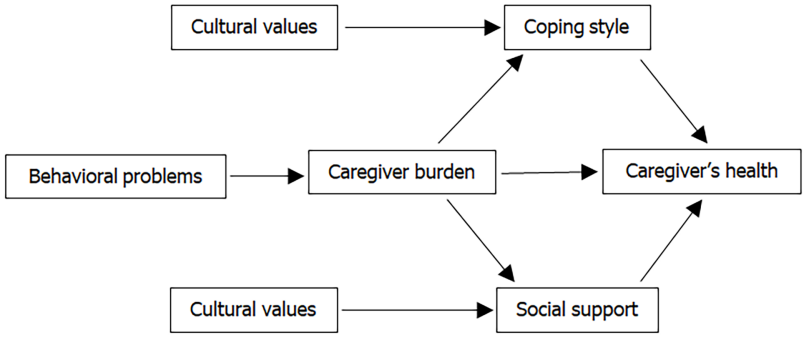


**Figure 1 The sociocultural stress and coping model is based on the core stress and coping model and further takes cultural values into consideration.**

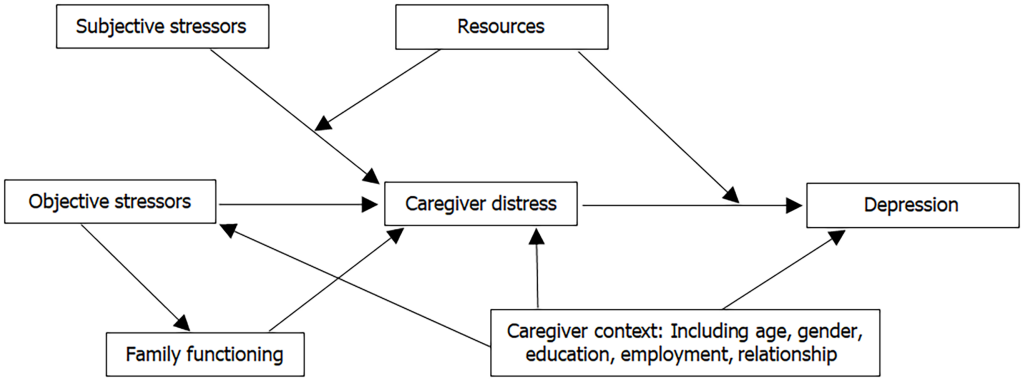


**Figure 2 Systemic family framework model is based on the stress process model and the family functioning is taken into consideration.**

caregiver depression.

### *Suffering-compassion model*

Previous studies suggest that caregivers' perceived suffering of the dementia patients was significantly associated with caregiver depression[38]. The Suffering-Compassion Model demonstrates the relations among the dementia patient's suffering, and the caregiver's perceived suffering, intrusive thoughts, and compassion. The contribution of caregivers' perceived suffering to caregiver depression is, however, mediated by their own personal intrusive thoughts. At the same time, caregiver compassion appears to moderate the relations of the caregiver's perceived suffering and intrusive thoughts. If the caregiver had higher compassion, he or she was more likely to experience greater intrusive thoughts. It should be noted that the physical suffering of dementia patients may be more easily recognized than their psychological suffering [39]. This could therefore cyclically mediate caregiver perception, reaction, emotion, *etc*.

In summary, the author merged the above 6 common models for explaining caregiver depression, as shown in Figure 3.

## FACTORS ASSOCIATED WITH CAREGIVER DEPRESSION

It is important to explore all factors that may be relevant to the development of dementia caregiver depression. By understanding the relevant factors, treatment may be designed to improve caregivers' mental health.

As dementia diseases progress, an individual's forethought, planning, organizing, and execution of instrumental and basic activities of daily living (ADL) deteriorate and ultimately require oversight, assistance, and then performance on behalf of the patient. Without caregiver assistance, a large proportion of patients with dementia would need nursing home care earlier in the disease process, and the costs of long-term care would increase. Depression is one of the most important issues for caregivers because it is related to poor quality of life, functional decline, and even mortality. Caregiver

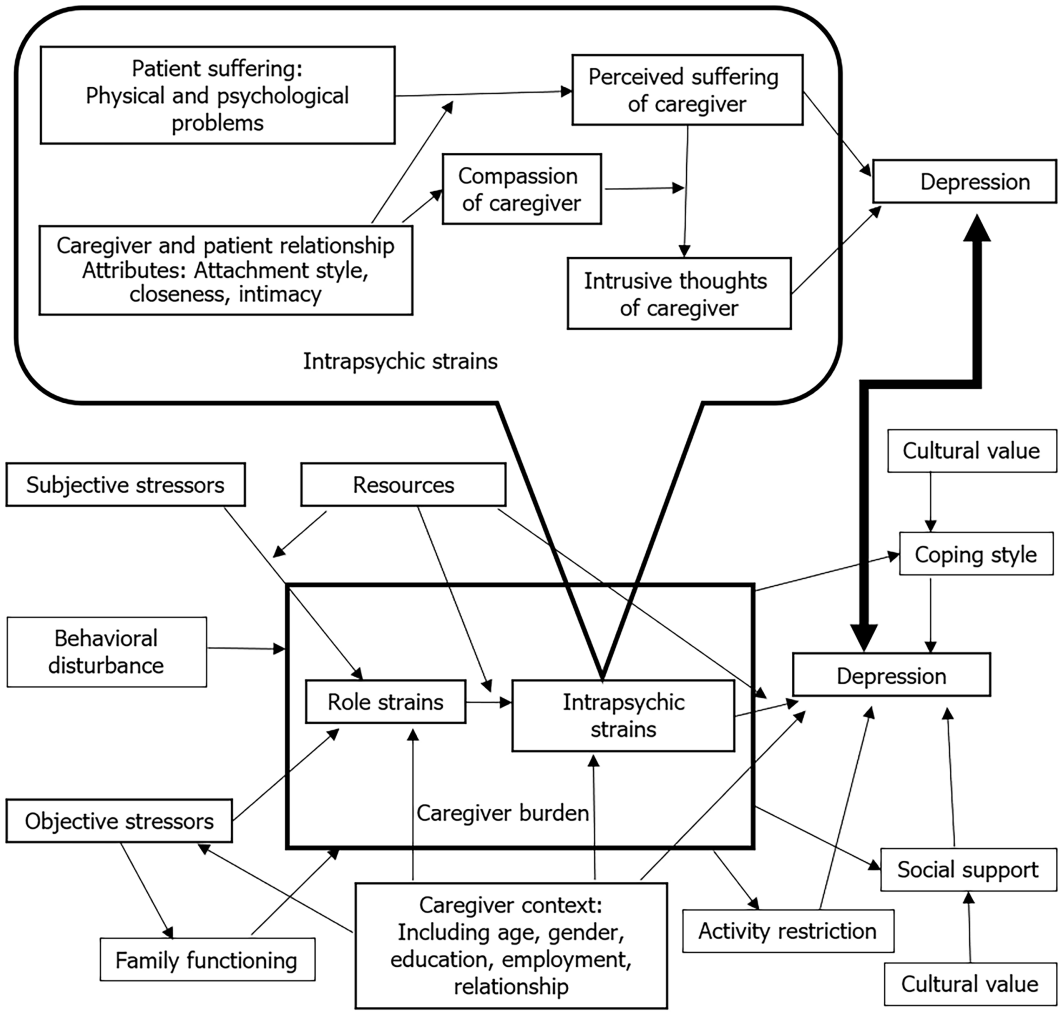


**Figure 3 A conceptual model includes the factors related to the caregiver depression.** The figure is based on the stress process model and combined with core stress and coping model, sociocultural stress and coping model, systemic family framework model, activity restriction model, and suffering-compassion model.

depression is thought to be a consequence of care due to a complex interplay of factors that comprises dimensions of the patient, caregiver, and cultural background.

### *Characteristics of patients with dementia*

Previous studies associated caregiver depression with being younger, having White or Hispanic ethnicity (compared to black ethnicity), having a lower educational level, and caring for a patient with ADL dependence[40,41], and behavioral disturbances[41,42]. There is significant evidence that BPSD influence depression in caregivers and may be more influential than the severity of cognitive deficits seen or perceived in the patient [43,44]. Different dementia types are also associated with caregiver depression. Liu *et al*[45] reported that the severity of patients' BPSD and caregivers' perceived stress contributed to the increased caregiver burden. Caregivers for patients with fronto-temporal lobar degeneration and dementia with Lewy bodies are likely to have more caregiver burdens than those who care for patients with Alzheimer's disease.

Apart from cognitive and functional impairment, BPSD affect a large proportion of patients with dementia at some point in their disease course. Behavioral disturbances are highly challenging for patients with dementia, their caregivers, and their physicians, as some BPSD are difficult to manage and associated with a greater caregiver burden, higher risk for nursing home placement, prolonged hospitalization, and reduced quality of life. Huang *et al*[46] suggested that agitation, aggression, anxiety, nighttime behavior disturbances, irritability, and hallucinations are the five leading BPSD that are significantly related to caregiver depression. Choi *et al*[47] suggested that different BPSD clusters have a differential impact on caregivers' mental health. Care providers should first distinguish between rejection of care, aggression, and agitation in patients with dementia and then manage those problematic behaviors

to decrease the risk of caregiver depression.

Some studies have found anosognosia in patients with dementia to be related to caregiver burden and depression[48-50]. Anosognosia is characterized by the phenomenon of obvious unawareness, misinterpretation, or total denial of an illness. It is a common symptom of dementia[51]. One explanation is that a patient's higher level of anosognosia results in a higher burden and depression of the caregiver. Anosognosia would increase caregivers' social isolation and tension related to obtaining and receiving patient care[50]. Another possible explanation could be that the depression of the caregiver may distort the perceived health status of the dementia patient and possibly cause a more negative assessment of caregiver-rated dementia problems[52].

Other than the patients' demographics, the subjective feelings of the dementia patients may also be an important topic to be studied, such as the patient's sensation of suffering. In a longitudinal analysis[53], increases in patients' suffering were associated with higher caregiver depression. Several studies suggest that measurable manifestations of suffering comprise (1) Physical symptoms such as chronic or acute pain, nausea, and dyspnea; (2) Psychological symptoms such as depressive symptomatology and anxiety; and (3) Spiritual well-being including inner harmony, meaning of life, and the extent to which people find comfort and strength in religious beliefs[54-56].

### Characteristics of the caregivers

For dementia caregivers, factors associated with depression risk include having a low income, spending more hours caregiving (40 to 79 h/wk compared to less than 40 h/wk)[40], being female[41], having a spousal relationship[40,57], living with the patient[41,44,58], having poorer health status[44,58], and having a higher caregiver distress sensation[44,58,59]. It has been reported that approximately 80% of caregivers have some form of sleep disturbance. Poor sleep is independently associated with greater depressive symptoms[60].

Robinowitz *et al*[61] suggested that self-efficacy may be an important factor for recognizing caregiver depression risk. Measurements of self-efficacy in caregivers for dealing with memory decline and behavioral disturbances may be valuable to providers who may care for either or both dementia patients and caregivers. Caregiver self-efficacy relates to their conviction about his or her adaptive ability and skills to manage caregiving problems that may arise. Greater self-efficacy has been associated with better psychological and physical health outcomes in dementia caregivers, including decreased depression and anxiety[62].

It has also been suggested that social support and perceived caregiving competency are significant protective factors for caregiver depression[47].

The commitment to the caregiving role, leisure, and work was associated with the formation of guilt feelings. A higher commitment to the caregiving role has been reported to contribute to lower levels of guilt[63]. Higher levels of guilty feelings are related to lower levels of commitment to the caregiving role and to leisure and higher commitment to work. Feelings of guilt may have resulted in caregivers' distress and depression[64].

### Impact of cultural issues and values

In some regions and cultures around the globe, symptoms of dementia may be regarded as normal aging or even as a consequence of previous wrongdoing. It has also been reported that some South Asian regions tend to consider dementia an outcome of family conflict or impaired family support. On the other hand, African Americans, due in part to religious beliefs, are prone to rely more on prayer and reconstruction of difficult circumstances during challenging times. Dementia is also thought to be influenced by negative spiritual forces. Cultural factors may influence the conceptualization and help-seeking behaviors of patients with dementia and the caregivers that control their access to care. Indeed, cultural factors affect caregiver responses to the cognitive and noncognitive symptoms of dementia and the consequences of adherence or nonadherence to treatment recommendations[65].

Understanding caregiver stress has become an emerging, relevant cultural value [66]. Based on the sociocultural stress and coping model[32], Losada *et al*[66] explained the association between cultural values and caregiving distress. Traditional beliefs about family obligations, such as the values systems of Asian and Latino/Hispanic regions, may result in psychological strain from a greater than average emphasis on the caregiving role and the encouragement to overlook one's own needs and feelings. When caregivers feel stress about performing duties and their personal needs are ignored, avoidant coping styles may therefore arise. Avoidant coping strategies may be the mediating factor between familial obligations and cultural values toward

caregiver depression[67].

Youn *et al*[68] suggested that Korean and Korean American caregivers had higher levels of familism and burden than white American caregivers. It is indicated that first-generation employed caregivers appear to have less flexibility and accommodations in their work environments and are more likely to leave their positions when performing caregiving roles than second-generation caregivers. Challenges in utilizing health care systems and language barriers are also higher within the groups of first-generation caregivers[69].

Factors associated with higher rates of dementia caregiver depression, as seen in the literature review, are listed in Table 1.

## MANAGEMENT FOR CAREGIVER DEPRESSION

Regarding dementia patients, there are few effective interventions to slow and stop the progression of cognitive impairment. However, there are many interventions designed to treat BPSD and therefore alleviate caregiver burden. Multicomponent nonpharmacological treatments, including caregiver education and support, problem solving training, and assistance in comprehending and managing specific behavioral problems, have been suggested to be effective in treating behavioral disturbances and increasing the quality of life of patients with dementia and their caregivers[70].

Numerous studies have been designed to improve depression in dementia family caregivers. We summarized types of caregiver interventions that have been classified by psychoeducation[71-77], leisure and physical activity[37,78-80], counseling[81-90], cognitive-behavioral approaches[91-94], mindfulness-based interventions[95], and psychological and social support[96-99], as shown in Table 2. We also observed and highlighted interventions utilizing telephone and technologies to deliver nonface-to-face management below.

Various interventions and key clinical content elements identified in the literature review are listed below in Table 2.

### *Psychoeducation*

In this intervention, caregivers are educated on suitable skills to deal with caregiving requirements and stress using structured content and are often performed by small groups, including time for practice. The topics in these sessions usually comprise knowledge of dementia, learning to reserve time for self, enhancement of communication and interaction with family members, skills for managing BPSD, and related community services. More specialized topics, such as emotional management, thought and behavioral modification, and pleasant activity scheduling, may also be involved in some studies.

### *Leisure and physical activity*

Daily pleasant experiences can create balance between "self-life" and caring for patients and help caregivers to maintain positive points of view while serving in the caregiving role. Leisure or physical activities may also serve to transform the caregivers' negative experiences[37]. It is challenging to incorporate activities in the daily lives of caregivers for dementia patients because of their heavy workloads. Moreover, stressed individuals may diminish the skills to engage in positive interactions. The behavioral theory of depression interprets depression as a result of a series of negative reinforcements. Multiple factors create a downward spiral toward the further disruption of a healthy lifestyle and its biological rhythms and social activities, resulting in more severe depressive symptoms.

### *Counseling*

Individual and family counseling is provided by trained providers to help caregivers manage stress and crises. This intervention is performed face to face or through telephone calls.

### *Psychotherapy and cognitive behavioral approaches*

Psychotherapy and cognitive behavioral approaches are performed by trained health care providers to help caregivers manage stress and to treat distress and depression. These interventions are often used for caregivers with clinical depression or other significant mental health problems. They can be performed in individual or group circumstances.

**Table 1 Factors associated with increased depression in caregivers of patients with dementia in the literature**

| Dimension | Less modifiable factors | More modifiable factors |
|---|---|---|
| Patient | Younger age, white and Hispanic ethnicity, less educational level, type of dementia (frontotemporal lobar degeneration and dementia with Lewy bodies) | More activities of daily living dependence, behavioral disturbances, higher levels of anosognosia, more physical and psychological suffering |
| Caregiver | Low income, more hours spent caregiving, female sex, spousal relationship, living with the patient, poorer health status | Higher distress sensations, sleep disturbances, lower self-efficacy, lower levels of commitment to the caregiving role, guilty feelings |
| Cultural | Familism, family obligation, language barriers | Misunderstandings, coping style, less flexibility and accommodations in their work environments |

**Table 2 Types of intervention for dementia caregiver depression in the studies**

| Type of intervention | Content of program |
|---|---|
| Psychoeducation | Information about dementia and the different stages of dementia severity[71-73], understanding and managing behavioral problems [71,73-76], problem-solving techniques[73], coping strategies for emotional problems[73-75], communication skills[71,73-75], crisis management[73], resource information[73], targeting pain and distress (mood problems, lack of engagement in activities)[74,75,77] |
| Leisure and physical activity | Education on how to monitor time spent in leisure activities[78,79], identification of enjoyable leisure activities[78,79], prioritizing activities[79], scheduling/participating in leisure activities[79], fostering physical activity[78], individualized goal setting[78], behavioral modification skill training, behavioral activation[37,80], increasing pleasant activities[37,79] |
| Counseling | Care consultation[81-90], managing dementia symptoms[81,82,84,85,87,88], accessing community support services[81,82,86], telephone-based use of logbooks[83], information about dementia and legal issues and resources for social support[83,86] |
| Cognitive behavioral approaches | Cognitive reappraisal[91], controlling upsetting thoughts[27], enhancing self-efficacy[27,28], cognitive restructuring[92], assertive skills[92], relaxation[92], acceptance of aversive internal events and circumstances[92], choosing meaningful courses of action[92], telephone-based identification and expression of painful thoughts and emotions[93], managing painful emotions[93], accepting thoughts and emotions[93], redefinition of the relationship[92], reactivation of resources[93], adaptation to bereavement[93,94] |
| Mindfulness-based interventions | A range of practices with a focus on stress reduction, such as gentle mindful movement (awareness of the body), a body scan (to nurture awareness of the body region by region), and meditation (awareness of the breath)[95] |
| Psychological and social support | Providing information on formal social support[96,97], mutual sharing of emotions[96-98], creating an appropriate social network and home environment for the caregiver[96], support group participation[96], family role and strength rebuilding[99] |

### *Mindfulness-based interventions*

In this treatment model, caregivers are trained in mindfulness and meditation strategies with the basic purpose of concentrating on the present experience nonjudgmentally. Thoughts, emotions, and behaviors are observed without being judged as good or bad with a final aim of relieving suffering. Mindfulness-based interventions are based on acceptance, receptiveness of the current situation, and establishing a balanced coexistence with personal feelings and thoughts, instead of attempting change from the beginning. Mindfulness-based stress reduction is a widely used program that involves practices with a focus on stress reduction, including gentle mindful movement (awareness of the body), a body scan (to foster awareness of the body), and meditation (awareness of the breath)[100]. Dementia not only affects the person who suffers from it but also has an impact on the patients' caregivers. Caregivers of dementia patients are groups that experience mindfulness problems[101] and symptoms of stress and depression.

### *Psychological and social support*

The support group is characterized by a type of mutual helping that comprises a group of people to share experiences and deal with common problems. Studies have shown that support groups can be valuable resources to the families of dementia patients, and include care information and psychological support[99]. Several studies show that caregiver support groups are able to help individuals relieve the distress of caregiving and decrease depressive symptoms[102].

We divided factors associated with caregiver depression into three dimensions: patient, caregiver, and cultural background according to the literature and matched them with the treatment plan for each factor. The appropriate treatment content corresponding to each factor is listed for reference in Table 3. However, this table needs more clinical research for validation.

**Table 3 Interventions and modifications for caregiver depression in reviewed literature, classified and matched according to the associated factors and dimensions**

| | |
|---|---|
| **Patient with dementia** | |
| Address physical care domain | |
| | Psychoeducation |
| | Counseling |
| | Environmental modification |
| | Access to community resources |
| | Relief pain |
| Address psychological domain | |
| | Psychoeducation |
| | Cognitive Behavioral approaches |
| | Strategies to treat and compensate cognitive deficits |
| | Reality and insight enhancements |
| Address behavioral and psychological symptoms | |
| | Psychoeducation |
| | Counseling |
| | Pharmacological treatments |
| **Caregiver** | |
| Address distress sensation | |
| | Leisure and physical activity |
| | Counseling |
| | Mindfulness-Based Interventions |
| | Psychological and social support |
| Address self-efficacy | |
| | Counseling |
| | Cognitive Behavioral approaches |
| | Communication skills |
| | Behavioral management skills |
| | Problem-solving techniques |
| | Crisis management |
| | Training on nursing care |
| Address commitment to caregiving role | |
| | Counseling |
| | Psychological and social support |
| Address guilty feelings | |
| | Leisure and physical activity |
| | Counseling |
| | Cognitive Behavioral approaches |
| | Psychological and social support |
| Address sleep problems | |
| | Leisure and physical activity |
| | Cognitive Behavioral approaches |

| | |
|---|---|
| | Mindfulness-Based Interventions |
| Address coping strategies | |
| | Psychoeducation |
| | Leisure and physical activity |
| | Counseling |
| | Psychological and social support |
| | Coping with loss and grief |
| Address accommodations in work environment | |
| | Counseling |
| | Psychological and social support |

Key factors (listed in Table 1) considered include: (1) For patients: Activities of daily living dependence, behavioral disturbances, higher levels of anosognosia, physical, and psychological suffering; (2) For caregivers: Higher caregiver distress sensations, sleep disturbances, lower self-efficacy, lower levels of commitment to the caregiving role, guilty feelings; and (3) For cultural background: Coping style, less flexibility, and accommodations in their work environments.

## DELIVERY OF TREATMENT FOR CAREGIVER DEPRESSION

Because of dementia caregiving duties or conflicts with other schedules, face-to-face interventions for caregivers are not practical in certain situations. Family caregivers may also have difficulties leaving the patient to participate in intervention activities in certain places. Furthermore, interventions for caregivers are possibly not available or difficult to participate in many communities around the world, such as rural or underdeveloped communities. Nonface-to-face interventions may also be practical in the current clinical environment with the coronavirus disease 2019 pandemic.

### *Telephone-based intervention*

As dementia progresses, caregivers may become isolated and need a prolonged period of time to meet caregiving demands. This condition can make it difficult for them to leave their homes to seek support and resources through face-to-face interventions. To overcome these barriers, telephone-based interventions targeted to increase accessibility for caregivers are recommended. Telephone-based interventions have been demonstrated to promote the physical and mental health of caregivers[86,87]. Furthermore, telephone-based intervention is an alternative for caregivers for whom certain services are not available locally[89].

Telephone coaching also has the advantage of offering individualized recommendations for the caregiver. This is not always possible in a group setting, such as a large educational group. In some crisis situations, caregivers wanted to meet face-to-face with their instructors for suggestions. Interventions combining telephone and video have been introduced and performed[103].

### *Technology-driven interventions*

Interventions for depression using eHealth or Connected Health (CH) largely employ information and communication technologies for caregivers. These evaluations, interventions, and treatments are performed *via* the internet[104]. For instance, these interventions can be provided in the form of an online course on the computer. Healthcare providers can also utilize smartphone or tablet applications designed to provide newer information and psychological support from peers as well as professionals. The care model is assisted by technology, and all the associated disciplines involved in patient care can be communicated through a health portal that offers beneficial information between formal and informal caregivers. Additionally, some programs for technology-driven interventions use technologies such as body-worn and monitoring devices. Health care professionals can help informal caregivers monitor dementia patients' health status using these devices. The devices can provide an event alert (such as a fall or other emergency event) and facilitate communication. Technology-driven models could provide a handy and lower cost intervention compared to traditional home care, supply a family caregiver with social interaction and emotional support and facilitate information exchange with other caregivers and professionals. It could also ameliorate the decision-making process for matters about

patient care[105]. The literature also suggests that dementia caregiver burden and stress could be reduced through technology-driven interventions[106]. At the same time, the self-efficacy and quality of life of caregivers will be improved by this type of intervention[105].

A study performed in Ireland[107,108] used a Connected Health Sustaining Home Stay Model for caring for patients with dementia and their caregivers. The purpose of the study was to (1) Assess the effectiveness of the platform in supporting caregivers at home; (2) Study the potential improvement of patients with dementia and their family caregivers' mental and physical health; and (3) Investigate the platform's usability and user experience. Another example is the system named the A Technology Platform for the Assisted Living of Dementia Elderly Individuals and their Carers[109]. It is a digital platform designed to offer support to the informal caregiver.

### *Case management*

Patient-centered care planning is essential for case management. It includes identification and outreach, comprehensive individualized assessments, care planning, care coordination, service provisions, monitoring, evaluation and fulfilling individualized needs[110].

Due to the complexity of the symptoms of dementia, the model using a multidisciplinary approach and integrated working is beneficial in care for dementia patients. Case managers, nurses, psychiatrists, pharmacists, psychologists, occupational therapists, and social workers are all involved in decision making and supporting the caregivers living with people with dementia[111].

## CONCLUSION

Overall, the prevalence of depression among dementia caregivers is higher than that seen in the general population. A structured way to study and verify associated factors and etiologies for caregivers' depression is based on the stress coping model, which may then be expanded by adding relevant important variables. The activity restriction model in the mechanism of caregiver depression also provides an important theoretical basis for interventions and management, such as behavioral activation, leisure, and physical activities. There are many interventions used to manage caregiver depression in the literature, but after further reviewing the intervention methods, it was found that most recommended treatment plans incorporated multicomponent interventions.

The following points provide some perspective and a few suggestions to address currently unmet gaps in treatment adequacy for depression in caregivers of patients with dementia.

Understanding the clinical mechanisms of depression requires investigating psychosocial, physiological, and biological contributions. Is there a difference between depression in caregivers of dementia patients and the general population in imaging studies or in brain neuroendocrine studies? These questions need further exploration.

Most of the current research utilized psychosocial approaches. What should be further studied is whether there will be a meaningful improvement if the caregiver's depression is also given pharmacological treatment such as antidepressants. Is there a difference in antidepressant efficacy between dementia caregivers and the general population? For individual depression symptoms, are there differences in the treatment response of these two groups?

Additionally, many current clinical studies available for review were based on cross-sectional research designs. The behavioral symptoms and daily life functions of dementia deteriorate over time. More long-term follow-up studies are needed to track whether the depressive symptoms of caregivers also change over time.

Dementia is known to occur in many different forms, each having different symptoms and disease courses. For instance, patients with vascular dementia have more obvious physical disabilities and often experience stepwise cognitive declines following each clinically diagnosed stroke event. Cognitive functioning in those with Alzheimer's disease degrades slowly, from instrumental ADL to the most basic ADL. Different types of dementia may very well have different impacts on the moods and daily lives of their caregivers.

Many clinical studies assessed the depression of caregivers by using self-rated scales or scales asking about subjective feelings as the main outcome. One such instrument is the Center for Epidemiologic Studies Depression Scale[112], whose reliability and validity have been proven. Maintaining reliability and validity is best assured by

objective evaluation by trained researchers. Two scales also recommended as appropriate evaluation tools are the Hamilton Depression Rating Scale[113] and the Montgomery–Asberg Depression Rating Scale[114].

The clinical problems of patients with dementia are individual and unique. The author believes that the formulation and implementation of individualized treatment plans are an important component of addressing dementia caregiver depression. Therefore, the case management model for people with dementia and their caregivers needs promotion and the opportunity to evolve to meet these populations' needs.

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*REVIEW*

# Brain-derived neurotrophic factor and inflammation in depression: Pathogenic partners in crime?

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## Abstract

Major depressive disorder is a debilitating disorder affecting millions of people each year. Brain-derived neurotrophic factor (BDNF) and inflammation are two prominent biologic risk factors in the pathogenesis of depression that have received considerable attention. Many clinical and animal studies have highlighted associations between low levels of BDNF or high levels of inflammatory markers and the development of behavioral symptoms of depression. However, less is known about potential interaction between BDNF and inflammation, particularly within the central nervous system. Emerging evidence suggests that there is bidirectional regulation between these factors with important implications for the development of depressive symptoms and antidepressant response. Elevated levels of inflammatory mediators have been shown to reduce expression of BDNF, and BDNF may play an important negative regulatory role on inflammation within the brain. Understanding this interaction more fully within the context of neuropsychiatric disease is important for both developing a fuller understanding of biological pathogenesis of depression and for identifying novel therapeutic opportunities. Here we review these two prominent risk factors for depression with a particular focus on pathogenic implications of their interaction.

**Key Words:** Brain-derived neurotrophic factor; Microglia; Neuroinflammation; Growth factors; Depression

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**Core Tip:** Low levels of brain-derived neurotrophic factor (BDNF) and high inflammation have both been implicated as risk factors in the pathogenesis of major depressive disorder. Here we review the role BDNF and inflammation play in the etiology of depression and the interaction between them. Recent evidence suggests a bidirectional connection between these two risk factors: inflammation reduces BDNF expression, and BDNF may have a negative regulatory role in resolving neuroinflammation. Understanding of this interaction in the context of neuropsychiatric disease is important for a fuller understanding of biological pathogenesis of depression and for identifying novel therapeutic opportunities.

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## INTRODUCTION

Research has made important advances in recent decades towards the understanding and treatment of major depressive disorder, a debilitating disorder with a heterogeneous range of symptoms. Despite these advancements, depression remains a leading cause of disability with an estimated 264 million individuals worldwide affected by the disorder[1]. In the United States, the economic burden of major depressive disorder is an estimated 210.5 billion dollar[2] with substantial lost productivity and diminished quality of life for affected patients and their families. Recent interest has turned to biomarker and genetic analysis to predict those who may be vulnerable to developing depression and to understand the etiology of patients' existing diagnosis in order to better prevent and treat this debilitating disorder. Two notable biological risk factors for depression are of particular interest: A deficiency in brain-derived neurotrophic factor (BDNF) and inflammation. In this review, we will highlight the mechanisms by which these factors are known to contribute to the development of depression and summarize emerging evidence suggesting that interactions between these two factors within the brain are important in the pathogenesis of depression.

## BRAIN DERIVED NEUROTROPHIC FACTOR

BDNF, a member of the neurotrophin family of growth factors, has been well-studied for its role in the pathogenesis of major depressive disorder and antidepressant efficacy. BDNF is a small protein expressed by the *bdnf* gene on chromosome 11 in humans[3]. Transcription of the *bdnf* gene is controlled by nine distinct promoters. The *bdnf* gene contains up to 11 exons; exons II, III, IV, and VII are brain-specific[4]. BDNF is first synthesized as the precursor pre-proBDNF in the endoplasmic reticulum. The pre- domain is cleaved off and proBDNF is transported to the Golgi apparatus. ProBDNF may be secreted in the precursor form or proteolytically cleaved intracellularly or extracellularly to form mature BDNF (mBDNF)[5,6]. Both pro- and mature forms of the BDNF protein are neuroactive, though the activity of proBDNF and mBDNF have largely opposite effects. ProBDNF binds and activates the pan-neurotrophin receptor $p75^{NTR}$, a member of the tumor necrosis factor receptor family, promoting apoptosis[7]. mBDNF binds with high affinity to the tyrosine kinase receptor tropomycin receptor kinase B (TrkB).

When mature BDNF, or neurotrophins with lesser affinity for TrkB including neurotrophin-4 and neurotrophin-3, bind to the extracellular domain of TrkB, the intracellular domains of the receptor dimerize and autophosphorylate one of three tyrosine residues. Phosphorylation at each residue initiates a distinct signaling cascade: Ras-PI3K-Akt, Ras-MAP kinase-Erk, or phospholipase Cγ[8]. These signaling cascades activate transcription factors such as CREB, resulting in cell proliferation, cell survival, synaptogenesis, and memory formation (Figure 1).

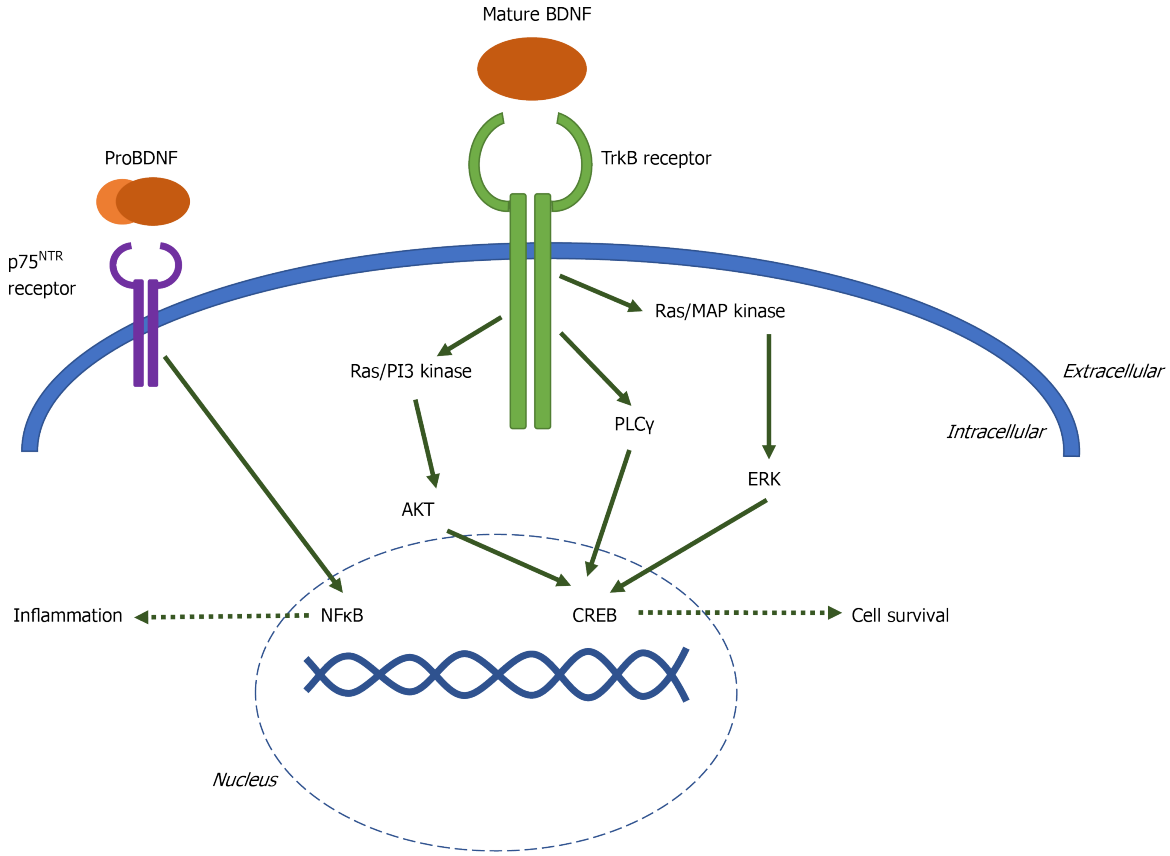


**Figure 1 Brain-derived neurotrophic factor signaling cascade diagram**. When TrkB is activated by binding mature brain-derived neurotrophic factor (BDNF), the intracellular domains of the receptor dimerize and autophosphorylate one of three tyrosine residues. Phosphorylation at each residue initiates a distinct signaling cascade: Ras-PI3K-Akt, Ras-MAP kinase-Erk, or phospholipase Cγ. These signaling cascades activate transcription factor CREB, resulting in cell proliferation, cell survival, synaptogenesis, and memory formation. ProBDNF binds to pan-neurotrophin receptor $P75^{NTR}$. $P75^{NTR}$ signaling activates transcription factor NFκB, leading to inflammation and apoptosis. BDNF: Brain-derived neurotrophic factor.

BDNF and TrkB are expressed both peripherally and within the central nervous system. In the periphery, BDNF has been detected in the heart and spleen[9], expressed by myoblasts[10], dorsal root ganglion cells[11], vascular endothelial cells [12], leukocytes[13] and is stored in platelets[14]. In the brain, BDNF is expressed by neurons, astrocytes[15], and microglia[16]. BDNF is highly expressed in the hippocampus and is found in lower concentrations in the cerebral cortex and brainstem[17]. TrkB is expressed in neurons, microglia, and astrocytes throughout the brain[18,19].

A number of factors may modulate BDNF expression or function. Prenatal, early life, social, and unpredictable stress are all associated with reduced BDNF expression or protein levels[20]. Exercise increases BDNF expression[21] and environmental enrichment protects against the effects of stress and early life inflammation on BDNF expression[22,23]. BDNF levels may also decline with age[24,25] and low BDNF levels are associated with age-related neurodegenerative disorders such as Alzheimer's and Parkinson's disease[26,27]. However, some studies suggest BDNF expression does not change with age[28,29].

While a number of genetic factors may contribute to a reduction of BDNF expression or function[30-33], the val66met mutation has garnered considerable attention due to its relevance in psychiatric conditions like bi-polar disorder and suicidality[34,35]. The single nucleotide polymorphism (SNP; rs6265) at nucleotide 196 (G/A) occurs on the 5′ pro-BDNF sequence, producing a valine to methionine substitution within codon 66. This SNP does not appear to alter BDNF expression or biological activity, but impairs translocation and activity-dependent secretion[36], thus reducing BDNF- TrkB signaling. The val66met SNP is also associated with reduced serum BDNF protein levels in the periphery[37].

## BDNF IN DEPRESSION

The negative correlation between BDNF levels and symptoms of depression have been well established; researchers have been interested in BDNF as a biomarker for depression for decades[38-40]. Clinical data has often demonstrated that patients suffering from major depression disorder are more likely to have alterations in their BDNF-TrkB signaling activity. Numerous studies have found that depressed or suicidal patients have lower BDNF levels than healthy controls[41-48]. Keller *et al*[30] found that suicide victims were more likely to have DNA methylation in the *BDNF* promotor/exon IV compared to control subjects, suggesting a link between epigenetic down-regulation of BDNF and suicidal behavior. Further, psychosocial stress, a known precursor to depression and anxiety, reduces BDNF levels[20].

Genetic analysis reveals several polymorphisms that are associated with susceptibility to developing depression or suicide, such as rs12273363, rs7124442, rs10767664, rs962369, rs908867[31,33]. Of these polymorphisms, the rs6265 SNP known as val66met has been most extensively studied in psychiatric conditions. Some studies suggest that individuals carrying the val66met polymorphism are more vulnerable to developing depression[37,49-52], suicidality[53,54], or to be nonresponsive to antidepressant treatment[55]. However, others dispute this association[55-60]. The val66met polymorphism has been linked to depression in breast cancer patients/survivors[61, 62], but also appears to be protective against chemotherapy-associated cognitive impairments in breast cancer patients[63]. The mixed findings pertaining to association between the val66met SNP and psychiatric disorders suggest that the mutation alone is likely not sufficient to cause pathology. Rather it is a risk factor that interacts with other genetic or environmental factors to contribute to pathogenesis of depression or depressive symptoms.

Clinical studies investigating BDNF have been limited to measuring BDNF in the blood or cerebral spinal fluid, direct measurement of mRNA or protein in the brain being only available in post-mortem tissue samples. However, BDNF does cross the blood-brain barrier (BBB)[64], and Karege *et al*[65] found that brain and serum levels of BDNF are positively correlated in rats. For this reason, measuring peripheral BDNF levels are a feasible indicator of central BDNF expression. Moreover, there is a negative correlation between serum BDNF stored in platelets and depression in humans[66]. BDNF release from platelets may be impaired in depressed patients[67] while antidepressants increase BDNF release from platelets[68], suggesting platelet-derived BDNF is a contributing factor to the interaction between peripheral BDNF levels and depression.

Recent preclinical studies revealed that mice heterozygous for the BDNF allele, which reduces BDNF levels within the brain by about half[69], are susceptible to depressive-like phenotypes after a challenge such as mild stress or acute inflammation [70,71,201]. Direct infusion of BDNF into the rodent brain[72,73] and periphery[74] is protective against the behavioral consequences of stress in the forced swim test and learned helplessness models of depressive-like despair behavior. Further, manipulation of the BDNF-TrkB signaling activity through TrkB agonist 7,8-dihydroxyflavone (DHF)[75] reduces depressive-like behavioral changes induced by social defeat stress [76] and acute inflammation[77]. Many antidepressant treatments increase levels of circulating BDNF[46,68,78-84]. In the brain, anti-depressant treatment induces BDNF mRNA expression in neurons[85], astrocytes[86-88], and microglia[88]. Up-regulation of BDNF may be necessary for the anti-depressant response[89-93].

## INFLAMMATION IN THE PERIPHERY AND THE BRAIN

As suggested above, dysregulation in the BDNF-TrkB system may not be a pathological factor that acts alone, rather perturbation within this neurotrophic factor expression/signaling may engender a foundation of vulnerability to subsequent insults to increase the risk of depression or lead to pathology (Figure 2). Inflammation is one risk factor that may well fit this profile.

The ancient Roman encyclopedist Celcus defined inflammation by the presence of "rubor, calor, dolor, tumor", or redness, heat, pain, and swelling. Modern scientists have a deeper understanding of inflammation as a consequence of the innate immune system's activation in response to an irritant or loss of homeostatic control due to factors such as stress, obesity, and aging. Acute inflammation occurs when a tissue injury, pathogen, or noxious stimuli is detected. Leukocytes travel to the impacted region to remove the stimuli and repair damage. Chronic inflammation is a persistent

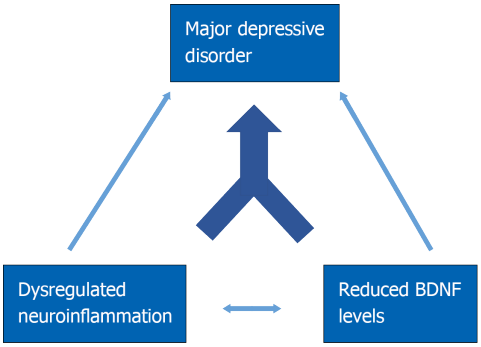


**Figure 2 Hypothesis diagram.** Brain-derived neurotrophic factor (BDNF) deficiency and elevated or chronic neuroinflammation independently confer vulnerability to development of major depressive disorder. BDNF plays a negative regulatory role in resolving neuroinflammation, and high inflammation reduces BDNF expression. BDNF: Brain-derived neurotrophic factor. BDNF: Brain-derived neurotrophic factor.

and maladaptive response that can be caused by many factors, such as chronic somatic diseases, advancing age, obesity, smoking, and high fat diets. In addition to contributing directly to risk of depression, chronic inflammation may lead to chronic illnesses such as allergies, arthritis, and autoimmune disease that also have high comorbidity with depression.

Invading pathogens or signals released by damaged cells are detected by toll-like receptors (TLR) in the plasma membrane of innate immune cells. TLRs are classified as pattern recognition receptors (PRRs). PRRs recognize and bind pathogen-associated molecular patterns (PAMPs)[94], such as lipopolysaccharide (LPS) on the gram-negative bacterial cell wall, or damage-associated molecular patterns (DAMPs) in a pathogen-independent process known as "sterile inflammation". Activation of TLRs initiate an intracellular signaling cascade, activating the transcription factor NFκB, causing up-regulation of pro-inflammatory mediators including cytokines, chemokines, cellular adhesion molecules[95], and downstream induction of reactive oxygen species[96]. Of these mediators, macrophage-derived TNFα, IL-1β, IL-6, and IL-10 have received extensive attention due their roles in regulating the immune system and their effects on the body[97].

Inflammation as a function of the immune response is necessary to protect the life of the organism. Recently, intentional induction of inflammation has been wielded as a promising tool against cancer as immunotherapy[98]. However, numerous studies have shown prolonged and elevated immune activation has significant impacts on physiological, metabolic, and neural/behavioral processes. The effects of peripheral inflammation or immune challenge do not remain in the periphery; inflammatory conditions impact the CNS through several possible mechanisms. The BBB created by the tight junctions of brain endothelium restricts diffusion of pathogens and non-select solutes from the blood into the brain. Peripheral inflammation may disrupt this boundary, increasing the permeability of the BBB and allowing infiltration by circulating monocytes, cytokines, and other substances[99,100]. Cytokines and monocytes attracted by the expression of chemokines such as monocyte chemoattractant protein 1 will travel to the brain and enter through leaky regions of the BBB or through active transport systems. Peripheral cytokines, PAMPs, and DAMPs can also impact brain homeostasis by signaling through the vagus nerve[101] or by signaling through PRRs on the BBB endothelial cells[102,103]. These inflammatory signaling pathways across the BBB initiate the neuroinflammatory response within the brain.

Numerous animal studies have demonstrated that microglia, the resident immune cell in the brain, adopt an "activated" phenotype following peripheral inflammation induced by LPS and live or heat-killed pathogens[100]. In their resting state, microglia are "ramified" with small somas and long highly branched processes. Once microglia detect an immune challenge, their morphology shifts toward an "amoeboid" shape with enlarged soma and shorter, thicker processes. Microglia are the primary source for brain-borne cytokines and other inflammatory mediators.

In addition to producing cytokines, inflammatory microglia also synthesize metabolites of the tryptophan-kynurenine pathway associated with oxidative stress. Tryptophan is converted to kynurenine by the enzyme indolamine-2,3 dioxygenase. Kynurenine metabolism then splits into distinct branches: Kyurenic acid, a metabolite with NMDA receptor antagonist activity, is produced in astrocytes by the enzyme kynurenine aminotransferase, while the enzyme kynurenine monooxygenase (KMO) produces 3-hydroxykynurenine (3-HK) in microglia (Figure 3). 3-HK is further

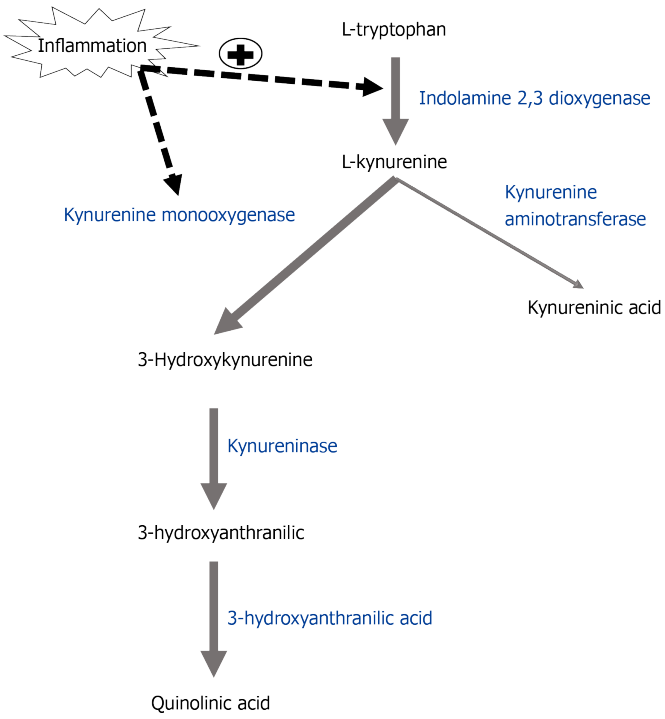


**Figure 3 Inflammation shifts kynurenine metabolism pathway towards oxidative stress-associated metabolites.** The enzyme indolamine-2,3-dioxygenase (IDO) converts tryptophan to kynurenine. Kynurenine aminotransferase converts kynurenine to kynureninic acid in astrocytes while kynurenine monooxygenase (KMO) metabolizes kynurenine to 3-hyroxykynurenine (3-HK) in microglia. 3-HK is metabolized by kynureninase to 3-hydroxyanthranilic acid and 3-hydroxyanthranilic acid dioxygenase to quinolinic acid. Inflammation up-regulates the enzymes IDO and KMO, resulting in increased levels of KMO-dependent metabolites associated with oxidative stress and depression. IDO: Indolamine-2,3-dioxygenase; KAT: Kynurenine aminotransferase; KMO: Kynurenine monooxygenase; 3-HK: 3-hyroxykynurenine; KYNU: Kynureninase; HAAO: 3-hydroxyanthranilic acid dioxygenase; QA: Quinolinic acid.

metabolized by the enzyme 3-hydroxyanthranilate 3,4-dioxygenase (HAAO) into the neuroactive NMDA receptor agonist quinolinic acid (QA). 3-HK and QA are also free radical inducers and are necessary for the development of inflammation-induced development of depressive-like phenotypes[104], described below.

## NEUROINFLAMMATION IN DEPRESSION

Symptoms of typical "sickness behaviors" which cease upon recovery – fatigue, loss of appetite, pain sensitivity, anhedonia, cognitive deficits, social withdrawal – have significant overlap with symptoms of major depressive disorder[105]. In fact, a subset of patients with chronic inflammatory diseases will suffer from longer-lasting symptoms of depression[106]. Individuals suffering from depression but who are otherwise medically healthy often have higher baseline levels of circulating pro-inflammatory mediators, particularly TNFα and IL-6[82,107-110]. Some anti-depressant treatments may reduce neuroinflammation[111,112], but most studies suggest that conventional antidepressants have reduced efficacy in depressed patients who have high inflammation. Conversely, while direct TNFα inhibition was ineffective as an anti-depressant in treatment resistant depression patients with low-moderate CRP levels, it was quite effective in treatment resistant patients with high inflammation[113]. This finding underscores the notion that anti-depressant treatment decisions and efficacy may be improved by integrating understanding of a patient's inflammatory status. At the cellular/molecular level, post-mortem studies indicate that microglia density in the dorsolateral prefrontal cortex, anterior cingulate cortex, and mediodorsal thalamus[114,115], expression levels of IL-1β, IL-6, and TNFα in the prefrontal cortex[116,117] and blood[118], and production of QA in the ACC[119] is significantly higher in suicide victims compared to non-suicide controls. Further, anti-depressants with secondary anti-inflammatory properties are more effective in treatment-resistant patients with high baseline levels of inflammatory markers IL-6 and C-reactive protein[120]. These studies suggest a strong association between inflammation and the development of depression.

Inflammation on its own may be sufficient to promote the development of depressive symptoms. Subsets of patients report feelings of depression following cytokine treatment for hepatitis or cancer[121,122]. Experimental treatment with endotoxin[123] or *Salmonella typhi* vaccine in healthy subjects similarly induced symptoms of depression and anxiety alongside acute inflammation[124] and increased kynurenine pathway metabolism. Numerous rodent studies have likewise demonstrated that inflammation can induce depressive-like phenotypes[125].

Inflammation can arise from multiple sources and events. In humans and rodents, acute and chronic stress is known to promote activation of the innate immune system [126,127] and induce microglial activation[115,128]. Psychological stress, a frequent trigger for depression and suicidality in humans, is commonly modeled in rodents using acute or chronic stressors such as social defeat, restraint, or home cage disruption. You *et al*[129] found that rats exposed to chronic mild stress have elevated central and peripheral pro-inflammatory cytokines, reduced neurogenesis in the hippocampus, and display anhedonia-like behavior as measured by the sucrose preference test. Hodes *et al*[109] found that mice with higher baseline levels of circulating IL-6 are more susceptible to developing depressive-like behavioral phenotypes after chronic social stress; IL-6$^{-/-}$ mice were resilient to the effects of social stress. Aging similarly increases vulnerability to neuroinflammation and subsequent depressive-like behaviors. Peripheral LPS treatment promotes a more robust inflammatory responses and sickness behavior in aged mice compared to young adults[130, 131]. Culley *et al*[132] found that LPS increases pro-inflammatory cytokine expression in the prefrontal cortex and impairments in prefrontal cortex-dependent cognition in aged rats. Inflammation associated with obesity[133] and alcohol consumption[134] have similarly been shown to induce depressive symptoms and behaviors in humans and animals.

Researchers have extensively studied depressive-like behavioral changes induced by peripheral immune challenge in rodents[125]. The viral mimetic Poly:IC, attenuated bacterial strain Bacillus Calmette-Guerin (BCG), and LPS are common models used to induce chronic or acute innate immune activation in animal models. Poly:IC increases expression of IL-1β, TNFα, and CD11b and elevates kynurenine levels in the rat brain, followed by a reduction in saccharin preference up to 72 h after treatment[135]. BCG inoculation induces chronic inflammation, up-regulates TNFα, INFy, and the tryptophan-kynurenine enzymes IDO and HAAO, and drives despair-like behavior measured by immobility in forced swim test and tail suspension test one week after infection[136,137]. LPS treatment models acute inflammation: Pro-inflammatory cytokine up-regulation and sickness behaviors resolve within 24 h after administration. Once motor activity and food intake is restored at 24 h, mice continue to display anhedonia-like, despair-like, and anxiety-like behavior[131,138,139]. Anti-inflammatory compounds ameliorate the depressive-like behaviors after LPS[138,140-144]. Moreover, many of these effects appear to be dependent on neurotoxic kynurenine metabolism. Inhibition of, or targeted deletion of, the gene for the rate-limiting enzyme IDO prevents development of LPS- and BCG-induced depressive-like behaviors, despite the elevation of pro-inflammatory cytokines[136,145,146]. KMO$^{-/-}$ and HAAO$^{-/-}$ mice are likewise are protected against many of the depressive-like behavioral effects of LPS, while direct administration of 3-HK provokes immobility in the tail suspension test and hippocampal-dependent cognitive impairment in the y-maze without an increase in pro-inflammatory cytokines[147], suggesting a causative role of downstream metabolites 3-HK and QA.

However, of the total human population that is exposed to high levels of inflammation, only a relatively small subset goes on to develop symptoms of major depressive disorder. For this reason, researchers have lately turned to investigating the environmental and genetic risk factors that contribute to a patient's vulnerability to developing depression. Recent research has revealed a role for BDNF in modulating the effects of neuroinflammation in a psychiatric context. A deficiency in BDNF may prime the system to develop neuropsychiatric symptoms in a maladaptive response to neuroinflammation-induced sickness behavior (Figure 2).

## PATHOGENIC TUG OF WAR?

Mounting evidence has revealed negative correlations between BDNF and neuroinflammation, particularly in psychiatric populations[148,149]. Depression is frequently comorbid with chronic inflammatory conditions, and BDNF deficiency has been identified as a risk factor. Breast cancer survivors are more likely to suffer from inflam-

mation-associated depression if they carry the Met allele in the val66met SNP[62]. BDNF expression is reduced in animals models and patients with rheumatoid arthritis, a disease characterized by chronic inflammation, and associated with major depressive disorders[150]. In Hepatitis C patients undergoing IFNα therapy, elevated cytokine levels are predictive of lower BDNF levels, and both BDNF and cytokine expression are associated with depressive symptoms[151]. Uint *et al*[152] found that elevated levels of both IL-1β and BDNF were predictive of treatment-resistant depression, but posited that this relationship may be due to the patients' long-term use of anti-depressant medications buoying their BDNF levels. Treating rats with viral mimetic Poly:IC increases expression of IL-1β, TNFα, IL-6, and CD11b and decreases BDNF and TrkB in the frontal cortex and hippocampus and reduces saccharin preference (anhedonia-like behavior)[135].

Numerous anti-inflammatory treatments have shown promising effects in alleviating depressive-like symptoms and increasing BDNF. Clinically, zinc monotherapy decreases depressive symptoms and increases BDNF in obese subjects[153]. In pre-clinical studies, insulin-like growth factor-1[81] and drugs such as resveratrol[140, 154], imipramine[89,144], doxycycline[144], fluoxetine[155], etazolate[156], chaihu-shugan-san[157], dihydromyricetin[158], minocycline[159], ketamine[160], and caffeine [161] all inhibit inflammation, increase BDNF, and improve depressive-like behavioral phenotypes.

BDNF activity likewise appears to impact stress or inflammation-induced depression. Mice with genetically reduced baseline levels of BDNF ($BDNF^{+/-}$ mice) develop an exaggerated neuroinflammatory and anhedonia-like response to peripheral LPS challenge compared to wild-type controls[201] and increased despair-like behavior in the forced swim test after acute mild stress[71]. Both the TrkB agonist DHF and the TrkB antagonist ANA-12 are anti-depressant in mice treated with LPS, likely due to opposing effects of BDNF-TrkB activity between the hippocampus and nucleus accumbens[77]. INFα therapy patients with the Val66Met polymorphism display symptoms of suicidal ideation and depression compared to those with the Val allele[162]. Mice with the humanized val66met polymorphism (Val/Met mice) are more sensitive to LPS-induced depressive-like behaviors than Val/Val mice and exhibit microglia with an already primed morphology (unpublished data).

Additionally, investigating the interaction between BDNF-TrkB system and inflammation may be relevant for addressing the sex differences in the presentation of depression. Women report experiencing depression at up to twice the rate of men. BDNF is expressed differentially in various regions of the CNS between males and females and environmental conditions modulate BDNF expression differentially between males and females, although circulating levels of peripheral BDNF appear consistent between sexes[163]. Female BDNF conditional KO mice display more depressive-like behaviors and attenuated anti-depressant response than male BDNF conditional KO mice[164]. Women may also be more vulnerable to developing inflammation-induced depression. Females tend to have higher baseline levels of inflammation than males[165] and have a larger pro-inflammatory and depressive response to endotoxin exposure[166]. In the brain, while male microglia appear to be more reactive early in life than female microglia, female microglia may be reactive and inflammatory later in life, when neuropsychiatric disorders tend to manifest[167]. Estrogen may also play a role: Rodent models of estrogen deficiency results in increased depressive-like behaviors, pro-inflammatory cytokine expression, and increased levels of kynurenine pathway enzyme IDO in the hippocampus[168]. There is also evidence that estrogen regulates expression of BDNF and that the estrogen receptor may be necessary for the protective effects of TrkB activation[163]. These findings suggest the relationship between BDNF, inflammation, and sex warrants further investigation.

## BDNF AND NEUROINFLAMMATION: BI-DIRECTIONAL MODULATION

Mounting evidence suggests that the connection between BDNF expression and neuroinflammation regulation is bi-directional in nature (Figure 2). Interestingly, Gomes *et al*[169] found *in vitro* that microglia acutely increase extracellular secretion of BDNF in response to LPS, leading to reduced intracellular levels of BDNF. Cultured human monocyte cells constitutively secrete BDNF, and BDNF secretion is increased when monocytes are stimulated by TNFα or IL-6, although no change in BDNF mRNA was detected[170]. Astrocytes likewise express BDNF when stimulated by TNFα[15] and increase expression of BDNF, TNFα, and IL-6 after LPS treatment[171]. BDNF

regulates proliferation and survival of microglia[172]. This acutely elevated BDNF secretion may be necessary for microglia proliferation and activation after immune challenge[173].

Alternatively, increased BDNF secretion may be a means of inhibitory feedback, as BDNF dampens microglial activation. In spinal cord injury, locally applied BDNF reduces microglial density and inhibits free radical production around injury site [174]. Exogenous BDNF infusion dampens microglial activation by LPS in the substantia nigra in aged mice[175]. In a mouse model of Type I diabetes, overexpressing BDNF in the hippocampus suppressed microglial activation and expression of TNFα and IL-6 induced by hyperglycemia[176]. Further, hypermethylation of BDNF is associated with higher levels of serum IL-6 in patients with acute coronary syndrome[177]. Exogenous BDNF administration significantly decreases TNFα and increases expression of the anti-inflammatory cytokine IL-10 in rodent models of stroke, multiple sclerosis, and pneumococcal meningitis[178-181]. Along this line, $BDNF^{+/-}$ mice have reduced expression of IL-10 and kynurenic acid levels while 3-HK is increased in the brain compared to wild-type controls following chronic mild stress [182]. After LPS treatment, $BDNF^{+/-}$ mice have increased expression of pro-inflammatory cytokines IL-1β and TNFα and elevated levels of kynurenine and QA[201]. Reduced BDNF after viral mimetic poly:IC treatment is likewise accompanied by a shift in the tryptophan/kynurenine ratio[135]. *In vitro* studies in BV2 microglia by Park *et al*[183] have demonstrated that TrkB activation by the agonist DHF inhibits production of nitric oxide, TNFα, and IL-1β, and translocation and transcriptional activity of NFκB. These data suggest a role for BDNF-TrkB activity in modulating and resolving the neuroinflammatory response to immune challenge with implications for the development of the depressive-like behavioral phenotypes (Figure 4).

While BDNF secretion may be acutely increased after immune challenge, long-term BDNF expression is hindered in an inflammatory environment. Patients undergoing INFα treatment have significantly reduced BDNF levels[151,162], and Lotrich *et al*[162] found this effect was largest in those with the Val66Met genotype. In rodents, BDNF mRNA is significantly reduced after peripheral injection of LPS in the hippocampus [184,185], substantia nigra[186], and in the whole brain[161]. Similarly, poly I:C also reduces BDNF expression in the brain[135] and E. coli treatment down-regulated BDNF and reduced levels of phosphorylated TrkB receptors in the hippocampus of aged animals[187].

Down-regulation of BDNF may be driven by the pro-inflammatory cytokines IL-1β. *In vitro* experiments have shown that IL-1β treatment inhibits the neuroprotective effects of BDNF through the PI3-K and MAPK pathways and activity of the CREB transcription factor[188]. In rodents, exogenous IL-1β treatment blocks BDNF expression in the hippocampus[189-191], and while BDNF expression was not directly measured, chronic inflammation induced by BCG reduces neurogenesis[192] which is a BDNF-TrkB dependent process and correlate of anti-depressant efficacy.

## THERAPEUTIC IMPLICATIONS

BDNF as a treatment target for inflammation-associated depression has its challenges. While BDNF and TrkB ligands do cross the b BBB[64,193], BDNF has opposing effects in different cell types and brain regions. For example, LPS treatment down-regulates BDNF in the hippocampus but up-regulates BDNF in the nucleus accumbens[77]. BDNF and TrkB agonists have anti-depressant-like effects in the hippocampus, but pro-depressive-like effects in the nucleus accumbens; inhibiting TrkB activation is anti-depressant in the nucleus accumbens[77]. Further, peripheral infusion of BDNF induces hyperalgesia[194] which, together with differential regionally-distinct CNS effects, precludes the therapeutic utility of systemic BDNF infusion and flooding the CNS with BDNF or TrkB ligands. However, intranasal ketamine, which was recently approved for anti-depressant use, activates BDNF-TrkB signaling directly in the brain, suggesting that therapeutic strategies that deliver BDNF-TrkB modulators directly to target regions within the CNS could prove efficacious.

Peripheral levels of BDNF and inflammatory markers may be useful as biomarkers for treatment-resistant depression, although this approach also is not without challenge. An ideal biomarker of risk or diagnosis should be reliably sensitive to predicting the disease in an asymptomatic individual and be specific to the disorder in question with little to no overlap with other diseases[195]. While low BDNF and high inflammation markers are frequently measured together in depressed individuals, there are many individuals who meet criteria but report no symptoms of depression,

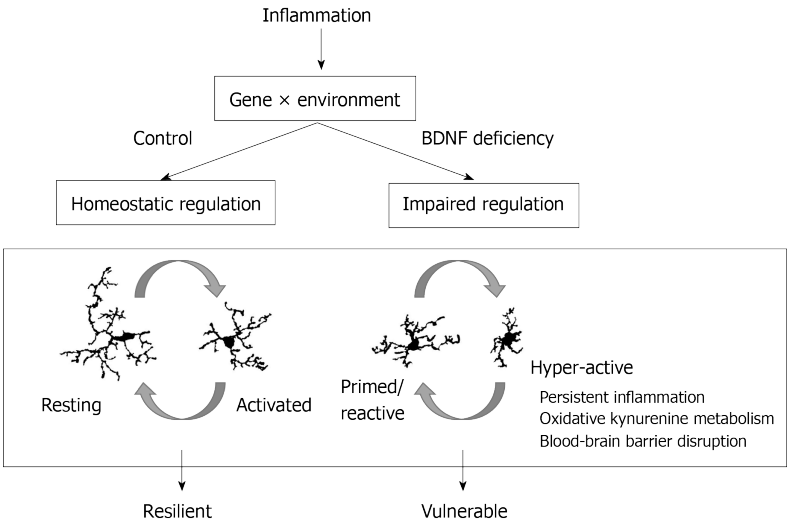


**Figure 4 Brain-derived neurotrophic factor deficiency impairs resolution of microglial inflammatory phenotypes.** Brain-derived neurotrophic factor (BDNF) levels are altered by genetics and environmental circumstances. Reduced levels of BDNF impair microglia regulation after inflammation. Hyper-active microglia contribute to blood-brain barrier disruption and express higher levels of pro-inflammatory cytokines and kynurenine metabolism pathway enzymes. Individuals with hyper-active microglia are vulnerable to developing symptoms of depression after inflammatory challenge. BDNF: Brain-derived neurotrophic factor.

or become depressed without diverging from average serum levels of each marker. Additionally, low peripheral BDNF and elevated inflammatory markers are reported in other neurodegenerative or neuropsychiatric disorders, including Parkinson's disease, bi-polar disorder, and schizophrenia[196-198]. Epigenetic patterns that disrupt inflammatory homeostasis or functional immunoreactivity of circulating immune cells may provide better prognostic value in predicting vulnerability.

Despite the obstacles, the association between BDNF and inflammation may have utility in deciding treatment options for depressed patients. Patients with inflammation and dysregulation of their BDNF-TrkB system may respond better to anti-depressant drugs with known anti-inflammatory properties, or anti-inflammatory drugs that incidentally have anti-depressant actions, and are able to elevate BDNF levels. Further mechanistic investigations of the interaction between BDNF expression and secretion and pro-inflammatory microglial responses may illuminate potentials targets for novel anti-depressant medication. One emerging approach that has yielded positive results in neurodegenerative disease is to use genetically modified hematopoietic stem cells that express growth factor and traffic specifically to the areas of the brain where pathology occurs[199,200]. While this approach has not yet been tested, it could be viable in cases of severe treatment-resistant depression.

## CONCLUSION

Researchers have long recognized BDNF and neuroinflammation as key players in the development of neuropsychiatric conditions, notably major depressive disorder. Recent research has uncovered bi-directional modulation between these two risk factors in the development of depression with promising implications for predicting vulnerability to and treatment of depression. Future studies exploring the mechanisms of BDNF modulation by inflammatory signals, and the anti-inflammatory effects of BDNF in the brain, will provide greater insight into the complex pathogenesis of depression and other neuropsychiatric disorders.

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*MINIREVIEWS*

# Molecular typing of familial temporal lobe epilepsy

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## Abstract

The pathogenesis of temporal lobe epilepsy (TLE) was originally considered to be acquired. However, some reports showed that TLE was clustered in some families, indicating a genetic etiology. With the popularity of genetic testing technology, eleven different types of familial TLE (FTLE), including ETL1-ETL11, have been reported, of which ETL9-ETL11 had not yet been included in the OMIM database. These types of FTLE were caused by different genes/Loci and had distinct characteristics. ETL1, ETL7 and ETL10 were characterized by auditory, visual and aphasia seizures, leading to the diagnosis of familial lateral TLE. ETL2, ETL3 and ETL6 showed prominent autonomic symptom and automatism with or without hippocampal abnormalities, indicating a mesial temporal origin. Febrile seizures were common in FTLEs such as ETL2, ETL5, ETL6 and ETL11. ETL4 was diagnosed as occipitotemporal lobe epilepsy with a high incidence of migraine and visual aura. Considering the diversity and complexity of the symptoms of TLE, neurologists enquiring about the family history of epilepsy should ask whether the relatives of the proband had experienced unnoticeable seizures and whether there is a family history of other neurological diseases carefully. Most FTLE patients had a good prognosis with or without anti-seizure medication treatment, with the exception of patients with heterozygous mutations of the *CPA6* gene. The pathogenic mechanism was diverse among these genes and spans disturbances of neuron development, differentiation and synaptic signaling. In this article, we describe the research progress on eleven different types of FTLE. The precise molecular typing of FTLE would facilitate the diagnosis and treatment of FTLE and genetic counseling for this disorder.

**Key Words:** Temporal lobe epilepsy; Gene mutation; Gene locus; Phenotypes; Prognosis

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**Core Tip:** Eleven types of familial temporal lobe epilepsy (FTLE) caused by single gene mutations or specific gene loci had been identified to date. The phenotype of FTLE was heterogenous and includes typical temporal lobe seizures and specific symptoms. We herein describe the etiology, inheritance, phenotype and prognosis of each type of FTLE and summarize their similarities and differences.

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## INTRODUCTION

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate two unprovoked seizures > 24 h apart[1]. Epilepsy could be classified as focal, generalized, combined generalized and focal, and unknown according to the origin of the seizures[2]. Epilepsy affected approximately 50 million people worldwide, among which up to 60%-70% of affected individuals had focal epilepsy[3,4]. Epilepsy and its comorbidities, such as memory and psychiatric disorders, severely lower the quality of life of patients[5]. Temporal lobe epilepsy (TLE), including mesial TLE (MTLE) and lateral TLE (LTLE), was the most common type of focal epilepsy, especially in adults[6]. The causes of TLE were heterogeneous, and the overall prognosis of TLE was far from satisfactory[7].

The first description of an instance of familial TLE (FTLE) could be traced back to 1895, before TLE had been defined[8,9]. In 1994, Berkovic *et al*[10] provided the first report of familial TLE, in which four individuals in two generations were diagnosed with TLE. The family aggregation of TLE indicated a genetic etiology. Although the characteristics of TLE had been extensively studied, the genetic etiology of TLE remains unclear, and the incidence of FTLE were severely underestimated due to the high rates of misdiagnosis and missed diagnosis in individuals with subtle symptoms [11]. Leucine-rich glioma inactivated-1 (*LGI1*) mutations was identified in approximately 50% of families with LTLE and 3% of sporadic LTLE cases[12,13]. Those findings had led to the hypothesis that LTLE was commonly caused by gene mutations and promoted the exploration of the genetic causes of LTLE[14]. Seventy percent of MTLE cases were considered to be caused by hippocampal sclerosis (HS) and was drug-refractory[15]. Most patients with drug-refractory MTLE had to undergo costly surgery, although 30% of such patients experience relapse within two years[16]. Many reports had shown that HS and MTLE were inheritable[17,18]. The mechanism seemed polygenic and was affected by multiple factors[19]. Further exploration of the underlying pathogenic genes and molecular mechanisms was critical for precision medicine.

Eleven genes/Loci responsible for FTLE have been reported to date (Table 1), including the genes *LGI1*, carboxypeptidase A6 (*CPA6*), reelin (*RELN*), galanin and GMAP prepropeptide (*GAL*), DEP domain containing 5 (*DEPDC5*), microtubule associated monooxygenase, calponin and LIM domain containing 1 (*MICAL-1*) and sodium voltage-gated channel alpha subunit 1 (*SCN1A*), along with gene loci on chromosomes (Chr) 12q22-q23.3, 4q13.2-q21.3, 9q21-q22, and 3q25-q26. These genes were involved in different biological processes. In this article, we describe the research progress on eleven types of FTLE, ETL1-ETL11, caused by these genes/Loci, of which ETL9-ETL11 had not yet been recorded in the OMIM database.

## ETL1, RELATED TO LGI1 GENE MUTATION

ETL1 (OMIM 600512) was first reported by Ottman *et al*[20] in a family in which 11 members in three generations had seizures, with most seizures having auditory features, suggesting a neocortical (or lateral) temporal lobe origin. Linkage analysis

**Table 1 Eleven different types of familial temporal lobe epilepsy**

| Phenotype | OMIM ID | Gene/locus | Inheritance | Age at seizure onset (yr) | Seizure types | EEG | MRI | Epilepsy types | Prognosis | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|
| ETL1 | 600512 | LGI1 | AD | 4-50 | Aud, Aph, FBTCS | T ea | Nor | LTLE | Responsive to ASM | [20,24, 25] |
| ETL2 | 608096 | Chr12q22-q23.3 | AD | 0.75-35 | FS, FBTCS; Cog, Aut | Nor, T ea | HM | MTLE | Responsive to ASM or SR | [27,28] |
| ETL3 | 611630 | Chr4q13.2-q21.3 | AD | 5-18 | Cog, FBCTS, FIAS | Nor, T ea | Nor | MTLE | Responsive to ASM or SR | [32] |
| ETL4 | 611631 | Chr9q21-q22 | AD | 0.58-63 | Focal Mot; Cog, Sen, Aut, FIAS, FBCTS | Nor | Nor | OTLE | Responsive to ASM or SR; migraine 5/Mo – 2/y | [33] |
| ETL5 | 614417 | CPA6 | AR | 0.75-5 | FS, FBECTS, FIAS | T ea | T atr, HS | TLE | Responsive to ASM or SR | [36] |
| | | | AD | 1.25-23 | FS | - | T atr | TLE | Drug-refractory | [36] |
| ETL6 | 615697 | Chr3q25-q26 | AD | 3-46 | FS, FIAS, Cog, Sen, Aut, FBTCS | Nor, T ea, sa | Nor | MTLE | Responsive to ASMs | [37] |
| ETL7 | 616436 | RELN | AD | 8-40 | Vis, Aud, FBECTS, FIAS | T ea | Nor | LTLE | Responsive to ASM or SR | [38,40] |
| ETL8 | 616461 | GAL | AD | 13 | FIAS, Cog, Sen, Aut, FBTCS | T ea | Nor | TLE | Responsive to ASM | [43] |
| ETL9 | - | DEPDC5 | AD | 8-13 | FS,Cog, Sen,focal Mot; FBECTS | T ea | Nor | TLE | Responsive to ASM | [44,46, 47] |
| ETL10 | - | MICAL-1 | AD | 6-30 | Aud, Aph, FBECTS | T or FT ea | Nor | LTLE | Responsive to ASM | [48] |
| ETL11 | - | SCN1A | AD | 10-13 | FS, FIAS, Aut; focal Mot, FBECTS | T ea | HS | TLE | Responsive to ASM | [50] |

AD: Autosomal dominant; Aph: Aphasia; AR: Autosomal recessive; ASMs: Anti-seizure medications; atr: Atrophy; Aud: Auditory; Aut: Autonomic; Chr: Chromosome; CPA6: Carboxypeptidase A6; Cog: Cognitive; DEPDC5: DEP domain containing 5; ea: Epileptic activity; EEG: Electroencephalogram; Emo: Emotional; ETL: Epilepsy, familial temporal lobe; FBTCS: Focal to bilateral tonic-clonic seizures; FIAS: Focal impaired awareness seizure; FS: Febrile seizures; FT: Frontotemporal; GAL: Galanin and GMAP prepropeptide; HM: Hippocampal malrotation; HS: Hippocampal sclerosis; LGI1: Leucine-rich glioma inactivated-1; LTLE: Lateral TLE; MICAL-1: Microtubule associated monooxygenase, calponin and LIM domain containing 1; MTLE: Mesial TLE; Mot: Motor; MRI: Magnetic Resonance Imaging; Nor: Normal; OTLE: Occipitotemporal lobe Epilepsy; RELN: Reelin; sa: Slow activity; SCN1A: Sodium voltage-gated channel alpha subunit 1; Sen: Sensory; SR: Spontaneous remission; T: Temporal; TLE: Temporal lobe Epilepsy; Vis: Visual.

revealed that the candidate epilepsy gene was located on Chr 10q22–q24. In 2002, an *LGI1* gene mutation on Chr 10q22–q24 was identified as the pathogenic cause[21]. LGI1 is a 60-kDa secreted protein that is predominantly expressed in neuronal cells in the brain and is involved in cortical neuronal migration, neuronal excitability and synaptic transmission. *LGI1* mutations could lead to protein folding failure and destroy the interaction with its ligand, *ADAM22*[22].

More than 40 *LGI1* variants related to ETL1 had been detected to date[23]. The variants were usually inherited from the affected parents and were rarely de novo, and the overall penetrance of the disorder was 61%-67%. The age of seizure onset was 4-50 years, usually 12-30 years[24]. Auditory and/or sensory aphasia seizures were the most common seizure types, and interictal electroencephalogram (EEG) showed temporal lobe origin, which supports the diagnosis of LTLE. The auditory symptoms ranged from unformed sounds, such as humming and ringing, to distortions and volume changes. Autonomic symptoms were less common. Most patients had experienced focal to bilateral tonic-clonic seizures (FBCTS). The prognosis was good with anti-seizure medications (ASMs), such as phenytoin and carbamazepine[25]. Some research has shown that treatment with the chemical corrector 4-phenylbutylate

ameliorates the increased seizure susceptibility of *LGI1* mutant mice, which provides potential new therapeutic options for *LGI1*-mediated epilepsy[26].

## ETL2, RELATED TO THE 12Q22-Q23.3 LOCUS

Depondt *et al*[27] reported a 5-generation family in which 22 members had TLE and febrile seizures without HS. Claes *et al*[28] linked this phenotype, namely, ETL2 (OMIM 608096), to Chr 12q22-q23.3, which includes 280 genes. ETL2 was autosomal dominant inherited, and the penetrance was approximately 80%. Those patients had a high incidence of febrile seizures, and all febrile seizures disappeared before 6 years of age. The mean age at onset of afebrile seizures was 8 years. The most common seizure types included focal seizures with or without impaired awareness, such as sensation in the head, fear, confusion and viscerosensory and tonic-clonic seizures. Ten of the patients were diagnosed with MTLE. Hippocampal malrotation was common in this family, even in individuals without seizures. The prognosis was good, with 11 individuals experiencing spontaneous remission. In addition, there was a report of a family in which seven members had febrile seizures that evolved to tonic-clonic seizures. The genetic linkage analysis mapped to Chr 12q22-q23.3[29]. Recently, Maria *et al*[30] reported a sporadic case with TLE and febrile seizures who had a 12 Mb duplication at Chr12q22-q23.3. She presented with growth retardation. Her seizure was well controlled with carbamazepine. These findings indicated that Chr 12q22-q23.3 had a broad phenotypic spectrum, similar to most well-known epileptogenic genes[31]. The symptoms of patients from the same family showed high similarity, which might be related to the common mutation sites and genetic backgrounds. The exact pathogenic mechanism required further research.

## ETL3, RELATED TO THE 4Q13.2-Q21.3 LOCUS

Hedera *et al*[32] reported a 4-generation family in which 11 individuals were diagnosed with MTLE or ETL3 (OMIM 611630). Linkage analysis mapped the phenotype to Chr 4q13.2-q21.3, which include 359 genes without homology to the well-known epileptic genes. ETL3 showed autosomal dominant inheritance with incomplete penetrance. The age of seizure onset was 5-18 years and most patients were 10-20 years. Ten individuals had focal cognitive seizures with feelings of déjà vu associated with dizziness or nausea, and 8 also had focal seizures with altered awareness and staring. Four individuals had FBCTS. Brain magnetic resonance imaging (MRI) was performed on 3 patients and the findings were not significant. EEG was performed on 6 patients, of whom 5 patients exhibited normal EEG and 1 had left anterior temporal sharp waves. Only 4 patients were treated with ASMs.

## ETL4, RELATED TO THE 9Q21-Q22 LOCUS

ETL4 (OMIM 611631) was reported in a 5-generation family of which 14 individuals had occipitotemporal lobe epilepsy and migraine with visual aura[33]. Genome-wide linkage and haplotype analysis mapped the phenotype to Chr 9q21-q22, which include 604 genes. ETL4 was autosomal dominant and was inherited with a low penetrance of 75%. The age at seizure onset ranged from 7 mo to 63 years, and the median age was 21 years. Age at migraine onset ranged from 30 to 65 years, with a median age of 42 years. Ten individuals had occipitotemporal lobe epilepsy and 5 of them also had migraine with aura. Nine of the 10 patients had focal motor or nonmotor seizures, such as visual, autonomic, and somatosensory symptoms, olfactory and auditory hallucinations, and cognitive seizures excluding déjà vu. Three of the 10 patients had focal seizures with altered awareness and 3 had FBCTS. Four had a single isolated seizure, and 1 of them also had migraine with aura. Seizures and migraine attacks were temporally independent in all patients except one. EEG and brain MRI were normal except in 2 patients with age-related white matter changes.

Approximately 6% of migraine patients have seizures, and 8%-15% of epilepsy patients have migraines[34]. Tikka-Kleemola *et al*[35] reported that among 33 families of patients experiencing migraine with visual aura, 22 families were linked to Chr 9q21-q22. None of these family members had seizures. These findings indicated that epilepsy and migraine have a common genetic basis and that Chr 9q21-q22 was closely

related to epilepsy and migraine.

## ETL5, RELATED TO CPA6 GENE MUTATION

Salzmann *et al*[36] reported four children with recessive familial forms of febrile seizures and TLE born to healthy first-cousin parents. A *CPA6* gene homozygous mutation was found associated with the phenotype and was named ETL5 (OMIM 614417). All 4 patients had febrile seizure onset before 4 years of age. One of them had TLE. His MRI showed right temporal atrophy, and EEG showed right temporal spikes and waves. They all became seizure-free with or without ASMs. In vitro research showed that *CPA6* variants reduced the level of protein expression and secretion and/or destroyed carboxypeptidase activity. Salzmann *et al*[36] also reported a sporadic case with drug-refractory TLE carrying compound heterozygous mutations in the *CPA6* gene. MRI showed cavernous malformation. His grandfather had a history of febrile seizures. Four unrelated patients with febrile seizures and refractory TLE carrying *CPA6* gene heterozygous mutations were also reported, suggesting that ETL5 was both recessively and dominantly inherited[36]. The seizure onset of these 4 patients ranged from 15 mo to 23 years of age. Among them, one had febrile seizures and left temporal lobe origin seizures with HS. His brother had a history of febrile seizures. Two patients had temporal lobe seizures originating from the temporo-parietal junction and bitemporal lobes. These two patients had neonatal sequelae and bitemporal atrophy on MRI. The last patient had febrile seizures, and his mother also had a history of febrile seizures. The prognosis of patients with homozygous mutations seemed to be better than that of patients with heterozygous mutations.

## ETL6, RELATED TO THE 3Q25-Q26 LOCUS

Only one ETL6 (OMIM 615697) family had been reported to date by Chahine *et al*[37] in 2013. In the 4-generation family surveyed in the study, 7 individuals had TLE, and 4 had febrile seizures during childhood but no subsequent epilepsy. Genetic linkage analysis linked the phenotype to Chr 3q25-q26 containing 453 genes. ETL6 was autosomal dominant and inherited with incomplete penetrance. The age of onset of temporal seizures ranged from 3 to 46 years. The 4 patients with isolated febrile seizures had onset between 5 mo to 5 years of age. Seizure types included focal aware seizures, focal impaired awareness seizures, FBCTS and rarely status epilepticus. Many of the seizures were suggestive of a mesial temporal origin, and occurred with auras including abdominal discomfort, rising numbness, floating sensation, strange grabbing feeling, déjà vu and dizziness. Brain MRI, performed in 3 patients, was normal. EEG was normal except in 1 patient who exhibited sharp right temporal waves and irregular slow activity. The seizures of the patients were responsive to ASMs.

## ETL7, RELATED TO RELN GENE MUTATION

Dazzo *et al*[38] identified seven different heterozygous missense mutations in the *RELN* gene in 7 unrelated families with LTLE or ETL7 (OMIM 616436). The RELN gene is crucial for the correct cytoarchitecture of laminated structures during embryonic development and modulates dendritic growth and synaptic plasticity in the postnatal and adult stages[39]. Their research revealed that the expression of reelin was reduced in the hippocampus of ETL7 patients and reelin promoter methylation was greater with severe granule cell dispersion, which supports a compromised reelin signaling pathway and identifies promoter methylation as an epigenetic mechanism in the pathogenesis of ETL7[38]. The clinical features of ETL7 were found to be similar to those of ETL1[40]. The mean age at seizure onset was 20 years. Seizure types included focal visual seizures, auditory seizures, déjà vu, FBTCS and focal seizures with impairment of consciousness. These patients were seizure-free with or without ASMs treatment. Previous work revealed that homozygous *RELN* gene mutations caused lissencephaly with cerebellar hypoplasia[41]. Three small consanguineous LCH-affected families had been reported thus far. The heterozygous individuals in these families exhibited reduced levels of reelin in their sera and were reported to be clinically normal[42]. The apparent normal phenotype of these individuals was

consistent with the low penetrance of *RELN* mutations.

## ETL8, RELATED TO GAL GENE MUTATION

ETL8 (OMIM 616461) was reported by Guipponi *et al*[43] in a pair of monozygotic twin brothers with TLE carrying a heterozygous missense mutation in the *GAL* gene. The *GAL* gene encodes galanin, which is a neuropeptide highly expressed in the central nervous system. The mutant galanin identified in their study led to antagonistic activity against GALR1-mediated responses, decreased binding affinity and reduced agonist properties for GALR2 in vitro, suggesting that the variants impaired galanin signaling in the hippocampus and led to increased glutamatergic excitation[43]. The age of seizure onset was 13 years in both patients. Both had focal abdominal sensory seizures, incoherent speech, blurred vision, auditory hallucinations, slow ideation déjà vu and occasional FBCTS. Brain MRI findings were normal. Seizures were well controlled by ASMs.

## ETL9, A DEPDC5- RELATED FTLE

In 2013, Shida *et al*[44] reported two families with TLE caused by *DEPDC5* gene heterogenous mutations. The patients had focal nonmotor and motor seizures and their interictal EEG showed slow waves and sharp waves in the temporal lobes[45]. DEPDC5 proteins have no homology with ion channel proteins. DEPDC5 protein formed a GATOR1 complex with NPRL2 and NPRL3, which inhibited the aggregation of mTORC1. In vitro, mutant mRNA products are degraded by the nonsense-mediated decay system, and DEPDC5 haploinsufficiency was likely to be the cause of the disease [44]. Striano *et al*[46] detected a *DEPDC5* gene nonsense mutation, p.Tyr306*, in a family with two individuals diagnosed with MTLE. In the proband and her mother, the seizures were characterized by déjà vu, anxiety, derealization and epigastric sensation. During follow-up, the proband showed significant auditory seizures weekly, suggesting a diagnosis of LTLE[47]. The reports to date indicated that the phenotype of *DEPDC5*-related TLE was variable and that *DEPDC5* variants were responsible for both MTLE and LTLE.

## ETL10, AN MICAL-1-RELATED FAMILIAL LTLE

Dazzo *et al*[48] identified three different *MICAL-1* gene heterozygous missense mutations in three LTE families without *LGI1* or *RELN* gene mutations. The *MICAL-1* gene is expressed ubiquitously, with higher expression levels in the embryonic and nervous systems. In vitro, the variants significantly increased *MICAL-1* oxidoreductase activity and induced cell contraction, which likely resulted from deregulation of F-actin dynamics[49]. These results suggested that the dysregulation of actin cytoskeleton dynamics was a likely mechanism by which *MICAL-1* gene pathogenic variants led to LTE. The seizure onset age was 6-30 years, with most patients experiencing onset at 6-10 years. Affected individuals had auditory auras and some of them had aphasic symptoms. Most patients had FBCTS. EEG revealed temporal or fronto-temporal abnormal epileptic activity. Their 1.5-Tesla brain MRI scans were unremarkable. Seizures were well controlled with ASMs such as carbamazepine, methylhydantoin and vigabatrin.

## ETL11, AN SCN1A-RELATED FTLE

In 2007, a southern Italian family was reported by Colosimo *et al*[50], in which 13 members over 3 generations had febrile seizures and TLE associated with the *SCN1A* p.M145T mutation. The *SCN1A* gene encodes the alpha subunit of the NaV1.1 sodium channel and is highly expressed in the central nervous system. *SCN1A* gene mutations were associated with a broad spectrum of epilepsy phenotypes and were commonly reported in epilepsies characterized by frequent febrile seizures during childhood; few had been reported in TLE[51]. The *SCN1A* p.M145T mutation was the first missense mutation found in DIS1 of *SCN1A* and caused a loss of function of the NaV1.1 channel

[52]. All 13 living members had febrile seizures onset from 5 to 45 mo. Nine subjects were affected with only febrile seizures and had normal EEG. Three individuals later developed TLE with epileptiform temporal spikes on EEG, and two of them had HS. The onset age of TLE was 10-13 years. Seizure types included focal seizures with or without awareness and rare nocturnal FBCTS. Seizures in the patient without HS were completely controlled with valproate. Seizures in 1 patient with HS were well controlled with the combination of carbamazepine and primidone. In another patient with HS, seizures continued despite treatment with the combination of topiramate and phenobarbital.

## CONCLUSION

FTLE was always underestimated due to itsheterogeneous intrafamily clinical manifestations. Some family members with subtle symptoms had not received a diagnosis of epilepsy prior to detailed enquiry by a neurologist[11]. Eleven types of FTLE have been identified thus far (Table 1).

In addition to typical temporal lobe seizures, special phenotypes also exist within some types of FTLE, such as migraine and febrile seizures. In 2000, Gambardella *et al* [53] reported a family with ETL4, in which migraine was a common phenotype among the TLE patients. Chr. 9q21-q22, harboring 604 genes, was correlated with both migraine and ETL4. Understanding of the pathogenetic mechanisms requires the identification of the genes responsible for the phenotype. ETL2, ETL5, ETL6 and ETL11 were associated with a high incidence of febrile seizures, which was also found to be a prominent feature in a number of genetically determined epilepsy cases[54]. Febrile seizures affect approximately 3% of children and increase the risk of developing HS [55]. Moreover, febrile seizures and TLE were associated with common genetic variation, such as the *CPA6* and *SCN1A* genes[36,56]. The prognosis of FTLE with a high incidence of febrile seizures was almost good. However, in some patients with genetically based MTLE-HS and histories of febrile seizures, the prognosis was poor, and the underlying pathogenic genes remain unknown[57]. A growing number of studies had proven that HS and MTLE had polygenic or multifactorial modes of inheritance. The mechanism involves neuron development, differentiation, synaptic signaling, immune response and vascular development, which might provide directions for therapy of MTLE-HS[19].

LTLE was mostly genetic in etiology related to *LGI1*, *RELN*, *MICAL-1* and *DEPDC5* gene mutations. *LGI1* and *RELN* mutations were reported in approximately 35 and 17.5 % of LTLE families respectively[12,38]. The phenotypes of familial LTLE caused by pathogenic mutations of the *LGI1*, *RELN* and *MICAL-1* genes were similar. However, the molecular functions of these genes were discrepant, indicating that the mechanism of LTLE was complicated. Notably, some candidate loci were also gradually being recognized, such as the Chr 9q13.11–q13.31 Locus (not mentioned above), which was related to familial LTLE with a higher frequency of febrile seizures and migraine and a lower recurrence of focal to bilateral seizures than ETL1, ETL7 and ETL10[58].

Four gene loci on Chr 12q22-q23.3, 4q13.2-q21.3, 9q21-q22, and 3q25-q26, were closely related to FTLE. These loci each contain 280-604 genes, but the specific pathogenic genes for TLE had not yet been identified. Reports on each type of FTLE were rare, which limits our knowledge and hinders in-depth research. Reaching a complete understanding of the genetics of TLE is still a long-term prospect.

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*MINIREVIEWS*

# Emergence of bariatric psychiatry as a new subspecialty

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## Abstract

Bariatric surgery is the branch of surgery aimed at helping a person with obesity lose weight. The implementation of surgical treatment of obesity is growing at an impressive rate. As expected, the expanding implementation of bariatric procedures has progres-sively revealed critical issues that were not evident when the number of obese patients treated with surgery was relatively small. One critical issue is the importance of mental health assessment and care of bariatric patients. The aim of this review is to provide readers with an up-to-date summary of the goals, methods, and clinical strategies of bariatric psychiatry. The aims can be grouped into three distinct categories. First, to ascertain that there are no psychiatric contraindications to safe bariatric surgery. Second, to diagnose and treat pre-surgery mental conditions that could predict poor weight loss. Third, to diagnose and treat post-surgery mental conditions associated with poor quality of life. Although bariatric psychiatry has gained the status of a new subspecialty within the field of mental health and psychopathology, many clinical questions remain unsolved. We need more long-term data on outcome measures such as quality of life, adherence to behavioral guidelines, risk of suicide, and post-surgery prevalence of psychological disturbances and mental disorders.

**Key Words:** Bariatric surgery; Psychiatry; Weight loss; Mental health; Quality of life; Preoperative assessment; Postoperative follow-up

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**Core Tip:** Bariatric psychiatry has gained the status of a new subspecialty within the field of mental health and psychopathology. The aims of bariatric psychiatry can be grouped into three distinct categories. First, to ascertain that there are no psychiatric contraindications to safe bariatric surgery. Second, to diagnose and treat pre-surgery mental conditions that could predict poor weight loss. Third, to diagnose and treat post-surgery mental conditions associated with poor quality of life. Future research should

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focus on post-surgery quality of life, adherence to behavioral guidelines, risk of suicide, and prevalence of psychological disturbances and mental disorders.

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## INTRODUCTION

Bariatric surgery is the branch of surgery aimed at helping a person with obesity lose weight. Compared to traditional treatments of obesity (*e.g.*, diet, exercise, behavior modifications, and weight loss medications), bariatric surgery generally leads to more consistent outcomes in terms of significant and long-lasting weight loss, up to 30% of total body weight[1]. Another peculiarity of bariatric surgery is its favorable impact on metabolic complications associated with obesity (*e.g.*, type 2 diabetes). Thus, some reports refer to bariatric surgery as "weight and metabolic surgery".

Bariatric surgery includes different surgical procedures (*i.e.*, sleeve gastrectomy, Roux-en-Y gastric bypass abbreviated to RYGB, biliopancreatic diversion, adjustable gastric banding and intragastric balloons) almost always done *via* laparoscopic surgery. The implementation of surgical treatment of obesity is growing at an impressive rate. The data reported by the American Society for Metabolic and Bariatric Surgery (ASMBS) show that, in the years between 2011 and 2019, the number of patients who underwent weight loss surgery in the United States rose from 158000 to 256000[2]. The latest edition of the Global Registry published by the International Federation for the Surgery of Obesity and Related Disorders (IFSO, 2019) reports that worldwide operations increased from 100092 in 2014 to 833687 in 2019[3].

As expected, the expanding implementation of bariatric procedures has progressively revealed critical issues that were not evident when the number of obese patients treated with surgery was relatively small. One critical issue is the importance of mental health assessment and care of bariatric patients. Bariatric surgery is not a hit-and-run technical operation like many other surgical procedures. Rather, it is a "voyage" affecting patients' life for years. After surgery, patients experience major changes in their physiological functions, psychological processes, lifestyle habits, and social interactions. Therefore, they need extensive and prolonged interactions with mental health professionals that should start in the preoperative stage and continue throughout the postoperative years. In spite of their importance in the multi-disciplinary teams that take care of patients seeking weight-loss surgery, often psychologists and psychiatrists still play a marginal or poorly defined role in preoperative assessment and postoperative follow-up.

Fortunately, in the last decade, many studies focusing on a variety of aspects related to preoperative assessment and postoperative follow-up have partially reduced the gap between bariatric surgery and psychiatry. The body of evidence derived from these studies is so large and diverse to allow the conclusion that bariatric psychiatry has gained the status of a new subspecialty within the field of mental health and psychopathology[4].

The aim of this review is to provide readers with an up-to-date summary of the goals, methods, and clinical strategies of bariatric psychiatry. The review is organized as follows. The first section outlines the *raison d'être* of bariatric psychiatry. The following three sections summarize the clinical issues addressed by preoperative and postoperative psychiatric assessment. The final section focuses on the specific skills required to mental health professionals who take care of bariatric patients before and after surgery.

## THE AIMS OF BARIATRIC PSYCHIATRY

It is unusual for patients undergoing surgical operations to be interviewed by a psychiatrist before surgery and to be re-evaluated over time after surgery. So, why should bariatric patients follow a different route from that usual for other surgical

patients? Most bariatric candidates ask such a question and need an explanation that clarifies the aims of mental health assessment. The aims can be grouped into three distinct categories. First, to ascertain that there are no psychiatric contraindications to safe bariatric surgery. Second, to diagnose and treat pre-surgery mental conditions that could predict poor weight loss. Third, to diagnose and treat post-surgery mental conditions associated with poor quality of life.

The definition of the three categories listed above has been a gradual acquisition since the rise of bariatric surgery. Initially, for many years, the only reason for mental health assessment was the exclusion of patients with psychiatric disorders that could increase the risk of medical complications. Later on, it became clear that the primary goal of bariatric surgery (*i.e.*, weight loss) was influenced by a variety of psychological and behavioral variables. As a result, the identification of these variables in the individual patient became an additional task for the examining psychiatrist. Still today, weight loss is the only measure of success in many follow-up studies focusing on the psychological predictors of bariatric outcome. Yet, in the last few years, researchers and clinicians have begun to pay greater attention to the post-surgery quality of life of patients. Successful bariatric surgery should not only be safe and cause significant weight loss but it should also improve patients' quality of life. Below, I will briefly discuss each of the three aims of contemporary bariatric psychiatry (Table 1).

## DEFINING PSYCHIATRIC CONTRAINDICATIONS

Although, at the dawn of bariatric surgery, the definition of psychiatric contraindications was the only task of mental health assessment, still today there is no clear consensus among official guidelines regarding which psychiatric conditions merit recommending delay or denial of surgery. For example, the *Interdisciplinary European Guidelines on Metabolic and Bariatric Surgery*[5] list non-stabilized psychotic disorders, severe depression, personality and eating disorders, alcohol abuse or drug dependencies as definite contraindications to bariatric surgery. Likewise, the *Resource Document on Bariatric Surgery and Psychiatric Care* of the American Psychiatric Association[6] states: "*The most common reasons for deferring bariatric surgery are significant psychopathology such as active psychosis (including thought disorder symptoms), current substance dependence, untreated eating disorders (specifically anorexia nervosa or bulimia nervosa), untreated depression and/or active suicidal ideation*." (p. 2). Yet, a diligent reading of these documents reveals that the sole presence of any particular psychiatric symptom or syndrome is not a sufficient element for contraindicating surgery because clinicians should make their determinations based on a more comprehensive assessment. The European document specifies that the conditions listed above are contraindications "*unless specifically advised by a psychiatrist experienced in obesity*" (p. 453) and the American document states that "*a psychiatric disorder per se should not be viewed as an exclusion criterion for bariatric surgery*." (p. 2).

Regardless of the ambiguity of the recommendations reported by different guidelines, a fact that emerges clearly from the most recent reports addressing the issue of psychiatric contraindications is a progressive expansion of eligibility criteria [4]. Conditions that in the past were considered contraindications are now judged as compatible with bariatric surgery. Two reasons may explain such a progressive expansion of eligibility criteria. First, the decline in the medical complications associated with bariatric surgery[7]. Second, the emphasis on weight loss as the primary measure of successful outcome. Yet, the view that a psychiatric condition is a contraindication only if it increases medical risks and/or impairs weight loss is questionable. Such a permissive approach ignores the recent finding that, over a 10-year study period, there was an increase in mental health service presentations after surgery, particularly among those who had prior psychiatric illnesses[8].

We need standardized guidelines for psychiatric eligibility based on longitudinal data that focus not only on medical complications and weight loss but also on post-surgery mental health and quality of life. Standardized guidelines are needed to protect both patients and health professionals. The lack of unambiguous and agreed-upon recommendations specifying which individual factors turn a potential psychiatric contraindication into a manageable pre-surgery condition exposes evaluating clinicians to the risk of facing a medical malpractice lawsuit and charge them with the burden of deciding case-by-case.

**Table 1 The aims of bariatric psychiatry**

| Aims of bariatric psychiatry |
|---|
| To ascertain that there are no psychiatric contraindications to safe bariatric surgery |
| To diagnose and treat pre-surgery mental conditions that predict poor weight loss |
| To diagnose and treat post-surgery mental conditions associated with poor quality of life |

## PREDICTING WEIGHT LOSS

Weight loss is the primary goal of bariatric psychiatry and the key measure of successful outcome. A recent study[9] defined a favorable weight loss response as ≥ 50% excess weight loss or ≥ 20% total weight loss. Among the wide range of individual variables that can impact weight loss, personality traits and psychiatric conditions play a relevant role.

Two recent systematic reviews have analyzed the relationship between personality traits and bariatric surgery outcomes[10,11]. Better weight loss response is predicted by a combination of different personality traits including high cooperativeness, high persistence, low novelty seeking, low impulsivity, an internal locus of control, a low tendency toward externalizing behaviors, a secure attachment style, and low levels of alexithymia. Each of these personality traits is associated with a variety of individual and social behaviors that promote successful postoperative treatment plans including the capacity and willingness to modify dietary habits, to increase levels of routine physical activity, to restrain alcohol consumption, and to attend monitoring appointments. Thus, during preoperative clinical interviews, personality assessment should integrate diagnostic procedures aimed at detecting the presence of those psychiatric syndromes that impact negatively on weight loss. Eating, depressive, and anxiety disorders are the psychiatric syndromes most analyzed by follow-up studies.

Obese patients seeking bariatric surgery have a high prevalence of eating disordered behavior. In particular, binge eating disorder (BED) is frequently diagnosed in bariatric candidates but there is no definitive evidence on the association between preoperative BED and weight loss outcomes after surgery. There are studies showing that patients with and without BED show similar outcomes in terms of after-surgery weight loss and weight regain[12]. However, other studies identified a diagnosis of BED as a negative predictor of outcome. Ivezaj *et al*[13] have described the "Bariatric Binge-Eating Disorder" (Bar-BED) defined as an eating pathology meeting all criteria for BED, except for the requirement of an unusually large amount of food. In their study, the outcome of patients who underwent sleeve gastrectomy surgery and developed Bar-BED was worse than the outcome of patients without such a diagnosis. Thus, it is likely that a pejorative impact of BED on bariatric outcome is exclusive to, or more frequent in, those patients who retain their pre-surgery eating pathology[14].

Whereas the relationship between eating disorders and the outcome of bariatric surgery has been largely investigated, fewer studies have analyzed the impact of preoperative depression and anxiety. Some studies based on small samples reported a negative association between baseline depression and postoperative weigh loss. For example, de Zwaan *et al*[15] found that the presence of a depressive disorder was significantly associated with a lower degree of weight loss at 24-36 mo, but not at 6-12 mo ($n$ = 107). By contrast, Gill *et al*[16] concluded that preoperative depression scores did not predict outcomes of postoperative body mass index (BMI). A possible confounding variable is the chronological course of affective and mood symptoms. de Zwaan *et al*[15] reported a differential effect of lifetime and current anxiety disorders on weight loss. Whereas current anxiety disorders had no impact, lifetime anxiety disorders were of negative prognostic value for postoperative weight loss. However, when successful outcome is measured in terms of weight loss, the majority of prospective studies shows that the impact of preoperative anxiety is negligible[16].

## MONITORING POST-SURGERY MENTAL HEALTH AND QUALITY OF LIFE

Bariatric surgery is a turning point in patients' lives. Patients are typically faced with initial dietary restrictions, permanent changes in eating and dietary habits, altered body sensations and experiences, shifting body image and self-care behaviors, new

cognitions and feelings, and an emerging and different lifestyle. In addition, they may sometimes realize unexpected and significant changes in relationships that may result in marked stress[17]. All these changes inevitably impact patients' mental health and quality of life, for better or worse. After an initial improvement in psychiatric symptoms and psychosocial functioning (the honeymoon phase lasting about 2 years), some patients show a progressive decline in their mental wellbeing. One of the major tasks of contemporary bariatric psychiatry is to improve our understanding of which individual variables can predict and explain such a biphasic post-surgery course.

Doubtless, pre-existing psychiatric disorders are a risk factor for post-surgery mental disturbance. The increase in mental health service presentations reported by Morgan *et al*[8] over a 10-year study period after surgery involved especially those patients who had prior psychiatric illnesses. Psychiatric disorders are common among patients seeking surgical treatment of obesity, as shown by Dawes *et al*[18] in their meta-analysis of 59 studies reporting the preoperative prevalence of mental health conditions in 65363 bariatric candidates. The three most common individual diagnoses, based on random-effects estimates of prevalence, were depression (19%), BED (17%) and anxiety disorders (12%). Whereas anxiety symptoms do not improve after surgery, eating pathology and depression tend to remit during the first 2 years and to recur thereafter[4].

The scope of preoperative assessment is not limited to psychiatric diagnosis and should be expanded to include patients' motivations and expectations. Poor satisfaction with surgery outcomes often derives from unrealistic expectations and may cause postoperative frustration, depression and opposition to implement behavioral changes[19]. In the preoperative phase, it is important to discuss and correct naïve hopes that surgery would simply "fix" things including bad eating habits without personal effort. Common beliefs among bariatric candidates are that they have lost control over their own diet and the ability to lose weight, and this control cannot be regained through personal effort. Choosing to undergo bariatric surgery is seen as a way to end the never-ending, unwinnable struggle with food and weight, and hand control over to a surgeon who will release them from obesity by changing how their body works[20]. If not modified, such a passive attitude may undermine patients' collaboration with postoperative treatment strategies.

Post-surgery decline in mental wellbeing is not necessarily related to unmet expectations about weight loss and eating behavior. Mental health professionals taking care of bariatric patients should be aware that weight loss is not the only variable making the difference in terms of psychological well-being. Personal characteristics can offset the psychological reward of weight loss. A good example is child maltreatment. Bariatric patients with a history of child maltreatment experience weight loss similar to those without histories of abuse. However, they often report greater levels of depression as well as mood and anxiety disorders both prior to and following surgery. Additionally, victims of childhood adverse experiences are more vulnerable to psychiatric hospitalizations and suicidal behavior following surgery, especially those who are suffering from mood or substance use disorders[21].

Another psychological variable largely independent from weight loss is body dissatisfaction. In most cases, body image improves after bariatric surgery. However, some aspects of body image do not improve with weight loss or do not reach norms (*e.g.*, average scores of people with BMIs in the normal range and no eating disorder). The way patients feel and think about their physical appearance may lag behind the rapid changes in weight and body shape following surgery. Thus, the process of rebuilding a positive body image may be lengthy and complicated, although a decrease of body dissatisfaction is generally expected after surgery[22].

Although symptoms reflecting anxiety, depression, disordered eating and body dissatisfaction require prompt diagnosis and treatment, the two most alarming psychiatric complications of bariatric surgery are suicide and addiction. There is a growing concern that post-bariatric surgery patients may have an increased risk for completed suicide, attempted suicide and self-harm compared to age-, sex-, and BMI-matched controls[23,24]. A variety of pre- and post-surgical psychosocial, pharmacokinetic, physiologic, and medical factors may be involved in increasing self-harm and suicide risk[25]. A meta-analysis published in 2019 and based on 32 studies with 148643 subjects reports the most recent data on completed suicide, attempted suicide and self-harm in post-bariatric surgery patients[26]. Mortality from suicide after bariatric surgery was 2.7 per 1000 patients and the suicide attempt/self-harm event rate was 17 per 1000 patients. The calculated event rate in post-bariatric surgery patients was eight times higher than average suicide rates in the general populations from countries with the highest suicide rates in the world. The strongest predictor of post-surgery risk was a lifetime history of suicide ideation and/or self-injurious

behavior. Therefore, preoperative assessment conducted by an expert mental health professional is crucial for effective prevention of self-harm and suicide in bariatric patients. The 2016 edition of the guidelines of the Italian Society of Bariatric Surgery [27] includes a lifetime history of attempted suicide among the absolute contraindications to bariatric surgery.

Post-surgery substance use disorders are emerging as one of the most critical psychiatric complications of bariatric surgery[28,29]. Long-term studies indicate that these problems tend to develop after a relatively long latency following surgery, typically about 1 year to 2 years after surgery, and some evidence suggests that the risk for onset of such problems continues to increase, rather than decrease, over many years following surgery[30]. Risk factors for post-surgery substance use disorders have been consistently described and include type of surgery, a personal history of substance use disorder, a family history of substance use disorder, a history of early trauma, pre-existing psychiatric disorders, low social support, younger age, male sex and alcohol sensitization after surgery. By contrast, the mechanisms linking bariatric surgery and substance use disorders are not fully understood. Several hypotheses have been advanced to explain post-surgery increased risk. Prevalent explanations focus on altered pharmacokinetics induced by the anatomical and physiological changes that result from surgical procedures. Addiction transfer is an alternative (or complementary) explanation. The hypothesis assumes that, being physically prevented from comfort eating after bariatric surgery, some patients employ substances or compulsive behaviors as a way to manage the problem of their unmet emotional and psychological needs.

## WHY A SUBSPECIALTY?

The title of the present review elevates bariatric psychiatry to the rank of subspecialty. The emergence of a new medical subspecialty is justified if knowledge in the field expands so rapidly to impose the further specialization of clinicians. Subspecialization allows clinicians to focus their abilities and learn more about the best strategies to diagnose and treat patients with specific medical problems. Psychological assessment and care of bariatric patients have reached such a level of complexity to require dedicated programs conducted by mental health professionals with a high degree of expertise. This was clearly stated as early as 2004 by the American Society for Bariatric Surgery[31]: "*ASBS believes that the application and interpretation of objective tests, the ability to identify discrete risk factors not amenable to testing, as well as the capacity to conduct pertinent clinical interviews and to organize this information in a way that directly speaks to the adjustment of the individual after surgery requires a particular level and kind of experience that is specific to bariatric surgery.*" (p. 15).

I refer the reader to my recent book[5] for a detailed discussion of the clinical skills required to psychiatrists who take care of bariatric patients. Here, I will summarize the basic aspects that differentiate the clinical care of bariatric patients from standard psychiatric practice (Table 2).

The evaluating psychiatrist should be aware of the complexity of informed consent in bariatric psychiatry[32]. Patients should be able to articulate their rationale for surgery and why it is right at this time in their life. The psychiatrist should ascertain if the patient has a good understanding: (1) Of the nature and mechanics of surgery as well as the possible risks and complications of the procedure; and (2) Of what is expected postoperatively, including diet, exercise, follow-up, support group attendance, *etc.* If patients are unable to demonstrate a basic and clear understanding of these factors, they are referred back to the surgeon and/or nutritionist for additional counseling. It is clear that, in order to conduct an accurate investigation of patients' motivations and expectations, the evaluating psychiatrist should have a solid knowledge of the physiological and psychological changes caused by bariatric surgery.

Another critical aspect that makes preoperative evaluation different from standard psychiatric interview is the dependability of the information reported by patients. Bariatric surgery candidates tend to present themselves in an overly favorable light during the psychological evaluation. This response style is associated with less reporting of psychological problems and might interfere with the accurate assessment of patient mental condition[33]. Mental health professionals interviewing bariatric candidates should be trained to circumvent patients' reticence in sharing information that could make them not eligible for bariatric surgery. This can be made by explaining the importance of psychological assessment for postoperative long-term well-being and by assessing personality traits (*e.g.*, impulsivity or attachment style)

**Table 2 Specific skills required to bariatric psychiatrists**

| Specific skills |
|---|
| Understanding the complexity of informed consent by bariatric candidates |
| Capacity to circumvent patients' reticence in sharing information that could make them not eligible for bariatric surgery |
| Ability to detect and diagnose problematic eating behaviors other than bulimia nervosa, anorexia nervosa and binge eating disorder |
| In-depth understanding of psychiatric medication absorption and altered pharmacokinetics after surgery, as well as the impact of psychiatric medication on weight loss |

that, compared to symptoms, are less subjected to conscious alteration.

As explained previously, bariatric surgery candidates often report problematic and/or eating disordered behaviors. For most patients, these eating behaviors improve after surgery. A subset, however, experience a recurrence or new onset of problematic eating behaviors as early as 2 mo to 18 mo after surgery, which can result in compromised weight loss/excessive weight regain[34]. During standard diagnostic interviews, clinical psychiatrists generally limit their assessment to symptoms reflecting bulimia nervosa, anorexia nervosa or BED. When interviewing bariatric patients, the diagnostic scope should be widened to include other problematic eating behaviors that are not yet included in official classifications such as grazing, night eating, emotional eating, and food addiction.

Finally, psychiatric care of bariatric patients requires a solid background in psychopharmacology. Studies have estimated that approximately 35%-38% of bariatric surgery candidates were taking psychiatric medications before surgery[35]. Many of these patients continue to take psychotropic medications after surgery. The complex management of drug therapy after surgery require an in-depth understanding of psychiatric medication absorption and altered pharmacokinetics, as well as the impact of psychiatric medications on weight loss and psychiatric symptoms after surgery[36].

## CONCLUSION

Bariatric psychiatry is on the move. The role of mental health professionals is currently more important than in the recent past and it is likely to gain even greater responsibility in the future. Yet, many clinical questions remain unsolved. We need more long-term data on outcome measures such as quality of life, adherence to behavioral guidelines, risk of suicide, and post-surgery prevalence of psychological disturbances and mental disorders. These data will be instrumental in deciding "how much psychiatry is too much" for bariatric patients. In fact, whereas some authors have argued for more intensive preoperative and postoperative psychosocial interventions [37], others have even criticized the requirement of preoperative psychological evaluation for all patients seeking bariatric surgery[38].

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*MINIREVIEWS*

# Mental health promotion for elderly populations in World Health Organization South-East Asia Region: Needs and resource gaps

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## Abstract

The accelerated population growth of the elderly (individuals aged 60 years or more) across the globe has many indications, including changes in demography, health, the psycho-social milieu, and economic security. This transition has given rise to varied challenges; significant changes have been observed in regard to developing strategies for health care systems across the globe. The World Health Organization (WHO) is also engaging in initiatives and mediating processes. Furthermore, advocacy is being conducted regarding a shift toward the salutogenic model from the pathogenic model. The concept behind this move was to shift from disablement to enablement and from illness to wellness, with the notion of mental health promotion (MHP) being promoted. This article attempts to discuss the MHP of elderly individuals, with special reference to the need to disseminate knowledge and awareness in the community by utilizing the resources of the health sector available in the WHO South-East Asia Region countries. We have tried to present the current knowledge gap by exploring the existing infrastructure, human resources, and financial resources. There is much to do to promote the mental health of the elderly, but inadequate facilities are available. Based on available resources, a roadmap for MHP in elderly individuals is discussed.

**Key Words:** Mental health promotion; Elderly; Mental healthcare needs; Resource gaps; World health organization

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Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
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Grade E (Poor): 0

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**Core Tip:** In gross domestic product South-East Asia Region Organization (SEARO) countries, the aging population is increasing exponentially; with this increment, mental health issues and care needs are increasing drastically. The mental health promotion of elderly people needs adequate awareness, enough human resources and infrastructure, good psychosocial support, the use of innovations in care, research, and reasonable funding. The mental health care needs of the elderly in SEARO countries are tremendously high, and there is a considerable gap in terms of trained human resources and infrastructure. Thus, there is a need to recognize both at-risk activities and the current care deficiencies that need to be resolved in the right direction for the potential boom that we foresee occurring in the elderly population.

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## INTRODUCTION

### *Demographic scenario*

The global population is aging, and life expectancy is following an increasing trend. With an increased global growth rate of the elderly population (aged 60 years and older), the mental health issues of this group need thoughtful attention. The enormous mental health morbidity in this population group gives rise to a higher number of consumers of mental health care services. Thus, mental health care needs are also increasing. As per the World Health Organization (WHO) report, the global elderly population is expected to double by 2050 from the baseline level reported in 2015[1]. It is likely that by 2050, four out of every five elderly individuals will be located in low- and middle-income countries[1]. By 2019, the number of people in the world who were older than 60 years was reportedly 1 billion; this number is expected to increase to 1.4 billion by 2030 and 2.1 billion by 2050[2]. As the number of elderly individuals in the South-East Asia Region Organization (SEARO) is increasing rapidly, their mental health care needs will also increase significantly in the days to come.

### *The era of MHP and healthy aging*

Health promotion refers to the process that empowers a person to improve his or her strengths to retain health[3]. In contrast, MHP advocates maintaining one's psychological well-being by adopting a scheduled routine, lifestyle, and a helpful environment[4,5]. In the late 19$^{th}$ century, the concept of preventing illness by promoting health came into existence after a conference held in Ottawa[3]. Mental health promotion (MHP) for elderly individuals stipulates a procedure that attempts to develop an integrated approach for providing quality of life to the elderly population so that they can lead their life in a meaningful way with dignity. Studies suggest that socializing and upgrading one's emotional and functional potentials for MHP may be glorified[6].

The WHO's document entitled "*Decade of Healthy Aging 2021–2030*" discusses the concept of healthy aging and emphasizes enhancing the functional abilities of the elderly population to promote healthy aging[7]. This document also discusses the vision for healthy aging by 2030 and appeals to the government and various other stakeholders to invest in and monitor healthy aging among the general population in the community[7]. The global strategy and action plan for aging and health (2016–2020) emphasizes the long and healthy life of every elderly population in the world[8]. The Sustainable Development Goals (SDGs), adopted by the United Nations member states, emphasize the good health and well-being of every individual, including those who are elderly[9].

Including 11 member states (Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste), the SEARO is one of the most heavily populated regions of the world[10]. The WHO SEARO caters to nearly one-fourth of the global population and is primarily

affected by war, terrorism, political crisis, natural calamities, unemployment, and poverty[10]. The training for and teaching about geriatric mental health in the medical curriculum in South-East Asia are also inadequate, which affects the care of the elderly population[11]. Another major challenge of developing countries is that a large chunk of the geriatric population seeks help from nonqualified persons and traditional healers for their mental ailments[11]. Many South Asian countries, such as Japan, Singapore, China, Malaysia, and Thailand, have undertaken initiatives to develop country-specific policies to protect the rights of the elderly population and provide them with quality care[12]. The Ministry of Social Justice and Empowerment, Government of India, also developed a national policy for older persons in 1999, which was subsequently amended as per the needs of the elderly population[13].

### *Aging and mental health in the SEARO*

The significant bulk of the population in the SEARO resides in India. In India, the elderly population comprises approximately 104 million individuals, which corresponds to 9% of the nation's total population[14]. It has been projected that by 2026, the elderly population (> 60 years) will rise to 14% of the total population, and by 2050, it is expected to be 19% of the total population[14].

Older adults globally face several challenges in regard to their deteriorating general physical health and increased risk of mental health issues, including neurocognitive disorders, loss of job, grief, loneliness, isolation, and abuse[14,15]. All these challenges compromise the quality of life of an individual. Commonly encountered mental health issues in the elderly are depression, other mood disorders and neurocognitive disorders[15-17]. Elderly populations are also victims of negatively expressed emotions[15].

There is a lack of resources and infrastructure for the care of the elderly population [18], which is evident in almost all WHO SEARO regions. In regard to the mental health care of the geriatric population, there are even fewer facilities[18]; the same/worse scenario is found everywhere in WHO SEARO countries. Generally, the geriatric population receives health care facilities from the general health care system, alternative medicine, home-based care, and other resources. Unfortunately, a more significant proportion of older adults are deprived of timely care for their health ailments[15].

### *The Mental health challenges of elderly*

Existing shreds of evidence suggest a massive burden of mental health issues among the elderly population. However, in low-income countries, resource scarcity is more serious and affects the geriatric population's mental health care[19]. In South-East Asia, several countries fall into the group of low-income countries, and their health care systems struggle with the scarcity of human resources and infrastructure. It has also been reported that the prevailing infrastructure necessary to meet mental health care needs among the elderly is sparse in India[20]. As a result of this vast gap in health care delivery, the existing health care sectors are overburdened, and older adults in need of help are deprived of care. A significant chunk of people with dementia live in developing countries. It is expected that by 2040, the exponential growth of people living with dementia in South-East Asian countries will exceed 300% of the baseline figure reported in 2001[19]. It has also been reported that loneliness is commonly seen among 3/4$^{th}$ of older adults suffering from depression[20]. Furthermore, loneliness is a common issue among the elderly and is a well-known risk factor for depression. Thus, it may influence perceived social support among the elderly population.

Another challenge found in developing countries is the lack or poor implementation of policies and programs that facilitate the care and protection of the elderly[21]. However, some countries lack specified indicators or targets against which the implementation of these policies/programs could be monitored, and some places hardly have any existing programs. Resources in terms of budgetary allocations and physical and human infrastructure are also questionable in some WHO SEARO countries. Such problems may be resolved by promoting the mental health of the elderly population, which attempts to sustain the psychological well-being of elderly individuals by committed efforts, for which an in-depth need availability vis. a vis. gap analysis in terms of various domains, such as housing, safety, security, financial, psychosocial, emotional, health, and other ancillary needs, would be required. This article attempts to discuss the various dimensions of MHP for the aging population in WHO SEARO countries in view of the available mental health resources, needs, and existing gaps.

## APPROACH ADOPTED TO UNDERSTAND MHP FOR AGING POPULATIONS IN WHO SEARO COUNTRIES

We aimed to accomplish this review with a broad focus on MHP, including general and specific questions that are suitable for a comprehensive analysis of the subject. We aimed to conduct this review research in view of our own experiences and the existing literature on the topic to explore the needs, available resources, and gaps. This led us to provide a roadmap for further developments in the field of MHP in elderly individuals. The review was conducted in a phasewise manner.

**Stage 1-Preparatory phase:** First, the corresponding author approached four mental health professionals with experience in the field and discussed writing the manuscript. After obtaining consent from each participating author, we performed two subsequent meetings. Subsequently, the following research questions were identified: what are the mental health issues of the elderly population in general, and generally, how are they handled? What is needed for the better mental health of the elderly population? What services are available to balance the mental health and well-being of the elderly population? What health promotion strategies exist to maintain the mental health of the elderly population? The discussion led to identifying our research topic. With consensus, the topic was finalized as "*Mental health promotion for the aging population in WHO SEARO countries: Needs and resource gaps*." After identifying our review topic and question, we discussed the aim and objectives and finalized them. Then, decisions were made regarding strings to search the literature, time, and language.

**Stage 2-Identification of related articles:** With the help of keywords—mental health, promotion, and (older adults or Geriatrics or elderly)—two of the authors (VKL and NS) started including manuscripts (original and review) initially with the help of PubMed. A total of 195 articles were extracted from PubMed; of these, only six articles were suitable. Then, using an exact keyword search of articles, PubMed Central (PMC) was utilized. PMC revealed 51322 articles, and exploring articles from this huge bulk in a limited period was difficult; thus, the string was changed to MHP AND elderly OR Older adults AND WHO SEAR, which revealed 327 articles. Of these, only one article was found to be relevant. The selection of articles was limited to peer-reviewed and pragmatic research related to the goal of our study to make an evidence-based foundation to understand the MHP status in WHO SEARO countries.

Furthermore, as per the document's significance, a decision was made to include supplementary data from other sources. Documentation of the essential details was also performed simultaneously. The primary focus was on MHP, existing MHP programs, and related stakeholders. We tried to include almost all the articles and references with relevant documentation to avoid missing any related information obtained from the subsequent supplementary search.

## MHP IN WHO SEARO COUNTRIES-THE STATUS

**MHP needs:** The WHO states that the basic tenet of MHP for the elderly population is active and healthy aging itself[22]. Peace, shelter, education, food, income, a stable ecosystem, sustainable resources, equity, and social justice are prerequisites for health. Health promotion is not just the health sector's responsibility; rather, it goes beyond healthy lifestyles to well-being[23]. With advancing age, few specific issues affect mental health, such as physical ailments, financial insecurity, and inadequate social support[24]. Promoting mental health in the elderly population depends on helping them meet these specific needs, such as financial security, adequate housing, social support, general health care, and protection against ageism and abuse[22]. Some of these needs are universal and address the whole population, while others are selected and as indicated, target those with significant risks[25]. Promoting general health, preventing disease, and managing chronic illnesses go a long way in promoting the mental health of the elderly population. Therefore, training all health providers in working with issues and disorders related to aging is essential. Effective, community-level primary mental health care for older people is crucial. Health care training, education, and support to the caregivers must be provided[22].

The WHO considers the scope for interventions that address the risk factors for poor health and modify unhealthy behaviors and functional status to promote the health of the elderly population in general. Strategies have been recommended in the manual for primary care physicians under Integrated Care for Older People (ICOPE) [26]. Apart from this, the WHO has also provided recommendations, strategies, and support to member states/government agencies at the global level under different comprehensive action plans, including health promotion in general and specific strategies for promoting mental health.

**Resources available for MHP:** To understand the needs of MHP, the overall resource gaps and the ways to mitigate them, it is necessary first to have a general overview of the available mental health resources available in all eleven SEARO countries.

Table 1 depicts the availability of facilities in terms of policy, plan, legislation, and budgetary allocations[27]. The table is generated based on the Mental Health Atlas of 2017 and information available about the SDGs of SEARO countries[27-38]. Table 1 reveals that except for the Maldives and Nepal, most countries spend 5% or less of their total gross domestic product (GDP).

Table 1 and Figure 1 also indicate that mental health policies or plans containing specified indicators or targets against which the implementation of these plans and policies can be monitored are present in most nations but not implemented in Bangladesh, the Maldives, and Sri Lanka. However, the stand-alone law for mental health is available in all SEAR countries except Bhutan, the Maldives, Myanmar, Nepal, and Timor-Leste. However, a dedicated authority or independent body to assess the compliance of mental health legislation with international human rights exists only in India, Korea, and Thailand. This also provides the periodic inspections of facilities and the partial enforcement of mental health legislation (Table 1 and Figure 1). Regarding the financial aspects, the government's total expenditure on mental health as a % of the total government health expenditure is also below par in most SEARO nations, ranging from as low as 0.30% in Thailand to 1.50% in India and 6% in Indonesia. The WHO recommends that the mental health budget accounts for 5%–15 % of a country's health care expenditures (Table 1).

Table 2 shows the mental health human resources (rate per 100000 population) of the SEARO countries[27]. The total mental health workers per 100000 population ranged from as low as 0.64 in Bhutan to 14.36 in Thailand, but the number of psychiatrists available per 1 Lakh population in all SEARO countries showed alarming data of even less than one, except in Korea and the Maldives, where it was 5.79 and 2.39, respectively. Additionally, among the psychiatrists available, those trained to deal appropriately with the complexities of geriatric mental health are scarce.

Table 3 shows the availability of physical infrastructure and its uptake in SEARO nations[27]. The outpatient facilities attached to a hospital and community-based/nonhospital mental health outpatient available are not on par per the population of these respective nations. It is also alarming that countries such as Bangladesh, Sri Lanka, and Nepal have such a considerable scarcity of mental hospitals. Table 3 shows that MHP and prevention strategies are not functional. Data regarding the existence of at least two functioning programs are not available for Indonesia, Myanmar, and Nepal.

The gap: Table 4 and Figures 2, 3.

The objective of MHP comprises those activities that can enhance one's psychological well-being. To improve the elderly population's psychological well-being, we need to have inclusive legislation, proper mental health services in terms of physical and human infrastructure, social and financial security, and an elderly individual-friendly environment. We have tried to search for such exclusively available resources, but there are hardly any in existence. Thus, we have considered overall the available facilities for mental health care and other services. The recommendations gap for overall human resources are estimated based on the available literature[18,39].

## ROADMAP TO THE WAY FORWARD

**The WHO recommendations for the ICOPE:** To accomplish the MHP activities of the elderly, we have to look into the recommendations made by the WHO. These recommendations are related to various domains of individual life linked to essential and psychosocial, financial, and environmental amendments.

**Nutrition and dietary advice:** Although the requirement for energy declines with age, due to diminishing sensory faculties such as taste and smell and dental issues, the elderly population is at risk for malnutrition. Adequate protein and limited salt intake are recommended, and foods with antioxidant properties such as green, yellow, and orange vegetables and fruits are recommended. The typical nutritional deficiencies are iron, fiber, folic acid, vitamin C, vitamin D, vitamin B12, calcium, zinc, riboflavin, and vitamin A[40]. The intake of calcium and vitamin D found in milk, curds, cheese, small fish, and certain green vegetables is advised. Exposure to sunlight is necessary to make the skin produce vitamin D. The routine prescription of multivitamins to be avoided, but vegetarians require vitamin B12 supplementation[40]. These findings have implications for physical well-being, specifically in terms of preventing cognitive decline and maintaining mood. Further, older adults need proper and suitable remedies for their

**Table 1 Existing health facilities with special reference to mental health (policy/plans/budgetary allocations) in World Health Organization South- East Asia Region Organization countries**

| Mental health policies and implementations | India | Bangladesh | Bhutan | Indonesia | Korea | Maldives | Myanmar | Nepal | Sri Lanka | Thailand | Timor-leste |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Current health expenditure as share of GDP | 3.6% | 2.4% | 3.5% | 3.1% | Not found | 10.6% | 5.1% | 6.3% | 4.2% | 3.7% | 2.4% |
| Domestic general government health expenditure | 3.1 | 3.4 | 8.3 | 8.3 | - | 20.2 | 4.8 | 5.3 | 8.6 | 15.3 | 3.2 |
| Health worker density (per 10000 population) | 27.5 | 8.3 | 19.3 | 24.4 | 81 | 50 | 17.9 | 33.5 | 31.7 | 38.15 | 25.04 |
| Stand-alone policy or plan for mental health | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| The mental health policy/plan | Yes | No | Yes | Yes | Yes | No | Yes | Yes | No | Yes | Yes |
| Policy/plan in line with human rights covenants | 5 | 4 | 3 | 5 | 4 | 5 | 4 | 5 | 4 | 5 | 4 |
| Stand-alone law for mental health | Yes | Yes | No | Yes | Yes | No | Yes | No | Yes | Yes | No |
| Dedicated authority or independent body assessing the compliance | Yes | No | No | Not found | Yes | Not found | Nonfunctional | Not found | Not found | Irregular and partial | Not found |
| Law is in line with human rights covenants | 5 | 2 | 2 | 5 | 3 | Not found | Not found | Not found | 5 | 4 | 5 |
| Existence of at least two functioning programs | Yes | Yes | Yes | Not found | Yes | Not found | Not found | Not found | Yes | Yes | Yes |
| Existence of a suicide prevention strategy | No | No | Yes | Not found | Yes | No | No | No | Yes | Yes | Yes |
| Total mental health expenditure/-person (reported currency) | 4 INR | 2.4 BDT (2.0 INR) | 6.73 BTN (6.73 INR) | Not found | 76370.40 KRW (5014 INR) | Not found | 58.92 MMK (3 INR) | Not found | Not found | 46.48 THB (112.4 INR) | Not found |
| The government's expenditure on mental health as % of total health expenditure | 1.30% | 0.50% | 0.30% | 6.00% | 3.80% | Not found | 0.36% | Not found | Not found | 0.30% | Not found |

GDP: Gross domestic product; BDT: Currency code of Bangladesh; INR: Indian Ruppee; KRW: Korea won; MMK: Official currency of Myanmar; THB: Thailand Baht.

health and psychological wellbeing within their limits, which is hard to approach in low and middle-income countries[41].

**Exercise:** Compared to older individuals who exercise and those who do not, the former have better physical health and better cognitive functioning. Older people should perform at least 150 min of moderate-intensity aerobic physical activity throughout the week. When older people cannot perform the recommended amount of physical activity due to their health condition, they should be as physically active as their abilities and conditions allow[42]. A lower frequency of vigorous physical activity is significantly associated with higher rates of diagnosed depression in the elderly population[43].

**Social support and interaction:** Social networks and interactions help promote older people's mental health and prevent mental illness. Social support to promote health must provide a sense of belonging and intimacy. It also helps people be more competent and self-efficacious[43].

**Prevention of substance abuse:** Chewing tobacco is a common practice among the elderly in the South-East Asian region, as is smoking. The intake of alcohol is also

**Table 2 Availability of mental health manpower in World Health Organization South- East Asia Region Organization countries**

| Mental health human resources[1] (per 100000 population) | India | Bangladesh | Bhutan | Indonesia | Korea | Maldives | Myanmar | Nepal | Sri Lanka | Thailand | Timor-leste |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Total number of mental health professionals (government and non government) | 25312 | 1893 | 5 | 7751 | 20301 | 27 | 627 | 413 | 1480 | 9436 | 45 |
| Total mental health workers | 1.93 | 1.17 | 0.64 | 3.00 | 40.13 | 6.45 | 1.20 | 1.44 | 7.14 | 14.36 | 3.63 |
| Psychiatrists | 0.29 | 0.13 | 0.51 | 0.31 | 5.79 | 2.39 | 0.38 | 0.36 | 0.52 | 0.99 | 0.08 |
| Child psychiatrists | 0 | 0 | Not found | Not found | 0.38 | Not found | Not found | 0.003 | 0.03 | 0.26 | 0.24 |
| Geriatric psychiatrists | 24 | Hardly available | | | | | | | | | |
| Other specialist doctors | 0.15 | 0.01 | Not found | Not found | Not found | Not found | Not found | Not found | 1.47 | 1.24 | Not found |
| Mental health nurses | 0.80 | 0.87 | 0.13 | 2.52 | 13.66 | Not found | 0.32 | 0.56 | 3.28 | 6.74 | 1.37 |
| Psychologists | 0.07 | 0.12 | Not found | 0.17 | 1.59 | 2.15 | 0 | 0.52 | 0.25 | 0.75 | 0.08 |
| Social workers | 0.06 | 0 | Not found | Not found | 8.40 | 0.48 | 0.01 | Not found | 0.28 | 0.91 | 1.61 |
| Occupational therapists | 0.03 | 0 | Not found | Not found | 0.08 | 0.24 | 0 | Not found | 0.22 | 0.98 | 0.16 |
| Speech therapists | 0.17 | 0 | Not found | Not found | Not found | 1.20 | Not found | Not found | 0.05 | 0.19 | 0.08 |
| Other paid mental health workers | 0.36 | 0.03 | Not found | Not found | 10.21 | Not found | 0.47 | Not found | 1.04 | 1893.45 | Not found |

[1]This includes trained geriatric psychiatrists only.

**Table 3 Available physical infrastructure for providing mental health services in South- East Asia Region Organization countries**

| Mental health infrastructure | India | Bangladesh | Bhutan | Indonesia | Korea | Maldives | Myanmar | Nepal | Sri Lanka | Thailand | Timorleste |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mental hospitals | 136 | 2 | Not found | 48 | 181 | Not found | 2 | 6 | 1 | 19 | Not found |
| Psychiatric units in general hospitals | 389 | 56 | 1 | 269 | 197 | 1 | 22 | 18 | 31 | 104 | 1 |
| Mental health outpatient facilities attached to a hospital | 952 | 69 | 28 | Not found | 518 | 6 | 33 | 29 | 230 | 830 | 6 |
| Private practitioners | 1217 | Not found | Not found | Not found | 313 | Not found | 3 | Not found | 20 | 2 | 69 |

prevalent. Apart from these issues, benzodiazepine abuse is also common, which adds to cognitive and mood deterioration in the long term[24]. Managing these conditions would work as a mental health-promoting strategy by reducing the risk of cognitive decline and mood dysregulation[40].

**Prevention of polypharmacy:** Polypharmacy increases cognitive deterioration and other geriatric syndromes. The indiscriminate use of appetite stimulants, high-calorie nutritional supplements, benzodiazepines, and antimicrobials to treat bacteriuria without specific symptoms of urinary tract infections should be avoided as much as possible[40].

**Table 4 Estimated human resource requirements for mental health care of elderly individuals in World Health Organization South- East Asia Region Organization countries**

| Human resources requirement norms for the general population[37] | Human resources requirement for total population of WHO SEARO countries on Feburary 18, 2021(2537079071)[a] | Human resources requirement for elderly population 248633749[b] (@ 9.8%-WHO) SEARO countries as per norms of general population | Older adults with mental health problems @ 20% (tiwari and pandey, 2012) in SEARO 49726750 population as per general population norms | Availability of manpower in WHO SEARO countries | The gap (requirement - availability) |
|---|---|---|---|---|---|
| Psychiatrists (1 per 50000 population) | 50741.6 | 4972.7 | (4972.7 × 5) 24863.5 | 994.5 × 5 = 4972.5 | 9945.2 |
| Clinical psychologists 1 per 25000 population | 10148316 | 9945.3 | (9945.3 × 5) 49726.5 | 1989.7 × 5 = 9948.5 | 19893.8 |
| Psychiatric social workers 1 for 25000 population | 10148316 | 9945.3 | (9945.3 × 5) 49726.5 | 1989.7 × 5 = 9948.5 | 19893.8 |
| Psychiatric nurses 1 per 25 000 population | 10148316 | 9945.3 | (9945.3 × 5) 49726.5 | 1989.7 × 5 = 9948.5 | 19893.8 |

[a]https://www.worldometers.info/world-population/asia-population/ accessed on Feburary 18, 2021.
[b]https://www.WHO.int/southeastasia/health-topics/ageing#:~:text=the%20population%20in%20WHO%20south,2030%20and%20by%202050%2c%20respectively. Accessed on Feburary 18, 2021.
WHO: World health organization; SEARO: South-east asia region organization.

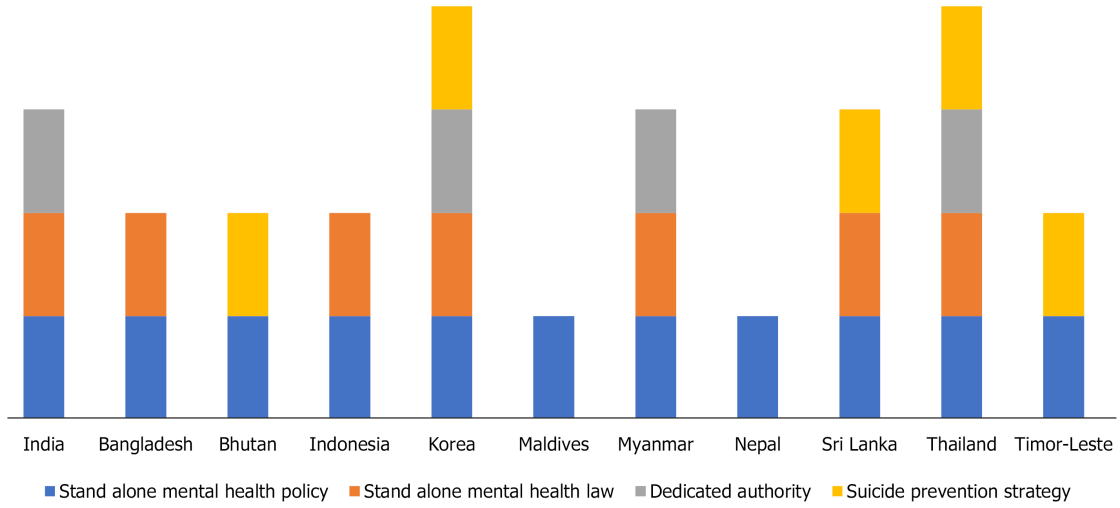


**Figure 1 Status of available mental health policy, law, authority and suicide prevention strategies in World Health Organization South-East Asia Region Organization countries.**

### *The WHO recommendations and support to governments at the global level*

The WHO supports member states in strengthening and promoting mental health in the elderly population; it also advocates for integrating effective strategies into policies and plans. The World Health Assembly adopted the Global Strategy and Action Plan on Aging and Health in 2016[41], the objectives of which include the following[42]: Commitment to action on *healthy aging* in every country; Developing age-friendly environments; Aligning health systems to the needs of older populations; Developing sustainable and equitable systems for providing long-term care (home, communities, institutions); and Improving measurement, monitoring, and research on *healthy aging*.

In May 2017, the World Health Assembly endorsed the Global Action Plan on the Public Health Response to Dementia 2017–2025[44]. This plan provides a comprehensive blueprint for action, including increasing the awareness of dementia and reducing the risk for dementia. Apart from this, the WHO Mental Health Gap Action

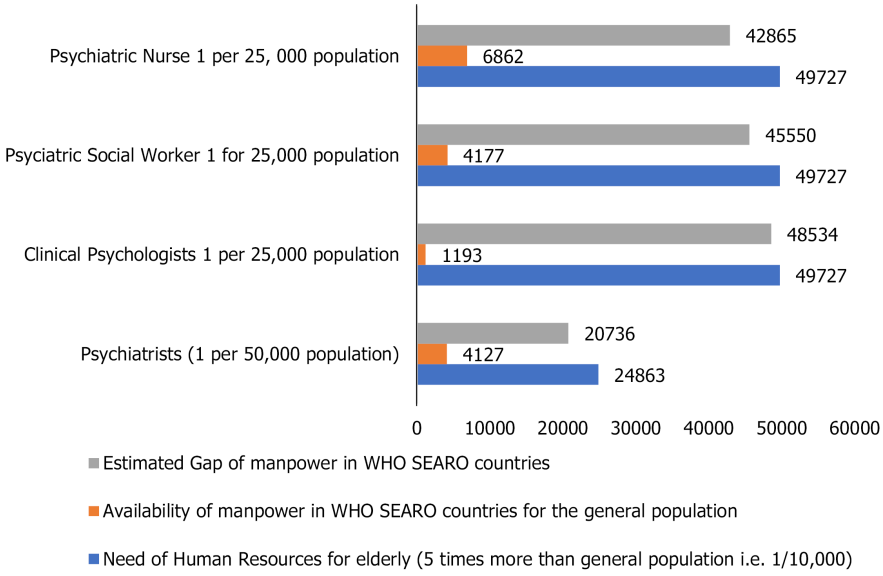


**Figure 2 Estimated requirement and gap of human resources in World Health Organization South- East Asia Region Organization countries.**

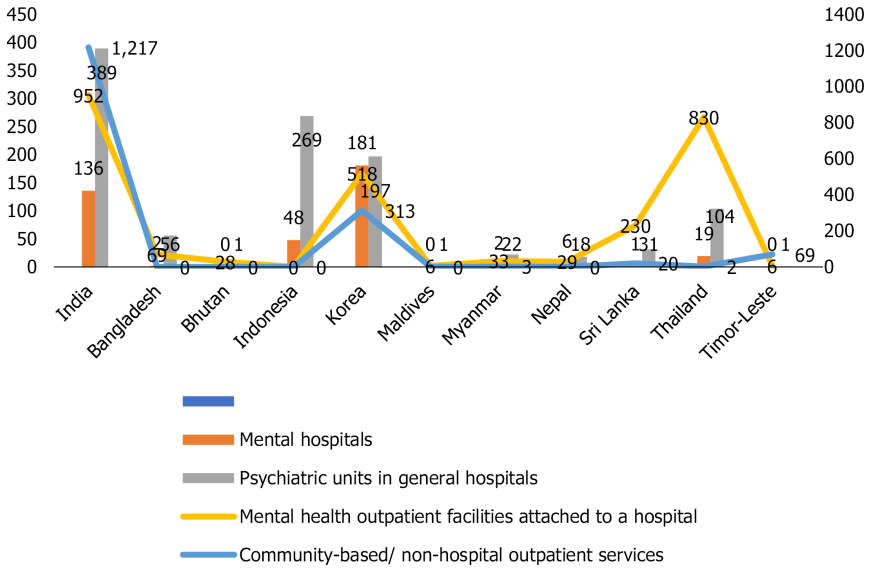


**Figure 3 Available physical infrastructure for providing mental health services in South- East Asia Region Organization countries.**

Programme (mhGAP) package consists of interventions for the prevention and management of priority conditions such as depression, psychosis, suicide, and substance use disorders in nonspecialized health settings, including those for older people[45]. Under universal health coverage, the WHO also recommends protecting the elderly population from financial risks, designing age-friendly benefit packages, and extending social insurance schemes for older people[46], which is another way to promote mental health in older people.

### *Limitation*

This article provides an overview regarding the available resources in mental health in order to promote the mental health of the elderly population, which can be utilized in the community by generating awareness. However, we did not discuss the availability, needs, and gaps of various resources, such as housing facilities, social safety, support, financial security, *etc.* Articles were sourced from the PubMed and WHO websites.

## CONCLUSION

### *Conclusion and Future Implications*

With the rapidly shifting aging demographic and changing family dynamics, the elderly population forms a sector of the population that needs specific focus. The sound mental health of elderly individuals is a cornerstone in ensuring quality and dignity of life. Thus, it is crucial to understand the sociocultural and economic factors that contribute to their mental well-being. MHP plays a vital role in establishing healthy practices, which in the long run sensitize and protect the elderly population against the deterioration of overall functionality. Elderly individuals located in the WHO SEARO region share remarkably similar sociocultural profiles. The research available in this area provides actionable data and clear pathways of MHP to improve the existing conditions for the elderly populations in these countries. There is a need to identify at-risk behavior and the existing gaps for providing care to elderly individuals. At present, we need to address these issues and challenges to maintain societal equilibrium and correct the future boom we expect in regard to the population of older adults.

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*MINIREVIEWS*

# Current progress in neuroimaging research for the treatment of major depression with electroconvulsive therapy

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## Abstract

Electroconvulsive therapy (ECT) uses a certain amount of electric current to pass through the head of the patient, causing convulsions throughout the body, to relieve the symptoms of the disease and achieve the purpose of treatment. ECT can effectively improve the clinical symptoms of patients with major depression, but its therapeutic mechanism is still unclear. With the rapid development of neuroimaging technology, it is necessary to explore the neurobiological mechanism of major depression from the aspects of brain structure, brain function and brain metabolism, and to find that ECT can improve the brain function, metabolism and even brain structure of patients to a certain extent. Currently, an increasing number of neuroimaging studies adopt various neuroimaging techniques including functional magnetic resonance imaging (MRI), positron emission tomography, magnetic resonance spectroscopy, structural MRI, and diffusion tensor imaging to reveal the neural effects of ECT. This article reviews the recent progress in neuroimaging research on ECT for major depression. The results suggest that the neurobiological mechanism of ECT may be to modulate the functional activity and connectivity or neural structural plasticity in specific brain regions to the normal level, to achieve the therapeutic effect.

**Key Words:** Neuroimaging; Major depression; Electroconvulsive therapy; Magnetic resonance imaging; Positron emission tomography; Magnetic resonance spectroscopy

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**Core tip:** Longitudinal neuroimaging studies in patients with major depression before

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and after electroconvulsive therapy (ECT) have shown that ECT has effects on specific brain areas. However, these ECT-regulated brain regions and their changes are uncertain. Based on recent studies with various neuroimaging techniques, this paper reviews longitudinal neuroimaging findings in recent years and discusses the relatively consistent results.

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## INTRODUCTION

Major depressive disorder (MDD) has become a major public health problem throughout the world. Approximately 322 million people suffer from depression worldwide, with a prevalence rate of 4.4%. More than 1 million people commit suicide due to depression every year[1]. Neuroimaging studies have shown that the structural and functional alterations in frontal lobe, cingulate gyrus (CG), hippocampus, basal ganglia and other brain regions are closely related to the pathogenesis of depression [2].

Electroconvulsive therapy (ECT) is essentially a method of using electrical current to induce epileptiform discharges in the cortex, causing a systemic seizure to control mental symptoms. Since ECT was invented by Italian scientists Cerletti and Bini in 1938, it has been extensively applied to the treatment of mental disorders for > 80 years[3]. At present, ECT is an indispensable treatment in the field of psychiatry. It is still the first choice for patients with severe depression with stubborn suicidal thoughts, delusions, and food refusal, followed by schizophrenia and mania[4]. ECT has attracted increasing attention in neurologic diseases due to its rapid and high response rate in patients with depression[5,6].

Currently, the neural mechanisms underlying the clinical response to ECT for MDD remain uncertain, and there are no widely accepted biomarkers that can be used to assist in the diagnosis or treatment options for individual patients. It only relies on subjective judgments based on clinical features and lacks objective and reliable evidence[7]. To facilitate treatment development, a clearer understanding of the neural correlates of successful antidepressant responses is essential[8]. Neuroimaging technology has the potential to identify objective neurobiological markers that reflect the underlying pathophysiological process in a given mental illness, and it is a noninvasive research method for observing brain changes. Various neuroimaging techniques such as positron emission tomography (PET) and magnetic resonance imaging (MRI) have promoted research on neuropsychiatric diseases. At the same time, this provides a new window for the study of the therapeutic mechanism of ECT in depression.

Longitudinal studies of neuroimaging in patients with major depression before and after ECT have shown that ECT has effects on specific brain regions and circuits. Some studies in the late 1980s focused on refuting the hypothesis that ECT caused brain damage and found no overall evidence of structural changes or harmful effects[9-11]. After the first high-resolution (1 $mm^3$) MRI study determined ECT-induced structural changes by detecting the increase in hippocampal volume[12], several subsequent studies confirmed that ECT can also induce alterations in hippocampal structure and other brain regions[13-16]. Recent research using machine learning and MRI can help patients and psychiatrists make more informed decisions about ECT as a treatment option[17,18]. These studies use machine learning algorithms to identify patients who are most likely to benefit from ECT at the individual level. Using these methods also helps to discover biomarkers in the brain that can predict the response to ECT treatment.

Although an increasing number of neuroimaging studies have attempted to reveal the neurological effects of ECT, these ECT-regulated brain regions and their changes are usually inconsistent. Therefore, based on recent longitudinal neuroimaging findings related to ECT treatment in depression, we investigated the progress made in these studies.

## BRAIN FUNCTIONAL IMAGING STUDY FOR DEPRESSION WITH ECT

### *Functional MRI*

Blood oxygenation level-dependent functional MRI (BOLD-fMRI) has been applied in the field of brain function research since the 1990s and has become the most rapidly developing functional detection technology. BOLD-fMRI has the advantages of being noninvasive, nonradioactive, repeatable, and having high temporal and spatial resolution. It also allows analysis on a single-subject basis to reflect the dynamic activity of neurons and the different patterns of response between adjacent cortices throughout the process. The spontaneous low-frequency activity information collected in the resting state is defined as the baseline brain function information, which reflects the spontaneous functional activities of the central nervous system in the basic state [19,20]. Therefore, fMRI in the resting state has obvious clinical advantages. Resting-state fMRI (rs-fMRI) is also particularly suitable for the study of patients with major depression because it does not require the patient to perform a specific task. Thus, rs-fMRI is increasingly widely used in the study of brain function in depression.

ECT can cause changes in the functional connectivity (FC) in specific brain regions in patients with depression. These changes may reveal that the clinical improvement of depression is related to the treatment effect of ECT through fMRI. Assessing changes in FC requires analyzing the differences before and after ECT. In recent years, different results have been reported[21]. In the voxel-analysis method, the CG is generally regarded as an important area related to ECT. There were significant changes in ECT, including a decrease in resting state FC (rsFC) in the left dorsal anterior cingulate cortex (dACC) and an increase in rsFC in the bilateral posterior cingulate cortex (PCC). Other important areas found in the rsFC after ECT are the frontal cortex, parietal cortex and temporal cortex, including the bilateral anterior central gyrus, dorsomedial prefrontal cortex, bilateral superior frontal gyrus (SFG), left angular gyrus (LAG), left precuneus, bilateral hippocampus, right superior temporal gyrus, right island, and cerebellum[21]. For instance, Wei *et al*[22] adopted FC strength (FCS) to identify brain hubs through resting-state fMRI at three time points, *i.e.*, prior to ECT, at the completion of ECT, and 1 mo after the completion of ECT. The results showed that the FCS of the LAG of patients with depression after ECT was significantly increased. Mo *et al*[23] found that the FC of the LAG with the bilateral inferior temporal gyrus (ITG), bilateral middle frontal gyrus, and other areas was significantly increased, accompanied by emotional improvement. Sun *et al*[24] used fMRI data to make preliminary predictions of individual response to ECT, and the results showed that the predictive areas were concentrated in the prefrontal and temporal cortices and the subcortical nuclei.

In seed-based analysis, CG is usually also selected as the seed region. After ECT, it was found that rsFC of the left subgenual anterior cingulate cortex (sgACC) with the left parahippocampal gyrus (PHG) increased, while rsFC of the contralateral temporal pole decreased[25]. During ECT treatment, rsFC of the subcallosal cingulate cortex with bilateral hippocampus, bilateral temporal poles, and ventral prefrontal cortex was significantly reduced[26]. Some studies also pointed out that rsFC of the sgACC with the amygdala and fusiform gyrus changed significantly after ECT treatment. Using fMRI data, Leaver *et al*[27] found that rsFC between the left dorsolateral prefrontal cortex (DLPFC) and sgACC was probably an important feature of the ECT response to depression. With regard to network-based and region-of-interest (ROI) analysis, the changes in rsFC in the left cerebellum, default mode network, ACC, and PCC were more frequent after ECT treatment.

ECT can also cause regional functional activity changes in patients with depression. It is an important method to study the regional functional activity changes in brain regions through fMRI. The indicators include amplitude of low frequency fluctuations (ALFF), fractional ALFF (fALFF), and regional homogeneity (ReHo). Qiu *et al*[28] found that ReHo of rs-fMRI showed significant differences in brain activity before and after ECT. MDD patients who received eight courses of ECT showed higher ReHo values in the bilateral frontal lobes, bilateral parietal lobes, and right caudate nucleus. Decreased ReHo values were observed in the left anterior cerebellar lobe, right CG, right superior temporal gyrus, and right medial temporal gyrus. Argyelan *et al*[29] used rs-fMRI to compare patients with treatment-resistant depression before ECT with normal controls and found that the fALFF of the right cingulate cortex increased significantly in patients, suggesting that local brain functional activity is hyperactive. The fALFF in the cingulate cortex in patients after ECT was significantly lower than that before ECT, and there was no significant difference compared with normal controls, indicating that ECT can significantly improve abnormal brain function activities. In addition, ReHo of the LAG[23] and ALFF of the dorsal medial prefrontal

cortex[30] in MDD patients increased significantly after ECT treatment. In a sham-controlled fMRI study, Miskowiak *et al*[31] found that the regulation of medial prefrontal hyperactivity during the encoding of negative affectional information may be a common mechanism for different biological depression treatments. In response to negative emotional stimulation for depression, the activity in the amygdala increases abnormally. Redlich *et al*[32] used fMRI data to find that the patient's amygdala function normalized after ECT.

### PET

PET is a modern imaging technology to detect and identify metabolic changes that occur prior to structural changes in tissues and organs under disease conditions at the molecular level. It measures and displays the biological activities of cells and molecules by injecting radioisotope drugs with appropriate half-life into the body. According to the concentration of the tracer, cerebral blood perfusion and glucose and neurotransmitter metabolism levels can be inferred, and it has the advantages of high sensitivity and accurate quantitative analysis.

PET is currently used to study changes in specific neurotransmitter receptors after ECT. Masuoka *et al*[33] used [$^{18}$F]FE-PE2I PET to examine MDD patients before, during and after treatment and found that all patients had a reduced striatal dopamine transporter-binding potential ($BP_{ND}$). Combined with the patient's clinical response, it has been proven that the dopamine nervous system is part of the mechanism of ECT. Tiger *et al*[34] used PET and [$^{11}$C]raclopride to examine patients with severe MDD before and after ECT, and healthy controls. Compared with the control group, the [$^{11}$C]raclopride binding rate in all three parts of the striatum decreased significantly in the patients. However, there was no significant effect of ECT on $D_2/D_3$ binding in the patients. Baldinger-Melich *et al*[35] used PET and radioligand [$^{11}$C]harmine to evaluate cerebral monoamine oxidase A (MAO-A) distribution volumes ($V_T$). The results showed no significant difference in MAO-A $V_T$ between patients with post-ECT treatment-resistant depression and healthy controls at baseline. This suggested that MAO-A $V_T$ is not related to the clinically relevant mechanism of action of ECT. Using [$^{18}$F]Setoperone PET, Yatham *et al*[36] found that serotonin$_2$ (5-$HT_2$) receptor binding was extensively reduced in all cortical regions of MDD patients after ECT. Furthermore, the reduction in the 5-$HT_2$ receptor in the right PHG, right lingual gyrus and right medial frontal gyrus was correlated with the improvement of depressive symptoms. These results were consistent with research on antidepressants[37-39]. Lanzenberger *et al*[40] used highly selective radioligand [carbonyl-$^{11}$C] WY100635-PET scans and compared the voxels of serotonin-1A (5-$HT_{1A}$) receptor binding ($BP_{ND}$) before and after ECT. The results showed extensive decreases in cortical and subcortical areas, except for the cerebellum and the occipital cortex. This PET study proposed the whole-brain involvement of postsynaptic 5-$HT_{1A}$ receptor binding in ECT effects.

PET is utilized to evaluate ECT-related changes in [$^{18}$F]-fluorodeoxyglucose (FDG) to measure the rate of local brain metabolism of glucose. The most consistent finding in pre- and post-ECT comparisons was decreased glucose metabolism in the bilateral frontal medial and inferior frontal areas and right frontal operculum[41]. The areas with increased glucose metabolism included the hippocampus, middle temporal lobe, left occipital lobe, parietal lobe and pons. Bak *et al*[42] used [$^{18}$F]-FDG PET to study the efficacy of ECT in a 55-year-old woman with late-onset depression. $^{18}$F-FDG PET/computed tomography (CT) images of the patient's brain showed a diffuse decrease in brain metabolism. After the patient's symptoms were improved by ECT, her PET imaging showed her brain metabolism was normal. After improving the patient's symptoms through ECT, PET imaging showed that her brain metabolism was normal. Hassamal *et al*[43] adopted $^{18}$F-FDG-PET/CT before ECT to show extensive hypometabolism in the frontal, parietal and temporal cortices. After eight sessions of ECT, symptoms of psychosis and anxiety symptoms as well as cognitive impairment were resolved. $^{18}$F-FDG-PET/CT showed improvement in hypometabolism of the cerebral cortex, especially in the left parietal cortex, left temporal/occipital cortex, and bilateral frontal areas. The improvement of brain glucose hypometabolism may represent the neurophysiological mechanism of ECT for the treatment of psychotic episodes. However, Reininghaus *et al*[6] reported inconsistent results. They employed FDG-PET scans to measure the effects of a series of ECT treatments on brain glucose metabolism in depressed subjects before and after treatment. They found that there was almost no change in brain glucose metabolism. Therefore, they did not think that FDG-PET can evaluate the functional brain changes that may occur after ECT.

### *Magnetic resonance spectroscopy*

Magnetic resonance spectroscopy (MRS) is used to determine abnormal metabolic conditions in tissues by measuring changes in the concentration of metabolites in the human body and observing different peaks and ratios of the spectrum curve. MRS is a noninvasive detection technology that can measure neurobiochemical information in specific brain functional areas and analyze the content of neurobiochemical substances. These compounds include γ-aminobutyric acid (GABA), glutamate (Glu), choline-containing compounds, N-acetyl-L-aspartic acid (NAA), glutamine (Gln), myoinositol, and creatine (Cr).

Glu plays a key role in the pathophysiology of depression[44]. There was evidence that the levels of Glu and Gln in pgACC were reduced[45,46], while the concentration of Glu in the DLPFC was unchanged[47,48]. ECT caused changes in glutamatergic neurotransmission that seem to be closely related to its antidepressant effects[49,50]. Njau *et al*[51] reported that Glx (Glu and Gln) increased in sgACC but decreased in the left hippocampus in patients with depression after ECT treatment, and these changes were related to the improvement of mood. Glx disorders in MDD patients and the regulation of Glx levels by ECT vary from region to region. Although some studies reported increased Glx levels in the DLPFC and ACC after ECT[49,52], one study was unable to replicate these findings[48]. There were similar contradictory reports for the hippocampus. A recent study reported the correlation between elevated hippocampal Glx and ECT response in patients with medication-resistant depression[53], while another report was unable to confirm these results[54]. In general, brain metabolism of Glu has been an important component of ECT efficacy, but there are differences in the exact mechanism.

In addition, reduced levels of GABA in cerebrospinal fluid and plasma, as well as in the frontal cortex, were reported in patients with depression[55]. Thus, increased serum levels and occipital GABA concentrations were observed after ECT[56,57]. However, Knudsen *et al*[58] used MRS to measure GABA changes in the prefrontal and occipital cortex in patients before and after ECT. There were no significant differences in GABA/Cr levels in the prefrontal cortex or occipital lobe between baseline patients and healthy subjects, and there was no statistically significant difference in GABA, Glu, glutamine, choline or GSH before and after ECT. They concluded that GABA should not be considered a key factor in the treatment of major depression with ECT.

NAA is a marker of neurons and axons, and its concentration can reflect the number and functional status of neurons. Proton MRS (H-MRS) showed that ECT can increase the content of NAA in the anterior CG and amygdala, suggesting that ECT has a nerve-promoting effect. Njau *et al*[51] detected MDD patients with ECT through $^{1}$H-MRS and found that compared with the control group, the content of NAA in the left hippocampus of the patients was reduced before treatment. Meanwhile, the NAA levels of the dACC and right hippocampus also decreased significantly after ECT treatment.

Tosun *et al*[59] observed the metabolic changes of ACC in MDD patients after ECT through $^{1}$H-MRS. There was no significant difference in the levels of ACC metabolites between the patients and the control group at baseline. ECT was associated with a statistically significant decrease in the NAA/Cr ratio in ACC. All patients responded to ECT treatment as measured by the clinical scale. These results suggest that a relative increase in Cr levels after ECT in MDD appears to be associated with an improvement in clinical severity. However, Ende *et al*[60] found that hippocampal NAA did not change after ECT, and the choline content increased, indicating that ECT may be related to increased membrane transformation and may reflect neurogenesis.

Because the different neurotransmitter systems involved in the antidepressant effect of ECT are connected to each other through a complex signal transduction network and the changes in the content of neurobiochemical substances are also complicated, the above findings based on MRS have presented inconsistent results.

## BRAIN STRUCTURAL IMAGING STUDY FOR DEPRESSION WITH ECT

### *Structural MRI*

ECT can improve brain function and change the brain structure in patients with depression. Many MRI structural studies in patients with MDD have shown morphological abnormalities, mainly manifested as cortical thickness, gray matter volume, and white matter integrity[61]. Longitudinal structural neuroimaging studies have proven that ECT increases the volume of the hippocampus, amygdala, caudate

nucleus, and temporal lobe. Some studies have found that ECT increases the volume of the hippocampus and amygdala in the temporal lobe system in patients with depression[62-64]. The strongest evidence of structural changes in the brain after ECT was an increase in the volume of the temporal lobe and subcortical structures, such as the hippocampal-amygdala complex, anterior cingulate cortex and striatum[65].

Voxel-based morphology (VBM) is a powerful and objective method for studying brain structural changes in patients with depression before and after ECT through MRI. Due to its simplicity of use, VBM has inspired many neuroscientists to characterize specific abnormalities in brain gray matter volume in MDD[66,67].

Some studies have used ROI methods to analyze brain regions closely associated with depression. Tendolkar *et al*[62] took the bilateral hippocampus and amygdala as regions of interest and found that ECT could increase the gray matter volume of the bilateral hippocampus and amygdala in patients with refractory depression. Accordingly, the Hamilton Depression Scale score was significantly reduced after ECT, and the severity of depressive symptoms was reduced. Gryglewski *et al*[68] found that structural changes were observed in the hippocampal subregions and amygdala after ECT. These structural changes are particularly involved in the pathophysiology of depression and stress-related diseases and still have high neuroplasticity in adulthood. Cao *et al*[69] used the latest hippocampal segmentation method and found that ECT induced cornu ammonis subfields, granule cell layer, molecular layer, and hypothalamic volume increases. It also accurately predicted the quantitative efficacy of ECT for each patient. Joshi *et al*[70] used FreeSurfer to segment the hippocampus and amygdala and found that ECT induced neuroplasticity processes related to clinical responses, which can correct the reduction in the structure of the hippocampus and amygdala associated with MDD. Patients with small hippocampal volumes were most likely to show an increase in volume and improve clinical response. Therefore, changes in the structure of the hippocampus and amygdala could serve as potential biomarkers for the development of other rapidly effective therapies. Jorgensen *et al*[54] used structural MRI (sMRI) of the hippocampus, amygdala, DLPFC, orbitofrontal cortex, and hypothalamus and found that the hippocampus and amygdala volume increased in patients with major depression after ECT, while the volume of the DLPFC decreased slightly. However, due to the lack of correlation between these changes and the antidepressant effect, this remodeling of the brain structure does not appear to directly affect the antidepressant effect of ECT. Wade *et al*[8] conducted a longitudinal study on the cortical volume, cortical thickness and cortical surface area of the caudate nucleus, putamen, pallidum, and nucleus accumbens through surface-based morphometry. Compared with the control group, the volume of the nucleus accumbens and nucleus pallidum were smaller in MDD patients. ECT caused an increase in the volume of the left putamen. In patients defined as responders to treatment, there was an increase in overall nucleus accumbens volume and local changes in globus pallidus and caudate nucleus volume. Thus, ECT induces structural plasticity in the dorsal and ventral striatum/pallium.

In some studies, VBM has been effectively used to evaluate anatomical abnormalities in the whole brain. Ota *et al*[71] found that the volume of the bilateral medial temporal cortex, inferior temporal cortex and right anterior CG increased significantly after ECT. In addition, the rate of increase was associated with clinical improvement as measured by the Hamilton Depression Scale. Van Eijndhoven *et al*[72] compared the brain images of treatment-resistant MDD patients before and after ECT with normal controls and found that there was no significant difference in the thickness of the whole cerebral cortex between patients before ECT and normal controls. After ECT, the patients had increased cerebral cortex thickness in the left temporal pole, left middle temporal gyrus, and right insula compared with the control group. Meanwhile, the Hamilton Depression Scale score was significantly lower than before treatment, with an average decrease of 57%. Sartorius *et al*[16] analyzed sMRI before and after ECT and found that the gray matter volume of the whole brain increased in most patients after ECT, while the white matter volume of the brain did not significantly change. Further voxel-based morphological analysis showed that the volume of gray matter in the bilateral temporal lobe, the middle CG, the insular lobe and the putamen increased after treatment. Jiang *et al*[73] adopted six GM areas including the right hippocampus/parahippocampus, the right orbitofrontal gyrus, the right ITG, the left posterior middle gyrus/anterior process, the left auxiliary motor area and the left lingual gyrus to be identified as predictors of ECT response. They revealed that GM density only increased in the left auxiliary motor cortex and the left middle posterior gyrus/protrusion after ECT. The results indicate that the treatment prediction area and the treatment response area may be anatomically different. Pirnia *et al*[74] found that the thickness increased in the bilateral anterior cingulate cortex,

superior temporal cortex *etc*. ECT resulted in extensive neuroplasticity in the neocortex, limbic and paralimbic areas. Moreover, changes in ACC thickness can distinguish treatment responders and predict early responses during ECT.

Gbyl and Videbech[75] concluded that current MRI studies do not support the hypothesis that ECT causes brain damage. They confirmed that ECT causes an increase in the volume of the limbic area of the frontal lobe, and further research should explore the relationship between these increases and treatment effects and cognitive side effects. Many studies have shown an increase in hippocampal volume following ECT, but there are conflicting results as to whether the increase in hippocampal volume is associated with clinical response. Other studies have found increased GMV or cortical thickness in areas such as the amygdala, frontotemporal cortex, lingual gyrus, thalamus, and striatum.

### *Diffusion tensor imaging*

Diffusion tensor imaging (DTI) is a derivative technique of diffusion-weighted imaging that can noninvasively detect the direction and integrity of white matter tracts by evaluating the diffusion of water molecules in nerve tissue. It has important applications in neuroimaging research.

Chen *et al*[76] performed a meta-analysis of microstructural brain abnormalities in drug-naïve patients with major depression through DTI. They observed that the main areas of fractional anisotropy reduction included the bilateral anterior limb of the internal capsule, body of the corpus callosum, right SFG, and right ITG. Gbyl and Videbech[74] found that an ECT-induced increase in the integrity of the white matter pathways in the frontal and temporal lobes through a meta-analysis of DTI, but the correlation between the increase in volume and the treatment effect and the mechanism of action of ECT are still uncertain. Yrondi *et al*[77] found a reduction in the hippocampus and left amygdala during ECT in patients with treatment-resistant depression using mean diffusivity (MD) measure. They concluded that ECT can correct the microstructural integrity of these structures. Gryglewski *et al*[78] conducted a DTI study on patients with treatment-resistant depression using unilateral ECT and found that axial diffusivity was increased in the posterior limb of the internal capsule in the right hemisphere. Compared with the left hemisphere, the increase in this region was higher on the right. However, no correlation between this effect and treatment response was found. Repple *et al*[79] used DTI to analyze the alterations in the white matter structure in patients with depression before and after ECT and found that MD of the right hemisphere increased after ECT, which was a specific effect in the ECT group. Kubicki *et al*[80] revealed alterations in the structural connections of the hippocampal neural circuits after ECT. It also means that glial, neurotrophic or inflammatory response mechanisms affect the integrity of the axons. Lyden *et al*[81] observed a significant increase in fractional anisotropy in the dorsal frontolimbic circuits including the anterior cingulate, forceps, and left superior longitudinal fascia between baseline and transition to maintenance therapy. Radial and MD in overlapping regions and anterior thalamic radiation were reduced. Changes in DTI indicators related to treatment response indicated that ECT effects significantly differed between MDD and control groups. Alterations in white matter microstructure in the pathways connecting the frontal and limbic regions that occur in MDD are regulated by ECT and are associated with treatment response.

## CONCLUSION

In recent years, the rapid development of neuroimaging technologies represented by MRI has played a major role in promoting the study of neurological mechanisms of mental diseases. With the continuous emergence of new technologies, they have been able to provide different levels of physiological and pathological information from macroscopic tissue morphology to microscopic subcellular structure, and from blood flow and energy metabolism to high-level brain functional networks, which embodies the characteristics of multidimensional and multimodal information. Research on the neural effects of ECT needs to consider the physical and mental state of patients with major depression to adopt appropriate neuroimaging technology. At present, MRI is the most commonly used method, and there are very few studies using single-photon emission CT.

In general, the findings of current neuroimaging studies are inconsistent. The main reasons are as follows: (1) The operating methods of ECT such as electrode position, electric dose, and treatment times are different; (2) Data collection and analysis

**Table 1 Consistent findings in neuroimaging research on electroconvulsive therapy effects**

| Neuroimaging technologies | Methods/measures | Relatively consistent findings |
|---|---|---|
| fMRI | Functional connectivity strength | Changes in cingulate cortex, frontal cortex, and left angel gyrus |
| | Functional activity of local brain regions | Changes in cingulate cortex and prefrontal cortex |
| PET | Neurotransmitters | Downregulation of brain serotonin receptors |
| | Glucose metabolism | Reduction in glucose metabolism after ECT in bilateral anterior and posterior frontal areas |
| MRS | Gln/Glx, GABA, NAA, Cho, mI, Cr | None |
| sMRI | Gray matter volumn | Increase in hippocampus and amygdala |
| DTI | White matter | Alterations in microstructure and pathways |

fMRI: Functional magnetic resonance imaging; PET: Positron emission tomography; MRS: Magnetic resonance spectroscopy; sMRI: Structural magnetic resonance imaging; DTI: Diffusion tensor imaging; Gln: Glutamine; Glx: Glutamate and Gln; GABA: γ-aminobutyric acid; NAA: N-acetyl-L-aspartic acid; Cho: Choline-containing compounds; mI: Myoinositol; Cr: Creatine; ECT: Electroconvulsive therapy.

methods are different; (3) Sample size collected for research is too small; and (4) Physiological disorders of patients with depression are heterogeneous. Despite these shortcomings, it is not possible to fully understand how ECT works, and there are still some encouraging findings. Table 1 gives a summary of relatively consistent findings. In the fMRI study of ECT treatment, the significant changes in the functional connection strength of the cingulate cortex, frontal cortex, and left angel gyrus were relatively consistent. Significant changes in the functional activity of the cingulate cortex and frontal cortex are also response markers for ECT treatment. For PET studies, consistent conclusions include a reduction in glucose metabolism after ECT in the bilateral anterior and posterior frontal areas and downregulation of brain serotonin receptors. Due to the complex neurobiochemical alterations in the brain, no consistent results have been obtained in the current studies on the treatment of depression with ECT based on MRS. Many sMRI studies have found that the increased volumes of the hippocampus and amygdala are the most important imaging markers for improving depression after ECT. Among white matter DTI studies, much evidence supports an increase in white matter pathway integrity after ECT.

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ORIGINAL ARTICLE

**Observational Study**

# Prevalence and clinical characteristics of COVID-19 in inpatients with schizophrenia in Wuhan, China

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**Author contributions:** Zhang XY, Zhou YJ, and Sheng HW designed the study; Sheng HY, Wu J, Huo LJ, and Huang W were responsible for collecting the clinical data; Wang HG and Wang CZ collected the literature and cleaned the data; Zhou YJ and Zeng LY did statistical analysis; Zhou YJ and Sheng HW wrote the manuscript; Zhang XY reviewed and revised the manuscript.

**Institutional review board statement:** The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The Wuhan Youfu Hospital received approval for this study from the institutional review board of the Institute of Psychology, Chinese Academy of Sciences. Given the urgent need for data collection and retrospective research, no written informed consent was required for these

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## Abstract

***BACKGROUND***

In contrast to many Western countries, China has maintained its large psychiatric hospitals. The prevalence and clinical characteristics of coronavirus disease 2019 (COVID-19) in inpatients with schizophrenia (SCZ) are unclear.

***AIM***

To assess the prevalence of COVID-19 among inpatients with SCZ and compare the infected to uninfected SCZ patients in a Wuhan psychiatric hospital.

***METHODS***

We retrospectively collected demographic characteristics and clinical profiles of all SCZ patients with COVID-19 at Wuhan's Youfu Hospital.

***RESULTS***

Among the 504 SCZ patients, 84 had COVID-19, and we randomly sampled 174 who were uninfected as a comparison group. The overall prevalence of COVID-19 in SCZ patients was 16.7%. Among the 84 SCZ patients with confirmed COVID-19, the median age was 54 years and 76.2% were male. The most common

symptom was fever (82%), and less common symptoms were cough (31%), poor appetite (20%), and fatigue (16%). Compared with SCZ patients without COVID-19, those with COVID-19 were older ($P$ = 0.006) and significantly lighter ($P$ = 0.002), and had more comorbid physical diseases ($P$ = 0.001). Surprisingly, those infected were less likely to be smokers (< 0.001) or to be treated with clozapine ($P$ = 0.03). Further logistic regression showed that smoking [odds ratio (OR) = 5.61], clozapine treated (OR = 2.95), and male (OR = 3.48) patients with relatively fewer comorbid physical diseases (OR = 0.098) were at a lower risk for COVID-19. SCZ patients with COVID-19 presented primarily with fever, but only one-third had a cough, which might otherwise be the most common mode of transmission between individuals.

*CONCLUSION*

Two unexpected protective factors for COVID-19 among SCZ inpatients are smoking and clozapine treatment.

**Key Words:** Mental health; Schizophrenia; Inpatient; Epidemiology

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**Core Tip:** In contrast to many Western countries, China has maintained its large psychiatric hospitals. The prevalence and clinical characteristics of coronavirus disease 2019 (COVID-19) in inpatients with schizophrenia (SCZ) are unclear. Our aim was to assess the prevalence of COVID-19 among inpatients with SCZ and compare the infected to uninfected SCZ patients in a Wuhan psychiatric hospital. Two unexpected protective factors for COVID-19 among SCZ inpatients are smoking and clozapine treatment.

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## INTRODUCTION

On December 8, 2019, several cases of acute respiratory illness with unknown etiology were reported in Wuhan, Hubei Province, China[1-4], which is now well-known as coronavirus disease 2019 (COVID-19) pneumonia (CP)[4-6]. By early January, 2020, the Chinese Center for Disease Control and Prevention (CDC) identified the coronavirus from samples of bronchoalveolar lavage fluid of a patient in Wuhan[2]. Among the initially identified COVID-19 patients, most (73%) were men, and their clinical symptoms included fever (98%), cough (76%), dyspnoea (55%), and myalgia or fatigue (44%) with less common symptoms being secretion of sputum, headache, and diarrhea. All CP patients had abnormal chest CT manifestations, and 63% had lymphopenia. Some CP patients had complications such as acute respiratory distress syndrome (ARDS), acute cardiac injury, and secondary infection. Six (15%) of the 41 hospitalized CP cases died[1]. A subsequent study of COVID-19 patients confirmed the association in older men with medical comorbidities[3]. Common symptoms included fever (99%), fatigue (70%), and dry cough (59%). Laboratory tests showed that 70% had lymphopenia, and chest CT displayed bilateral patchy shadows or ground glass opacity in the lungs of all patients. As of February 3, the overall mortality was 4.3%[4]. The most recent report from the Chinese CDC on the initially confirmed 425 CP patients in Wuhan found a slightly higher percentage of men (56%) and a median age of 59 years. The estimated contagion number was 2.2 with a 95% confidence interval (CI) of 1.4-3.9[5], which is substantially greater than that of influenza or severe acute respiratory syndrome (SARS), and predicts robust human to human transmission through respiratory spread[7-8].

current analyses.

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Schizophrenia (SCZ) is one of the most common severe mental disorders, characterized by positive and negative symptoms and cognitive impairment, affecting about 1% of the world's population[9-10]. In China, the prevalence of SCZ is similar, suggesting that genetic factors may play a critical role in the occurrence of this disease [11-12]. Given the huge population of 1.3 billion in China, the number of SCZ individuals is very large. Compared with the number of 20000 psychiatrists in China, the number of SCZ patients is much larger. Therefore, in the large mental health hospitals in China, the resources for managing this COVID-19 epidemic are very limited, and these SCZ inpatients are expected to be highly contagious.

Therefore, we investigated the CP situation among SCZ inpatients in one of the major psychiatric hospitals in Wuhan during this COVID-19 pandemic with several major objectives. First, we sought to estimate the prevalence and clinical characteristics of the hospitalized SCZ patients with confirmed CP in Wuhan's public psychiatric hospitals. Second, we compared the clinical profiles, especially the potential risk and protective factors, among SCZ patients with *vs* without symptomatic COVID-19, some of whom went on to develop CP and a smaller percentage died from CP.

## MATERIALS AND METHODS

### Subjects

The Wuhan Youfu Hospital (Wuhan, Hubei Province, China) housed 586 psychiatric inpatients during the COVID epidemic. The first confirmed case of CP at this hospital occurred on January 8, 2020. As of February 29, 2020, there were 84 confirmed SCZ cases with CP at the hospital, and we included all CP cases in this study. After the first case emerged, the hospital set up isolation wards for COVID-19 patients, with airborne preventive measures, and immediately transferred all confirmed patients to these special wards.

There were eight wards in the hospital. In one ward, there were ten rooms with 60-80 hospitalized patients. The patients met each other among rooms in one ward. If one patient had COVID-19, he or she had an equal opportunity to make all other patients in the same room or at the same ward infected. Once a patient was found to have symptoms of fever or infection, the entire room was isolated on the spot. Then, the fever patient was transferred to a separate ward for isolation treatment, and other patients in the ward where the fever patient was located were isolated and observed in the room for 14 d.

Just 3 to 4 mo before the outbreak of COVID-19 in September, 2019, the Institute of Psychology, Chinese Academy of Sciences randomly recruited 174 patients with SCZ from Wuhan Youfu Hospital to conduct another study, which we used as an approximately two to one control group for comparison to the 84 schizophrenics with COVID-19 in this study.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The Wuhan Youfu Hospital received approval for this study from the institutional review board of the Institute of Psychology, Chinese Academy of Sciences. Given the urgent need for data collection and retrospective research, no written informed consent was required for these current analyses.

### Data collection

We designed a special Case Record Form to collect general information, socio-demographic data, and clinical, laboratory, radiological, and treatment data from electronic medical records for all psychiatric patients with and without confirmed COVID-19. Two researchers independently reviewed the data collection forms to confirm the accuracy of the data collected. If there were any ambiguous data related to COVID-19, such as epidemiological data, we made additional interviews with patients or their family members.

COVID-19 was diagnosed according to the World Health Organization (WHO) interim guidelines[13], and was confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) or next-generation sequencing assay of throat swab specimens[1]. The Wuhan CDC Laboratory confirmed COVID-19 before January 23, 2020, and the diagnosis was subsequently confirmed in certified tertiary care hospitals. RT-PCR testing followed the protocol set up by the WHO. Of 84 SCZ cases, 58 were laboratory-confirmed and the others were confirmed by chest radiography or computed tomography (CT) plus clinical symptoms. In addition, we defined the degree of severity of COVID-19 (severe *vs* non-severe) at the time of admission using the American Thoracic Society guidelines for community-acquired pneumonia[14].

We extracted additional data related to novel coronavirus from electronic medical records: History of exposure to novel coronavirus and possible pathway, clinical symptoms or signs, laboratory results, and chest radiologic assessments. Laboratory assessments included whole blood cell count, coagulation profile, and blood biochemical analysis (such as C-reactive protein, albumin/globulin ratio, creatinine kinase, myocardial enzymes, liver and renal function, blood glucose and lipid profiles, and electrolytes). In addition, we tested for seven types of common viruses (including influenza, avian influenza, respiratory syncytial virus, adenovirus, parainfluenza virus, SARS-CoV, and MERS-CoV) in throat swab specimens using real-time RT-PCR methods. Finally, most patients underwent chest CT or radiography as well as electrocardiograms when their physical condition indicated such testing.

### Study outcomes

The main endpoints were transfer to a designated COVID-19 hospital due to development of a serious condition requiring a ventilator, or death. The secondary endpoints were the rate of death and the time from symptom onset to the main endpoints[6].

We defined ARDS and shock according to the WHO interim guidelines.

### Statistical analysis

We express continuous variables as medians and interquartile ranges or simple ranges, as appropriate, and categorical variables as the number and percentages. Since all the demographic and clinical data are normally distributed (Kolmogorov-Smirnov one-sample test, $P > 0.05$), comparisons of demographic and clinical variables between different groups were performed using analysis of variance for continuous variables and chi-square test for categorical variables. We used analysis of covariance to control for confounding factors. We describe the prevalence of COVID-19 in both sexes with percentages and analyzed them by chi-square tests. A binary logistic regression analysis was performed to assess which factors were independently associated with COVID-19. We applied Bonferroni corrections to each test to adjust for multiple testing, and used SPSS (version 18.0, Chicago, IL, United States) to do all statistical analyses with a two-tailed significance level at 0.05.

## RESULTS

### Demographic and clinical features

By February 29, 2020, we identified 84 SCZ inpatients with COVID-19 at Wuhan Youfu Hospital. Of the 84 cases, 58 were laboratory-confirmed and the other 26 were confirmed by chest radiography or CT plus clinical symptoms. The prevalence of COVID-19 among the SCZ inpatients was 16.7% (84/504). The first two SCZ patients were diagnosed with COVID-19 on January 8, 2020. Table 1 shows the data for all 101 psychiatric patients with COVID-19.

Among all the 84 SCZ patients, 64 were male, and the age ranged from 19 to 81 years with a median age of 54 years. Besides their SCZ disorders, more than half ($n$ = 44) of the patients with COVID-19 had comorbid physical diseases before they had COVID-19, including hypertension ($n$ = 22), diabetes ($n$ = 8), anemia ($n$ = 7), leukopenia ($n$ = 7), and cerebral infarction ($n$ = 2).

The most common symptoms of the COVID-19 patients were fever (82%; the highest temperature of 40.5 °C, with 4 patients having a temperature ≥ 40 °C), cough (31%), poor appetite (20%), and fatigue (16%). Their fewer common symptoms were chest tightness (15%) and shortness of breath (11%); however, no patients reported nausea, vomiting, or diarrhea.

### Radiologic and laboratory measurements

Among the 84 patients, 58 had CT scans, with 50 (86%) having abnormal manifestations. Among the 58 patients with CT scans, 38 (66%) had bilateral lung involvement. The most common manifestations of chest CT were ground-glass opacity (51%) and bilateral patchy shadowing (46%).

Blood samples were available from 81 patients and 46% had lymphocytopenia, 36% had neutropenia, 34% had leukopenia, and 12% had thrombocytopenia. In addition, 68% of patients had elevated C-reactive protein levels.

**Table 1 Clinical characteristics of psychiatric inpatients with coronavirus disease 2019 based on disease severity**

| | All patients (*n* = 101) | Severe (*n* = 17) | Non-severe (*n* = 84) | $F/\chi^2$ | *P* |
|---|---|---|---|---|---|
| Age | 54.8 ± 12.0 | 61.3 ± 14.1 | 53.4 ± 11.2 | 9.63 | 0.003 |
| Median (IQR), years | 56 (48-63) | 65 (57-70) | 55 (47-61) | | |
| Distribution, years (%) | | | | 14.50 | 0.001 |
| 20-49 | 30 (29.7%) | 2 (11.8%) | 28 (33.3%) | | |
| 50-64 | 51 (50.5%) | 6 (35.3%) | 45 (53.6%) | | |
| ≥ 65 | 20 (19.8%) | 9 (52.9%) | 11 (13.1%) | | |
| Male/female | 72/29 (71.3%/28.7%) | 10/7 (58.8%/41.2%) | 62/22 (73.8%/26.2%) | 1.55 | 0.21 |
| Blood pressure | | | | | |
| Systolic pressure | 122.2 ± 7.2 | 119.6 ± 6.8 | 122.8 ± 7.2 | 2.80 | 0.09 |
| Diastolic pressure | 77.2 ± 5.5 | 76.9 ± 4.4 | 77.2 ± 5.7 | 0.06 | 0.81 |
| Diagnosis | | | | | |
| Schizophrenia | 84 | 10 | 74 | | |
| Bipolar disorder | 4 | 1 | 3 | | |
| Alzheimer's Disease | 4 | 4 | 0 | | |
| Mental retardation | 3 | 1 | 2 | | |
| Epileptic psychosis | 3 | 0 | 3 | | |
| Organic mental disorder | 3 | 1 | 2 | | |
| Weight (kg) | 62.1 ± 10.3 | 55.8 ± 7.7 | 63.2 ± 10.4 | 1.62 | 0.21 |
| Smoker/non-smoker | 14/76 | 1/10 | 13/66 | 0.40 | 0.53 |
| Duration of illness (yr) | 27.9 ± 11.8 | 31.7 ± 14.4 | 27.4 ± 11.4 | 1.41 | 0.24 |
| Age of onset (yr) | 26.9 ± 11.0 | 34.3 ± 17.5 | 25.8 ± 9.4 | 2.56 | 0.11 |
| Comorbid physical diseases | 43 (48.8%) | 13 (76.5%) | 40 (47.6%) | 4.72 | 0.03 |
| Antipsychotics | | | | | |
| Clozapine | 14 (13.9%) | 3 (17.6%) | 11 (13.1%) | 0.25 | 0.62 |
| Non-clozapine | 87 (86.1%) | 14 (82.4%) | 73 (86.9%) | | |
| Antipsychotic dose (mg) (chlorpromazine equivalents) | 239.2 ± 156.2 | 191.0 ± 164.1 | 264.4 ± 160.8 | 3.16 | 0.08 |

COVID-19: Coronavirus disease 2019; IQR: The interquartile range.

### *Treatment*

The hospital established isolation wards and once a patient showed suspicious symptoms of COVID-19, he/she received laboratory or radiological confirmation, and was transferred to these isolation wards. Among all the 84 patients, 70 received intravenous or oral antibiotic therapy; 55 took oseltamivir at 75 mg-150 mg/d, and 10 took umifenovir at 0.3-0.6 g/d. In addition, 14 and 3 patients received cephalosporin antibiotics and azithromycin, respectively, in combination with oseltamivir or alone. Finally, 17 patients received oxygen therapy and 3 received glucocorticoids.

Among all 84 patients, 13 developed respiratory distress syndrome (RDS), and the median duration from onset of COVID to RDS was 8 d (interquartile range, 5-13). Finally, 11 patients (13.1%) were admitted to an ICU at another hospital and 8 (9.5%) died.

### *Comparison of SCZ patients with and without COVID-19*

Table 1 shows the demographic and clinical characteristics of the SCZ patients with and without COVID-19. Compared to patients without COVID-19, patients with COVID-19 were older ($P = 0.006$), had significantly lower weight ($P = 0.002$) and lower systolic pressure ($P = 0.005$), had more comorbid physical diseases ($P = 0.001$), and were less likely to be smokers ($P < 0.001$). Since there was a significant difference in

antipsychotic treatment between the two groups ($F$ = 14.1, DF = 6, $P$ = 0.03), we further divided the patients into a clozapine and non-clozapine treated group, and found a significant difference in the infection rates between the two groups (32% in non-COVID-19 *vs* 18% in COVID-19; $\chi^2$ = 5.42, $P$ = 0.02). All these significant differences passed the Bonferroni corrections ($P$ < 0.05) except for clozapine treatment ($P$ > 0.05). In addition, there was a trend towards a higher proportion of female patients with COVID-19 ($P$ = 0.07).

Table 2 shows results using logistic regression to adjust for these several significant characteristics distinguishing those with and without COVID-19. The following differences remained significant independent predictors: Comorbid physical diseases, smoking, clozapine treatment, and sex. As indicated by the odds ratios and beta weights, the schizophrenic patients with a lower risk for COVID-19 were clozapine treated males who smoked and had fewer comorbid physical diseases.

## DISCUSSION

This first report about COVID-19 among SCZ inpatients contains three key findings. First, and most importantly, the mortality rate from CP of 9.5% among these SCZ inpatients is remarkably higher than that from COVID-19 found in the general population of this epidemic region[5-6]. Second, the most common symptom of COVID-19 in these patients was fever (82%) and the less common symptoms included cough (31%), poor appetite (20%), and fatigue (16%). Third, some unusual and relatively unexpected protective factors for lower rates of COVID-19 included being male and treatment with clozapine, as well as more smoking among these SCZ patients. In contrast to men and smokers, the general population is at a greater risk of contracting COVID-19 and its complications. The other association of risk for COVID-19 with more comorbid physical diseases is consistent with the general population during this epidemic.

The death rate of 9.5% in these SCZ patients with COVID-19 was much higher than the death rate of 1.4%-3.2% in the general Wuhan population with COVID-19[6]. These striking 3 to 7 fold differences in death rates and failure to survive severe complications with 62% (8/13) dying once they developed severe complications suggest that these SCZ patients may be more vulnerable to more direct progression from severe complications to death from COVID-19 and overall less responsive to attempts at treating this infection. A large number of epidemiological studies have shown that high rates of smoking[14-16], obesity[17-18], diabetes[19-20], and cardiovascular diseases[21] occur in SCZ patients, especially in those chronic and medicated patients, and that these comorbid disorders may contribute to a 15%-20% reduction in life expectancy reported in this population[15-21]. Therefore, the chronic SCZ patients in this study may have been vulnerable to higher mortality from COVID-19 based primarily on these other illnesses.

Another remarkable feature in our patients with COVID-19 is the relatively low contagion rate, in spite of almost all patients having clear and repeated contacts with infected patients before these infected patients showed clinical symptoms. We did not test for COVID-19 in all 504 patients so we do not know the actual rate of infection in this group, but relatively few (17%) showed any signs of COVID-19. This low disease rate was remarkable in spite of obvious potential for human-to-human transmission in the hospital with its densely populated wards that had 4-6 people in one room. COVID-19 may be spread through the respiratory or gastrointestinal tract, but gastrointestinal tract symptoms, such as nausea, vomiting, or diarrhea were uncommon in these patients, making upper respiratory tract contagion most likely.

While the most common symptom of fever in 82% of our CP patients was consistent with the 89% community rate, cough frequency (31%), which was much less than the community rate of 68%, might have contributed to the relatively lower contagion rate in these hospitalized patients[1-6]. Moreover, the cough frequency may have been low because of the sedative influence of antipsychotic medication. Additionally, fewer of our patients had gastrointestinal symptoms like nausea or vomiting (5%) and diarrhea (4%) than found in the community[6]. Reasons for these symptom differences may include biological differences in the disease of SCZ and specific medication effects. For example, antipsychotic agents can reduce nausea, vomiting, and diarrhea[22], masking these symptoms in COVID-19, and we found a specific effect of clozapine in reducing risk of COVID-19 induced symptoms and possibly infection itself. From another perspective, we found that nearly half of our patients with COVID-19 exhibited reduced white cell counts, including 46% with lymphocytopenia, 36% with leuko-

**Table 2 Characteristics of schizophrenia patients with or without coronavirus disease 2019**

| | COVID-19 patients (*n* = 84) | Non-COVID-19 patients (*n* = 174) | *F*, *Z* or χ | *P* |
|---|---|---|---|---|
| Age (yr) | 54.6 ± 9.5 | 51.1 ± 9.5 | 7.65 | 0.006 |
| Gender (Male/ Female) | 64/20 (76.2%/23.8%) | 137/31 (78.7%/17.8%) | 3.36 | 0.07 |
| Marital status | | | 1.06 | 0.59 |
| Single | 45/75 (60.0%) | 104/160 (65.0%) | | |
| Married | 9/75 (12.0%) | 21/160 (13.1%) | | |
| Divorced | 21/75 (28.0%) | 35/160 (21.9%) | | |
| Weight (kg) | 62.0 ± 10.3 | 67.8 ± 16.6 | 9.40 | 0.002 |
| Blood pressure | | | | |
| Systolic pressure | 122.5 ± 7.2 | 125.5 ± 8.0 | 7.98 | 0.005 |
| Diastolic pressure | 77.3 ± 5.7 | 76.6 ± 6.0 | 0.81 | 0.37 |
| Smoker/non-smoker | 11/65 | 92/74 | 35.8 | 0.000 |
| Duration of illness (years) | 29.4 ± 11.0 | 27.4 ± 10.3 | 2.09 | 0.14 |
| Age of onset (years) | 25.4 ± 7.9 | 23.8 ± 7.3 | 2.06 | 0.15 |
| Comorbid physical diseases | 43 (48.8%) | 44/164 (26.8%) | 11.9 | 0.001 |
| Antipsychotics | | | 14.1 | 0.03 |
| Olanzapine | 18 (21.4%) | 16 (9.2%) | | |
| Risperidone | 16 (19.0%) | 45 (25.9%) | | |
| Clozapine | 15 (17.9%) | 55 (31.6%) | | |
| Quetiapine | 13 (15.5%) | 18 (10.3%) | | |
| Aripiprazole | 11 (13.1%) | 17 (9.8%) | | |
| Ziprasidone | 4 (4.8%) | 5 (2.9%) | | |
| Typicals | 7 (8.3%) | 18 (10.3%) | | |
| Antipsychotic dose (mg/d) (chlorpromazine equivalents) | 264.4 ± 160.8 | 226.9 ± 152.8 | 3.16 | 0.08 |

COVID-19: Coronavirus disease 2019.

penia, and 34% with neutropenia, and 12% had thrombocytopenia and 68% had elevated C-reactive protein levels. While these findings are consistent with community patient reductions during COVID-19[1,3,6], antipsychotic drugs, especially clozapine, also are associated with low blood cell counts[23-25]. Therefore, protective effects of clozapine in our patients remain interesting, but in need of replication, while adverse factors in our SCZ patients, such as physical diseases, older age, and lower weight (caused by malnutrition), clearly appear to be risk factors for COVID-19 and its severe complications including death.

The three protective clinical factors of clozapine treatment, smoking, and being male have remarkable associations with COVID-19 among our SCZ inpatients. Moreover, the logistic analysis found significant independent contributions from these three factors for developing COVID-19 symptoms and complications. Biological mechanisms that might contribute to clozapine's association are its anti-inflammatory effects by inhibiting a NOD-like receptor family and the pyrin domain-containing protein-3 inflammasome[26]. Immunosuppression and anti-inflammatory effects of nicotine and smoking may also be a mechanism for the protective effects of smoking on COVID-19. We previously found that SCZ smokers had significantly decreased IL-2 and IL-6 levels, supporting that nicotine may cause immunosuppression in SCZ patients[27].

The association between smoking and COVID-19 has become a controversial topic in the world [28-29]. It is well known that smoking is harmful to health, and COVID-19 is just another example of how smoking may cause lung damage and makes a person at higher risk for COVID-19 and its complications. However, the most recent epidemiological survey demonstrates that current smoking status may protect against COVID-19[30], which may be based on the molecular biology of nicotinic receptor[31]. A recent

hypothesis has proposed that the nicotinic acetylcholine receptor may play a pivotal role in the pathophysiology of COVID-19, and nicotine and nicotinic agents may be a possible treatment for COVID-19[30]. Thus, our finding that smoking had a protective effect on COVID-19 among the SCZ inpatients appears to provide the new clinical support for this hypothesis. However, due to the limited sample size in this study, our finding should be replicated in a larger sample of smoking SCZ patients in further investigation. In addition, angiotensin-converting enzyme-2 (ACE2) receptor is a novel adhesion molecule through which SARS-CoV-2 can invade target cells causing COVID-19[32,33]. Interestingly, some recent studies found a connection between smoking and COVID-19[34]. Moreover, smokers had higher ACE2 gene expression than never-smokers, while nicotine may up-regulate ACE2 receptors, suggesting that smokers may be more susceptible to COVID-19, and smoking may exacerbates mortality[35]. Taken together, the relationship between smoking and COVID-19 is still contradictory, which deserves further study.

Our study has some limitations. First, a few cases had missing or incomplete symptom data due to the urgent situation in providing treatments. Second, about one-third of patients did not have COVID-19 laboratory tests to confirm their diagnosis due to restrictions in testing availability. Third, due to the much older age of the SCZ patients with COVID-19, some had unavoidable recall problems with some clinical data. Fourth, since many patients were still in the hospital when we extracted the data, and the outcome was unknown at the time of data cutoff, we were only able to use data about their clinical outcome at the time of data analysis. More patients may have died, for example, beyond the window of this study timeframe, and we did not have data on the prevalence of asymptomatic COVID-19 within this inpatient population to enable an accurate assessment of contagion among these inpatients. Fifth, there is a lack of the data on the possible change of mental clinical state in the infected patients. Hence, we did not know whether there was any change in their symptoms of SCZ at the time of their infection.

## CONCLUSION

In summary, we have found a seemingly higher prevalence of COVID-19 among the SCZ inpatients than that in the general population in Wuhan. Moreover, the 9.5% mortality of these patients with CP is remarkably higher than that in the general population from this region. These findings suggest that these primarily SCZ patients may be more vulnerable to death from severe complications of COVID-19 and need rapid and intensive interventions once clinicians detect COVID-19. While some symptoms like fever occurred at similar rates in our patients and in the community, other symptoms like cough and gastrointestinal symptoms were less common, and other symptoms, such as poor appetite and fatigue, were substantially more common in our SCZ patients. Less coughing may have reduced contagion and lack of vomiting and diarrhea may have limited fecal spread. Finally, our SCZ patients with COVID-19 had several high risk factors. These infected patients were older, had lower weight and more comorbid physical diseases, and unexpectedly, had a less smoking rate and less treatment with clozapine. It appears that clozapine treatment and smoking may be protective for COVID-19 among SCZ inpatients, perhaps related to nicotine and clozapine immunosuppression, which deserves further exploration.

## ARTICLE HIGHLIGHTS

### *Research background*

In contrast to many Western countries, China has maintained its large psychiatric hospitals. The prevalence and clinical characteristics of coronavirus disease 2019 (COVID-19) in inpatients with schizophrenia (SCZ) are unclear.

### *Research motivation*

In the large mental health hospitals in China, the resources for managing this COVID-19 epidemic are very limited, and these SCZ inpatients are expected to be highly contagious.

### Research objectives

To assess the prevalence of COVID-19 among inpatients with SCZ and compare the infected to uninfected SCZ patients in a Wuhan psychiatric hospital.

### Research methods

We retrospectively collected demographic characteristics and clinical profiles of all SCZ patients with COVID-19 at Wuhan's Youfu Hospital.

### Research results

Among the 504 SCZ patients, 84 had COVID-19, and we randomly sampled 174 who were uninfected as a comparison group. The overall prevalence of COVID-19 in SCZ inpatients was 16.7%. Among these 84 SCZ patients with confirmed COVID-19, the median age was 54 years and 76.2% were male. The most common symptom was fever (82%), and less common symptoms were cough (31%), poor appetite (20%), and fatigue (16%). Compared with SCZ patients without COVID-19, patients with COVID-19 were older ($P$ = 0.006), significantly lighter ($P$ = 0.002), and had more comorbid physical diseases ($P$ = 0.001). Surprisingly, those infected were less likely to be smokers (< 0.001) or to be treated with clozapine ($P$ = 0.03). Further logistic regression showed that smoking [odds ratio (OR) = 5.61], clozapine treated (OR = 2.95), and male (OR = 3.48) patients with relatively fewer comorbid physical diseases (OR = 0.098) were at lower risk of COVID-19. The SCZ patients with COVID-19 presented primarily with fever, but only one-third had a cough, which might otherwise be the most common mode of transmission between individuals.

### Research conclusions

Two unexpected protective factors for COVID-19 among these SCZ inpatients are smoking and clozapine treatment.

### Research perspectives

Clozapine treatment and smoking may be protective for COVID-19 among SCZ inpatients, perhaps related to nicotine and clozapine immunosuppression, which deserves further exploration.


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SYSTEMATIC REVIEWS

# Neurobiological mechanisms underlying delayed expression of posttraumatic stress disorder: A scoping review

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## Abstract

### *BACKGROUND*

The capacity of posttraumatic stress disorder (PTSD) to occur with delayed onset has been documented in several systematic reviews and meta-analyses. Neurobiological models of PTSD may provide insight into the mechanisms underlying the progressive increase in PTSD symptoms over time as well as into occasional occurrences of long-delayed PTSD with few prodromal symptoms.

### *AIM*

To obtain an overview of key concepts explaining and types of evidence supporting neurobiological underpinnings of delayed PTSD.

### *METHODS*

A scoping review of studies reporting neurobiological findings relevant to delayed PTSD was performed, which included 38 studies in the qualitative synthesis.

### *RESULTS*

Neurobiological mechanisms underlying PTSD symptoms, onset, and course involve several interconnected systems. Neural mechanisms involve the neurocircuitry of fear, comprising several structures, such as the hippocampus, amygdala, and prefrontal cortex, that are amenable to time-dependent increases in activity

**Peer-review report's scientific quality classification**

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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through sensitization and kindling. Neural network models explain generalization of the fear response. Neuroendocrine mechanisms consist of autonomic nervous system and hypothalamic-pituitary-adrenocortical axis responses, both of which may be involved in sensitization to stress. Neuroinflammatory mechanisms are characterized by immune activation, which is sometimes due to the effects of traumatic brain injury. Finally, neurobehavioral/contextual mechanisms involve the effects of intervening stressors and mental and physical disorder comorbidities, and these may be particularly relevant in cases of long-delayed PTSD.

*CONCLUSION*
Thus, delayed PTSD may result from multiple underlying neurobiological mechanisms that may influence the likelihood of developing prodromal symptoms preceding the onset of full-blown PTSD.

**Key Words:** Posttraumatic stress disorder; Delayed expression; Sensitization; Neurobiology; Neuroendocrine; Neuroinflammatory

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**Core Tip:** Multiple neurobiological mechanisms underlying delayed expression of posttraumatic stress disorder contribute to sensitization, kindling, and generalization leading to increasing symptoms, through epigenetic, neuroinflammatory, neuroendocrine, and neural interactions.

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## INTRODUCTION

Posttraumatic stress disorder (PTSD) with delayed expression (also known as delayed PTSD or delayed-onset PTSD) is a diagnostic category that applies to people who first meet the criteria for a PTSD diagnosis at least 6 mo following exposure to a traumatic event[1]. While the majority of people who develop PTSD do so within the first wk or mo following the traumatic encounter, a significant minority of people with PTSD present delayed expression of the disorder[2-4]. Since the inclusion of the PTSD diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) in 1980, a delayed category has been discerned[5]. Subsequently, the capacity of PTSD to occur with delayed expression has been documented in several systematic reviews and meta-analyses[2-4]. A proper understanding of the neurobiological basis for delayed expression of PTSD is clinically useful since it has implications for diagnostic assessment in both treatment and forensic settings and in the context of litigation. Specifically, neurobiological models of PTSD may explain variability in the progressive increase in PTSD symptoms over time following exposure to trauma that characterizes PTSD with delayed expression. Neurobiological mechanisms and systems are likely to play a central role in determining the duration of the prodromal phase, the presence of prodromal symptoms and mental and physical disorder comorbidities.

Because delayed expression is the exception rather than the rule, neurobiological mechanisms underlying delayed PTSD have received limited research attention. We therefore conducted a scoping review to obtain an overview of key concepts explaining and types of evidence supporting neurobiological underpinnings of delayed PTSD. The research questions were to determine what role neurobiological mechanisms have in the delayed expression of PTSD, and how neurobiological mechanisms contribute to explaining the occurrence of delayed PTSD following a long asymptomatic interval.

## MATERIALS AND METHODS

### Search strategy

Since our aim was to provide an overview of key concepts and types of evidence, we performed a scoping review[6]. We searched for publications examining the role of neurobiological mechanisms in developing delayed PTSD. The PRISMA scoping reviews checklist[7] was used to ensure correct reporting. We did not register the review protocol. The search was performed in early December 2020 in the following databases (all in the Ovid platform): PsycINFO; Ovid Medline ALL, Ovid Evidence Based Medicine Reviews (EBM Reviews - Cochrane Database of Systematic Reviews and EBM Reviews - Database of Abstracts of Reviews of Effects) and Embase. We based the search strategy on the two research questions and several lead articles (which we presented to Ovid Citation Analyzer to harvest search terms). We built a search strategy in PsycINFO (Ovid), which we then adapted to the other databases. The full search strategy for PsycINFO can be found in Supplementary Table 1. The search terms were grouped into clusters. For Question 1 (the role of neurobiological mechanisms in developing delayed PTSD), we had these clusters: etiology and neurobiological factors (sets 1 through 5), late-onset PTSD (set 6), and study types (sets 8 through 11). For Question 2 (delayed PTSD with a long-term asymptomatic interval), we used the following clusters: late-onset PTSD (set 6), remission and asymptomatic periods (set 7) and study types (sets 8 through 11). These clusters were combined using Boolean operators, and the combined clusters for question 1 (set 12) and question 2 (set 13) were combined. The search results were imported into Endnote and deduplicated using the method outlined elsewhere[8]. Supplementary Table 2 shows the number of items retrieved in each search system, the number of duplicates and thus the new articles collected. These articles were then screened for inclusion in this review.

### Study selection

To screen and select articles, we used Rayyan, a web-based program for systematic reviews[9]. The screening process consisted of three phases: (1) Stepwise inclusion of records based on titles and abstracts with the aid of automatic Rayyan keywords for inclusion; (2) Manual inclusion and exclusion of records based on the inclusion and exclusion criteria; and (3) Manual exclusion of articles based on the full text. Records were eligible if they were: (1) About trauma and PTSD; (2) About delayed onset; (3) About neurobiology; and (4) About causal mechanisms or risk factors. Therefore, records were excluded if they reported studies that were: (1) Not about trauma and PTSD; (2) Not about delayed onset; (3) Not about neurobiology; or (4) Not about causal mechanisms or risk factors. Additionally, duplicate items were excluded. During the first phase, the references including the keywords in Table 1 were retained. In the second phase, two researchers (GS and JL) independently reviewed the titles and abstracts of the remaining 438 items, which had been preselected based on the keywords. In this phase, we used the same criteria as earlier, as outlined in Table 2. After this phase, 60 articles were screened based on the full text by the first author. Twenty-two articles were excluded, thus arriving at a final selection of 38 articles. Figure 1 shows a PRISMA diagram for an overview of the process.

### Statistical analysis

The selected articles were divided into human studies ($n$ = 22), animal studies ($n$ = 4), and review studies ($n$ = 12). From human studies, we abstracted the following data: population (N), the type of trauma or stressor, assessment times, type of PTSD assessment, prevalence of PTSD and delayed PTSD, and neurobiological observation methods. From animal studies, we abstracted the following data: types of animals (N), type of trauma or stressor, assessment times, observed anxiety and delayed effects, and neurobiological observation methods. From review studies, we abstracted the included study types (human and/or animal) and summarized the review focus. An overview of the included human, animal, and review studies is presented in Tables 3, 4 and 5, respectively. A detailed overview of human studies is provided in Supplementary Table 3.

## RESULTS

The included studies reported three types of neurobiological mechanisms, specifically neural, neuroendocrine and neuroinflammatory mechanisms. In addition, included

**Table 1 Study Selection Phase 1: Keywords used for stepwise including (and thus excluding) items**

| Criterion | Input for this criterion | Automatic keyword screening (Rayyan): Used keywords for include | Included | Thus excluded |
|---|---|---|---|---|
| 1 | 5659 | Trauma; traumas; traumatic; traumatized; traumatised; posttraumatic; PTSD | 5194 | 465 |
| 2 | 5194 | Asymptomatic; bridging; delayed; dormant; emerge; emerges; emerging; increase; increases; increasing; interval; late; latency; latent; onset; progression; progressive; symptom-free | 2287 | 2907 |
| 3 | 2287 | Adrenal; adrenalin; allostatic; ANS; autonomous; biochemical; biological; biology; biomarker; biomarkers; brain; cell; ceruleus; chemokine; coeruleus; cortex; cortisol; corticosteroids; corticosteroid; CT; cytokine; cytokines; DNA; epicortisol; epigenetic; epigenomic; epinephrine; frontal; genetic; hippocampus; hippocampal; HPA; hydrocortisone; hypothalamic; hypothalamus; imaging; immune; immunological; inflammation; LC; marker; markers; MRI; NE; nervous; neurobiological; neurobiology; neuroimaging; noradrenalin; norepinephrine; parasympathetic; PET; phenotype; phenotypical; pituitary; PNS; prefrontal; psychobiological; psychobiology; SNS; SPECT; stem; sympathetic | 716 | 1571 |
| 4 | 716 | Amnesia; amnesic; amnestic; cause; causal; dissociation; dissociative; factor; mechanism; mechanisms; predictor; protective; risk; sensitisation; sensitised; sensitization; sensitized; stage; staging; susceptibility; trigger; vulnerability | 455 | 261 |
| | 455 | Deduplication | 438 | 17 |

ANS: Autonomous nervous system; CT: Computed tomography; HPA: Hypothalamic-pituitary axis; LC: Locus coeruleus; MRI: Magnetic resonance imaging; NE: Norepinephrine; PET: Positron emission tomography; PNS: Parasympathetic nervous system; SNS: Sympathetic nervous system; SPECT: Single photon emission computed tomography; PTSD: Posttraumatic stress disorder.

**Table 2 Study Selection Phase 2: Manual title and abstract screening, inclusion and exclusion**

| Criterion | Input for this criterion | Manual title and abstract screening: Record refers to | Inclusion | Exclusion |
|---|---|---|---|---|
| 1 | 438 | Trauma and PTSD | 308 | 130 |
| 2 | 308 | Delayed onset | 73 | 235 |
| 3 | 73 | Neurobiology | 62 | 11 |
| 4 | 62 | Causal mechanisms or risk factors | 60 | 2 |
| | 60 | Full-text articles assessed for eligibility | 60 | |

PTSD: Posttraumatic stress disorder.

studies reported neurobehavioral/contextual pathways. The following sections will summarize the findings for each of these types of mechanisms and pathways. An overview of the interconnected neural, neuroendocrine, neuroinflammatory, and neurobehavioral/contextual systems is presented in Figure 2.

### *Neural mechanisms*

Studies of neural mechanisms of PTSD have focused on identifying brain structures involved in fear learning and modeling structural and functional characteristics underlying PTSD symptoms, onset, and course.

### *The neurocircuitry of fear*

Animal research has identified the amygdala, medial prefrontal cortex (PFC), and hippocampus (the so-called limbofrontal neurocircuitry of fear) as the key regions involved in the acquisition, regulation, and extinction of conditioned fear[10].

**Amygdala:** The most consistent functional abnormality in human PTSD studies is increased amygdalar responsiveness to emotional stimuli, which may or may not be trauma specific. A hyperactive amygdala has been associated with the heightened fear and hyperarousal of patients with PTSD[11]. Consolidation of cued and contextual fear conditioning has been found to be mediated by epigenetic modifications in the amygdala[12].

In a study of healthy trauma-exposed rescue ambulance workers, an increased volume in the left amygdala was found. Left amygdalar volumes positively correlated with suppressed morning salivary cortisol concentrations[13], suggesting amygdalar

**Table 3 Overview of Human Studies**

| Ref. | Population (*n*) | Trauma/stressor | Assessment times |
|---|---|---|---|
| Admon *et al*[14], 2013 | Soldiers (33) | Treating a fellow soldier with severe combat injury | Pre-deployment and 18 mo later |
| Alway *et al*[30], 2016 | TBI patients (85) | Motor vehicle accidents (76.5%), other accidents, assaults | 6 mo, 1-, 2-, 3-, and 4-yr post-injury |
| Bryant *et al*[29], 2009 | Traumatic injury patients with no (708) or mild TBI (459) | Transport accident, assault, fall, work injury, other injury | During hospital admission and at 3 mo post-injury |
| Bryant *et al*[28], 2013 | Road traffic accident survivors admitted to trauma hospital (1084) | Transport accident, assault, fall, work injury, other injury | During hospital admission and at 3-, 12-, and 24 mos post-injury |
| Busso *et al*[21], 2014 | Adolescents exposed to bombing (78) | Terrorist attack at the 2013 Boston marathon | 1 year prior to trauma ($n$ = 44), 4-6 wk posttrauma ($n$ = 78) |
| Cacciaglia *et al*[13], 2017 | Healthy rescue ambulance workers (18), non-exposed matched controls (18) | Exposed group: vehicle accident (41%), traumatic loss of a loved one, domestic violence, childhood abuse | Cross-sectional; trauma occurred a mean of 7.41 yr ago |
| Chase *et al*[39], 2015 | Help-seeking veterans (16) and family members (10) | Exposure to blast during employment to combat-intense settings | Cross-sectional; > 7 yr after exposure |
| Do Prado *et al*[31], 2017 | Adolescents with childhood trauma (30), controls without history of early life stress (27) | Sexual abuse, physical abuse, emotional abuse, physical neglect, emotional neglect | Cross-sectional; maltreatment ended > 12 mo ago |
| Gandubert *et al*[19], 2016 | Emergency room patients (123) | Physical assault, sexual assault, serious accident, other | During the first week and at 1-, 4-, and 12 mos post-trauma |
| Gil *et al*[35], 2005 | Traumatic brain injury patients (120) | Traffic accident | < 1 week, 3 mo, and 6 mo later |
| Glenn *et al*[27], 2017 | Soldiers deployed to Afghanistan (852) | Combat experience, difficult living and working environment | 4 wk before and 22 wk after deployment |
| Jung *et al*[47], 2019 | Community-dwelling women (nurses) (50020) | Various self-reported on Brief Trauma Questionnaire | Biennial from enrollment |
| Monfort and Trehel[44], 2017 | 93-year-old veteran (1) | WW II combat experiences | 65 years later |
| Roy *et al*[36], 2015 | Combat veterans without PTSD, depression, or post-concussive syndrome < 2 mo after return (81) | Deployment to Iraq or Afghanistan > 3 mo | < 2 mo after return, 3, 6, and 12 mo |
| Smid *et al*[26], 2015 | Deployed soldiers (693) | 4 mo deployment to Afghanistan | 2 mo prior to deployment and 1-, 6-, 12-, and 24 mo following deployment |
| Solomon and Mikulincer[42], 2006 | Combat veterans with combat stress reaction (CSR) (131) or without (83) | 1982 Lebanon War | 1, 2, 3, and 20 yr after the war |
| Solomon *et al*[41], 2017 | Ex-prisoners of war (101), combat controls (15) | 1973 Yom Kippur War | 18, 30, 35, 42 yr after the war |
| Stein *et al*[43], 2013 | Community-dwelling (25,018) | Lifetime exposure to 27 traumatic events | Cross-sectional |
| Uddin *et al*[32], 2010 | PTSD-affected (23) and -unaffected individuals (77) from large sample | Lifetime exposure to 19 traumatic events | Cross-sectional |
| Vaiva *et al*[20], 2005 | Hospitalized traumatology patients (78) | Road traffic accident | 1 and 6 wk, 12 mo |
| Wang *et al*[33], 2015 | Blunt chest trauma patients (57) | Motor vehicle accidents (61.4%), falls, other accidents | 1, 3, 6 mo |
| Waszczuk *et al*[46], 2020 | First responders (1490) | Working at the World Trade Center site, New York following the 9/11, 2001 terrorist attacks | Mean = 7.75 monitoring visits per 1.49 yr, PTSD diagnosis at 12 yr |

involvement in sensitized neuroendocrine responses (see below).

**Hippocampus:** Guided by evidence from animal studies demonstrating how stress can have a destructive effect on the hippocampus, a brain structure critical for learning and memory, studies in humans have frequently reported reduced hippocampal volume in patients with PTSD[11]. An abnormal hippocampus has been suggested to mediate PTSD-related deficits in the appreciation of safe contexts and contextual memory[11]. Indeed, epigenetic modifications in the hippocampus have been shown

**Table 4 Overview of animal studies**

| Ref. | Animals (*n*) | Trauma/stressor | Assessment times | Anxiety and delayed effects | Neurobiological observation methods |
|---|---|---|---|---|---|
| Ardi *et al*[15], 2014 | Rats: naïve (12), swim (12), swim + reminder (R) (12), UWT (12), UWT + R (12) | Rats were given daily 1-minute swim trials for 5 days. On day 6, 'swim' rats had an additional swim trial, and 'UWT' rats were swimming and then held underwater for 30 s using a net. On day 7, rats from the 'reminder' groups were exposed to 30 s of swimming | Following the 'reminder', rats were tested after 30 min.; 'swim' and 'UWT' rats were tested on day 7 | Undergoing UWT results in reduced exploration in the open field even 24 h after the trauma compared to 'swim' and 'naïve' groups. Exposure to the reminder resulted in significantly enhanced anxiety behavior | electrophysiological recordings of hippocampal dentate gyrus GABA-ergic local circuit activity: paired-pulse inhibition (reflecting feedback inhibition), frequency-dependent inhibition (reflecting feed-forward inhibition), long-term potentiation; biochemical analysis: amygdala extracellular-signal-regulated kinase activity |
| Justice *et al* [45], 2015 | Mice: wild type controls (43) and PTSD-group (65), Alzheimer's Disease model controls (76) and PTSD-group (145) | Mice in the PTSD group were immobilized for 2h on boards with tape in a brightly lit area. For the reminder, the procedure was repeated during 15 min. | 2–3 mo and 6–12 mo | Animals displayed elevated anxiety and slightly elevated startle amplitudes | resting and peak plasma corticosteroid levels, cerebrospinal fluid beta-amyloid levels |
| Serova *et al* [25], 2019 | Rats: 1 wk following stress (57), 2 wk following stress (42), controls (56) | Rats were immobilized for 2 h on a board by taping the limbs and restricting motion of the head, then subjected to forced swim for 20 min. | 1 or 2 wk following stress | At 1 week, 17.5%, and at 2 wk, 57.1% of animals displayed severe anxiety | Gene expression in the mediobasal hypothalamus and locus coeruleus (LC), immunohistochemistry |
| Wilson *et al* [34], 2013 | Rats: PTSD-group (10), controls (10) | PTSD group rats were secured in plexiglas cylinders and placed in a cage with a cat for one hour on days 1 and 11 of a 31-day stress regimen, and their cage cohort was changed daily | day 0, day 12, day 31 | The PTSD group displayed significantly higher anxiety than the control group, and significantly diminished growthrate over the 31-day stress period | Growth, plasma (corticosterone), adrenal glands (weight, oxidative stress), and hippocampus, amygdala, and pre-frontal cortex (oxidative stress and inflammatory markers: interleukin-1β, NALP3-inflammosome, glyceraldehyde 3-phosphate dehydrogenase) |

UWT: Underwater trauma; GABA: Gamma aminobutyric acid; NALP3: NACHT, LRR and PYD domains-containing protein 3 (also: nucleotide-binding domain, leucine-rich repeat family pyrin domain containing 3); PTSD: Posttraumatic stress disorder.

to be specifically involved in mediating contextual fear learning[12]. In deployed soldiers, reductions in hippocampal volume and connectivity with the ventromedial PFC from pre- to postdeployment were found to be related to concurrent increases in PTSD symptoms, whereas predeployment low hippocampal volume was not associated with outcomes in terms of PTSD symptoms[14]. However, this latter finding should not be regarded as contradicting prior evidence from homozygotic twins suggesting that smaller hippocampal volume is a predisposing risk factor for PTSD[11,14]. Probably, the effects of predisposing and acquired neural abnormalities are interrelated, such that reduced hippocampal volume may predispose to PTSD, yet at the same time development of PTSD can cause a secondary loss of hippocampal volume over time[11].

Animal research on hippocampal involvement in fear learning revealed time frames related to hippocampal fear memory processing. Consolidation of hippocampus-dependent fear memory can be evaluated 24 h after training, whereas consolidation of remote memory becomes evident at least 7 days after training, when memories from the hippocampus have been integrated for maintenance in the cortex[12]. In animal models of PTSD based on fear conditioning following shock exposure, exposure to a novel, neutral tone provides an index of fear sensitization[12]. Importantly, the expression of sensitized fear to a novel auditory cue has been found to increase with time after shock exposure[12].

A study in rats following underwater trauma exposure and subsequent exposure to a trauma reminder one week later[15] demonstrated the impact of trauma reminders on both the hippocampus and amygdala. While exposure to underwater trauma resulted in increased local circuit inhibitory feedback activity in the hippocampal dentate gyrus, exposure to the trauma reminder resulted in an additional increase in local circuit inhibitory feed-forward activity. Reminder exposure also resulted in impaired hippocampal dentate gyrus long-term potentiation and amygdalar extracellular-signal-regulated-kinase-2 (ERK2) activation, supporting the notion that under emotional conditions, the amygdala modulates stress-induced alterations in the dentate gyrus through the modulation of hippocampal ERK signaling[15].

**Table 5 Overview of review studies**

| Ref. | Study types | Review focus |
|---|---|---|
| Admon *et al*[11], 2013 | Human | Reviews predisposing and acquired neural abnormalities that can be discerned based on PTSD neuroimaging studies that include genetic, environmental, twin, and prospective data |
| Belda *et al*[22], 2015 | Animal | Reviews sensitization: A phenomenon whereby exposure to a particular stimulus triggers a state of hyperresponsiveness |
| Kim *et al*[18], 2019 | Human, animal | Reviews influences of chronic exposure to stress on the immune system, resulting in increased proinflammatory cytokine levels. Focuses on changes in the amygdala, hippocampus, PFC, and insula, that are particularly influenced by excess cytokines |
| McFarlane[17], 2000 | Human | Focuses on people who develop PTSD de novo, *i.e.*, without preexisting disorder at the time of the traumatic event that may have acted as a risk factor to the onset of PTSD |
| McFarlane[23], 2010 | Human | Examines the issue of the timing of the onset of PTSD following exposure to traumatic events |
| McFarlane *et al* [16], 2002 | Human | Reviews the knowledge from neural networks to model a framework for exploring the relationship between neurobiology, cognition, and behavior in PTSD |
| McFarlane *et al* [40], 2017 | Human | Argues that major advances in the biological treatments of PTSD depend on a more sophisticated classification of PTSD that acknowledges the heterogeneity of this condition |
| Michopoulos *et al* [24], 2015 | Human | Reviews putative PTSD biomarkers with specific emphasis on the interaction between neurobiological influences on disease risk and symptom progression |
| Smid *et al*[38], 2003 | Human | Reviews risk factors for delayed PTSD, including combat trauma, stressful events after the trauma and previous emotional problems |
| Soreq[37], 2010 | Human, animal | Reviews effects that are often reported yr after prophylactic treatment with cholinesterase inhibitors for protection under threat of chemical warfare, *e.g.*, during the Gulf War, and their similarity to symptoms of PTSD |
| Wilker and Kolassa[10], 2013 | Human, animal | Reviews genetic risk factors in PTSD etiology from the perspective of a psychobiological model, which proposes that intrusive memories, the core PTSD symptom, result from the formation of an associative neural fear network, which stores sensory-perceptual representations of traumatic memories |
| Zovkic *et al*[12], 2013 | Human, animal | Discusses epigenetic regulation of PTSD in human studies and in animal models and ways in which these models can be expanded. Reviews the literature that directly addresses the involvement of epigenetics in PTSD and puts it into the broader context of epigenetics in stress and fear learning |

PTSD: Posttraumatic stress disorder; PFC: Prefrontal cortex.

**Prefrontal cortex:** The PFC has been found to display abnormal function and structure in PTSD patients. Specifically, aspects of the medial sections of the medial PFC and anterior cingulate cortex (ACC) have been associated with patients' deficits in emotional regulation[11]. Connectivity studies, either functional or structural, have shown deficient connectivity between the amygdala and/or the hippocampus to the frontal lobe, which could contribute to difficulties that patients with PTSD have in integrating cognitive control over the emotional neural system[11]. Abnormal structure of the amygdala and dorsal ACC and their heightened responsivity to emotionally negative stimuli may represent predisposing neural abnormalities that increase the likelihood of developing PTSD following exposure to trauma[11]. Reduced volumes in medial PFC structures (specifically, the rostral ACC, ventromedial PFC, and orbitofrontal cortex), as well as reduced ventromedial PFC connectivity with the hippocampus, if acquired following exposure to trauma, may lead to PTSD susceptibility[11].

### *Neural network models*

According to neural network models of PTSD, the structure of the neural networks involved in the processing of traumatic memories becomes progressively modified by the repeated replay of these memories through iterative learning, top-down activation and pruning[16]. Noradrenergic neurons play a central role in coordinating the interaction of multiple cortical regions, and functional alterations in the noradrenergic system leading to dysfunctional modulation of working memory in PTSD contribute to intrusive traumatic recollection[16]. Modifications of neural networks have a secondary effect of kindling in the hippocampus that further moderates the individual's sensitivity to a range of stressors[16]. The fear network model assumes that every new trauma activates the same memory structure, given that different

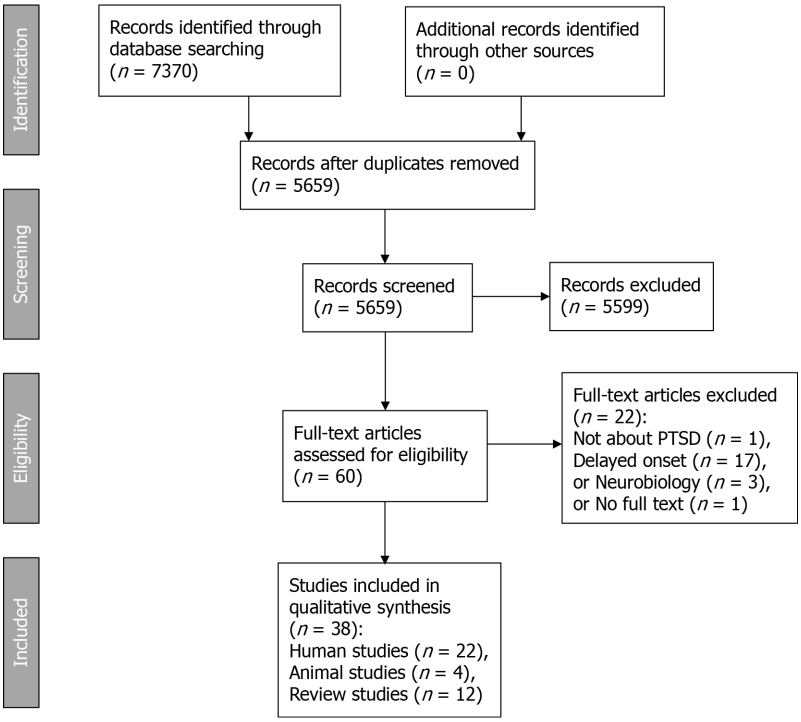


**Figure 1 PRISMA flow chart.** PTSD: Posttraumatic stress disorder.

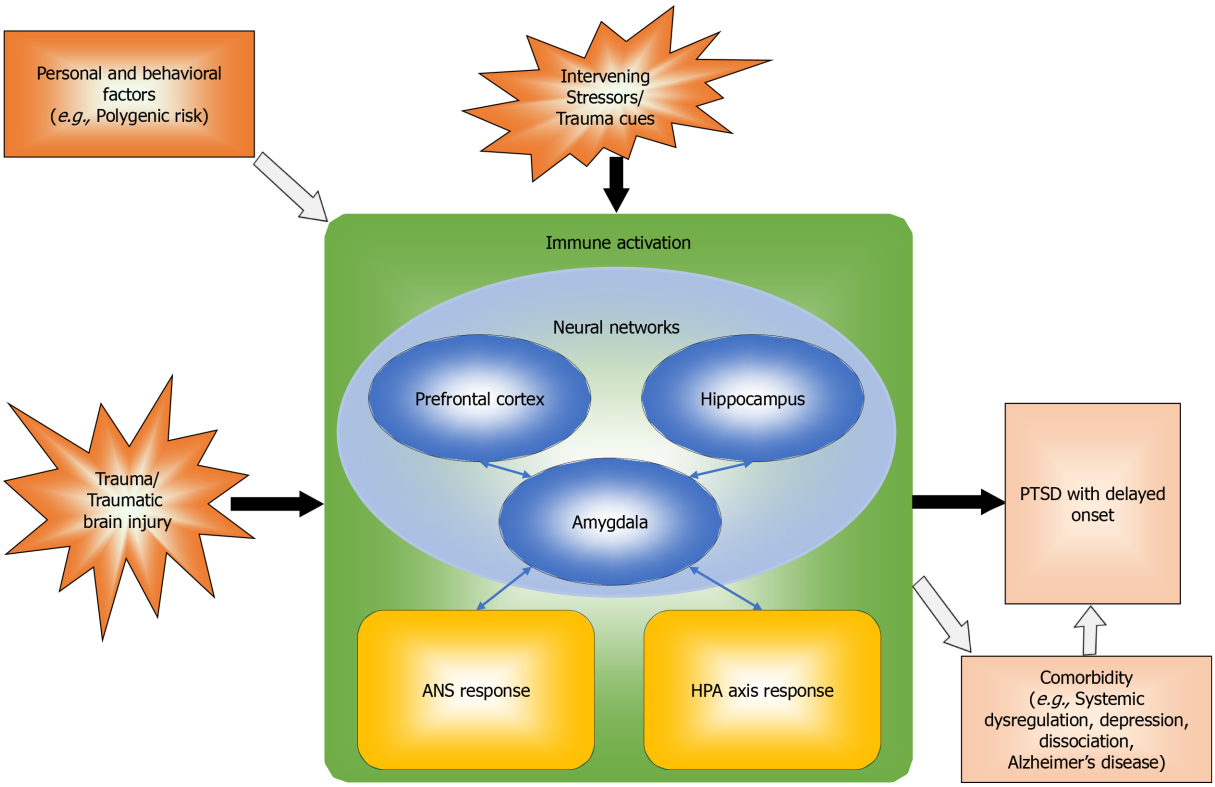


**Figure 2 Neural, neuroendocrine, neuroinflammatory, and contextual mechanisms underlying delayed expression of posttraumatic stress disorder.** Solid arrows indicate direct effects, open arrows indicate indirect effects. ANS: Autonomic nervous system; HPA: Hypothalamic-pituitary-adrenal; PTSD: Posttraumatic stress disorder.

traumatic experiences share important elements[10]. With each new traumatic event, sensory-perceptional elements are added, and the interconnections of the emerging fear network strengthen. With multiple traumatic events, the network will contain conflicting contextual information from different events. Hence, the memory for

context weakens with increasing traumatic load, followed by the emergence of intrusive symptoms[10]. An individual exposed to sequential trauma who has developed PTSD after a particular traumatic event may develop intrusive and distressing memories of previously experienced traumatic events that had not previously led to symptoms. Due to the pruning of dendrites, inappropriate fusion of memory networks occurs, which explains how a particular traumatic event can serve as an activator of previous traumatic memories[16]. Furthermore, the triggers for intrusive traumatic memories become increasingly more subtle and generalized[16].

### Neuroendocrine mechanisms

Neuroendocrine mechanisms involve both neural and endocrine (hormonal) components. Two major neuroendocrine systems have been implicated in the stress response, one involving the autonomic nervous system and the other involving the hypothalamic-pituitary-adrenocortical (HPA) axis. Below, findings relevant to delayed PTSD regarding both neuroendocrine systems are summarized.

### Autonomic nervous system responses

The autonomic nervous system responses to stressor exposure involves activation of neurons in the locus coeruleus (LC), the major noradrenergic (norepinephrinergic) nucleus of the brain involved in the regulation of arousal and autonomic activity, leading to adrenalin (epinephrine) release *via* the sympatho-adrenal medullary pathway. Autonomic hyperarousal is a risk factor predicting the course of PTSD[17]. Decreased activity of the parasympathetic nervous system, along with increased activity of the sympathetic nervous system, have been observed in PTSD[18]. In emergency room patients, the waist-to-hip ratio and systolic blood pressure were associated with PTSD 4 and 12 mo later; both measures are biomarkers of autonomic nervous system responses. A higher level of overnight urinary norepinephrine predicted PTSD at 4 mo, and body mass index at baseline was associated with a 12 mo PTSD diagnosis[19]. Gamma amino-butyric acid (GABA) is inversely associated with the intensity and duration of the central hyperadrenergic response in times of high stress. In hospitalized traumatology patients, lower GABA levels one week after hospitalization predicted PTSD 12 mo later. Among victims without PTSD at 6 wk, 80% of subjects with GABA levels below 0.20 nmol/mL developed delayed-onset PTSD[20]. Adolescents who were exposed to a terrorist bombing attack and who had had high levels of sympathetic reactivity during a Trier Social Stress Test (specifically, shorter preejection period on impedance cardiography) preceding the attack exhibited an elevated risk for PTSD symptoms compared to adolescents with low sympathetic reactivity in a context of low levels of exposure to media coverage of the attacks. In the context of high levels of media exposure, youth with high and low sympathetic reactivity exhibited equally high levels of PTSD symptoms. Thus, adolescents with low sympathetic reactivity developed PTSD symptoms only following high exposure to media coverage of the attack[21]. These results suggest that in the absence of pre-exposure vulnerability for PTSD, additional superimposed stress may be needed to trigger PTSD symptom onset.

### HPA axis response

The HPA axis response to stressor exposure in humans involves activation of neurons in the hypothalamus that secrete releasing hormones, such as corticotrophin releasing hormone (CRH), that act on the pituitary to promote the secretion of adrenocorticotropic hormone (ACTH), which in turn acts on the adrenal cortex to initiate the synthesis and release of glucocorticoid hormones, specifically cortisol. Exposure to systemic or high-intensity emotional stressors is followed by HPA axis sensitization. In some studies, with acute immune stressors, HPA sensitization appears to develop over time (incubation), but most studies find a strong initial sensitization that progressively declines over the days[22]. HPA axis cross-sensitization to heterotypic stressors is best observed with short duration (5-15 min) novel challenging stressors[22]. In addition to HPA axis (cross-) sensitization, behavioral sensitization, reflected in different types of animal tests related to fear conditioning and anxiety-like behavior, can be observed, especially following the imposition of a new, brief stressor. Behavioral sensitization appears to persist longer than that of the HPA axis, suggesting long-term latent effects of the initial exposure[22].

In the domain of the HPA axis, the process of sensitization explains why individuals with PTSD become unusually reactive to stress, which is manifested as exaggerated behavioral and biological responses to environmental challenge[23]. A study of healthy trauma-exposed rescue ambulance workers reported hyposuppression of

salivary cortisol in a dexamethasone challenge test. HPA axis sensitization appeared to be associated with amygdalar activity. Specifically, left amygdalar enlargement correlated with suppressed morning salivary cortisol[13]. These findings suggest that asymptomatic, trauma-exposed individuals develop neurobiological features similar to those in patients with PTSD. However, it is unclear whether and how prior trauma exposure affects the time of onset of PTSD symptoms following exposure to subsequent traumatic events.

Emerging genetic and epigenetic findings related to PTSD risk *vs* resilience have focused on modulators of HPA axis function prior to and following trauma[24]. In a study of gene expression in HPA axis-related brain regions in rats exposed to a single prolonged stressor, the percentage of animals displaying severe anxiety increased strongly from 17.5% at one week to 57.1% two wk after stress. This single prolonged stressor elicited time-dependent changes in gene expression for CRH and neuropeptide Y (NPY) systems in the locus coeruleus and hypothalamus. The locus coeruleus displayed prolonged activation, with enhanced gene expression for CRH receptor 1 and reduced gene expression for NPY and Y2 receptors. In the mediobasal hypothalamus, sustained increased CRH gene expression was found, but there was a flip in alterations of gene expression for glucocorticoid receptor (GR), FK506 binding protein 5 (FKBP5) and NPY receptor at two wk compared to one week. Although gene expression for GR and FKBP5 was increased over levels in unstressed rats at 1 wk, it was downregulated by 2 wk. Similarly, robust increases in Y2 receptor and Y5 receptor gene expression were observed at 1 wk, but after 2 wk, only the Y5 receptor differed from the unstressed levels and was downregulated to half the levels that were observed in unstressed rats[25]. These findings illustrate the cascade of neurobiological alterations underlying progressive symptom development following trauma.

### Neuroinflammatory mechanisms

An accumulating body of evidence suggests that cytokines play a role in processes such as fear learning and memory that are involved in the pathogenesis of PTSD[18,26,27]. High levels of proinflammatory cytokines associated with injury, inflammation, and severe psychological stress have been shown to exert direct detrimental effects on memory functioning and neural plasticity[18,26]. Studies of traumatic brain injury (TBI) survivors have yielded additional insights into PTSD progression over time[28-30].

### Immune activation

Different mechanisms have been suggested to underlie immune activation following exposure to psychological trauma. In adolescents exposed to childhood maltreatment [31], evidence of immune activation and proinflammatory profiles was found, as well as more circulating lymphocyte subsets associated with cell activation and signs of early immunological aging. Underlying mechanisms included enhanced activation of both mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NFκB) signaling pathways and partial resistance to glucocorticoids, specifically, decreased lymphocyte sensitivity to dexamethasone[31]. In a cross-sectional study of PTSD-affected and PTSD-unaffected individuals, peripheral epigenomic and cytomegalovirus immune response profiles associated with PTSD were consistent with traumatic events inducing downstream alterations in immune function by reducing methylation levels of immune-related genes[32]. In hospitalized blunt chest trauma patients, transfusion, injury severity, and high-mobility group box 1 Levels, a key late mediator of systemic inflammation after one week, were predictive of PTSD at 6 mo, including delayed PTSD[33].

In soldiers reporting high combat stress exposure, both high mitogen-stimulated T-cell cytokine production and high innate cytokine production were associated with increases in PTSD symptoms in response to postdeployment stressful life events. In soldiers exposed to low combat stress and those with low cytokine production, postdeployment stressful life events were not associated with increases in PTSD symptoms. The effects of postdeployment stressful life events on the course of PTSD symptoms after a return from deployment largely depended on combat stress exposure as well as immune reactivity following return from deployment. High combat exposure does not by itself lead to increased sensitivity to postdeployment stressful life events but only in the presence of immune activation, as evidenced by high T-cell and innate cytokine production. Additionally, immune activation by itself is not sufficient to lead to increased reactivity to stressful life events, but only following high combat stress exposure. These findings suggest both beneficial and detrimental effects of high cytokine production, depending on the subsequent occurrence of stressful life events [26].

Heightened activity of the immune system may cause alterations in the structure and function of brain regions such as the amygdala, hippocampus, and PFC through changes in the levels of serotonin and kynurenine pathway metabolites and direct neurotoxic effects of cytokines[18]. Neurotoxic cytokine signaling may occur in conjunction with the production of reactive oxygen species (ROS). A study using a predator exposure/psychosocial stress animal model of PTSD found that proinflammatory cytokines and ROS were elevated in the amygdala, hippocampus, and PFC of the rat brain, indicating increased oxidative stress and inflammation. In addition, oxidative stress and inflammation were elevated systemically, as evidenced by increased ROS and proinflammatory cytokines in the adrenal glands and circulating blood. Importantly, within-group comparisons in the PTSD group of rats demonstrated that superoxide levels and total reactive oxygen species levels progressively increased during the stress regimen[34].

### *Traumatic brain injury*

Studies of TBI survivors contradict the idea that TBI and PTSD are nonoverlapping conditions, as the loss of consciousness and amnesia associated with TBI have been shown not to protect against PTSD. In a study of hospitalized trauma survivors with mild TBI, of the 55 participants with memory of the traumatic event, 13 (23%) developed PTSD, and of the 65 participants without memory of the traumatic event, there were still 4 (6%) who developed PTSD[35]. In another study of TBI patients, the duration of posttraumatic amnesia (PTA) did not significantly differ between participants with acute and delayed-onset PTSD[30]. In a prospective cohort study of traumatic injury patients, mild TBI patients were even more likely to develop PTSD at 3 mo following injury than non-TBI patients. No associations were found between the duration of PTA and PTSD symptoms, but longer PTA was associated with less severe intrusive memories at baseline[29]. The absence of early intrusive symptoms may be associated with an increased likelihood of delayed PTSD. Indeed, in long-term prospective follow-up assessments in the same cohort, in the group with no PTSD at 3 mo, PTSD severity at 24 mo was predicted by PTSD severity during hospitalization, the presence of mild TBI, and the number of days spent in the hospital[28].

In soldiers deployed to Afghanistan, TBI was found to be associated with alterations in fear learning and extinction[27]. Experiencing multiple TBIs within a 2- to 3-year time frame exacerbated conditioned fear, and elevated learned fear contributed to the risk for PTSD after TBI[27]. In combat veterans who had been deployed to Iraq or Afghanistan for over 3 mo and who had no PTSD, depression, or postconcussive syndrome within 2 mo after return, independent predictors of PTSD after one year were single nucleotide polymorphisms in the genes coding for two proteins related to neuronal recovery: myelin basic protein and brain-derived neurotrophic factor; MBP and BDNF may work in concert to protect against or enhance recovery from brain injury, thereby mediating the risk of long-term mechanical and psychological injury [36]. Additional predictive factors were elevated resting state connectivity on functional MRI between the right amygdala and left superior temporal gyrus and reduced volume on MRI of the right superior longitudinal fasciculus tract, connecting the frontal lobe with the parieto-temporal brain regions[36]. Elevated resting activity in the auditory cortex, which is part of the superior temporal gyrus, may prime the brain for enhanced vulnerability to sensory impressions.

In addition to traumatic brain injury, exposure to noxious agents may accompany psychological trauma, particularly in combat-exposed soldiers. An example was the prophylactic treatment with cholinesterase inhibitors, *e.g.*, as prescribed during the Gulf War for protection of soldiers under threat of chemical warfare[37]. Robust elevations in acetylcholine levels occur in both PTSD and during treatment with cholinesterase inhibitors. Acetylcholine interactions with receptors induce, through a calcium-dependent mechanism, the early immediate transcription factor c-Fos. This parallels the immediate stress response, since the expression of c-Fos is drastically elevated within minutes under stress[37]. Long-term, persistent brain changes occur at a very slow pace, sometimes over years. The initial phase of the feedback response probably leads to delayed cascades of the transcription of relevant genes[37].

### *Intervening stressors*

In a review of studies of delayed PTSD[38], several prospective studies provided evidence for stressful life events in the period following exposure to trauma to increase the risk of delayed PTSD. In a prospective cohort study of traumatic injury patients, in participants who had no PTSD at 3 mo, PTSD severity at 24 mo was predicted by the number of adverse life events after the 3 mo assessment, accounting for as much as 9% of the variance[28]. In deployed soldiers, the effects of postdeployment stressful life

events on the course of PTSD symptoms after return from deployment have been shown to depend on combat stress exposure as well as immune reactivity following return from deployment[26]. Postdeployment stressors occur in a context of readjustment to civilian life that may be complicated by a gradual unfolding of symptoms. In a study of veterans and their family members following deployment-relayed traumatic brain injury[39], participants reported that veterans "downplayed" their injuries and later "detached" themselves from friends, family, and communities and "denied" or were "oblivious" to their circumstances until a "wake-up call" pushed them to "get help." Most veterans said that they simply did not see that anything was wrong, while others usually attributed their issues, at least initially, to aging, stress, being tired or overworked or as a part of readjusting to civilian life[39].

### *Comorbidity*

Mental and physical disorder comorbidities may need to be considered as potentially impacting the onset and course of PTSD.

**Systemic dysregulation:** Based on prospective studies providing substantial evidence about biological abnormalities that precede the full-blown disorder, PTSD has been conceptualized as a systemic disorder characterized by metabolic and immune dysregulations that are reflected in increased rates of cardiovascular and autoimmune disease [40]. A staging model of PTSD has been proposed[40] with the initial stages being characterized by: (1) Asymptomatic downregulation of glucocorticoid receptor sensitivity and increased amygdalar reactivity; (2) Undifferentiated symptoms of mild anxiety and distress, inflammatory cytokine activation, and decreased response inhibition in the frontal cognitive systems; and (3) Subsyndromal distress with some behavioral and functional decline, increased physiological reactivity to trauma-related stimuli and startle response, and prolonged autonomic arousal on provocation[40]. A staging model implies that although an array of putative biomarkers associated with PTSD risk and symptom progression have been identified across distinct biological domains, specific biomarkers might be relevant at one time point, *e.g.*, heart rate immediately following trauma exposure, and not at another[24]. The severity of exposure to traumatic stress may be crucial in determining the risk of systemic comorbidity. In a long-term prospective study of combat soldiers and prisoners of war (POWs)[41], ex-POWs were almost 3 times more likely to develop metabolic syndrome than combat-exposed controls; blood levels of CRP were abnormally high in a large percentage of ex-POWs and were related to the level of physical and psychological stressors experienced during captivity. Chronic and delayed PTSD trajectories were associated with elevated CRP levels and metabolic syndrome[41].

**Combat stress reaction:** In a long-term prospective study of combat veterans with or without a combat stress reaction (CSR) diagnosis following participation in frontline battles with no indication of serious physical injury and other psychiatric disorders, CSR increased the risk of chronic but not delayed PTSD. Delayed PTSD, defined as onset at 2, 3, and/or 20 years after nonendorsement at year 1, was endorsed by 23.8% ( $n$ = 20) of the no-CSR group and 16.1% ($n$ = 21) of the CSR group[42].

**Dissociation:** Peritraumatic dissociation, *i.e.*, experiences of depersonalization or derealization during exposure to a traumatic event, has been suggested to predict the course of PTSD[17]. Dissociative amnesia, *i.e.*, awareness of 'time loss', may occur following exposure to trauma and may exist in delayed PTSD prior to the onset of symptoms[38]. In a large cross-sectional survey of dissociative symptoms in people with PTSD[43], depersonalization and derealization were associated with high incidence of re-experiencing symptoms. Dissociation among people with PTSD has been associated with childhood onset, exposure to a high number of prior traumatic events, and childhood adversities and is not related to trauma type[43].

**Depression:** Depressive disorders represent stress-responsive syndromes that often cooccur with PTSD, and PTSD and depressive disorders share several overlapping symptoms. A sensitization process to depressive states has been described, which predicts that with recurrent episodes of depression, there will be a progressive diminution of the role of environmental stressors[23]. The concepts of sensitization and kindling have been extensively studied in PTSD and a range of other psychiatric disorders and highlight the commonality of etiological mechanisms, particularly with depressive disorders[23].

**Alzheimer's disease:** A case report[44] described a WW2 veteran who, following several asymptomatic decades of successful adaptation to traumatic memories,

developed Alzheimer's disease and the associated cognitive autonomy loss, which subsequently led to the emergence of late-onset posttraumatic stress disorder. Animal research has provided evidence that stress biology interacts with biological mechanisms underlying neurodegenerative disease to produce comorbidities such as late-life PTSD. In a mouse model of Alzheimer's disease[45], exposure to PTSD-like inducing trauma elevated cerebrospinal fluid beta-amyloid levels in both the short (1–2 mo) and long term (6–12 mo), and Alzheimer's disease model mice displayed a stronger PTSD-like phenotype after trauma exposure than wild-type mice. An increase in beta-amyloid production was shown to directly activate corticotropin-releasing factor neurons to exacerbate HPA axis responses. Increased beta-amyloid levels might not only accelerate AD pathogenesis, leading to exacerbated amyloid plaque deposition, but also exacerbate chronic changes in behavior and corticosteroid regulation, resulting in a higher incidence of PTSD[45].

**Other behavioral and polygenic risk factors:** Polygenic risk scores based on multiple genetic variants known to contribute to psychopathology were calculated for individuals with European ancestry in a large, long-term prospective follow-up study of first responders working at the World Trade Center site (New York) following the 9/11/2001 terrorist attacks[46]. Re-experiencing, generalized anxiety, and schizophrenia polygenic risk scores were predictive of a severe PTSD symptom trajectory characterized by increasing incidence of chronic symptoms over the course of 17 years, and a depression polygenic risk score predicted a diagnosis of PTSD[46]. In a very large sample of community-dwelling women participating in the Nurses' Health Study[47], time spent viewing TV was analyzed in relation to the onset of PTSD symptoms following exposure to trauma. Among women who developed PTSD during follow-up, a significantly steeper increase in time spent viewing TV occurred prior to the onset of PTSD symptoms compared to women who did not go on to develop PTSD symptoms following trauma exposure. Women with high PTSD symptoms reported more TV viewing than trauma-unexposed women. TV viewing following trauma exposure may therefore be a marker of vulnerability for developing PTSD and a consequence of having PTSD[47].

## DISCUSSION

The neurobiological mechanisms underlying PTSD symptoms, onset, and course are heterogeneous, as they involve several interconnected systems. Studies of each of these underlying systems support their involvement in delayed reactions and/or the capacity for time-dependent increases in system reactivity. Neural mechanisms involve the neurocircuitry subserving fear conditioning, including but not limited to the hippocampus, amygdala, and prefrontal cortex. Studies in both humans and animal models consistently show time-dependent increases in activity within the neurocircuitry of fear. Neural network models emphasize the effects of iterative learning, pruning, and top-down coordination on generalization of the fear response and progressive symptom development in PTSD. Neuroendocrine mechanisms consist of autonomic nervous system responses and HPA axis responses, both of which contribute to hyperresponsiveness and sensitization to stress. Neuroinflammatory mechanisms involve immune activation due to massive psychological stress and/or the effects of traumatic brain injury, with crosstalk between the immune and endocrine systems and neurotoxic effects of excess immune system activity contributing to long-standing and delayed neuroinflammatory reactions. Finally, neurobehavioral/contextual mechanisms involve the effects of intervening stressors, multiple traumatic exposures, and mental and physical disorder comorbidities on delayed manifestations of remote traumatic exposure.

Crucial concepts emerging from the study of neurobiological mechanisms of delayed PTSD include sensitization, kindling, and generalization. Exposure to traumatic stressors may increase an individual's reactivity to subsequent stressors, a process that has been termed stress sensitization. The progressive development of symptoms of PTSD after exposure to traumatic events may be based on either neural, neuroendocrine, or neuroinflammatory sensitization to stress or combinations of these mechanisms. Heterogeneity in sensitization mechanisms may underlie differences with regard to the duration of the prodromal phase and/or the presence of prodromal symptoms.

Sensitization in conjunction with kindling may be linked to PTSD. Sensitization refers to externally induced reactions, *e.g.*, flashbacks of traumatic events induced by subsequent exposure to a similar stressor, whereas kindling refers to spontaneous activity occurring in the absence of an apparent cue. Kindling may follow sensitization, when reactions are triggered by progressively less severe stressors over time and eventually occur spontaneously. Finally, generalization that may result from the pruning of dendrites within neural fear networks leads to increased responsiveness to increasingly less specific contextual cues and cross sensitization to heterotypic stressors.

Long delayed effects of traumatic exposures are likely to also involve neurobehavioral and contextual mechanisms. Exposure to specific stressful life events resembling remote traumatic events may trigger specific memories that initiate a cascade of neurobiological dysregulation characteristic of PTSD. Indeed, the impact of repeated stressor exposures and contextual reminders has been demonstrated across several human and animal studies. The effects of stressors or trauma reminders may operate in concert with comorbid mental or physical disease and the associated sense of vulnerability that could increase the salience of the triggering event(s).

These findings have implications for diagnostic assessment in both treatment and forensic settings. Delayed expression of trauma- and stressor-related disorders requires careful individual assessment of the trauma history, intervening stressors, and development of symptoms of mental and physical disorders. In addition to PTSD, other specific trauma- and stressor-related disorders and mental and physical disorder comorbidities need to be evaluated with regard to the potential causal link between traumatic exposure and delayed symptoms, while taking into account the frequently substantial etiological overlap.

Subthreshold PTSD symptoms may indicate clinically significant distress and functional impairment. Findings from a Korean cross-sectional study among 45,698 active firefighters indicated that the presence of subthreshold PTSD symptoms was associated with suicidal behavior, depression, alcohol use problems, and functional impairment[48]. Assessment of a history of TBI is mandatory in help-seeking, trauma-exposed individuals, specifically in soldiers and veterans, who are at increased risk of PTSD with delayed expression[2-4]. Foreseeable stressors and resource losses, including unemployment and physical impairments, may be an effective target for secondary prevention of psychological distress. Pharmacological prevention of PTSD following exposure to potentially traumatic events is not generally recommended, and there is insufficient evidence to recommend selective, indicated pharmacological prevention[49], with the possible exception of hydrocortisone[50], a corticosteroid drug with immunosuppressive effects. Our data provide support for exploring the preventive potential of normalizing immune reactivity by pharmacological means.

Limitations of the current review need to be considered. These include the methodological limitations of some of the included studies, such as small sample sizes that may prevent studies from obtaining sufficient statistical power to detect associations relevant to delayed PTSD, the use of self-report measures possibly leading to response biases, memory bias in studies that rely on retrospective reporting, and limited durations of follow-up that prevented the detection of long-delayed cases. Indeed, there is a paucity of long-term prospective follow-up studies investigating the impact of intervening stressors on delayed PTSD onset. Limitations of the current review include the selection of studies addressing delayed expression of PTSD and neurobiology. Since these studies represent a subset of studies addressing the neurobiology of PTSD, this selection precludes exhaustive descriptions of the state of knowledge regarding all involved mechanisms.

## CONCLUSION

In conclusion, the capacity of PTSD to occur with delayed onset may result from the interaction of an array of underlying neurobiological mechanisms that may influence the likelihood of manifesting prodromal symptoms preceding the onset of full-blown PTSD. Highly specific contextual reminders, stressful life events or vulnerability associated with comorbid physical or mental disease may trigger the exacerbation of previously contained distress associated with traumatic memories.

## ARTICLE HIGHLIGHTS

### *Research background*

Posttraumatic stress disorder (PTSD) with delayed expression occurs in people who develop PTSD at least six mo following exposure to a potentially traumatic event. During the prodromal phase or delay interval between the traumatic event and the onset of the disorder, subthreshold symptoms are often present, although long delay intervals without prodromal symptoms have rarely been reported. This study reviews neurobiological mechanisms underpinning the occurrence of a prodromal phase with or without prodromal symptoms.

### *Research motivation*

Delayed expression of PTSD may present diagnostic challenges in clinical settings as well as in litigation contexts. Insight in neurobiological mechanisms is crucial to optimize diagnostic assessment and management.

### *Research objectives*

To identify and characterize neurobiological mechanisms and pathways underlying delayed expression of PTSD and to obtain an overview of types of supporting evidence.

### *Research methods*

We performed a scoping review of neurobiological studies in humans and animals and reviews of such studies. Records were eligible if they reported about studies on trauma and PTSD, delayed onset, neurobiology, and causal mechanisms or risk factors.

### *Research results*

Following the search and selection, 38 studies were included in the review. Neural, neuroendocrine, and neuroinflammatory mechanisms have been implicated in progressive PTSD symptom expression over time. Neurobehavioral and contextual pathways complement these mechanisms.

### *Research conclusions*

A variety of interconnected systems underlies the heterogeneity in PTSD symptom expression over time, contributing to sensitization, kindling, and generalization.

### *Research perspectives*

Delayed expression of trauma- and stressor-related disorders requires careful individual assessment of the trauma history, intervening stressors, and development of symptoms. Assessment of a history of TBI is mandatory in help-seeking, trauma-exposed individuals, specifically in soldiers and veterans, as this may be associated with symptom progression over time. Efforts to avert foreseeable stressors and resource losses may contribute to secondary prevention of psychological distress. Future research should explore the preventive potential of normalizing immune reactivity by pharmacological means.

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SYSTEMATIC REVIEWS

# Impacts of acupressure treatment on depression: A systematic review and meta-analysis

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## Abstract

### *BACKGROUND*

Depression is recognized as a major public health problem with a substantial impact on individuals and society. Complementary therapies such as acupressure may be considered a safe and cost-effective treatment for people with depression. An increasing body of research has been undertaken to assess the effectiveness of acupressure in various populations with depression, but the evidence thus far is inconclusive.

### *AIM*

To examine the efficacy of acupressure on depression.

### *METHODS*

A systematic literature search was performed on PubMed, PsycINFO, Scopus, Embase, MEDLINE, and China National Knowledge (CNKI). Randomized clinical trials (RCTs) or single-group trials in which acupressure was compared with control methods or baseline in people with depression were included. Data were synthesized using a random-effects or a fixed-effects model to analyze the impacts of acupressure treatment on depression and anxiety in people with depression. The primary outcome measures were set for depression symptoms. Subgroups were created, and meta-regression analyses were performed to explore which factors are relevant to the greater or lesser effects of treating symptoms.

### *RESULTS*

A total of 14 RCTs (1439 participants) were identified. Analysis of the between-group showed that acupressure was effective in reducing depression [Standardized mean differences (SMDs) = -0.58, 95%CI: -0.85 to -0.32, $P < 0.0001$] and anxiety (SMD = -0.67, 95%CI: -0.99 to -0.36, $P < 0.0001$) in participants with mild-to-moderate primary and secondary depression. Subgroup analyses suggested

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**
Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

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that acupressure significantly reduced depressive symptoms compared with different controlled conditions and in participants with different ages, clinical conditions, and duration of intervention. Adverse events, including hypotension, dizziness, palpitation, and headache, were reported in one study.

*CONCLUSION*
The evidence of acupressure for mild-to-moderate depressive symptoms was significant. Importantly, the findings should be interpreted with caution due to study limitations. Future research with a well-designed mixed method is required to consolidate the conclusion and provide an in-depth understanding of potential mechanisms underlying the effects.

**Key Words:** Acupressure; Depression; Mild-to-moderate depressive symptoms; Systematic review; Meta-analysis

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**Core Tip:** Acupressure is effective on mild-to-moderate depressive symptoms. However, no confirmed evidence is available about the impacts of acupressure on patients with severe depressive disorders. This is the first study investigating the impacts of acupressure on depression among clinical and general populations.

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## INTRODUCTION

Depression is a prevalent and debilitating mental disorder that is estimated to affect more than 264 million people worldwide[1]. Individuals with depression commonly experience dysfunctional symptoms, including undesirable mood, impaired concentration, poor quality of sleep, and a high risk of suicide. Up to 15% of clinically depressed patients eventually commit suicide[2]. Besides, depression is the commonest comorbidity of chronic physical illnesses, such as cardiovascular and respiratory diseases, diabetes, arthritis and osteoporosis, and cancer[3]. Moreover, evidence shows that depression is also a risk factor for physical illnesses[4]. It will become the second major contributor to the general medical service burden by 2030[5]. Thus, depression needs to be considered when providing integrated treatments for common chronic diseases.

In primary care, subthreshold and mild depression are most often managed with psychological interventions, such as cognitive-behavioral therapies, interpersonal therapy, and psychological counseling. Antidepressant medication is usually prescribed for moderate-to-severe depression[6]. However, medications are associated with drug dependence and side effects, which negatively impact adherence. Psychological therapies require considerable time and resources, resulting in high drop-out rates and unsustainable effects. Surveys have shown that self-help and complementary therapies for depression were extensively reported[7,8].

Acupressure is a non-invasive complementary and alternative technique that shares common characteristics with acupuncture[9]. It is defined as the stimulation on acupuncture points located along meridians (also known as "acupoints") using fingers, hands, knuckles, or dull instruments to exert pressure, leading to a sensation of soreness, numbness, and distention[10]. According to the core concept of traditional Chinese medicine (TCM) theory, acupressure stimulates the meridian. It restores health by balancing the "qi" flow, which could be described as bioenergy[11]. Results from studies of acupuncture have suggested that effects on neurotransmitter levels of serotonin and noradrenaline may be one of the potential mechanisms underlying the therapeutic effects. On the other hand, the pressure exerted on the acupoints regulates the sympathetic and parasympathetic nervous systems to create feelings of calm and

relaxation[12].

Acupressure has received increased attention for the alleviation of pain or discomfort associated with physical illnesses, injuries, and surgical operations in different populations, ranging from children[13] to the elderly[14]. Furthermore, the benefits of acupressure in psychological well-being have also been observed. While emerging evidence shows that acupressure has encouraging and promising effects on depression[15,16], there has been no systematic review and meta-analysis of its effectiveness for this condition. The present study aimed to synthesize findings of randomized clinical trials (RCTs) and quantify the effectiveness of acupressure for the treatment of depression in adults. Moreover, selection of acupoints and manipulation techniques, adverse events, drop-out rates, and quality of the included RCTs are described for treatment decision-making.

## MATERIALS AND METHODS

This systematic review and meta-analysis were performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guideline.

### *Literature search*

The following electronic databases were systematically searched until December 2020: PubMed, PsycINFO, Scopus, Embase, MEDLINE, and China National Knowledge (CNKI). The main keywords used were "acupressure" OR "finger massage" OR "acupoint massage" OR "shiatsu" AND "depress*" OR "mental health" OR "mental disorder*" OR "psychiatric disorder*" OR "mood disorder*" OR "bipolar disorder.*" Reference lists of retrieved studies and review articles were screened for additional references.

We screened the studies in two phases. First, two review authors (He J and Chen T) independently screened the titles and the abstracts. Second, the full text of potentially eligible studies was retrieved and assessed independently by the same two authors. Any disagreement between the review authors was resolved by a third review author (Lin J).

### *Study selection*

Inclusion criteria were defined using the PICO (Population, Intervention, Comparison, and Outcomes)[17]: (1) Were clinical trials, including RCTs and non RCTs that included acupressure as one of the study groups; (2) Used acupressure as the sole intervention compared with the control condition of either sham control or standard control (*e.g.*, standard care); (3) Used a sample of participants aged 18 years old or above; and (4) Were published in either English or Chinese.

Studies were excluded: (1) If they did not target depression as one of the outcome measures before and after acupressure intervention; or (2) If they used acupressure as part of a multi-component intervention.

### *Data extraction*

All data were extracted from studies by two review authors (He J and Chen T) according to predefined criteria, including: (1) The first author, year, and country of publication; (2) The number and characteristics of the participants; (3) The regimen of the experimental and control interventions; (4) The manipulation techniques of acupressure; (5) Drop-out rate; (6) Baseline depressive symptoms, and (7) Outcome measures. For the purpose of this review, our primary outcome was the change of depressive symptoms before and after an intervention. That was evaluated using any standardized clinical measures, including Beck Depression Inventory (BDI), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), Depression Anxiety Stress Scales (DASS), Major Depression Inventory (MDI), and Edinburgh Postnatal Depression Scale (EPDS). The anxiety level, manipulation, and frequency of acupressure, drop-out rate, and adverse events were reported as the secondary outcomes. Discrepancies between the two reviewers were resolved by consensus decision.

### *Quality and risk of bias evaluation*

The quality of reporting for the acupressure trials was evaluated independently by two authors (He J and Chen T) using revised STRICTA (Standards for Reporting

Interventions in Clinical Trials of Acupuncture). A total of 10 items were applicable to the acupressure studies, which covered acupressure rationale, pressure details (instead of needling details), treatment regimen, other components of treatment, practitioner background, and control intervention[18]. The acupressure procedure was considered well-reported if at least six out of the ten STRICTA items were reported.

The methodological quality of identified studies was assessed according to the six domains in the Cochrane risk of bias tool. These are random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, and selective outcome reporting. Each domain was rated as "high" (seriously weakens confidence in the results), "unclear," or "low" (unlikely to significantly alter the results). Given the nature of the intervention, it was difficult to blind the personnel who applied the acupressure, so only the participants and outcome assessors were blinded. To follow the guidelines recommended by the Cochrane Back Review Group, a compliance threshold of < 50% of the criteria was associated with bias[19]. Studies that met at least four domains with no serious flaws were considered as having a low risk of bias. If necessary, attempts were made to contact authors to obtain additional information.

Funnel plots were constructed to assess the risk of publication bias across series for all outcome measures. The Egger regression was used to test the asymmetry of the Funnel plots, with $P > 0.1$ indicating no publication bias.

### Data synthesis and statistical analysis

According to Jackson & Turner[20], meta-analysis was performed when at least five studies with similarities in clinical characteristics and with no domain rated as having a high risk of bias were included. Meta-analyses were conducted using the changes of the scores between pre- and post-intervention measured by different scales. Heterogeneity among studies was evaluated by calculating the $I^2$ statistic and $\chi^2$ test (assessing the $P$ value) using Review Manager 5 software (V5.4, The Nordic Cochrane Centre, Copenhagen). If the $P$ value was < 0.05 and $I^2 > 50\%$, we considered the heterogeneity to be substantial. A random-effect model was used to combine the data if significant heterogeneity existed. Standardized mean differences (SMDs) with 95%CI were used for continuous outcomes. The magnitude of the overall effect size was calculated based on the pooled SMD. Following Cohen's categories, the effect sizes of 0.20, 0.50, and 0.80 were considered small, medium, and large, respectively[21].

Sensitivity analyses and subgroup analyses were performed to investigate the effects of acupressure with different study designs, ages of participants, control conditions, and treatment duration. Meta-regression was also performed to identify the potential predictors of the effects of acupressure on depression.

## RESULTS

### Study selection

A PRISMA flow diagram is shown in Figure 1. The search initially found 552 articles. After screening the title and abstract, 46 of which were examined full text. Of these, 16 were excluded based on the inclusion/exclusion criteria, and 16 Chinese articles were excluded due to their low quality, resulting in a total of 14 eligible articles for systematic review. There was no publication bias based on the Funnel plots and Egger-regression test results (Figure 2). Fourteen RCTs involving 1439 participants were included for meta-analyses.

### Study characteristics

The main characteristics of the included studies are described in Table 1. The sample size of the 14 studies varied from 12 to 288. Four studies focused on old participants (aged 65 or above)[22-25], while the remaining studies recruited participants from 20-64 years. Ten studies recruited participants with chronic diseases, including chronic obstructive pulmonary disease[22], lung cancer[26], acute myocardial infarction[27], breast cancer[28], low back pain[29], multiple sclerosis[30], hemodialysis[31-33], and unilateral knee osteoarthritis[34]. Three studies recruited patients with depression[24,25,35]. One study was for patients with Alzheimer's disease comorbided with depression[23]. None of them included patients with major depressive disorders (MDD), and the overall severity of depressive symptoms in the participants was mild to moderate. The drop-out rate ranged from 0 to 28.8%, with a mean of 10.2%.

**Table 1 Characteristics of included studies**

| Ref. | Type of study | Participants (sample size, mean age ± SD) | Drop-out rate, *n* (%) | Treatment (frequency and duration) | Manupilation techniques (acupoints composition, and techniques used) | Control | Depressive symptoms at baseline M (SD) | Outcome measures |
|---|---|---|---|---|---|---|---|---|
| Bergmann *et al*[27], 2014 | RCT | Acute myocardial infarction with PPS acore ≥ 60 (213, 61.0 ± 8.1) | 32 (15.0) | Acupressure (45 min twice a day for 12 wk) | Figure pressure on two points at the sternum | Treat as usual (TAU) | MDI: 8.9 (7.4), PPS: 81 (13) | MDI, QOL, WHO-5's well-being index, PPS |
| Dehghanmehr *et al*[31], 2020 | RCT | Hemodialysis with no severe depression and anxiety (60, 39.2 ± 11.32) | 0 | Acupressure (8 min, 3 d weekly for 4 wk) | Figure pressure on acupoint Saiyinjiao | Sham, TAU | BDI: 31.44 (20.95), STAI: 47.60 (7.04) | STAI, BDI |
| Hmwe *et al*[32],2015 | RCT | Hemodialysis with depressive symptom (108, 58.06 ± 11.4) | 0 | Acupressure (12 min per session, 3 sessions weekly for 4 wk) | Figure pressure on acupoints Yintang, Shenmen, and Taixi | TAU | DASS depression: 10.93 (8.38), GHQ total: 25.33 (12.56) | DASS, GHQ-28 |
| Honda *et al*[35], 2012 | RCT | College students with depressive symptoms (25, 33.2 ± 10.0) | Not mentioned | Acupressure (30 seconds per session, 3 sessions daily for 4 wk) | Figure pressure on six points on the neck (three points on the left and right side each) | TAU | BDI: 55 (10) | BDI |
| Kalani *et al*[33], 2019 | RCT | Hemodialysis with BDI score ≥ 10 (96, 53.4 ± 13.9) | 0 | Acupressure (18 min per session, 3 sessions weekly for 4 wk) | Figure pressure on acupoints Sanyinjiao, Zusanli, Yanglingquan, Yongquan, Shenshu, and Shenmen | Sham, TAU | BDI: 27.5 (9.1) | BDI |
| Lanza *et al*[23], 2018 | RCT | Alzheimer with CDR score ≤ 2 (12, 80.0 ± 9.0) | 0 | Acupressure (40 min weekly for 40 wk) | Figure pressure on relevant trigger points of the meridians | TAU | GDS: 13 (2) | GDS, MMSE, ADL, IADL |
| Molassiotis *et al*[24], 2020 | RCT | Depression with GDS score ≥ 8 (118, 79.5 ± 14.5) | 34 (28.8) | Acupressure (5 min per session, twice weekly for 12 wk) | Figure pressure on acupoints Zusanli, Zhongfu, Shenmen, Taichong, Baihui | Sham, TAU | GDS: 10.6 (2.1), GHQ: 18.8 (5.9) | GDS, PSQI |
| Rahimi *et al*[30], 2020 | RCT | Multiple sclerosis with EDSS score = 0-5.5 (106, 20-45 years old) | 20 (18.9) | Acupressure (15 min every day for 4 wk) | Figure pressure on acupoints Shenmen and Yintang | Sham | DASS depression: 11.48 (3.1) | DASS, FSS |
| Rani *et al*[34], 2020 | RCT | Knee osteoarthritis with Kellgrene Lawrance scale grade 2 or 3 (212, 58.07 ± 11.22) | 11 (5.2) | Acupressure (15 min per session, 2 sessions per day, 5 d weekly for 32 wk) | Figure pressure on acupoints Liangqiu, Dubi, Zusanli, Yinglingquan, Xuehai, Yanglingquan | TAU | DASS depression: 14.56 (8.63) | DASS, VAS, GHQ-12, BMSWBI, WHOQOL-BREF |
| Tang *et al*[26], 2014 | RCT | Lung cancer undergoing chemotherapy (40, 64.4 ± 9.2) | 10 (25) | Acupressure (3 min once every morning for 20 wk) | Figure pressure on acupoints Hegu, Zusanli, and Sanyinjiao | Sham | HADS: 7.29 (4.39), ECOG-PSR: 11 (45.8) | HADS, TFRS, ECOG-PSR, PSQI |
| Tseng *et al*[25], 2020 | RCT | Depression with GDS score > 5 (47, 82.78 ± 6.88) | 8 (17.0) | Acupressure with a magnetic bead (7 d weekly for 2 wk) | Magnetic bead on ear Shenmen point | Sham | GDS: 8.71 (2.31) BAI: 13.63 (7.36) | GDS, BAI |
| Wu *et al*[22], 2007 | RCT | Chronic obstructive pulmonary disease with depressive symptom (44, 73.0 | 0 | Acupressure (16 min per session, 5 sessions weekly for 4 wk) | Figure pressure on acupoints Dazhui, Tiantu, Shousaili, Feishu, Shenshu | Sham | GDS score at basline not available | GDS, DVAS |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | ± 9.7) | | | | | | |
| Yu *et al*[29], 2020 | RCT | Postpartum wome with low back pain score ≥ 1 (70, 34.4 ± 4.8) | 0 | Acupressure (10 min per session, 5 sessions weekly for 4 wk) | Figure pressure on acupoints Shenhu, Dachangshu, Guanyuanshu, Weiyang, and Sanyinjiao | Sham | EPDS: 9.4 (4.5) | EPDS, RMDQ, ODI, VAS |
| Zick *et al*[28], 2018 | RCT | Breast cancer with depressive symptom (288, 60.5 ± 10.0) | Not mentioned | Acupressure (30 min every day for 10 wk) | Figure pressure on acupoints Hegu, Zusanli, Sanyinjiao, Taixi, Baihui, and Qihai | Sham, TAU | HADS: 6.2 (3.2) | VAS, BPI |

ADL: Activity of daily living; BAI: Beck anxiety inventory; BDI: Beck depression inventory; BMSWBI: Body-mind-spirit well-being inventory; BPI: Brief pain inventory; CDR: Clinical dementia rating; COPD: Chronic obstructive pulmonary disease; DASS: Depression anxiety stress scales; DVAS: Dyspnea visual analogue scale; ECOG-PSR: Eastern cooperative oncology group performance status rating; EDSS: Expanded disability status scale; EPDS: Edinburgh postnatal depression scale; FSS: Fatigue severity scale; GDS: Geriatric depression scale; GHQ: General health questionnaire; HADS: Hospital anxiety and depression scale; IADL: Instrumental ADL; MDI: Major depression inventory; MMSE: Mini mental state examination; ODI: Oswestry disability index; PFS: Piper fatigue scale; PPS: Pressure pain sensitivity; PSQI: Pittsburgh sleep quality index; QOL: SF-36 quality of life; RMDQ: Roland-morris disability questionnaire; STAI: Spielberger state-trait anxiety inventory; TAU: treat as usual; TFRS: Tang fatigue rating scale; VAS: Visual analog scale.

### *Quality and risk of bias assessment*

Table 2 describes the standards of reporting for the included trials. The standards reflect the revised STRICTA criteria (2010). All studies reported the frequency of treatment, the setting and context of intervention, and the control condition. Only one study did not mention the rationale of acupressure[27]. Three studies did not report the acupoints used in the intervention[23,27,35]. All studies provided a detailed description of the method/materials used for acupressure. All studies except two[23,25] specified the duration of pressure retention. Two studies reported other components, such as the details of other interventions[23,26].

Risk of bias was assessed and summarized in Figure 3. Fourteen studies were described as "randomized," of which eight studies reported detailed randomization methods[25,26,28,30-34]. All studies reported allocation concealment in detail. Blinding of outcome assessments was sufficiently carried out in 13 studies, with only one study providing no detailed description[26]. Five of them expressly stated a completion rate of their participants and were at low risk of attrition bias[22,24,26,27,34], while the others gave no details of missing data. All studies presented the outcomes clearly and were rated as having a low risk of selection bias. Overall, all studies were rated low in at least four domains, and therefore, were considered as having low risk of bias.

### *Rationale of acupoint selection*

Among the included studies, five of them applied three acupoints or fewer[25,26,30-32], and six studies applied more than three acupressure points[22,24,28,29,33,34]. However, three studies did not report the specific acupoints used for the intervention [23,27,35]. The most used acupoints were Zusanli, Sanyinjiao, and Shenmen.

**Table 2 Quality assessment using standards for reporting interventions in clinical trials of acupuncture for the included studies**

| Ref. | Acupressure details | | | | | | Other components of treatment | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Acupressure rationale | Acupoints used | Materials used for acupressure | Frequency of acupressure | Acupressure retention | Description of method/materials used for acupressure | Other components | Setting and context | Practitioner background | Control intervention |
| Bergmann (2014) | NR | NR | Y | Y | Y | Y | NR | Y | Y | Y |
| Dehghanmehr (2020) | Y | Y | Y | Y | Y | Y | NR | Y | NR | Y |
| Hmwe (2015) | Y | Y | NR | Y | Y | Y | NR | Y | NR | Y |
| Honda (2012) | Y | NR | NR | Y | Y | Y | NR | Y | Y | Y |
| Kalani (2019) | Y | Y | Y | Y | Y | Y | NR | Y | NR | Y |
| Lanza (2018) | Y | NR | NR | Y | NR | Y | Y | Y | NR | Y |
| Molassiotis (2020) | Y | Y | Y | Y | Y | Y | NR | Y | NR | Y |
| Rahimi (2020) | Y | Y | Y | Y | Y | Y | NR | Y | Y | Y |
| Rani (2020) | Y | Y | NR | Y | Y | Y | NR | Y | Y | Y |
| Tang (2014) | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Tseng (2020) | Y | Y | NR | Y | NR | Y | NR | Y | NR | Y |
| Wu (2007) | Y | Y | Y | Y | Y | Y | NR | Y | Y | Y |
| Yu (2020) | Y | Y | NR | Y | Y | Y | NR | Y | NR | Y |
| Zick (2018) | Y | Y | Y | Y | Y | Y | NR | Y | Y | Y |

NR: Not reported; Y: Reported.

All studies mentioned that selection of acupoints was based on the TCM principles and aimed to improve the body's natural self-healing capacity by regulating and balancing Qi. Three studies[22,24,29] selected the acupoints based on a thorough literature review of the effects of acupressure on depression. Hmwe *et al*[32] reported that two TCM specialists from local universities had reviewed the selection of acupoints.

### *Manipulation technique*

The duration of acupressure interventions varied across studies. They ranged from 5 s to 4 min on each acupressure point and from 30 s to 45 min per session, with an

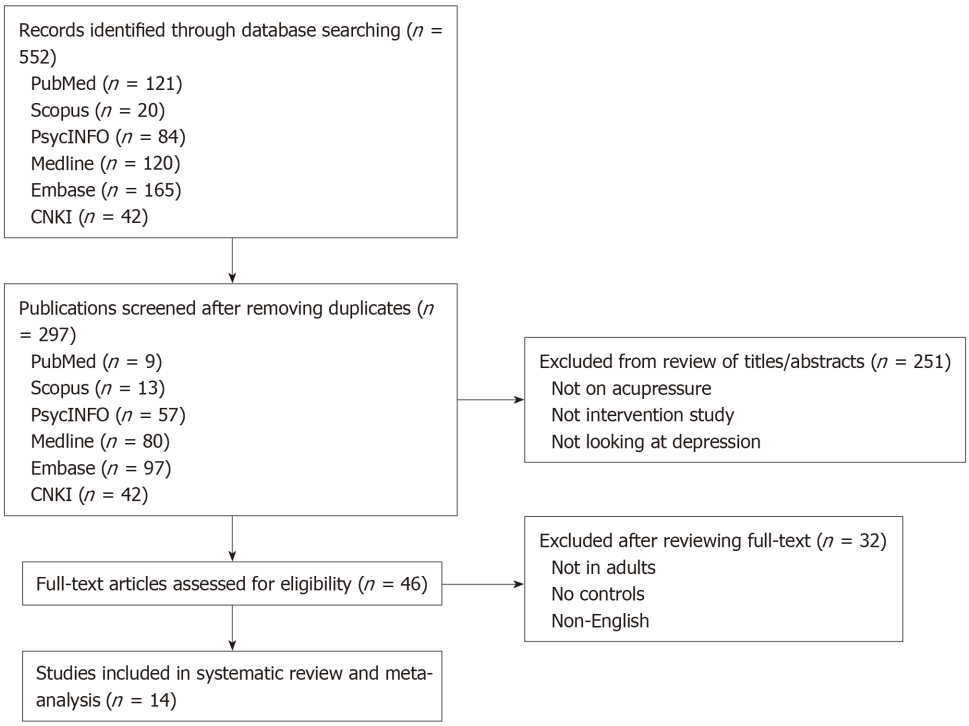


**Figure 1 Flow diagram for data collection and analysis.**

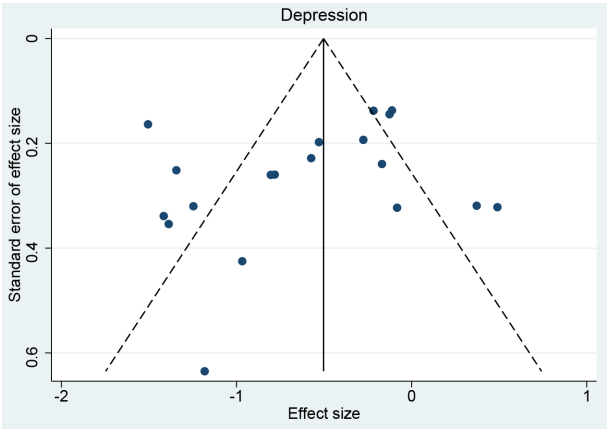


**Figure 2 Funnel plots of studies with depression outcomes.**

average of 15-20 min per session in most studies. The study duration ranged from 2 wk[25] to 40 wk[23]. All studies applied acupressure with finger pressure, except one study which applied the magnetic bead at relevant points[25].

The background of the therapists delivering acupressure differed in the included studies: Two trials involved research personnel[22,26], two trials employed allied health professionals[27,35], and three trials involved an acupuncturist[28,33,34]. Either "sham" or "treat as usual" (TAU) were used as controls. Nine studies employed sham stimulation that located around the true acupoints and were irrelevant to the treatment of depression[22,24-26,28-31,33]. Four studies had both a sham and a TAU control group[24,26,28,33]. The other studies used TAU as the control group.

### *Overall effectiveness of acupressure on depression*

Three trials adopted BDI[31,33,35]; four trials adopted GDS[22-25]; two trial used HADS[26,28]; three trials used DASS[30,32,34]; one trial used MDI[27], and the other trial used EPDS for depression[29]. Similar findings were reported in all studies that the acupressure group had a greater reduction in depression after treatment than the sham or the TAU control groups.

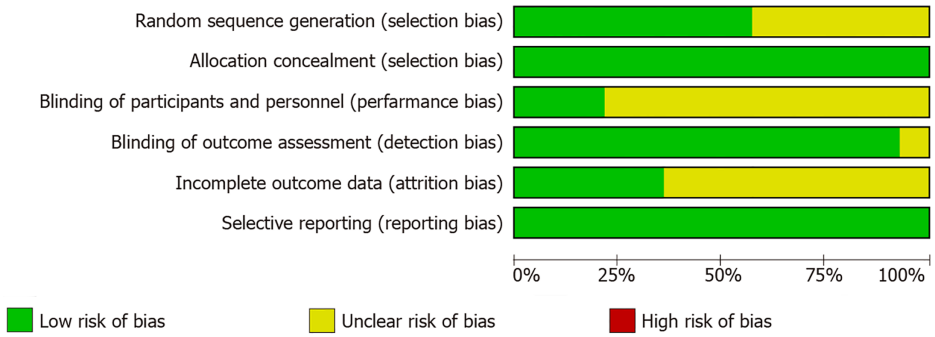


**Figure 3 Risk of bias evaluation for the included studies.**

Meta-analysis of these 14 RCTs suggested a lager overall improvement in the depression level in the acupressure group than sham or TAU control groups (SMD = -0.58; 95%CI = -0.85 to -0.32; $P < 0.0001$; $I^2 = 84\%$; $\chi^2 = 110.96$; $P < 0.0001$) (Figure 4). The combined effect size was 4.39, which equals to a small effect size according to Cohen's categories.

### *Effectiveness of acupressure on depression with different control conditions*

Subgroup analyses were performed in studies using different control groups (Figure 4). The combined results of 10 studies using TAU control groups showed a greater reduction in depression level in the acupressure group with a small effect size (SMD = -0.34; 95%CI = -0.63 to -0.05; $P = 0.02$; $I^2 = 76\%$; $\chi^2 = 37.78$; $P < 0.00001$; $Z = 2.33$). Similar results were shown in the nine studies using sham controls with a moderate effect size (SMD = -0.83; 95%CI = -1.2 to -0.46; $P < 0.00001$; $I^2 = 80\%$; $\chi^2 = 39.77$; $P < 0.00001$; $Z = 4.42$).

### *Effectiveness of acupressure on depression with different treatment durations*

Subgroup analyses were also performed in studies with different durations. The combined results of eight studies with a duration of 2-4 wk showed acupressure significantly reduced depression levels compared to sham or TAU controls with a moderate effect size (SMD = -0.67; 95%CI = -0.99 to -0.35; $P < 0.0001$; $I^2 = 71\%$; $\chi^2 = 30.82$; $P = 0.0003$; $Z = 4.16$) (Figure 5). Significant reductions in the depression levels were found in six studies with a duration of more than 4 wk in the acupressure group compared to the sham or TAU controls with a small effect size (SMD = -0.48; 95%CI = -0.9 to -0.07; $P = 0.02$; $I^2 = 90\%$; $\chi^2 = 78.05$; $P < 0.00001$; $Z = 2.28$) (Figure 6).

### *Effectiveness of acupressure on depression in different participants*

Subgroup analyses were also performed in studies with different participants. The combined results of eleven studies in participants with depressive symptoms comorbidded with chronic diseases showed acupressure significantly reduced depression level compared to sham or TAU controls with a small effect size (SMD = -0.48; 95%CI = -0.77 to -0.19; $P = 0.001$; $I^2 = 85\%$; $\chi^2 = 91.96$; $P < 0.00001$; $Z = 3.23$) (Figure 7). Significant reductions of depressive symptoms were also found in three studies in participants with depression with a moderate effect size (SMD = -1; 95%CI = -1.40 to -0.60; $P < 0.00001$; $I^2 = 48\%$; $\chi^2 = 5.79$; $P = 0.12$; $Z = 4.91$) (Figure 8).

### *Effectiveness of acupressure on depression in participants of different ages*

Subgroup analyses were also performed in studies with different ages. The combined results of ten studies with individuals aged 20-64 showed acupressure significantly reduced depression levels compared to the sham or TAU controls with a small effect size (SMD = -0.42; 95%CI = -0.71 to -0.14; $P = 0.004$; $I^2 = 85\%$; $\chi^2 = 84.08$; $P < 0.00001$; $Z = 2.89$) (Figure 9). Significant reductions in depression levels after acupressure interventions with a large effect size were also found in four studies in participants over 65 years old (SMD = -1.09; 95%CI = -1.45 to -0.72; $P < 0.00001$; heterogeneity: $I^2 = 43\%$; $\chi^2 = 7.01$; $P = 0.14$; $Z = 5.82$) (Figure 10).

### *Effects of acupressure on depression using different acupoints*

Subgroup analyses were performed in studies using different numbers of acupoints. The combined results of RCTs with no more than 3 acupoints (3 included) (SMD = -0.36; 95%CI = -0.56 to -0.17; $P < 0.0001$; $I^2 = 79\%$; $\chi^2 = 28.86$; $P = 0.0003$; $Z = 3.63$)

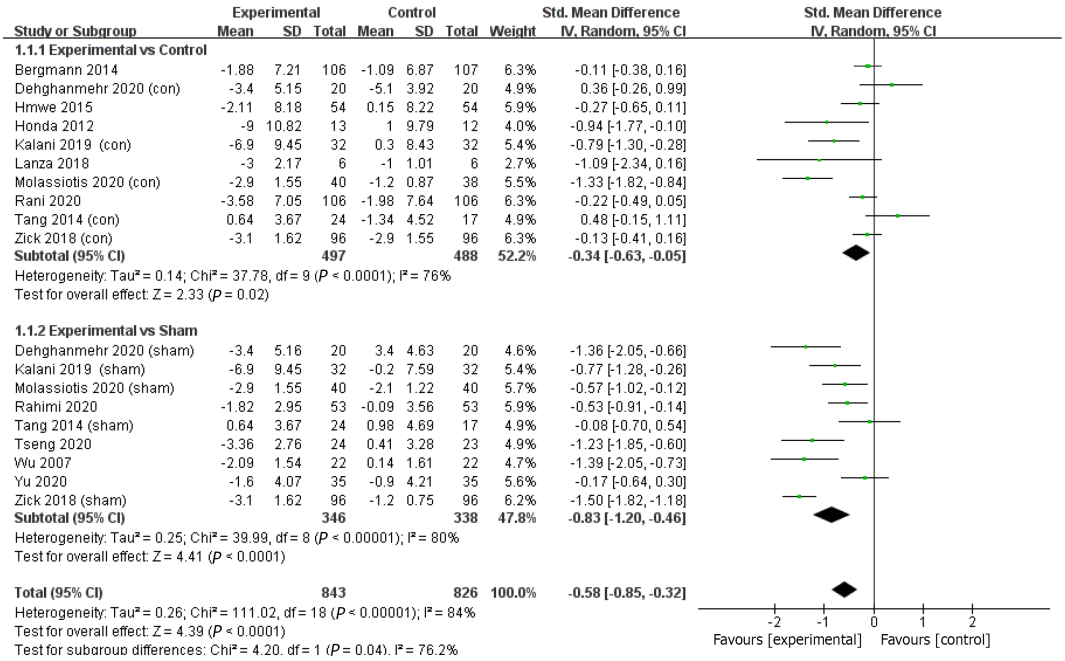


**Figure 4 Effects of acupressure on depression.** 1.1.1. Subgroup meta-analyses of studies using treat-as-usual (TAU) as controls; 1.1.2. Subgroup meta-analyses of studies using Sham controls.

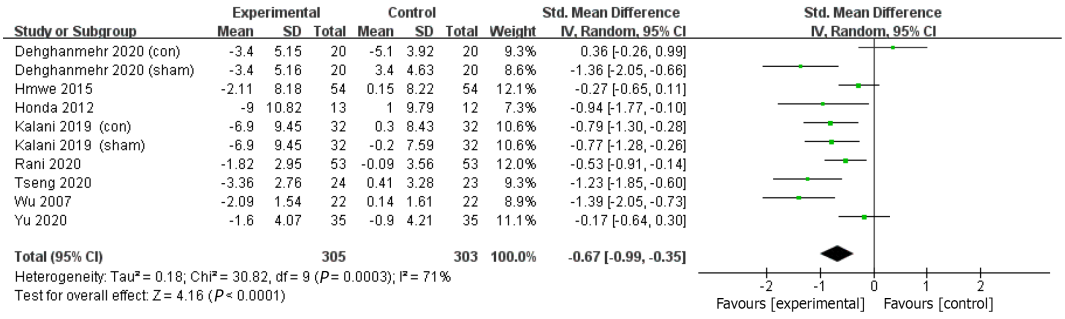


**Figure 5 Effects of acupressure on depression with treatment duration of 2 to 4 wk.**

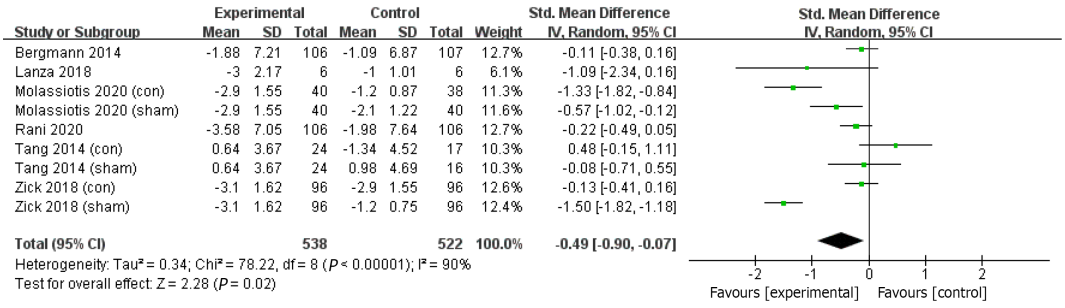


**Figure 6 Effects of acupressure on depression with treatment duration of more than 4 wk.**

(Figure 11), and more than 3 acupoints showed significant effects on depression in acupressure compared to controls with moderate effects (SMD = -0.74; 95%CI = -1.13 to -0.36; $P = 0.0002$; $I^2 = 88\%$; $\chi^2 = 66.63$; $P < 0.00001$; $Z = 3.75$) (Figure 12).

Subgroup analyses were also performed in studies using the three most used acupoints. The combined results of the studies showed significant beneficial effects on depression in the acupressure treatment group compared to controls, with a large effect size for Sanyinjiao (SMD = -0.54; 95%CI= -0.69 to -0.39; $P < 0.00001$; heterogeneity: $I^2 = 89\%$; $\chi^2 = 72.17$; $P < 0.00001$; $Z = 7.03$), a moderate effects size for Shenmen

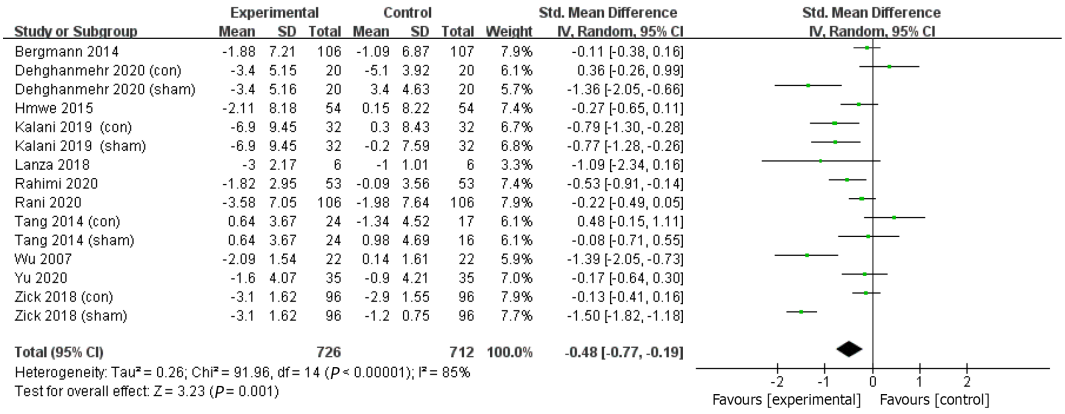


**Figure 7 Effects of acupressure on depressive symptoms in participants with chronic diseases.**

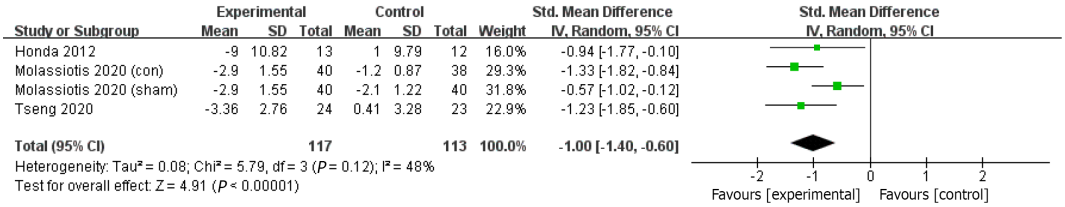


**Figure 8 Effects of acupressure on depressive symptoms in participants with primary depression.**

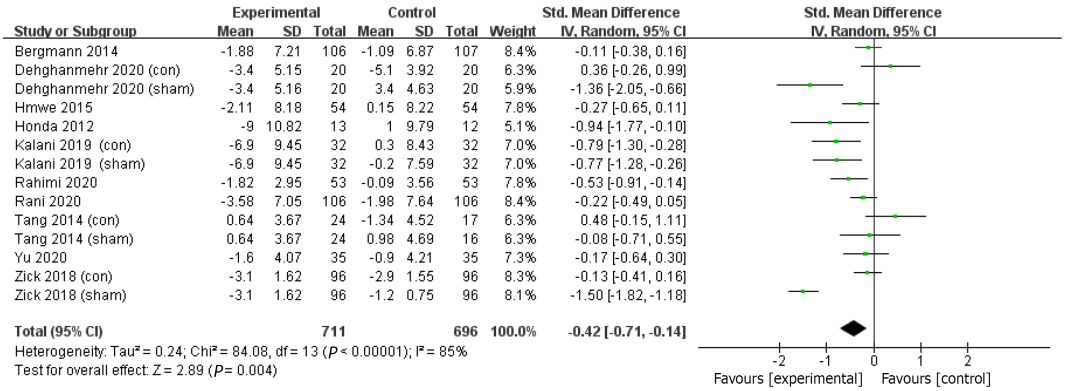


**Figure 9 Effects of acupressure on depression in participants aged 18-64 years old.**

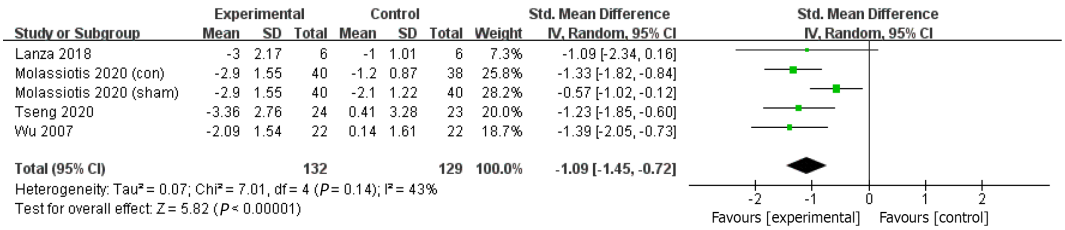


**Figure 10 Effects of acupressure on depression in participants aged 65 years old or above.**

(SMD = -0.75; 95%CI = -1.03 to -0.47; $P < 0.00001$; $I^2 = 60\%$; $\chi^2 = 15.14$; $P = 0.02$; $Z = 5.20$) and a small effect size for Zusanli (SMD = -0.56; 95%CI = -0.97 to -0.15; $P = 0.008$; $I^2 = 89\%$; $\chi^2 = 71.65$; $P < 0.00001$; $Z = 2.67$).

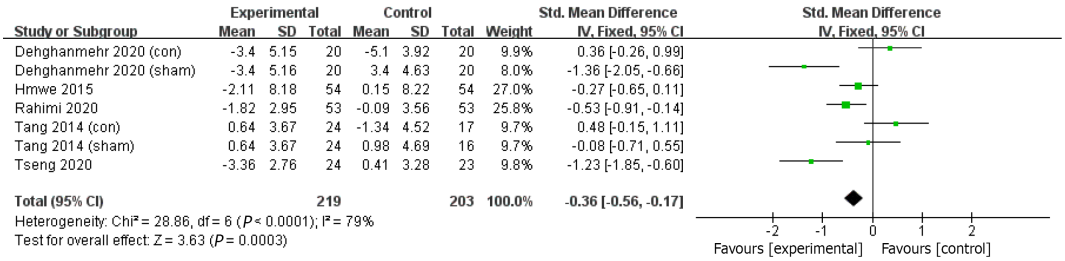


**Figure 11 Effects of acupressure using no more than 3 (3 included) acupoints on depression.**

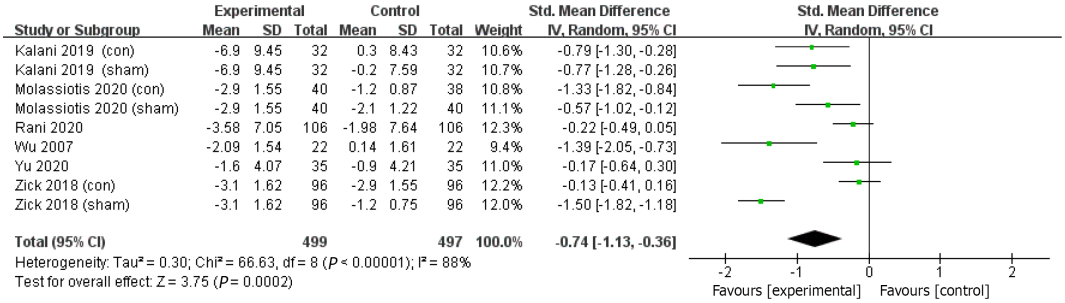


**Figure 12 Effects of acupressure using more than 3 acupoints on depression.**

### *Effect of acupressure on anxiety*

Three trials adopted HADS[26,28,31], one trial used Beck Anxiety Inventory (BAI)[25], and two trials used DASS[32,34] to measure anxiety level. Consistent findings were found in six studies that the acupressure group reported a greater reduction in anxiety after acupressure application than the sham or TAU controls. Meta-analyses of the six trials indicated an overall improvement in anxiety levels in the acupressure group compared with sham or TAU control groups with a small effect size (SMD = -0.67; 95%CI = -0.99 to -0.36; $P < 0.0001$; $I^2 = 79\%$; $\chi^2 = 37.82$; $P < 0.00001$; $Z = 4.16$) (Figure 13).

### *Adverse events*

Only one study[32] reported the adverse events of acupressure during four-week acupressure in patients with end-stage renal disease, including intradialytic hypotension ($n = 11$), dizziness ($n = 6$), palpitation ($n = 2$), and headache ($n = 1$). Intradialytic hypotension was reported to occur within 30 min after acupressure, and two participants discontinued the study in the final week due to the increased frequency of hypotension. The episodes of dizziness, palpitation, and headache occurred while acupressure was being applied. These side-effects disappeared within a few min and the acupressure treatment did not cease.

### *Sensitivity analyses*

Sensitivity analyses were performed after excluding one study[26], as it contained no description of blinding details. The results were similar to all the other studies involved (Figure 14).

### *Meta-regression analyses*

Meta-regression analyses were performed to investigate if there were any factors associated with the effects on depression. Age, the number of acupoints used, the total time of intervention, and the physical illnesses were included to investigate if there were any associated factors with the effects on depression. However, no significant results were found.

## DISCUSSION

We included in the systematic review and meta-analysis 14 RCTs with 1439 participants with depressive symptoms. Overall, the data showed that acupressure

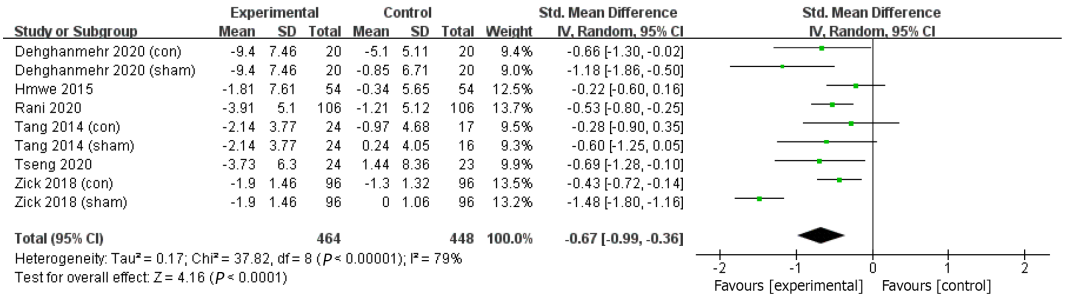


**Figure 13 Effects of acupressure on anxiety.**

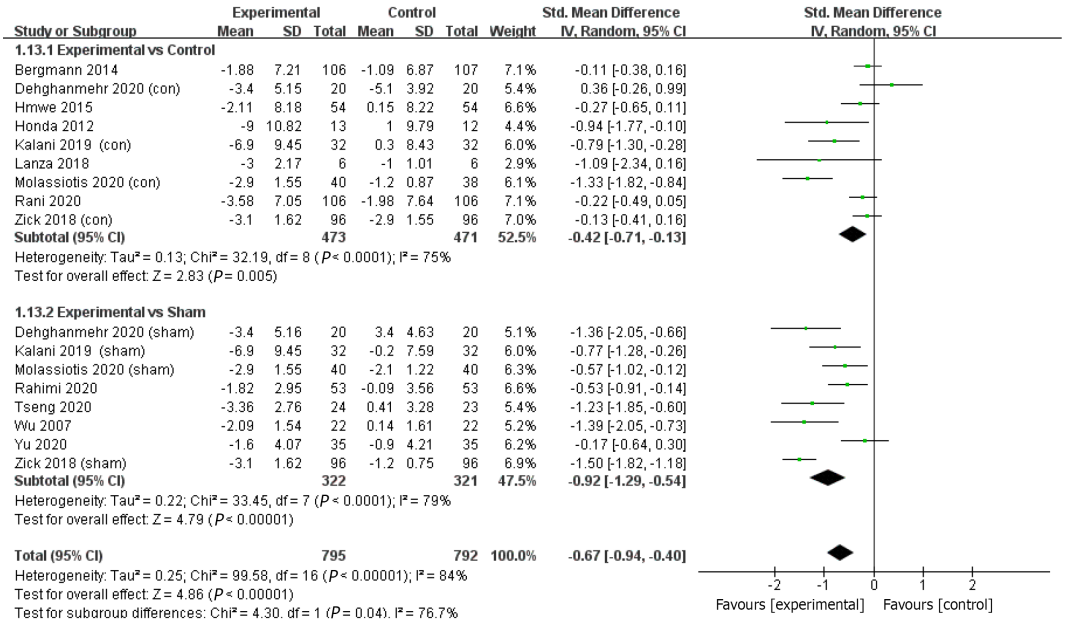


**Figure 14 Sensitivity analyses of acupressure on depression.**

had great potential to improve mild-to-moderate depressive symptoms in both primary and secondary depression. No systematic review and meta-analysis have been performed to assess the effectiveness of acupressure on depression in various clinical population. A recent integrative review showed that acupressure reduced depression in older people in the community, whether or not they had chronic illnesses[32]. Subgroup analyses in our meta-analysis consistently showed significant reductions in depression levels after acupressure treatment for adults with a large effect size in participants aged 65 years or above. Moreover, subgroup analyses also suggested that acupressure significantly reduced depression regardless of the clinical conditions. A recent scope review of six studies indicated that acupressure improved depression and psychological health in dementia[36], which is consistent with our findings in participants with Alzheimer's disease. However, these significant findings should be interpreted with caution due to the heterogeneity of the clinical conditions of the participants, manipulation techniques of acupressure, the selected acupoints, and the outcome measures.

Most studies in our review investigated the effects of acupressure on mild-to-moderate secondary depression in patients with chronic diseases. Three studies examined in patients with mild-to-moderate primary depression and all reported significant improvement in symptoms. However, it is not clear if acupressure is effective for patients with moderate-to-severe primary depressive disorders. Furthermore, none of the studies included in our meta-analysis mentioned specifically which symptom domains of depression were improved by acupressure treatment. Future research may focus on the effects of acupressure for moderate-to-severe depressive disorders and specific symptom domains.

Data showed a wide range of durations in acupressure interventions, ranging from 2 wk to 40 wk. More than half the studies (57.1%) involved acupressure treatment for 2-4 wk. The subgroup analyses suggested significant reductions in depression after either less than or more than 4 wk, indicating that acupressure benefits psychological well-being even after short-term treatment.

The acupressure manipulation applied in the included studies differed widely, and no confirmative conclusion could be drawn on the most effective acupressure technique. In general, 15 to 20-min sessions and 4-wk durations were commonly adopted. The majority of studies applied more than three acupoints, and the commonest acupoints used for depression are Yintang, Sanyinjiao, and Zusanli. Future research may compare the effects on depression among different acupoints to ascertain the effect of acupressure using specific acupoints. The most fundamental technique of acupressure is firm pressure on the acupoints. No included studies mentioned the amount of pressure on the acupoint, which is related to the thickness of skin, muscle, and fatty tissue at the point. The intensity of the pressure may be associated with the effect of acupressure due to the potential mechanism of stimulating the nerve systems; this needs to be clarified. Furthermore, adjusting the intensity of pressure based on the individual's tolerance is important in clinical practice.

All studies mentioned that the selection of acupoints was based on the TCM principles of balancing the "qi" flow in the body to promote inner self-recovery abilities. However, none of the included studies measured "qi" which may be a confounding factor for the outcomes, and none of them specified the particular neuro-mechanisms underlying the selection of acupoints. According to TCM, the "qi" circulates through 12 principal meridians between different organs of the body. There are 361 acupoints distributed along the meridians, and each is associated with a specific part of the body. Selecting acupoints along the meridian is the vital principle for acupressure treatment in depression. The application of specific acupoints related to refreshing the brain and soothing the liver function is the primary procedure across all the studies.

Acupressure also reduced anxiety in participants with psychiatric disorders, sclerosis, uremia, and osteoarthritis in both clinical and community settings. The findings were consistent with a previous systematic review and meta-analysis of acupressure on anxiety by Au *et al*[16]. However, Hmwe *et al*[32] suggested inconsistent findings on the effects of acupressure on anxiety and agitation in older people. Anxiety is a common comorbidity of depression, and the generalization of the effects of acupressure on anxiety needs to be further explored.

Ten of the 14 studies reported drop-out rates ranging from 0 to 28.8%, with a mean drop-out rate of 10.2%. Only one study reported the number that dropped out from each group and the reasons for withdrawal[24]. The completion rate was similar to previous studies of acupressure in older people in both clinical and community settings[32]. It was relatively lower than psychological treatment in depression[37]. It should be noted that none of the included studies had long-term follow-up. Furthermore, only one study reported adverse events, including hypotension, dizziness, palpitation, and headache, but without details. Addressing the effects during medium and long-term follow-up periods and the detailed adverse events of acupressure are the priorities suggested for future studies.

Only one study included in our review suggested the potential mechanisms through which the stimulation of particular acupoints on the skin can reduce depression and anxiety by altering the concentration of neurotransmitters, reducing the levels of adrenocorticotrophic hormones and hydroxytryptamine-5 in the brain, resulting in calmness[31]. Previous studies of acupuncture, which shared the same TCM theory with acupressure but used different manipulation technique (acupuncture uses needle), suggested that antidepressant effects of acupuncture are the result of the interaction inbetween multiple targets and levels in neural system. Acupuncture not only improves monoamine neurotransmitters, inhibits the hyperactive HPA axis, but also activates neurotrophic pathways, improves hippocampal neurogenesis, and inhibits inflammatory cytokines[38]. A study of electroacupuncture of acupoints "Baihui" and "Sanyingjiao" in chronically stressed rates significantly increased the activities of 5-HT by increasing the bingding site of $5\text{-HT}_{1A}$ receptors in the hippocampus of depressed rats[39]. A clinical study of acupuncture in women with menopausal depression showed significant increases in serum levels of Norepinephrine and Dopamine[40]. Furthermore, acupuncture at acupoints "Baihui" and "Yintang" combined with 5-HT reuptake inhibitors in older adults with depression significantly increased the serum Brain-derived Neurotrophic Factor (BDNF) level [41]. Song *et al*[42] found that electroacupuncture can significantly reduce the levels of serum interleukin IL-1β and tumor necrosis privacy (TNF-α) in patients with

depression, and the ratio of interferon to IL-4.

### *Limitations of the review*

The first systematic review and meta-analysis of acupressure in depression showed a significantly greater overall effect than the controls. However, it is important to be aware of several limitations when interpreting the results.

We excluded 16 Chinese studies that reported poorly, and we were unable to find complete details of study design features relevant to the risk of bias assessment. Thus, trials meeting our inclusion criteria beyond those identified may exist.

Also, only three included trials focused on mild-to-moderate primary depression, and no evidence was found in patients with moderate or severe depression, making generalizability to this patient group difficult.

The included studies differ substantially with regard to participants, treatment frequency and duration, and acupoints selected. Meanwhile, the exact techniques of acupressure and therapeutic composition of acupoints were less undermined and inclusive, making comparisons between these included RCT studies difficult.

No study included in our meta-analysis measured "qi", which is the primary rationale for the selection of acupoints, and may be a confounding factor for the interpretation of the findings. Even though, we could still perform a meta-analysis and a quantitative synthesis of the included studies.

### *Implications for clinical practice and further research*

As a non-invasive, safe and simple technique, acupressure has the potential to be promoted in clinical practice. The present study found that acupressure is feasible to improve depression and anxiety. Integration of this technique in the care of people vulnerable to mental illnesses, such as older people and postnatal women, would promote their emotional well-being and quality of life. That should further reduce the costs and side effects of conventional medication treatment in the standard care system. However, well-designed trials are recommended to provide more solid evidences on the effectiveness of acupressure for mental health promotion.

It is apparent that research in acupressure for mental health is still in its infancy, and further studies of high quality, with large sample sizes and medium- to long-term follow-ups, are warranted to examine the impacts on depression with different severity. Furthermore, effects of different acupoints and pressure retention on depression should be further examined for better understanding of the underlying mechanisms of acupressure in depression. Preliminary findings from our review suggested the potential mechanisms of acupressure may be associated with sympathetic and parasympathetic activities and the concentration of neurotransmitters and hormones in the neural networks. Future studies investigating the neurophysiological changes using imaging techniques (*e.g.*, fNIRS and MRI) are suggested.

## CONCLUSION

This review found emerging evidence to support certain positive effects of acupressure for adults suffering from mild-to-moderate depression. Future well-designed research is needed to provide robust evidence for clinical practice and recommendation for its application, and an in-depth understanding of acupressure treatment in the context of integrative care as well.

## ARTICLE HIGHLIGHTS

### *Research background*

Originated from traditional Chinese medicine (TCM), acupressure is a safe and cost-effective complementary treatment for depression.

### *Research motivation*

An increase body of research has been undertaken to assess effectiveness of acupressure in depression, but the evidence thus far is inconclusive.

### *Research objectives*

Via the systematic review and meta-analysis, we compared clinical data using

acupressure and controls with usual care or sham treatment.

### Research methods

The databases PubMed, PsycINFO, Scopus, Embase, MEDLINE, and China National Knowledge (CNKI) were searched. Randomized clinical trials (RCTs) or single-group trials in which acupressure was compared with control methods or baseline in people with depressive symptoms were included. The primary outcomes were the change between pre- and post-treatment in depression measures. Data were synthesized using a random-effects or a fixed-effects model to analyze the impacts of acupressure treatment on depression and anxiety in people with depression.

### Research results

A total of 14 RCTs (1439 participants) were identified. Analysis of the between-group showed that acupressure was effective in reducing depression (SMD = -0.58, 95%CI: -0.85 to -0.32, $P < 0.0001$) and anxiety (SMD = -0.67, 95%CI: -0.99 to -0.36, $P < 0.0001$) in clinical patients with depressive symptoms. The evidence of acupressure for mild-to-moderate depressive symptoms in patients with chronic diseases was significant. The evidence of certainty in moderate-to-severe primary depression was low. No severe adverse events were reported.

### Research conclusions

This present review indicated acupressure to be safe and exert certain positive effects in people with mild-to-moderate depressive symptoms. Importantly, the findings should be interpreted with caution due to study limitaitons, including heterogeneity of participants, treatment frequency and duration, the selected acupoints, and sample size.

### Research perspectives

Future research with a well-designed mixed method is required to provide stronger evidence for clinical decisions and recommendations for its application, as well as an in-depth understanding of acupressure mechanisms and symptoms domains in depression.

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SYSTEMATIC REVIEWS

# Risk factors for suicidal behaviour in late-life depression: A systematic review

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## Abstract

### *BACKGROUND*

Suicide is a leading cause of preventable death worldwide, with its peak of maximum incidence in later life. Depression often puts an individual at higher risk for suicidal behaviour. In turn, depression deserves particular interest in old age due to its high prevalence and dramatic impact on health and wellbeing.

### *AIM*

To gather integrated evidence on the potential risk factors for suicide behaviour development in depressive older adults, and to examine the effects of depression treatment to tackle suicide behaviour in this population.

### *METHODS*

A systematic review of empirical studies, published from 2000 onwards, was conducted. Suicidal behaviour was addressed considering its varying forms (*i.e.*,

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Grade C (Good): 0
Grade D (Fair): D
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wish to die, ideation, attempt, and completed suicide).

*RESULTS*
Thirty-five papers were selected for review, comprising both clinical and epidemiological studies. Most of studies focused on suicidal ideation (60%). The studies consistently pointed out that the risk was related to depressive episode severity, psychiatric comorbidity (anxiety or substance use disorders), poorer health status, and loss of functionality. Reduced social support and loneliness were also associated with suicide behaviour in depressive older adults. Finally, the intervention studies showed that suicidal behaviour was a robust predictor of depression treatment response. Reductions in suicidal ideation were moderated by reductions in risk factors for suicide symptoms.

*CONCLUSION*
To sum up, common and age-specific risk factors seem to be involved in suicide development in depressive older adults. A major effort should be made to tackle this serious public health concern so as to promote older people to age healthily and well.

**Key Words:** Late-life depression; Suicide behaviour; Disability; Chronic disease; Loneliness

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**Core Tip:** Suicide constitutes a global health concern. In this regard, suicide is one of the leading ten causes of death in five of the 21 Global Burden of Disease defined regions. Suicide mortality is more prevalent in older adults in comparison to younger adults, due to the cumulated influence of multiple risk factors over time. The role of depression in late-life suicide deserves particular interest due to its elevated prevalence and relationship with functional disability and chronic disease development. Results from this study may contribute to planning intensive assessment protocols in older adults with depression to target suicide, as well as to monitoring suicide behaviour as a key indicator of depression treatment success.

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## INTRODUCTION

Over 700000 deaths are attributed to suicide every year, making it the second leading cause of preventable death across the world and a serious public health concern[1]. An increasing trend of suicide death has also been reported between 2000 and 2017, with the highest rate of completed suicide observed in men older than 85 years[2-5].

Suicide should be considered a multifactorial phenomenon, involving dreadful consequences at varying levels, such as medical, legal, psychological, and economic levels among others[6]. Furthermore, it should be noted that psychiatric patients are more likely to die by suicide than the general population individuals[7-9].

Major depression deserves particular attention in old age as over 16% of community-dwelling older adults may experience an episode of clinically-relevant depressive symptoms susceptible for a clinical diagnosis, although not all report suicidal symptoms[10,11]. Some authors claim for considering the distinctive features of depression in old age. In this sense, a greater burden of somatic symptoms (*e.g.*, agitation, insomnia, and weight loss) may be evident in late-life depression[12]. Moreover, a higher risk of depressive episode onset may be observed among people with a history of depression in comparison to those who do not show any previous

episode. Since first episodes tend to appear from adolescence to middle age, late-life depression relapses may adopt more enduring statuses with a poorer prognosis in comparison to other life periods[13,14].

Besides, neurodegenerative and other ageing-related processes have to be taken into account in later life[15,16]. From this perspective, ageing-related frailty (*i.e.*, decreased physiological reserves, leading to adverse effects on health) and related disability have been extensively associated with poorer health status, including a higher rate of falls, increased health care service utilization, and mortality. Some studies have also linked limitations in activities of daily living with some somatic symptoms also seen in depression (*e.g.*, fatigue and agitation) as well as with risk factors for depressive symptom aggravation, such as reduced social participation and feelings of loneliness. On the other hand, the increased risk of showing metabolic diseases (*e.g.*, diabetes, hypercholesterolemia, and hypertension) and their daily management may decisively lead to emotional distress and depression development in late life[17,18]. Finally, the aging-related cognitive decline and its pathological evolution to dementia may be expected to increase the risk of late-life depression development[19].

Evidence is mixed regarding the contribution of aging-related factors (*e.g.*, increased metabolic and cognitive decline risk and loss of functionality) on the emergence of suicidal behavior symptoms in late-life depression[20-22]. Note that suicide behaviour should be understood more widely, comprising its varying forms (*i.e.*, wish to die, suicidal ideation, planning, attempt, and completed suicide) falling over the suicidality continuum. In this regard, it is relevant to mention that the strongest risk factors for death by suicide are the engagement in suicidal attempt and suicidal ideation[10].

Each suicidality form may have a distinctive way of expression[23]. Likewise, each form may be influenced by specific risk factors. For instance, suicidal ideation in old age was proven to be associated with sociodemographic factors (*e.g.*, lower educational attainment, living alone, and economic hassles) as well as some clinical factors, such as history of childhood abuse, poor self-perceived health, psychiatric comorbidity, and poorer social support (leading to loneliness and isolation) among others[2,24]. On the other hand, persistent suicidal ideation may be a major risk factor for suicide attempt, as well as other sociodemographic and clinical features, such as being White Caucasian, higher impulsivity levels, and suffering from chronic pain syndromes[21,25,26]. Unfortunately, inconsistencies have been described between the studies focused on suicide behaviour development and its related risk factors in depressive older adults.

This systematic review aimed to gather evidence on the risk of engaging in suicide behaviour among older adults with late-life depression. Moreover, it intended to investigate form-specific nuances of suicidality among older adults with depression, by studying the influence of sociodemographic, clinical, and psychological risk factors on suicidality form risk. Finally, we were interested in exploring the effect of interventions to reduce suicide behaviour on depressive symptoms.

## MATERIALS AND METHODS

This study was conducted following the guidelines proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) initiative[27,28]. Moreover, this systematic review was registered in PROSPERO platform (ID: CRD42021223897).

### *Article selection criteria*

Studies were selected according to PICOS strategy in line with PRISMA-P 2015 guidelines. In this sense, the population criteria guided to select the following studies: Studies focused on human samples of older individuals (aged 65 years or higher) with a diagnosis of major depression disorder (MDD), according to a diagnostic manual of (mental) diseases. To satisfy intervention criteria, studies should assess suicide behaviour (by means of interviews, self-reports, or hospital/local or national records). Control criteria guided to select studies that comprised a control group of individuals who had been diagnosed with a MDD (and no suicide behaviour). In longitudinal studies, a baseline assessment of MDD patients would serve as a control condition. Regarding the outcome criteria, study should have a measure of suicide in its varying forms: Ideation, plan, attempt, and completed suicide. In addition, the passive wish to die was also considered as an outcome, as it can be understood as a passive form of suicidal ideation[29-31]. Composite scores derived from integrating multiple suicidality forms (*e.g.*, suicidality risk) were also considered. Finally, criteria on study

item were: Empirical studies published in scientific literature in Spanish or English, from 2000 onwards.

### Search strategy

Papers were located following a two-way approach: An ascendant approach which involves scientific databases being consulted. The consulted databases were: Web of Science, PubMed, PsycInfo, and SCOPUS. The database search was conducted between November and December 2020. Queries were created combining three main key terms and their respective thesaurus (see the search queries in the Supplementary Table 1): Suicide (related MeSH terms: "Suicide, Attempted" and "Suicide, Completed"), depression (related MeSH terms: "Depressive Disorder", OR "Depressive Disorder, Treatment-Resistant" and "Depressive Disorder, Major"), and old age (exact MeSH term: 'Aged').

Articles were screened by a reviewer on an initial review of title, abstract, and keywords. Pre-selected papers were fully read by an independent reviewer to ratify the selection. A third peer reviewer approved the adequate selection of every paper to be included in this study. Discrepancies on paper selection were resolved by discussion.

### Data extraction and bias assessment

Relevant data were extracted from each article using a coding manual by an independent coder (different from the reviewers who selected the article). Data from these variables were extracted: Age, sex, sample size, depression status, presence of a psychiatric comorbidity, chronic diseases, and disability; loneliness feelings, self-esteem, mental health treatment, follow-up length (longitudinal studies), and results of the study.

The Newcastle–Ottawa Quality Assessment Scale (NOQAS) was used to measure methodological quality of studies as a way to control for publication bias[32].

## RESULTS

Database searches resulted in a total of 16431 hits retrieved. Over 64% ($n$ = 10495) of them were duplicated records (Figure 1). A total of 5936 articles were excluded in the screening phase (*i.e.*, title, abstract, and keyword reading). A final sample size of 35 articles were reviewed after the full-text review phase.

The selected articles and their main features are displayed in Table 1. Over 54% of articles were published in 2010 onwards. On the other hand, 42.86% of articles were led by United States research groups, far followed by studies conducted in the United Kingdom and Taiwan (8.57% of studies in both cases). Study sample size ranged from 24[33] to 654232[34], with a mean of 22211.77 (SD: 109023.38). Male/female ratio was also quite diverse across studies, with a percentage of female participants ranging from 0[2,35,36] to 74%[37]. Mean age fluctuated between studies from 69.51[38] to 84.37 years[39], with an overall mean age of 72.5 (SD: 0.5) years. Finally, the methodological quality of studies ranged from 2 to 9 (Table 1).

Most studies (60%) selected examined suicidal ideation outcome[3,10,20-22,25,36,38-52]. On the other hand, suicide attempt was assessed in 40% of studies[2,3,21,35,37,41,44,52-57]. Finally, nine studies (25.71%) addressed death by suicide[2,33,34,37,54,56], three (8.57%) assessed wish to die[22,39,58], two (5.71% of studies) focused on suicidality risk[59,60], and only one evaluated suicide planning[45]. The most commonly used scale to measure suicidal ideation was the Hamilton depression rating scale (HDRS)[61] in 23.81% of suicidal ideation studies; a clinical interview relied on the Diagnostic and Statistical Manual of Mental Disorders (DSM)[62], and the Beck scale for suicidal ideation (SSI)[63], both used in 14.29% of studies measuring suicidal ideation. In suicide attempt studies, most of studies collected data on attempts from either national or local registers (42.86% of these studies) due to hospital admission.

Regarding sociodemographic risk factors, Barnow *et al*[39] showed a relationship between increased levels of wish to die and age among German seniors. Moreover, some studies have highlighted a higher risk of suicidal behaviour in women[39,52] and White Caucasian[25]. In the same vein, Lohman *et al*[47] observed lower scores in the HDRS among older adults from ethnic minority groups. On the other hand, the study by Bartels *et al*[41] reported higher scores of suicidal ideation among older Americans from Asian ethnic groups (in comparison to those from the African ethnic group). These authors also found that suicidal ideation was associated with comorbid anxiety disorder, fewer social support, and more medical comorbidity. Moreover, the level of

**Table 1 Summary of studies included in the review**

| Ref. | Sample size | Sex (% female) | Mean age (yr) | Methodological quality | Suicide outcome | Suicide assessment | Treatment study testing and result | Depression-related factors | Significant risk factors |
|---|---|---|---|---|---|---|---|---|---|
| Almeida *et al*[2], 2016 | 38170 | 0 | 72 | 5 | Suicide attempt and completed suicide | National register | | | Chronic diseases (+) |
| Arslanoglou *et al* [20], 2019 | 63 | 73.02 | 80.52 | 4 | Suicidal ideation | Scale: HDRS | Psychological: PATH. Better outcomes for the PATH intervention *vs* supportive care | Depressive episode onset (-) | Cognitive function, (+) disability, (-) and social factors (social support) (-) |
| Aslan *et al*[3], 2019 | 150 | 72.7 | 71.3 | 4 | Suicidal ideation and suicide attempt | Clinical interview: DSM-IV | | | Education attainment, (-) anxiety symptoms (+) |
| Awata *et al*[40], 2005 | 1145 | 58.07 | 76.29 | 4 | Suicidal ideation | Clinical interview: DSM-IV | | Depressive symptoms (+) | Disability (+) and social factors (social support) (+) |
| Barak *et al*[53], 2006 | 202 | 58.41 | 76.55 | 5 | Suicide attempt | Local/regional register | | Antidepressant use (-) | |
| Barnow *et al*[39], 2004 | 516 | 48.1 | 84.37 | 4 | Wish to die and suicidal ideation | Scale: HDRS, GMS-A | | | Age, (+) sex (female), (+) subjective health status (-) |
| Bartels *et al*[41], 2002 | 2240 | 23.9 | | 5 | Suicidal ideation and suicide attempt | Scale: PSS | | | Ethnic group (Asians), (+)[1] medical diseases, (+) social factors (social support), (-) comorbid anxiety disorder (+) |
| Bakkane Bendixen *et al* [59], 2018 | 218 | 67 | 75.6 | 4 | Suicidality risk | Scale: MADRS | | | Anxiety symptoms (+) |
| Bickford *et al*[42], 2021 | 88 | 62.5 | 71.5 | 4 | Suicidal ideation | Scale: GSIS | | Depressive symptoms (+) | Frailty and disability (+) |
| Bickford *et al*[10], 2020 | 225 | 64.9 | 71.4 | 4 | Suicidal ideation | Scale: GSIS | | | Perceived stress (+) |
| Bonnewyn *et al* [58], 2017 | 68 | 59.29 | 73.87 | 5 | Wish to die | Scale: SSI | | | |
| Brådvik and Berglund[54], 2009 | 1206 | | | 5 | Suicide attempt and completed suicide | National register | | | |
| Bruce *et al*[43], 2004 | 412 | | | 6 | Suicidal ideation | Scale: SSI | Pharmacological: PROSPECT. Reductions in suicidal ideation due to treatment | | |
| Cole *et al*[44], 2006 | 113 | 63.4 | 79.2 | 5 | Suicidal ideation and suicide | Clinical interview: DSM-IV | | Major depression (+) | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | attempt | | | | |
| Coupland *et al* [55], 2011 | 60746 | 66.7 | 75 | 6 | Suicide attempt | Local/regional register | Pharmacological: Antidepressants. No effect of treatments on suicidal outcomes | Antidepressant use (+) | Self-harm (+) |
| Hwang *et al*[35], 2010 | 70 | 0 | 79.4 | 6 | Suicide attempt | Clinical interview | | | Brain volume (*i.e.*, reductions in dorsal medial prefrontal cortex) (+) |
| Innamorati *et al* [56], 2014 | 331 | 24.4 | | 4 | Suicide attempt and completed suicide | Autopsy | | | Social factors: Widowhood, (+) loneliness, (+) social support. (-) Life stressors (+) |
| Jokinen and Nordström[37], 2008 | 99 | 73.73 | 73 | 5 | Suicide attempt and completed suicide | National register | | | Dexamethasone suppression (-) |
| Kiosses *et al*[45], 2017 | 74 | 73.66 | 80.90 | 4 | Suicidal ideation and plan | Scale: MADRS | Psychological: PATH. Better outcomes for the PATH intervention *vs* supportive care | | Negative emotions, (+) cognitive function (-) |
| La Pia *et al*[46], 2001 | 36 | 55.55 | | 4 | Suicidal ideation | Scale: HDRS | Pharmacological: Fluoxetine. Suicidal ideation reductions as a robust predictor of response | | |
| Lee *et al*[21], 2003 | 156 | 32.69 | 73.6 | 2 | Suicidal ideation and suicide attempt | Scale: HDRS; Clinical interview: DSM-IV | | Delusional symptoms, (+) depressive symptoms (+) | Cognitive function, (-) disability (+) |
| Liu *et al*[36], 2020 | 47 | 0 | 83.8 | 5 | Suicidal ideation | Scale: SSI | | Depressive symptoms (+) | Chemokines (MCP-2/CCL8) (+) |
| Lohman *et al*[47], 2016 | 112 | 69.6 | 76.5 | 6 | Suicidal ideation | Scale: HDRS | Nurse-based: CAREPATH. Lower proportions (31.3%) of CAREPATH patients showing suicidal ideation at follow-up, *vs* TAU patients (63.6%) | | Ethnic group (minorities), (-) disability, (+) burdensomeness (+) |
| Lutz *et al*[48], 2021 | 75 | 66 | 71.57 | 4 | Suicidal ideation | Scale: GSIS | Psychological: 12-wk problem-solving therapy. Changes in functional disability predicted the changes in suicidal ideation | | Disability (+) |
| Lynch *et al*[38], 2004 | 77 | 62.3 | 69.51 | 3 | Suicidal ideation | Scale: ASIQ | | Hopelesness (+) | Negative affect intensity and reactivity (+) |
| Mansour *et al*[25], 2020 | 5546 | 61.5 | 76.8 | 7 | Suicidal ideation | Clinical Interview: ICD-10 | | | Ethnic group (White) (+) |
| McIntyre *et al* [22], 2008 | 1763 | 28.59 | 73.68 | 4 | Wish to die and suicidal ideation | Scale: GSIS | | | Subjective health status, (-) medical conditions, (+) disability, (+) health service utilization, (+) anxiety disorder (+) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Meeks *et al*[49], 2008 | 148 | 60 | 80.3 | 5 | Suicidal ideation | Center admission record | | Sleep difficulty (+) | Chronic pain, (+) |
| Morse and Lynch [50], 2004 | 65 | 69.2 | 70.3 | 4 | Suicidal ideation | Scale: ASIQ | | | |
| Nishida *et al*[33], 2015 | 24 | 41.67 | 78.7 | 8 | Completed suicide | Autopsy | | | Stroke severity (+) |
| Richard-Devantoy *et al*[57], 2012 | 40 | 62.5 | 76.5 | 9 | Suicide attempt | Clinical interview: DSM-IV | | | Cognitive function (-) |
| Sacco *et al*[60], 2015 | 8480 | 52.97 | 75.91 | 5 | Suicidality risk | Clinical Interview: ICD-10 | | Depressive symptoms (+) | Alcohol use disorder, (+) liver disease (+) |
| Szanto *et al*[51], 2003 | 395 | 72.91 | 71.4 | 4 | Suicidal ideation | Scale: HDRS | Pharmacological and psychological: Paroxetine, nortriptyline with or without psychotherapy. Participants with a higher risk of suicidality needed a greater time for suicidal ideation reduction | Depressive episode onset, (-) number of episodes, (+) depressive symptoms, (+) recurrence of depressive episode (+) | Psychiatric inpatient (+) |
| Tan and Wong [52], 2008 | 80 | 69.1 | 72.7 | 5 | Suicidal ideation and suicide attempt | Scale: BDI, SSI. Clinical interview (not specified) | | History of suicide behavior (+) | Sex (female), (+) psychiatric inpatient treatment (-) |
| Zivin *et al*[34], 2007 | 654232 | | | 7 | Completed suicide | National register | | | Substance use disorder, (+) PTSD (-) |

[1]In comparison to black participants.

The methodological quality of the studies was assessed by means of the Newcastle-Ottawa Quality Assessment Scale. The relationships between the depression-related and risk factors with the suicide outcome were positive (+), indicating the higher the level of the factor (or the presence of this condition), the higher the risk of the suicide outcome. An inverse relationship between the depression-related and risk factors with the suicide outcome was indicated by (-), with higher levels of the factor (or the presence of this condition) associated with a lower suicide outcome risk. ASIQ: Adult suicidal ideation questionnaire; DSM: Diagnostic and statistical manual of mental disorders; BDI: Beck depression inventory; GMS-A: Geriatric mental state examination; GSIS: Geriatric suicide ideation scale; HDRS: Hamilton depression rating scale; ICD: International classification of diseases manual; MADRS: Montgomery-Asberg depression rating scale; SSI: Beck scale for suicidal ideation.

education was negatively associated with a higher risk of suicide behaviour engagement (*i.e.*, suicidal ideation and attempt), as Aslan *et al*[3] reported.

In terms of depression features, the studies showed a higher risk of suicide in depressive episodes with earlier onset[20,51]. On the other hand, the use of antidepressants was associated with a lower risk of suicide behaviour[53], but results did not seem to be conclusive due to divergences with other studies. In this vein, Coupland *et al*[55] observed a higher probability to show suicide behaviour in patients under antidepressant treatment. Finally, the severity of depressive symptoms was strongly associated with higher suicide behaviour across studies[36,40,42,51,60]. Meeks *et al*[49] highlighted the relationship between sleep difficulty and suicidal ideation. More concretely, the study aimed to assess whether chronic pain would be associated with comorbidity, length of hospitalisation, suicidal ideation, and sleep duration in depressive geriatric inpatients. As a result, the authors found an elevated prevalence

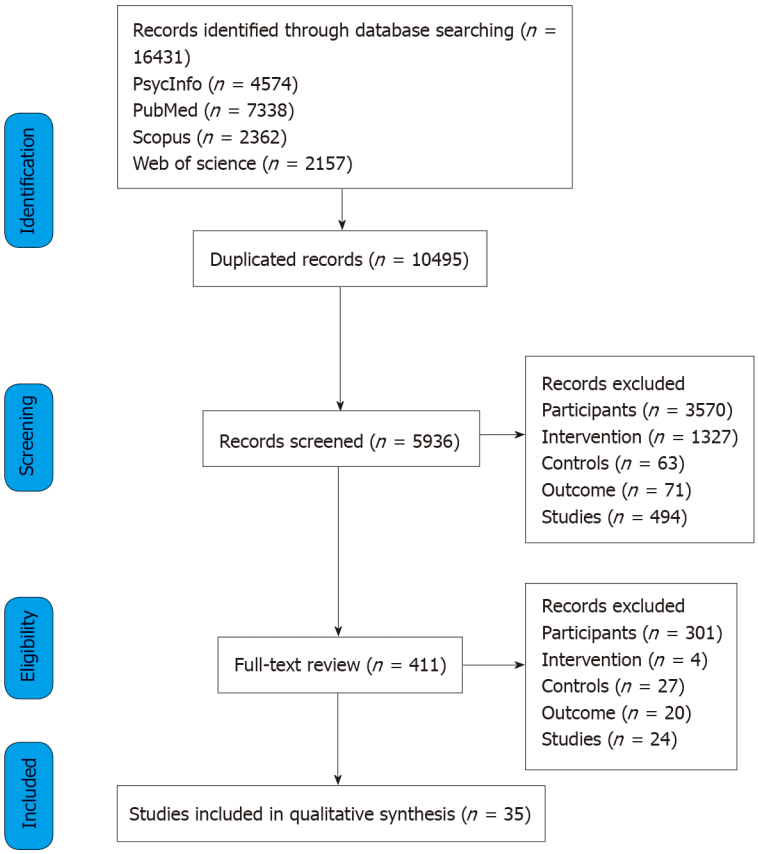


**Figure 1 Flow diagram of study selection**

of chronic pain among these patients (62% of patients). Moreover, patients with comorbid depression and chronic pain showed a higher risk of suicidal ideation than patients without chronic pain. Other factors associated with suicidal ideation in this study were the diagnosis of a personality disorder, more elevated medical burden, and total sleep time decrease.

The study by Lynch *et al*[38] provided some evidence in line with the well-known relationship between suicidal ideation and hopelessness. Finally, other studies point to a higher risk of suicidal behaviour in patient with both history of depressive episodes ( *i.e.*, number of episodes and recurrence) and number of suicide episodes[51,52].

Regarding clinical factors, studies agree in highlighting the relationship between health status indicators and suicidality forms. First, some studies showed an increased risk of suicidality in psychiatric inpatients[34,52]. Moreover, mounting evidence has suggested a consistent relationship between anxiety (*i.e.*, comorbid anxiety disorder or elevated anxiety symptoms) and suicide, regardless of suicidality form[3,22,41,59]. Other studies focused on comorbidity with other psychiatric disorders. In this vein, Zivin *et al*[34] highlighted a reduced risk of death by suicide among veterans with comorbid depression and posttraumatic stress disorder. However, this result was moderated by age, as younger veterans did show a higher suicide rate than their older counterparts. Results were contradictory regarding personality traits. As aforementioned, Meeks *et al*[49] did find a positive relationship between suicidal ideation and a diagnosis of a personality disorder in depressive older adults with chronic pain. However, Morse and Lynch[50] failed to identify positive correlations between pathological personality traits (*i.e.*, paranoid, schizotypic, narcissistic, borderline, and avoidant) and suicidal ideation. On the other hand, the presence of co-occurring substance abuse disorder was associated with a higher suicide risk in this sample. Sacco *et al*[60] also found a significant relationship with alcohol use disorder. The association between cognitive decline and suicidal ideation seems to be evident as shown by Kiosses *et al*[45] and Richard-Devantoy *et al*[57], even though none of the studies addressing cognitive function included samples with either dementia or mild cognitive impairment.

Several studies showed an increased risk for suicidal behaviour with higher disability levels[20,22,40,42,47,48], poorer health status[22,39], and multimorbidity[41,47]. Almeida *et al*[2] studied the relationship of multiple clinical factors with suicide

attempt and completed suicide among older men from Australia. The authors found that more than 57% of depressive men who completed suicide showed physical multimorbidity (*i.e.*, five or more health conditions). McIntyre *et al*[22] aimed at providing some evidence on the influence of comorbid anxiety on suicidal risk of depressive patients. The authors concluded that anxiety and depression co-occurrence may represent a gradient of clinical severity, leading to increasing levels of poorer self-reported health status, higher number of medical disorders, worse mental functioning, and greater use of emergency services. On the other hand, as aforementioned, chronic pain was associated with increased suicidal ideation[49]. Finally, the postmortem study by Nishida *et al*[33] revealed a clear relationship between stroke severity and completed suicide in older adults who had presented acute poststroke depression. More concretely, suicide victims were more likely to have shown progressive supranuclear palsy with argyrophilic grain disease.

In terms of psychosocial factors, the lack of social support has been systematically associated with suicidality across studies, particularly with suicidal ideation[20,40,41]. Innamorati *et al*[56] conducted a postmortem study comparing data from psychological interviews of patients who died by suicide and psychiatric outpatients who did not engage in suicide attempt. The study revealed higher levels of loneliness and lack of social support among suicide victims. Moreover, victims were more likely to be widowed and living alone before death. Finally, higher levels of stress were found among suicide victims. Bickford *et al*[42] also highlighted the relationship between perceived stress levels and suicidal ideation. Jokinen and Nordström[37] provided a piece of evidence connecting physiological stress response and suicide. The study analysed how the dexamethasone test (DST) may be useful to predict suicide attempt or death by suicide among depressed inpatients. A total of 24 patients (24.24% of sample participants) committed a suicide attempt and six patients died by suicide. The DST no-suppression was proven to be able to distinguish between suicide victims and survivors. On the other hand, Liu *et al*[36] explored how inflammatory factors and chemokines (the hypothalamus-pituitary-adrenal axis is involved in regulation of inflammatory factors) may distinguish between depressive men with and without suicidal ideation. As a result, participants with suicidal ideation showed higher levels of MCP-2/CCL8 chemokines than healthy controls and depressive men without suicidal ideation, as well as a higher number of depressive symptoms.

Finally, interventions to deal with depression and suicide behaviour deserve being mentioned. Eight studies analysed the effects of interventions to ameliorate depressive symptoms, targeting suicidal behaviour (*i.e.*, ideation and attempting). Three studies tested psychological interventions[20,45,48], and three were focused on pharmacological interventions[43,46,55]; the study by Lohman *et al*[47] analysed the effects of a nursing-based intervention (the CAREPATH). On the other hand, the study by Szanto *et al*[51] included data from two primary trials on antidepressant treatments (*i.e.*, paroxetine and nortriptyline) and another trial combining pharmacological and psychological treatment. The 12-wk problem adaptation therapy (PATH) programme was studied by Kiosses *et al*[45] and Arslanoglou *et al*[20]. The intervention was focused on providing emotion regulation skills. The PATH yielded reductions in suicidal ideation during the course of treatment, in comparison to supportive therapy. On the other hand, Lutz *et al*[48] evaluated factors related to suicide ideation due to a psychological treatment delivery (12-wk problem-solving therapy). As a result, they found that the changes in functional disability derived from the intervention predicted the reductions in suicidal ideation.

Regarding pharmacological interventions, results were mixed. First, Coupland *et al*[55] showed that the use of antidepressants (regardless of typologies: Tricyclic antidepressants or selective serotonin reuptake inhibitors) was associated with the presence of suicide attempts among the patients. However, Bruce *et al*[43] found beneficial effects of the use of antidepressants following the PROSPECT clinical algorithm (citalopram and psychiatric sessions, with training for clinicians to better manage late-life depression) on suicidal ideation. La Pia *et al*[46] studied the effect of fluoxetine on late-life depression. The authors found that suicidal ideation change was a robust predictor of treatment response. Szanto *et al*[51] pointed that symptom amelioration due to pharmacological intervention (with or without psychotherapy) was slower in depressive patients with a higher suicidality risk.

Lohman *et al*[47] analysed the effectiveness of the nurse-based depression management intervention (CAREPATH) in older adults with depression. The authors found a decreased risk of suicidal ideation in the CAREPATH group (only 31.3% of patients showing suicidal ideation in the 1-year follow-up), in comparison to controls (63.6% of them showing suicidal ideation). The decreased risk of suicidal ideation was associated with being an ethnic minority member, and lower limitations in instru-

mental activities of daily living and burdensomeness.

## DISCUSSION

This systematic review aimed to gain insight into the risk factors for suicide behaviour development in older people with depression. From a lifelong perspective, suicide behaviour may reach its level of maximum incidence rate in late life[5,10]. Depression constitutes a main contributor to suicide behaviour development across the lifespan[8,64,65]. A total of 35 manuscripts were selected from our robust methodological approach, covering both clinical studies[20,33,55] and epidemiological studies[34]. Despite the wide heterogeneity observed between the studies, our review revealed that most papers focused on suicidal ideation, mainly using self-reported measures, followed by suicide-attempt studies. Very few studies addressed risk factors for early forms of suicidality, such as passive suicidal ideation (*i.e.*, wish to die ideation)[22,39,58], as well as completed suicide and its potential risk factors[2,33,56].

Our study focused on the role of four types of risk factors for suicide behaviour: Sociodemographic factors, factors related to depressive episodes (current episode and history of episodes), other clinical factors (both psychiatric and organic factors), and psychosocial factors. In addition, the effect of mental health interventions was studied. First, it highlighted the influence of some sociodemographic factors on suicidal ideation among depressive older adults: Being woman and White Caucasian[39,47,52]. According to the integrated motivational-volitional model (IVM)[23], the genetic, biologically-based vulnerabilities may put individuals at higher risk of particular suicidality forms. In this vein, findings derived from the studies reviewed suggest that sex (being woman) and ethnic factors may show an age-invariant effect on suicidal ideation among depressive individuals, in line with other studies across the lifespan [64,65]. Unfortunately, data exploring the relationship between sociodemographic factors and other suicidality forms (*i.e.*, attempt and completed suicide) were not available for late-life depression patients. The exception that proves the rule only comprises two studies. First, Aslan *et al*[3] found a relationship between elevated suicidal ideation and attempt, and lower education level. Innamorati *et al*[56] showed that widowhood may be associated with a higher risk of engaging in suicide attempt and death by suicide. Widowhood may make social networks and participation become limited, with the subsequent emergence of feelings of loneliness and other mediators of suicide behavior[23]. Difficulties in emotion regulation and disease management may be related with a lower education level in old age[17,66]. In other words, lower education level may therefore be associated with poorer coping strategies. In line with the IVM[63], deficits in coping strategies may increase motivational moderators of suicidal ideation (*i.e.*, feeling of defeat, hopelessness, humiliation, or entrapment). The difficulties in emotion regulation may also be seen in depressive older individuals with cognitive decline[67].

Some episode-related factors may be involved in the emergence of suicide behaviour symptoms. These factors may boost the influence of motivational moderators on suicidal ideation and may increase the probability of ideation turning into attempt subsequently. The history of recurrent depression deserves being mentioned. First, depressive older adults are very likely to show a history of previous episodes[13]. Moreover, a depressive episode tends to be associated with a poorer prognosis and enduring symptoms in late life[68,69]. The studies included in this review were quite consistent in highlighting an increased risk of suicidal ideation among people with more severe episodes (*i.e.*, episode with an earlier onset, more severe symptoms, and treatment resistance) and those with a history of depressive episodes[20,36,42,46,51,60]. Conversion of suicidal ideation into suicide attempt may be boosted by the history of self-harm and suicide episodes, due to habituation processes and increased physical pain tolerance[55]. In this vein, people may erroneously learn that the suicide attempt constitutes an optimal strategy to cope with hassles and problematic situations[63].

Other clinical factors highlighted in our study were the presence of either a comorbid anxiety disorder or a co-occurring substance use disorder. Both types of disorders have been strongly associated with suicide behaviour symptoms[70,71]. Of particular interest is the relationship found between comorbid depressive and anxious symptoms and suicide among community-dwelling older adults, even from earlier subclinical stages[72,73]. On the other hand, alcohol-related disorders are strongly associated with suicide, both at the individual level (*e.g.*, up to six times more likelihood to engage in suicide behaviour in alcohol abusers) and population (*i.e.*,

increasing population drinking trends are associated with raising suicide rates) level [74,75]. Conversely, the debate is still open on the relationship between pathological personality traits and suicide among depressive older adults, due to the low number of studies and mixed evidence obtained[49,50]. Some mediating factors (*e.g.*, impulsivity or emotion dysregulation) are very likely to play a relevant role in the relationship between personality and suicide[23].

Multimorbidity and poorer health status have been systematically associated with suicide behaviour symptoms across studies[2,41,47]. In the similar vein, disease burden and difficulties in activities of daily living have proven to put depressive older adults at higher risk of suicide behaviour, regardless of suicidality form[20,42,48]. Disability and chronic diseases have shown a main, independent association with suicide, apart from depression[76,77]. However, these results should be considered more cautiously due to the influence of multiple ageing-related processes (*e.g.*, inflammatory imbalance and metabolic dysregulation) on both depression and chronic disease development[78,79]. Anyway, disability and chronic disease management may be particularly challenging and stressful for older adults due to progressive functional losses, increased economic costs, and frequent hospital admission[80,81]. Elevated stress has also been associated with a higher risk of suicidality across the reviewed studies[10,56]. In line with the IVM, recurrent exposure to stressors and daily hassles may increase the salience and cognitive accessibility of suicide triggering individuals engaging in suicide attempt[23].

Regarding the psychosocial factors, the reviewed studies identified the lack of social support and increased feelings of loneliness as main contributors to suicide behaviour in depressive older adults[20,41,56]. Social participation and social support may buffer the impact of stress in late life. In turn, social resources may work as protective factors that prevent depressive symptom aggravation and suicide behaviour emergence[82,83]. On the other hand, social isolation and related emotional states (*i.e.*, loneliness) may lead to systematic deficient emotion regulation due to its impact on cognitive bias development (*e.g.*, selective retrieval of negative memories), as well as metabolic dysregulation due to loss of adherence to healthy lifestyle habits[84-86].

Finally, eight intervention papers were reviewed in our study. Some of the papers analysed the effect of targeted treatments on suicide behaviour[45,47], and others (pharmacological treatments, mainly) focused on wide depressive symptoms[46,51]. As a main conclusion of these studies, the reductions in suicidal behaviour (suicidal ideation) were moderated by changes in risk factors (*e.g.*, functional disability and burdensomeness) that may presumably involve deactivation of suicide-related cognitive mediators (*e.g.*, hopelessness and feelings of entrapment). Unfortunately, further studies should be done to support this speculation. On the other hand, it was found that a robust predictor of treatment response to antidepressants was the reduction of suicidal ideation. Some studies postulate the role of suicide ideation as a central symptom of depression whose amelioration may lead to improvement in other symptoms, due to contagion mechanisms[87,88]. Therefore, all these studies stress the key role of suicide behaviour in the maintenance of a depressive disorder in late life.

The present study comes from a robust framework to systematically review the risk factors of suicide behaviour emergence, maintenance, and remission in depressive older adults. Depression constitutes a highly prevalent mental disorder with a dreadful impact in late life[89,90]. Suicide behaviour has been consistently associated with depression, leading to worse outcome. Our study examined suicide in depressive older adults considering varying suicidality forms (*i.e.*, wish to die, suicidal ideation, attempt, and completed suicide). Moreover, a wide variety of risk factors were studied. On the other hand, the present study has some limitations that deserve mentioning. First, conclusions from this systematic review are essentially qualitative. Further studies should address the relationship between depression and suicide from a more analytical standpoint (*i.e.*, meta-analysis). Furthermore, our review was focused on recent literature covering the period from 2000 onwards. In this regard, the present study serves as an updated picture of the existing literature on depression and suicide in older adults. On the other hand, subthreshold depression was not addressed in this study. Some studies have demonstrated an evident relationship between subclinical depression statuses and suicide in old age[73,91,92]. In this regard, full-blown depressive disorders are related to a higher risk of negative outcomes and usually show a poorer prognosis in late life[89,93]. Finally, this study came from defining older adults as individuals who are 65 years or older. Our definition goes in line with that proposed by the World Health Organization[94]. Although we are aware that this definition might be narrowed, we decided to adopt a robust criterion for older age definition due to the huge variability of definitions across cultures[95].

## CONCLUSION

Some clinical implications may be derived from our study. First, further research should be done to disentangle specific mechanisms involved in some forms of suicidality. In this vein, it is particularly relevant to gain insight into potential risk factors for dangerous suicidality forms (*e.g.*, suicide attempt and re-attempt) in a vulnerable population as older adults are. Second, policy makers may have a decisive role in tackling suicide in old age by promoting multicomponent prevention strategies, addressing both health-related and social factors (*e.g.*, strategies to promote social participation). Finally, suicide-targeted interventions should be developed and delivered on a wider basis to tackle the excess of mortality by suicide and to treat depression syndromes in older adults. In the same vein, suicide behaviour should be prioritised as a key therapeutic goal, even from its earliest forms (*i.e.*, wish to die).

## ARTICLE HIGHLIGHTS

### *Research background*

Suicide is one of the most relevant health hazards worldwide, particularly in old age with elevated rates of mortality by suicide. Depression constitutes the most prevalent mental health condition in old age, affecting almost one in five older adults at a community level. Depression is one of the most relevant risk factor for suicide behaviour in its multiple forms (*i.e.*, ideation, attempt, and completed suicide).

### *Research motivation*

This study comes from the interest in reinforcing lines on research at community and clinical levels so as to improve the quality of life of older patients that may show severe mental health conditions: Older adults with depression and suicidal ideation and behaviour.

### *Research objectives*

This study aimed to analyse the relationship between risk factors for suicide behaviour development and late-life depression, as well as to explore the effects of depression treatment on suicide behaviour.

### *Research methods*

A systematic review was conducted covering the period from 2000 onwards, by selecting scientific papers on the relationship between late-life depression and suicide. The review was conducted following the guidelines proposed by the PRISMA-P 2015 statement.

### *Research results*

Factors related to depressive episode severity, psychiatric comorbidity, poorer health status, and disability were highlighted to be related with the emergence of suicide behaviour among depressive older adults. Psychosocial factors were also involved in suicide behaviour emergence. Finally, suicidal behaviour was proven to be a key predictor of depression treatment response.

### *Research conclusions*

Very few studies were focused on severe suicidal behaviour. For that reason, further research is needed to accurately disentangle the pathways involved in the transition between ideation and suicide attempt to prevent death by suicide. Changes in suicidal ideation seem to be decisive in terms of depressive disorder prognosis in late life.

### *Research perspectives*

The results may help increase the awareness on the study of mechanisms involved in suicide from people at risk, as those with a depressive disorder, an actual lure in late life, taking into account its devastating impact in terms of mental health and wellbeing.

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EDITORIAL

# Screening dementia and predicting high dementia risk groups using machine learning

Haewon Byeon

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## Abstract

New technologies such as artificial intelligence, the internet of things, big data, and cloud computing have changed the overall society and economy, and the medical field particularly has tried to combine traditional examination methods and new technologies. The most remarkable field in medical research is the technology of predicting high dementia risk group using big data and artificial intelligence. This review introduces: (1) the definition, main concepts, and classification of machine learning and overall distinction of it from traditional statistical analysis models; and (2) the latest studies in mental science to detect dementia and predict high-risk groups in order to help competent researchers who are challenging medical artificial intelligence in the field of psychiatry. As a result of reviewing 4 studies that used machine learning to discriminate high-risk groups of dementia, various machine learning algorithms such as boosting model, artificial neural network, and random forest were used for predicting dementia. The development of machine learning algorithms will change primary care by applying advanced machine learning algorithms to detect high dementia risk groups in the future.

**Key Words:** Dementia; Artificial intelligence; Clinical decision support system; Machine learning; Mild cognitive impairment

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**Core Tip:** The predictive performance of machine learning techniques varies among studies because of the difference in machine data (especially, Y variables) imbalance, characteristics of features included in the model, and measurement methods of outcome variables. Therefore, further studies are continuously needed to check the predictive performance of each algorithm because, although some studies have proven that the performance of a specific machine learning algorithm is excellent, the results cannot be generalized for all types of data.

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## INTRODUCTION

New technologies such as artificial intelligence, the internet of things, big data, and cloud computing have appeared with the advent of the Fourth Industrial Revolution. These new technologies have changed the overall society and economy, and the medical field particularly has tried to combine traditional examination methods and new technologies. The most remarkable field in medical research is the technology of predicting high-risk groups using big data and artificial intelligence. The picture archiving and communication system and electrical medical records have been implemented in hospitals over the past 20 years, and it has accumulated an enormous amount of medical data. However, there is a limit to analyzing patterns or characteristics of the data using only traditional statistical methods due to the size (volume) and complexity of such medical big data.

However, studies have persistently predicted dementia based on machine learning[1-5] over the past 10 years by using cognitive abilities such as neuropsychological tests, in addition to brain imaging and image analysis, which has shown new possibilities for screening dementia and predicting groups with high dementia risk based on medical artificial intelligence. It is expected that the clinical decision support system (CDSS) using artificial intelligence including machine learning will be widely introduced in medical research and it will affect disease prediction and early detection. It is critical to collect high-quality data and analyze the data with an appropriate machine learning technique suitable for the properties of the data to create safe and meaningful medical artificial intelligence. It is necessary to understand the characteristics of machine learning algorithms, different from traditional statistical methods, in order to develop a CDSS that is scientifically meaningful and shows good performance with the participation of medical experts in this process.

Machine learning has been widely used over the past 20 years mainly because of the emergence of big data[6]. It is because the performance of machine learning mostly depends on the quantity and quality of data, and the required level of data has become available only recently. The amount of digital data produced worldwide has been skyrocketing, and it is forecasted that it will be 163 zettabytes per year in 2025[7]. Big data that can be used for medical research include electronic medical record and picture archiving and communication system data individually constructed by a medical institution, insurance claim data of the Health Insurance Corporation, and epidemiological data such as the National Health and Nutrition Examination Survey data. More mental science studies[8,9] have tried to identify risk factors for mental disorders such as depression and cognitive disorders such as dementia using these epidemiological data.

Machine learning algorithms have been successfully applied in medical image processing fields such as neurology and neurosurgery. However, mental science, which mainly deals with clinical data (structured data) such as cognition and emotion, has relatively fewer studies on disease prediction using machine learning. Furthermore, researchers in mental science do not have a deep understanding on machine learning, either. This review introduces: (1) The definition, main concepts, and classification of machine learning and overall distinction of it from traditional statistical analysis models; and (2) The latest studies in mental science to detect dementia and predict high-risk groups in order to help competent researchers who are challenging medical artificial intelligence in the field of psychiatry.

## DEFINITION OF MACHINE LEARNING

The machine learning technique is a representative method for exploring the risk factors or high-risk groups of a disease by analyzing medical big data (Figure 1). Many studies mix the concepts of artificial intelligence, machine learning, and deep learning. Machine learning means the algorithm for data classification and prediction, while deep learning is the algorithm that is composed of an input layer, multiple hidden layers, and an output layer, imitating human neurons, among many machine learning

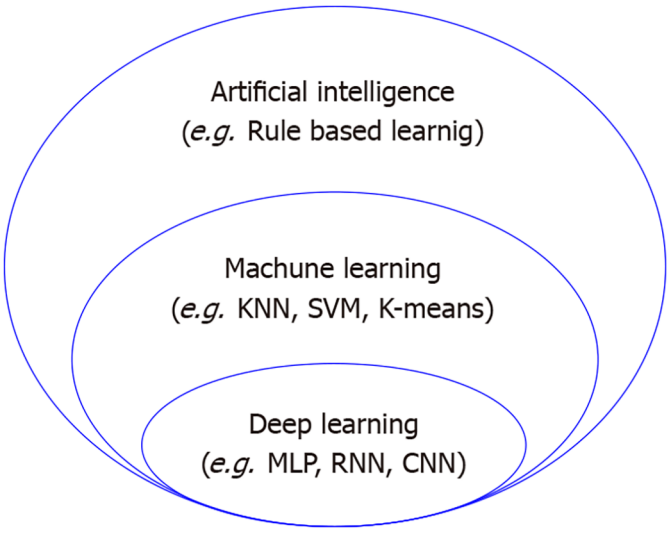


**Figure 1 Diagram for concepts of artificial intelligence, deep learning and machine learning.** KNN: K-nearest neighbors; SVM: Support vector machine; RNN: Recurrent neural network; MLP: Multilayer perceptron; CNN: Convolutional neural network.

algorithms. Moreover, artificial intelligence can be defined as the highest concept encompassing both deep learning and machine learning. Traditional statistical techniques such as analysis of variance and regression analysis can also be used for analyzing big data. However, traditional statistical techniques cannot identify the complex linear relationships among variables well because big data contain multiple independent variables, and they are limited in analyzing data with many missing values.

Machine learning refers to a method of improving the performance of an algorithm by itself through learning from data. Mitchell[10], a world-renowned machine learning scientist, defined machine learning using task, experience, and performance measure. If there is a computer program, which gradually performs a task better as it accumulates experience through performance measures, it is considered that learning has been accomplished in that computer program. In other words, machine learning is a method that allows a computer to learn using data and finds an optimal solution as a result of it.

In general, machine learning algorithms develop various machine learning models to predict disease risk factors and select the model showing the best performance as the final model. While traditional statistical techniques such as regression analysis use the significance probability to evaluate the predictive performance of models, machine learning algorithms use a loss function. Mean squared errors and mean absolute errors are used as loss functions to evaluate the performance of machine learning for continuous variables, while cross entropy is used for categorical variables[11]. If there are many model parameters or there is a possibility to misrepresent the result due to biased parameters, regularization, a method of adding a penalty to a loss function, is used. L1 (lasso) regularization and L2 (ridge) regularization are representative regularizations used in machine learning, and the Akaike information criterion and Bayesian information criterion are also used[12].

## EVALUATING THE PREDICTIVE PERFORMANCE OF MACHINE LEARNING MODELS

Generally, hold-out validation and k-fold validation are mainly used to evaluate the predictive performance of machine learning models. Hold-out validation validates the accuracy by separating the dataset into a training dataset and a test dataset (Figure 2A). For example, 80% of the dataset is used as a training dataset to train a learning model, and the remaining 20% is used as a test dataset to evaluate predictive performance (accuracy). However, if the size of data is not large enough, the hold-out validation may suffer from overfitting. The k-fold validation can be used as an alternative to overcoming the limitation of the hold-out validation. The k-fold validation divides the data into k groups, uses each group as a verification group, and selects the model with the smallest mean error (Figure 2B).

## THE STRENGTH OF MACHINE LEARNING IN PREDICTING HIGH DEMENTIA RISK GROUPS

Many previous studies[4,5] did not define the high dementia risk group as a dementia group because

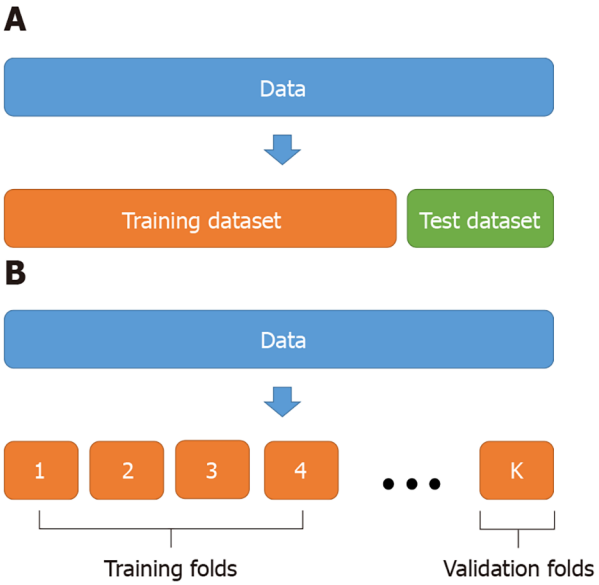


**Figure 2 The concept of two validations.** A: The concept of hold-out validation; B: The concept of k-fold validation.

although their memory or cognitive functions were lower than the group with the same age and education level in a standardized cognitive test, the ability to perform daily life (*e.g.* activities of daily living) was preserved. In other words, since it is the preclinical stage of dementia, it has been receiving attention in terms of early detection and prevention of dementia.

In general, the main goals of data analysis for predicting high dementia risk groups are inference and prediction. The inference is based on theories and previous studies, and it assumes that data is generated by a specific statistical-based model and tests hypotheses established by the researcher. Even though traditional statistical analyses emphasize inference, prediction using machine learning, unlike inference, often does not establish hypotheses or does not conduct hypothesis testing. Therefore, statistical learning can be considered more advantageous than machine learning in analyzing social science data (or mental science data) emphasizing the relationship between variables. However, as convergence studies on disease prediction have been active recently, this comparison is gradually becoming meaningless. In other words, it has become more common not to strictly distinguish terminologies such as machine learning, statistical analysis, and predictive analysis. Nevertheless, the followings are the strengths of machine learning over traditional statistical analyses. First, it is important to build a predictive model and identify the relationship between key variables associated with the issue in traditional statistical analyses. On the other hand, machine learning focuses on identifying patterns and exploring predictive factors of dementia rather than testing a specific hypothesis. Therefore, machine learning techniques can be applied more flexibly to more diverse data than traditional statistical analysis techniques.

Second, while traditional statistical analysis techniques focus on linear models, machine learning has the advantage of handling nonlinear models and complex interactions between variables[13].

Third, machine learning can analyze a large amount of data that are difficult to handle with traditional statistical methods. Data generally used in statistics are called “long data” and they refer to data in which the number of cases exceeds the number of variables, while “wide data” indicate data in which the number of variables is larger than the number of cases[14]. Even though it is hard to analyze wide data with traditional statistical techniques, machine learning has the advantage that it can analyze long data as well as wide data easily. In other words, while traditional statistical techniques are optimized to analyze data collected through researchers' research design, machine learning can analyze large volumes of data collected without a specific intention.

## LIMITATIONS OF MACHINE LEARNING IN PREDICTING HIGH DEMENTIA RISK GROUP

The limitations of machine learning in detecting dementia or predicting high dementia risk groups are as follows. First, it is difficult to interpret the relationship between explanatory variables and response variables with black-box techniques (*e.g.*, boosting models, artificial neural networks, and random forests) among machine learning techniques. While traditional statistical analysis techniques aim to explain (interpret) the relationship between independent and dependent variables, the goal of machine learning techniques is to predict. For example, studies that aim to infer high dementia risk groups develop a study model based on theories and previous studies and test hypotheses. It is possible to

**Table 1 Summary of studies**

| Ref. | Data | Features | Models/algoritms | Results |
|---|---|---|---|---|
| Bansal *et al*[2] | Total of 416 subjects in cross-sectional data and 373 records in longitudinal data | Age, sex, education, socioeconomic status, mini-mental state examination, clinical dementia rating, atlas scaling factor, estimated total intracranial volume, and normalized whole-brain volume | J48, naive Bayes, random forest, multilayer perceptron | Classification accuracy; J48: 99.52%; Naive Bayes: 99.28%; Random forest: 92.55%; Multilayer perceptron: 96.88% |
| Bhagyashree *et al*[3] | Total of 466 men and women, health and ageing, in South India | Consortium to establish a registry for Alzheimer's disease, community screening instrument fordementia | Jrip, naive Bayes, random forest and J48, synthetic minority oversampling technique | Sensitivity; Word list recall (WLR) score lower than the population mean: 92.5%; cog-score/verbal fluency/WLR score lower than 0.5 SD lower than population mean: 85.1% |
| Zhu *et al*[4] | Total of 5272 patients were analyzed. Normal cognition, mild cognitive impairment, very mild dementia | History of cognitive status, objective assessments including the clinical dementia rating, cognitive abilities screening instrument, and montreal cognitive assessment | Random forest, AdaBoost, LogitBoost, neural network, naive Bayes, and support vector machine (SVM) | Overall performance of the diagnostic models; Overall accuracy; Random forest: 0.86; AdaBoost: 0.83; LogitBoost: 0.81; Multilayer perceptron: 0.87; Naive Bayes: 0.87; SVM: 0.87 |
| Jammeh *et al*[5] | Total of 26483 patients aged > 65 yr (National Health Service data) | Total of 15469 read codes, of which 4301 were diagnosis codes, 5028 process of care codes, and 6101 medication codes | SVM, naive Bayes, random forest, logistic regression | Naive Bayes classifier gave the best performance with a sensitivity and specificity of 84.47% and 86.67%; The area under the curve naive Bayes: 0.869 |

WLR: Word list recall; SVM: Support vector machine.

explain the characteristics of these high dementia risk groups through the model. On the other hand, studies that aim to predict usually don't have a clear study model and often don't test a hypothesis. However, it is possible to confirm which variables are critical to predicting dementia. In particular, when there are new learning data, even if dementia does not develop, it has the advantage of providing the necessary help to the high dementia risk group by categorizing the elderly in the community into a high-risk group and a low-risk group. In summary, traditional statistical analyses emphasize inference, and machine learning focuses on prediction. Machine learning models such as random forests and neural networks partially overcome the issues of the black box by visually presenting the relative importance of variables using "variable importance" and "partial dependence plot". However, it still has limitations in interpreting the relationship or causality between variables.

Second, it may be difficult for mental science researchers to understand machine learning techniques that emphasize the accuracy of prediction rather than explaining the relationship between variables and do not focus on inference of hypotheses. Among the machine learning techniques, the penalized regression model, which is relatively close to the traditional statistical model, presents which explanatory variable is related to the response variable in which direction and how much, but it generally does not show the statistical significance of the explanatory variable like the linear regression model.

Third, unlike the traditional statistical model that models a small number of variables for a theoretical test, the machine learning technique is data-driven. Therefore, unless the data are unbiased good quality data, it is highly likely that biased results will be derived.

## TYPES OF MACHINE LEARNING

### *Regression algorithm*

Regression models based on stepwise selection have very poor performance in high-dimensional models. Therefore, it is compensated by using the regulation method, which gives a penalty every time the number of variables is increased. Lasso regression is a representative method[15]. In order to reduce the effect of outliers or singularity in the data, a robust regression technique that selects and trains a part of the data and reiterates this process can also be used[16].

### *Clustering algorithms*

The clustering algorithm classifies data into a specified number of clusters according to the similarity of the attributes. Since the data have only attribute values and labels do not exist, it is called unsupervised learning. The k-means algorithm is a representative clustering algorithm.

### Classification algorithms

Classification algorithms include decision tree (DT), support vector machine (SVM), k-nearest neighbor, and multilayer perceptron (MLP) ensemble learning. It is important to treat the imbalance of y-class when applying the classification algorithm. If there is an imbalance of classes, the group with a larger number of data is treated as more important, and the predictive performance decreases. Undersampling, oversampling, and synthetic minority over-sampling technique (SMOTE) methods are mainly used to deal with data imbalance[17], and it has been reported that the performance of SMOTE is generally better than that of undersampling and oversampling[18].

### DT

DT is a classifier that repeats binary classification based on the threshold value of a specific variable to the desired depth. Classification criteria variables and values are automatically learned from the data. The classification and regression tree algorithm is used for the learning of DT, instead of gradient descent. This method adds nodes step by step to minimize Shannon entropy or Gini index. The advantage of DT is that the learned classification results can be easily understood by people.

### SVM

SVM is a machine learning algorithm that finds the optimal decision boundary through linear separation that separates the hyperplane optimally. If data have a non-linear relationship, the same method is applied after transforming the input variable using a kernel function. SVM solves nonlinear problems related to input space (*e.g.*, two-dimension) by transforming it into a high-dimensional feature space. For example, when A = (a, d) and B = (b, c) are non-linearly separable in 2D, it has linearly separable characteristics if they are mapped in 3D. Thus, when adequate nonlinear mapping is used in a sufficiently large dimension, data with two classes can always be separated in the maximum-margin hyperplane. The advantage of SVM is that it can model complex nonlinear decision-making domains.

### MLP

Until the late 20$^{th}$ century, studies using artificial neural networks used shallow networks with two or less hidden layers[19]. However, as the effectiveness of deep neural networks was confirmed in the 21$^{st}$ century[19], the dropout technique and a rectified linear unit function were developed after 2010[20]. Through them, the era of deep learning has begun. The advantage of MLP is its excellent accuracy. Since the accuracy of deep neural networks is generally higher than that of shallow networks[21], it is recommended to apply deep neural networks to obtain more accurate classification or prediction in disease data. Although deep neural networks generally have slightly higher accuracy than other machine learning models, the learning time of it is longer[22]. Therefore, researchers need to select an algorithm suitable for the purpose when developing a machine learning model.

### Ensemble learning methods

Ensemble learning refers to a method to learn many models using only some samples or some variables of the data and use these models at the same time, which usually provides better predictive performance than when using a single model. Bootstrap aggregating (bagging) and boosting are representative ensemble learning techniques. Bagging is a method of determining the final output by fitting the result variables several times using some samples or only some variables of the training dataset[23]. Bagging shows good performance because as the number of classifiers increases, the variance of the prediction means of the classifiers decreases. Boosting refers to a method of sequentially generating multiple classifiers. The bagging of DT and random forest are typical examples of the ensemble learning technique. Fernandez-Delgado *et al*[24] compared the performance of classifiers for 121 datasets and reported that random forest impressively outperformed the rest 179 classifiers.

## STUDIES OF PREDICTING DEMENTIA BASED ON MACHINE LEARNING

Most of the previous studies[25,26] on the detection of dementia and the prediction of high-risk groups used traditional statistical methods such as regression analysis or structural equation models, but some studies[2-5] applied machine learning (Table 1). Previous studies using machine learning techniques for the elderly with dementia predicted dementia, mild cognitive impairment, and very mild dementia using various features including demographic information[2], medical records[2-5], dementia test scores [3,4], and normalized whole-brain volume[2]. Previous studies have shown that machine learning models had different predictive performance. Bansal *et al*[2] reported that the accuracy (99.52) of the DT model (J48) had the highest accuracy compared to other machine learning models (*e.g.*, naïve Bayes, random forest, and MLP). On the other hand, Zhu *et al*[4] revealed that the accuracy (predictive performance) of MLP (87%), naive Bayes (87%), and SVM (87%) was excellent. Jammeh *et al*[5] confirmed that the area under the curve (AUC) (predictive performance) of naive Bayes (AUC = 0.869) was the best compared to other machine learning models. The predictive performance of machine

learning techniques varies among studies because of the difference in machine data (especially, Y variables) imbalance, characteristics of features included in the model, and measurement methods of outcome variables. Therefore, further studies are continuously needed to check the predictive performance of each algorithm because, although some studies have proven that the performance of a specific machine learning algorithm is excellent, the results cannot be generalized for all types of data.

## CONCLUSION

This study introduced the definition and classification of machine learning techniques and case studies of predicting dementia based on machine learning. Various machine learning algorithms such as boosting model, artificial neural network, and random forest were used for predicting dementia. After the concept of deep learning was introduced, multilayer perceptron has been mainly used for recognizing the patterns of diseases. The development of machine learning algorithms will change primary care by applying advanced machine learning algorithms to detect high dementia risk groups in the future. If researchers pay attention to machine learning and make an effort to learn it while coping with these changes, artificial intelligence technology can be used as a powerful tool (method) for conducting mental science studies.

## FOOTNOTES

**Author contributions:** Byeon H designed the study, involved in data interpretation, preformed the statistical analysis, and assisted with writing the article.

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*REVIEW*

# Prenatal nicotine alters development of the laterodorsal tegmentum: Possible role for attention-deficit/hyperactivity disorder and drug dependence

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## Abstract

As we cycle between the states of wakefulness and sleep, a bilateral cholinergic nucleus in the pontine brain stem, the laterodorsal tegmentum (LDT), plays a critical role in controlling salience processing, attention, behavioral arousal, and electrophysiological signatures of the sub- and microstates of sleep. Disorders involving abnormal alterations in behavioral and motivated states, such as drug dependence, likely involve dysfunctions in LDT signaling. In addition, as the LDT exhibits connectivity with the thalamus and mesocortical circuits, as well as receives direct, excitatory input from the prefrontal cortex, a role for the LDT in cognitive symptoms characterizing attention-deficit/hyperactivity disorder (ADHD) including impulsivity, inflexibility, and dysfunctions of attention is suggested. Prenatal nicotine exposure (PNE) is associated with a higher risk for later life development of drug dependence and ADHD, suggesting alteration in development of brain regions involved in these behaviors. PNE has been shown to alter glutamate and cholinergic signaling within the LDT. As glutamate and acetylcholine are major excitatory mediators, these alterations would likely alter excitatory output to target regions in limbic motivational circuits and to thalamic and cortical networks mediating executive control. Further, PNE alters neuronal development and transmission within prefrontal cortex and limbic areas that send input to the LDT, which would compound effects of differential processing within the PNE LDT. When taken together, alterations in signaling in the LDT are likely to play a role in negative behavioral outcomes seen in PNE individuals, including a heightened risk of drug dependence and ADHD behaviors.

**Key Words:** Prenatal nicotine exposure; Pregnancy outcome; Addiction risk; Laterodorsal tegmentum; Arousal; Attention

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**Core Tip:** Offspring of women who used nicotine-containing products while pregnant exhibit risk factors for later-life development of cognitive deficits, including attention deficit/hyperactivity disorder and drug dependence. This suggests that circuits that play a role in cognition are being altered by nicotine. The laterodorsal tegmental nucleus of the pons plays a role in attention, motivation, and other cognitive-related processes, and nicotine during gestation has been shown in animal studies to alter functioning of this nucleus. In this review, we discuss the human and animal literature that indicate that alterations in functioning of the laterodorsal tegmental nucleus could arise following prenatal nicotine exposure, and that these alterations could play a role in the negative risks associated with early-life nicotine exposure.

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## INTRODUCTION

### *Prenatal nicotine and the contribution of the laterodorsal tegmentum to executive control*

Smoking during pregnancy exposes the fetus to a variety of chemicals known to have effects on development. Arguably, the most influential of these is nicotine, which crosses the placenta and sequesters within the fetal compartment, which is unfortunate as nicotine is a known teratogen likely involved in differences seen in the development of neural structures characterized in functional imaging studies (for review, see[1]). Many of the brain regions that have been found to be altered are known to play a role in cognitive processing and behavioral control, and differences in their development associated with prenatal nicotine exposure (PNE) could underlie negative cognitive and other behavioral outcomes. Clinically, among other maladaptive, neurally-based behavioral outcomes, PNE individuals exhibit a higher degree of drug dependence[2-6], impulsivity[7,8], and dysfunctions in attention[9-12]. Given the occurrence of these later two behaviors in PNE, an association between attention-deficit/hyperactivity disorder (ADHD) and PNE has been explicitly examined, with studies suggesting that there is a higher incidence of ADHD in offspring of women who smoked while pregnant[10,12-14]. Although few studies have addressed the topic, some reports detail sex-based differences in behavioral outcomes following PNE, which could be due to hormonally-based differential sensitivities to nicotine's ability to alter structural development[15]. In studies examining the damaging neural effects of nicotine that could underlie negative behavioral outcomes, the focus has been directed to changes within neural structures well known to play a role in cognition- and motivation control, such as the prefrontal cortex (PFC), amygdala, hippocampus, and mesoaccumbal circuits comprising the nucleus accumbens (NAc) and the ventral tegmental area (VTA). Unsurprisingly, the role of changes imposed by PNE in the brain stem in PNE-associated behavioral risks has been much less well studied.

While the literature supporting a role of the brain stem in cognitive functioning is scant, since the 1930s, it has been known that damage to the brain stem causes dysfunctions in executive control, suggesting that the brain stem transmits signals that are incorporated into high-order, cognitive processing[16,17]. While sparse, anatomical lesion, pharmacological, and stimulation data began to emerge supporting the interpretation that the brain stem plays a role that extends beyond simply receiving information, and its role may include participation as an inherent functional player in shaping cognitive function. Thanks in large part to the advent of optogenetics, which allows selective dissection of cellular contributions to behavior, the amount of data showing a role of the laterodorsal tegmentum (LDT) in cognitive-based behaviors has exploded, and when taken together, suggest that the brain stem is an integral functional component of the circuits that are involved with executive functions[18-20]. Specifically, determination of the role played by neurons within the LDT of the pons in motivation, attention, and other facets of goal-directed behaviors[21-25] suggests that a re-evaluation is warranted of the perception that the brain stem receives input from top-down circuits and passively transmits it onwards. At this time, it appears clear that the LDT is not a region that passively complies with and executes commands from higher order centers, but rather that the LDT plays a significant role in the coding of information in associative circuits in a bottom-up direction. Further, data suggest that the LDT could be involved in behavioral and mental behaviors known to be altered in PNE individuals. In this review, we discuss data from recent studies that should lead to redefinitions of the extent of control of behavior played by what is considered the most ancestral region of the brain, the brain stem. In addition, results from these studies should raise alarm that early life exposures to nicotine could alter the way by which the LDT responds to input, which would subsequently impact LDT output. This alteration could participate in the generation of PNE-associated behavioral abnormalities in motivation and executive control.

## COGNITION RELIES ON ACETYLCHOLINE, AND ONE OF THE MAJOR SOURCES OF ACETYLCHOLINE IS THE LDT

Cognitive functioning, including that involved in attention, relies on acetylcholine (ACh) acting at neuronal nicotinic ACh receptors (nAChRs) and muscarinic ACh receptors. Cholinergic dysfunction has been correlated with impairment of long-term memory[26-28], and manipulations of cholinergic systems have been shown to play a role in attentional states[29]. In humans, augmentation of cholinergic signaling at nAChRs in individuals not sensitized by nicotine has been shown to improve cognitive functions, such as memory and attention[30,31]. Transdermal nicotine delivery in non-smoking subjects increases attention by reducing omission errors and response time variability in the human continuous performance task[32]. Further, nicotine has been shown to improve attentional performance in a variety of cognitive disorders in non-sensitized adults, including ADHD[33], Alzheimer's disease[34], and schizophrenia[35]. These and other studies have focused on the development of cognitive enhancing drugs based upon agonism or potentiation of nAChRs.

While nicotine is an excellent agonist for the nAChR, endogenous signaling at nAChRs is mediated by ACh. The majority of neuronal ACh is sourced from two main clusters in the brain, one within the forebrain and another within the pontine brain stem, with both clusters sending diffuse projections to a variety of targets. The LDT and the pedunculopontine tegmental nucleus (PPT) comprise the cholinergic cluster in the pontine brain stem and send ACh projections widely to both caudal and rostral targets. Both the PPT and the LDT participate in the reticular activating system and, as part of it, exert cholinergic control over the thalamus, which has been implicated in behavioral state control and electro-encephalographic states of arousal and attention. Both cholinergic brain stem nuclei also play a role in sensorimotor integration, reinforcement, and learning; however, their contribution to the control of these processes differs, which is supported by the distinct segregation in the projection patterns of the two nuclei and by divergent functional outcomes upon stimulation[18,36]. The PPT appears particularly involved in control of gait and posture, which is supported by a heavy innervation of structures involved in motor functions, and findings that, when stimulated, the PPT modulates activity in the basal ganglia as well as in the formation and updating of action-outcome associations and rapid decision making[37,38]. The LDT does send projections to the substantia nigra, suggesting it could participate in control of movement; however, optogenetic stimulation of this projection did not result in locomotion, which provides functional evidence in line with the interpretation that the projection from the LDT to the portion of the striatum involved in motor control is not as involved as the PPT projections are in movement control[18,25]. The LDT appears to be more involved than the PPT in the control of cognition and behavior, as suggested from a plethora of anatomical, behavioral, and stimulation studies. This control appears to be exerted directly *via* connectivity of the LDT to limbic structures as well as indirectly *via* synapses within specific thalamic nuclei (Figure 1).

### *Role of LDT cholinergic transmission in thalamic control*

Projections from the LDT synapsing within the principle relay nuclei of the thalamus suggest control of the LDT over thalamic cellular activity that would impact output to cortical regions *via* thalamo-cortical tracts. Thalamo-cortical radiations are involved in relaying information critical in mediation of consciousness, arousal, and alertness. While thought to be a passive relay station, recent evidence suggests the possibility that the thalamus may govern amplification of cortical signaling and therefore be involved more centrally in cognitive behaviors, including behavioral flexibility, than previously appreciated. The more active role emerging of the thalamus in cognitive processes highlights that afferent input to the thalamus, such as that sourcing from the LDT, likely plays a modulatory role in cognitive control[39]. Retrograde studies revealed that the major cholinergic input into the thalamus, particularly in the cognitive-relevant anterior, reticular, ventroposterior, mediodorsal, and central medial nuclei, sources from LDT neurons through both ipsi- and counter-lateral projections[40-43]. Double retrograde labeling approaches showed that many of the LDT neurons that send projections to the thalamus also send collaterals to extra thalamic targets. One of these extra thalamic targets is the VTA, which is also involved in cognitive and limbic functioning through dopamine (DA)-mediated transmission in the mesoaccumbal and mesocortical pathways[18]. Since both the thalamus and VTA project to the NAc, a central nucleus in limbic processing that sends input both to the thalamus and to cortical targets *via* the mesocortical pathway, this collateralized projection pattern provides the LDT with direct and indirect control of striatal regions that project to and release DA within the cortex. Therefore, regulation of cognitive functions *via* variations in DA levels in the PFC, which exerts executive functioning, could occur *via* LDT actions within the thalamus or, more indirectly, *via* LDT collaterals in the VTA, suggesting a complex potential for LDT control over DA transmission. However, this dual projection pattern is not consistently seen in all LDT thalamic targets.

The anterior thalamus, which is known to be involved in alertness, learning, and memory, receives cholinergic projections from the LDT that arise from a different population of cholinergic LDT cells than those sending input to the VTA, suggesting presence of distinct sub-populations of LDT cells[44].

Functional activation of the LDT-thalamic pathway has been shown. LDT cholinergic neurons fire action potentials most vigorously during rapid eye movement sleep and aroused wakefulness[45,46],

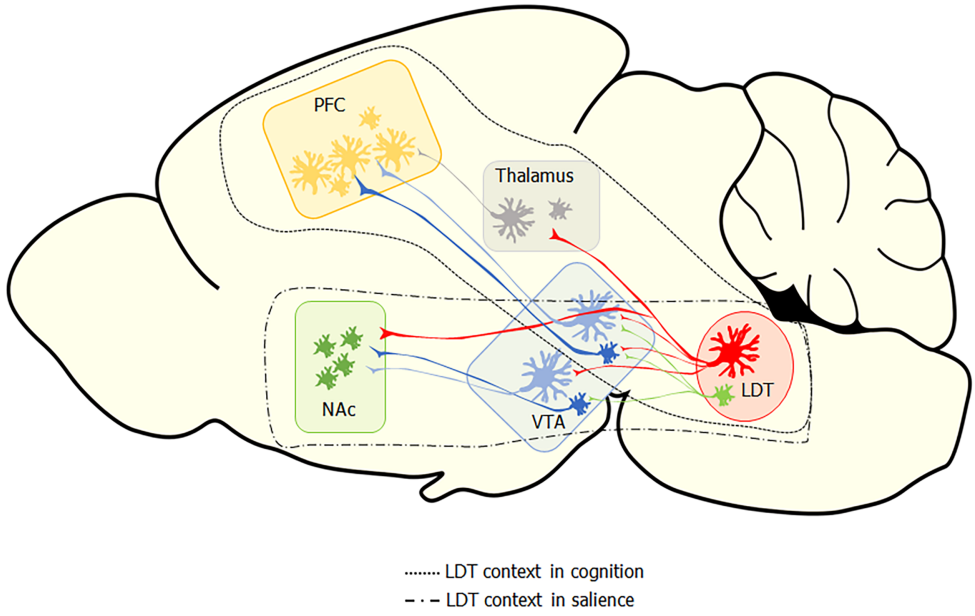


**Figure 1 Overview of laterodorsal tegmental nucleus efferent to reward-related brain areas and to thalamic centers involved in modulating cortical function.** PFC: Prefrontal cortex; Thal: Thalamus; NAc: Nucleus accumbens; VTA: Ventral tegmental area; LDT: Laterodorsal tegmental nucleus.

which has been shown with *in vivo* micro dialysis to result in increases in the levels of ACh within the thalamus during these states[47]. Functional connections between the LDT and different thalamic centers have also been shown by *in vivo* electrophysiology, combined with pharmacological approaches. Electrical stimulation of the LDT, as well as pharmacological stimulation of the thalamus *via* application of the muscarinic ACh receptor agonist carbachol, enhanced firing rates of ventroposterior medial thalamic cells, indirectly modulating sensory-related cortical areas involved in selective attention[19,48]. Actions of cholinergic agonists in the ventroposterior medial thalamus were associated with modulation of tonic firing patterns and activation of thalamic-cortical projecting centers, such as the somatosensory cortex responsible for processing sensory perception[49,50]. Lesions of the mediodorsal thalamic nucleus, one of the thalamic regions that receives the heaviest cholinergic inputs from the LDT and exhibits reciprocal innervation with the PFC, resulted in working memory deficits in rats, as assayed by impaired radial maze performance[51]. Injection of cholinergic agents enhanced mediodorsal thalamus-PFC synaptic plasticity and inhibited mechanisms underlying depotentiation, which is a mechanism behind the weakening of strength of synapses[52]. Weak *in vivo* stimulation of the LDT nucleus was shown to eliminate spontaneous and evoked burst-firing in the reticular nucleus of the thalamus in anesthetized rats, whereas strong LDT activation induced discharge within this region[53]. In addition, pulse trains injected within the LDT enhanced the responsiveness of anterior thalamic neurons to cortical stimuli[54]. Further, lesions of the anterior or central thalamic nuclei reduced performance in memory testing and diminished attention, which were effects also seen upon local infusion of cholinergic antagonists at these sites, thereby linking the deficits in ACh in the thalamus to working memory and attentional impairments[55-57]. Functional imaging studies in humans have shown that the improvement of attention induced by nicotine is associated with increased activation of the thalamus[58,59], and, furthermore, functional magnetic resonance imaging has provided evidence that more general cognitive improvements observed upon nicotine exposure could be due to activation of nAChRs in the thalamus[60]. When taken together, it is clear that cholinergic actions in the thalamus are involved in attention and cognition, and cholinergic input is provided by a functional connection between the LDT and the thalamus. Therefore, LDT-thalamic cholinergic projections confer upon the LDT an indirect control of cortical excitability through thalamic relay centers and could be involved in amplification of cognitive processing controlled by the thalamus.

### *Role of cholinergic and GABAergic transmission from the LDT to limbic control pathways*

Besides participating in cholinergic modulation of cortico-thalamic circuits, ultrastructural, immunolabeling, and optogenetic studies indicate that the LDT exerts a cholinergic modulatory role within structures and circuits associated with the limbic system that underlie motivation and salience, including the VTA and the NAc[61,62]. The LDT has been shown to be the main source of cholinergic inputs into the NAc core and the VTA, and studies have suggested that LDT cholinergic inputs onto VTA cells modulate activity of DA-containing VTA neurons that participate in both the mesocortical and mesoaccumbal pathways[61-65]. The LDT has been shown to form mainly asymmetric, putatively excitatory, synapses within the striatal complex, particularly onto DA-containing VTA cells and within

the NAc core[64]. While the majority of VTA neurons are DA-containing, 35% of the cells in the VTA are non-dopaminergic, with 25 % of these being inhibitory gamma-aminobutyric acid (GABA)ergic neurons [66]. GABAergic VTA neurons in both mesoaccumbal and mesocortical pathways were found to receive symmetric synapses, putatively inhibitory inputs, from LDT projections, which led to the suggestion that the LDT could participate in disinhibitory mechanisms by inhibiting striatal GABAergic interneurons[22,63]. This point was reinforced by findings that following optogenetic activation of LDT cholinergic cells projecting to DA VTA neurons, a late activation could be observed, consistent with a rebound excitation after the stimulation of GABAergic interneurons[18]. Inhibitory input from the LDT directed to GABAergic cells of the mesocortical pathways could also participate in disinhibitory processes occurring indirectly between the LDT and PFC[63], which could occur in combination with thalamic inhibitory input. Interestingly, symmetric synapses from the LDT were selectively found on DA neurons in the mesocortical pathway, as there was no evidence for their presence in mesoaccumbal DA neurons, indicating that directly mediated, inhibitory influences of the LDT on limbic DA output are mainly targeted to mesocortical DA pathways[63].

## ROLE OF DA, THE VTA, AND THE LDT IN DRUG DEPENDENCE

Activation of the mesoaccumbal DA system resulting in DA output to the NAc is involved in reward reinforcement to natural stimuli including sex[67], social interaction[68], and food[69]. Large rises in DA encode a positive valence to these triggering stimuli, which is reinforcing and leads to incentive for repeat of behaviors leading to acquisition of the triggering stimulus. However, in addition to activation of this system by stimuli promotive of health and continuation of our species, drugs of abuse also activate this system and do so to a greater extent than natural stimuli, leading to rises in DA of several fold greater than those evoked by non-drug stimuli[70]. All drugs of abuse share the common ability to activate the mesoaccumbal system, whereas this property is not shared by the majority of drugs that do not exhibit dependence-inducing effects[70]. While drugs of abuse lead to rises in DA, diverse pharmacologic properties across drug classes confer differences in the way by which rises in DA are elicited. The pharmacologic actions leading to rises in DA can be directly-mediated excitatory cellular effects on DA cells, or actions can be indirectly-mediated *via* afferent input to DA cells, which can include cells within the VTA that are not DA-containing neurons, including GABAergic cells and glutamate cells[71] or non VTA sourced projections. Following a large body of studies showing the critical role of VTA DA in incentive salience, the central paradigm regarding the neural processes underlying development of dependence to drugs of abuse involves a high degree of drug-induced DA activation of the mesoaccumbal pathway *via* actions on the heterogenous VTA cell population but also activation of extra-VTA input terminating in the VTA or NAc.

### *Excitatory LDT cells*

Extensive evidence shows that the connectivity of the LDT to the VTA and NAc plays a role in drug addiction behaviors suggestive of drug actions on the LDT-VTA-NAc circuit. Early microdialysis studies showed that electrical stimulation of the LDT resulted in large rises in DA in the NAc, which was reduced by intra-VTA application of nAChR, muscarinic ACh receptor, and ionotropic glutamate receptor antagonists, suggesting ACh and glutamate output from the LDT play a role in DA rises[21]. Further, rises in DA induced by morphine were reduced in LDT lesioned rats[72]. Behaviorally relevant, large rises in DA were found to result from high frequency, burst firing of VTA DA neurons, which was a firing pattern impossible to elicit in VTA brain slices[73-76]. This finding suggested that afferent input severed in the slice preparation was crucial for firing activity of VTA DA-neurons. Consistent with this, *in vivo* studies revealed that DA VTA burst firing was reliant on an intact LDT, since pharmacologic inactivation of the LDT eliminated this firing pattern[77]. The influence of the LDT was thought to be mediated *via* cholinergic inputs[77], and further work showed that cholinergic output from the LDT shapes the firing of VTA neurons and biases VTA activity towards a burst pattern from a more disorganized discharge that likely results in higher release of DA to levels sufficient to underlie the encoding of value of stimulus value, as the rises were associated with evidence of changes in motivated behaviors[18].

Initial optogenetic studies of the role of the LDT in motivated behaviors showed that stimulation of the LDT engendered conditioned place preference (CPP), a model of both associative learning and drug-dependent behavior, which was an effect attributed to the demonstrated presence of glutamatergic output in the LDT-VTA circuit, albeit direct *in vivo* evidence of the role of this circuit in behavioral outcome was not provided[22]. Further optogenetic work confirmed the ability of stimulation of the LDT to induce CPP, and a role of the cholinergic LDT population was shown[64,78]. The role of the cholinergic LDT cells in motivated behaviors mediated by the VTA was additionally supported by loss of CPP conditioning to cocaine when associated with pharmacologic inactivation of the cholinergic LDT cells as well as failure to induce CPP when muscarinic and nicotinic receptors were blocked in the VTA [79]. In addition, photo excitation of LDT cholinergic terminals in the VTA was shown to cause positive reinforcement as subjects spent more time in the compartment in which they received photo

stimulation, which was an effect similar to that induced when cholinergic LDT-NAc input was activated [25]. In a study designed to tease apart the relative contribution of excitatory LDT neurons to motivated behavior, the role in CPP of both glutamate and cholinergic LDT cell populations was examined under identical laboratory conditions[80]. Selective activation of either the glutamate or cholinergic LDT projections to the VTA by light pulses resulted in induction of CPP in mice, leading to the conclusion that both glutamate and cholinergic LDT inputs to the VTA play a role in the net rewarding effects of drugs of abuse[80]. However, the role played by the two excitatory transmitters was found to differ, suggesting that glutamatergic LDT projections may be important for initial reinforcement of place preference, whereas cholinergic mechanisms underlie continued reinforcement, as longer stays in the light drug-paired chamber were seen upon stimulation of cholinergic LDT projections[80]. Glutamatergic neurons, which exhibit very different connectivity to limbic structures and different firing patterns due to differences in intrinsic membrane properties to that exhibited by cholinergic neurons, likely do play a role in the control of VTA neurons, but that role is probably complementary to that served by ACh-containing cells[18,80]. Whether or not the ACh or the glutamatergic LDT afferents to the VTA play a more relevant role in drug dependence behaviors remains an open and very interesting question to address, especially vis a vis treatment targets; however, what is clear from the data is that the LDT can control DA efflux from the VTA in a behaviorally relevant fashion *via* both major excitatory transmitter systems that project to the mesoaccumbal pathway.

### *Inhibitory LDT cells*

The role of the GABAergic LDT neurons, which can be local or projecting, and their impact on eventual VTA DA efflux have been less well examined. A role of LDT-mediated disinhibition of VTA GABAergic cells, especially those within mesocortical circuits, has been proposed[63]. Stimulation of GABAergic VTA cells was found to inhibit firing of DA cells, whereas their optogenetic activation led to conditioned place aversion, a behavioral model of aversive stimulation, suggesting that their inhibition would be promotive of DA release and the encoding of stimuli with a positive valence[81,82]. However, excitation of GABAergic LDT neurons was found to mediate innate fear responses following exposure to predator odorant in rodents[81]. This action was found to be mediated by the lateral habenula, which sends input to the VTA and the GABAergic rostromedial tegmental nucleus, also identified as the tail of the VTA, known to mediate aversive responses. While direct evidence is needed, this raises the interpretation that GABAergic LDT neurons projecting to the VTA do not play a functionally relevant role in inhibiting GABAergic VTA cells, leading to rises in DA sufficient for reinforcement. It is also possible that they inhibit a subset of the remaining 75% of the non-GABAergic VTA population, and/or LDT input directed to the lateral habenula and rostromedial tegmental nucleus supersedes any effect of local VTA disinhibition. A non-mutually exclusive possibility is that different populations of LDT GABAergic projection neurons exist. The role of the local GABAergic interneurons in the LDT, which abut the cholinergic neurons, and their impact on excitatory output are unexplored. When taken together, while it remains to be determined how the three main neuronal phenotypes of the LDT work in concert as a whole, output from the LDT results in significant changes in DA-VTA neuronal activity. As rises in DA efflux from the VTA are involved in reward prediction of salient stimuli and the LDT has been shown to control DA VTA output, the LDT is believed to be critically involved in DA-mediated striatal-control of behavior[83].

### *Role of DA and the LDT in PFC-controlled behaviors: A role of the LDT in ADHD?*

In addition to the heavy projections in the mesoaccumbal pathway, the LDT also provides the major cholinergic input to VTA neurons participating in the mesocortical pathway, which suggests the LDT has control over DA output to cortical regions as the direct projection from the striatum to the PFC of the mesocortical pathway provides the major DA innervation of the PFC. Connections from PFC back to limbic regions are present, creating a striatum cortical loop that is importantly involved in controlling behavioral flexibility and decision making[22,63,65]. Two such loops, comprised of dorsolateral PFC-striatum and anterior cingulate cortex-striatum connections, are suggested to control sustained and selective attention, respectively[84-86]. Dysfunctions within the mesocortical loop have been associated in humans with the expression of ADHD cardinal phenotypes. ADHD is a predominantly childhood mental disorder characterized by a combination of persistent maladaptive behaviors, including hyperactivity as well as cognitive impairments leading to failure to sustain directed attention and impulsivity, which involves decision making before full cognitive processing has occurred[87,88]. The classic triad of symptoms can manifest in several different negative ways, however, effects on emotionality and cognition tend to become exacerbated with age, likely due to increased stresses, whereas motor overactivity tends to abate in adulthood, which are clinical features relevant to note in animal experimentation of ADHD mechanisms[88].

Given the role of striatal cortical loops in control of behavior and the role of DA within behavioral controlling networks, DA dysfunctions within the PFC have been hypothesized to be involved in ADHD[87,89,90]. One of the most compelling findings supporting the hypothesis of a role of DA in ADHD is that stimulants of catecholaminergic systems have been among the most successful treatment of ADHD patients[90]. In addition, reductions in striatal DA transmission have been reported in ADHD patients[91]. Several animal studies have implicated DA function in mesocortical circuits encompassing

the PFC as involved in control of executive functions shown to be altered in ADHD as well as in the control of one of the hallmarks of ADHD, hyperactivity. Lesions of DA-containing mesocortical inputs to the PFC were associated with a hyperactive phenotype in rats[92]. Extracellular DA levels were increased in the PFC during the training phase of a radial maze task in rats, which assays working memory performance[93]. In addition, DA depletion in the PFC was associated with working memory deficits in a T-maze paradigm[94], and similar cognitive deficits were seen after intra-PFC administration of type I DR receptor (DR1) antagonists[95,96]. Depletion of DA release into the PFC was shown to induce cognitive deficits in rhesus monkeys[97], and subsequent studies found that application of D1R antagonists into the PFC promoted deficits in oculomotor delay responses and working memory tasks[98,99]. Behavioral flexibility and decision making were reduced following antagonism of D1R and type 2 DA receptors in the PFC[65]. Interestingly, while D1R agonists injected at low doses within the PFC increased visual attentional performance in rats[100], increased activation by higher concentrations of the D1R agonists impaired performance in both rodents and primates, suggesting optimal D1R activation in the PFC is necessary for proper working memory performance[101-104]. These data support the hypothesis that DA levels within the PFC exert cognitive effects; however, this control is likely exerted in an "inverted U shape" manner, as originally suggested more than 100 years ago[105]. According to this suggestion, optimal dopamine levels within the PFC are believed to be associated with maximum behavioral performance, and either hyper- or hypo-DA function in this brain region compromises executive behaviors[106].

Since PFC-projecting DA VTA neurons contribute to the DA tone of cortical circuits brain regions, which modulate mesocortical VTA activity, the LDT could indirectly contribute to cortical DA functioning. Therefore, activity in the LDT could be indirectly involved in ADHD behaviors *via* the control exerted on mesocortical pathways *via* excitatory synapses on DA mesocortical VTA cells directed to the PFC. A role of the LDT in control of PFC DA levels is indirectly supported by findings that local infusions of nAChR antagonists in the rat VTA resulted in deficits in PFC-controlled behaviors that are DA dependent[107]. Further, control of PFC DA levels could be exerted by the LDT *via* disinhibitory mechanisms mediated by inhibitory LDT inputs directed to GABAergic mesocortical neurons controlling PFC function[63]. In addition, non-DA control of the LDT in ADHD behaviors could be mediated by LDT-thalamic connections, since thalamic-cortical circuits associated with ADHD-related hyperactivity receive input from the LDT[84-86,88]. In addition, the LDT could be involved in other ADHD features, including impulsive behavior. This conclusion is supported by findings that reductions in activation in thalamic relay nuclei are seen in gamblers exhibiting poor impulse control[108]. When taken together, altered neurotransmitter signaling from the LDT could be involved in increasing susceptibility for dysfunctions of attention and cognition. Thus, although no direct evidence has linked LDT function or dysfunction with ADHD-related phenotypes, studies investigating dysfunction of DA mesocortical, mesostriatal, and thalamo-cortical pathways in working memory and other cognitive-related behaviors support the assumption that alterations in the LDT-VTA and LDT-thalamic circuitry could contribute to ADHD-related behavioral deficits. In support of this hypothesis, the brain stem reticular activating system has been suggested to contribute to attention and filtration of interfering stimuli and, accordingly, was thought to play a potential role in disorders involving disorganization in cognitive processes[109]. However, detection of structural abnormities in the brain stem of human patients suffering from ADHD-associated cognitive dysfunctions awaits as these structures have proven to be more challenging than forebrain structures to image[87].

## AFFERENT INPUT TO THE LDT IS LIKELY TO INFLUENCE LDT OUTPUT

When taken together, anatomical and functional studies suggest a complex and regulatory role of LDT neurons on VTA functioning and provide further support of the influence of the LDT on mesoaccumbal DA transmission as a relevant step in encoding the valence of environmental stimuli[21]. In addition, these data suggest that the LDT plays a regulatory role in other cognitive functions *via* actions in PFC through direct striatal influence on DA transmission or through indirect actions mediated by thalamic relay centers. However, the circuits in which the LDT participates are not one way, and the LDT receives dense afferent input from many extra-LDT regions throughout the brain (Figure 2). A high number of LDT inputs were shown to source from pontine and midbrain nuclei, including the PPT, central gray, and deep mesencephalic nucleus[61]. In addition, afferents sourcing from cerebellum, spinal cord, basal ganglia, medulla, the bed nucleus of the stria terminalis, and the hypothalamus, particularly from the lateral hypothalamus that houses neurons importantly involved in state-control, were noted[61,110]. Relevant to circuits involved in motivated behaviors and cognition, substantial projections sourced from the VTA as well as the cerebral cortex, including the medial and orbitofrontal PFC[61,111]. These studies demonstrate that LDT afferents source from cortical, limbic, and somatosensory systems, which do, in some cases, themselves receive projections from the LDT. If the LDT passively transmitted information from higher order brain regions, alterations in LDT functioning would not be expected to have a significant impact on downstream signals. However, as the LDT processes signals before they are transmitted, alterations in LDT functioning would be expected to have

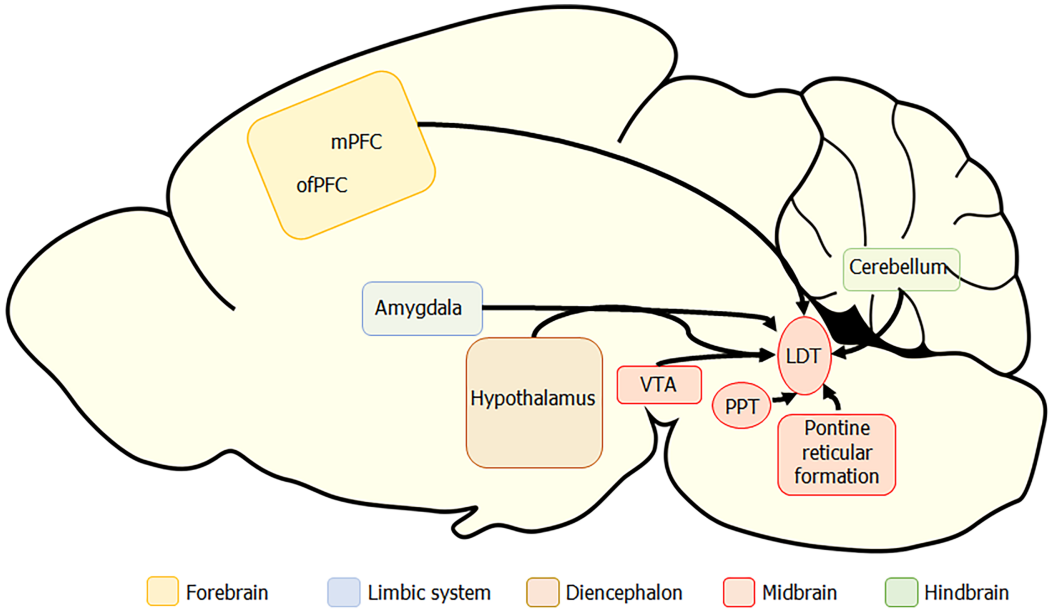


**Figure 2 Overview of input sourcing from cognitive and limbic regions synapsing within the laterodorsal tegmental nucleus.** PFC: Prefrontal cortex; Hippoc: Hippocampus; NAc: Nucleus accumbens; VTA: Ventral tegmental area; LDT: Laterodorsal tegmental nucleus.

an exponential effect on signal transmission if processing occurs on signals that themselves are altered. Therefore, in dysfunctional conditions, the effect of alterations in LDT functioning would be expected to have a high degree of impact *via* alteration of input and output transmission within networks important in behavioral outputs.

## PNE EFFECTS ON COGNITIVE-BASED BEHAVIORS THAT COULD INVOLVE THE LDT

### *PNE animal models*

PNE has been associated with a higher risk of several adverse behaviors that are controlled by signaling in the striatum, thalamus, and PFC. Functional and anatomical studies have shown that molecular, cellular, and structural changes present in these regions are found following PNE. Control over these regions is exerted by the LDT either *via* direct or indirect pathways. When taken together with the fact that there is currently no human data available regarding structural development within the LDT associated with PNE, experimentally examining the issue of PNE-associated changes in the LDT is warranted if we wish to understand fully the mechanisms underlying the higher risk of these maladaptive, cognitive-based behaviors in PNE individuals. While three-dimensional human-derived brain organoid models have recently been used to examine effects on neural development of environmental factors, including nicotine, they do not allow for examination of behavioral associations[112] (for review, see[113]). Accordingly, for studies examining synaptic changes that could underlie behavioral outcomes, we require animal models of PNE in which both cellular and behavioral studies can be conducted. However, PNE animal models vary in several very important factors, making it difficult to choose the model best suited for translational significance.

One major difference in PNE models to date in the choice and breed of animal that have been used, which is a not insignificant confound as different species, and strains within the same species can respond with diverse behavioral outcomes suggestive of different cellular changes[114]. PNE studies also have varied in the experimental design regarding the method by which nicotine was applied, which has included subcutaneous application either *via* injection or implantation of osmotic mini pumps, intravenous application, intraperitoneal injection, or inhalation of cigarette smoke. In a less invasive approach, nicotine can be applied *via* the drinking water of the pregnant dams. Each of these methods would be expected to result in blood nicotine levels that are different and perhaps not similar in kinetics to those seen in humans, as nicotine concentrations in the blood of regular smokers are usually constant during periods of wakefulness in order to abate symptoms of withdrawal.

Other variations in the model utilized have sourced from differences in the nicotine dose utilized, the age at which the animal behaviors were assessed, the behavioral tests which were employed, and the time during pregnancy at which nicotine exposure occurred. This later point is relevant to physiological, peripheral effects engendered by first time exposures to nicotine, and concern of induction of stress, which is known to induce neural changes in offspring and maternal behaviors, as nicotine can be aversive in drug naïve individuals. If the first-time exposure occurs to the pregnant dam during the

gestational period, which has been necessary in experimental designs when pumps with limited lifetimes have been utilized, the confound of stress' role in physiological responses complicate attribution of effects to nicotine. As it is known that sex plays a role in PNE behavioral outcomes, interpretation of data where sexes have been pooled, or extrapolation to the opposite sex when single sex selective studies have been conducted, limits applicability of the data. These and other variables inherent to any laboratory study with rodents make it difficult to compare results across studies and further complicate determination as to which is the superior model in order to make conclusions relevant to the human situation [see[115] for a full discussion of the issue].

Despite these complications, examination of results from many PNE studies has led to the conclusion that the most robust rodent model of PNE is the oral nicotine intake method during pregnancy[115]. Arguments for this model include that it reflects pharmacodynamics/kinetics observed in human smokers, ADHD- and addiction-related behaviors have been seen in the rodent offspring with features similar to those seen in humans exposed to nicotine *in utero*, the nicotine exposure pattern is very similar to that seen in humans as it occurs during wakefulness, and stress levels are minimized, as no manipulations or surgical procedures are required. Finally, it avoids the issue of first-time exposure to nicotine to the dam occurring during gestational periods, which could introduce confounding factors. Accordingly, this model has been utilized by many laboratories to examine alterations in excitatory signaling within several brain regions associated with PNE. Further, in work conducted in the LDT, an outbred strain of mouse, the Naval Medical Research Institute (NMRI) mouse, was used in our investigations in order to attempt to reflect better the genetic diversity of the human population.

### *Behavioral alterations in PNE rodent models and in humans exposed gestationally to nicotine*

Validation of the PNE NMRI model *via* maternal drinking water model was provided by evaluation and detection of high cotinine levels in newborn PNE pups, confirming the gestational nicotine exposure of the fetus following maternal ingestion of nicotine *via* the drinking water[116]. Behavioral tasks were also employed in order to characterize the behavioral phenotype associated with early-life exposure to nicotine *via* the drinking water[116]. Although an extensive review of the behavioral deficits associated with PNE treatment in rodents is beyond the scope of this article, it is of interest when comparing dysfunctions of behaviors in which the LDT plays a role to compare sex-based findings of PNE-associated effects on affective state, cognition, and locomotion in the NMRI mouse exposed to nicotine *via* maternal drinking water with data from other laboratories using different PNE models, and with human clinical data, in order to evaluate the face validity of the oral NMRI PNE model.

**Anxiety and PNE:** Within young adulthood [postnatal day (PND)42-48], PNE treatment in NMRI mice was associated with anxiety-like behaviors that were effects only seen in male offspring[116]. In inbred C57BL/6J mice exposed to nicotine *via* maternal drinking water, anxiety levels of males have been reported to be increased[114,117]. However, it appears that the nicotine concentration is relevant for the anxiolytic action, since in another study using lower concentrations PNE did not alter anxiety levels in the offspring[118]. The method of nicotine administration is also likely important, as failure to detect anxiolytic-like behavior is common in studies in which nicotine was administered subcutaneously[119-121]. Early life exposures to nicotine have been suggested to heighten the risk of anxiety disorders in humans[122]. However, very few studies have been conducted examining the influence of smoking during pregnancy on anxiety in offspring, and in those conducted, mixed results have been reported with no gender segregation[123-125]. In perhaps the largest and well-characterized cohort examined, the Norwegian Mother and Child Cohort (1999-2009), maternal smoking was associated with an increase in externalizing behaviors, including anxiety; however, unfortunately, sex-based effects were not taken into account[122]. Interestingly, a larger impact was noted when the amount of cigarettes was considered as well as the time during gestation when smoking was present, with a more negative effect on anxiety the earlier nicotine was present in the pregnancy. This later finding was supported by a study of a much smaller population of Australian mother and child pairs[124-126]. In conclusion, while an enhanced risk of anxiety-like behavior remains a point to be examined in both human and animal studies, available data suggest that the PNE mouse model, in which nicotine is provided in the drinking water, represents a reasonable, translational model that can be used to study the mechanistic neural link between anxiety and PNE.

**Hyperactivity and PNE:** The oral administration method of PNE in NMRI mice was associated with hyperactivity in the offspring of both sexes in the open arena test (PND42-48)[116]. When nicotine was delivered *via* drinking water to pregnant rodent dams in other studies, PNE treatment was associated with hyperactivity in males, albeit some data showed that this effect could be present in both sexes or it could be linked to the genetic background of the mouse employed[114,127-130]. Differences can also be due to strain, as in a study using outbred mice, hyperactivity was seen in male PNE Swiss mice during late adolescence[119]. Further, it is relevant to consider the nicotine concentrations employed to draw associations between PNE and locomotor behavior, as no locomotor effects were seen in both sexes in a study employing a lower nicotine level before and during pregnancy[118], contrasting with previous findings showing PNE hyperactivity in similar models and ages investigated when higher doses of nicotine were utilized[116,127,130,131]. Although one study reported greater hyperactivity in 3-year-old

boys following exposure to tobacco during gestation[132], another study suggested that prenatal tobacco exposure could have a causal relationship with hyperactivity seen in both adolescent and adult women[8]. Thus, the sex-dependency of hyperactive effects on offspring following PNE in experimental studies and prenatal tobacco exposure in clinical investigations is still unclear. Further, sex-dependent effects on motor activity of nicotine exposure *via* e-cigarette usage during pregnancy need to be examined as neurobehavioral evaluation of a small population of neonates exposed to e-cigarettes reported abnormal motor reflexes linked to later life motor development that were similar to those seen in prenatally cigarette exposed infants[133]. The small sample size precluded sex-based comparisons.

**Cognitive deficits, ADHD, and PNE:** In the oral PNE NMRI model, poorer outcomes have been detected in the spontaneous alternate behavior test, which is a Y-maze based test quantifying performance of a cognitive-dependent behavior. Scores indicative of cognitive impairments and working memory deficits were found in both sexes in young adult NMRI PNE offspring. In the outbred NMRI PNE model, both male and female offspring displayed deficits in the percentage of correct alternate behavior in the Y-maze, suggesting deficits in hippocampal-dependent working memory[116]. Moreover, this same model was associated with performance impairments in the rodent continuous performance task, particularly in scores related with learning, impulsivity, and attention, but only male offspring were investigated[134]. In inbred mice in which nicotine was delivered *via* drinking water of pregnant dams, deficits in the spontaneous alternate behavior performance assessed in adult offspring were seen only in males[118,135]. However, another study using twice the concentration of nicotine in the same inbred strain found that PNE cognitive deficits in this test were present in both PNE males and females[131], suggesting that the concentration of nicotine given could play a role in the sex-dependent outcomes. Further, young adult rats exposed prenatally to nicotine through the drinking water displayed impaired performance in another test of working spatial memory, the radial maze test. This effect was seen in both sexes[136], but little or no effect was found in PNE models using minipumps or subcutaneous injections[137-139]. A higher risk of cognitive deficits has been found in children born from pregnant smokers[9,12,140]. This association was also found in a study with a cohort of 574 children born from mothers who used NRTs during pregnancy[141]. Additionally, children prenatally exposed to smoke exhibited alterations in cognitive control circuitry and exhibited attention dysfunctions[142]. When taken together, the data strongly support the conclusion that nicotine during the prenatal period is associated with cognitive deficits. PNE individuals show up to a three-fold higher risk of ADHD, and a strong association has been made between nicotine levels in the mother during the first and second trimesters and diagnosis of ADHD[9]. Interestingly, ADHD has shown a sex bias, with reports of the male/female ratio being 4:1. However, carefully controlled, large population studies indicate the ratio is more likely 2:1 in adolescence, which was a proportion maintained into adulthood, leading the authors to suggest the possibility that males exhibit a greater level of hyperactivity/impulsive symptoms that are disruptive than manifestations of these behaviors in females, and that female ADHD behaviors tend to be more cognitive-based and require more probing to detect[143]. Although clinical studies have employed both sexes to draw associations between prenatal tobacco exposure and ADHD, sex-dependent effects in the offspring were not taken into consideration to date in these studies, as genders were pooled together[144]. Our findings and others suggest that perhaps more clinical investigative attempts to identify and better recognize ADHD symptoms, especially in females, are warranted.

**Conclusions on the animal models of PNE:** In conclusion, we found a greater level of anxiety, locomotion, and cognitive deficiencies, with sex-specificity regarding emotional behaviors, in young adult NMRI mice prenatally exposed to nicotine *via* the drinking water[116,134]. The behavioral associations seen reproduced some of the relevant features observed in ADHD patients, which are associated with exposures prenatally to nicotine. When taken together, behavioral outcomes associated with PNE models in which gestational nicotine exposure occurs *via* maternal drinking water suggest that this model provides reasonable face validity relative to others by recapitulation of risk outcomes of individuals exposed to prenatal tobacco which have been seen in epidemiological investigations. This conclusion leads us to suggest that this model displays high translational potential for research focused on the connection of developmental exposure to nicotine to later-life appearance of ADHD-associated symptoms,= as well as in the search of relevant brain circuit alterations that could contribute to this phenotype. Studies using other rodent models of PNE have provided data that these models do exhibit characteristics of drug dependence and in some cases, recapitulate sex-differences seen in humans[3,145-147]. However, whether the NMRI PNE drinking water model exhibits features seen related to drug dependence and whether sex-based differences exist remains an open question which must be experimentally addressed.

## SYNAPTIC AND CELLULAR ALTERATIONS IN PNE LDT NEURONS

The oral administration PNE NMRI model has demonstrated many of the behavioral risks associated

with gestational nicotine exposure in humans that could involve the LDT, and other models of PNE have shown the heightened risk of drug dependency, suggesting a role of nicotine in this outcome. This model has been utilized to explore the molecular changes occurring in the LDT during development when nicotine is present in order to gain insight into alterations that could contribute to the behavioral risks found in PNE individuals in which this brain stem nucleus is implicated.

### *Cholinergic signaling is altered in PNE LDT neurons*

We have reported that gestational exposure to nicotine induces cellular changes in cholinergic signaling within the LDT that are findings in line with other studies, which have shown alterations in players in cholinergic transmission in diverse regions of the brain using alternative PNE models[145,148]. Indeed, reductions in the expression of nAChRs in different regions of the PNE brain, including the brain stem= as well as lower striatal and cortical DA levels[149-151], led to the suggestion that alterations in nAChRs induced by PNE are involved in dysfunctions in DA functioning in these regions underlying the higher drug dependence and ADHD risks in PNE individuals[152], which could involve changes in function of nAChRs in the LDT. Consistent with this, we have provided evidence that PNE is associated with alterations in functioning of nAChRs in the LDT. Nicotine application *ex vivo* in LDT-containing brain slices resulted in significantly smaller rises in calcium in LDT cells from PNE individuals when compared to rises elicited in control LDT cells. Further, in the PNE LDT, a reduced proportion of cells responded with rises in calcium upon nicotine application[153]. Although the mechanism of altered nAChR-stimulated calcium was not examined, changes in calcium responses seen could be due to reductions in numbers of nAChRs and/or could be due to alterations in nAChR subunit composition, as the subunit composition determines calcium permeability.

### *Glutamate signaling is altered in LDT neurons of PNE mice*

Glutamate transmission was also altered in the LDT of PNE mice, which has been seen in other regions of the rodent brain examined across several different PNE models. Glutamate mediates fast excitatory transmission *via* actions at three ionotropic receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-D-aspartate (NMDA), and kainate. AMPA receptors (AMPARs) are tetramers composed of different assemblies of subunits (GluA1-4)[154], exhibit widespread expression in the brain, and are the major mediators of fast glutamate synaptic transmission[155]. Further, expression of AMPAR subunits follows a distinct ontogenetic pattern, which suggests specific functional roles at different periods during development. In the rat hippocampus, GluA1 expression remains constant until young adulthood, whereas GluA3 increases, and both GluA2 and GluA4 expressions are reduced over time[156], with GluA2 expression mostly limited to interneurons[157]. Within the VTA, electrophysiological evidence has suggested that GluA2-lacking AMPARs are abundant during the first postnatal days with a reduction in functional presence across age, with similar findings in cortical pyramidal cells and other brain areas[158-160]. NMDA receptors (NMDARs) are composed of heteromeric assemblies of GluN1-3 subunits, with obligatory presence of GluN1 with four GluN2 (GluN2A, GluN2B, GluN2C and GluN2D) and two GluN3 (GluN3A and GluN3B) possible isoforms. NMDAR subunit expression levels also shift during ontogeny, particularly among GluN2 and GluN3 subunits. GluN2A expression starts after birth, with a steady rise during development so that levels are at their highest in the adult brain. GluN2B/D subunits are expressed during the intra-uterine period, with GluN2B expression maintained at high levels up to the first postnatal week, and progressively decreasing in expression across age, culminating gradually in a limited restriction of presence within the forebrain, whereas GluN2D is markedly reduced in expression immediately after birth. GluN2C subunits appear late during development, at PND10, and exhibit a restricted expression and are primarily found within cerebellum and olfactory bulb. Finally, GluN3A subunits increase expression following birth, but thereafter, decline progressively to low levels; whereas, conversely, GluN3B expression shows a slow and steady increase throughout development[161-164].

Investigations from other laboratories have reported alterations in glutamate receptor subunit expression from expected patterns in the PNE brain. Differences in levels of expression of the GluA2, GluN1, and GluN2C subunits were seen in the PNE hippocampus at PND63 following osmotic pump-mediated PNE for 14 gestational days, whereas changes in glutamate signaling-related molecules were observed at younger ages[165]. Using a similar PNE model in which nicotine exposure was also provided by osmotic minipumps, a reduced expression of GluA1 subunits, smaller amplitudes in glutamate-mediated, miniature postsynaptic excitatory currents, reduced long-term potentiation, and increased long-term depression in hippocampal CA1 neurons associated with PNE treatment were reported[166-168]. As changes in synaptic strength are mediated by alterations in AMPA and NMDA receptor functioning, PNE-associated differences in long-term potentiation and long-term depression suggest changes in the functionality of glutamate receptors. Further, PNE from gestational day 5 was associated with a reduced frequency of excitatory postsynaptic currents and altered AMPA-mediated synaptic transmission in hypoglossal motoneurons in brain slices from rat neonates[169,170]. In addition, reduced glutamatergic input was found in the PNE auditory brainstem[171]. Finally, gestational nicotine exposure was associated with suppression of progenitor cell differentiation in the glutamatergic-projecting granule cells within the hippocampal dentate gyrus at PND21 in rats[172] as well as with the impairment of progenitor cell proliferation during gestation, resulting in reductions in

the availability of pyramidal glutamate neurons within the postnatal medial PFC in mice[173]. Overall, these studies indicate that the teratogenic effects of nicotine can affect glutamate signaling in different brain regions, which could affect both pre- and postsynaptic mechanisms in neuronal circuits.

Our studies in the LDT extend the observations of PNE effects on glutamate functionality. When the effects of PNE treatment in the NMRI model in male offspring were examined, early life exposure to nicotine was associated with larger, AMPA receptor-mediated intracellular calcium rises and inward currents in LDT cells (Figure 3)[174]. Pharmacological examination suggested a delayed switching of GluA2-lacking AMPA receptors in PNE LDT neurons, suggesting a time lag in appropriate development of AMPA receptors associated with early exposure to nicotine. Presynaptic release of glutamate was lower in PNE LDT cells, which would contribute to reductions in postsynaptic excitability of these neurons[174]. Notably, an unpublished observation in our group was that, despite the finding that PNE LDT neurons exhibited significantly higher AMPAR-stimulated current amplitudes, enhanced membrane responsiveness was not sufficient to activate these neurons to fire action potentials to the same extent as observed in control cells, further suggesting reduced excitability. NMDA receptors in the LDT were also shown to be associated with alterations in functionality following PNE. Our data indicated that PNE was associated with changes in both synaptic and extrasynaptic NMDAR function, which was cell-type specific. In putatively GABAergic inhibitory LDT cells, PNE treatment was associated with higher functional presence of GluN2B-containing synaptic NMDARs and higher levels of silent synapses, without major functional effects detected in extrasynaptic NMDARs. Further, putatively cholinergic cells displayed reduced functional presence of GluN2B subunits in synaptic NMDARs, and changes in extrasynaptic NMDARs[175]. Our electrophysiological findings were in line with a previous calcium imaging study conducted in our group that did not include electrophysiology, suggesting lower intracellular calcium increases upon a second bath application of NMDA, which was interpreted to reflect a shift in properties of NMDARs in LDT cells following PNE treatment[176].

### *Membrane property differences leading to alterations in excitability*

Passive and active properties of cholinergic neurons of the LDT were also examined in the PNE as membrane properties underlie cellular excitability. Lower neuronal excitability among LDT cells in PNE mice was exhibited in several different paradigms. PNE LDT neurons exhibited a higher rheobase, which is defined as the minimum amount of current necessary to elicit an action potential[177], and smaller activity-induced rises in calcium putatively due to PNE-associated alterations in voltage-operated calcium channels, although this point was not directly examined[174]. Examination of the action potential revealed a broader spike in the PNE, due to a slower decay slope that was likely reflective of differences in ionic conductance underlying the kinetics of the rise and decay times. Further studies revealed data consistent with a reduction in function of $K^+$-channels activated by $Ca^{+2}$[174]. In addition, the amplitude of the afterhyperpolarization was significantly larger in the PNE, which also suggested alterations in ionic conductance[153]. When taken together, the effects on the kinetics of the action potential and the amplitude of the afterhyperpolarization would likely result in a limitation in the firing frequency.

### *Summary of the impact of cellular changes associated with PNE in the LDT*

In summary, our studies of PNE LDT neurons found reductions in membrane excitability, effects on the action potential kinetics and the amplitude of the afterhyperpolarization that likely resulted in limitations in firing frequency, reductions in nAChR-induced calcium rises suggestive of a reduction in excitability mediated by nAChRs, and changes in glutamate signaling that would lead to decreases in excitability in cholinergic neurons, with concurrent increases in activity of GABAergic cells, which could be local or projection neurons. Interestingly, some of these changes were present in young animals but did not persist into adulthood, suggesting that nicotine-associated alterations in development of LDT transmission would result in changes in output that would participate differentially across ontogeny and thereby, affect neuronal excitability differentially across age. When taken together, our studies have led us to the working hypothesis that PNE is associated with a hypofunctioning LDT, which would lead to reductions in output of excitatory neurotransmitters onto projection targets, including those within the VTA, NAc, and thalamus.

## LDT TARGETS INVOLVED IN DA-MEDIATED BEHAVIORS: RELEVANCE TO THE HIGHER RISK OF DRUG DEPENDENCE AND ADHD AFTER PNE

Reductions in cholinergic transmission from the LDT to target areas would be expected to have a significant effect on behaviors controlled by those target regions. Data from the oral NMRI PNE model have led to our development of the 'hypocholinergic hypothesis', and predictions from this hypothesis could mechanistically play a role in adverse behavioral outcomes associated with PNE.

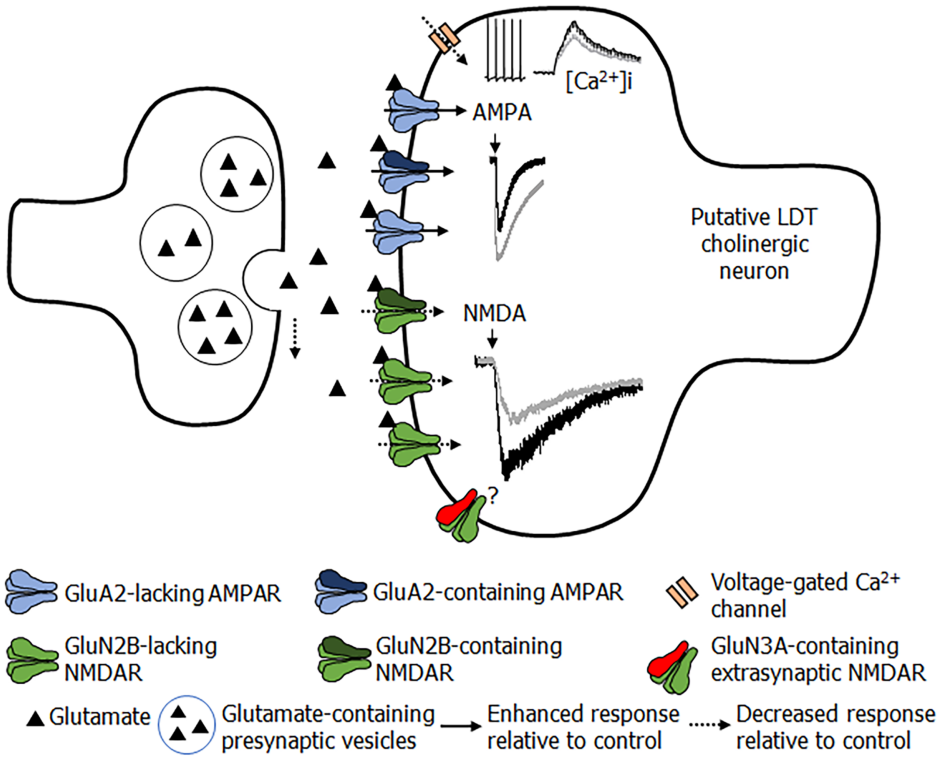


**Figure 3 Overview of input sourcing from cognitive and limbic regions synapsing within the Laterodorsal tegmental nucleus.** PFC: Prefrontal cortex; Hippoc: Hippocampus; NAc: Nucleus accumbens; VTA: Ventral tegmental area; LDT: Laterodorsal tegmental nucleus.

### *Drug dependence and the hypocholinergic hypothesis*

PNE has been associated with a higher risk of later life development of drug dependence, especially to nicotine as well as a higher risk of drug experimentation and abuse, which is an association seen in studies correcting for confounds such as maternal cigarette consumption after birth[2-5]. Importantly, an increased risk for nicotine dependence was also seen in investigations including sibling-pairs discordant for prenatal tobacco exposure that were controlled for such confounds as postnatal maternal smoking, which linked prenatal cigarette exposure with increased liability for nicotine addiction[178-180]. Gestational exposure to nicotine has been associated with a higher likelihood for abusing drugs, particularly during the adolescent time, including marijuana and cocaine, which is only explained in part by increased experimentation during the adolescent period and incomplete development of cortical regions of the brain[6,181]. An association has also been found during adulthood, in which gestationally-exposed young adults displayed significantly higher rates of cigarette smoking and nicotine dependence, which has been shown in independent studies[3,182].

As burst firing in mesoaccumbal circuits leads to behaviorally relevant levels and temporal patterns of DA in the NAc, which signal salience and engender continued usage of drugs, if PNE was associated with alterations in DA VTA burst firing engendered by exposure to drugs of abuse, or endogenous rewarding stimuli, this could alter coding of salience to the triggering stimuli. Interestingly, PNE was associated with alterations in the burst firing pattern of DA-VTA neurons of adolescent rats who were exposed to nicotine prenatally *via* mini-pump implantation[183], and several different models have identified an association between PNE treatment with lower DA release within the striatum[149,151,184]. When findings from these and other PNE cellular studies conducted in the VTA are taken together with our PNE LDT data, it is tempting to speculate that since the LDT is a critical modulator of burst firing in the VTA[77], PNE-associated alterations in LDT excitability are likely involved in differences seen in VTA neuronal firing in PNE. As a working hypothesis, our LDT cellular data have led us to propose that the alterations seen in the PNE LDT would result in a reduced cholinergic tone into target brain areas upon activation of the LDT following exposure to drugs of abuse. As ACh is excitatory to DA VTA neurons, among other consequences, a hypocholinergic tone from the LDT in PNE individuals would be expected to reduce, or at least drastically alter, behaviorally relevant, excitatory drive mediated, phasic DA VTA firing in response to stimuli. This hypothesis is also in line with very recent findings that inhibition of cholinergic transmission from the LDT influences neuronal firing of striatal neurons, associated with blockade of goal-directed behaviors, resulting in a more habitually-directed brain reflective of reduced flexibility in development of action strategies[18]. This hypothesis is somewhat in line with the 'hypoexcitability hypothesis' of drug dependence, which postulates that individuals with a higher liability for drug dependence possess a hypodopaminergic function within the mesolimbic circuit, a condition that could be due to genetic and epigenetic factors as well as *in utero*

insults, including drug exposure[178,185-188]. Arguably, hypodopaminergic functioning within the mesoaccumbal circuit could lead to a bias towards coding a relatively higher reward value upon drug intake when compared to natural rewards, or when compared to coding conferred by normal functioning of the mesolimbic circuit[189], and this higher reinforcement could underlie continuous usage and engender escalation in drug consumption[190,191]. Further, a progressive development towards a switch to habitual and non-flexible responses to stimuli, rather than development of novel adaptive strategies integrated within experienced behaviors, has been noted as a feature of drug dependence, although drug dependency can be seen perhaps more correctly as an imbalance between habit and goal-directed behaviors[192]. Neuroimaging studies are in line with our hypothesis, since a weaker response in striatum to reward anticipation was noted in adolescents born to smoking mothers, which was suggested to contribute to an increased risk factor for substance dependence[193]. Although our hypothesis requires experimental validation, it places the PNE-associated changes in the LDT as critically involved in the negative behavioral outcomes related to a higher risk of drug dependence in this population.

### *ADHD and the hypocholinergic hypothesis*

PNE has also been associated with a higher risk of later life development of ADHD-like behaviors. Modulation of catecholamine levels within the PFC has provided compelling experimental evidence of the role of DA pathways in impulsivity and attention deficits in behavioral performances[87,89,90]. Studies employing the PNE model in which nicotine was delivered *via* drinking water reported a reduced DA content in the PFC of adolescent male PNE mice[151], which corroborates findings of lower levels of DA in the cortex associated with PNE induced by minipump nicotine delivery model, an effect more pronounced at juvenile and adolescent stages[184], but which does not support findings in a later study with the minipump method in which DA levels were greater in the PFC of males and female offspring; however, the turnover ratio from DA to the DA metabolite homovanillic acid (HVA) was reduced only in the PNE males, suggestive of a sex-based PFC DA alteration[194]. Gestational tobacco smoke exposure was associated with a reduction in the DA and tyrosine hydroxylase levels within the striatum of PTE adult mice[149]. In adult PNE mice born to mothers exposed to nicotine *via* the drinking water, microdialysis of medial PFC showed reduced basal extracellular levels of DA[151]. Reductions in tyrosine hydroxylase, which catalyzes the conversion of L-tyrosine to L-DOPA, a precursor of DA, were detected using immunohistochemistry in DA-positive cells in the medial PFC and in the NAc core and shell in PNE animals[151].

As further evidence that alterations in DA signaling might be a common outcome following PNE, diminished levels of HVA were noted in the PFC in the mouse and rat PNE[151,195], which interestingly, while seen in the males of another study, was not noted in the female mice in that same work[194]. As lower HVA levels in spinal fluid and urine has been seen in clinical studies with both children and adult ADHD patients[196,197], alterations in DA turnover in the PFC could represent a common signaling dysfunction in both PNE and ADHD individuals. Accordingly, alterations in DA levels within the PFC seen in PNE rodents could underlie the higher risk of ADHD-type behaviors following early life exposure to nicotine. While it remains to be explored, alterations in LDT output to the DA cells of the mesocortical pathway could be involved in alterations of DA release in the PFC and NAc, which could represent a circuit-based alteration with great relevance for the heightened risks seen in PNE individuals to the development of ADHD. In line with this possibility, imaging studies on ADHD individuals have reported reduced activation of the ventral striatum in response to rewards, which is a similar response detected following PTE[193,198].

### *The thalamus and the hypocholinergic hypothesis*

The ascending cholinergic projections which encompass LDT output to thalamic regions suggest that the LDT could play a role in cognitive functions by modulating cortico-projecting thalamic neurons. Therefore, changes induced by gestational nicotine associated with synaptic alterations in the LDT could lead to alterations in cholinergic output terminating in the thalamus, which could also play a role in ADHD-like phenotypes associated with PNE. Interestingly, it has been hypothesized that alterations in cholinergic signaling in corticothalamic circuits induced by PNE could underlie deficits in sensory processing, contributing to the behavioral alterations seen in these individuals in response to environmental stimuli, including ADHD related behaviors[199]. The majority of studies of effects of PNE on cholinergic transmission in cognition-associated regions have focused on alterations in nAChRs; however, deficits suggestive of reduced cholinergic transmission were noted in cerebral regions[145,199]. When taken together, PNE-induced alterations in neuronal excitability and cholinergic and glutamate signaling within the LDT nucleus presumably affect LDT cholinergic input to thalamic relay nuclei. Our working hypothesis is that cholinergic output from the LDT to targets including those within the thalamo-cortical circuit is reduced in PNE, altering cortical activation in this network, leading to higher risks in this population of negative, cognitive behaviors controlled by the cortex. This conclusion is paralleled by findings of a reduced activation of the thalamus seen in conditions exhibiting poor impulse control characteristic of both ADHD and drug dependence[108]. Interestingly, PNE-associated alterations in cortical transmission were found to be sex-dependent, with a striking effect in males[145]. Although females were not as affected, PNE appeared to sensitize females to a greater

extent as they exhibited poorer cognitive outcomes upon later life exposure to nicotine when compared to those in males[145]. In summary, PNE-induced alterations in excitability, cholinergic, and glutamate signaling within the LDT nucleus would presumably affect LDT cholinergic tone present in thalamic centers leading to a dysfunction in thalamo-cortical brain circuits. This dysfunction in input could lead to altered processing of sensory stimuli and to cognitive deficits seen in ADHD present in those gestationally exposed to nicotine. Further, while this effect might be more prominent in males, early life exposure appears to leave behind a liability in females, in that later life exposure to nicotine could result in reductions in cholinergic transmission, which could have deleterious behavioral consequences on processes controlled by cortico-thalamic loops.

## CONCLUSION

While the brain stem might not be the obvious neural target in studies interested in cognitive processing, or in studies focused on cognitively-based disorders, over time, irrefutable evidence of the role the LDT plays in cognitive processes has been provided, and accordingly, alterations in LDT neuronal output could play a significant role in dysfunctions of cognitively-based behaviors. As regions of the brain known to modulate psychomotor, reward, memory, and attentional behaviors[93,200-202] are altered in PNE, and since the LDT exerts direct or indirect control over these regions, it would be expected that changes in glutamate and cholinergic receptor signaling, as well as in excitatory membrane processes in this nucleus seen in experimental models of gestational exposure to nicotine, would lead to reductions in excitatory cholinergic and glutamatergic output from the LDT to target regions. This scenario would lead in the PNE to a hypodopaminergic midbrain function, lower cholinergic tone in the NAc, and reduced cholinergic strength within ascending reticular activating system participating pathways to thalamic relay centers. Many of the regions targeted by LDT afferent input are DA releasing, which strongly suggests that DA release would be altered, as has been seen in the PNE brain. In addition, ACh stimulatory input to thalamic nuclei that control the cortex, including the PFC, would be altered, implying that changes in DA are also likely to be accompanied by non-DA changes due to PNE-associated differences in cholinergic tone within cortico-thalamic circuits. Finally, resulting postsynaptic processing of afferent input to the LDT would be altered, as cellular changes impacting on synaptic integration would likely be affected in this nucleus. Given the neural regions under control by activity of the LDT, PNE-associated alterations in LDT function would likely contribute to the enhanced risk of drug dependence and ADHD-like behaviors seen in PNE individuals, placing the brain stem as notably involved in these cognitively-based risks following PNE.

Increases in magnetic strength is allowing functional magnetic resonance imaging to reveal unprecedented details of the human brain, and as improvements are made in spatial resolution, it may become possible to conduct studies in humans to evaluate potential structural changes in LDT in PNE. Moreover, powerful *in vivo* electrophysiological techniques such as utilization of Neuropixels probes have emerged, allowing unprecedented recordings of deep brain structures in rodent models. Future studies employing *in vivo* electrophysiology, pharmacology, and optogenetic approaches in animal models should be used to determine the extent of LDT involvement in demonstrated PNE-induced alterations of midbrain DA functioning. Such studies could also dissect the effects of the LDT-thalamo-cortical pathway in cognitive and behavioral control. If our working hypothesis of PNE-associated reductions in ACh transmission sourcing from the LDT is confirmed, data obtained from future studies could identify a target brain substrate for therapeutic interventions involving cholinergic function within the LDT to VTA, NAc, and thalamic circuits in order to ameliorate drug dependence and ADHD-like associated behaviors, such as those seen in PNE individuals.

## FOOTNOTES

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*REVIEW*

# Drug-induced stuttering: A comprehensive literature review

Naemeh Nikvarz, Salehe Sabouri

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## Abstract

Drug-induced stuttering (DIS) is a type of neurogenic stuttering (NS). Although DIS has not been reported as frequently as other cases of NS in the literature, it is not a negligible adverse drug reaction (ADR) which can significantly affect the quality of life if not treated. This literature review aims to evaluate the epidemiological and clinical characteristics of DIS and suggests some pathophysiological mechanisms for this ADR. Relevant English-language reports in Google Scholar, PubMed, Web of Science, and Scopus were identified and assessed without time restriction. Finally, a total of 62 reports were included. Twenty-seven drugs caused 86 episodes of stuttering in 82 cases. The most episodes of DIS were related to antipsychotic drugs (57%), mostly including clozapine, followed by central nervous system agents (11.6%) and anticonvulsant drugs (9.3%). The majority of the cases were male and between the ages of 31 and 40 years. Repetitions were the most frequent core manifestations of DIS. In 55.8% of the episodes of DIS, the offending drug was withdrawn to manage stuttering, which resulted in significant improvement or complete relief of stuttering in all cases. Based on the suggested pathophysiological mechanisms for developmental stuttering and neurotransmitters dysfunctions involved in speech dysfluency, it seems that the abnormalities of several neurotransmitters, especially dopamine and glutamate, in different circuits and areas of the brain, including cortico-basal ganglia-thalamocortical loop and white matter fiber tracts, may be engaged in the pathogenesis of DIS.

**Key Words:** Drug; Dysfluency; Dysphemia; Psychotropics; Speech; Stammering

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**Core Tip:** Stuttering has two main types, developmental and acquired stuttering. Acquired stuttering is a manifestation of psychogenic or neurogenic disorders. Neurogenic stuttering is caused by brain injury, stroke, drugs, *etc.* Because most drugs inducing stuttering are used in the management of psychiatric and/or neurologic disorders, clinicians may merely attribute a new-onset stuttering to the worsening of the underlying disorder and neglect drugs as the causes of stuttering. Therefore, in this review, reports of drug-induced stuttering (DIS) are collected to provide information about epidemiological and clinical characteristics of DIS. Moreover, some pathophysiological changes are proposed as the underlying mechanisms of DIS.

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## INTRODUCTION

Speech production is a complex process involving various areas of the brain. Stuttering is a fluency disorder classified as developmental or acquired stuttering. Developmental stuttering, which is mentioned as childhood-onset fluency disorder in the diagnostic and statistical manual of mental disorders, fifth edition[1], often manifests between the ages of 2 and 6 years and spontaneously remits in most cases[2,3]. Acquired stuttering which has a secondary cause can occur in both children and adults. There are two types of acquired stuttering, psychogenic and neurogenic stuttering (NS). NS is caused by the traumatic brain injury, stroke, neurodegenerative disorders like Parkinson's disease (PD) and multiple sclerosis, seizure disorders, drugs, *etc.*[4]. In contrast to the other cases of NS, in which injuries to the brain areas involved in the speech production result in neuroanatomical and neurochemical abnormalities leading to stuttering, in the cases of drug-induced stuttering (DIS), short intervals between the initiation of culprit drug and the occurrence of stuttering and also between the dose reduction or discontinuation of the drug and the relief of stuttering suggest that DIS may be caused merely by neurochemical changes in the brain[5].

Although DIS has not been reported as frequently as other cases of NS in the literature, it is not a rare and negligible adverse drug reaction as Trenque *et al*[6] have reported that 724 individual case safety reports (ICSRs) containing the lowest level terms "stuttering" or "stutter" have been registered in Vigibase, the world health organization international pharmacovigilance database, up to May 31, 2020. The aim of this review is to describe the reported cases of DIS, including their demographic characteristics, medical history, predominant manifestations of stuttering, and the interventions done to manage stuttering and propose some probable pathophysiological mechanisms of this type of NS.

## SEARCH STRATEGY

The electronic databases Google Scholar, PubMed, Web of Science, and Scopus were searched by two reviewers without time limitation to find the relevant data. The keywords "stutter", "stuttering", "speech dysfluency", "drug-induced stuttering", "medication-induced stuttering", "psychotropics" "antipsychotics", "antiepileptics", "antiseizure drug", "anticonvulsants", "antidepressants", "clozapine", and "mood stabilizers" were used as search terms. The references of published articles were also examined to find any additional relevant reports. Case reports and case series were included. The reports whose full texts were not available and those being written in non-English language were excluded. According to the above-mentioned inclusion and exclusion criteria, 63 articles reporting DIS in 82 cases were considered in this review.

Twenty-seven drugs caused 86 episodes of stuttering in 82 cases. In four cases, two drugs caused stuttering[8-11]. Of 86 episodes of DIS, 49 (57%) were caused by antipsychotic drugs, followed by 10 (11.6%) by central nervous system (CNS) agents and 8 (9.3%) by anticonvulsant drugs (Table 1). As mentioned above, Trenque *et al*[6] have done a disproportionality analysis using reports registered in Vigibase to estimate the association between exposure to a drug and occurrence of stuttering. Of 22632669 reports registered in this database, 724 ICSRs contained the lowest level term "stuttering" or "stutter". Consistent with our findings, the most reports of stuttering were related to clozapine ($n$ = 40), pregabalin ($n$ = 33) methylphenidate ($n$ = 27), adalimumab ($n$ = 26), and olanzapine ($n$ = 25)[6]. The results of the disproportionality analysis done by Trenque *et al*[6] showed that the following drugs had the highest reported odds ratio: Methylphenidate (19.57; 95%CI: 13.3-28.7); topiramate (12.48; 95%CI: 7.1-22.1); olanzapine (11.98; 95%CI: 8-17.9); golimumab (10.25; 95%CI: 5.5-19.1); clozapine (8.44; 95%CI: 6.1-11.6); and pregabalin (8.36; 95%CI: 5.9-11.9).

**Table 1 Number of episodes of drug-induced stuttering reported in the online literature and included in the present review**

| Therapeutic category | Number of episodes of stuttering, *n* = 86 (%) |
|---|---|
| Antipsychotics | |
| Clozapine | 30 (34.9) |
| Olanzapine | 8 (9.3) |
| Risperidone | 4 (4.6) |
| Aripiprazole | 3 (3.5) |
| Trifluoperazine | 1 (1.2) |
| Chlorpromazine | 1 (1.2) |
| Fluphenazine | 1 (1.2) |
| Levomepromazine | 1 (1.2) |
| Anticonvulsants | |
| Phenytoin | 2 (2.3) |
| Divalproex | 2 (2.3) |
| Pregabalin | 2 (2.3) |
| Gabapentin | 1 (1.2) |
| Lamotrigine | 1 (1.2) |
| Central nervous system agents | |
| Methylphenidate | 3 (3.5) |
| Memantine | 2 (2.3) |
| Levodopa | 4 (4.6) |
| Dextroamphetamine and amphetamine salts (Adderall®) | 1 (1.2) |
| Atomoxetine | 1 (1.2) |
| Pemoline | 1 (1.2) |
| Antidepressants | |
| Sertraline | 3 (3.5) |
| Bupropion | 3 (3.5) |
| Desipramine | 1 (1.2) |
| Bipolar agents | |
| Lithium | 3 (3.5) |
| Respiratory tract agents | |
| Theophylline | 4 (4.6) |
| Anxiolytics | |
| Alprazolam | 1 (1.2) |
| Antineoplastics | |
| Methotrexate | 1 (1.2) |
| Pyrethrin | 1 (1.2) |
| Total | 86 (100) |

## DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS

Twenty-eight (34.6%) cases were female. Most patients were in the age range of 31 to 40 years. Fifteen cases were less than 12 years old. Gender and age of a patient were not reported in one case report[12] (Table 2).

**Table 2 Demographic characteristics and clinical history of patients**

| Characteristic/history[1] | *n* (%) |
|---|---|
| Gender | |
| Female | 28 (34.6) |
| Male | 53 (65.4) |
| Age (yr) | |
| < 12 | 15 (18.5) |
| 12-20 | 3 (3.7) |
| 21-30 | 15 (18.5) |
| 31-40 | 16 (19.7) |
| 41-50 | 13 (16) |
| 51-60 | 10 (12.3) |
| > 60 | 9 (11.1) |
| History of speech dysfluency | 11 (13.4) |

[1]The total number of the patients is 82, but the age and gender of one patient was not reported.

## MANIFESTATIONS OF STUTTERING

The primary or core behaviors of stuttering include sound, syllables, and monosyllabic whole-word repetitions, sound prolongations, and speech blocks[4]. The core behaviors were described only in 40 cases. Repetitions ($n$ = 42) were the most frequent primary behavior, followed by blockages ($n$ = 21) and sound prolongations ($n$ = 16). Twenty-one cases had more than one type of primary behavior (Table 3).

Individuals with developmental stuttering and persistent developmental stuttering (PDS) have anxiety related to stuttering[4]. However, patients with acquired stuttering may be annoyed by stuttering but do not experience anxiety. None of the reports included in this review described the psychological presentations of patients when producing a dysfluent speech.

Individuals with developmental stuttering[4,13] as well as patients with NS[13-15] often develop secondary behaviors including eye blinking, facial grimacing, interjections, word or phrase substitution, *etc*. The secondary behaviors are acts that are learnt in long term to cope with stuttering[13]. In the cases included in the present review, the secondary behaviors related to the stuttering were not reported. It may not be unusual because in comparison to the developmental stuttering, secondary behaviors are less prominent in the acquired stuttering[13]. Furthermore, we believe that since the development of the secondary behaviors requires a sufficient period, it is unlikely that patients with DIS have enough time to present these behaviors because interventions such as dose reduction or discontinuation of the culprit drug are carried out as soon as possible, which result in the complete relief or significant improvement of stuttering.

## MANAGEMENT

Therapeutic measures that resulted in significant improvement or complete relief of stuttering were drug withdrawal in 48 (55.8%) episodes, dose reduction in 18 (21%), addition of a new drug in three (3.6%), addition of a new drug besides dose reduction of the culprit drug in three (3.5%), and slow dose titration in two (2.3%). Moreover, in three (3.5%) episodes, the stuttering spontaneously remitted despite continuation of the offending drug with no dose reduction[16-18]. However, three (3.5%) episodes did not respond to the dose reduction[19-21]. For four (4.6%) episodes, the authors did not describe the actions taken to manage stuttering[22-25]. In two (2.3%) cases with PDS and PD, stuttering was exacerbated during levodopa-on periods, and levodopa was not discontinued[26,27] (Table 3).

## PATHOPHYSIOLOGY

In this section, the abnormalities suggested in the pathogenesis of developmental stuttering and PDS are described. Then, we propose some mechanisms for DIS based on the underlying impairments involved in the pathogenesis of PDS and developmental stuttering.

**Table 3 Summary of the case reports of drug-induced stuttering**

| Offending drug (dosage) | Patients' gender/age (yr) | Main indication of drug administration | Concomitant medications (dosage) | Onset/aggravation of stuttering | Primary behaviors | Concomitant symptoms | Management, response | Recurrence of stuttering after medication resumption | Concomitant disorders | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|
| Adderall XR® (20 mg/d) | Male/10 | ADHA | No other drugs | Within two weeks after the initiation of Adderall XR® | Single word and syllable repetitions and audible/silent sound prolongations | Increased tic behaviors, increased levels of social anxiety and communication related frustration | DC of Adderall XR® and start of atomoxetine (10 mg/d), significant reduction of stuttering | NR | Developmental stuttering, Tourette Syndrome, allergies, chronic ear infections, frequent phonic and motor tics | Donaher *et al* [82] |
| Alprazolam (1 mg) | Female/22 | Anxiety and depression | No other drugs | Shortly after increasing the dose | Not restricted to initial syllables, occurred on small grammatical words and substantive words, persisted during singing, not associated with secondary symptomatology such as facial grimacing or fist clenching | A right carotid bruit and a grade II/IV systolic murmur without a click, Minimal late systolic mitral valve prolapse and mild stenosis of both internal carotid arteries | DC of alprazolam, complete relief after two days | Within one hour after a single morning dose of 0.5 mg alprazolam, stuttering started, then 10 to 12 h later it was stopped. Stuttering did not happen with placebo | No history of speech dysfluency | Elliott *et al* [83] |
| Aripiprazole (2 mg/d) | Male/8 | ADHD combined-type | Atomoxetine (25 mg/d) | After 10 d of starting aripiprazole | NR | NR | DC of Aripiprazole, complete relief | NR | Developmental stuttering | Ünay *et al*[84] |
| Aripiprazole (10 mg/d) | Male/11 | Mild intellectual disability | No other drugs | 4 wk after increasing the dose to 10 mg/d | NR | Addition of clonazepam 0.75 mg/d, no improvement. Reduction of aripiprazole dose to 5 mg, complete relief over 10 d | NR | Increasing the dose to 10 mg resulted in re-emergence of stuttering which responded to DC of aripirazole | No history of speech dysfluency | Naguy *et al* [85] |
| Atomoxetine (started at 25 mg/d and gradually increased to 40 mg/d) | Male/14 | ADHD | No other drugs | Three weeks after the initiation of atomoxetine | NR | NR | Dose reduction to 25 mg/d, no improvement. DC of atomoxetine and initiation of methylphenidate, complete relief of atomoxetine-induced stuttering and | NR | Developmental stuttering since the age of 7 yr. ADHD predominantly inattentive | Cicek *et al*[86] |

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| | | | | | | | considerable reduction of developmental stuttering | | | |
| Bupropion (SR) 150 mg BID | Female/59 | Major depressive disorder | No other drugs | Four days after starting the drug | Sound prolongations, silent blocking, word production with excess physical tension, and monosyllabic whole-word repetitions. The stuttering was anxiogenic and restricted to initial syllables | Slight finger dysdiadochokinesia | DC of bupropion, complete relief of stuttering after 2 d | NR | No history of speech dysfluency | Fetterolf *et al* [78] |
| Bupropion SR (300 mg/d) | Male/38 | Major depressive disorder | No other drugs | Two days after increasing the dosage from 150 to 300 mg/d | Involuntary silent pauses or blocks, repetitions, prolongations of sounds, syllables, and words, affected rhythm of speech | NR | DC of bupropion, complete relief of stuttering | Re-administration of bupropion 150 mg after 1 wk caused stammering, and the drug was stopped immediately | A history of occasional smoking, no history of speech dysfluency | Bhatia *et al* [79] |
| Bupropion XL (300 mg/d) | Male/53 | Depression | No other drugs | After increasing the dosage of Bupropion | Difficulty starting words and repetition of syllables | NR | Administration of 5 mg oral haloperidol, stuttering was improved after 3 h and completely relieved after 7 h | Medication was continued | No history of speech dysfluency | McAllister *et al*[80] |
| Clozapine (up to 400 mg/d) | Female/32 | Paranoid schizophrenia | No other drugs | 4 wk after the initiation of clozapine | NR | Pharyngeal dystonia and buccolingual and facial dyskinesia associated with laryngeal dystonia | DC of clozapine, complete relief after 5 d | Clozapine was reintroduced at 100 mg/d. All symptoms reoccurred and relieved by clozapine cessation | History of neuroleptic-induced parkinsonism but not concomitant with dysarthria, no history of speech dysfluency | Thomas *et al* [63] |
| Clozapine (was initiated at 400 mg/d and gradually increased to 900 mg/d) | Female/28 | schizoaffective disorder | No other drugs | Shortly after the initiation of clozapine at 400 mg/d and not relieved during the gradual increase in the dosage to 900 mg/d | NR | NR | Dosage reduction to ≤ 700 mg/d, complete relief | The dose was not increased again | No history of speech dysfluency | Ebeling *et al* [87] |
| Clozapine (450-750 mg/d) | Female/49 | Psychosis | No other drugs | Stuttering was initiated when the clozapine dosage was | NR | Generalized seizure followed by myoclonic jerks of | The addition of phenytoin and then sodium valproate and | Clozapine was continued at 600 mg/d in addition to sodium | History of neuroleptic-induced acute | Supprian *et al* [59] |

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| | | | | increased to 700 mg/d | | her arms at the clozapine dosage of 750 mg/d | the reduction of clozapine dosage to 600 mg/d, complete relief | valproate 900 mg/d with no recurrence of stuttering | dystonia, no history of speech dysfluency | |
| Clozapine (300 mg/d) | Male/28 | Paranoid schizophrenia | No other drugs | Stuttering was initiated when the dosage of clozapine was increased from 150 mg to 300 mg/d and worsened with further increases in the clozapine dosage | NR | Generalized tonic colonic seizure at 425 mg/d along with the increased severity of stuttering | The reduction in the dosage of clozapine to 200 mg/d and addition of sodium valproate, significant improvement | The clozapine dosage was increased to 300 mg/d, but stuttering was not reoccurred albeit in the presence of sodium valproate 800 mg/d | No history of speech dysfluency | Duggal *et al* [64] |
| Clozapine (300 mg/d) | Male/57 | Schizoaffective disorder | Lithium (900 mg/d), sodium valproate (600 mg/d) | Four days after the initiation of clozapine | NR | NR | Dose reduction and DC of clozapine, complete relief after 7 d | NR | History of alcohol dependency, diabetes mellitus, no history of speech dysfluency | Bar *et al*[15] |
| Clozapine (up to 500 mg/d) | Not mentioned | Schizophrenia | No other drugs | A few days after the initiation of clozapine at 300 mg/d | NR | Myoclonic jerks at night and facial tics | Addition of sodium valproate, significant improvement, reducing the dosage of clozapine from 500 to 300 mg/d, complete relief | Clozapine was not discontinued | No history of speech dysfluency | Begum *et al* [11] |
| Clozapine (700 mg/d) | Female/33 | Schizophrenia | No other drugs | After reaching the daily dose to 700 mg (interval was not reported) | NR | Facial tics, seizure (seizure was initiated after the occurrence of stuttering) | Reduction in the dosage of clozapine to 600 mg/d, remarkable improvement, addition of sodium valproate to control seizure, no effect on stuttering | Clozapine was not discontinued | No history of speech dysfluency | Hallahan *et al* [58] |
| Clozapine (300 mg/d) | Female/34 | Schizophrenia | No other drugs | 2 wk after the initiation of clozapine | NR | Orofacial dyskinesia | Clozapine dosage reduction to 50 mg/d, complete relief | Clozapine was not discontinued | No history of speech dysfluency | Hallahan *et al* [58] |
| Clozapine (50-125 mg) | Male/62 | Delusional disorder | No other drugs | NR | Unsustained phonation, hesitation, irregular articulatory break down, sound repetition (not related to any specific sound, occurred at irregular word positions) | Orofacial dyskinesia, laryngeal and pharyngeal tardive dystonia, harsh and strangulated voice | Addition of tetrabenazine, patient could not tolerate the clozapine dosages more than 100 mg/d, DC of clozapine, complete relief | Clozapine was not restarted | No history of speech dysfluency | Lyall *et al*[9] |

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|---|---|---|---|---|---|---|---|---|---|---|
| Risperidone and then clozapine (450 mg/d and 75 mg/d) | Male/55 | Schizophrenia | No other drugs | NR | Occasional blocking, prolongation on word-initial sounds and repetitions of speech elements including one-syllable words at the beginning of his speech utterances | Stammering and unusual limb and trunk movements related to risperidone, belching, persistent hiccupping, worsening of the facial tic, and the orofacial dyskinesia involving the lips and tongue related to clozapine | Risperidone-induced stuttering: NR, the first episode of clozapine-induced stuttering, dose reduction to 125 mg/d and cessation of clozapine; significant improvement and complete relief of stuttering; the second time of clozapine-induced stuttering: addition of sodium valproate, considerable improvement | Clozapine was restarted at 75 mg/d, recurrence of stuttering, the addition of sodium valproate, 600 mg/d, significant improvement in the stuttering | History of head injury resulting in problems with executive functioning and a significant discrepancy, between the patient's verbal and performance IQ, making various clicking noises and blowing sounds when speaking before the initiation of antipsychotic drugs | Lyall *et al*[9] |
| Clozapine (up to 600 mg/d) | Male/35 | Schizotypal personality disorder | No other drugs | At clozapine dosage of 250 mg/d and progressive worsening with dose escalation | NR | NR | Reducing the dosage of clozapine to 200 mg/d, complete relief | Clozapine was continued at 200 mg/d without causing stuttering | History of trifluoperazine-induced truncal dystonia, no history of speech dysfluency | Krishnakanth *et al*[88] |
| Clozapine (200 mg/d) | Male/24 | Paranoid schizophrenia | No other drugs | After increase in the dosage of clozapine to 200 mg/d | NR | NR | DC of clozapine, complete relief | Clozapine was not restarted, amisulpiride was started and did not cause stuttering | No history of speech dysfluency | Krishnakanth *et al*[88] |
| Clozapine (250 mg/d) | Male/23 | Paranoid schizophrenia | No other drugs | At clozapine dosage of 250 mg/d (interval was not reported) | NR | NR | Clozapine dosage reduction to 150 mg/d, complete relief | Clozapine was not discontinued | History of neuroleptic-induced tardive dyskinesia, no history of speech dysfluency | Krishnakanth *et al*[88] |
| Clozapine (350 mg/d) | Male/15 | Undifferentiated schizophrenia | Clomipramine (225 mg/d) | Three years after the initiation of clozapine and clomipramine | Repetitions of syllables and transient accelerations of speech rate | Involuntary paroxysmal perioral movements, facial tic-like movements, myoclonic jerks of the upper limbs, GTC seizure | Addition of valproic acid at 500 mg/d, complete relief of stuttering within days | Clozapine was continued with valproic acid without reoccurrence of seizure and speech dysfluency during 2 yrs of follow-up | Symptoms of obsessive-compulsive disorder, no history of epilepsy or speech dysfluency | Horga *et al* [66] |
| Clozapine (up to 250 mg/d) | Male/29 | Undifferentiated schizophrenia | No other drugs | After the clozapine dosage titration from 137.5 mg/d to 150 mg/d | Frequent repetition and prolongation of syllables or words with frequent hesitations, blocking and | No focal dystonia or any evidence of seizure-like activity | Reducing and splitting the dose of clozapine to 50 mg in morning and 75 mg at night, improvement of stuttering | Reoccurrence of stuttering at clozapine dosage of 250 mg/d, improvement of stuttering after dose reduction to 225 mg/d, a later increase in the | History of antipsychotic-induced extrapyramidal symptoms, no history of speech dysfluency | Grover *et al* [61] |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | pauses | | | dosage to 300 mg/d did not cause recurrence of stuttering | | |
| Clozapine (400 mg/d) | Female/33 | Severe MDD with psychotic features | No other drugs | Stuttering was started after increasing the dosage of clozapine to 400 mg/d and worsened when the dosage was increase to 450 mg/d | Excessive prolongation of syllables or words | Sialorrhea | Addition of benztropine, no improvement. Reduction of the dosage of clozapine to 350 mg/d, complete relief | Stuttering recurred 16 d after increasing the clozapine dosage to 400 mg/d, but completely relieved after dosage reduction to 300 mg/d | None | Kumar *et al* [89] |
| Clozapine (up to 650 mg/d) | Male/32 | Paranoid schizophrenia | Sertraline (300 mg/d), lamotrigine (500 mg/d), haloperidol (4 mg/d), clonazepam (1 mg/d) | Noticeable stuttering at clozapine dosages of ≥ 600 mg/d | Expressive speech dysfluency with hesitancy and frequent pauses | Involuntary twitching of muscles of jaw | Clozapine dose reduction by 25 mg, improvement of stuttering | Clozapine was not discontinued | No history of speech dysfluency | Murphy *et al* [20] |
| Clozapine (400 mg/d) | Male/43 | Schizoaffective disorder | Paroxetine (20 mg/d) | Stuttering became noticeable when the clozapine daily dose was increased to more than 350 mg | Expressive speech dysfluency | NR | Clozapine dose reduction by 50 mg, improvement of stuttering | Clozapine was not discontinued | No history of speech dysfluency | Murphy *et al* [20] |
| Clozapine (450 mg/d) | Male/33 | Paranoid schizophrenia | No other drugs | Stuttering was developed during the initiation and dose titration of clozapine | Intermittent stuttering of speech | NR | Reducing the rate of dose titration, improvement of stuttering | Clozapine was not discontinued | No history of speech dysfluency | Murphy *et al* [20] |
| Clozapine (up to 300 mg/d) | Female/46 | Delusional disorder | No other drugs | Stuttering was developed during the initiation and dose titration of clozapine | Hesitancy with specific syllables | Orofacial dyskinesia | Clozapine dose reduction to 50 mg, improvement of stuttering | Clozapine was not discontinued | No history of speech dysfluency | Murphy *et al* [20] |
| Clozapine (325 mg/d) | Male/67 | Schizoaffective disorder | Duloxetine (60 mg/d), hyoscine (30 mg/d), aripiprazole (10 mg/d) | Stuttering was developed during the initiation and dose titration of clozapine | Expressive speech dysfluency | Orofacial twitching, upper limb jerking, hypersalivation | Reducing the rate of clozapine dose titration, improvement of stuttering | The clozapine dose was increased again to control psychotic symptoms, but nothing about the recurrence of stuttering was reported | Hearing impairment, hypertension | Murphy *et al* [20] |
| Clozapine (650 mg) | Female/63 | Paranoid schizophrenia | Amisulpride 200 mg/d, amitriptyline 25 mg/d, paroxetine 20 mg/d, zopiclone 3.75 mg/d | Stuttering was developed on a stable dose of clozapine | Expressive speech dysfluency with hesitancy | NR | Reducing the dose of clozapine by 50 mg, no improvement | Clozapine at 650 mg/d was recommenced, but authors did not report its effects on the recurrence of stuttering | No history of speech dysfluency | Murphy *et al* [20] |
| Clozapine (100 mg), aripiprazole (7.5 | Female/21 | Schizophrenia | No other drugs | At clozapine dosage of 100 mg/d and | NR | NR | Reduction of the dose of clozapine and | The drugs were not discontinued | Turner syndrome, no history of | Ertekin *et al* [8] |

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| mg/d) | | | | aripiprazole dosage of 7.5 mg/d | | | addition of aripiprazole (5 mg/d), complete relief. Reduction of the dose of aripiprazole from 5 to 7.5 mg/d, complete relief | | speech dysfluency | |
| Clozapine (gradually increased to 450 mg/d) | Male/16 | Schizoaffective disorder | Citalopram (NR), clonazepam (NR), atenolol (NR), lithium (NR) | Approximately 22 d after increasing the clozapine dosage to 400 mg/d | Persistent stuttering (difficulties with the pronunciation of letters "I," "D," and "T") | Orofacial dyskinesia with perioral twitching (started at clozapine dosage of 350 mg/d), microseizure according to EEG (at clozapine dosage of 400 mg/d) | Substituting lithium with divalproex sodium, improvement in stuttering 4 wk after receiving divalproex sodium at 500 mg BID | Clozapine was not discontinued because of its considerable therapeutic effects | History of type 1 DM, DKA with episodic hallucinations, GERD, cerebral contusion, occasional cocaine use, anxiety-induced intermittent stuttering, family history of stuttering | Rachamallu *et al*[62] |
| Clozapine (up to 600 mg/d) | Female/22 | Schizophrenia | Fluoxetine (60 mg/d) | Stuttering was developed after the clozapine dose escalation to 300 mg/d | NR | NR | Reduction in the clozapine dose and initiation of ECT, minimal improvement | Clozapine was not discontinued | NR | Das *et al*[19] |
| Clozapine (450 mg/d) | Man/in early 40s | NR | No other drugs | After increasing the clozapine daily dose from 400 mg to 450 mg | NR | Marked increase in seizure activity | DC of clozapine, nothing was clearly reported by the authors | NR | NR | Kranidiotis *et al*[24] |
| Clozapine (200 mg/d) | Male/38 | Schizophrenia | No other drugs | Stuttering was evident at 200 mg/d and became so disabling at 350 mg/d | NR | NR | Dose reduction of clozapine and addition of amisulpiride and BDZ, reduction of stuttering, DC of clozapine, complete relief | Clozapine was not restarted | NR | Kranidiotis *et al*[24] |
| Clozapine (300 mg BID) | Male/57 | Paranoid schizophrenia | Risperidone, IM injection (37.5 mg every 2 wk), Risperidone, oral (1.5 mg/d which increased to 2 mg BID on admission) | Two days after admission (the dosage of clozapine, 300 mg BID, was not changed on admission) | NR | Orofacial and extremities myoclonic jerks, drop attacks | Clozapine dosage reduction to 100 mg BID, resolution of stuttering within two days | The patient was discharged on clozapine 150 mg BID, but author reported nothing about stuttering at follow-up | History of COPD, hypertension, DM, and chronic back pain, cigarette smoking | Chochol *et al*[60] |
| Clozapine (125 mg/d) | Male/29 | Schizophrenia | No other drugs | A few days after titrating the clozapine dosage to 125 mg/d | Frequent repetitions of words that included broken words | NR | Reducing the clozapine dosage to 100 mg/d, significant improvement | Clozapine dosage was not re-escalated | No history of speech dysfluency | Nagendrappa *et al*[90] |

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| Clozapine (up to 200 mg/d) | female/25 | Schizophrenia | No other drugs | At clozapine dosage dose of 150 mg/d (interval was not mentioned) | NR | Tonic-clonic epileptic seizure | DC of clozapine and start of amisulpiride and biperiden, complete relief of stuttering and seizure | Clozapine was not rechallenged | No history of speech dysfluency | Gica *et al*[65] |
| Divalproex sodium (600 mg/d) | Male/45 | Affective instability and irritability | Citalopram (30 mg/d), promazine (100 mg/d) | Four days after initiation of divalproex sodium | Sound repetitions and prolongations (not restricted to the initial syllable and caused pronounced difficulty in starting and completing his sentences) | NR | DC of divalproex, complete relief after 3 d | Divalproex sodium was not restarted | A 10-yr history of post-traumatic stress disorder and alcoholism, no history of speech dysfluency | Aukst-Margetić *et al* [91] |
| Divalproex sodium (1500 mg/d in divided dose) | Male/56 | Bipolar affective disorder | Olanzapine (10 mg/d), lorazepam (4 mg/d, gradually stopped along with increase in the dose of divalproex) | Two weeks after increasing the dosage of divalproex from 1000 to 1500 mg/d | A moderately pressured speech, articulation of speech, alterations in intensity and timings of utterance segments, Involuntary repetitions and prolongations of sounds, syllables, words or phrases, involuntary silent pauses or blocks | NR | DC of divalproex, instant amelioration of the stuttering | Re-initiation of the drug after one week caused resurgence of symptoms, so the drug was stopped | No history of speech dysfluency | Mukherj *et al* [92] |
| Desipramin (300 mg/d) | Male/28 | Dystimia, primary type, major depression | Doxepin (50 mg at bed time) | Two months after increasing the dosage of desipramine | Stuttering with difficulty in articulation | Minimal dryness of mouth before stuttering, myoclonic jerking (twitching movements around his jaw) concomitant with stuttering | DC of both drugs, complete relief after 48 h | Twenty-four hours after restarting both drugs stuttering happened again, the desipramin dosage was decreased to 250 mg/d, but stuttering was persisted occasionally, on 4 different occasions, desipramin was discontinued and stuttering was solved within 24-48 h; an increase in the doxepin dosage to 200 mg at bed time had not resulted in stuttering | Opiate and alcohol dependence in remission, retinal detachment and ruptured disc and chronic back pain in the past, no history of speech dysfluency | Masand *et al* [93] |
| Fluphenazine (up to 50 mg/d) | Male/35 | Schizophrenia | Benztropine mesylate (4 mg/d) | 12 d after increasing fluphenazine dosage to 50 mg/d | NR | EPS | Dosage reduction to 30 mg/d, complete relief | Increasing the dosage of fluphenazine to 40 mg/d caused stuttering | No history of speech dysfluency | Nurnberg *et al*[10] |

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| | | | | | | | | recurrence | | |
| Gabapentin (NR) | Female/58 | Intractable seizure | Phenytoin (NR) | NR | NR | NR | DC of gabapentin, relief after 4 d | NR | No history of speech dysfluency | Nissani *et al* [94] |
| Lamotrigine (up to 5 mg/kg/d) | Female/5 | BECTS | Valproic acid (30 mg/kg/d) | Stuttering was initiated after increasing the dosage of lamotrigine to 5 mg/kg/d | NR | Frequent diurnal absence seizures, poor concentration and forgetfulness, clumsiness and poor coordination, emotional lability, dysarthria, and slurred speech | DC of lamotrigine, speech improvement in a couple of days | Lamotrigine was not rechallenged | NR | Catania *et al* [95] |
| Levodopa/carbidopa (100/25 mg TID) | Male/44 | PD | NR | Patient had a history of PDS, and stuttering was exacerbated during on periods, 1 h after levodopa/carbidopa intake | NR | Dyskinesia during drug-on phases and akinesia, bradykinesia, resting tremors, and rigidity in drug-off phases | The severity of stuttering return to baseline during levodopa-off periods | Levodopa was not discontinued | PDS | Anderson *et al*[25] |
| Levodopa (200 mg/d) | Male/72 | PD | None | Nearly one month after increasing the dosage to 200 mg/d | NR | Palilalia, speech freezing | DC of levodopa and initiation of pramipexole, return to the baseline level of dysfluency | Reinitiating levodopa caused stuttering | Speech dysfluency due to PD | Louis *et al*[22] |
| Levodopa (up to 1000 mg/d) | Male/42 | PD | Pergolide (1.5 mg/d), quetiapine (50 mg at bed time) | After increasing the levodopa dosage to 300 mg/d | Pressured speech and sound repetition | Palilalia, speech freezing | NR | NR | None | Louis *et al*[22] |
| Levodopa 600 mg/d | Male/57 | PD | Cabergoline (4 mg/d), selegeline (10 mg/d), amantadine (300 mg/d) | Patient had a history of PDS, and stuttering was exacerbated during on phases after levodopa consumption | Speech repetitions and speech blocks | Speech problems associated with PD including hypokinetic dysarthria and hypophonia occurred during levodopa-off phases | Severity of stuttering return to baseline during levodopa-off periods | Levodopa was not discontinued | PDS | Burghause *et al*[26] |
| Levomepromazine (50 mg at bed time) | Male/65 | Bipolar disorder | Quetiapine (NR), valproate semisodium (NR), zolpidem, moxonidin (NR), propafenone (NR), insulin (NR) | Five days after the initiation of levomepromazin | NR | NR | DC of Levomepromazin, complete relief three days later | Levomepromazin was not recommenced | History of drug induced EPS, supraventricular tachycardia, type 2 DM, HTN, and mild cognitive impairment | Margeticet al [96,97] |
| Lithium (1200 mg at bed time) | Male/48 | Bipolar affective disorder | Fluoxetine (20 mg/d) | One month after the initiation of lithium | Worsening his developmental stuttering, a repetitive word | Lightheadedness, hand tremor | Tapering off lithium, stuttering returned to baseline within a few weeks | Valproic acid (2750 mg/d) was started instead of lithium | PDS, depression | Netski *et al* [98] |

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| | | | | | stutter that severely limited his verbal communication ability | | | | | |
| Lithium (900 mg twice daily) | Male/10 | Bipolar disorder | Risperidone (4 mg bed time), clonidine (0.1 mg 3 times daily), melatonin (3 mg at bed time), famotidine (20 mg BID) | Two days after increasing the dose of lithium, stuttering was worsened | Syllable repetitions, occurred only at the beginning of sentences | NR | Dose adjustment of lithium to 600 mg in the morning and 900 mg at night, stuttering returned to baseline after 2 d | Lithium was not discontinued | History of developmental stuttering, bipolar disorder not otherwise specified, ADHD, and conduct disorder | Gulack *et al* [99] |
| Lithium (the dose was not mentioned, but lithium was used for a long time) | Female/86 | Bipolar disorder | Donepezil (NR), primidone (NR), risperidone (NR) | After a chronic use of lithium, stuttering was started and stayed for 3 more mo. The lithium level was elevated (2.0 mmol/L) | Starting a few words fluently, then repeating syllables and words and terminating the sentence abruptly | NR | DC of lithium, complete relief of stuttering after two weeks | Lithium was not restarted | Past medical history of dementia and epilepsy, no history of speech dysfluency | Sabillo *et al* [100] |
| Memantine (10 mg/d) | Male/9 | Autistic disorder | No other drugs | After increasing the dose | Deterioration of primary behaviors of developmental stuttering includingsound repetition, and sound prolongation on first and middle vowels, and difficulty for starting to speak. His parents explained that the child could only start to speak after a deep and audible breath | NR | Reduction of memantine dosage to 7.5 mg/d, improvement of acquired stuttering after several days. DC of memantine, stuttering was reduced to baseline after 3 wk | Risperidone was used instead | Developmental stuttering | Alaghband-Rad *et al*[17] |
| Memantine (5 mg/d) | Male/4 | Autism | No other drugs | After increasing the dose | The difficulty was with the start of the speech and the child could only start to speak after a deep and audible breath | NR | The drug was continued at the same dose as the difficulty was tolerable, and gradually was increased to 7.5 mg/d, relief of speech difficulty | Medication was continued, and its dose was gradually increased | No history of speech dysfluency | Alaghband-Rad *et al*[17] |
| Methotrexate (cumulative dose of 62.5 mg, IT) | Female/22 | Pre-B acute lymphoblastic leukemia | NR | After achieving cumulative dose of 62.5 mg (26 d after | NR | Dysphasia progressed to aphasia, mild | Three months after initiation of symptoms (no intervention was | NR | No history of speech dysfluency | Shuster *et al* [21] |

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| | | | | initiating IT MTX) | | headache, low-grade fever, behavioral problems | described) | | | |
| Methylphenidate (10 mg/d) | Male/7 | ADHD | No other drugs | 10 d after the initiation of the drug | Sound prolongations, silent blocking, word production with excess physical tension, monosyllabic whole-word repetitions | NR | DC of methylphenidate, speech returned to normal after 1 wk | Atomoxetine was used instead | No history of speech dysfluency | Alpaslan *et al* [101] |
| Methylphenidate (5 mg in the morning and 5 mgat noon) | Male/7 | ADHD | No other drugs | One day after drug initiation | Troubles during the pronouncing the first syllables and repetitions of some syllables | NR | DC of Methylphenidate, improvement after 10 d | Methylphenidate was restarted at 10 mg in the morning and5 mg at noon. After 10 d, stuttering was returned | NR | Copur *et al* [102] |
| Methylphenidate (2.5 mg BID) and pemoline (9.375 mg/d) after DC of methylphenidate | Girl/3 | Pervasive hyperactivity | None | Three days after starting methylphenidate, four days after starting pemoline | Repetition of the first syllable of word which gradually worsened | NR | DC of methylphenidate, relief of stuttering, DC of pemoline, relief of stuttering | Methylphenidate and pemoline were not restarted | NR | Burd *et al*[7] |
| Olanzapine (15 mg/d) | Male/56 | Depression | Intrathecal morphine (7.5 mg/d), clomipramine (225 mg/d) | Four days after the initiation of clozapine | Constant word repetition (acquired) | NR | DC of olanzapine, complete relief after two days | NR | Chronic pain syndrome, no history of speech dysfluency | Bar *et al*[15] |
| Olanzapine (7.5-10 mg/d) | Male/72 | Psychotic depression | Clomipramine (50-150 mg/d) | 3 wk after the initiation of olanzapine | Repetition and retention of first syllables and prolongation of phonemes | NR | DC of olanzapine, complete relief after 5 d | NR | Brain cortical atrophy, no history of speech dysfluency | Bar *et al*[15] |
| Olanzapine (5 mg/d) | Female/36 | Manic episode | Sodium valproate (300 mg/d), prednisolone (75 mg/d) | 7 d after the initiation of olanzapine | Repetition of syllables and words | NR | DC of olanzapine, complete relief after 4 d | NR | Ulcerative colitis and celiac disease, no history of speech dysfluency | Bar *et al*[15] |
| Olanzapine (10 mg/d) | Female/43 | Schizophrenia | No other drugs | Approximately 21 d after the initiation of olanzapine | Repetition of first syllables and word prolongation | NR | DC of olanzapine, complete relief after 3-5 d | NR | Mild cluttering at the age of 19 | Bar *et al*[15] |
| Olanzapine (2.5 mg/d) | Female/51 | Depression | Sertraline (100 mg/d), promethazine (50 mg at night); both was started 14 wk before initiation of | 14 d after the initiation of olanzapine | Blocking of speech and prolongation of phonemes | NR | Increase in olanzapine dose to 5 mg/d, relief of stuttering during the next weeks | Olanzapine was not discontinued | Symmetrical cerebellar hypoplasia and generalized cortical atrophy, no history of | Bar *et al*[15] |

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| | | | olanzapine | | | | | | speech dysfluency | |
| Olanzapine (10 mg/d) | Male/42 | Schizophrenia | Zopiclone (7.5 mg/d) | Two days after the initiation of olanzapine | Difficulty in articulating words properly | NR | DC of olanzapine, complete relief after two days | NR (patient was not followed-up) | A fall without loss of consciousness 2 d before initiation of stuttering, no history of speech dysfluency | Bar *et al*[15] |
| Olanzapine (10 mg/d) | Male/42 | Paranoid ideation | Venlafaxine (150 mg/d), promazine (200 mg/d) | Four days after the initiation of olanzapine | Repetition and retention of first syllables and prolongation of phonemes | NR | DC of olanzapine, complete relief after two days | | PTSD, adjustment disorders, no history of speech dysfluency | Lasic *et al* [103] |
| Olanzapine (10 mg/d) | Male/21 | Psychotic disorder | No other drugs | Three days after the initiation of olanzapine | disturbance in the fluency and time patterning of speech, repetition of sounds and syllables, blocking between words | NR | DC of olanzapine and start of quetiapine, complete relief after three days | Olanzapine was not restarted | No history of speech dysfluency | Asan *et al* [104] |
| Phenytoin (200 mg/d) | Male/42 | Seizure due to head injury | No other drugs | Shortly after initiation of phenytoin | Predominantly part-word repetitions and prolongation | Abnormality of speech muscle fine motor control | Addition of CBZ and gradual DC of phenytoin, sustain decrease in the frequency of dysfluencies and improved motor performance | Phenytoin was not restarted | No history of speech dysfluency | Mcclean *et al* [105] |
| Phenytoin (20 mg/kg LD and 5 mg/kg/d MD) | Male/3 | GTC seizure due to head trauma | No other drugs | 10 d after the initiation of phenytoin | NR | NR | DC of phenytoin and initiation of sodium valproate, complete relief 10 d after DC of phenytoin | Phenytoin was not rechallenged | No history of speech dysfluency | Ekici *et al* [106] |
| Pregabalin (75 mg twice daily) | Female/31 | Complex regional pain syndrome | No other drugs | After taking the second dose of pregabalin on the first day | A slurred speech | NR | DC of pregabalin, complete relief after one week | Pregabalin was not restarted | No history of speech dysfluency | Giray *et al* [107] |
| Pregabalin (75 mg twice daily) | Female/68 | Herpes zoster | Acyclovir (800 mg five times daily) | Three days after the initiation of pregabalin | NR | Frequent blepharospasm | DC of pregabalin;alleviated of symptoms after four days and complete relief after one week | A 75 mg pregabalin capsule consumption after 4 wk resulted in stuttering and frequent blepharospasm | No history of speech dysfluency | Ge *et al*[108] |
| Pyrethrin product containing 0.33% pyrethrum extract and 4% piperonyl butoxide (3 times | Female/2 (the child's mother, who was breastfeeding | Repeated episodes of head lice | No other drugs | Two days after the last period of mother's treatment | An acute onset of stuttering especially at the initiation of the speech | An increase in clumsiness, slight erythematous rash ofapproximately 3 cm × 2 cm on the | Six weeks postexposure | Pyrethrin was not repeated | No history of speech dysfluency | Hammond *et al*[81] |

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| overa period of 12 d left on the scalp for 10 min) | her atleast one time per day, were receiving this topical product) | | | | | occiput of the scalp | | | | |
| Risperidone (4 mg/d, then 8 mg/d) | Male/32 | Aggravated psychotic disorder | Lorazepam (1 mg/d) | Stuttering was initiated after the dose increase to 4 mg/d, and worsened 16 d after the dose increase to 8 mg/d | Severe sound repetitions and interjections in a way that it was difficult to understand his words | Slight akathisia-like symptoms such as anxiety and restlessness (not prominent) | No action, stuttering diminished 23 d later | He continued taking risperidone at 8 mg/d with only a slight stuttering | A 10-yr history of Schizophrenia. His friend during junior high school was a stutter, and the patient used to mimic his stuttering. He began stuttering at that time for 1 yr | Lee *et al*[16] |
| Risperidone (4 mg) | Female/48 | Psychosis | Lorazepam (1 mg PRN), procyclidine (5 mg BID for treatment of EPS) | 11 d after taking risperidone | Repetitions in the speech, pausing within a word and her speech, an excess of physical tension in the speech | NR | A little decrease in risperidone dose, a bit reduction in stuttering | Risperidone was not discontinued | No history of speech dysfluency | Yadav *et al* [18] |
| Risperidone (at a dose of 1 mg/d for 2 yr) | Male/21 | Behavioral disorder | No other drugs | After chronic treatment with low-dose of risperidone | Prolongation of sounds, hearable blocks, repetitions of single-syllable words | NR | No action, stuttering was decreased to a minimal level after 17 d | Risperidone was not discontinued | Moderate mental retardation because of perinatal asphyxia, no history of speech dysfluency | İnci *et al*[23] |
| Sertraline (100 mg daily) | Male/36 | Major depression | Alprazolam (0.25 mg 3 TID) | Two weeks after increasing the dosage from 50 to 100 mg/d | Normal vocabulary, decreased rate of speech, normal tone, interrupted words | NR | DC of serteraline, speech problem resolved after one day | Medication was not restarted. Later, administering phenelzine, imipramine, and fluoxetine caused milder speech hesitancy | No history of speech dysfluency | Makela *et al* [109] |
| Sertraline (50 mg daily) | Female/32 | Recurrent depression | No other drugs | During the third week of starting the drug, stuttering occurred and worsened over a 3-d period | Difficulty in starting and completing the sentences | Feeling nervous, increased restlessness, and insomnia two days before the onset of stuttering | DC of sertraline, complete relief of stuttering after 3 d | Previously, patient has received sertraline and experienced stuttering, so discontinued the medication. Medication was not restarted. Desipramine was started and did not cause stuttering | No history of speech dysfluency | Christensen *et al*[76] |

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| Sertraline (150 mg daily) | Female/22 | Bulimia nervosa, anorexia nervosa, posttraumatic stress disorder, recurrent depression, panic disorder | Clonazepam (0.5 mg QID), trimethoprim-sulfamethoxazole (BID) | One week after increasing the dosage of sertraline | NR | Hyperreflexia and mild tremulousness, generalized muscle twitching (myoclonus), restlessness, and mild confusion | DC of sertraline and Antibiotic, gradual normalization of speech over two to three days | Seven days after restarting sertraline at 50 mg/d, stuttering and other symptoms returned, then the drug was discontinued | No history of speech dysfluency | Brewerton *et al*[77] |
| Theophylline (200 mg BID to 100 mg QID) | Male/the age of the onset of theophylline-induced stuttering was not reported, but it surely occurred when he was between 1.5 and 4 yr old | Asthma | Nothing was clearly mentioned | The patient only experienced stuttering during the autumn when he was receiving theophylline for the management of asthma attacks | Repeating whole words, six or seven times usually at the beginnings of the sentences, no dysfluency while singing | Being tense, havinginsomnia, and be frustrated by his speech problem | DC of theophylline at the end of autumn before age 4 yr, complete relief of stuttering. Changing the dosage from 100 mg QID to 200 mg BID at age 4 yr, complete relief after 7 d with no recurrence of stuttering | The patients had stuttered each time that he was on Theophyllineregimen 200 mg BID | No history of speech dysfluency | Rosenfield *et al*[110] |
| Theophylline (130 mg TID and sometimes QID) | Female/6.5 | Asthma | Metaproterenol sulphate (PRN) | Within a few days after increasing the theophylline dosage to 130 mg TID | Multiple repetitions of the word "I", especially at the beginning of sentences, she could speak better when speak more slowly. Stuttering was worse when she was excited | NR | DC of theophylline, complete relief within two days | Resumption of theophylline resulted in the recurrence of stuttering which responded to drug withdrawal. Several months after the discontinuation of theophylline, the drug was resumed without causing any dysfluency | No history of speech dysfluency | Rosenfield *et al*[110] |
| Theophylline 200 mg BID to 200 mg TID | Male/4 yr and 3 mo | Asthma | Beclomethasone dipropionate and Theo-Dur sprinkle (200 mg BID) (at age 4 yr and 4 mo). Addition of metaproterenol sulphate, isoetharine HCL andatropine (at age 4 yr and 10 mo, DC of all drugs and initiation of cromolyn capsules (20 mg TID) (at age 5 yr) | Nine months after the initiation of theophylline | Repeating "ah, ah, ah" in the middle of sentences, stuttering was worse when he was excited | Anxiety, sleep problems | Withdrawal of theophylline at age 5 yr, complete relief within two weeks | After complete relief of stuttering, the patient only received theophylline during asthma attacks and experienced no stuttering | No history of speech dysfluency | Rosenfield *et al*[110] |
| Theophylline (400 mg BID) | Male/73 | A long-standing chronic obstructive lung | Steroids and ranitidine as well as being on oxygen | One month after the introduction of theophylline | An intense tonic-clonic stuttering without any | NR | DC of theophylline, stuttering was diminished within 48 | Theophylline was readministered 2 wk later at the same | No history of speech dysfluency | Gerard *et al* [111] |

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| | | disease secondary to pneumoconiosis | | | extrapyramidal components | | h | dosage, and the same speech disorder recurred within a few daysand persisted until treatment was stopped | | |
| 1. Trifluoperazine (30 mg/d)<br>2. Chlorpromazine (up to 800 mg/d) | Male/40 | Schizophrenia | Trihexyphenidyl (5 mg/d) | 1. Four days after increasing the trifluoperazine dosage to 30 mg/d<br>2. After increasing chlorpromazine dosage to 800 mg/d | NR | NR | 1. Increasing dosage of trihexyphenidyl, no improvement. DC of trifluoperazine, complete relief<br>2. Addition of benztropine, no improvement. Reduction of chlorpromazine dose to 400 mg/d, complete relief | Increasing the dosage of chlorpromazine to 700 mg/d caused the return of stuttering; reducing the dosage of chlorpromazine to 400 mg/d caused cessation of stuttering | No history of speech dysfluency | Nurnberg *et al*[10] |

ADHD: Attention-deficit hyperactivity disorder; BECTS: Benign focal epilepsy of childhood with centrotemporal spikes; BID: Two times per day; BDZ: Benzodiazepine; CBZ: Carbamazepine; COPD: Chronic obstructive pulmonary disease; DC: Discontinue, DM: Diabetes mellitus; EPS: Extrapyramidal side effect; GERD: Gastroesophageal reflux disease; GTC: Generalized tonic-colonic seizure; HTN: Hypertension; IM: Intramuscular; IT: Intrathecal; IV: Intravenous; LD: Loading dose; MD: Maintenance dose; MDD: Major Depressive Disorder; MTX: Methotrexate; NR: Not reported; PD: Parkinson disease; PDS: Persistent developmental stuttering; PRN: Pro re nata (as needed); QID: Four times a day; TID: Three times a day; VPA: Valproic acid.

For producing a fluent speech, orofacial as well as respiratory muscles must work properly. Different areas of the brain including several parts of the cerebral cortex and subcortical structures such as the basal ganglia (BG) and cerebellum are involved in speech production. Functional abnormalities of each part of these areas may cause speech dysfluency. It has been suggested that dysfunction in the different parts and networks of cerebral cortex engaged in speech production[28], the impairments in the neural connections between the cerebral cortex, the BG, and the thalamus, which are called cortico-BG-thalamocortical circuit (CBTC)[28,29], and/or the dysfunction of the BG are involved in the pathogenesis of developmental stuttering[28,29].

## CBTC AND STUTTERING

Several neural circuits are engaged in the process of speech production. One of these circuits that has received much attention in the pathogenesis of stuttering is CBTC[28,29]. The BG consist of input, intrinsic, and output nuclei. The input nuclei receive information from different parts of the brain, especially the cerebral cortex, the thalamus, and the substantia nigra, and send signals to the intrinsic nuclei for further processing and then to the output nuclei. The output nuclei relay signals to the thalamus which sends signals back to the part of the cerebral cortex from which the primary signal was originated. The input nuclei consist of the putamen and the caudate nucleus, collectively named the striatum. The intrinsic nuclei consist of the external segment of the globus pallidus (GPe), the subthalamic nucleus (STN), and the substantia nigra pars compacta (SNpc). The internal segment of the

globus pallidus (GPi) and the substantia nigra pars reticulata (SNpr) make the output nuclei[30].

The striatum has two types of neurons including gamma-aminobutyric acid-ergic (GABAergic) medium-sized spiny neurons (MSNs) representing 90%-95% of the striatal neurons and GABA-ergic/cholinergic interneurons. The striatum receives inputs from different parts of the brain including excitatory glutamatergic inputs from different parts of the cerebral cortex, motor cortex, supplementary motor area (SMA), pre-SMA, auditory cortex, somatosensory cortex, and the thalamus and dopaminergic inputs from SNpc[30]. BG match motor, sensory, and cognitive context received from different parts of the cerebral cortex[31] and send signals to the thalamus to stimulate the cerebral cortex to initiate the desired movement, *e.g.*, terminating production of the previous phoneme and initiating the next phoneme in the case of speaking, and inhibit competing movements[32]. The cerebral cortex sends signals through corticobulbar tracts to the orofacial and respiratory muscles including the muscles of larynx, pharynx, lips, and tongue[33], activates the proper group of muscles, and inhibits competing muscles whose activation interferes with the production of the desired movement.

The signals that are received by the input nuclei of BG are transmitted *via* two pathways: Direct and indirect. The activation of the direct pathway stimulates the cerebral cortex and therefore activates the right motor program while the activation of the indirect pathway inhibits the cerebral cortex and therefore, all other competing motor programs[2,28].

In the direct pathway, MSNs, which have N-methyl-D-aspartate (NMDA) glutamate receptors, D1 dopamine receptors, A1 adenosine receptors, and M4 muscarinic receptors[34] and release gamma-aminobutyric acid (GABA), substance P, and dynorphin[35], project to the SNpr and GPi, the output nucleus of BG. MSNs are stimulated by glutamatergic projections from the cerebral cortex. The activated MSNs release GABA, which inhibits the output nucleus. GABAergic projections from the output nucleus inhibit the glutamatergic neurons of the thalamus. Therefore, the inhibition of the output nucleus by MSNs disinhibits thalamic neurons which ultimately activate the cerebral cortex and increase locomotor activity[35] (Figure 1).

MSNs in the indirect pathway, which have NMDA glutamate receptors, D2 dopamine receptors, A2A adenosine receptors, and M1 muscarinic receptors[34] and release GABA and enkephalin, project to the output nucleus through the GPe and STN. The GPe has GABAergic neurons that inhibit STN neurons which are glutamatergic cells. The release of glutamate because of the activation of the cerebral cortex stimulates MSNs in the indirect pathway to release GABA. GABA inhibits the GPe and therefore disinhibits the STN. Release of glutamate from the STN stimulates the inhibitory GABAergic neurons of the output nucleus, which inhibits thalamic neurons and therefore cerebral cortex, resulting in decreased locomotor activity (Figure 1). It has been proposed that the direct and indirect pathways have interactions with each other, and their integration and balanced activation during movement selection is required for the proper execution of motor programs[36,37].

## ROLE OF DOPAMINE IN THE BG MOTOR CIRCUIT

As mentioned above, D1, A1, and M4 receptors are colocalized on MSNs in the direct pathway[34]. The stimulation of D1 receptors activates MSNs in the direct pathway and stimulates this pathway[28]. Blocking A1 and M4 receptors facilitates the dopamine neurotransmission. Therefore, A1 and M4 antagonists also stimulate the direct pathway[34]. Neurons of the indirect pathway have D2, A2A, and M1 receptors[34]. The activation of D2 receptors inhibits the indirect pathway[28]. A2A and M1 receptors antagonists also increase the dopamine signaling and therefore suppress the indirect pathway. Since these two pathways have a cross talk and coordinated activity, disturbing their coordination can cause movement disorders such as dystonia, dyskinesia, and stuttering. Therefore, both increased and decreased dopamine neurotransmission in the striatum may cause stuttering by impairing the balance between the direct and indirect pathways.

## WHITE MATTER FIBER TRACTS AND STUTTERING

Other changes that can affect connectivity between different areas of the brain involved in the speech motor control are the white matter abnormalities. The white matter tracts, bundles of myelinated axons, relay signals between different areas of the brain and therefore coordinate their communication and function[38]. Several *in vitro* and animal studies and a small number of human studies have found multiple neurotransmitters, including glutamate, adenosine, GABA, glycine, dopamine, serotonin, acetyl choline, histamine, norepinephrine, and substance P, and their receptors in the white matter. It has been proposed that glutamate and purine signaling have the most prominent effects on the white matter functioning; however, it seems that the white matter requires a coordinated action of all of these neurotransmitters for conduction of action potentials and maintaining signal integrity through very long signal transmission axonal pathways[38]. Different studies in adults[33,39] and adolescents and young people[40] with developmental stuttering demonstrated the reduced integrity of the white matter fiber tracts. It may be proposed that an agent that impairs the normal activity of one or some of the

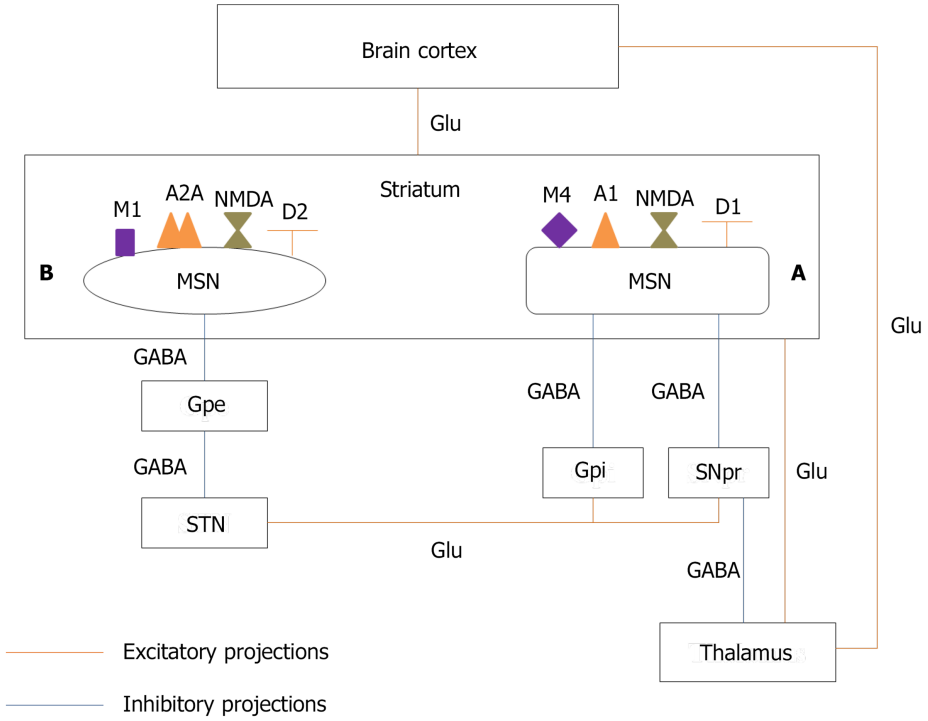


**Figure 1 Schematic graph of direct and indirect pathways of basal ganglia.** A: Direct pathway; B: Indirect pathway. A1: A1 adenosine receptor; A2A: A2A adenosine receptor; D1: D1 dopamine receptor; D2: D2 dopamine receptor; GABA: Gamma-aminobutyric acid; Glu: Glutamate; Gpe: External segment of the globus pallidus; Gpi: Internal segment of the globus pallidus; M1: M1 muscarinic receptor; M4: M4 muscarinic receptor; MSN: Medium-sized spiny neurons; NMDA: N-methyl-D-aspartate receptor; SNpr: Substantia nigra pars reticulate; STN: Subthalamic nucleus.

neurotransmitters in the white matter may impair signal transmission between different areas of the brain engaged in speech motor control and result in stuttering. Moreover, in some psychiatric disorders such as schizophrenia and bipolar disorder, one of the pathological findings in the CNS is myelin loss or disruption[41]. Of cases included in the present review, 25, 5, and 6 had schizophrenia, schizoaffective disorder, and bipolar disorder, respectively. As a result, it can be suggested that drugs disrupting normal neurotransmitter balance in the white matter, which already has an underlying impairment in these patients, may exacerbate white matter dysfunction.

## STUTTERING INDUCED BY DRUGS AFFECTING DOPAMINE NEUROTRANSMISSION

### *Increased dopamine neurotransmission in BG and stuttering*

Evidence that supports the role of the dopamine excess in the pathophysiology of stuttering includes the reduction of stuttering by antipsychotic drugs, which are dopamine blockers, such as haloperidol, risperidone, olanzapine, aripiprazole, and asenapine[42], the finding of Wu *et al*[43] that showed the excessive striatal dopamine activity and increased uptake of fluoro-l-3, 4-dihydroxy-phenylalanine, a precursor of dopamine, in several parts of the brain in persons who stutter in comparison to healthy controls, and computational modeling of stuttering by Civier *et al*[44]. Furthermore, it has been shown that children aged 2.5-3 years, the age of onset of developmental stuttering in most children, have more density of D2 than D1 receptors and therefore low D1/D2 density in the striatum in comparison to older children. Therefore, drugs like haloperidol, which is a highly selective D2 antagonist, decrease this D1/D2 imbalance and the severity of stuttering. Besides the above-mentioned studies conducted in persons with developmental stuttering, cases of exacerbation of stuttering by levodopa in patients with PD[23,26,27] also propose a role for dopamine excess in the pathogenesis of NS. Chang *et al*[28] have suggested that the inhibition of the indirect pathway in the states of dopamine excess decreases the suppressing effect of this pathway on the competing motor programs. Therefore, choosing correct motor program over incorrect ones becomes difficult, which could ultimately delay the initiation of the right motor program. This delay may cause speech blockage or sound prolongation. Furthermore, in this situation, the proper signal that originated from the direct pathway and stimulates the right motor program may be initiated but suffers premature termination which may lead to the repetitions[28].

In conclusion, drugs such as levodopa, a precursor of dopamine, methylphenidate that increases the extracellular level of dopamine in the striatum[45], amphetamines that increase the release of catecholamines mainly dopamine and nerve-end particles (NEP) from presynaptic nerves and inhibit

the reuptake of dopamine and NEP into presynaptic neurons[46], and phenytoin that has been proposed as a dopamine enhancer in the BG pathways may cause stuttering by increasing the dopamine neurotransmission in BG[47,48].

### *Decreased dopamine neurotransmission in BG and stuttering*

Reduced dopamine neurotransmission in the striatum also can cause stuttering. For example, some patients with PD, the disorder that is mainly characterized by the dopamine depletion from BG, experience new-onset NS[49], exacerbation of PDS[26,27], or re-emergence of developmental stuttering [50]. Chang *et al*[28] proposed that in this state, the decreased excitation of the direct pathway results in reduced stimulation of the correct motor program and its ability to compete other motor programs. This also may result in unstable or delayed production of signals initiating the right speech motor program.

## ANTIPSYCHOTICS-INDUCED STUTTERING

Although some studies have shown the relative efficacy of antipsychotic drugs in the treatment of stuttering[42], there are case reports of antipsychotics-induced stuttering. All studies that reported efficacy of antipsychotic drugs in reducing stuttering were conducted in patients with PDS. However, all cases of antipsychotics-induced stuttering had a psychotic disorder, which was schizophrenia in the majority of them. Elevated dopamine levels and excessive dopamine activity in the striatum are present in both developmental stuttering[42,43] and schizophrenia. Therefore, the opposite effects of dopamine blockers in these disorders, improving stuttering in some cases of developmental stuttering but causing stuttering in some patients with schizophrenia, indicate that effects of these drugs on the dopamine activity in other parts of the brain and on other neurotransmitters may be responsible for their different effects on speech motor control. Furthermore, abnormalities in the brain of patients with psychotic disorders are extensive and are not comparable to persons with developmental stuttering. These differences also may justify why a dopamine blocker can be a therapeutic option in PDS but a causative agent of stuttering in the psychotic disorders.

However, it should be noted that studies by Fish *et al*[51] and Langova *et al*[52] demonstrated that not all persons with developmental stuttering respond to the dopamine blockers. In the study conducted by Fish *et al*[51], 14 out of 28 persons who stuttered Prader-Willi syndrome (PWS) and received amphetamine experienced improvement in stuttering while two got worse. Of 12 PWS who did not improve by amphetamine, eight got better on trifluoperazine, a D2 blocker. Four participants did not show any improvement neither by each medication nor by their combination. Similarly, in the study conducted by Langova *et al*[52], 88% of PWS got better on phenmetrazine, a stimulant, while 67% deteriorated using chlorpromazine. These findings have led to the suggestion of the hypothesis that persons with developmental stuttering may be classified as the dopamine blocker-responsive or stimulant-responsive[29].

In the present review and study conducted by Trenque *et al*[6], the majority of cases of DIS were caused by clozapine. Regarding the effects of antipsychotics on dopamine receptors, all antipsychotics except than clozapine, olanzapine, ziprasidone, and asenapine have a higher affinity for D2 receptors than D1 receptors. Clozapine, olanzapine, ziprasidone, and asenapine equally block both D1 and D2 receptors. Furthermore, clozapine and asenapine have a lower affinity for dopamine receptors in comparison to olanzapine and ziprasidone[53]. Clozapine is one of the most effective antipsychotic drugs[54]; however, because of its serious side effects such as agranulocytosis, seizure, and cardiovascular adverse effects[55], clozapine is considered as one of the last options in the treatment of schizophrenia and other psychotic disorders. Therefore, many patients had received several antipsychotics prior to the initiation of clozapine. Long-term blockage of D2 receptors while sparing D1 receptors caused by other antipsychotics results in the supersensitivity of D2 receptors[56]. The affinity of clozapine for blocking D2 receptors is lower than that of many other antipsychotics[53]. Therefore, after the initiation of clozapine, decreased D2 blocking combined with the supersensitivity of D2 receptors creates a state of increased D2 stimulation which finally inhibits the indirect pathway. On the other hand, antagonizing the D1 receptors inhibits the direct pathway. The inhibition of the indirect pathway impairs the suppression of the competing motor programs. Besides, the inhibition of the direct pathway decreases cerebral cortex stimulation and locomotor activity, which causes difficulties in initiating next segment in a movement sequence like speaking. Clozapine also is a $5HT_{2a}$ and $5HT_{2c}$ receptor blocker[55]. Reducing the serotonin neurotransmission increases the dopamine transmission in the prefrontal cortex, which may also cause stuttering. Although clozapine is a potent M1 antagonist [55], the effect that facilitates the dopamine neurotransmission in the direct pathway, the final result of antagonizing all above-mentioned receptors is the inhibition of both direct and indirect pathways and therefore impaired speech motor control. Moreover, changing the normal function of dopamine, serotonin, acetylcholine, and norepinephrine, by blocking α1 receptors, and histamine, by blocking H1 receptors[55], can disturb normal functions of the white matter and cause stuttering.

Other antipsychotics that are included in the present review are olanzapine, risperidone, aripiprazole, chlorpromazine, fluphenazine, and trifluoperazine. Olanzapine is very similar to clozapine regarding

the affinity for different receptors including D1, D2, $5HT_{2A}$, $5HT_{2C}$, M1, α1, and H1 receptors[57]. Other antipsychotics such as risperidone, chlorpromazine, and fluphenazine are potent inhibitors of D2 receptors without any considerable effect on D1 receptors. Chlorpromazine also is a potent M1 antagonist while risperidone and fluphenazine have no considerable effect on M1 receptor. The efficacy of risperidone in antagonizing 5HT receptors is comparable to that of olanzapine and more than the efficacy of chlorpromazine, fluphenazine, and trifluoperazine. Aripiprazole is a partial agonist of D2 and $5HT_{1A}$ receptors and antagonist of $5HT_{2A}$ receptor[57]. We suggest that these antipsychotics can cause extrapyramidal side effects (EPS) which may manifest as stuttering as well as other movement disorders by impairing the balanced and coordinated activity of the direct and indirect pathways. Furthermore, increasing the dopamine neurotransmission in the prefrontal cortex by blocking the serotonin effects as well as disturbing neurotransmitters' functioning in the white matter can be the other underlying mechanisms of the antipsychotics-induced stuttering.

The following section is focused on clozapine as the most prevalent cause of DIS.

## CLOZAPINE-INDUCED STUTTERING

Clozapine is the drug with most reports of inducing a new episode of stuttering or worsening pre-existing stuttering both in the present review and analysis carried out by Trenque *et al*[6]. In the cases included in this review, clozapine induced stuttering in a wide variety of dosages ranging from 50 mg/d[10] to 700 mg/d[58,59]. However, in most cases, clozapine caused stuttering at the daily doses of 250 mg to 450 mg. It seems that stuttering is a dose-dependent adverse effect of clozapine as in 13 (43.3%) cases stuttering was significantly improved or completely vanished following dose reduction (Table 3).

We have suggested likely mechanisms of clozapine-induced stuttering in the previous section. Furthermore, based on the concomitant signs and symptoms that patients experienced with stuttering, it has been proposed that clozapine-induced stuttering may be a manifestation of the movement disorders such as focal segmental dystonia in orofacial muscles, akathisia, or dyskinesia[10,21,58,60-63] or a seizure disorder.

Although clozapine is an antipsychotic with a low potential for causing EPS[55], of 30 cases, seven experienced a type of movement disorder concomitant with stuttering[10,21,58]. Grover *et al*[61] reported a case who experienced clozapine-induced stuttering and had a history of EPS associated with other antipsychotics. Although clozapine did not cause other manifestations of EPS, they proposed that stuttering might be a symptom of movement disorders induced by clozapine. Concerning the management of clozapine-induced stuttering the dose reduction or withdrawal of clozapine resulted in significant improvement or complete relief of both stuttering and the movement disorders in two cases [58]. In contrast, in one case reported by Lyall *et al*[10], substitution of clozapine with zuclopenthixol decanoate relieved stuttering but not dyskinetic movements, and restarting clozapine resulted in reoccurrence of stuttering which responded to sodium valproate despite no electroencephalogram (EEG) abnormality. For four cases, the authors did not report whether their intervention improved the movement disorders in addition to stuttering or not[10,21].

Regarding the other likely mechanisms of clozapine-induced stuttering, it has been suggested that stuttering may be a manifestation of seizure. Clozapine-induced stuttering was associated with seizure or EEG abnormalities without typical symptoms of seizure in nine out of 30 case reports[12,25,59,60,62-66], and stuttering was significantly improved or completely relieved by addition of sodium valproate and the dose reduction of clozapine in five cases[12,59,62,64,66]. In the other four cases[25,60,63,65], anticonvulsant drugs were not tried, but discontinuation or dose reduction of clozapine resulted in complete relief of stuttering in three cases[60,63,65]. In contrast, one of the cases reported by Hallahan *et al*[58] experienced seizure after the development of stuttering. After the addition of sodium valproate, the patient had no seizure, but stuttering did not improve. It is worth mentioning that three cases had stuttering with both movement disorders and EEG abnormalities[60,62,63], which may demonstrate that some movement disorders induced by clozapine may be due to the epileptiform activity in the brain rather than EPS.

Collectively, the mechanism of clozapine-induced stuttering is multifactorial. Any of the following impairments or a combination of them can be a cause of clozapine-induced stuttering: Imbalance between direct and indirect pathways in the BG which may cause just stuttering or other movement disorders in addition to stuttering, abnormalities in the white matter neurotransmitters, and seizure or EEG abnormalities.

Finally, we suggest that in the cases of clozapine-induced stuttering at first, clinicians must do the electroencephalography to rule out any abnormal electrical activity of the brain which may progress to convulsion. If the patient has seizure or any abnormalities in EEG, the addition of sodium valproate is recommended. Even Varma *et al*[67] have recommended that one of the indications of initiating sodium valproate in patients receiving clozapine is stuttering with or without any types of seizure or EEG abnormalities. After ruling out the abnormal electrical brain activities, considering stuttering as an EPS and typical management of these side effects or dose reduction or discontinuation of clozapine may be

considered if stuttering is annoying the patient.

## STUTTERING INDUCED BY DRUGS AFFECTING GLUTAMATE NEUROTRANSMISSION

As described above, as the input nucleus of the BG, the striatum receives glutamatergic projection from different parts of the cerebral cortex and thalamus. Furthermore, the STN stimulates inhibitory GABAergic neurons of the output nuclei of the BG by releasing glutamate. All ionotropic NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, and kainite, and metabotropic glutamate receptors, mGlu1-8, are expressed in the BG, and glutamate is one of the important neurotransmitters that mediate signal transmission in the BG motor circuit. In addition, the computational modeling of stuttering[44] and the data of diffusion tensor imaging obtained from children who stutter[44] indicate that there is an impaired connectivity between different parts of the cerebral cortex and striatum in developmental stuttering. This impaired connection causes that BG cannot optimally detect cognitive and sensory motor context to terminate the previous phoneme and initiate the next phoneme[29] in a timely manner to produce a fluent speech. Therefore, drugs like memantine by inhibiting NMDA receptors[68] and pregabalin, gabapentin, and lamotrigine by inhibiting the release of glutamate[69,70] change the normal function of glutamate in corticostriatal pathway or in the different parts of the BG motor circuit can impair balance between the direct and indirect pathways and cause motor abnormalities like stuttering. Moreover, glutamate is the main neurotransmitter in the white matter and antagonizing its effects also disturbs signal transmission through white matter fiber tracts.

### *Theophylline*

Theophylline increases dopamine release and transmission by inhibiting GABA receptors on the SNpc and adenosine receptors on MSNs of both direct and indirect pathways. Theophylline also increases glutamate release. Therefore, it can disturb the normal balance between the mentioned neurotransmitters in the BG and cause stuttering. Another mechanism may be impairing the normal function of neurotransmitters in the white matter by increasing glutamate, the main neurotransmitter of the white matter[5].

## STUTTERING INDUCED BY OTHER DRUGS

### *Divalproex*

Although the main mechanism of action of valproate is the blockage of voltage-dependent sodium channels[71], it has several other mechanisms of action that justify its broad anticonvulsant activity, effects in the prophylaxis of migraine headache, and mood stabilizing properties. Animal studies in rats have demonstrated that valproate increases GABA concentration in both the striatum and substantia nigra, but its effect is more pronounced in the substantia nigra[72]. Valproate also increases the firing pattern and frequency of neurons of the SNpr[73]. We propose that an increased level of GABA in the substantia nigra increases its inhibitory effects on the thalamus through the direct pathway, and therefore, reduces the brain cortex stimulation to execute the desired movement which may cause stuttering.

### *Atomoxetine*

Atomoxetine is a selective NEP reuptake inhibitor. It increases the extracellular concentrations of NEP and dopamine in the prefrontal cortex[45]. However, studies that examined the effects of atomoxetine on the concentration of dopamine in the striatum obtained opposite results[45,74]. Because of uncertainty about the effect of atomoxetine on the dopamine levels in the striatum, we do not focus on dopamine as a mediator of likely effects of atomoxetine on speech motor control and stuttering. A study measured the blood oxygenation level dependent response using pharmacological magnetic resonance imaging in different regions of the rat brain following acute administration of atomoxetine. That study showed that atomoxetine increased SNpr and STN activity in the BG[75]. These increased activities decrease the stimulatory activity of the thalamocortical pathway. Therefore, we suggest that because of the decreased stimulation of the cerebral cortex, the favorable motor program is not executed, which can result in the inappropriate activation of the orofacial muscles and cause stuttering.

### *Sertraline*

It is proposed that sertraline-induced stuttering may be related to the serotonergic inhibition of the dopaminergic neurons. The cell bodies of these neurons are located in the ventral tegmental area. Therefore, inhibition of the dopamine pathways in the nigrostriatum can be considered as a mechanism of promoting stuttering by sertraline or selective serotonin reuptake inhibitors drugs in general[76,77].

### *Bupropion*

Bupropion is able to increase dopamine levels in the prefrontal cortex, which may cause stuttering[78-80].

### *Pyrethrin*

It seems that the stuttering induced by a topical pyrethrin product in a child is related to its neurotoxicity since the metabolism of pyrethrin in children is slow. The product also had contained piperonyl butoxide, which can inhibit the hepatic metabolism of the compound and potentiate the toxicity[81].

## CONCLUSION

In this review, 82 cases of DIS were collected. Most cases were related to antipsychotic drugs. Similar to the developmental stuttering, the majority of persons who experienced an episode of DIS were male. The repetitions followed by speech blocks were the most frequent core manifestations of stuttering. In 55.8% of cases, drug withdrawal was the therapeutic measure that was used to manage the stuttering.

Although we tried to provide a complete feature of the epidemiological and clinical characteristics of DIS, much information such as the core behaviors of stuttering, the interval between the initiation or increase in the dose of offending medications and the occurrence of stuttering and between the drug withdrawal or dose reduction and the improvement of stuttering, and concurrent psychological symptoms with stuttering was not reported in several cases. As a result, future cases of DIS must be reported with more detailed information since these data give others a comprehensive feature of this type of the NS.

By focusing on the cortico-BG-thalamocortical loop and the white matter fiber tracts and their neurotransmitters such as dopamine and glutamate, we suggest some likely mechanisms for DIS. However, dysfunctions in other areas of the brain like the cerebral cortex and cerebellum and other neurotransmitters are not addressed in this review. In addition, we consider stuttering as a speech motor disorder, but cognitive and sensory disorders may also play roles in the pathogenesis of DIS. Therefore, it is suggested that these subjects should be considered in the future papers discussing the underlying mechanisms of DIS. In spite of many hypotheses that can be proposed for the pathogenesis of DIS, experimental studies will provide the most robust evidence in this field. Since advanced brain imaging facilities may not be available in every setting where clinicians encounter a case of DIS to find the areas of the brain that act abnormally, animal studies evaluating the changes in the functions of the brain and different neurotransmitters are required to shed a light on the underlying mechanisms of DIS.

## FOOTNOTES

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*REVIEW*

# Insights into myelin dysfunction in schizophrenia and bipolar disorder

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## Abstract

Schizophrenia and bipolar disorder are disabling psychiatric disorders with a worldwide prevalence of approximately 1%. Both disorders present chronic and deteriorating prognoses that impose a large burden, not only on patients but also on society and health systems. These mental illnesses share several clinical and neurobiological traits; of these traits, oligodendroglial dysfunction and alterations to white matter (WM) tracts could underlie the disconnection between brain regions related to their symptomatic domains. WM is mainly composed of heavily myelinated axons and glial cells. Myelin internodes are discrete axon-wrapping membrane sheaths formed by oligodendrocyte processes. Myelin ensheathment allows fast and efficient conduction of nerve impulses through the nodes of Ranvier, improving the overall function of neuronal circuits. Rapid and precisely synchronized nerve impulse conduction through fibers that connect distant brain structures is crucial for higher-level functions, such as cognition, memory, mood,

and language. Several cellular and subcellular anomalies related to myelin and oligodendrocytes have been found in postmortem samples from patients with schizophrenia or bipolar disorder, and neuroimaging techniques have revealed consistent alterations at the macroscale connectomic level in both disorders. In this work, evidence regarding these multilevel alterations in oligodendrocytes and myelinated tracts is discussed, and the involvement of proteins in key functions of the oligodendroglial lineage, such as oligodendrogenesis and myelination, is highlighted. The molecular components of the axo-myelin unit could be important targets for novel therapeutic approaches to schizophrenia and bipolar disorder.

**Key Words:** Myelin sheath; Oligodendroglia; Schizophrenia; Bipolar disorder; White matter

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**Core Tip:** Schizophrenia and bipolar disorder are multifactorial neuropsychiatric entities that share clinical manifestations as well as alterations to brain structure and function, genetic characteristics, and neurobiological pathways. Among the main pathophysiological mechanisms shared by these conditions is oligodendroglial dysfunction. Scientific evidence that ranges from the microscale cellular and subcellular levels to the macroscale connectomic level strongly supports overall myelin dysfunction and brain disconnection as hallmarks of schizophrenia and bipolar disorder.

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## INTRODUCTION

Currently, it is widely understood that optimal functioning of the central nervous system (CNS) depends on synaptic connections and multidirectional interactions between neuronal and glial cells. One of the closest glial-neuronal interactions in the CNS occurs between oligodendrocytes and neurons through myelination. Myelin ensheathment induces axonal compartmentalization to form nodes of Ranvier, *i.e.*, specialized domains that increase the conduction speed of action potentials. The saltatory propagation and speed of these electrical impulses depends on axon caliber, but primarily on myelin features such as the number and length of internodes as well as myelin width and compaction[1]. Therefore, myelination allows neuronal circuits to be finely tuned and synchronized and, as such, plays a key role in maintaining the proper connectivity between brain structures to support higher integrating processes, such as perception, memory, or cognition. Furthermore, through myelination, oligodendrocytes also provide metabolic support to axons[2,3], contributing to their structural and functional integrity, which is a requirement for homeostasis of the human brain.

Myelination is a neurodevelopmental process that begins during the third trimester of pregnancy and increases steadily during childhood and early youth until it reaches a slow-increasing plateau in adult life[4,5]. This process is adaptive, with neural activity being one of the main factors driving myelin plasticity[6]. Moreover, because the myelin sheath is a specialized structure made up of multiple layers of plasma membrane, from which most cytoplasm is extruded, its composition is enriched with lipids (approximately 70% of its content) and proteins[7]. These proteins have important functional roles, such as providing anchorage between myelin lamellae, attaching axons and myelin at paranodal regions, signaling and interacting with cytoskeletal elements within oligodendrocytes[7,8]. As with any other cell type, the plasma membrane in oligodendrocytes is subject to homeostatic turnover; thus, to manage this large energy requirement, their metabolic rate is higher than that of other cell types[9]. This characteristic renders myelinating oligodendrocytes more vulnerable to cellular stress and oxidative damage generated by reactive oxygen/nitrogen species[10]. In the case of injury and myelin loss (demyelination), endogenous repair mechanisms are triggered and remyelination occurs. For either developmental/adaptive myelination or remyelination to occur, oligodendrocyte precursor cells (OPCs) distributed along the brain must differentiate and mature to acquire myelinating capacity[11,12]. Oligodendrogenesis involves differential expression of proteins and other molecules and a dramatic increase in morphologic complexity, which implies crucial and extensive rearrangements of the oligodendroglial cytoskeleton[13,14].

Due to the intrinsic complexity of oligodendrocyte morphology and functioning and the importance of myelination/remyelination processes for CNS homeostasis, impairments in oligodendroglial lineage may be associated with brain disorders. Within the last two decades, great effort has been made to determine and describe neuronal and glial alterations that contribute to the etiology of mental illnesses [15-18]. Of the studied mental disorders, we focused on schizophrenia and bipolar disorder because these neuropsychiatric illnesses present a chronic and deteriorating course that imposes a large burden, not only on patients but also on society and health systems. These disorders are long-lasting, severe mental health conditions that share genetic characteristics and alterations to brain structure and function, and neurobiological pathways[19-21]. Among the main pathophysiological mechanisms shared by these conditions is glial dysfunction[22,23], specifically related to myelination, which is the focus of this text.

Taking the above information into account, the aim of this work was to gather and discuss the evidence that myelin dysfunction at the cellular and subcellular levels may underlie the white matter (WM) macroscale connectome alterations evidenced by neuroimaging in schizophrenia and bipolar disorder, thereby supporting the disconnection hypothesis that explains the symptomatic domains of these clinical entities. For this purpose, we first provide a brief overview of the main structural features of myelin. Next, we present the evidence of myelin alterations at the microscale levels (cellular and subcellular) found in postmortem samples from schizophrenia and bipolar disorder patients. Then, we briefly compare the main findings at these levels. Finally, we review evidence at the macroscale level from neuroimaging techniques and find consistent support for dysconnectivity among key brain regions in these disorders. These neuroimaging techniques are the main methods that allow us to obtain information about brain structure and function from patients during the course of their illnesses.

## BRIEF OVERVIEW OF MYELIN STRUCTURAL FEATURES

Each myelin internode is a specialized structure of multiple membrane lamellae. The first membrane layer-closest to the axon-is called the adaxonal membrane. Between the axon and the adaxonal membrane is the periaxonal space[7]. Flanking each internode, paranodal loops make contact with the axon through the cell adhesion proteins neurofascin 155 (NF155; on the oligodendrocyte) and contactin-associated protein 1 (Caspr1)/contactin 1 (on the axon). In juxtaparanodal regions, myelin-axon interactions are mediated by contactin 2 and Caspr2, and the voltage-gated $K^+$ channels Kv1.1/1.2 are enriched at the axolemma. Contactin's cytoplasmic domains provide anchors for scaffold molecules of the paranodal-nodal-paranodal cytoskeleton, specifically for the 4.1B protein, the αII/β2SP heterotetramers (both actin-interacting proteins) and ankyrin B (AnkB)[24].

In a mature myelin internode, the adaxonal layer is relatively loose compared with the tightly compacted myelin lamellae, and its cytoplasmic content is slightly higher, which allows the functional presence of signal transduction molecules and oligodendroglial cytoskeletal components such as septin filaments[25]. These components are also present at paranodal loops. In contrast, the structure of compact myelin is almost withdrawn from the cytoplasm; thus, intracellular membranes are in tight apposition, with myelin basic protein (MBP) playing a key role in regulating the hydrophobic forces between them[7].

As previously mentioned, the molecular composition of myelin is highly enriched in lipids, which account for approximately 70% of its wet weight. Myelin membranes have a higher cholesterol content than other membranes (at approximately 1.6-fold) and are characteristically enriched with galactosphingolipids and plasmalogens, which are asymmetrically distributed among the bilayer leaflets. The extracellular leaflet is enriched in galactosylceramide and its sulfated form, sulfatide, as well as phosphatidylcholine and sphingomyelin, whereas the intracellular leaflet is rich in ethanolamine plasmalogen and other phospholipids. The lipid components of the extracellular leaflet form discrete domains known as lipid rafts, which often contain membrane proteins and are frequently involved in signaling and/or myelin component turnover. For further review of myelin lipids, see[26,27].

Myelin-specific structural proteins also are distributed according to their functions. Interestingly, at least five out of eleven CNS myelin-specific proteins are categorized as intrinsically disordered proteins. This set of physicochemical attributes accounts for their flexibility and multifunctionality, which are important for a plastic structure such as myelin[28]. An exhaustive description of the structural and functional features of every myelin-specific protein is beyond the scope of this review and has been further addressed elsewhere[8,29]. Figure 1 illustrates the main CNS myelin-specific proteins at their common locations in the myelin sheath, as well as the lipidic composition of myelin membranes.

## EVIDENCE OF MYELIN ALTERATIONS AND OLIGODENDROGLIAL DYSFUNCTION IN POSTMORTEM SAMPLES OBTAINED FROM SCHIZOPHRENIA PATIENTS

The analysis of postmortem samples provides valuable information about the structural and

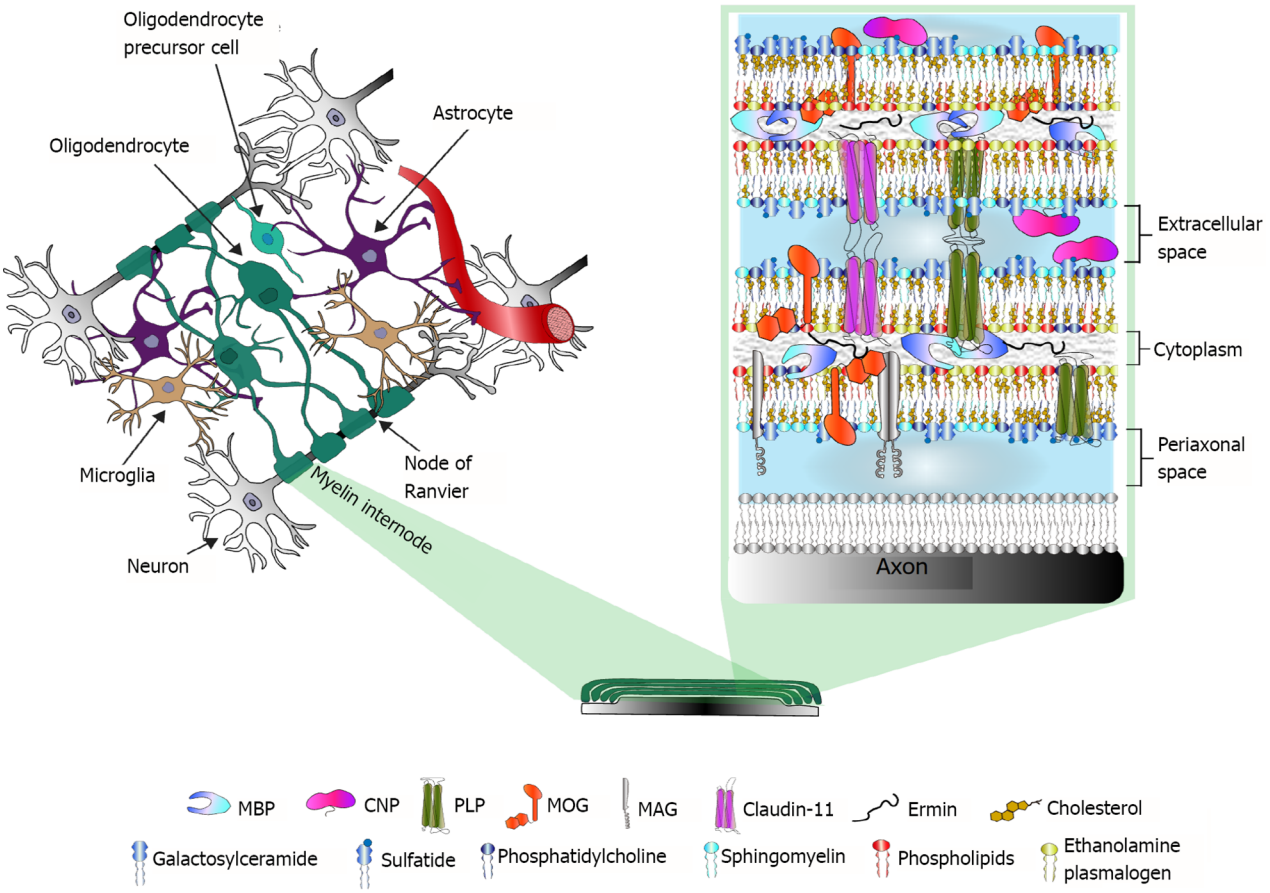


**Figure 1 Myelin in the central nervous system.** Left, a schematic representation of central nervous system (CNS) cells and their multidirectional interactions. Right, the main protein and lipid components of CNS myelin. Proteomic studies have revealed altered expression of myelin proteins in postmortem brain samples from patients with schizophrenia or bipolar disorder. MBP: Myelin basic protein; CNP: 2',3'-cyclic nucleotide 3'-phosphodiesterase; PLP: Proteolipid protein; MOG: Myelin-oligodendrocyte glycoprotein; MAG: Myelin-associated glycoprotein.

biochemical alterations present in the brains of patients with neuropsychiatric disorders. In the last 20 years, several reports by Uranova *et al*[30] have described the main ultrastructural alterations in oligodendrocytes and myelinated fibers found in patients with schizophrenia.

With electron microscopy and morphometry or with a stereological approach and Nissl-stained sections, they extensively analyzed the prefrontal cortex (PFC), specifically the gray matter layers of Brodmann's area 9 (BA9) and BA10[30-33] and their adjacent WM[34-36], as well as the caudate nucleus [21,33,37,38], hippocampus[33,38,39] and anterior putamen[40].

Their analysis of myelinated fibers found concentric lamellar bodies and interlamellar abnormal inclusions, swelling of periaxonal oligodendrocyte processes and ultrastructural signs of axonal atrophy [21,33,38,39]. They characterized six types of abnormal myelinated fibers that were present in patients with schizophrenia and that could correlate with the predominant presence of positive or negative symptoms, age or illness duration[35].

Oligodendrocytes showed consistent signs of dystrophia, apoptosis and/or necrosis, and in most of the studies, their numerical density was significantly reduced in patient samples[31,33,37,40]. Oligodendrocyte clusters, which are thought to be involved in activity-dependent myelination, were also consistently reduced[37,40]. In the oligodendrocytes, mitochondria were the main altered organelle, with a significant reduction in numeric and volume density and even intramitochondrial accumulation of lipofuscin granules[30,34,36,38]. These findings suggest that not only is the numerical density of oligodendrocytes affected in schizophrenia, but that their energy and redox metabolism is also compromised.

Interestingly, both perineuronal and pericapillar oligodendrocytes showed signs of dystrophy in patient samples[33,34] suggesting that oligodendrocytes may be involved both in the disrupted transmission of neuronal information and in metabolic dysregulation. In addition, these studies found dystrophic ameboid microglia adjacent to dystrophic oligodendrocytes[30,34] and myelin concentric lamellar bodies engulfed by astrocytes[21], implying the involvement of other glial cells in myelin pathology in schizophrenia patients.

Hof *et al*[41,42] found a significant decrease in both the total number of oligodendrocytes and the number of oligodendrocytes expressing the 2',3'-Cyclic-nucleotide 3'-phosphodiesterase (CNP) marker

in cortical layer III of BA9 and the WM of the superior frontal gyrus with a stereological analysis on samples from patients with schizophrenia. Additionally, the number of oligodendrocyte clusters in the WM was significantly reduced[42]. Other studies reported a decreased number of oligodendrocytes in the anterior principal thalamic nucleus[43,44], centromedian thalamic nucleus[44], thalamic internal capsule[45], hippocampus[46,47] and anterior cingulate WM[48] of schizophrenia patient samples. In the latter structure, oligodendrocytes expressing disintegrin and metalloproteinase domain-containing protein 12 (ADAM12) were examined[48]. ADAM12 is predominantly expressed in oligodendrocytes and has been suggested to play a role in myelination and neurodevelopmental processes, as well as in higher cognitive functions[49].

Not all neuropathological studies of postmortem schizophrenia brain samples showed significant differences in oligodendrocyte densities, *e.g.*, in the cingulum bundle[50], BA9 adjacent WM[23,51], and BA10 adjacent WM[34], no changes in oligodendrocyte cell densities were found between schizophrenia and control samples. In contrast, an increased density of prohibitin$^{(+)}$-oligodendrocytes was reported in the right dorsolateral prefrontal WM of schizophrenia patients[52]. The authors suggested that prohibitin may be upregulated in oligodendrocytes as a result of mitochondrial stress and/or dysfunction in schizophrenia.

mRNA expression of neural/glial antigen 2 (NG2) was augmented in the putamen of schizophrenia patients[53], suggesting that there could be an increased density of OPCs. Additionally, a study by Kerns *et al*[45] supported the hypothesis that in schizophrenia OPCs may fail to exit the cell cycle and differentiate into mature myelinating oligodendrocytes. In BA9 WM, there was no significant difference in NG2$^{(+)}$-cells but a significant reduction in cells expressing oligodendrocyte transcription factor 2 (OLIG2), suggesting an overall reduction in the oligodendroglial lineage[54].

## MYELIN SUBCELLULAR/BIOCHEMICAL ALTERATIONS IN POSTMORTEM SAMPLES OF PATIENTS WITH SCHIZOPHRENIA

Proteomic approaches have been used to determine that the main myelin structural proteins are differentially expressed in schizophrenia postmortem brain samples; in most of the studies, these proteins were significantly downregulated. For most of the myelin structural proteins, altered transcriptomic levels have consistently been reported[53,55-57], and in some cases, single-nucleotide polymorphisms (SNPs) at their codifying genes have been associated with schizophrenia (Table 1). This is the case for MBP[58-61], CNP[57,60-63], proteolipid protein (PLP)[60,62,64], myelin-associated glycoprotein (MAG)[62,64,65], and transferrin[66-68]. The latter is not a structural myelin protein, but is essential for oligodendrocyte homeostasis and survival[69,70]. Downregulation of myelin oligodendrocyte glycoprotein (MOG)[58,60-62,71] and claudin-11[62,64] at the proteomic and transcriptomic levels has been reported, although no SNPs of the corresponding codifying genes have been associated with schizophrenia. Several brain regions have been analyzed by proteomic studies, such as the dorsolateral PFC BA46[59,62,71], PFC BA9 gray and WM[68], PFC BA10[60], anterior PFC[65], orbitofrontal cortex[64], anterior temporal lobe[58], corpus callosum[61], cerebellum, posterior cingulate cortex and caudate nucleus[63].

Consistent with findings of overall downregulation of myelin-specific proteins, mRNA levels of *OLIG1*[22], *OLIG2*[22,55,72-74] and *SOX10*[22,55,72], corresponding to oligodendroglial lineage transcription factors, were significantly reduced in postmortem schizophrenia brain samples. Additionally, the expression of the *NG2*, *PGDFRA* and *GALC* genes (the former two coding for markers of OPCs and the latter for a marker of immature oligodendrocytes), was consistently downregulated in patient samples[22]. Quaking (QKI), an RNA-binding protein with a key role in the posttranscriptional regulation of myelin-specific genes, mRNA levels were significantly reduced in postmortem samples of schizophrenia patients[72,75-77]. Moreover, SNPs in both *OLIG2* and *QKI* genes have been associated with this mental disorder.

In addition to the previously mentioned gene association studies, a functional glial-specific gene set analysis based on genome-wide association data reported three main oligodendroglial gene sets, *i.e.*, lipid metabolism, gene transcription and oxidation–reduction, which were strongly associated with an increased risk for schizophrenia[78]. Furthermore, gene expression profile analysis of CNP$^{(+)}$-cells revealed nine differentially regulated signaling pathways associated with oligodendrocyte differentiation[54], strongly suggesting oligodendrogenesis impairment in schizophrenia.

Proteomic studies of schizophrenia-derived postmortem brain samples have also consistently revealed that many cytoskeletal components are differentially expressed in this disorder. Dynamic cytoskeletal rearrangements are crucial for oligodendrogenesis since this process implies a dramatic increase in oligodendroglial morphologic complexity. Additionally, actin-cytoskeleton dynamic assembly and disassembly are critical for axon ensheathment during the myelination process[79-81]. Several actin-interacting proteins are involved in these rearrangements, including gelsolin and cofilin, actin filament-severing proteins that drive actin cytoskeleton disassembly, which is essential for proper myelin wrapping[79]. Gelsolin is specifically expressed in myelin-forming cells[82] and is present in the different stages of oligodendroglial lineage differentiation[83]. Transcriptomic and proteomic analyses

**Table 1 Studies that reported single-nucleotide polymorphisms associated with schizophrenia in myelin/oligodendrocyte genes**

| Protein name | Gene | SNPs | Ref. |
|---|---|---|---|
| Myelin basic protein | *MBP* | rs12458282; rs2008323; rs721286 | Baruch *et al*[185], 2009 |
| 2′,3′-Cyclic nucleotide 3′-phosphodiesterase | *CNP* | rs2070106 | Peirce *et al*[186], 2006 |
| | | | Voineskos *et al*[187], 2008 |
| | | | Voineskos *et al*[175], 2013 |
| Proteolipid protein | *PLP* | rs475827 | Qin *et al*[188], 2005 |
| Myelin-associated glycoprotein | *MAG* | rs720308; rs720309; rs756796; rs2301600 | Wan *et al*[189], 2005 |
| | | | Yang *et al*[190], 2005 |
| | | | Voineskos *et al*[187], 2008 |
| Transferrin | *TF* | rs3811655; rs448115 | Qu *et al*[191], 2008 |
| | | | Huo *et al*[192], 2019 |
| Oligodendrocyte lineage transcription factor 2 | *OLIG2* | rs1059004; rs9653711 | Georgieva *et al*[73], 2006 |
| | | | Voineskos *et al*[175], 2013 |
| | | | Huo *et al*[192], 2019 |
| | | | Komatsu *et al*[74], 2020 |
| Quaking | *QKI* | rs2784865 | Voineskos *et al*[175], 2013 |

SNP: Single-nucleotide polymorphisms.

of postmortem brain samples have shown that both gelsolin[61,68,72] and cofilin[59,63,64] are dysregulated in schizophrenia. Similarly, the oligodendrocyte-specific protein ermin, also known as juxtanodin, is downregulated in the anterior temporal lobe and upregulated in the dorsolateral PFC in patients with schizophrenia[58,59]. Ermin is an F-actin binding protein that is expressed at late stages of oligodendrocyte maturation. It may play a key role in the formation of multiple oligodendroglial processes and the dramatic changes in morphology as these cells acquire the capacity for myelination [84,85].

Septin heteromeric filaments (SEPT2/SEPT4/SEPT7/SEPT8) form at the adaxonal myelin layer and at paranodal loops. These filaments act as molecular scaffolds, mediating axo-glial signaling and compartmentalization of mature myelin. Their loss or deficit has been associated with the formation of myelin outfoldings that impair the rapid propagation of nerve impulses[25,86,87]. The four septins involved in these filaments are differentially expressed in proteomic analyses of postmortem schizophrenia brain samples[62,63].

α/β-Spectrin oligomers are important components of the membrane-bound cytoskeleton at the axolemma. At the paranodal and juxtaparanodal regions of the axon beneath a myelin internode, these oligomers interact with proteins such as 4.1B, adducin and AnkB to form a scaffold that mediates the interaction of the cytoplasmic tails of contactins and other axo-glial adhesion molecules with the actin filaments and the actin rings found along the axon. These proteins are also relevant because they are crucial for the paranodal-nodal-paranodal cytoskeleton, which is a specific arrangement of cytoskeletal protein oligomers and polymers underlying the proper assembly and plasticity of the nodes of Ranvier [24]. All of these proteins are differentially regulated in schizophrenia postmortem brain samples[58,59,62-64].

Neurofilaments are important axonal cytoskeletal components. They belong to the intermediate filament IV category, and their composition is heteromeric, with light (NEFL), medium (NEFM) and heavy (NEFH) polypeptides as their main constituents. Internexin (INA) is also a component of these axonal structural filaments. Repelling forces among negatively charged phosphorylated residues on the neurofilaments contribute to the enlargement of axon caliber, *e.g.*, at internodes (Figure 2). Thus, phosphorylation/dephosphorylation of neurofilament polypeptides is a mechanism that regulates axon caliber, which influences molecular trafficking as well as the speed of nerve impulse conduction. Proteomic studies have found that the three neurofilament polypeptides NEFL, NEFM, and NEFH, as well as INA, are differentially regulated in postmortem brain samples from schizophrenia patients[57,61-64].

As expected, the actin and tubulin monomeric components of microfilaments and microtubules, respectively, as well as various microtubule-associated proteins, are altered in schizophrenia brain samples[58,61-63]. The cytoskeleton mediates the essential functions of every cell in the organism. In the axo-myelin functional unit[88], the cytoskeleton is crucial for the following: Oligodendrogenesis; myelin

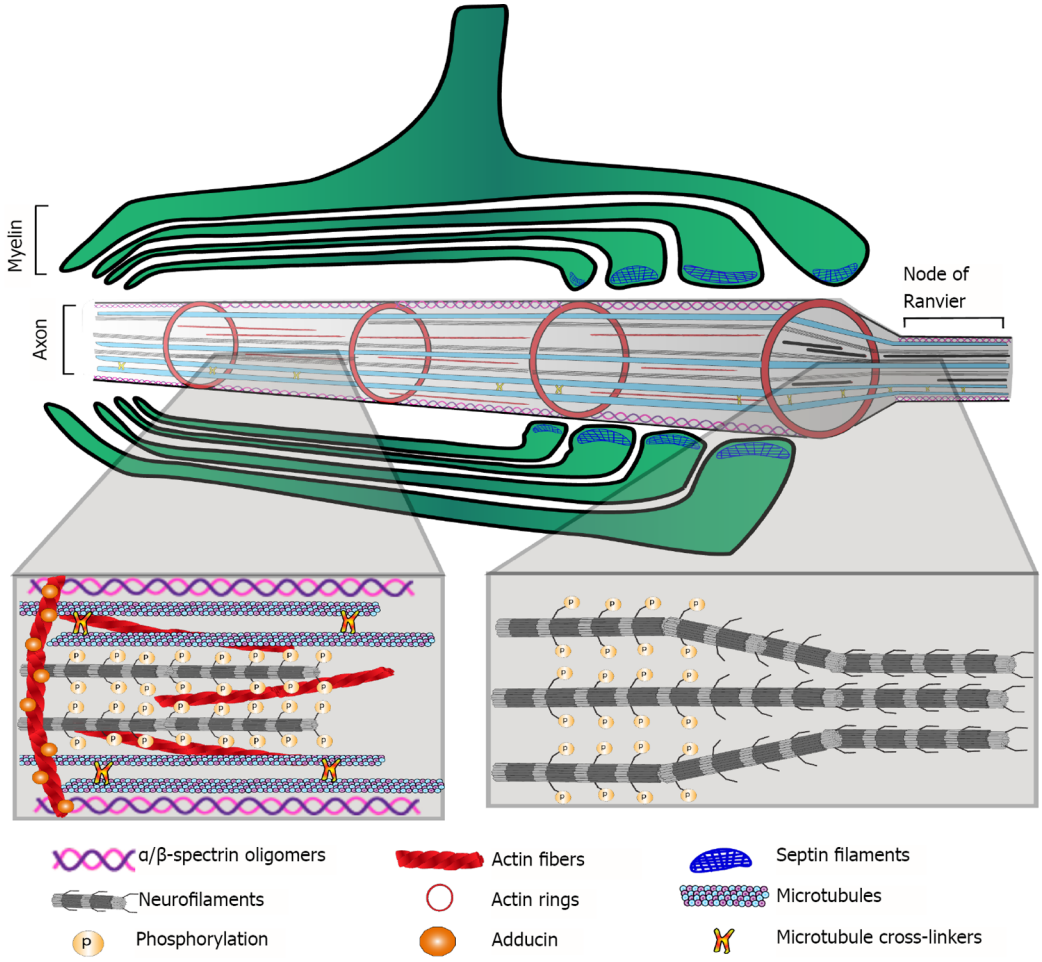


**Figure 2 Main cytoskeletal components of the myelinated axon.** Proteomic approaches revealed alterations in most of these components in postmortem brain samples of schizophrenia patients.

formation, turnover and plasticity; assembly and remodeling of axonal specialized domains, such as the axon initial segment and nodes of Ranvier; myelin and axonal compartmentalization; anchorage for cell adhesion molecules involved in axo-glial junctions; and scaffolds for molecules involved in signal transduction.

As most of the myelin structural proteins are affected by schizophrenia and most of the cytoskeletal components are dysregulated, it is plausible to infer that overall dysfunction of the axo-myelin unit may underlie the compromised integrity of gray and WM and thus the functional disconnection observed in schizophrenia.

Metabolic dysfunction in schizophrenia has been suggested by positron emission tomography (PET) and magnetic resonance imaging (MRI), and mitochondrial alterations have been documented as mentioned above. At the proteomic level, dysregulation in the expression of enzymes involved in energy metabolism and the antioxidant system has been observed. For example, Martins-de-Souza *et al* [59,89] found alterations in proteins involved in glycolysis (fructose-bisphosphate aldolase C and phosphoglycerate kinase 1), the Krebs cycle (citrate hydrolyase), the malate-aspartate shuttle (cytosolic malate dehydrogenase) and oxidative phosphorylation (mitochondrial ATP synthase F1 and F0 complexes) in postmortem dorsolateral PFC samples from schizophrenia patients[59,89]. In addition, four subunits of mitochondrial respiratory complex I (NADH dehydrogenase [ubiquinone] (NDU) flavoprotein 2 (NDUFV2), iron-sulfur protein 3 (NDUFS3) and 6 (NDUFS6), and 1 beta subcomplex subunit 5 (NDUFB5)) are downregulated in the anterior temporal lobe of schizophrenia patients[58,89].

Increased amounts of oxidative reactive species are produced under high energy demand or mitochondrial dysfunction, as is suggested to occur in schizophrenia. Therefore, antioxidant enzymatic systems in schizophrenia are expected to be upregulated to counteract oxidative damage. However, the expression levels of three members of the glutathione transferase (GST) family (GSTM3, GSTTLp28, and GSTP1), carbonyl reductase 1 (CBR1), carbonyl reductase 3 (CBR3) and quinoid dihydropteridine reductase (QDPR), are reduced in the thalamus and PFC of schizophrenia patients (reviewed in[89]). As these results were obtained from brain homogenates, an interesting follow-up would be to assess whether these metabolic and redox alterations are present in oligodendrocytes. For this purpose, enriched cultures of patient-derived oligodendrocytes differentiated from induced pluripotential stem

cells (iPSCs) and/or cocultures of these induced oligodendrocytes with neurons and other glial cells could be useful *in vitro* tools for studying alterations in the oligodendroglial lineage in schizophrenia.

## MYELIN ALTERATIONS AND OLIGODENDROGLIAL DYSFUNCTION EVIDENCE IN POSTMORTEM SAMPLES OBTAINED FROM BIPOLAR DISORDER PATIENTS

Uranova *et al*[51] also analyzed samples from patients with bipolar disorder, examining BA9 of the PFC, layers III and VI and the adjacent WM, BA10, the caudate nucleus and the anterior putamen. A stereological approach with Nissl-stained samples revealed a significant reduction in the numerical density of oligodendrocytes in the caudate nucleus and in the gray matter layers of BA9[32,37,51]. In the adjacent WM, they found no difference between bipolar disorder samples and samples from control subjects[51]. The number of oligodendrocyte clusters was also significantly reduced in the caudate nucleus[37] and in the anterior putamen, but the latter difference was observed only in male subjects [40]. Electron microscopy analysis of the samples showed ultrastructural signs of apoptosis and necrosis of oligodendrocytes[21].

Oligodendrocyte numbers were significantly reduced in the thalamic anterior principal and centromedian nuclei, in postmortem samples from bipolar disorder patients with a clinical history of psychotic episodes[44]. The age-related increase in oligodendrocyte number observed in control subjects was attenuated in this group of patients. The latter effect was also observed by Vostrikov and Uranova[90]. Vostrikov and Uranova[90] also found significantly reduced oligodendrocyte densities in samples from BA9 Layer VI from bipolar disorder patients younger than 50 years old compared with those from corresponding age-matched controls[90]. Hayashi *et al*[91] found a significant reduction in $OLIG2^{(+)}$-cells using a flow cytometry approach in unfixed postmortem gray matter BA10 samples from bipolar disorder patients, which suggests an overall deficit in the oligodendroglial lineage. $S100B^{(+)}$-oligodendrocyte density was decreased in the left alveus of the hippocampus from bipolar disorder patients[92]. In contrast, Hercher *et al*[23] found increased oligodendrocyte density and CNP protein levels in BA9-adjacent WM in bipolar disorder patients compared with control samples. A further study also showed an increase in oligodendrocyte density along with deficits in axonal markers in prefrontal WM in bipolar disorder patients[93]. In a systematic review of postmortem brain studies in bipolar disorder, Gigase *et al*[94] found no difference in either neurons or glial cells and suggested that findings from existing studies should be validated.

Significantly less intense myelin staining of the deep prefrontal WM was shown in bipolar disorder patients than in control subjects[95]. Additionally, MBP immunostaining revealed decreased myelination of the hippocampal formation in female bipolar disorder patients than a corresponding sex-matched control group[96]. In contrast, male patients showed increased MBP staining in the superior medullary lamina, which suggests sex differences in myelin alterations[96]. To the best of our knowledge, no ultrastructural analysis of myelinated fibers has been conducted on bipolar disorder postmortem samples.

Perineuronal oligodendrocytes are located in the cerebral gray matter in close proximity to neuronal perikarya and less frequently near dendrites and neurites. Although their morphology is indistinguishable from that of other oligodendrocytes, it remains unknown whether perineuronal oligodendrocytes have a similar or different cell signature from that of typical myelinating oligodendroglial cells[97]. Bipolar disorder patients showed cytochemical abnormalities of prefrontal perineuronal oligodendrocytes, correlating with cytochemical alterations of calbindin-containing GABAergic neurons and changes in gene expression levels[98].

## MYELIN SUBCELLULAR/BIOCHEMICAL ALTERATIONS IN POSTMORTEM SAMPLES OF PATIENTS WITH BIPOLAR DISORDER

Myelin structural proteins MBP, CNP, PLP and MOG were downregulated in postmortem brain samples from bipolar disorder patients[60]. Consistent downregulation at the transcriptomic level was reported for *MBP* and *CNP*, and at this level *MAG*, *PLP*, *CLDN11*, *MOG*, and *MOBP* were also downregulated[22]. Reduced mRNA levels were also reported for *TF*[22,53]. The gene expression of the oligodendroglial lineage transcription factors *OLIG1*, *OLIG2* and *SOX10* was downregulated. Additionally, transcript levels of *NG2* and *GALC*, which correspond to markers of OPCs and immature oligodendrocytes, respectively, were significantly lower in bipolar disorder samples than in control samples[22].

Differential expression of cytoskeletal components of the axo-myelin unit has been reported in postmortem brain samples of bipolar disorder patients. In the WM adjacent to BA9, the β-tubulin protein level assessed by Western blot was significantly lower in patient samples than in controls[93]. A proteomic approach found that the NEFL level was downregulated in bipolar disorder samples of BA10 [60]. Similarly, the neurofilament units NEFL and NEFM and INA, α-spectrin (SPTAN1), SEPT11 and

tubulin polymerization-promoting protein (TPPP) were downregulated, whereas β-actin (ACBT) and the ARPC5 subunit of the actin-binding Arp2/3 complex were upregulated in hippocampal samples from bipolar disorder patients[99,100]. The actin-bundling protein fascin (FASC) was also dysregulated in these samples[99]. In samples of the dorsolateral PFC, NEFL, NEFM and INA were consistently downregulated, while α- and β-tubulins as well as SEPT5, SEPT6 and SEPT11 were upregulated[67].

As in schizophrenia, alterations in metabolic and redox pathways have been described for bipolar disorder. Studies using magnetic resonance spectroscopy have found a reduction in phosphocreatine and ATP in the frontal lobes and basal ganglia, while an increase in lactate levels was reported in postmortem gray matter samples from bipolar disorder patients. In addition, mitochondrial structure is altered, and mutations or polymorphisms in mitochondrial DNA associated with the respiratory chain have been reported[101]. Furthermore, high levels of lipid peroxidation, nitric oxide concentration, and DNA and RNA oxidative damage were found in patient samples[102]. There is evidence of dysfunctional attachment of the hexokinase 1 protein to the outer mitochondrial membrane in patient samples, which results in abnormal generation of mitochondrial reactive oxygen species and cellular oxidative stress[103]. Additionally, impairment of redox modulation pathways in the frontal cortex is found in bipolar disorder patients[104]. The antioxidant molecule glutathione has been reported at low concentrations in some brain regions and could contribute to oxidative stress[105,106]; however, some patients present a significant increase in this molecule in the anterior cingulate cortex[107]. These apparently contradictory results could reflect differential redox regulation or antioxidant capacity in diverse brain regions.

Due to their high metabolic rate and high lipid content in myelin-forming membranes, oligodendrocytes are especially vulnerable to oxidative stress. Therefore, a microenvironment prone to the generation of high amounts of oxidative molecules and an impaired antioxidant capacity, which seems to be characteristic of patients with schizophrenia or bipolar disorder, would certainly contribute to the dysfunction of the axo-myelin unit and subsequently impact the proper conduction of nerve impulses.

## COMPARISON OF ALTERED FEATURES OF OLIGODENDROCYTES AND MYELIN IN SCHIZOPHRENIA AND BIPOLAR DISORDER

Several features are similarly altered by schizophrenia and bipolar disorder at the cellular level. Ultrastructural studies have revealed signs of oligodendrocyte apoptosis and necrosis[21], oligodendrocyte numerical density was significantly reduced in the caudate nucleus[37] and in BA9 gray matter layers of the PFC[32,51], and significantly fewer oligodendrocyte clusters were found in the caudate nucleus[37] and the anterior putamen[40]. In BA9-adjacent WM, a stereological analysis found no differences in oligodendrocyte numerical density in either schizophrenia or bipolar disorder patients compared to that of the control samples[51]. However, in schizophrenia, studies have reported decreased oligodendrocyte numerical density in the BA9- and BA10-adjacent WM[33,108], a significant reduction of $OLIG2^{(+)}$-cells in the former[54], and a significant decrease in both total and $CNP^{(+)}$-oligodendrocytes in the WM of the superior frontal gyrus[41,42]. Additionally, significantly fewer $ADAM12^{(+)}$-oligodendrocytes were found in the anterior cingulate WM[48]. In contrast, two different studies reported increased oligodendrocyte density in the prefrontal WM in postmortem samples from bipolar disorder patients[23,93]. One of these studies reported a concomitant decrease in axonal markers [93], which may imply axonal degeneration due to demyelination, which is consistent with an increase in oligodendrocytes at early stages of differentiation. In schizophrenia-derived samples, significantly more oligodendrocytes expressing prohibitin were found in the right dorsolateral prefrontal WM[52]. Although prohibitin proteins can be found in other cell compartments, such as the nucleus or plasma membrane, their role in the inner mitochondrial membranes is key for modulating cell proliferation or apoptosis and for overall mitochondrial homeostasis[109-112]. Therefore, altered oligodendroglial prohibitin expression is consistent with a previous work suggesting dysregulation of the cell cycle in oligodendrocytes in schizophrenia[113]. Based on the findings of that work, Katsel *et al*[113] suggested that postmitotic oligodendrocytes may abnormally re-enter the cell cycle, while a significantly increased level of NG2 in the putamen of schizophrenia patients suggested that OPCs failed to exit the cell cycle. Dysregulation of p57Kip2 gene expression in schizophrenia patient samples[113] could also be related to impaired oligodendrocyte maturation, since this protein has been characterized as an oligodendroglial differentiation competence marker[114-116].

At the subcellular level, proteomic analyses have revealed that the four most abundant myelin structural proteins[117] (PLP, MBP, CNP, and MOG) are significantly reduced in schizophrenia and bipolar disorder. At the transcriptomic level, almost all myelin structural proteins, as well as the main oligodendroglial lineage markers and OPC markers, were significantly downregulated. This evidence strongly suggests that the oligodendroglial lineage is compromised at all differentiation stages in these disorders. Moreover, several axonal and oligodendroglial cytoskeletal components and cytoskeletal-interacting proteins are dysregulated in both schizophrenia and bipolar disorder. A deficit of myelin structural and cytoskeletal proteins in the axo-myelin functional unit may compromise myelin formation, compaction, remodeling and its overall integrity and functionality, which may imply a

concomitant compromise in the assembly and functioning of the nodes of Ranvier and other axonal functional rearrangements. If nervous impulses are not properly conducted in terms of speed and precise timing, some connections would not be reinforced and could be lost, influencing the local connectome. At the macroscale connectomic level, which comprises long-range tracts, fine-tuning and synchronization of nervous impulse conduction is crucial, and even subtle alterations of myelin structural and functional features may have a detrimental impact on information processing and thus on cognitive functions and behavior.

These findings suggest that altered myelination, loss of oligodendrocytes and compromised energy and redox metabolism in oligodendrocytes of schizophrenia and bipolar disorder patients could correlate with the WM alterations observed by neuroimaging techniques. These mechanisms could explain, at least partially, the clinical manifestations observed in schizophrenia and bipolar disorder patients. The relationship between myelin and oligodendrocytes, WM and symptom domains can be systematically studied. In the following sections, we will address the evidence from imaging studies on dysfunctions in the nervous tracts and how the main symptoms correlate with these alterations, giving rise to the hypothesis of disconnection in mental disorders.

## EVIDENCE OF WM ALTERATIONS IN SCHIZOPHRENIA AND BIPOLAR DISORDER IN BRAIN IMAGING STUDIES

Structural and functional neuroimaging findings provide evidence of connectivity alterations that might be related to myelin dysfunction; the most extensive evidence comes from MRI studies[118]. In the field of structural magnetic resonance imaging (sMRI), WM volume and density have been measured using techniques such as voxel-based morphometry (VBM)[119]. VBM studies have found diminished WM volume and density in several brain regions of patients with schizophrenia, with main decreases in the frontal and temporal regions. A meta-analysis of VBM studies reported decreased WM in 150 foci. The affected tracts included the corpus callosum, internal capsule, fornix, anterior commissure, and an additional sixteen tracts[120].

Additionally, WM alterations have been detected by diffusion tensor imaging (DTI); this method evaluates subtle changes in WM, determining fractional anisotropy (FA). FA expresses the diffusion of water molecules along neural fibers. Water movement is inhibited when myelin sheaths are thick and well preserved (FA = 1); in contrast, water moves easily along fibers in any direction when the myelin sheath is damaged (FA = 0)[118]. Although FA can indeed reflect changes in myelination, it could also reflect other tract properties, such as axonal ordering and axonal density[121]. Therefore, Jones *et al*[121] urge caution when interpretating DTI-based measurements and not assume that they are direct indicators of WM integrity[121]. Bearing this in mind, DTI studies have reported that patients with schizophrenia have a widespread decrease in FA[122]. For instance, the ENIGMA-Schizophrenia DTI group analyzed 4321 individuals and found widespread FA reductions in 20 of the 25 analyzed regions in schizophrenia patients when compared with those of the controls[123]. In addition, at least three meta-analyses have reported reduced FA in schizophrenia patients; they conclude that the tracts more frequently affected in these patients are the anterior corona radiata, the corpus callosum, the cingulate bundle, and the uncinate and arcuate fascicles[120,123,124] (Figure 3). Furthermore, functional MRI (fMRI) studies have also reported connectivity alterations in several circuits connecting frontal, limbic, temporal, and parietal regions in schizophrenia subjects, as well as alterations to the default network [125,126].

As the evidence is extensive and complex, we will discuss the neuroimaging evidence of WM alterations in schizophrenia based on each of its main clinical domains. This will integrate the findings and highlight the importance of WM. The structural and functional WM alterations associated with the psychotic domain of schizophrenia include tracts and circuits that connect the frontal, temporal, and parietal cortexes[127]. For instance, the arcuate fasciculus (AF) is frequently studied in regard to the psychotic domain; the AF connects temporal and parietal regions with the frontal lobe and is considered the main language processing tract of the brain because it connects Wernicke's and Broca's areas[128]. DTI studies on schizophrenia patients have reported diminished FA on the AF when compared with that of controls[123]. Additionally, some studies have related the decrease in AF integrity with thought disturbances, language alterations, and auditory hallucinations[129-131].

Furthermore, psychotic symptoms are related to functional connectivity alterations in the fronto-striatal, frontotemporal, and frontoparietal circuits[132]. The frontostriatal circuit comprises the connections between the PFC and basal ganglia[128]. These regions have been extensively studied in relation to the dopaminergic hypothesis of schizophrenia[133]. Some studies of resting-state fMRI analysis have indicated functional dysconnectivity between the dorsolateral PFC and basal ganglia in patients with schizophrenia, which is related not only to psychotic symptoms but also to cognitive alterations[134]. In contrast, the frontotemporal circuit comprises connections from the PFC to temporal structures, including the auditory cortex and Wernicke's area[128]. Functional connectivity alterations in this circuit have been related to auditory hallucinations and the perceived reality of those hallucinations [134].

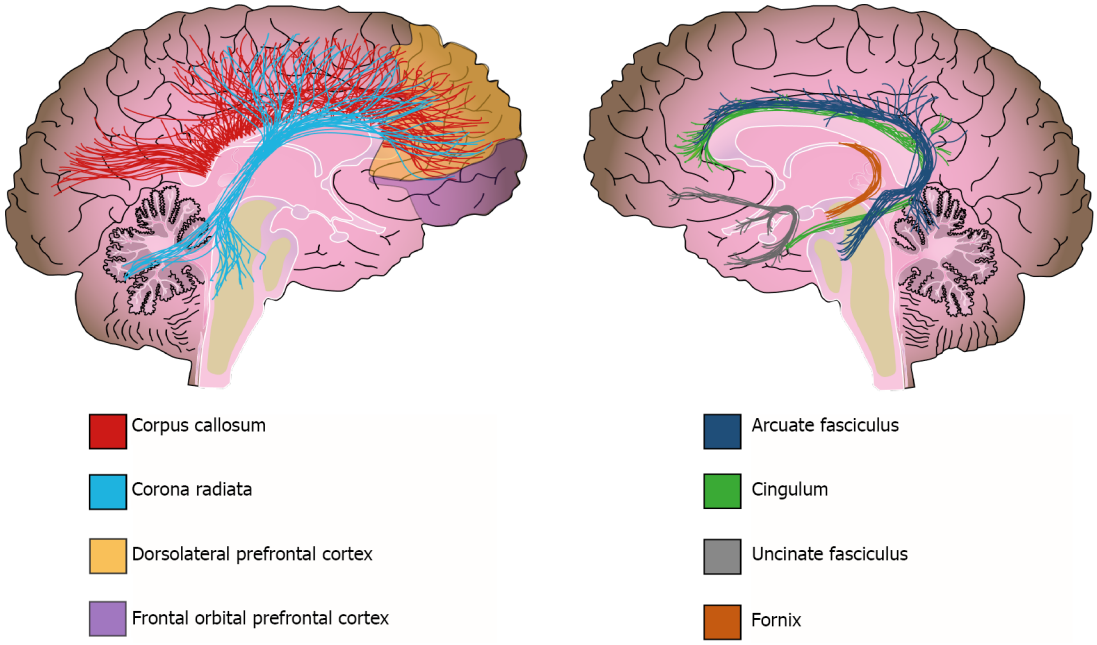


**Figure 3 White matter alterations in schizophrenia.** Solid lines represent the path of the affected white matter tracts, whereas shadowed areas (purple and yellow) show brain regions with diminished white matter density.

Alterations to the cingulum bundle, fornix, and inferior fronto-occipital fascicle are related to cognitive symptoms of schizophrenia[127,135]. The cingulum bundle is a major connector between limbic, paralimbic, and neocortical structures, including the dorsolateral PFC, amygdala, paralimbic gyrus, and cingulate gyrus. This tract is implicated in self-monitoring, spatial orientation, and memory [128]. Subjects with schizophrenia have lower FA on the cingulum bundle than controls, which has also been linked with executive dysfunction and impaired working memory in these same patients[136,137]. The fornix is another WM structure implicated in cognitive function; this tract connects the hippocampus with other cortical structures and is implicated in memory and spatial learning[128]. Patients with schizophrenia have compromised fornix integrity and disrupted functional connectivity between the PFC and the hippocampus[138,139]. Further analysis of functional connectivity has provided evidence of alterations in the frontostriatal and frontoparietal circuits that are also related to cognitive dysfunctions in schizophrenia subjects[132].

Connectivity alterations have been associated with altered tract integrity of the uncinate fascicle; this tract connects the orbitofrontal and anterior dorsolateral cortex with the temporal lobe and is related to negative symptoms[128]. At least two studies have demonstrated an association between low FA of this tract and flattened affect and lack of social engagement[140,141]. As WM decline can be a consequence of demyelination, all of these neuroimaging results (that report WM reduction in important tracts underlying highly integrative brain functions) support the hypothesis that demyelination may be a key factor in explaining, at least in part, the symptoms of schizophrenia.

There are also extensive data on gray and WM changes that are associated with clinical characteristics, genetics, functional impairment, and treatment response for bipolar disorder[142,143]. Currently, one of the main hypotheses about the neurobiology of this disease centers on the disconnection of prefrontal-subcortical networks and limbic structures associated with mood regulation[144]. Diverse prefrontal-striatal-thalamic circuits that regulate the expression of sensorial, cognitive, and emotional data from cortical regions are altered in bipolar disorder patients. It is believed that the dysfunction of these networks explains the cognitive, behavioral, and affective manifestations of this disorder[145]. The current fronto-limbic circuit disconnection model highlights the importance of WM in bipolar disorder. Evidence of WM alterations can be provided through structural or functional findings from neuroimaging techniques, with the most extensive evidence coming from MRI studies.

White matter hyperintensities (WMHs) are evident bright areas on T2 MRI sequences. These alterations are one of the most replicated findings in bipolar disorder[144]. WMHs are lesions that are associated with vascular anomalies and neurodegenerative processes, such as demyelination, axon loss, or necrosis[146]. These lesions are frequently found around the lateral ventricles (periventricular), deep WM, and subcortical gray matter (basal ganglia, thalamus)[147,148]. At least three meta-analyses have linked the presence of WMHs with bipolar disorder, and it is estimated that approximately 39% of bipolar disorder patients have these lesions, compared with 18% of controls[149-151]. The presence of WMHs in patients has been associated with the worst outcomes of the disease, such as hospitalizations, psychotic symptoms, suicide attempts, cognitive impairment, and treatment resistance[151-155].

In addition to WMH, there is also extensive evidence about WM volume alterations from different methodologies[156]. Two meta-analyses that used a region-of-interest (ROI) approach reported a volume reduction in the corpus callosum of bipolar disorder patients, which is a structure of crucial importance for interhemispheric connectivity and is implicated in higher cognitive functions such as attention, memory, and language[124,156,157]. However, no clear association was found between altered corpus callosum volumes and psychotic symptoms or suicidal ideation in patients[157-159]. In contrast, Lavagnino *et al*[160] reported an association between volume reduction of the posterior corpus callosum and a higher number of affective episodes, hospitalizations, and incomplete remission of symptoms in female patients[160]. Other studies and meta-analyses used VBM to evaluate the whole brain and reported a reduction in WM volume of the corpus callosum, corona radiata, posterior cingulum, and inferior longitudinal fasciculus in bipolar disorder[142,161] (Figure 4).

DTI studies of bipolar disorder have reported diffuse WM microstructural alterations[124,162,163], which are evident when tract integrity and WM volume are measured. Recent meta-analyses have found FA reductions in all major classes of WM tracts (commissural, association and projection fibers) with frequent reports of alterations in temporoparietal WM, the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and left cingulum[124,164]. A mega- and meta-analysis of the ENIGMA group revealed decreased FA in 29 ROIs, with the greatest effect sizes in the corpus callosum and cingulum of patients compared with those of controls[162]. Voxel-based analysis of DTI (VBA-DTI) data has also found clusters of decreased FA and WM volume in prefrontal, temporal and parietal regions [164-166]. Emsell *et al*[165] conducted a study on euthymic bipolar disorder patients and found a cluster extending from the prefrontal WM to the splenium of the corpus callosum and posterior cingulum bundle[165], whereas a VBA-DTI meta-analysis reported another two clusters in areas involved in emotional processing[164]. Nortje's meta-analysis identified a large cluster of decreased FA and mean diffusivity in the right temporoparietal WM, a region that is crossed by the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus[164]. The evidence suggests that the posterior WM contributes to cognitive deficits, while the alterations of anterior fibers are associated with affective symptoms of bipolar disorder[164,167]. In conclusion, the previously discussed evidence suggests not only alterations to fronto-limbic connectivity but also dysfunction in parietal, fronto-occipital and interhemispheric connections, which may explain the cognitive and emotional manifestations of this disorder[167].

## THE DISCONNECTION PARADIGM AND WM DYSFUNCTION IN SCHIZOPHRENIA AND BIPOLAR DISORDER

Taken together, the evidence discussed above highlights the importance of oligodendroglial cells for brain function; through myelin formation, they are involved in the precise synchronization of electrical impulses that propagate along nerve fibers connecting brain structures[168-170]. Most long-distance connecting tracts in the CNS are heavily myelinated and comprise the WM. Although structural and functional WM alterations have been described in other mental illnesses, such as major depression, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, autism spectrum disorders, Alzheimer's disease, and drug addiction[16,171], in this review, we focused on schizophrenia and bipolar disorder because these two neuropsychiatric illnesses share several clinical and patho-physiological features.

As can be inferred from the previously mentioned findings, the focus of investigations on the pathophysiology of schizophrenia and bipolar disorder has changed from alterations in specific regions to dysfunction in the connectivity of brain structures. This shift occurred first for schizophrenia, when the disconnection hypothesis was postulated more than twenty years ago, in response to the fact that several manifestations of schizophrenia, such as negative symptoms, cannot be fully explained by structural alterations to a specific cortical area[172-174]. Researchers subsequently hypothesized that the clinical domains of schizophrenia might be due to widespread network dysfunction instead of only specific morphological alterations of specialized cortical regions[125]. This paradigm shift in schizophrenia research quickly translated to other psychiatric conditions, and many studies have since tested the disconnection hypothesis in bipolar disorder[153]. Functional MRI and DTI studies have reported an association between compromised WM integrity and clinical manifestations of these disorders[126,167].

In the following years, many neuroimaging studies have associated WM alterations found in psychiatric patients with executive function, functional impairment, affective symptoms, treatment response or resistance, suicidal thoughts and attempts, and the severity of symptoms, to name only a few traits[123,145,161,175]. This overwhelming evidence has helped researchers to frame schizophrenia and bipolar disorder as multidimensional conditions with strong brain correlates at the macroscale connectomic level[125]. Undoubtedly, further research from a neuroglial integrative perspective is necessary to unravel the anomalies at the cellular/subcellular level, *i.e.*, the microscale connectomic level that may underlie the complex clinical manifestations of these patients.

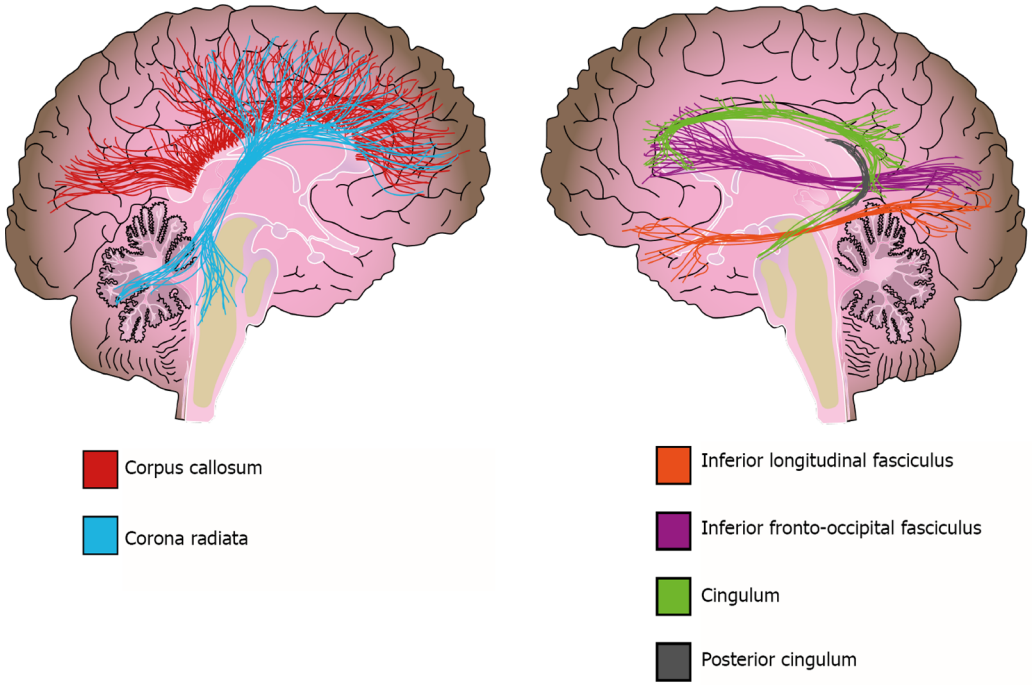


**Figure 4 White matter alterations in bipolar disorder.** Solid lines represent the path of the affected white matter tracts.

## PERSPECTIVES: MYELINATION IS NOT AN EXCLUSIVE OLIGODENDROGLIAL-NEURONAL RELATIONSHIP

The axo-myelin interaction is so close that, by itself, it constitutes a functional unit with a complex and deeply intermingled physiology. However, both astrocytes and microglia interact with axo-myelin units and influence their function[176-179]. Metabolic homeostasis and *de novo* formation or plasticity of myelin internodes and nodes of Ranvier are modulated by astrocytes and microglia. The main glial-mediated modulatory mechanisms of myelin homeostasis include physical intercellular interactions through gap junctions, secretion of soluble factors and clearance of myelin debris. Dysregulation of these modulatory mechanisms may also underlie the pathophysiology of mental illnesses such as schizophrenia and bipolar disorder; however, scientific research on this topic is still limited.

During the last two decades, great advances have been made in our understanding of human CNS physiology and pathophysiology, and glial cells have been recognized as key players in neuropsychiatric disorders[15,180-182]. Nevertheless, scientific psychiatry and patients with mental disorders would definitely benefit from a more integrative point of view at all research levels.

## CONCLUSION

Schizophrenia and bipolar disorder are multifactorial neuropsychiatric illnesses that share clinical manifestations and alterations to brain structure and function, genetic characteristics, and neurobiological pathways. Both are chronic and severe conditions that cause disability, reduce lifespan and impose a high burden on patients and society. The disconnection hypothesis of the pathophysiology of these two disorders is supported by alterations in WM tracts revealed by neuroimaging techniques. Alterations at the macroscale connectome level strongly correlated with the multidimensional clinical manifestations of these disorders; however, to better understand the correlates at the cellular and subcellular levels, it is necessary to obtain deeper insight into the main components of WM, *i.e.*, myelinated axons. Therefore, the pathophysiology of both the neuronal and oligodendroglial components of neural circuits and networks needs to be investigated. Twenty years since the first hypothesis implying oligodendrocyte/myelin failure as a hallmark of schizophrenia[183], a large amount of evidence at the connectomic, microscopic, proteomic, transcriptomic and genomic levels has accumulated for overall dysfunction of the axo-myelin functional unit in these patients. Although oligodendrocyte/myelin dysfunction has also been consistently reported in bipolar disorder, the same amount of scientific knowledge about axo-myelin pathophysiology in this psychiatric disorder is lacking, at least at the cellular and subcellular levels. Further research on schizophrenia and bipolar disorder is needed to better understand the axo-myelin molecular pathways that are dysregulated and to identify potential targets for the development of novel therapeutic alternatives. Several recent studies

have focused on the effects of commonly prescribed antipsychotic drugs on oligodendrocytes/myelin [184]. However, testing the effects of novel compounds intended to induce oligodendrogenesis and (re)myelination[116] in preclinical models of schizophrenia and bipolar disorder could also hold great promise for future research.

## FOOTNOTES

**Author contributions:** Valdés-Tovar M contributed to the overall conception and design of the study; all authors carried out comprehensive literature search and wrote the first draft; Rodríguez-Ramírez AM contributed to the clinical perspective and figure design; Sotelo-Ramírez CE contributed to figure creation; Solís-Chagoyán H critically revised the manuscript; Valdés-Tovar M and Camarena B obtained funding; all authors assisted in a thorough revision of the manuscript and approved its final version.

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*MINIREVIEWS*

# Common outcome, different pathways: Social information-processing deficits in autism spectrum disorder and attention-deficit/hyperactivity disorder

Janice K Y Chan, Patrick W L Leung

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## Abstract

Social functioning is a key domain of impairment in both autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). This review adopts the social information-processing model as the theoretical framework to compare and contrast the deficits of ASD and ADHD at each of the six steps of social information-processing. Both disorders show deficits at each step, but the nature and origins of the deficits are different. Thus, while both disorders exhibit a common outcome of social impairment, the exact pathways that each disorder traverses along the six steps of social information-processing are different. For ASD, there is a social knowledge/behaviour deficit arising from difficulties in social/emotional cue detection, encoding, and interpretation, leading to problems in joining and initiating social interaction. For ADHD, there is a performance deficit incurred by disruption arising from the ADHD symptoms of inattention and hyperactivity/impulsivity, while its acquisition capacity on social knowledge is relatively intact. The inattentive, intrusive, and impulsive behaviours of ADHD unsettle social interaction. Finally, this review proposes training targets for intervention along the six steps of the social information-processing model for ASD and ADHD, as well as areas for future research in further elucidating the social impairment of the two disorders.

**Key Words:** Autism spectrum disorder; Attention deficit/hyperactivity disorder; Social information-processing; Social impairment; Social skills training; Social outcome

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**Core Tip:** Both autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) show deficits in social information-processing, but their nature and origins are different. While both disorders exhibit a common outcome of social impairment, the exact pathways that each disorder traverses along the social information-processing steps are different. For ASD, there is a social knowledge/behaviour deficit arising from difficulties in social/emotional cue detection, encoding, and interpretation, which lead to problems in joining and initiating social interaction. For ADHD, there is a performance deficit incurred by disruption arising from the ADHD symptoms of inattention and hyperactivity/impulsivity. The inattentive, intrusive, and impulsive behaviours of ADHD unsettle social interaction.

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## INTRODUCTION

Social functioning is a key domain of impairment in both autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD)[1]. For the diagnosis of ASD, social impairment is a defining feature and a core diagnostic criterion. Findings consistently indicate significant deficits in fundamental aspects of social cognition including weakness in emotion recognition skills and theory of mind compared to typically developing peers. These in turn are significant contributing factors for suboptimal social behaviour and social outcome in ASD.

Social impairment is also well-documented in children with ADHD and has often been conceptualized as a manifested outcome of its core symptoms of inattention, hyperactivity, and impulsivity. Children with ADHD demonstrate a failure to modulate behaviour according to the social contexts and more frequently engage in inappropriate social behaviours such as paying less attention to peers (inattention) or interrupting others out of turn (impulsivity) during their social interactions[2,3]. These problems in social behaviours are seen as contributed by ADHD symptoms, giving rise to inconsistent or inappropriate behavioural responses and regulation[2,4], and often result in higher rates of peer rejection and friendship failures.

Since both children with ASD and those with ADHD present with social impairment, it is important to better understand the processes that underlie this common outcome between the two disorders. A recent review by Mikami *et al*[1] extensively examined the characteristics and aetiologies of social impairment in these two disorders. Across the broad domains of social functioning including social cognition, social behaviour, and peer regard, it was found that both ASD and ADHD shared transdiagnostic impairment in all of these areas, yet were also distinct in the different areas of difficulties. For instance, while both disorders exhibited problems in peer regard, the social difficulties of ADHD were characterized by disruptive and negative behaviours in peer situations, while ASD children might lack the positive or prosocial behaviours to initiate and maintain peer relationships. In other words, there is a distinctiveness of deficiency in knowledge and skills in ASD compared to relatively intact skills but problematic performance in ADHD. While this recent review describes well the potential different bases of deficits leading to impairment in overt social behaviours across the two disorders, it has not organized the underlying deficits under a coherent and comprehensive theoretical framework of social information-processing that characterizes in sequential steps how an individual first attends and processes incoming stimuli in a social situation, including the thoughts and feelings of others, to be followed by decision-making, and then choice and enactment of an appropriate social response at the end. These underlying social cognitive processes are the mechanisms and pathways that translate a social situation into a social outcome. A social information-processing model, proposed by Crick and Dodge[5], has been put forward to explain social behaviours with a series of hierarchical, stepwise cognitive processes that serve the above-described cognitive functions in responding to social situations or events. This series of cognitive processes, which are based largely on biologically determined capabilities in social cognition, as well as past learning experiences, shape the eventual social interaction. Thus, any deficits along this hierarchy of sequential steps can contribute to social impairment[4].

This review will adopt the social information-processing model by Crick and Dodge[5] as its theoretical framework, which is well-defined and well-tested, to elucidate the social cognitive processes that underlie the common outcome of social impairment in ASD and ADHD. The identified deficits can become viable training targets to be alleviated for enhancement of social behaviours in ASD and ADHD.

## THE SOCIAL INFORMATION-PROCESSING MODEL

The social information-processing model proposed by Crick and Dodge[5] describes a hierarchy of covert, mental mechanisms that are employed to translate external social cues (inputs) to overt behavioural responses (outputs). It provides a theoretical framework to better understand the social cognitive abilities and social adjustment of children. The model includes five cognitive steps followed by the sixth step of behavioural response enactment: (1) Encoding of internal and external social cues; (2) Interpretation and mental representation of cues; (3) Clarification or selection of goals; (4) Response construction; (5) Response decision; and (6) Behavioural enactment[5,6]. Each step is guided by biologically determined capabilities in cognitive functioning, as well as a memory database of learned social experiences, which informs of social rules, schemas, and knowledge/skills of social behaviours.

Upon encountering a social situation, children enter the initial steps of social information-processing, whereby they selectively attend to, encode, and interpret social cues (steps 1 and 2). Essentially, steps 1 and 2 help the children create a mental representation of the presenting social situation or event - what is happening (attend and encode) and why it is happening (interpretation), including inferences about the perspectives and intentions of others involved. Deficits in these early stages of social information-processing, such as inaccurate encoding and interpreting of social cues, can create a biased mental representation of the social situation upon which behavioural responses are chosen for.

After creating a mental representation, children clarify and select a goal or desired outcome for the social situation in step 3. For instance, if they encode aggressive cues and interpret the situation as provocative or hostile, the children may determine whether their goal is to get even or avoid the provocation; whilst if they interpret the situation as friendly, the children may then consider more pro-social goals. The intention is to produce certain desired outcomes in a social situation.

After the children clarify their goals, they then need to construct a range of potential behavioural responses (step 4), either selecting from their existing pool of behaviour repertoire or generating a new piece of behaviour if the situation calls for it due to its novelty. Subsequently, at step 5, children evaluate their response choices and decide upon the most appropriate behaviour based on various expectations, including outcomes expectation, sense of self-efficacy and response appropriateness. Finally, at step 6, the chosen response is behaviourally enacted, producing a social outcome. Yet, children may produce suboptimal social responses should they have very limited behaviour repertoire, bad judgement on evaluating and deciding on the appropriateness of the responses, or over/underestimation of their self-efficacy in enacting the responses to the social situation. All these lead to impairment in social interaction.

### *Role of emotions in social information-processing*

Crick and Dodge[5]'s model also recognizes the importance that emotions play in social information-processing by highlighting the interactions between emotions and cognitions[7]. Each step of the social information-processing is intertwined with emotional processes. The biologically determined cognitive capabilities and the memory database of past learning experiences that guide social information-processing also include a predisposition to emotionality. The emotional states will affect the children's mood-congruent cued recall of past experiences, for instance, which in turn affects the information-processing. In encoding and interpreting cues, emotion recognition ability can play an important role in which emotion cues become encoded and interpreted; as such, inaccurate or selective encoding and interpretation of others' emotions, such as the tendency to encode and interpret ambiguous cues as anger, may generate more hostile responses than if the cues were encoded and interpreted as more neutral. The encoding and interpretation of cues can also be influenced by pre-existing mood states and levels of emotional arousal during the interaction, such that children are more likely to notice and recall mood-congruent information. Emotions can also have an impact in the determination of goals and the construction and choice of behavioural responses, whereby children with high emotional reactivity may choose goals and responses that primarily help to reduce emotional arousal, such as avoidant or hostile goals and actions. Children who are weak in reading and interpreting others' emotional cues, on the other hand, may tend to determine goals and choose responses that are less considerate of others' emotions and less likely to maintain relationship. Overall, while the social information-processing model describes primarily a social cognitive mechanism to explain social outcomes, there is a strong interplay with emotional processing, such that differences in emotionality or emotion recognition can influence each step of social information-processing toward the outcomes.

### *Studies of social information-processing in children*

Children with both externalizing and internalizing problems have been found with deficits along each step of the social information-processing model. For example, children with externalizing problems such as aggression were more likely to attend and encode cues related to aggressive or aversive acts in social situations (step 1)[8]. When interpreting social cues (step 2), aggressive children, as compared to non-aggressive peers, also showed hostile attributional biases and viewed others' actions and motivation as driven by hostile intent even when the situations were presented as ambiguous[5,8]. Research comparing behavioural responses of children with and without externalizing problems also

found differences in the quality and quantity of responses/solutions generated, whereby aggressive boys produced fewer assertive responses to solve social difficulties, but with an increased likelihood to engage in direct aggressive actions if the situations involved hostile provocation (steps 4-6).

Children with internalizing problems are also found with ineffective social information-processing patterns when compared to socially adjusted children. Depressed children, for instance, were less accurate in encoding relevant social cues and showed hostile attribution biases when interpreting social cues in unfamiliar situations (steps 1 and 2)[5,9]. In terms of behavioural responses, depressed children viewed assertive responses as associated with less positive and more negative outcomes, and thus tended towards constructing fewer assertive responses (steps 4 and 5)[10].

Conversely, social information-processing patterns for prosocial behaviour in children showed that they were more likely to interpret social cues positively, with a preference for maintaining positive relationship in the goal clarification step (step 3) even in face of provocation. Children who were accepted by their peers provided more prosocial and effective solutions and responses than children of lower peer status (step 4)[11].

Overall, the literature demonstrates that the social information-processing model by Crick and Dodge [5] is a helpful theoretical framework for understanding the underlying cognitive and behavioural processes contributing to differences in social behaviours and outcomes in children. It highlights the hierarchical nature as well as the interconnectedness of each step of the processes in contributing to the effectiveness and appropriateness of social responses to social situations, and how deficits in any of the steps can culminate into problematic social behavioural outcomes. It has proven validity in explaining and predicting externalizing, internalizing, and prosocial behaviours. This review will adopt this model to elucidate how the social information-processing deficits of children with ASD or ADHD can lead to their social impairment in six steps.

## SOCIAL INFORMATION-PROCESSING DEFICITS IN ASD AND ADHD

Although the social information-processing model by Crick and Dodge[5] has been applied to study the social deficits in ASD and ADHD, the number of available studies has not been plentiful. Furthermore, most studies conduct their investigation separately with ASD and ADHD; studies directly comparing the social information-processing patterns of the two disorders remain sparse to date. One general consensus emerging in the literature is that social information-processing deficits do emerge in ASD and ADHD, and they in turn contribute to the social impairment of both disorders. However, as we systematically review below studies at each step of social information-processing, the deficits identified are of different nature for ASD and ADHD, providing insight into how these disorder-specific deficits, though traversing different pathways along the hierarchically determined steps of social information-processing, eventually cumulate into a final common outcome of social impairment for both disorders.

### *Step 1: Encoding of social cues*

**Cue encoding and detection**: Cue encoding is the first step in social information-processing. A commonly used assessment tool for examining cue encoding is the social information processing interview (SIPI). It is a structured interview based on a series of vignettes or stories depicting negative peer social interactions (peer rejection or provocation). Children with ASD were found to score significantly lower on the efficient coding score of the SIPI, which measured the average level of details that could be accurately recalled by the children regarding the presented vignettes[6]. This indicated that children with ASD were encoding social information less accurately. This could potentially be due to their remembering fewer details (*i.e.*, encoding fewer cues) or remembering the details inaccurately (*i.e.*, tendency to code irrelevant cues), or both. Unfortunately, such error patterns were not captured by the SIPI and thus not reported. Nonetheless, the inefficiency in cue encoding by children with ASD means that they will in turn generate a less accurate mental representation of the social situations.

Children with ADHD were consistently found to encode fewer cues compared to control children when presented with the social vignettes[12]. Furthermore, they encoded lower percentages across positive, negative, and neutral cues, indicating that the inefficiency was non-specific and present across all valences[13]. Difficulties in attention and working memory, two fundamental deficits underlying ADHD symptomatology, were suggested for this non-specific pattern of inefficiency in cue encoding[12, 13]. It was hypothesized that children with ADHD might miss noticing cues due to inattentiveness or might fail to encode all relevant cues due to working memory deficit (*i.e.*, forgetting or failing to recall details of the social vignettes). Once again, the inefficiency in cue encoding in children with ADHD hinders them from developing a more balanced and accurate mental representation of the social situations.

Overall, cue encoding deficit is identified in both ASD and ADHD. However, since these findings are from separate studies, which use different (though similar) measures of cue encoding, it is difficult to conclude if the findings are directly comparable. Researchers also seem to speculate different origins of the encoding inefficiency in the two disorders. For the children with ASD, it is a fundamental deficit of ASD in encoding social cues, while the cue-encoding inefficiency of children with ADHD is a by-

product or a result of interruption arising from their ADHD symptoms, *i.e.*, inattention and working memory deficit.

**Social perception/cognition:** Those rare studies which directly compared social perception/cognition between ASD and ADHD suggested a more severe social perception/cognition deficit in ASD but a milder deficit in ADHD[14,15]. In particular, the evidence seems to suggest a larger contributing role of neurocognitive factors in social perception/cognition deficit in ADHD than ASD. Baribeau *et al*[15] compared the social perception/cognition abilities of children with ASD, ADHD, or obsessive-compulsive disorder and typically developing children using the Reading the Mind's Eyes test (RMET), a standardized test on decoding mental states which was based upon matching photographs of eyes with corresponding emotions and mental states being portrayed. Children with ASD were found to exhibit the most significant social perception/cognition deficit compared to other groups, while children with ADHD were found to display an intermediate level of social perception/cognition deficit, falling between the ASD and control groups in their performance. Furthermore, after controlling for intelligence quotient (IQ), there was a narrowing in the performance gap between the clinical groups and typically developing children. In particular, the accuracy scores of ADHD children became comparable to those of typically developing children. Drawing from these results, it seems that a large part of the social perception/cognition deficit in ADHD can be explained by lower general cognitive abilities, since ADHD children do have a lower IQ compared to typically developing peers[16]. For ASD, however, the effect of IQ can only explain part of the deficit. In the same study, features of hyperactivity and impulsivity were also found to be associated with deficit in social perception/cognition for all participant groups regardless of diagnosis; ADHD traits as measured by the strength and weaknesses of ADHD and normal behaviour rating scale had a significant negative effect on the RMET scores. The adverse impact of ADHD features in social perception/cognition was further substantiated by findings indicating that stimulants improved social perception/cognition in ADHD [14].

Another important differentiating factor when comparing social perceptual/cognitive deficits in ASD and ADHD is age. While paediatric samples demonstrated moderate effect sizes in social perception/cognition deficits for both ASD and ADHD, the effect sizes became smaller for adult ADHD samples, suggesting age-related improvement and catching-up in social perception/cognition for ADHD as they aged. Conversely, this age-related improvement was not found among the ASD population[14]. These differential findings across age support the speculation that social information-processing deficits of ADHD may be by-products of ADHD symptomatology whose age-related improvement also results in correspondingly age-related improvement in social perception/cognition.

**Facial emotion recognition:** Emotion recognition has been included as a fundamental process in social information-processing within the first step of cue encoding[7]. The encoding and interpretation of others' affective cues are an important source of information for processing. Facial emotion recognition has been studied extensively in ASD. The ability to recognise and discriminate facial emotional expressions is present in infants as young as 10 wk of age, but it is a key generalized deficit or delayed ability in children with ASD across all facial expressions, and may vary in magnitude for specific emotions, with more difficulty in the recognition of negative emotions, particularly fear and anger[17-19]. It persists through to adulthood[20]. This suggests a failure to develop specialization and expertise in emotional processing in ASD, and despite investing in efforts and resources to compensate, children with ASD are still unable to catch up in adulthood.

Findings on emotion recognition in ADHD also suggest weaker emotion recognition capability[19]. Yet, it has been speculated that emotion recognition deficit in ADHD may be due to a failure to attend to the appropriate cues of affect incurred by the inattention symptom of ADHD. In a study examining emotion recognition, it was found that boys with ADHD showed poorer performance across all tasks regardless of whether facial emotions were involved, indicating a more generalized difficulty involving deficit in attention control[21]. Furthermore, other studies found random error patterns and increased performance variability on emotion recognition performance for children with ADHD as well, which further implicated the role of inattentiveness in emotion recognition performance (*e.g.*, momentary lapses of attention characteristics of ADHD)[12,19]. Conversely, among children with ASD, performance in emotion recognition tasks was less variable with no random or variable error patterns[19], suggesting a performance profile less affected by momentary lapses of attention as in ADHD. These findings suggest a more pertinent role of inattentiveness in emotion recognition performance in children with ADHD, but not in children with ASD.

Yet, some studies do find inattention or distractibility as an important covariate for explaining facial emotion recognition deficits in both ASD and ADHD. However, it should be noted that in some of these studies, children with ASD were included regardless of the presence or absence of comorbid ADHD symptoms. For instance, in one study, up to one-third of the cases with a primary ASD diagnosis also fulfilled the criteria for ADHD[19]. Furthermore, the presence of ADHD aggravated the facial emotion recognition performance, including increased variability, in comorbid ASD and ADHD children, highlighting once again the negative role of inattentiveness in emotion recognition performance[22].

### *Step 2: Interpretation of cues*

Interpretation of cues involves attribution processes in which children make inferences about causal relationships, intents of others, *etc.* Children with ASD or ADHD have been suggested to show attributional biases in cue interpretation. A common and well-researched cognitive bias is the hostile attribution bias, which is the tendency to attribute malevolent or hostile intents when interpreting ambiguous or neutral social scenarios. For instance, preschool children with ASD were found to frequently interpret actions of others as hostile, which then led to the enactment of more aggressive responses[6]. However, the same bias was not consistently found among school-aged children and adolescents with ASD[23]. Instead, adolescents with ASD were more likely to show a negative, global attribution style in which they were more likely to view social outcomes as independent of their responses, making them less likely to assert prosocial responses but avoid or withdraw from interaction when faced with social situations[24]. The study reasoned that those repeated experiences of negative social interaction experienced by children with ASD, due to the well-known weakness in theory-of-mind in ASD, could lead to this negative, global attributional bias.

Attribution bias has also been studied among children with ADHD. They appeared to rely more heavily on their own opinions on what was happening in the social situations rather than on the observable, factual information[13]. This was suggested to be related to attentional problems, which hampered upstream cue encoding, contributing to fewer cues being encoded. Having less factual information to rely on, children with ADHD subsequently had to rely more on personal opinions. They were also more likely to show a recency effect when interpreting social situations by using the most recent contextual information[12]. This shallow interpretative process might also be related to attentional problems and working memory deficits, such that they were unable to hold and mentally manipulate all of the social cues, thus only relying on their most recent memories. Furthermore, a hostile attribution bias was generally not found in children with ADHD by comparison to typically developing peers[25,26]. Instead, children with ADHD were suggested to have a positive illusory attribution bias, whereby they tended to overestimate their abilities, leading them to choose unattainable or overly ambitious behavioural responses, as well as to underestimate their problems in the actual social situations. Such bias made the children with ADHD to be rated as less friendly, more inattentive, and less engaged in social situations[12].

Overall, in terms of cue interpretation, both ASD and ADHD show attribution biases, though the type of attribution biases and the underlying contributors differ between the two disorders. Children with ASD are more likely to show a negative, global attribution style contributed by repeated negative social experiences, which in turn drives withdrawal-based responses in social interaction. Children with ADHD are found to show positive illusory bias, making them less likely to consider the full impacts of their responses and outcomes, but more likely to engage in impulsive and overly ambitious responses with socially inappropriate behaviours. Also, the role of inattention and working memory deficits appears to be more relevant for cue misinterpretation in ADHD.

### *Step 3: Goal clarification*

In step 3 of the social information-processing model, children need to clarify their goals for the social situations. Social goals can be relationship enhancing or building, or conversely, can also be relationship damaging or retaliatory.

Unfortunately, this current review has not identified studies specific to goal clarification in ASD and ADHD. Some inferences can be made from some indirect findings. Adolescents with ASD were found to rate withdrawal as a preferred response compared to typically developing peers[24]. This may reflect a tendency to adopt a non-social, withdrawal/avoidant goal orientation. Given their positive illusory bias, as described above, children with ADHD might be overly confident of their competency and adopted the overly ambitious goal of confronting their problems in social situations[13].

### *Steps 4 and 5: Response construction and decision*

Findings on response construction and decision in adolescents with ASD found that the reduced breadth of social experiences and a higher proportion of harsh social experiences might be leading to limited availability of social problem-solving responses in their memory database. Consequently, adolescents with ASD were more likely to evaluate withdrawal responses as preferable in social scenarios and generate non-social withdrawal responses to avoid problems in social interaction[24]. These findings may be reflective of the real-life difficulties in initiating and responding to social situations experienced by individuals with ASD.

Children with ADHD tended to generate a lower proportion of positive responses and higher proportion of negative responses in social situations[13]. Children with ADHD had significantly higher rates of negative interactions with peers, including a higher rate of peer rejection. Thus, they were less likely to have positive responses in store in their memory database, but instead, they had many negative responses.

### *Step 6: Behavioural enactment*

Behavioural enactment is the last step of the social information-processing model and is generally

conceptualized as the behavioural outcomes of the five previous cognitive steps upstream. Naturally, the culmination of deficits in those previous steps will lead to suboptimal behaviours being enacted, thus impairing social functioning in children with ASD or ADHD.

Children with ASD show deficits in observable social behaviours, including less social play and fewer social initiation, as well as poorer verbal and nonverbal social communication that reduces the effectiveness of their social interactions[1]. This absence of positive social behaviours in ASD can be seen as the result of upstream social cognitive and emotion recognition deficits, creating an inappropriate mental representation of the social situations combined with a tendency to choose and positively evaluate non-social withdrawal responses.

It has been suggested that children with ADHD may have adequate social knowledge but experience difficulty in enacting social behaviours appropriately[27,28]. This suggestion collaborates well with findings that children with ADHD are noted with relatively milder deficits in social perception/cognition compared to children with ASD[14,15]. Instead, they showed more inconsistency and variability in their social behaviours which appeared to be more strongly influenced by the core features of ADHD - inattention, hyperactivity, and impulsivity[12,19]. For example, children with ADHD were found to show elevated negative social behaviours such as barging in and poor sportsmanship, which were contributed by the core symptoms of hyperactivity/impulsivity. Due to inattentiveness, they were also found to demonstrate an absence of positive behaviours such as missing the pace and content of conversation[1]. One study demonstrated that social problems in ADHD primarily reflected inconsistent performance rather than the lack of knowledge and skills[2]. Using the social skill improvement system, a parent-rated measure of observable social behaviours, Aduen *et al*[2] found that children with ADHD exhibited more social performance problems than children without, while rates of social acquisition problems were relatively rare and idiosyncratic. These findings suggested that children with ADHD failed in fact to perform learned social skills consistently across settings. Another study also pointed to a social performance deficit in ADHD, as opposed to the lack of social knowledge and inherent social communication deficits seen in ASD[3]. For instance, while both ASD and ADHD groups exhibited significant social behavioural difficulties, deficits in children with ASD were characterized by significantly less adaptive and appropriate social behaviours, which was a reflection of a knowledge deficit, while children with ADHD were found to have more inappropriate assertiveness, a reflection of impulsivity. Table 1 summarizes the social information-processing deficits in ASD and ADHD.

## COMMON OUTCOME, DIFFERENT PATHWAYS

Both ASD and ADHD have been well known for social impairment, exhibiting difficulties in relating with others. This is the common social outcome for the two disorders. However, the above review organized under the social information-processing model by Crick and Dodge[5] suggests different pathways traversing along the six steps of information-processing for children with ASD or ADHD to arrive at the common outcome.

Children with ASD start with an inefficiency in cue encoding and deficits in facial emotion recognition. They also exhibit a more severe deficit in social perception/cognition, which persists into adulthood without any sign of abatement. These encoding deficits, *e.g.*, well known as theory-of-mind deficits in the literature of ASD, consequently lead ASD children to generate a less accurate mental representation of the social situations in which they find themselves.

Regarding the interpretation of cues, children with ASD develop over time a negative, global attribution style in which they see themselves as helpless in effecting the social outcome. With this interpretation, they tend to opt for withdrawn and avoidance responses. There goes a vicious cycle in which these withdrawn/avoidance responses limit the breadth and positivity of the social experiences. These in turn reduce the availability or construction of positive social problem-solving responses to cope with the challenges in social situations. In the end, children with ASD, harbouring a withdrawn and avoidant response tendency, display less social play and fewer social initiation which thwart their social interaction.

Children with ADHD also start with a cue encoding deficit. This is followed by difficulties in social perception/cognition and facial emotion recognition. However, researchers speculate different origins of these encoding difficulties. For children with ASD, these encoding difficulties are cognitive deficits to social and emotion stimuli inherent to ASD, while for children with ADHD, they are by-products originating from interruption incurred by ADHD symptoms of inattention and hyperactivity/impulsivity. The latter suggestion is based on the observation that the encoding difficulties are random, non-specific, or variable across all valences, reflective of those momentary lapses of attention typical of ADHD. Children with ADHD thus display a performance deficit due to interruption by ADHD symptoms, but little acquisition problems on social knowledge. When the symptoms of ADHD are treated with stimulant medication, performance in social perception/cognition improves. Furthermore, an age-related improvement is also seen, in parallel with the age-related improvement in ADHD symptoms. All these point to an influential role of ADHD symptoms in hindering social information-processing. In the interpretation of social cues, children with ADHD also show a positive illusory bias,

which is of a different type from that of children with ASD. Such bias eventually leads to overly ambitious responses of confronting their problems in social situations. Once again, as in the case of children with ASD, children with ADHD are also locked in a vicious cycle in which inadequate social responses and negative social experiences are reinforcing each other and thus hinder the choice and construction of proper behaviour responses. Eventually, children with ADHD enact impulsive and inattentive behaviour, disrupting their social interaction with others.

In short, both disorders, ASD and ADHD, show social information-processing problems right from the very beginning and end with behaviour enactment that disrupts social interaction. However, as described above, the common social outcome is arrived at from different pathways that traverse along the six steps of social information-processing, invoking two cascading chains of deficits along the six steps. These eventually cumulate in suboptimal responses that hinder social relating, namely, withdrawn/avoidant responses from children with ASD, but intrusive/impulsive responses from children with ADHD. In brief, ASD does display inherent encoding deficits in social and emotion processing (*e.g.*, theory-of-mind deficits), while ADHD symptoms mar performance in social information-processing, despite a fairly intact pool of social knowledge acquired, *i.e.*, a social performance deficit rather than a knowledge deficit in ADHD.

## CLINICAL IMPLICATIONS ON SOCIAL SKILL TRAINING FOR ASD AND ADHD

Social information-processing has been a focus of intervention to reduce aggressive and violent behaviours and increase prosocial behaviours in children[8]. The social skill training programs thus devised involve explicit teaching of social problem-solving steps using developmentally appropriate teaching strategies such as skill modelling, role play, and feedback. These programs are well studied with positive findings in relation to increased prosocial behaviours and reduced aggressive behaviours [8].

Fewer studies are conducted using specifically social information-processing as a model for social skill training with ASD and ADHD. One study that did so in a small group of five children with ASD found post-intervention improvement across multiple domains of social skills[29]. Another study with 27 children with ADHD also found improvement in social competency[30]. The scarcity and the small sample size of these studies mean that further intervention studies should be conducted to explore the usefulness of the social information-processing model in guiding the design and implementation of intervention programs for children with ASD or ADHD.

### *Proposed social information-processing treatment targets*

The current review identifies in the social information-processing framework viable treatment targets for ASD and ADHD. At the early steps of social information-processing, children with ASD or ADHD both show reduced cue detection and encoding efficiency, specifically for detecting and recognizing emotion cues. Treatment that brings attention to and teaches the detection of relevant social cues (keeping attention on relevant and appropriate social and emotional cues, while screening out irrelevant cues) should be considered. Particularly for children with ASD, which show specific deficits in cue-encoding, strategies to increase their motivation to attend to and encode emotion-specific cues are more warranted, while for children with ADHD, maintaining overall attentiveness to social and emotion cues in social situations should be one overarching goal.

This review finds that children with ASD tend to show a more negative, depressive attributional style, while children with ADHD a positive illusory bias. Overall, both groups of children suffer from a biased interpretation of social cues contributing to an inaccurate mental representation of the social situations, and training should be targeted at improving the accuracy of interpretation, with consideration on the different biases that are more prevalent for the two disorders separately.

With respect to response generation and evaluation, children with ASD or ADHD both show a tendency to generate more negative responses, the former tending toward withdrawn/avoidant responses, while the latter toward more impulsive/intrusive responses. A common limiting factor for both groups of children is the absence of positive social experiences that allow these children to practice, evaluate, and receive feedback on generating and enacting positive social responses. Thus, the provision of positive social experiences should be incorporated in social skill training to expand the breadth of the social exposure of children with ASD or ADHD, in which more pro-social behaviours can be modelled/constructed, enacted, evaluated, and thus stored in the memory database for future use.

Finally, at the last step of behavioural enactment, the social difficulties of ASD and ADHD are of a social knowledge deficit *vs* a performance deficit. For children with ASD, the cumulative effects of deficits in cue encoding, interpretation, and response construction have produced a void in social knowledge and behaviour repertoire in coping with the demands of various social situations. Thus, knowledge-based social skill training to increase the pool of social knowledge and behaviours is essential to address the social impairment of children with ASD. For children with ADHD, the social impairment is of a performance deficit, caused by disruption arising from the inherent ADHD-related deficits in attention, working memory, and behavioural inhibition, as well as a generally lower IQ in

**Table 1 Summary of social information-processing deficits in autism spectrum disorder and attention-deficit/hyperactivity disorder**

| Social information processing steps | ASD | ADHD |
|---|---|---|
| Step 1: Encoding of social cues | | |
| Cue encoding and detection | Children with ASD found to be less accurate in cue encoding in social situations | Children with ADHD found to encode fewer social cues, and this inefficiency non-specific across all valences, suggesting involvement of attention and working memory difficulties |
| Social perception/cognition | Children with ASD showing more severe social perception/cognition deficits than children with ADHD and typically developing children | A larger contributing role of neurocognitive factors in social perception/cognition deficits in ADHD, including lower intelligence and ADHD symptomatology |
| Facial emotional recognition | Children with ASD showing generalized deficits in facial emotion recognition across all emotions with difficulties persisting into adulthood, suggesting a failure to develop specialization and expertise in facial emotional processing | Children with ADHD showing weaker emotion recognition but with increased performance variability and random errors, suggesting contributory role of inattentiveness in failure to attend to the appropriate cues of affects |
| Step 2: Interpretation of cues | Children with ASD showing a negative, global attribution style contributed by repeated negative social experiences, driving in turn withdrawal-based responses in social interaction | Children with ADHD showing a positive illusory bias to engage in impulsive and overly ambitious responses; inattention and working memory deficits playing an important role in cue misinterpretation |
| Step 3: Goal clarification | Adopting a non-social, withdrawal/avoidant goal orientation | Adopting an overly ambitious goal of confronting problems in social situations |
| Steps 4 and 5: Response construction and decision | Adolescents with ASD evaluating withdrawal responses as preferable and generating such responses to avoid problems in social interaction; reduced breadth of positive social experiences limiting availability of appropriate social responses in their memory database | Children with ADHD generating a lower proportion of positive responses and a higher proportion of negative responses in social situations; higher rates of negative interactions with peers resulting in fewer positive responses stored in their memory database |
| Step 6: Behavioural enactment | Children with ASD showing a social knowledge deficit affecting the enactment of social responses, resulting in social responses consistently less adaptive and appropriate | Children with ADHD showing a performance deficit with increased inconsistency and variability in enactment of social behaviours, incurred by the core symptomatology of ADHD |

ASD: Autism spectrum disorder; ADHD: Attention-deficit/hyperactivity disorder.

each step of social information-processing. Thus, there is a strong argument for the need to address attention and behavioural control in the management of social deficits in ADHD. Given the proven efficacy of stimulant medication on ADHD[31], such intervention should also produce beneficial effects on the social performance in children with ADHD. Indeed, there is evidence for this[14], but existing studies are few and some are inconclusive or inconsistent[32]. Behavioural training and scaffolding techniques that are also proven to manage ADHD symptoms[33] are the alternatives to be considered to deal with deficits in attention and working memory as well as behavioural disinhibition during social interaction. A recent meta-analytic review has indeed demonstrated the similar efficacy of both stimulant medication and behavioural treatment on the core ADHD symptoms[34]. Thus, future study should further examine if the social information-processing deficits of ADHD can be improved upon the alleviation of the core ADHD symptoms by existing efficacious medication and behavioural treatment.

## CRITIQUES AND FUTURE DIRECTIONS

The social information-processing model is initially theorized and applied to explain aggressive behaviours in children independent of any specific clinical groups. As such, many assessment methods are specifically designed to elucidate social cognitive mechanisms underlying aggressive behaviours. For example, the SIPI which is designed specifically to assess social information-processing patterns of aggressive behaviours mainly includes negative social scenarios of peer provocation or peer rejection [6]. Furthermore, the vignettes and the interview-based method are not designed in consideration of the special needs of individuals with mentalistic functioning or language deficits such as those with ASD. As such, the interview-based SIPI and similar tools which rely on verbal comprehension and expression abilities to provide responses to the questions, and which require respondents to 'imagine' their involvement in hypothetical situations may prove difficult for children/youths with ASD and confound the assessment[24]. There is also concern on the limited ecological validity of these measures, using hypothetical situations; development and the use of more ecologically valid measures are thus suggested[13].

Despite the view that children with ADHD display a performance deficit in social functioning due to the impact of ADHD symptoms and a lower general IQ, not many studies have actually investigated or controlled the impact of these variables. Future studies should consider doing so, including the invest-

igation of whether the efficacious stimulant medication and behavioural treatments of ADHD symptoms can in turn also improve the social functioning of ADHD children, as hypothesized above.

A sizable subgroup of children with ADHD (25%-75%) have comorbid oppositional defiant disorder (ODD)[35], which is also well known to be associated with social functioning deficits. Previously, treatment of ODD has been challenging, relying mainly on behavioural treatment. However, a recent study has suggested potential beneficial medication treatment[36]. Once again, it is intriguing to examine if the successful alleviation of comorbid ODD in children with ADHD may also help their social functioning.

This review finds few studies that directly compare children with ASD against children with ADHD. This makes exact comparison of the deficits of the two clinical groups difficult. For those few studies which include both clinical groups, more exacting group differences are revealed. For example, Baribeau *et al*[15] found that children with ASD had the worst social perception/cognition deficits, while those of children with ADHD were milder. Furthermore, the social perception/cognition deficits of children with ADHD improved with age, while those of children with ASD did not[14]. Thus, more future studies should involve direct comparison between the two disorders in order to provide more exacting contrast to uncover the common and differentiating deficits contributing to their social impairment.

The social information-processing model has been applied successfully in a wide range of prevention and intervention programs to reduce aggression and promote prosocial behaviour[8]. Yet, few studies apply the social information-processing model to social skill training for ASD and ADHD. This review has made a series of suggestions above to identify viable targets for intervention. They should inform the design and implementation of potentially beneficial intervention programs for ASD and ADHD, respectively.

Finally, there is a recent concern regarding misdiagnosis of some medical conditions, *e.g.*, autoimmune encephalitis, for ASD[37]. Unfortunately, most existing literature in ASD does not address this disorder in the definition and recruitment of participants in their study so that we cannot estimate how far the conclusion of this current review is affected by the inclusion of participants with autoimmune encephalitis.

## CONCLUSION

ASD and ADHD are both characterized by social impairment. This review applies the social information-processing model by Crick and Dodge[5] to define and compare the underlying deficits in the social cognitive mechanisms that contribute to the common outcome of social impairment in both disorders. It is found that both disorders show deficits at each step of social information-processing, but the nature and origins of the deficits may be different for the two disorders. In other words, the same outcome in social impairment may be arrived at by different pathways along the six steps of social information-processing. For ASD, there are difficulties in social/emotion cue detection, encoding, and interpretation, leading to a social knowledge/behaviour deficit that limits the availability and construction of behaviours to join or initiate social interaction. For ADHD, there is a performance deficit caused by disruption arising from ADHD symptoms of inattention and hyperactivity/impulsivity, leading to intrusive and impulsive behaviours that unsettle social interaction. Our conclusion essentially matches well with that of a recent review by Mikami *et al*[1], but our current review is framed under a coherent, well-developed model of social information-processing[5]. Social skill training that targets different loci of the social information-processing deficits of ASD and ADHD is well advised.

## FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

# Associated mortality risk of atypical antipsychotic medication in individuals with dementia

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## Abstract

*BACKGROUND*

Antipsychotic medications such as risperidone, olanzapine and aripiprazole are used to treat psychological and behavioural symptoms among dementia patients. Current evidence indicate prescription rates for antipsychotics vary and wider consensus to evaluate clinical epidemiological outcomes is limited.

*AIM*

To investigate the potential impact of atypical antipsychotics on the mortality of patients with dementia.

*METHODS*

A retrospective clinical cohort study was developed to review United Kingdom Clinical Record Interactive Search system based data between January 1, 2013 to

December 31, 2017. A descriptive statistical method was used to analyse the data. Mini Mental State Examination (MMSE) scores were used to assess the severity and stage of disease progression. A cox proportional hazards model was developed to evaluate the relationship between survival following diagnosis and other variables.

***RESULTS***

A total of 1692 patients were identified using natural language processing of which, 587 were prescribed olanzapine, quetiapine or risperidone (common group) whilst 893 (control group) were not prescribed any antipsychotics. Patients prescribed olanzapine showed an increased risk of death [hazard ratio (HR) = 1.32; 95% confidence interval (CI): 1.08-1.60; $P < 0.01$], as did those with risperidone (HR = 1.35; 95%CI: 1.18-1.54; $P < 0.001$). Patients prescribed quetiapine showed no significant association (HR = 1.09; 95%CI: 0.90-1.34; $P = 0.38$). Factors associated with a lower risk of death were: High MMSE score at diagnosis (HR = 0.72; 95%CI: 0.62-0.83; $P < 0.001$), identifying as female (HR = 0.73; 95%CI: 0.64-0.82; $P < 0.001$), and being of a White-British ethnic group (HR = 0.82; 95%CI: 0.72-0.94; $P < 0.01$).

***CONCLUSION***

A significant mortality risk was identified among those prescribed olanzapine and risperidone which contradicts previous findings although the study designs used were different. Comprehensive research should be conducted to better assess clinical epidemiological outcomes associated with diagnosis and therapies to improve clinical management of these patients.

**Key Words:** Dementia; Antipsychotics; Mortality; Vascular; Alzheimer's disease; Frontotemporal dementia; Lewy bodies; Parkinson's and mixed

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**Core Tip:** Antipsychotic medication is widely prescribed to patients with dementia displaying neuropsychiatric symptoms. Treatment with olanzapine and risperidone was associated with an increased mortality risk. In comparison, quetiapine showed a relatively lower, non-significant association with the mortality risk in those with dementia. Clinicians need to be aware of the potential heterogeneous relationship between dementias, antipsychotic medication, and mortality when creating a psychopharmacological treatment plan for their patients.

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## INTRODUCTION

Antipsychotic prescribing in older adults must be made with caution as there are age related changes in pharmacokinetics and pharmacodynamics that can result in an increased sensitivity to drugs and their side effects. This is evident in both typical and atypical antipsychotic prescribing within this population. Thus, Landi *et al*[1] demonstrated a 47% elevation of falls in elderly adults being prescribed typical antipsychotics, whilst atypical antipsychotic drugs have been associated with higher hospitalisation rates with acute kidney injury[2] and an increased 90 d risk of non-vertebral osteoporotic fracture, hip fracture and various other fractures and falls[3]. Similarly, the concerns around the safety and effectiveness of aripiprazole, olanzapine, quetiapine and risperidone (four specific antipsychotics) have been also raised for older patients in a clinical trial setting[4].

Antipsychotics are also used to treat anxiety, agitation and psychotic experiences presenting in dementia, the majority of whom are elderly. Patients with dementia are considered particularly vulnerable to the effects of antipsychotics[5]. In particular, those using antipsychotics extensively would have an increased susceptibility to venous thrombolytic episodes, hip fractures and strokes[6].

Due to the perceived risk of mortality and of side-effects, typical antipsychotics have begun to be replaced by atypicals in the last decade[5]. However, whilst there appears strong evidence for an associated risk of adverse events of both typical and atypical antipsychotic medication in the elderly, and in those with dementia, the evidence around increased mortality is less clear. Some of the literature suggests that there is an increased morality risk in dementia patients from both typical and atypical

antipsychotics accounting for an additional 1800 deaths per year[5]. However, others have argued that typical antipsychotics have a greater mortality risk than atypicals for those individuals with dementia[7] yet a meta-analysis of all cause dementia, indicated that there was a small increased risk of death from atypical antipsychotics compared to those on a placebo[8]. Furthermore, a retrospective study on a cohort of vascular dementia patients have found that there was no significant increases of mortality risk with those exposed to atypical antipsychotics to those with no exposure[9].

The present study investigates the risk of antipsychotics on mortality in all forms of dementia including vascular dementia. We hope this will help inform clinical practice and contribute to the development of training packages on prescribing antipsychotics in dementia.

## MATERIALS AND METHODS

### Study design

A retrospective clinical cohort study was designed to review data gathered over a 5-year period (January 1, 2013 to December 31, 2017) in a National Health Service (NHS) setting. The aim of the study was to investigate the potential impact of atypical antipsychotics on the mortality of patients with dementia. Health Research Authority (HRA) provided guidance to the Akrivia Health and all data controllers that neither ethics nor HRA approval (legal & governance) is required for the establishment of the Clinical Record Interactive Search (CRIS) system or using de-identified data (from the system) for research purposes in March 2020. Local approvals were obtained from the Southern Health NHS Foundation Trust (SHFT) patient-led oversight committee.

### Cohort inclusion and exclusion criteria

The CRIS platform was used to identify suitable participants for this study as per the inclusion/exclusion criteria. Patient records in the SHFT database were filtered to only include those: Older than 30 years at the beginning of the study period (January 1, 2013); having a first diagnosis of either Alzheimer's disease (G30), vascular dementia (F01), frontotemporal dementia (G31.0), unspecified dementia (F03) or dementia in other diseases (F02); have been assigned this first diagnosis between January 1, 2013 and December 31, 2016; and to never had a diagnosis of either schizophrenia (F20), schizoaffective disorder (F25) or bipolar disorder (F31). A total of 1770 patients were deemed eligible for this study.

### Data extraction

Akrivia Health provides the CRIS system to analyse de-identified data from the Southern Health NHS Foundation Trust Electronic Health Records (EHR). There are currently 14 NHS Mental Health Foundation Trusts in the United Kingdom using CRIS with 3.2 million anonymised patients' record. Each site has its own CRIS access port that ingests data from their own EHRs that is managed within a robust governance model in the form of an independent oversight committee. The SHFT CRIS system includes records of the Trust's patients except those that have opted out from having their de-identified records used for research and evaluation purposes that could improve clinical benefit. The accessible data include notes that are written by clinicians as a report on a patient's progress, including comments on medication. The CRIS platform extracts the free text (progress notes) in a de-identified format to enable researchers with appropriate approvals to conduct research. Given the scale of the cohort, it was not feasible to compile a medication history manually. Natural language processing (NLP) was employed to identify medications within the patient's notes using the Med-7 algorithm[10]. This data was used to refine the cohort into three groups; medication group prescribed olanzapine, quetiapine or risperidone, comparison group (not prescribed any antipsychotic), and exclusion group (prescribed an antipsychotic other than olanzapine, quetiapine or risperidone). Additional variables were obtained from CRIS, including: Mortality status, date of death, age at diagnosis, gender, and ethnicity.

### Data analysis

The CRIS database supports the Med-7 NLP algorithm[10]. The algorithm indicates phrases with medications. Both the de-identified patient electronic healthcare records and the Med-7 medication outputs were searched using Structured Query Language and the relevant data tables were then exported into Python 3.8[11]. Python was then used to carry out all the analyses and generate the figures, using the following packages: Pandas[12], Numpy[13], Lifelines[14] and Matplotlib[15].

### Proportional hazards assumption

To assess the relationship between survival since diagnosis and the other variables, a cox proportional hazard (CPH) model was built. This model used the 'death flag' as an event of interest, 'survival since diagnosis' as the duration, 'age at diagnosis' as a continuous covariate, and one-hot encoded covariates of 'gender', 'ethnicity' and 'MMSE Score'.

CPH models assume the time-independence of the proportional hazards, consequently assuming the hazard ratios (HR) are constant with time. In our case, a violation of this assumption would mean the HR are dependent on the time since diagnosis. For example, a specific medication could be associated with a temporary survival risk but be relatively safe in the long-term (or vice versa). Rulli *et al*[16] provide a detailed explanation of this issue. Particular care should be taken when comparing the results of multiple studies (*i.e.*, including our study in an aggregate), as the time dependence of results may vary across datasets.

The time-independence assumption of the proportional hazards was tested using scaled Schoenfeld residuals and a rank transformation of time[17-18]. The statistical significance of the deviation from time-independence was calculated using an approximation developed by Davidson-Pilon[14] with a *P*-value threshold of 0.01. All variables were above the threshold, with 'age at diagnosis' having a *P*-value of 0.0102 (see Figure 1). To address the possible violation, we model the CPH as a stratified model, using 'age at diagnosis' as a stratifying variable, separating patients into 5-year strata intervals.

## RESULTS

### Descriptive statistics

The NLP algorithm identified a total of 1692 patients with at least one medication entry. Of these, 587 patients were prescribed either olanzapine, quetiapine or risperidone (medication group), 893 were not prescribed any antipsychotic medication (comparison group) and 290 were prescribed an antipsychotic other than olanzapine, quetiapine and risperidone (exclusion group). Olanzapine was prescribed to 155 patients, quetiapine to 144 and risperidone to 450 patients. There were 153 patients who were prescribed at least two of the three antipsychotics over the study period. The demographic profiles and the MMSE scores for the study groups are shown in Table 1.

### Outcomes

MMSE scores from the time of first diagnosis were also obtained using NLP (regular expression search). Patient records were followed for up to 5 years after the first diagnosis, retrieving the date of death if present.

### Survival duration

1097 (74%) patients had a recorded death within 5 years of their first diagnosis (*i.e.*, patients with a 'death flag'). For these patients, the 'survival since diagnosis' was calculated, representing the duration in months between the first diagnosis and the date of death. The mean survival since diagnosis was 26.7 mo (SD = 19.9).

### CPH model

The stratified CPH model had a concordance of 0.60, with six of the included covariates showing a significant HR. The variable-level results are listed in Table 2. Specifically, patients prescribed olanzapine showed an increased risk of death within the study period [HR = 1.32; 95% confidence interval (CI): 1.08-1.60; $P < 0.01$]. Those prescribed risperidone showed a similar increased risk of death (HR = 1.35; 95%CI: 1.18-1.54; $P < 0.001$). Quetiapine showed no significant association with an increased risk of death (HR = 1.09; 95%CI: 0.90-1.34; $P = 0.38$).

Patients with a high MMSE score (20-30) at diagnosis showed a lower risk of death (HR = 0.72; 95%CI: 0.62-0.83; $P < 0.001$). Interestingly, the MMSE Score HR always trend in a negative direction, suggesting that patients with any mention of an MMSE score in their clinical notes, regardless of its value, have a decreased risk of death. To better understand this effect, a follow-up CPH model was built, with 'MMSE Missing' as a covariate instead of the 'MMSE Score' groups. In this model, patients who do not have any mention of an MMSE score in their clinical notes ($n = 872$) show a significantly higher risk of death (HR = 1.30; 95%CI: 1.14-1.47; $P < 0.001$).

Those identifying as female ($n = 766$) had a significantly lower HR (HR = 0.73; 95%CI: 0.64-0.82; $P < 0.001$) than those identifying as male ($n = 714$). Patients of the White-British ethnicity showed a significantly lower risk of death (HR = 0.82; 95%CI: 0.72-0.94; $P < 0.01$), suggesting better outcomes for patients in this group.

## DISCUSSION

The results show a significantly higher mortality risk for those prescribed olanzapine and risperidone. This supports previous findings of Gerhard *et al*[19], who showed that quetiapine had a lower mortality risk than risperidone, while olanzapine had a similar mortality rate to risperidone within the elderly population. Gerhard *et al*[19] argued that their findings could be due to less variance in dosing of quetiapine. In addition, higher doses of both olanzapine and risperidone were thought to have been

**Table 1 Demographic information for the two study cohorts**

| Demographic | Category | Total | Medication group | Comparison group |
|---|---|---|---|---|
| Number of patients | | 1480 | 587 | 893 |
| Age (mean ± SD) | | 82.6 ± 8.1 | 81.7 ± 8.4 | 83.3 ± 7.9 |
| Gender | Male | 714 (48.2%) | 294 (50.1%) | 420 (47.0%) |
| | Female | 766 (51.8%) | 293 (49.9%) | 473 (53.0%) |
| | Other/NA | 0 | 0 | 0 |
| Ethnicity | White-British | 1033 (69.8%) | 451 (76.8%) | 582 (65.2%) |
| | White-Irish | 5 (< 1%) | 4 (< 1%) | 1 (< 1%) |
| | White-Any other | 17 (1.1%) | 6 (1.0%) | 11 (1.2%) |
| | Mixed-White and Asian | 1 (< 1%) | 1 (< 1%) | 0 (< 1%) |
| | Asian-Indian | 6 (< 1%) | 2 (< 1%) | 4 (< 1%) |
| | Asian-Bangladeshi | 1 (< 1%) | 0 (< 1%) | 1 (< 1%) |
| | Asian-Any other | 10 (< 1%) | 5 (< 1%) | 5 (< 1%) |
| | Black-Caribbean | 2 (< 1%) | 1 (< 1%) | 1 (< 1%) |
| | Black-African | 2 (< 1%) | 1 (< 1%) | 1 (< 1%) |
| | Any other ethnic group | 2 (< 1%) | 2 (< 1%) | 0 (< 1%) |
| | Not stated/NA | 401 (27.1%) | 114 (19.4%) | 287 (32.1%) |
| MMSE | Number of patients with MMSE | 608 (41.1%) | 226 (38.5%) | 382 (42.8%) |
| | Number of patients without MMSE | 876 (58.9%) | 361 (61.5%) | 511 (57.2%) |
| MMSE score | 20-30 | 369 (60.7%) | 101 (44.7%) | 268 (70.2%) |
| | 10-19 | 199 (23.7%) | 98 (43.4%) | 101 (26.4%) |
| | < 10 | 40 (6.56%) | 27 (11.9%) | 13 (3.4%) |

The percentages listed are of the column totals (number of patients) for the respective group. The only exception is the Mini Mental State Examination (MMSE) Score percentages, which are a proportion of the 'number of patients with MMSE' count. The 'Ethnicity-Asian' and 'Ethnicity-Black' groups include the Asian British and Black British ethnicity groups. MMSE: Mini Mental State Examination.

linked to a higher risk of mortality.

Aside from dosing, the differences in mortality rate could be due to the risk of cerebrovascular events. Risperidone and olanzapine have been associated with greater risks of cerebrovascular events[20-24]. The mechanism by which risperidone and olanzapine may increase the risk of cerebrovascular adverse events could be related to high levels of prolactin. Olanzapine and risperidone have been associated with high levels of prolactin[25-26]. High levels of prolactin have been associated with cerebrovascular events[27]. Furthermore, hyperprolactinaemia has been reported to frequently complicate antipsychotic treatment[28].

It is worth noting that risperidone has not been reported to cause anticholinergic side effects in the elderly unlike other atypicals[29]. Within this population, anti-psychotics are used to treat agitation and psychotic phenomenon often presented in dementia. Olanzapine and risperidone as atypical antipsychotics are commonly prescribed due to their favourable side-effect and safer metabolic profiles [5,30] age related changes in pharmacokinetics and pharmacodynamics can lead to increased sensitivity to drugs and their side effects[31] consequently impacting on mortality rates.

Polypharmacy is another facet observed within this population of patients that could attribute to the findings of our study. A recent scoping review on the sex and gender differences in polypharmacy in this population could support this theory[32] notably for women with dementia, in comparison to men [32]. Similarly, dementia is implicated in the increased risk of polypharmacy within the elderly population with rates varying from over 65 years taking from 6 medications to more than 10 medications in those older than 85 years across the world.

This study results contradict the previous findings of Sultana *et al*[9], who found no increase in risk hazard across olanzapine, quetiapine and risperidone, there are several differences in our study design that may account for the differing outcomes.

**Table 2 Results of the cox proportional hazard model, with survival since diagnosis as the duration variable**

| Covariate | Total | Alive | Dead | Hazard ratio | *P* value |
|---|---|---|---|---|---|
| Medications | | | | | |
| Olanzapine | 155 | 33 (21.3%) | 122 (78.7%) | 1.32[a] (1.08-1.60) | < 0.01 |
| Quetiapine | 144 | 29 (20.1%) | 115 (79.9%) | 1.09 (0.90-1.34) | 0.38 |
| Risperidone | 450 | 82 (18.2%) | 368 (81.8%) | 1.35[b] (1.18-1.54) | < 0.001 |
| Gender | | | | | |
| Male | 714 | 165 (23.1%) | 549 (76.9%) | Baseline | |
| Female | 766 | 218 (28.5%) | 548 (71.5%) | 0.73[b] (0.64-0.82) | < 0.001 |
| Ethnicity | | | | | |
| White-British | 1033 | 275 (26.6%) | 758 (73.4%) | 0.82[a] (0.72-0.94) | < 0.01 |
| White-Irish | 5 | 2 (40.0%) | 3 (60.0%) | 0.51 (0.16-1.62) | 0.26 |
| White-Any other | 17 | 6 (35.3%) | 11 (64.7%) | 0.62 (0.34-1.13) | 0.12 |
| Mixed-White and Asian | - | - | - | - | - |
| Asian-Indian | 6 | 1 (16.7%) | 5 (83.3%) | 1.49 (0.61-3.63) | 0.38 |
| Asian-Bangladeshi | - | - | - | - | - |
| Asian-Any other | 10 | 6 (60.0%) | 4 (40.0%) | 0.17[a] (0.05-0.53) | < 0.01 |
| Black-Caribbean | - | - | - | - | - |
| Black-African | - | - | - | - | - |
| Any other ethnic group | - | - | - | - | - |
| MMSE score | | | | | |
| 20-30 | 369 | 123 (33.3%) | 246 (66.7%) | 0.72[b] (0.62-0.83) | < 0.001 |
| 10-19 | 199 | 45 (22.6%) | 154 (77.4%) | 0.87 (0.73-1.04) | 0.12 |
| < 10 | 40 | 11 (27.5%) | 29 (72.5%) | 0.81 (0.56-1.19) | 0.28 |

[a]Hazard ratio significant at the $P < 0.01$ level.
[b]Hazard ratio significant at the $P < 0.001$ level. The 'Alive' and 'Dead' percentages are a proportion of the 'Total' count. The hazard ratio is listed along with the 95% confidence interval. MMSE: Mini Mental State Examination.

The cohort in the present study covers five different International Classification of Diseases diagnosis sub-groups (G30, F01, G31.0, F03, F02), rather than vascular dementia (F01) exclusively. As such, the present results are representative of the shared patterns observed across differing dementias. Patients with Alzheimer's disease (G30) are known to show an increased mortality risk associated with long-term antipsychotic use[33]. This is a plausible finding observed across the dementia diagnoses, in particular among vascular dementia patients. A direct comparison of the individual dementia diagnosis sub-groups could assist establishing the homogeneity/heterogeneity of the mortality risk effect in future studies.

The geographical differences between the Southampton and South London population also play a vital role in our findings, given the variations in ethnicities and races. The non-medication results are comparable across both studies with women demonstrating a lower risk in comparison to men. In addition, the Caucasian group demonstrated a relatively lower risk compared to most other groups. Consistent with other studies[34], patients with high MMSE scores were also associated with lower risk of mortality. This may either mean the MMSE test is not used in patients with advanced dementias, or that there are systematic patterns due to missing data issues within electronic healthcare records in primary and secondary care organizations. These possible theories could be substantiated with prospective research studies.

### *Strengths and limitations*

A study design using de-identified EHR has implicit strengths and limitations. The study provides a direct look into patient-level effects without influencing the clinical trajectory of the participants. Similarly, this design enables the analysis of the whole patient population in the NHS Trust (except for those opting out of NHS research) which would be prohibitively time consuming using traditional

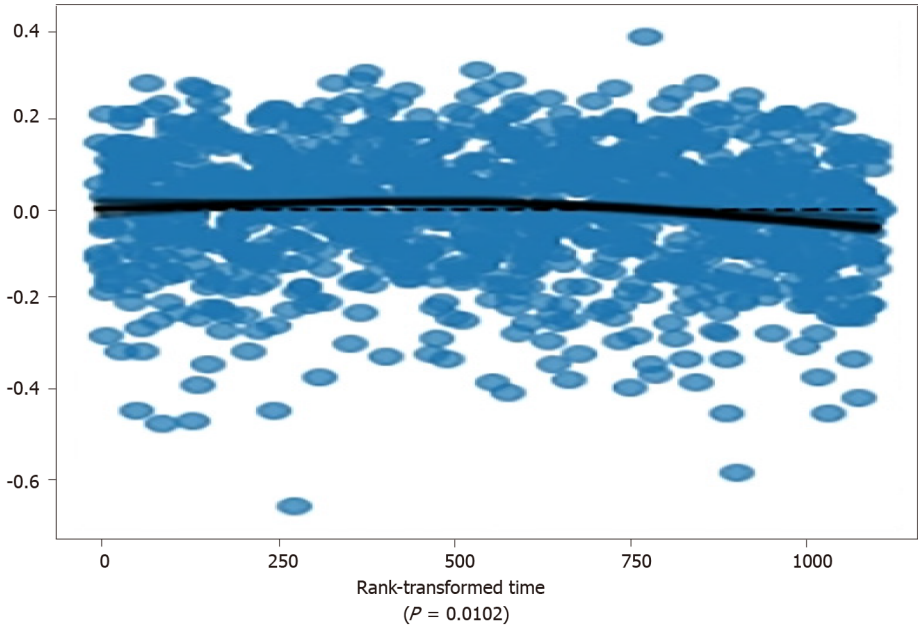


**Figure 1 Scaled Schoenfeld residuals for age at diagnosis, plotted against time ranks.**

patient recruitment methods. The use of NLP allows for the estimation of prescribed medication despite the fact that this information is rarely recorded in a structured format.

The strengths of using CRIS is that key features of the older adult population could be reviewed for this disease. Validating an original dataset by way of a secondary independent analysis is valuable to further future research within this area. On the other hand, it is important to appreciate that any retrospective EHR study is descriptive in nature. It is representative only of the cohort at hand, and any attempts at generalization should be accompanied by a robust theoretical underpinning of the observed effects. These are out of the scope of the current study, whereby the presented results aim to stimulate areas of further research, not inform clinical practice.

However, to strengthen the outcomes of this study, it was not feasible to develop an aggregated dataset which would have benefited the outcomes of this study. It is therefore recognized; future research should consider expanding the data collection during patient visits to better understand key clinical features and standardized scores in relation to the disease. A key data limitation is the under-representation of certain ethnic groups. Specifically, the 'White-British' group accounts for 95.7% of the patients who have an ethnicity on record. This makes it impossible to accurately estimate any ethnicity-related effects of the model, especially in the ethnicity groups that only include 1-5 patients. Gianfrancesco *et al*[35] provide a useful discussion on the potential bias associated with underrepresentation in EHRs. To investigate these effects, studies may benefit from specifically approaching the under-represented groups in order to generate more balanced cohorts.

A further limitation is that the method used within our paper is used in limited research papers due to differences with data gathering time points which impact the patients at risks at differing time points. Parmar *et al*[36] demonstrated similar methods could be used to estimate censored data along with a number of events at specific intervals although, the limitation with this is further assumptions would be made to generate estimates. The correlation tests based on Schoenfeld residuals is a positive step to assess the proportionality of hazards in standard cox models. Pseudo-likelihood was used to define Schoenfeld residuals at event times. Additionally, Kaplan-Meier estimates could have been completed if the event times and a ranking system was available at the point at which the dataset was furthered to assess the performance in a better way. Similarly, it would be beneficial to conduct simulation studies to address this issue although, this is a step to be completed as part of future research.

## CONCLUSION

The study showed an increased mortality risk associated with olanzapine and risperidone whilst quetiapine showed a relatively statistically insignificant association. This study reports a heterogeneous relationship between dementias, antipsychotic medication, and mortality, with some medication classes being more problematic than others. Antipsychotic use especially in the elderly population with dementia should only be prescribed when absolutely necessary given that such medication related adverse effects remain a significant source of mental and physical distress. Evidentiary argument implicates long-term antipsychotic use to progressive reduction in brain volume. As such, regulatory

warnings from the Food and Drug Administration and the European Medicines Agency on antipsychotics in population seem to be ineffective as usage has increased. Future comprehensive investigation is imperative, especially in understanding how the sub-diagnoses of dementias differ in their medication interactions and the effect of biological differences in sex and ethnicity that many intervene and further elucidate our findings. Further investigation to better assess clinical epidemiological outcomes associated with diagnosis and non-pharmacological therapies to improve clinical management of these patients is warranted.

## ARTICLE HIGHLIGHTS

### *Research background*

Antipsychotic medication is widely prescribed to patients with dementia displaying neuropsychiatric symptoms. The present study investigated the risk of antipsychotics on mortality in all forms of dementia including vascular dementia. It is anticipated the findings will help inform clinical practice and contribute to the development of training packages on prescribing antipsychotics in dementia.

### *Research motivation*

Antipsychotic prescribing in older adults must be made with caution as there are age related changes in pharmacokinetics and pharmacodynamics that can result in an increased sensitivity to drugs and their side effects. Similarly, the concerns around the safety and effectiveness of aripiprazole, olanzapine, quetiapine and risperidone (four specific antipsychotics) have been also raised for older patients in a clinical trial setting. Usage of antipsychotics in this population has increased despite regulatory warnings from the Food and Drug Administration and the European Medicines Agency.

### *Research objectives*

This study was developed with a primary objective to evaluate the impact of atypical antipsychotics associated with mortality in a dementia cohort.

### *Research methods*

A retrospective clinical cohort study was designed to review data from electrical health records (RIO system) gathered over a 5-year period (January 1, 2013 to December 31, 2017) in a National Health Service setting.

### *Research results*

Treatment with olanzapine and risperidone was associated with an increased mortality risk. In comparison, olanzapine showed a relatively lower non-significant association with the mortality risk in those with dementia.

### *Research conclusions*

Clinicians within primary and secondary care need to be aware of the potential heterogeneous relationship between dementia, antipsychotic medication and mortality when creating a psychopharmacological treatment plan for their patients.

### *Research perspectives*

Future comprehensive investigation is imperative, especially in understanding how the sub-diagnoses of dementias differ in their medication interactions and the effect of biological differences in sex and ethnicity that many intervene and further elucidate our findings.

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## FOOTNOTES

**Author contributions:** Phiri P and Carr H drafted the study protocol; Phiri P wrote the first draft of the manuscript version; Engelthaler T conducted the data extraction and analysis; all authors contributed to the critical revision of the manuscript and have approved the final manuscript.

**Institutional review board statement:** Health Research Authority (HRA) provided guidance to the Akrivia Health and all data controllers that neither ethics nor HRA approval (legal & governance) is required for the establishment of the Clinical Record Interactive Search (CRIS) system or using de-identified data (from the system) for research purposes in March 2020. Local approvals were obtained from the Southern Health NHS Foundation Trust (SHFT) patient-led oversight committee.

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous data that were obtained after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** Phiri P has received other, educational from Queen Mary University of London, Stanford University School of Medicine and other from John Wiley and Blackwell, outside the submitted work. Rathod S reports other from Janssen, Otsuka and Lundbeck outside the submitted work. All other authors report no conflict of interest.

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**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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ORIGINAL ARTICLE

Observational Study

# Reduced paraoxonase 1 activities may explain the comorbidities between temporal lobe epilepsy and depression, anxiety and psychosis

Ana Paula Michelin, Michael H J Maes, Thitiporn Supasitthumrong, Chusak Limotai, Andressa Keiko Matsumoto, Laura de Oliveira Semeão, João Victor de Lima Pedrão, Estefânia Gastaldello Moreira, Buranee Kanchanatawan, Décio Sabbatini Barbosa

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## Abstract

### *BACKGROUND*

Temporal lobe epilepsy (TLE) is the most common focal epilepsy subtype in adults and is frequently accompanied by depression, anxiety and psychosis. Aberrations in total paraoxonase 1 (PON1) status may occur in TLE and these psychiatric conditions.

### *AIM*

To examine PON1 status, namely Q192R PON1 genotypes and PON1 enzymatic activities, in TLE.

***METHODS***
We recruited 40 normal controls and 104 TLE patients, 27 without comorbidities and 77 with comorbidities including mood disorders ($n$ = 25), anxiety disorders ($n$ = 27) and psychosis ($n$ = 25).

***RESULTS***
Four-(chloromethyl)phenyl acetate hydrolysis (CMPAase) and arylesterase activities were significantly lower in TLE and mesial temporal sclerosis (MTS) with and without psychiatric comorbidities than those in normal controls. The areas under the receiver operating characteristic curve of CMPAase were 0.893 (0.037) for TLE and 0.895 (± 0.037) for MTS. Partial least squares path analysis showed that there were specific indirect effects of PON1 genotype on TLE severity ($P$ < 0.0001) and psychopathology ($P$ < 0.0001), which were both mediated by lowered CMPAase activity, while arylesterase activity was not significant. The severity of TLE was significantly associated with psychopathology scores. Furthermore, PON1 CMPAase activity was inversely associated with Mini Mental State Examination score.

***CONCLUSION***
The severity of TLE and comorbidities are to a large extent explained by reduced PON1 enzyme activities and by effects of the Q192R genotype, which are mediated by reduced CMPAase activity. Total PON1 status plays a key role in the pathophysiology of TLE, MTS and psychiatric comorbidities by increasing the risk of oxidative toxicity. PON1 enzyme activities are new drug targets in TLE to treat seizure frequency and psychiatric comorbidities.

**Key Words:** Antioxidants; Oxidative stress; Neuroimmune; Major depression; Mood disorders; Affective disorders

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**Core Tip:** The severity of temporal lobe epilepsy (TLE) and mesial temporal sclerosis and their psychiatric comorbidities including depression, anxiety and psychosis are largely explained by lowered paraoxonase 1 (PON1) enzyme activities, which mediate the effects of the Q192R PON1 genotype on psychopathology and epilepsy severity. It is argued that PON1 status may play a key role in the pathophysiology of TLE, mesial temporal sclerosis and its psychiatric comorbidities by increasing the risk of neuro-oxidative toxicity. It is concluded that PON1 enzyme activities are new drug targets to treat seizure frequency and psychiatric comorbidities in patients with TLE.

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## INTRODUCTION

Patients with epilepsy suffer from recurrent seizures originating from excessive and synchronous firing of groups of neurons in the brain[1,2]. Temporal lobe epilepsy (TLE) is the most common focal epilepsy subtype in adults, with a 40% incidence in relation to all types of epilepsy[3]. Hippocampal sclerosis or mesial temporal sclerosis (MTS), which is associated with neuronal loss and gliosis, is the most common primary pathology, accounting for 36% of all focal pathologies of epilepsy[4,5].

Neuropsychiatric disorders such as mood, anxiety and psychotic disorders are observed in about 30%-70% of TLE patients, and these comorbidities have a significant impact on the patient's quality of life[6-8]. In TLE, comorbid depression has the highest prevalence (42.9%) followed by anxiety disorders (18.4%), especially generalized anxiety disorder (GAD), while psychosis (PSY) shows a lower prevalence (around 5%-7%)[9,10].

In epilepsy, the first seizure may induce reactive oxygen and nitrogen species (ROS/RNS), and when these reactive species are produced in large quantities and exceed the antioxidant defense mechanisms, they may cause oxidative damage to lipids, proteins, DNA and mitochondria, excitotoxicity and neuroinflammation[11,12]. Oxidative neurotoxicity is particularly important in the central nervous system, since the brain is sensitive to oxidative stress due to its high energy and aerobic metabolic

demand[13-15]. Mitochondrial dysfunctions arising from ROS/RNS and the consequent oxidative lesions are frequently observed after seizures and during epileptogenesis and, additionally, are associated with neurodegeneration[13]. During seizures, performant antioxidant defenses are extremely important to protect brain tissues against oxidative damage ensuing from lipid peroxidation and aldehyde formation[15]. Experimental studies suggest that these oxidative pathways play an important role in the pathophysiology of TLE and TLE progression[16,17]. In addition, TLE is associated with decreases in antioxidant defenses as indicated by lowered superoxide dismutase[18] and glutathione levels in the hippocampus[19].

The enzyme paraoxonase 1 (PON1) is of particular importance because it is bound to high density lipoprotein (HDL) and has the ability to catalyze the hydrolysis of organic phosphates and lipid peroxides, protecting lipids, HDL and low density lipoprotein (LDL) from oxidation[20]. The PON1 Q192R single nucleotide polymorphism determines in part the catalytic activity and antioxidant properties of PON1 enzymes[21]. The alloenzyme R has a higher efficiency in detoxifying substrates such as paraoxon and 4-(chloromethyl) phenyl acetate (CMPA), and homozygous RR carriers metabolize lipids more efficiently than alloenzyme Q carriers, explaining their stronger protection against lipid peroxidation[22]. Nevertheless, there are only few studies that have examined total PON1 status (that is enzymatic activities and PON1 genotypes) in epilepsy. Dönmezdil *et al*[23] and Calik *et al*[24] found significantly lowered serum PON1 and arylesterase activities in patients with epilepsy, although these authors did not measure total PON1 status, which should include total enzyme activities and PON1 genotypes[25]. Moreover, no studies examined the associations between PON1 status and psychiatric comorbidities in TLE, although PON1 status is significantly associated with major depression, anxiety disorders and subtypes of PSY[25].

Hence, the objective of this study was to evaluate PON1 status, namely CMPAase and arylesterase activities as well as PON1 Q192R genotypes, in patients with TLE and MTS with and without comorbid PSY, depression and anxiety.

## MATERIALS AND METHODS

### *Participants*

For this case-control study, 104 patients with TLE and 40 normal controls were recruited. Patients with TLE were admitted to the outpatient clinic of the Comprehensive Epilepsy Unit of King Chulalongkorn Memorial Hospital, Bangkok, Thailand from December 2013 to December 2014. The patients were diagnosed with TLE by a senior neurologist specializing in epilepsy. The latter diagnosis was based on the history of clinical characteristics of seizures, electroencephalography records and magnetic resonance imaging scans performed in all patients. The patients with TLE were subdivided into four subgroups based on the presence of psychiatric comorbidities according to the criteria established in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR), namely: (1) Mood disorders due to TLE with depressive characteristics ($n$ = 25); (2) Anxiety Disorder Due to TLE with panic attacks, GAD or obsessive-compulsive symptoms ($n$ = 27); (3) Psychotic disorder due to TLE with delusions or hallucinations ($n$ = 25); and (4) "Pure TLE" when there were no psychiatric comorbidities ($n$ = 27).

Exclusion criteria for healthy controls were a diagnosis of epilepsy, febrile seizures in childhood and any other axis 1 psychiatric disorder and a positive family history of epilepsy, mood disorders or psychotic disorders. Exclusion criteria for TLE patients were: (1) Any other axis 1 disorder, except mood, anxiety and psychotic disorders due to TLE; and (2) Interictive dysphoric disorder. Exclusion criteria for patients with mood disorders due to TLE were anxiety and psychotic disorders. In the patient group with anxiety disorders due to TLE, we excluded patients with mood disorders or PSY, and, in the patient group with psychotic disorder due to TLE, we excluded patients with mood and anxiety disorders. In addition, patients with "pure TLE" did not suffer from any of the above-mentioned psychiatric comorbidities. Exclusion criteria for patients and controls were: (1) (Auto)immune diseases including diabetes, psoriasis, chronic obstructive pulmonary disease, inflammatory bowel disease; (2) Neurodegenerative and neuroinflammatory disorders, such as multiple sclerosis, Parkinson's disease and Alzheimer's disease; (3) Immune, inflammatory or allergic response 3 mo before the start of the study; (4) A lifetime history of treatment with immunomodulatory drugs; (5) Use of therapeutic doses of antioxidants or supplements containing ω3-polyunsaturated fatty acids 3 mo before inclusion in the study; and (6) Pregnant or lactating women.

Prior to participation in the research, all individuals signed a written informed consent form. The Institutional Review Board of the Faculty of Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand, gave their approval to this research (IRB number 305/56) in accordance with the International Guideline for the Protection of Human Research, as established by the Declaration of Helsinki, The Belmont Report, International Conference on Harmonization of Good Clinical Practice and Council for International Organizations of Medical Sciences Guideline.

### Measurements

Semi-structured interviews were conducted by a senior neurologist and a senior psychiatrist specialized in epilepsy. The neurologist collected sociodemographic data and TLE characteristics including family history of epilepsy, age at onset of TLE, type of epilepsy, location of the lesion, seizure frequency, seizure control (seizure free, fairly and poorly controlled seizures); history of post-ictal confusion, type of seizures and use of antiepileptic drugs (AEDs). The diagnosis of TLE was made based on the history of partial seizures and electroencephalography records of epileptiform activities in one or both temporal regions. In addition, the senior neurologist and a radiologist used results of magnetic resonance imaging scans to make the diagnosis of MTS or other types of TLE. Patients and controls were evaluated by the senior psychiatrist to identify psychotic symptoms, anxiety and depression, using DSM-IV-TR criteria. The diagnosis of mood disorders due to TLE comprises major depression in an acute episode or in partial remission and ictus-related depression. The diagnosis of anxiety disorder due to TLE comprises patients with panic, GAD, obsessive-compulsive symptoms and ictus-related anxiety such as fear and horror. Psychotic disorders due to TLE comprise delusions (persecutors, possessed, paranoid and reference ideas), hallucinations (auditory, taste, visual and olfactory) and ictus-related psychoses, as described by Kanchanatawan *et al*[26]. These psychoses can be ictal, pre-ictal, post-ictal, psychotic aura, peri-ictal, interictal or schizophrenic-like PSY. In this context, fear, horror, forced thoughts, out-of-body experiences and going crazy were not considered to be psychotic.

The senior psychiatrist (BK) also assessed the Brief Psychiatric Rating Scale (BPRS), the Hamilton Depression (HAM-D) and Anxiety (HAM-A) Rating Scale[27-29] and also assessed the Mini Mental State Examination (MMSE)[30] in patients and controls. The body mass index (BMI) was calculated using the ratio between body weight in (kg) and height ($m^2$) and tobacco use disorder was evaluated using the DSM-IV-TR criteria.

### PON1 assays

Blood samples were collected at 8:00 am, after an overnight fast, and serum was aliquoted and stored at -80 °C until thawed for PON1 status. Total PON1 activity was determined by the formation of phenyl acetate hydrolysis[22]. The rate of phenylacetate hydrolysis was determined on a Perkin Elmer® EnSpire model microplate reader (Waltham, MA, United States) at a wavelength of 270 nm measured over 4 min (16 readings at 15 s between readings) with the temperature maintained at 25 °C. Activity was expressed in U/mL based on the phenyl acetate molar extinction coefficient, which is 1.31 mmol/Lol/Lcm-1. For the stratification of the functional genotypes of the PON1Q192R polymorphism (PON1 192Q/Q, PON1 192Q/R, PON1 192R/R), we used CMPA (Sigma, St. Louis, MO, United States) and phenyl acetate (PA, Sigma). PON1 polymorphism confers differences in hydrolysis capacity, and this allows to stratify the genotypes after phenotypic analysis of enzyme activity. Isoform R has high hydrolysis activity on CMPA, whilst alloenzyme Q has lower hydrolytic activity on CMPA, and both alloforms hydrolyze PA with similar efficacy. Therefore, the reaction with PA is performed with high salt concentrations, which partially inhibits the activity of R allozyme, thereby providing a better distinction between the three functional genotypes. The rate of PA hydrolysis in low salt concentration by arylesterase was also measured.

### Statistics

We used analysis of variance to assess differences in scale variables between diagnostic groups and analysis of contingency tables ($\chi^2$-tests) to assess associations among categorical variables. We used multivariate general linear model (GLM) analysis to ascertain the associations between diagnosis and biomarkers while controlling for possible background variables including sex, age, BMI, smoking and the drug state. Consequently, tests for between-subject effects were employed to examine the associations between diagnosis and each of the biomarkers. Model-generated estimated marginal mean values were computed, and protected pair-wise comparisons among treatment means were employed to delineate the differences among the study groups. We used *P*-corrections for false discovery rate to control for multiple statistical tests[31]. Automatic binary regression analysis was employed to delineate the best biomarker prediction of TLE (controls as reference group). We employed automatic stepwise (step-up) multiple regression analysis to assess the most significant biomarkers predicting the BPRS, HAM-D, HAM-A and MMSE scores. Regression analyses were double-checked for collinearity and bootstrapped using 5000 samples, and the bootstrapped results are shown in case of discrepant results. All tests were two-tailed and a *P* value of 0.05 was used for statistical significance. IBM SPSS25 (Armonk, NY, United States) (for windows was used to analyze the data. The number of participants was established *a priori* using GPower: At least 138 people were required to achieve a power of 0.8 (effects size: 0.3; alpha = 0.05; four groups and four covariates) (analysis of covariance).

To examine the causal associations between PON1 genotype and PON1 enzyme activities and TLE characteristics and psychopathology, we performed partial least squares (PLS) path analysis employing SmartPLS[32]. SmartPLS is a structural equation modeling technique that allows to examine causal pathways explaining the effects of input variables (PON1 genotype) on output variables (PON1 activities and clinical aspects of TLS and comorbidities), whereby variables are entered as single indicator variables (PON1 genotype and enzyme activities) or as latent vectors (LV) extracted from TLE

features (TLE; aura; postictal confusion; TLE frequency; seizure free, fairly and poorly controlled seizures); and the three psychopathological rating scale scores (BPRS, HAM-A, HAM-D)[32]. We conducted PLS path analysis when the model complied with quality criteria, *i.e.* model SRMR < 0.080 and when the LVs showed adequate reliability validity as indicated by composite reliability > 0.7, rho_A > 0.8, Cronbach's alpha > 0.7 and average variance extracted (AVE) > 0.5; while the outer model factor loadings were > 0.6 with $P < 0.001$[32]. Consequently, we conducted complete and consistent PLS path analysis using 5.000 bootstrap samples to compute path coefficients (with $P$ values) and the significance of total, total indirect and specific indirect effects.

## RESULTS

### Demographic and clinical data

Table 1 shows the socio-demographic data of the participants in this study. There were no significant differences in age, BMI, marital status, or tobacco use disorder between the study groups. There was a trend towards more females in TLE patients with depression and anxiety. Subjects with TLE were somewhat less educated than the healthy controls. Therefore, we have statistically controlled for education in regressions with psychopathology ratings and MMSE as dependent variables. There were no significant differences in seizure frequency, age of onset of TLE, a history of aura, postictal confusion and control of seizures (free of seizures, fair and poor control) between the four TLE subgroups. Patients with psychotic disorder due to TLE showed a higher incidence of status epilepticus as compared with those with "pure TLE". Table 1 also shows the rating scale scores and MMSE scores in the five subgroups. The BPRS and HAM-A scores were significantly different between the five subgroups, with the lowest levels in controls and highest values in patients with TLE + PSY and TLE + anxiety, respectively. The HAM-D score was significantly higher in patients with TLE + depression than in all other study groups, while the MMSE was significantly lower in TLE patients than in controls, with the lowest scores being established in TLE + PSY.

### Associations between TLE with and without comorbidities and PON1 genotypes

The total study group (patients and controls) was at Hardy-Weinberg equilibrium ($\chi^2 = 1.086$, df = 1, $P = 0.297$), while also the control ($\chi^2 = 1.2013$, df = 1, $P = 0.273$) and the TLE ($\chi^2 = 0.530$, df = 1, $P = 0.467$) subgroups were at Hardy-Weinberg equilibrium. There was no significant association between PON1 Q192R genotypes and TLE subgroups ($\psi = 0.137$, $P = 0.251$), namely in controls: 1/17/22 *vs* 10/51/47 in TLE for the QQ, QR and RR genotypes, respectively. There were no significant associations between TLE and different genetic models of the *PON1* gene, including allelic, dominant, recessive and overdominant models.

### Associations between PON1 activity and diagnosis

We examined the associations between the activities and diagnosis using multivariate GLM analysis while adjusting for sex, age and BMI. We examined four PON1 activity indices namely PON1 CMPAase and AREase enzyme activities as measured in this study and their residualized values after covarying for PON1 genotypes. The latter explained 70.0% of the variance in PON1 CMPAase and arylesterase activities (F = 173.88, df = 2/145, $P < 0.001$), with the lowest CMPAase activities and the highest arylesterase activities in QQ carriers.

Multivariate GLM analysis showed that there was a significant association between PON1 activity and diagnosis (Table 2). Tests for between-subjects effects showed significant associations between diagnosis and CMPAase and the residualized CMPAase activities with an explained variance of around 43.7%-45.0%. The associations with arylesterase and the residualized arylesterase activity shared around 24.8%-33.0% of the variance. Table 3 shows the model-generated estimated marginal mean values, indicating that all PON1 activities were significantly lowered in TLE patients than in controls. These differences were highly significant, with a distance of around 1.586 standard deviations between controls and patients with TLE + PSY in residualized PON1 CMPAase activity. Figure 1 shows the box-plot of CMPAase activity values in controls, pure TLE and TLE with psychiatric comorbidities.

Binary logistic regression analysis with TLE as dependent variable (controls as reference group) showed that the residualized PON1 CMPAase activity was the most significant biomarker discriminating TLE from controls, with a sensitivity of 70.4%, specificity of 90.0% and accuracy of 75.7% ($\chi^2 = 69.74$, df = 1, $P < 0.001$, Nagelkerke = 0.546). The odds ratio was 0.111 (95% confidence interval: 0.053-0.230; Wald = 29.41, $P < 0.001$; B = 1.515, SE = 0.279).

Table 4 shows that CMPAase and arylesterase activities were significantly lower in MTS (with psychiatric comorbidities), "pure" TLE and "pure" MTS (both without psychiatric comorbidities) than those in controls. The strongest impact was established for CMPAase activity in MTS. The area under the receiver operating characteristic curve using reduced CMPAase activity as discriminatory variable was 0.893 (0.037) for TLE and 0.895 (± 0.037) for MTS.

**Table 1 Sociodemographic and clinical data of healthy controls and patients with temporal lobe epilepsy and patients with psychosis, depression and anxiety due to temporal lobe epilepsy (mean ± SD)**

| Variables | HC[1] | TLE[2] | TLE + PSY[3] | TLE + DEP[4] | TLE + ANX[5] | F/X[2] | df | *P* value |
|---|---|---|---|---|---|---|---|---|
| Age (yr) | 37.4 (12.8) | 40.0 (12.8) | 37.9 (10.5) | 39.0 (10.7) | 37.0 (8.2) | 0.34 | 4/141 | 0.849 |
| Sex (♂/♀) | 10/30 | 11/16 | 13/14 | 4/21 | 5/22 | 10.31 | 4 | 0.036 |
| BMI (kg/m$^2$) | 24.0 (4.3) | 24.1 (4.0) | 23.5 (3.7) | 23.9 (4.3) | 22.4 (4.3) | 0.79 | 4/140 | 0.535 |
| Married (No/Yes) | 26/14 | 18/9 | 20/7 | 20/5 | 15/11 | 3.58 | 4 | 0.466 |
| Education (yr) | 14.2 (4.9)[2,3,4,5] | 11.4 (4.7)[1] | 9.4 (4.4)[1] | 10.3 (5.4)[1] | 10.8 (4.5)[1] | 5.14 | 4/141 | 0.001 |
| TUD (No/Yes) | 38/2 | 24/3 | 23/4 | 21/4 | 23/4 | Ψ = 0.136 | - | 0.607 |
| Frequency seizures | - | 29.1 (84.7) | 19.1 (40.7) | 8.0 (17.0) | 9.7 (11.0) | 0.99 | 3/89 | 0.402 |
| Age onset TLE (yr) | - | 17.8 (12.6) | 12.2 (10.1) | 17.6 (8.9) | 16.1 (8.8) | 1.75 | 3/100 | 0.162 |
| Hx Aura (No/Yes) | - | 6/21 | 5/22 | 7/18 | 8/19 | 1.15 | 3 | 0.766 |
| Hx Postictal confusion (No/Yes) | - | 8/19 | 10/16 | 9/16 | 11/15 | 0.97 | 3 | 0.808 |
| Hx Status epilepticus (No/Yes) | - | 24/3[3] | 14/11[2] | 21/4 | 13/9 | 10.75 | 3 | 0.013 |
| Seizure control | - | 7/8/8 | 7/8/8 | 5/4/0 | 5/5/10 | Ψ = 0.309 | - | 0.307 |
| BPRS | 18.3 (1.1)[2,5] | 23.6 (3.3)[1,3,4,5] | 41.3 (5.9)[1,2,4,5] | 32.9 (6.7)[1,2,3,5] | 29.4 (50.)[1,2,3,4] | 115.64 | 4/141 | < 0.001 |
| HAM-D | 0.6 (2.0)[2,5] | 4.8 (2.5)[1,4,5] | 5.8 (2.9)[1,5] | 19.8 (4.9)[1,2,3,5] | 10.3 (3.8)[1,2,3,4] | 145.21 | 4/140 | < 0.001 |
| HAM-A | 2.6 (5.4)[2,5] | 7.8 (3.9)[1,3,4,5] | 11.6 (6.7)[1,2,3,5] | 18.9 (8.8)[1,2,3,5] | 23.8 (5.4)[1,2,3,4] | 59.69 | 4/141 | < 0.001 |
| MMSE | 28.3 (2.4)[2,5] | 25.1 (4.4)[1,3] | 22.4 (5.4)[1,2,4,5] | 25.7 (2.4)[1,3] | 25.8 (8.9)[1,3] | 11.06 | 4/140 | < 0.001 |

[1-5]Results of post-hoc comparisons among the five diagnostic groups.

[1]Indicates HC and "1" associated with column figures indicates that this value is different from HC.

[2]Indicates TLE and "2" associated with column figures indicates that this value is different from TLE.

[3]Indicates TLE + PSY and "3" associated with column figures indicates that this value is different from TLE + PSY.

[4]Indicates TLE + DEP and "4" associated with column figures indicates that this value is different from TLE + DEP.

[5]Indicates TLE + ANX and "5" associated with column figures indicates that this value is different from TLE + ANX.

BMI: Body mass index; TUD: Tobacco use disorder; Control seizures: Seizure free and fairly and poorly controlled seizures; BPRS: Brief Psychiatric Rating Scale; HAM-D: Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; MMSE: Mini Mental State Examination; HC: Healthy controls; TLE: Temporal lobe epilepsy; TLE: TLE without ant psychiatric comorbidities; TLE + PSY: Psychotic Disorder due to TLE; TLE + DEP: Mood Disorder due to TLE with depressive features; TLE + ANX: Anxiety Disorder due to TLE.

### *Effects of possible confounding variables*

As shown in Table 2, there were no significant effects of possible confounders including sex, age and BMI. There were also no significant effects of smoking (F = 0.48, df = 4/135, $P$ = 0.748) and the Fagerstrom score (F = 0.16, df = 4/135, $P$ = 0.960). We have also examined the possible effects of treatments with valproate ($n$ = 34), carbamazepine ($n$ = 61), phenytoin ($n$ = 38), levetiracetam ($n$ = 38), lamotrigine ($n$ = 27), phenobarbital ($n$ = 26), clonazepam ($n$ = 10), clobazam ($n$ = 58), topiramate ($n$ = 12), gabapentin ($n$ = 8), antipsychotics ($n$ = 9), antidepressants ($n$ = 16), anxiolytics ($n$ = 10), CaCo3 ($n$ = 13) and folic acid ($n$ = 27). These drug state variables were examined as dummy variables entered altogether in multivariate GLM analysis or one by one in univariate GLM analyses. However, both types of GLM analyses showed no significant effects, even without P-correction for multiple testing. There was no significant association (Spearman rank order correlation) between the number of AEDs and either CMPAase (-0.086, $P$ = 0.398, $n$ = 102) or arylesterase ($r$ = 0.052, $P$ = 0.605, $n$ = 102) activity.

### *Prediction of rating scale scores using biomarkers*

In order to examine the effects of biomarkers on the rating scale scores, we performed automatic multiple regression analysis with the rating scales as dependent variables and the four PON1 measurements (residualized and non-residualized CMPAase and AREase activities), the PON1 genetic models, age, sex as well as education (Table 5). Firstly, we examined associations with the BPRS and two symptoms profiles namely PSY that is sum of BPRS items 4 (conceptual disorganization), 11 (suspiciousness), 12 (hallucinations) and 15 (unusual thought disorders), and negative symptoms namely the sum of BPRS symptoms 3 (emotional withdrawal) and 16 (blunted affect). We found that 29.1% of the variance in the BPRS total score and 11.8% of the variance in PSY was predicted by PON1 CMPAase activity and education (both inversely). Figure 2A shows the inverse association between

**Table 2 Results of multivariate general linear model analysis examining the differences between diagnostic groups (diagnosis), namely healthy controls, temporal lobe epilepsy with and without comorbidities including depression, psychosis, and anxiety**

| Tests | Dependent variables | Exploratory variables | F | df | *P* value | Partial Eta squared |
|---|---|---|---|---|---|---|
| | All 4 biomarkers | | | | | |
| Multivariate | CMPAase | Diagnosis | 6.49 | 16/410 | < 0.001 | 0.158 |
| | Arylesterase | Sex | 1.22 | 4/134 | 0.306 | 0.035 |
| | Res CMPAase | Age | 0.61 | 4/134 | 0.654 | 0.018 |
| | Res Arylesterase | BMI | 1.07 | 4/134 | 0.375 | 0.031 |
| Between-subject effects | CMPAase | Diagnosis | 28.06 | 4/137 | < 0.001 | 0.450 |
| | Res CMPAase | Diagnosis | 26.60 | 4/137 | < 0.001 | 0.437 |
| | Arylesterase | Diagnosis | 11.31 | 4/137 | < 0.001 | 0.248 |
| | Res Arylesterase | Diagnosis | 16.90 | 4/137 | < 0.001 | 0.330 |

Diagnosis: Five diagnostic groups, namely Psychotic Disorder due to temporal lobe epilepsy (TLE), Mood Disorder due to TLE with depressive features, Anxiety Disorder due to TLE, "Pure TLE" (without any comorbidities) and healthy controls. PON1: Paraoxonase; CMPAase: 4-(chloromethyl)phenyl acetate hydrolysis; Res: Residualized (after regression on PON1 genotype); BMI: Body mass index.

**Table 3 Model-generated estimated marginal means of paraoxonase 1 levels in healthy controls and patients with temporal lobe epilepsy and psychosis, depression and anxiety due to temporal lobe epilepsy**

| Variables | HC[1] | TLE[2] | TLE + PSY[3] | TLE + DEP[4] | TLE + ANX[5] |
|---|---|---|---|---|---|
| CMPAase (U/mL) | 42.1 (1.3)[2,3,4,5] | 28.5 (1.6)[1] | 24.5 (1.6)[1] | 24.8 (1.7)[1] | 27.3 (1.7)[1] |
| Res CMPAase (z scores) | 1.041 (0.128)[2,3,4,5] | -0.196 (0.150)[1] | -0.545 (0.163)[1] | -0.545 (0.163)[1] | -0.375 (0.159)[1] |
| Arylesterase (U/mL) | 212.4 (9.0)[2,3,4,5] | 156.4 (10.5)[1] | 144.2 (10.4)[1] | 143.7 (11.4)[1] | 137.3 (11.2)[1] |
| Res Arylesterase (z scores) | 0.920 (0.140)[2,3,4,5] | -0.193 (0.163)[1] | -0.425 (0.162)[1] | -0.400 (0.177)[1] | -0.434 (0.174)[1] |

[1-5]Results of post-hoc comparisons among the five diagnostic groups.
[1]Indicates HC and "1" associated with column figures indicates that this value is different from HC.
[2]Indicates TLE and "2" associated with column figures indicates that this value is different from TLE.
[3]Indicates TLE + PSY and "3" associated with column figures indicates that this value is different from TLE + PSY.
[4]Indicates TLE + DEP and "4" associated with column figures indicates that this value is different from TLE + DEP.
[5]Indicates TLE + ANX and "5" associated with column figures indicates that this value is different from TLE + ANX.
TLE: Temporal lobe epilepsy; TLE: TLE without psychiatric comorbidities; TLE + PSY: Psychotic Disorder due to TLE; TLE + DEP: Mood Disorder due to TLE with depressive features; TLE + ANX: Anxiety Disorder due to TLE; HC: Healthy controls; PON1: Paraoxonase; CMPAase: 4-(chloromethyl)phenyl acetate hydrolysis; Res: Residualized values after regression on PON1 genotype.

total BPRS score and CMPAase activity (partial regression based on the first regression in Table 5). The best predictors of negative symptoms were the residualized CMPAase activity, age and education (all inversely correlated) and male sex. We found that 25.4% of the variance in the HAM-D score was predicted by PON1 CMPAase activity, education (both inversely), female sex and being a QQ or RR carrier. Figure 2B shows the partial regression of the total HAM-D score on CMPAase activity. A large part of the variance in suicidal ideation (item 3 of the HAM-D) was explained by QQ genotype and residualized CMPAase activity (inversely associated) combined. We also computed the associations between physiosomatic symptoms, namely the sum of the HAM-A items 11 (anxiety somatic), 12 (somatic symptoms GIS), 13 (somatic symptoms general), 14 (genital symptoms) and 15 (hypochondriasis) and found that 12.2% of its variance was explained by PON1 CMPAase activity (inversely associated). Consequently, we have computed an index of psychomotor retardation (PMR) as z values of item 8 of the HAM-D and item 13 of the BPRS (both PMR) and found that 29.5% of the variance in PMR was explained by residualized CMPAase activity, age and education (all inversely associated) and male sex. CMPAase activity combined with female sex predicted 15.3% of the variance in the total HAM-A score. We have computed an overall psychopathology index as the sum of the z values of the BPRS, HAM-D and HAM-A. This index was best predicted by PON1 CMPAase activity, education (both inversely), female sex and PON1 genotype. We found that 43.4% of the variance in the MMSE score was predicted by education and CMPAase activity (both positively associated).

**Table 4 Measurement of paraoxonase enzymatic activity in healthy controls and subgroups of temporal lobe epilepsy patients**

| PON1 activities | HC | Pure TLE | F | df | *P* value | Partial eta squared |
|---|---|---|---|---|---|---|
| CMPAase (U/mL) | 42.8 (1.7) | 28.8 (1.9) | 30.61 | 1/62 | < 0.001 | 0.331 |
| Arylesterase (U/mL) | 215.4 (10.8) | 156.4 (12.2) | 13.47 | 1/62 | 0.001 | 0.178 |
| | | **MTS** | | | | |
| CMPAase (U/mL) | 41.7 (1.5) | 25.6 (1.2) | 81.44 | 1/100 | < 0.001 | 0.449 |
| Arylesterase (U/mL) | 209.8 (9.4) | 139.4 (7.5) | 36.98 | 1/100 | < 0.001 | 0.270 |
| | | **Pure MTS** | | | | |
| CMPAase (U/mL) | 42.2 (1.8) | 27.3 (2.6) | 22.61 | 1/52 | < 0.001 | 0.303 |
| Arylesterase (U/mL) | 213.0 (10.8) | 139.5 | 14.65 | 1/52 | < 0.001 | 0.220 |

Data are results of univariate general linear model analysis and are shown as model-generated marginal estimated mean (SE) values after covarying for age, sex and body mass index. Pure TLE: Temporal lobe epilepsy without any psychiatric comorbidity; MTS: Established mesial temporal lobe sclerosis (thus including psychiatric comorbidities); Pure MTS: Established mesial temporal lobe sclerosis without any psychiatric comorbidity; TLE: Temporal lobe epilepsy; HC: Healthy controls; MTS: Mesial temporal sclerosis.

### *Results of path analysis*

Figure 3 shows the results of a consistent and complete PLS path analysis with the PON1 genotype (additive model) as input variable and a LV extracted from the three rating scale scores (BPRS, HAM-D and HAM-A) as final outcome in a multi-step mediation model with PON1 activities (CMPAase and arylesterase) and a LV extracted from TLE features (frequency, aura, controlled epilepsy and postictal confusion) as mediators. There were no significant effects of arylesterase (after considering the effects of CMPAase), and, therefore, only the latter are shown in this figure. The fit of the model was adequate with SRMR = 0.053, while the construct reliability validity of both LVs was adequate with composite reliability values of 0.890 and 0.855; Cronbach α values of 0.847 and 0.805, rho_A values of 0.898 and 0.810 and AVE values of 0.620 and 0.719 were determined for TLE and psychopathology LVs, respectively. All outer loadings of the indicators of both LVs were > 0.694 (all at $P < 0.0001$). We found that 46.0% of the variance in the psychopathology index was explained by the TLE LV (positively associated) and PON1 CMPAse activity (inversely associated), while 25.3% of the variance in the TLE LV was explained by CMPAase activity. Finally, the PON1 genotype additive model explained 9% of the variance in CMPAase activity. There were specific indirect effects of PON1 genotype on: (1) The TLE LV, which were mediated by CMPAase activity ($t = 4.07$, $P < 0.0001$); and (2) The psychopathology LV mediated by CMPAase activity ($t = 1.97$, $P = 0.048$) and the path from PON1 genotype→CMPAase activity→TLE LV→psychopathology LV ($t = 3.74$, $P < 0.0001$). Likewise, the PON1 genotype had significant total (indirect) effects on TLE LV ($t = 4.07$, $P < 0.0001$) and psychopathology LV ($t = 3.87$, $P < 0.0001$). We have also examined the total effects of the QQ, QR and RR genotypes on the TLE and psychopathology LVs and found that QQ ($t = 3.39$, $P = 0.001$ and $t = 3.20$, $P = 0.001$) and RR ($t = -3.35$, $P = 0.001$ and $t = -3.26$, $P = 0.001$), but not QR, had significant total effects on the TLE and psychopathology LVs, respectively.

## DISCUSSION

The first major finding of this study is that PON1 CMPAase and arylesterase activities were significantly decreased in patients with TLE, especially MTS, as compared with healthy controls. In our study, reduced levels of CMPAase yielded an area under the receiver operating characteristic curve of around 0.893 for TLE and MTS. These findings extend those of previous publications reporting significantly reduced levels of PON1 and arylesterase in patients with epilepsy when compared to healthy controls [24,33].

The second major finding of this study is that there were no significant differences in PON1 status between TLE without any comorbidities and depression, anxiety or PSY due to TLE, although severity of depression, PSY and anxiety were strongly associated with CMPAase activity. As such, CMPAase and, to a lesser degree, arylesterase activity are important in predicting the severity of psychopathology in TLE. We also observed that the severity of TLE predicts a general index of psychopathology.

Psychiatric comorbidities such as depression and anxiety are prevalent in patients with epilepsy and occur 2 to 3 times more frequently in this group of patients than in people who do not have the disease [34,35]. Some authors found a strong association between low levels of PON1 and CMPAase activities and major depression[36,37], whilst reduced activity of CMPAase was additionally associated with lower quality of life, increased disability and staging of illness[36,38], suggesting that reduced total

**Table 5 Results of multiple regression analysis with rating scales as dependent variables and paraoxonase status as explanatory variables**

| Dependent variables | Explanatory variables (model) | β | *t* value | *P* value | F model | Df | *P* value | Partial Eta squared |
|---|---|---|---|---|---|---|---|---|
| BPRS | CMPAase | -0.444 | -6.09 | < 0.001 | 29.35 | 2/143 | < 0.001 | 0.291 |
| | Education | -0.213 | -2.93 | 0.004 | | | | |
| Psychosis | CMPAase | -0.260 | -3.20 | 0.002 | 9.56 | 2/143 | < 0.001 | 0.118 |
| | Education | -0.167 | -2.06 | 0.041 | | | | |
| Negative symptoms | Education | -0.329 | -4.52 | < 0.001 | 12.75 | 4/141 | < 0.001 | 0.226 |
| | Sex | -0.329 | -4.29 | < 0.001 | | | | |
| | Res CMPAase | -0.189 | -2.56 | < 0.011 | | | | |
| | Age | -0.172 | -2.30 | 0.023 | | | | |
| HAM-D | CMPAase | -0.347 | -4.51 | < 0.001 | 11.95 | 4/140 | < 0.001 | 0.254 |
| | Education | -0.231 | -3.02 | 0.003 | | | | |
| | Overdominant model | -0.227 | -3.06 | 0.003 | | | | |
| | Sex | 0.170 | 2.31 | 0.023 | | | | |
| Suicidal ideation | Dominant model | 0.354 | 4.61 | < 0.001 | 13.21 | 2/143 | < 0.001 | 0.156 |
| | Res CMPAase | -0.173 | -2.26 | 0.025 | | | | |
| Physiosomatic symptoms | CMPAase | -0.349 | -4.47 | < 0.001 | 19.94 | 1/144 | < 0.001 | 0.122 |
| PMR | Education | -0.386 | -5.13 | < 0.001 | 14.75 | 4/141 | < 0.001 | 0.295 |
| | Sex | -0.252 | -3.54 | 0.001 | | | | |
| | Res CMPAase | -0.243 | -3.36 | 0.001 | | | | |
| | Age | -0.186 | -2.53 | 0.013 | | | | |
| HAM-A | CMPAase | -0.350 | -4.80 | < 0.001 | 12.93 | 2/143 | < 0.001 | 0.153 |
| | Sex | 0.163 | 2.10 | 0.037 | | | | |
| Psychopathology index | CMPAase | -0.430 | -5.83 | < 0.001 | 19.94 | 3/141 | < 0.001 | 0.298 |
| | Education | -0.250 | -3.41 | 0.002 | | | | |
| | Overdominant model | -0.148 | -2.07 | 0.040 | | | | |
| MMSE | Education | 0.593 | 9.09 | < 0.001 | 54.48 | 2/142 | < 0.001 | 0.434 |
| | CMPAase | 0.175 | 2.69 | 0.008 | | | | |

BPRS: Brief Psychiatric Rating Scale; HAM-D: Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; MMSE: Mini Mental State Examination; PMR: Psychomotor retardation; Res CMPAase: Residualized (after regression on PON1 genotype); CMPAase: 4-(chloromethyl)phenyl acetate hydrolysis; Dominant and overdominant model: PON1 Q192R genotype models.

PON1 and CMPAase activities may play a role in the pathophysiology and progression of mood disorders[36]. In patients with anxiety disorders, decreased levels of PON1 are accompanied by high levels of lipid hydroperoxides as compared with individuals without anxiety[39,40]. CMPAase activity is also inversely associated with symptoms characteristic of (deficit) schizophrenia including PSY, negative symptoms and PMR[37]. The latter authors reported that CMPAase activity was significantly reduced in patients with schizophrenia and that this effect was, to a large extent, determined by increased frequency of the QQ genotype. Noto *et al*[41] reported a significant decrease in PON1 activity in drug-naïve patients with first-episode PSY.

Our results show that PON1 CMPAase activity is positively associated with the MMSE score, which is significantly reduced in TLE patients, suggesting that PON1 activity protects against cognitive decline in TLE. In this regard, epilepsy *per se* is accompanied by a neurocognitive decline[42]. In patients with schizophrenia, reduced PON1 activity is strongly associated with neurocognitive deficits[37], whilst in mood disorders, reduced PON1 status is associated with staging of the disorder, which is characterized by increased neurocognitive deficits[43].

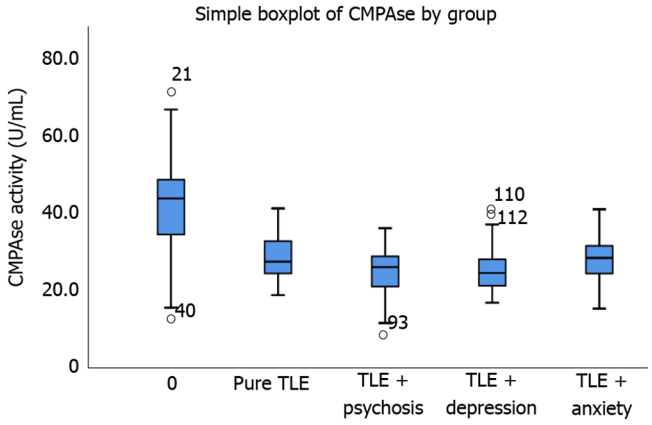


**Figure 1 Box plot of 4-(chloromethyl) phenyl acetate hydrolysis activity in controls (0), pure temporal lobe epilepsy (temporal lobe epilepsy: No comorbidities are present) and temporal lobe epilepsy with psychiatric comorbidities.** TLE: Temporal lobe epilepsy; CMPAase: 4-(chloromethyl)phenyl acetate hydrolysis.

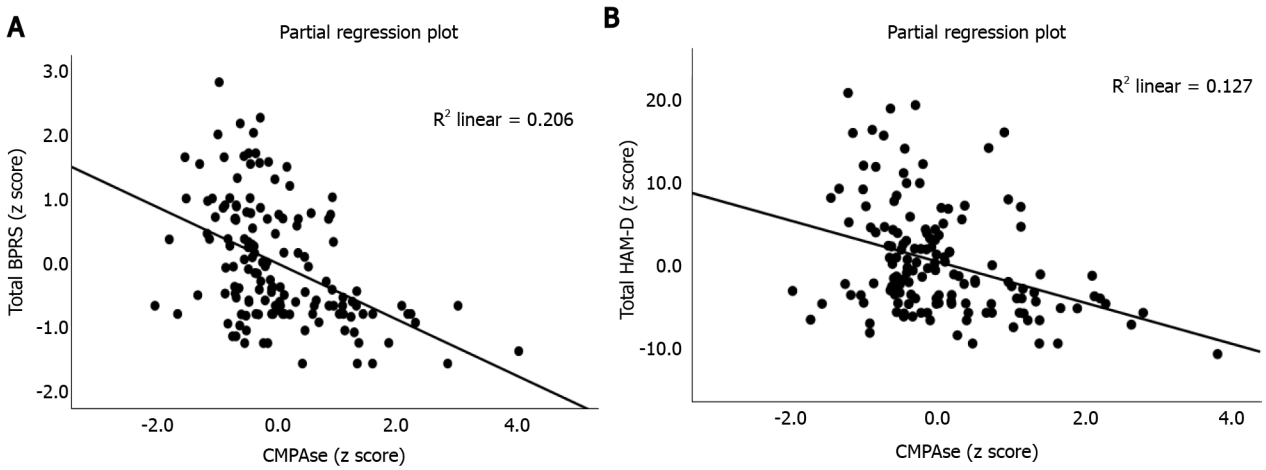


**Figure 2 The Brief Psychiatric Rating Scale score and total Hamilton Depression Rating Scale score on 4-(chloromethyl) phenyl acetate hydrolysis activity in 104 patients with temporal lobe epilepsy with and without comorbidities and 40 healthy controls.** A: Inverse association between the Brief Psychiatric Rating Scale score and 4-(chloromethyl) phenyl acetate hydrolysis activity in 104 patients with temporal lobe epilepsy with and without comorbidities and 40 healthy controls; B: The partial regression of the total Hamilton Depression Rating Scale score on 4-(chloromethyl) phenyl acetate hydrolysis activity in 104 patients with temporal lobe epilepsy with and without comorbidities and 40 healthy controls. BPRS: Brief Psychiatric Rating Scale; CMPAase: 4-(chloromethyl)phenyl acetate hydrolysis; HAM-D: Hamilton Depression Rating Scale.

The third major finding of this study is the significant association between the PON1 genotype and TLE features including seizure frequency, aura, postictal confusion, uncontrolled seizure type and TLE-associated psychopathology including severity of PSY, depression and anxiety. Thus, PLS path analysis revealed that the PON1 genotype, especially the QQ but also the QR, variants increase risk and severity of TLE and TLE-associated psychopathology and that the RR genotype is protective. Our study indicates that genetically determined decreases in PON1 CMPAase activity as well as reduced PON1 enzyme activities, which occur independently of the PON1 genotype, may be causally related to TLE and its psychiatric comorbidities. As such, alterations in CMPAase and PON1 activities, which are secondary to oxidative stressors[25,43], or environmental factors including nutritional factors and smoking may also be involved[25]. Nutritional factors that may affect PON1 activity include polyphenols, oleic acid, a Mediterranean diet, chokeberry and pomegranate juice, lipids, vitamin C and vitamin A[25]. Interestingly, tobacco use, which lowers PON1 activity, is associated with focal or generalized seizures[44,45], indicating that chemicals in tobacco smoke may have pro-convulsive effects [46]. Harmful and potentially harmful constituents in tobacco that may trigger seizures are carbon monoxide, toluene, cresol, arsenic, acetone, ammonia, lead and hexane[46].

PON1 is a detoxifying enzyme that is associated with HDL[40] and has anti-inflammatory[25] and antioxidant properties, including hydrolyzing lipid peroxides[47]. PON1 activity may protect against lipid, LDL and HDL oxidation and increase HDL's ability to increase cholesterol efflux from macrophages[48]. Furthermore, PON1 protects against macrophages' pro-oxidative effects, which produce free radicals and myeloperoxidase, resulting in the highly toxic peroxynitrite and hypochlorous

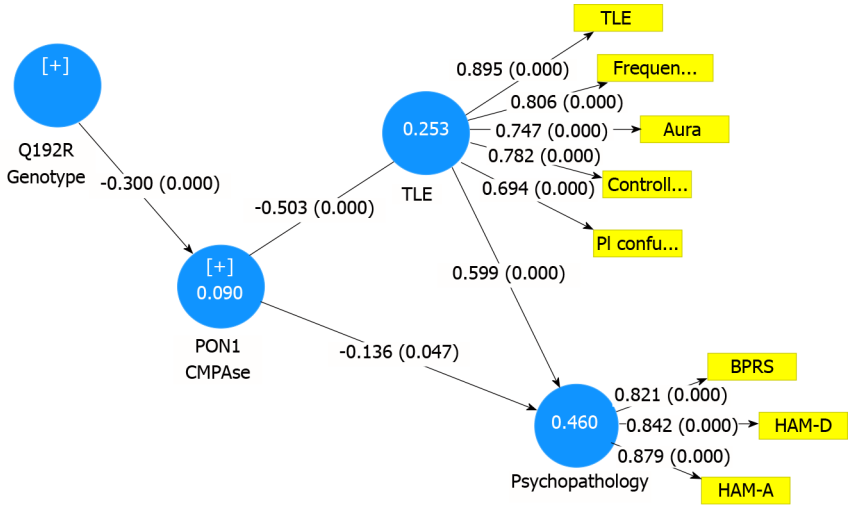


**Figure 3 Results of partial least squares path analysis with a latent vector extracted from three psychopathology dimensions as outcome variable and a latent vector extracted from temporal lobe epilepsy features, paraoxonase 1 activity and the Q19R paraoxonase 1 genotype (additive model) as input variables.** Shown are path coefficient with *P* value (between brackets). Frequency: Seizure frequency; Aura: Aura present or not; Controlled: Seizure free and fairly and poorly controlled seizures; PI confusion: History of post-ictal confusion; BPRS: Brief Psychiatric Rating Scale; HAM-D/HAM-A: Hamilton Depression and Anxiety Rating Scale scores; TLE: Temporal lobe epilepsy; CMPAase: 4-(chloromethyl)phenyl acetate hydrolysis.

acid[40]. Moreover, Borowczyk *et al*[49] reported that PON1 may hydrolyze homocysteine thiolactone, a toxic metabolite that can induce epileptic seizures in rats and is implicated in neurodegenerative disorders. Importantly, in oxidative stress conditions, PON1 may be damaged by increased myeloperoxidase activity and elevated production of peroxynitrite and hypochlorous acid, leading to reduced antioxidant defenses and thus an increased vulnerability to oxidation of LDL and HDL, which in turn will lower the protective effects of HDL[43]. Therefore, a well-functioning antioxidant system is important to prevent lipid peroxidation and conditions characterized by PON1 gene-associated decreases in PON1 activity (like TLE and MTS) are accompanied by increased risk to develop lipid oxidation.

There is now some evidence of increased oxidation of lipids[50,51] and lipid peroxidation occurring during TLE progression[15]. Moreover, experimental epilepsy/TLE models show increased hydroxyl radicals in the CNS[52], increased lipid peroxidation and reduced antioxidant defenses[15,15,53]. For example, Mojarad and Roghani[18] found increased lipid peroxidation and decreased superoxide dismutase activity in a kainic acid induced TLE model. The latter model is also accompanied by a decrease in the reduced form of glutathione in the hippocampus[19] and increased malondialdehyde, the end product of lipid peroxidation, in the piriform cortex[17]. Moreover, elevated malondialdehyde is associated with a greater vulnerability of the piriform cortex to seizure-induced damage. Lipid peroxidation can alter the permeability of the mitochondrial membrane and enzymes present in the membrane, possibly leading to neurodegenerative processes[12]. Therefore, the results of the current study suggest that reduced PON1 CMPAase activity, which is in part genetically determined, participates in the pathophysiology of TLE and MTS and the onset of comorbid psychopathology through increased oxidative stress. This mechanistic explanation may, at least in part, underpin the strong comorbidity between TLE and psychiatric symptoms. Moreover, the decrease in serum PON1 activity may explain the cognitive impairments in TLE/MTS. Previously, it was reported that reduced PON1 CMPAase activity is associated with cognitive deficits in schizophrenia and dementia[37]. For example, increased ROS levels may cause loss of inhibitory neurons in the hippocampus in patients with epilepsy and induce a hyperexcitability state, which can initiate reactive gliosis and, consequently, mitochondrial dysfunction leading to neurodegeneration[12].

### *Limitations*

Our results were adjusted for possible effects of sex, age, BMI and smoking, which may affect PON1 enzymatic activity and oxidative biomarkers[25]. All patients in the current study were medicated (AEDs or psychotropic drugs). Some studies, but not all, suggested that AED treatment may influence lipid peroxidation[54]. For example, treatment with levetiracetam may be accompanied by a decrease in serum PON1 and arylesterase activity and a significant increase in oxidized LDL[55]. Nevertheless, in our study, there were no significant effects of AEDs, antipsychotics or mood-stabilizing drugs on PON1 activity, and we found no associations between the number of AEDs patients were taking and PON1 enzymatic activity. Nevertheless, in the present study we did not control for duration of treatment with AEDs or antipsychotics on PON1 activities. Moreover, other studies found no significant differences in oxidative stress indicators between treated and untreated epilepsy patients[56,57]. Arylesterase activity

is not significantly different between chronically polymedicated psychiatric patients and controls, suggesting that treatment with psychotropic medications does not induce changes in arylesterase activity[25].

## CONCLUSION

The activities of CMPAse and arylesterase enzymes are significantly decreased in patients with TLE, especially MTS, as compared with healthy controls. The detrimental effects of the PON1 genotype on the severity of TLE, depression, PSY and anxiety are mediated by reduced CMPAase. The aberrations in PON1 status may play a key role in the oxidative pathophysiology of TLE, MTS and psychiatric comorbidities. PON1 enzymatic activity is a new drug target in TLE to treat seizure frequency and psychiatric comorbidities.

## ARTICLE HIGHLIGHTS

### *Research background*

Hippocampal sclerosis, also known as mesial temporal sclerosis (MTS), is the most common primary epileptic pathology, accounting for 36% of all focal epileptic pathologies. Depression, anxiety, and psychosis (PSY) affect between 30%–70% of temporal lobe epilepsy (TLE) patients. The pathophysiology of TLE, TLE progression, depression, anxiety and PSY is heavily influenced by oxidative pathways and decreased antioxidant defenses.

### *Research motivation*

The enzyme paraoxonase 1 (PON1) protects against lipid peroxidation, and its activity is influenced in part by a single nucleotide polymorphism in PON1. There has been no research that examined the links between PON1 status and mental comorbidities in TLE.

### *Research objectives*

The goal of this research was to look at PON1 status, namely 4-(chloromethyl) phenyl acetate CMPAase and arylesterase activities, as well as PON1 Q192R genotypes, in patients with TLE and MTS who had comorbid PSY, depression and anxiety.

### *Research methods*

This is a case-control study that examined 104 patients with TLE and 40 normal controls. TLE patients were divided according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision criteria into: (1) Mood disorders due to TLE with depressive features ($n$ = 25); (2) Anxiety disorders due to TLE ($n$ = 25); (3) Psychotic disorder due to TLE ($n$ = 25); and (4) "Pure TLE" when there were no psychiatric comorbidities. After an overnight fast, blood samples were obtained at 8:00 a.m., and serum was aliquoted and kept at -80 °C until thawed for total PON1 activity (PON1Q192R polymorphism, and arylesterase and CMPAase activities). Data were analyzed using partial least squares pathway analysis.

### *Research results*

PON1 activities were significantly lower in TLE patients than those in controls. The area under the receiver operating characteristic curve using lower CMPAase activity as discriminatory variable was 0.893 (0.037) for TLE and 0.895 (± 0.037) for MTS. We found that 46.0% of the variance in the severity of depressive, anxiety and psychotic symptoms was explained by the severity of TLE features and PON1 CMPAse activity while 25.3% of the variance in TLE severity was explained by CMPAase activity. PON1 QQ and RR, but not QR, had significant effects on severity of TLE and comorbid psychopathology.

### *Research conclusions*

In individuals with TLE, particularly MTS, the activity of CMPAse and arylesterase enzymes are much lower than in healthy controls. Reduced CMPAase mediates the negative effects of the PON1 genotype on TLE, depression, PSY and anxiety severity.

### *Research perspectives*

Changes in PON1 status play a role in pathophysiology of TLE, MTS and mental comorbidities. PON1 enzymatic activity is a novel therapeutic target in TLE for the treatment of seizure frequency and mental comorbidities.

## FOOTNOTES

**Author contributions:** All the contributing authors have participated in the manuscript; Kanchanatawan B and Maes MHJ designed the study; Kanchanatawan B and Limothai C recruited patients and completed diagnostic interviews and rating scale measurements; Maes MHJ carried out the statistical analyses; all authors contributed to interpretation of the data and writing of the manuscript and approved the final version of the manuscript; Kanchanatawan B and Barbosa DS shared senior authorship.

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**Informed consent statement:** All participants in this study gave written informed consent form before participating in the study.

**Conflict-of-interest statement:** The authors have no conflict of interest with any commercial or other association in connection with the submitted article.

**Data sharing statement:** The dataset generated during and/or analyzed during the current study will be available from the corresponding author upon reasonable request and once the dataset has been fully exploited by the authors.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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ORIGINAL ARTICLE

Observational Study

# Importance of communication in medical practice and medical education: An emphasis on empathy and attitudes and their possible influences

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## Abstract

*BACKGROUND*

Healthcare professionals need to be prepared to promote healthy lifestyles and care for patients. By focusing on what students should be able to perform one day as clinicians, we can bridge the gap between mere theoretical knowledge and its practical application. Gender aspects in clinical medicine also have to be considered when speaking of personalized medicine and learning curricula.

*AIM*

To determine sets of intellectual, personal, social, and emotional abilities that comprise core qualifications in medicine for performing well in anamnesis-taking, in order to identify training needs.

*METHODS*

An analysis of training clinicians' conceptions with respect to optimal medical history taking was performed. The chosen study design also aimed to assess gender effects. Structured interviews with supervising clinicians were carried out in a descriptive study at the Medical University of Vienna. Results were analyzed by conducting a qualitative computer-assisted content analysis of the interviews.

Inductive category formation was applied. The main questions posed to the supervisors dealt with (1) Observed competencies of students in medical history taking; and (2) The supervisor's own conceptions of "ideal medical history taking".

***RESULTS***

A total of 33 training clinicians ($n$ = 33), engaged in supervising medical students according to the MedUni Vienna's curriculum standards, agreed to be enrolled in the study and met inclusion criteria. The qualitative content analysis revealed the following themes relevant to taking an anamnesis: (1) Knowledge; (2) Soft skills (relationship-building abilities, trust, and attitude); (3) Methodical skills (structuring, precision, and completeness of information gathering); and (4) Environmental/contextual factors (language barrier, time pressure, interruptions). Overall, health care professionals consider empathy and attitude as critical features concerning the quality of medical history taking. When looking at physicians' theoretical conceptions, more general practitioners and psychiatrists mentioned attitude and empathy in the context of "ideal medical history taking", with a higher percentage of females. With respect to observations of students' history taking, a positive impact from attitude and empathy was mainly described by male health care professionals, whereas no predominance of specialty was found. Representatives of general medicine and internal medicine, when observing medical students, more often emphasized a negative impact on history taking when students lacked attitude or showed non-empathetic behavior; no gender-specific difference was detected for this finding.

***CONCLUSION***

The analysis reveals that for clinicians engaged in medical student education, only a combination of skills, including adequate knowledge and methodical implementations, is supposed to guarantee acceptable performance. This study's findings support the importance of concepts like relationship building, attitude, and empathy. However, there may be contextual factors in play as well, and transference of theoretical concepts into the clinical setting might prove challenging.

**Key Words:** Medical history taking; Attitude; Empathy; Training; Physicians' view

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**Core Tip:** The findings in this study underline the importance of paying attention to core competencies in medicine and medical students' socialization and training. Enriching self-assessments with observer-based reflections, as carried out in this investigation, seems to be a valid approach to identify training needs. Tolerance of ambiguity and openness to self-reflection, as demonstrated by the participants in our study, might be relevant in this context. Empathic relationships shape embodied empathy, result in embodied skills, and shift an individual's perception.

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## INTRODUCTION

Freud's advice for physicians practicing psychoanalysis was to not concentrate on details and rather surrender one's attention- the optimal mental state of an analyst: "withhold all conscious influences from his/her capacity to attend, and give himself/herself over completely to his/her 'unconscious memory'"[1].

This attitude differs a great deal from most clinical settings nowadays, due to necessary domain-based medical skills. The rapid medical technology developments in the last decade (*e.g.*, digital innovations like remote monitoring/mobile apps, medical devices, and robotic systems/machines controlled by a doctor and mixed reality in education) shape all healthcare fields. Nevertheless, as medicine is practiced for and by human beings, human factors are predominant in all interactions. To infer the workings of a patient's mind is a challenging task, and accepting uncertainty and incompleteness of our understanding is an unavoidable recognition[1,2]. Thus, personal and interpersonal competencies are relevant in meeting the needs of the health system, together with expert

knowledge and skills[3].

Interpersonal skills are especially relevant when taking a patient's history[4]. Guidelines for general medical history taking skills usually include a semi-structured interview manual that suggests a structured approach, in order to ensure professionalism[5,6]. In addition, communication components, such as relationship-building, trust, and respect, are established as markers for quality care[4]. The level of evidence supporting methods of developing these abilities, as well as medical professionalism, is limited[7,8]. Frameworks for communication-oriented curricula have been developed because the importance of building a relationship was found to be one of the core competencies in the physician-patient interaction[9-13].

An essential concept with a great impact on the quality of communication and professionalism is empathy. Empathy has been shown to be trainable but might depend on personality[14-18]. Through empathy, it is possible to improve the patients' compliance, satisfaction, clinical outcome, and decrease (interestingly enough) the possibility of a lawsuit[17-26]. Empathy describes a semi-voluntary, and in some conceptualizations, innate ability to share affective states with others, and requires a certain curiosity. Definitions of empathy overlap with another important concept, that of mentalization. Mentalizing (Theory of Mind) is the ability to interpret one's own and others'' mental states (*i.e.* intentions, beliefs)[27,28]. Key dimensions of empathy have been widely enumerated: emotive, cognitive, behavioral, and moral[29]. Such comprehension requires differentiating between one's own and others' mental states. This ability develops in repeating social interactions that result in the development of the Self, adequate affective regulation, and attachment patterns, and that mediate prosocial behavior[30,31]. Education of medical professionalism is compromised by a decline in empathy[32-34]. Protective factors and predictors of higher empathy include: resilience against stress, social support[35,36], agreeability, and conscientiousness[37].

Competency-based training in health care puts focus on applied knowledge and thus on improving practice[38,39]. More than 50% of patients support a participative approach with shared-decision making based on transparency[40,41]. In such a patient centered approach (PCA), the patient's values, perspective, and circumstances are respected[19,42-44]. Collaboration and coordination of available services at a systems level with resource allocation continuity and improved quality of services are other features of PCA[40]. The effects of PCA have been widely researched: increased adherence to therapy among patients has been demonstrated[45], as well as reduced recovery times[25], decreased mortality [46], improved quality of life[47], and improved general health[48]. To enable the patient to be part of the decision-making process, physicians must provide understandable information[49-51]. Compassion-based interventions and a relationship built on a solid affect-cognitive level are key features[44,49].

### Aim of the study

Developing core abilities in medical professionals is relevant to improving individualized medical care. The key questions are, (1) What are the core competencies in medical history taking; and (2) What are the prerequisites to ensuring a "good" anamnesis? From a theoretical point of view, we hypothesized that empathy might be one of the identifiable themes independent of specialty and that gender effects might exist.

## MATERIALS AND METHODS

### Study design and setting

A qualitative descriptive study was carried out at the Medical University of Vienna (MedUni Vienna) between June 2015 and April 2016. Assumptions and views of instructors regarding desirable core competencies in medical history taking were extracted from interviews with clinicians.

### Study population

All attending physicians had been practicing physicians for more than 10 years and had been instructors, mentors, and/or tutors at the MedUni Vienna.

### Inclusion and exclusion criteria

The exclusion criteria were (1) Missing written informed consent, and (2) Professional experience of fewer than 10 years. Health care professionals not engaged with medical student supervision and training were also excluded from the survey.

### Sampling methods

More than 5000 health care professionals were invited to participate in the study *via* an internal communication listserv for teaching clinicians and university teachers *via* MedUni Vienna-list.

The instructors were chosen by Löffler-Stastka H according to the representation of medical specialties in Vienna/Austria in order to reflect this real-life distribution. Unfortunately, the original aim of equal numbers of male and female physicians interviewed could not be met due to the actual

gender distribution of physicians in Vienna/Austria.

### Sample size

Thus, 33 attending physicians who both agreed to participate in the study and matched the required specialty-distribution were included.

### Instruments

The interview was standardized and semi-structured, with 16 open-ended questions developed by an interdisciplinary team. The questions allowed free association in order to carry out qualitative content analysis[52]. Questions about the interviewee's own experience in communication and medical history taking and their experience with and memory of their observed medical student's performance during training at their department were investigated. The interviews were all carried out personally at the MedUni Vienna; the setting did not change considerably (interview duration: 45 min). The attending physicians' interviews were all carried out by four different female interviewers (three medical students and one educational scientist). These interviewers were instructed and supervised by Löffler-Stastka H.

The interviews were audiotaped, transcribed, and imported into the program Atlas.ti[53]. Standard background questions (age/specialization of the attendant physician) were asked at the beginning of the interview.

### Analysis of the interviews

Results were analyzed by conducting a qualitative computer-based content analysis of the interviews [54] using the program Atlas.ti.

For more information about these methods and content analysis, please refer to the diploma thesis of Zervos, K[52].

### Ethical issues

The study design complies with the ethical standards set forth in the Declaration of Helsinki. This study was reviewed and approved by the Ethics Committee of the Medical University of Vienna (EK-Nr. 1381/2015).

As the questions did not include questions about any individual student's performance, but rather relied on the memory and experience of the interviewee, supervised students remained anonymous to the interviewers and the authors of the current study.

## RESULTS

As mentioned above, the distribution of specialties in this study is similar to the Viennese/Austrian population of clinicians[52]. Thirteen of the 33 interviewed attending physicians were female, and the remaining 20 were male. In Table 1 we present the distribution of attending physicians in terms of their specialties and sex.

### The "ideal patient history"

Associations of the participating attending physicians in this study can be arranged into positive (knowledge, ability to establish a relationship/trust, structure, accuracy and attitude/empathy; Figure 1) and negative ones (language barrier, lacking trust/relationship, or time, interruptions, incomplete) (Table 2).

"Knowledge" was the requirement most often identified in experts speaking about medical history taking; 24 participants mentioned knowledge. Physicians were allowed to mention themes several times. When counting the quotes per specialty/specialty group and correcting for the number of participants per group, general practitioners, pediatricians and non-surgical subspecialties (*e.g.*, psychiatrists, anesthetists, *etc.*) scored highest, while surgical specialties, surgical subspecialties and internists scored lower (Table 3). No gender-specific difference was found. The theme "structure" was mentioned by 20 participants, often in conjunction with "knowledge".

"Establishing a relationship" was another recurrent theme; it was found in 22 of the interviews, with a total of 53 quotes about it. The "ability to create trust" was mentioned in strong association with the attachment-related category. Most quotes on relationship-building were collected from interviews with non-surgical subspecialties, general surgeons, and pediatricians (Table 4). Interestingly, internists and surgeons from surgical subspecialties (ENT, gynecology) mentioned this ability the least often.

When asked about what they considered an ideal anamnesis, 19 attending physicians mentioned the health professionals' "attitude and personality" as important, with a presumably positive impact on the quality of the patients' history-taking process.

Furthermore, in 15 interviews, "empathy" was isolated as being important (21 quotes). Representatives of general medicine and psychiatry often mentioned quotes relating to "attitude" and "empathy" in ideal history taking (Figure 2). In regards to the mention of "attitude", we saw a minor gender-

**Table 1 Specialization and sex**

| Group | Specialty | Sex | | Total (*n* =32) |
|---|---|---|---|---|
| | | Female (*n* = 13) | Male (*n* = 19) | |
| Internal medicine | General internal medicine; Gastroenterology; Cardiology | 3 | 4 | 7 |
| Surgical specialties | General surgery; Neurosurgery; Visceral surgery; Thoracic surgery; Vascular surgery | 2 | 4 | 6 |
| Surgical subspecialties | Gynecology; ENT | 1 | 2 | 3 |
| Non-surgical subspecialties | Anesthesiology; Neurology; Psychiatry | 2 | 4 | 6 |
| Pediatrics | Pediatrics; Child and adolescent psychiatry | 0 | 3 | 3 |
| General medicine | General medicine | 5 | 2 | 7 |

Demographic data were assessed at the beginning of each interview for each participant *via* questionnaire. For one participant, the information regarding specialty was not available. This participant was included in the qualitative data analysis only when this information was not relevant.

**Table 2 Ingredients of the "ideal medical history taking": Identified themes**

| | | Percent | *n* = 33 |
|---|---|---|---|
| Positive associations | | | |
| Knowledge | | 72.73 | 24 |
| Relationship building: + | | 66.67 | 22 |
| | Trust: + | 39.40 | 13 |
| Structure | | 60.61 | 20 |
| Precision | | 60.61 | 20 |
| Attitude | Personality | 57.58 | 19 |
| | Empathy | 45.45 | 15 |
| Negative associations | | | |
| Language barrier | | 33.33 | 11 |
| Relationship building: - | | 48.48 | 16 |
| | Trust: - | 15.15 | 5 |
| Incomplete information gathering | | 27.27 | 9 |
| Time pressure | | 30.30 | 10 |
| Interruptions | | 18.18 | 6 |

Qualitative data analysis was carried out as explained in the method section (step model of inductive category development). Themes were extracted from the audiotaped interviews. The table shows the number and percentage of interviews a theme was identified within.

specific difference: 61.53% of questioned female attending physicians made quotes relating to "attitude" as an important tool in history taking as opposed to 55% of their male colleagues.

With respect to mentioning "empathy", we were able to identify a robust gender-specific frequency in favor of female attending physicians: 61.54% of questioned female attending physicians mentioned "empathy" in the context of a favorable influence on history taking, whereas only 35% of male colleagues made similar quotes.

The opposite was true for "precision", identified in 20 interviews (25 quotes). "Precision" was mostly mentioned by male physicians (70%). However, "precision" was, above all, found to be especially important to surgeons, with a higher percentage of males in this subgroup (66.67%).

### *Desirable student skills*

When remembering their students' overall performance and reflecting upon desirable characteristics in anamnesis taking, the importance of knowledge (69.70%, *n* = 23) and showing interest for the patient (63.64% *n* = 21), together with attitude (66.67%, *n* = 22), empathy (33.33%, *n* = 11), and structure (51.52%,

**Table 3 Quotes on the importance of knowledge**

| | % quotes | *n* quotes | *n* specialists | *n* (q)/*n* (s) |
|---|---|---|---|---|
| Internal medicine | 13.96 | 6 | 7 | 0.86 |
| General medicine | 27.90 | 12 | 7 | 1.71 |
| Non-surgical subspecialties | 20.93 | 9 | 6 | 1.50 |
| Paediatrics | 11.63 | 5 | 3 | 1.67 |
| Surgical specialities | 18.60 | 8 | 6 | 1.34 |
| Surgical sub-specialities | 6.98 | 3 | 3 | 1.00 |
| Total | 100 | 43 | 32 | |

The percentage and frequency of quotes about the importance of knowledge are shown for each specialist group. Multiple statements on each theme were possible for each participant. It is to be noted that considering the different number of specialists in each group, the number of quotes per group alone is not an accurate measure of the distribution of quotes in the groups. The quotient of the number of quotes in each group per number of specialists was highest for general medicine, pediatricians, and non-surgical subspecialties (1.71, 1.67, and 1.50 respectively).

**Table 4 Quotes on the importance of relationship establishment**

| | % quotes | *n* quotes | *n* specialists | *n* (q)/*n* (s) |
|---|---|---|---|---|
| Internal medicine | 7.55 | 4 | 7 | 0.57 |
| General medicine | 18.87 | 10 | 7 | 1.43 |
| Non-surgical subspecialties | 32.08 | 17 | 6 | 2.83 |
| Paediatrics | 11.32 | 6 | 3 | 2.00 |
| Surgical specialities | 26.42 | 14 | 6 | 2.33 |
| Surgical sub-specialities | 3.77 | 2 | 3 | 0.67 |
| Total | 100 | 53 | 32 | |

The percentage and frequency of quotes about the importance of relationship establishment are shown for each specialist group. Multiple statements on each theme were possible for each participant. It is to be noted that considering the different number of specialists in each group, the number of quotes per group alone is not an accurate measure of the distribution of quotes in the groups. The quotient of the number of quotes in each group per number of specialists was highest for non-surgical subspecialties, surgical specialties, and pediatricians (2.83, 2.33, and 2.00 respectively).

$n$ = 17) were mentioned more often than experience (36.36%, $n$ = 12).

### *Memories of observed skills*

When asked to remember one concrete example of a student taking a medical history, health care professionals described empathic behavior and a positive attitude as much as they did the lack of it. Concerning the students' performance, attitude and showing empathy/empathic behavior were included in one coding.

**Positive aspects:** Observed students' interest, motivation, and engagement were remembered by 16 attending physicians (48.48%).

Eleven of the attending physicians mentioned their students' attitude in the context of having a positive impact on the quality of their respective history taking (34.38%). Three of the physicians mentioning attitude were female and eight were male (*i.e.* 23.08% of all questioned female physicians, and 35% of all interviewed male physicians). We identify this as a gender-specific difference. These observations were equally distributed among all represented specialties.

**Negative aspects:** When asked to remember observations perceived as unfavorable, poor precision or incompleteness (54.55%; $n$ = 18), insufficient structure (due to inadequate knowledge 24.14% or failed clinical reasoning 15.15%) were often mentioned.

Attitude was observed to influence the medical history taking negatively by 11 (33.33%) of the attending physicians. No gender-specific effect was found.

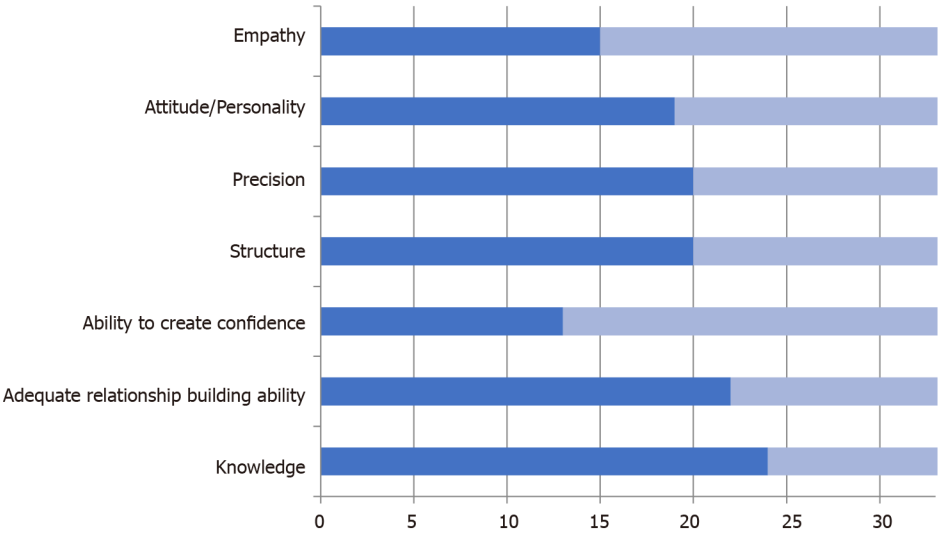


**Figure 1 Theoretical conception: Ingredients of the ideal medical history taking.** The figure shows theoretical conceptions about medical history taking only. The frequency with which a quote about a specific theme was identified in the qualitative analysis of the interviews is shown. Thus, multiple answers were possible for each participant.

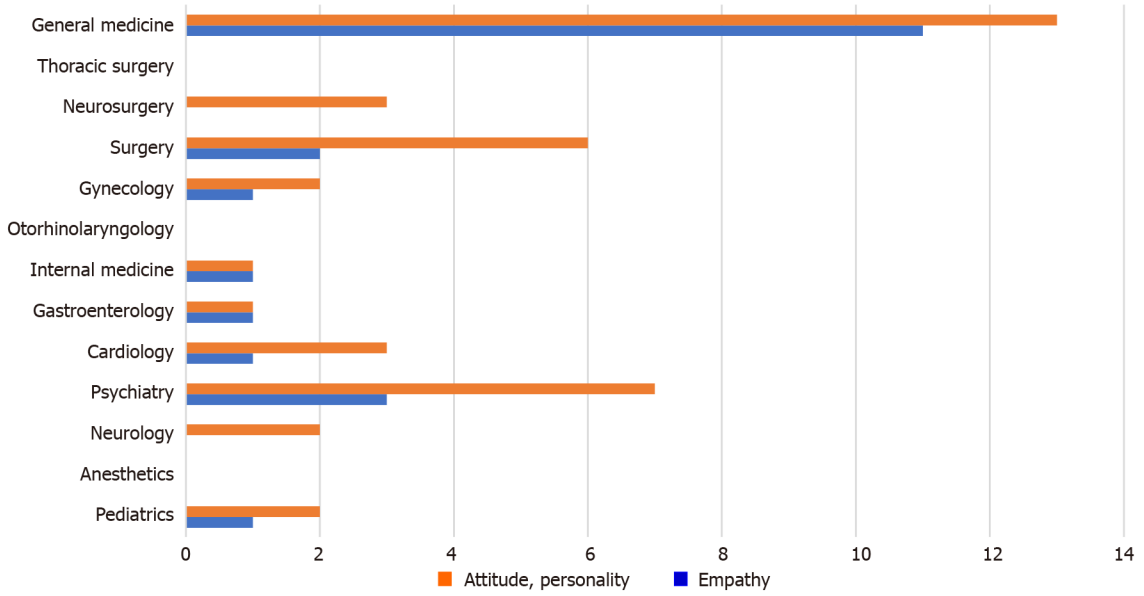


**Figure 2 Quotes about empathy and attitude.** Theoretical conceptualizations about necessary features required for a student's medical history taking were discussed in this part of the interview. The figure shows the frequency of quotes about empathy and attitude, identified per specialization as taken from the content analysis. Multiple quotes per participant and theme were possible. As mentioned in the results section, "attitude" was mentioned in 22 interviews (8 females, 14 male), while empathy was mentioned in 11 (6 females, 5 males).

## DISCUSSION

Dimensions identified as being relevant to anamnesis-taking included "knowledge" (mentioned by 24 participants), soft skills ("empathy", "relationship building ability", "trust", "attitude"), methodical approach ("structuring", "timing", "precision", "completeness of information-gathering"), as well as environmental ones ("time pressure", "interruptions", "language barrier").

As the interview asked about memories of ideal anamnesis-taking, and two categories were already given through the structure of the questions (*i.e.* positive *vs* negative associations), we suggest that future research should explore the identified dimensions along a continuum ranging from "ideal" to "abysmal".

One of the observations made in the present investigation was that negative associations were at first in timing, or more readily made by most participants when freely associating about taking an anamnesis. Thus, experience might lead to insight into the pitfalls of human conversations. Another explanation for this could be implicit bias found in the effects of supervision and quality control.

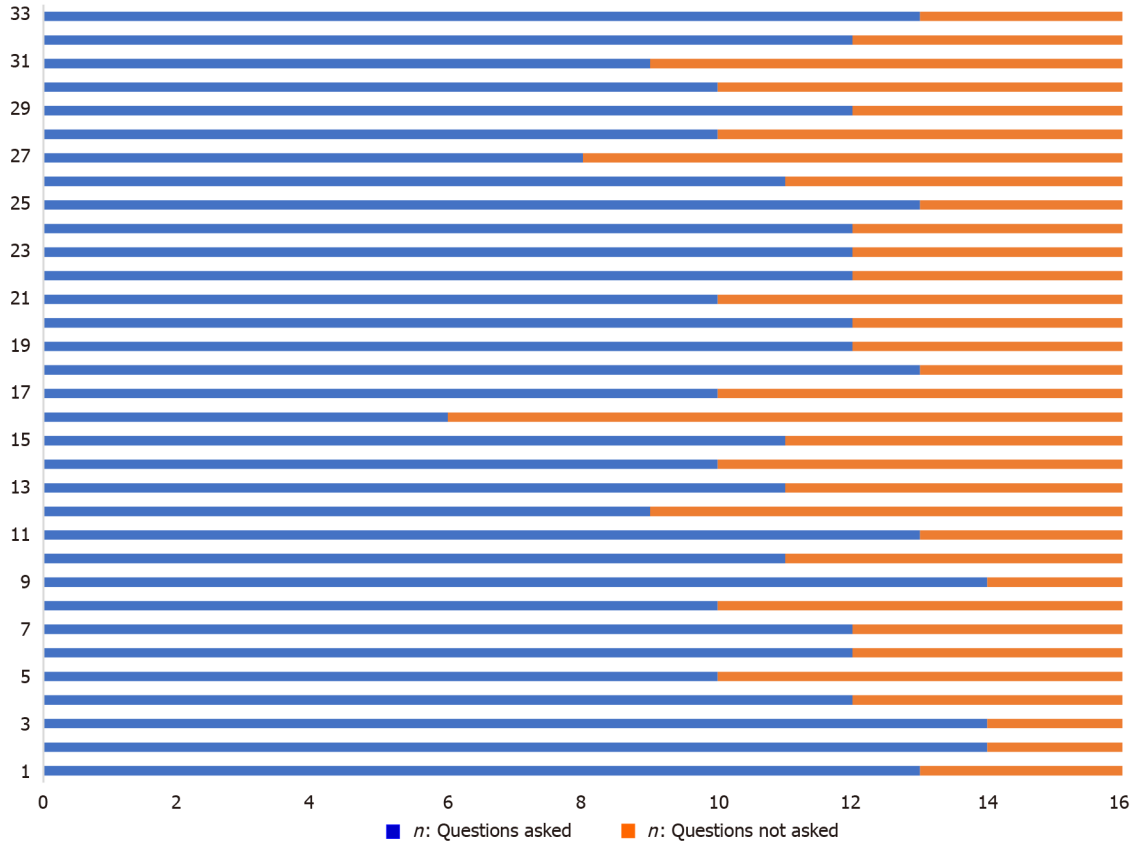


**Figure 3 Questions asked per interview.** This figure shows the number of questions asked per interview, as discussed in the limitation section. Blue: Number of questions asked in interview 1-33. Number of available questions: 16. Number of interviews: 33.

In assessing memories and observations, due to the known link between affective loading, accessibility, and storage of memory contents, the categories derived from this analysis are likely to be more accessible to clinicians in their actual clinical environment. An interview indirectly assesses the expert's ability to mentalize one's own and others' mental states. Overall, experts showed a reflected and integrated view, mentioning both positive and negative memories.

In the present qualitative analysis of interviews on memories regarding anamnesis, relationship-building was mentioned to be an important skill, as was empathy.

Although the frequency of quotes that emphasize the importance of knowledge, attitude, and empathy differed among the included specialty groups (*i.e.* *n* quotes about a specific theme/*n* participants of the group), this finding must be interpreted with caution. What does it really mean if a theme is mentioned more than once by a given participant in a semi-structured interview? One ability often mentioned in conjunction with "knowledge" by the participants in this actual study was the ability to structure a discourse. To discuss a matter in a structured way within a limited timeframe, it may be sufficient to mention the importance of a specific theme once and then proceed to the next. However, mentioning the importance of something multiple times could also be a way of addressing the importance of the subject. Thus, it might be the case that observed differences between specialties do exist (Table 3 and Table 4). The importance of knowledge was mentioned most often by general practitioners, pediatricians, and non-surgical specialties. The ability to establish a relationship was mentioned most often by non-surgical subspecialties, general surgeons, and pediatricians.

Integrating knowledge from different disciplines will become more challenging as scientific findings expand.

Interestingly, when asked to remember a concrete example of a student performing a good anamnesis, interest, motivation, and engagement were the main themes. Differing themes arose only when freely associating about theoretical history taking. Methodical issues prevailed when remembering a negative example (*i.e.* lacking precision, completeness, structure). Environmental aspects and explicitly pronounced relationship-building factors (besides engagement) were not mentioned in this context, either meaning that actual medical history taking does not usually lack these aspects, or that suppression impeded the memories of said aspects in contrast to when the task consisted predominantly of recall and theoretical conceptualization.

Interventions aiming to enhance students' communication skills often lack both effectiveness and comparative effectiveness analyses[55]; further research on this topic is needed.

Enhancing learning, especially the accessibility of learned memory contents when related to skills and applied knowledge (*i.e.* not to recall theoretical knowledge), has been extensively investigated. Accessibility of attitudes from memory seems to be a function of the manner of attitude formation. With regards to attitude, one can distinguish the process of attitude formation, attitude accessibility, and attitude-behavior consistency, such that one may begin to investigate how and which specific attitudes affect later behavior[56]. A meta-analysis assessing factors relevant to attitude-behavior relation found that direct behavioral experiences produce stronger object-evaluation associations and more accessible attitudes. Behavior is determined by attitudes that are accessible and stable over time, and that affirm effects of direct experience, attitude, and confidence based on one-sided information[57].

The role of affectivity in attitude formation and its role in knowledge and skill development is obvious. Emotion seems to guide attention in learning and determines the availability of memory contents[58]. The so-called "seeking system" initiates memory and learning, as well as generating positive emotions, hope, expectancy, and enthusiasm[59].

The relevance of embodied empathy for learning has also been suggested[60]. Observation and imitation in empathic social relationships lead to the acquisition of embodied skills. A synchronization of intentions and movements seems to occur in empathic relationships with skilled practitioners, shaping the student's perception[58]. Describing embodied knowledge is difficult, as it is not mediated through words alone, but rather learned through lived and shared experiences that established meaning.

Empathy has been classified as a basic relationship skill involving resonance and communication, and is especially relevant when aiming at patient-centered care[20,48,61]. An intrinsic disposition for empathy has been claimed and has been shown to be trainable[14-16,62-64].

Empathy levels in practitioners and therapists are quite variable. Health care professionals with high levels of empathy seem to be more vulnerable to stress-related mental conditions (*e.g.*, burn out/exhaustion and compassion fatigue)[65-67] with a protective role of compassion satisfaction, and sensory processing sensitivity as a risk factor[68].

Studies assessing empathy in students often rely on self-assessment. Self-perceived empathy declines during medical school[18,24,36,69-72] and seems to depend on specialty choice[33,34,72], with higher perceived empathy in patient-oriented specialties. The decrease in empathy can be attributed to increased negative emotions such as stress and anxiety, which are highly dependent on context (*e.g.*, workload, exposure to suffering and death, work hours, sleep deprivation) and impede empathy[18,35,70,73,74]. With the increase of negative affects during medical formation, remembering negative contents is more likely to influence accessible attitude.

How physicians spend their time during their workday has been analyzed for different specialties with very different profiles of work tasks and emphasis on communication skills, work-related stress, and job satisfaction[75-77].

Analysis of empathy profiles of psychotherapists shows a four-way dependence on competence in perspective taking, their tendency to experience personal distress, their fantasy (*i.e.* their ability to identify with fictional characters), and their empathic concern (*i.e.* the ability to feel compassion towards a person in distress)[78]. The profiles distinguish between types that may be characterized as "average", "insecure-self-absorbed", therapists showing "empathic immersion", and those who are "rational empathic". With experience, the "rational empathy" becomes more prevalent.

A given clinician's empathic range and flexibility seem to be modifiable independent of context; however, circumstances can influence them. Emergency settings, for example, have been shown to produce a high level of burnout frequency[79,80], which reduces predisposition for empathic behavior.

Especially interesting is the observation of students' positive attitude and empathic behavior and their positive impact on the quality of history taking as perceived across all specialties, instead of merely mentioning attitude and empathy as important tools on a theoretical level. Physicians mentioning attitude and empathy in the theoretical context of ideal history taking represent predominantly general medicine and psychiatry, and are mainly female. The observation of the positive impact of attitude and empathy on actual student history taking is described mainly by male health care professionals, without showing any predominance of specialty. Again, accessibility of memory contents depends on the content's affective links and its links to real experience[59,81,82]. Cognitive processes are influenced by emotions[83]: "Substantial evidence has established that emotional events are remembered more clearly, accurately, and for longer periods than are neutral events"[59]. Thus, contents normally less accessible are easier to remember when an actual experience is associated. The fact that more women mention attitude and empathy even when theorizing, whereas men only do so when remembering an actual observation, could indicate a difference in perceived value and importance of the theme, perhaps due to different socialization, among other things.

Observations of healthcare professionals are supported by extensive data describing the practitioners' positive impact on patient health, shortening the diagnostic process[23-26].

When dealing with embodied knowledge, there may be a gap between recalled themes and the actual performance of practitioners, particularly as evidence shows that empathic therapists show this (socially desirable) behavior rather automatically, independent from their conscious intention or personality. However, it is to be noted that even if attitude (including empathy) is described by fully one-third of the questioned attending physicians as having been observed among students (with positive impact on

their history taking), a similar proportion of them recognize deficits in this area. Interventions promoting empathy and improving attitudes, including underlying processes of self-reflection and mentalization, could enhance the acquisition of this skill[84-88].

Attitude is particularly influenced by those more senior than us[89]. Therefore, change cannot only be implemented at the undergraduate-level but must also impact the postgraduate system.

Whether perspective representation or simply a sensitivity to the perspective of others is necessary for successful communication has been questioned; however, the importance of perspective-taking for systematic success is well known[90]. Forming representations of the mental and affective states of others determines attachment and mind-reading abilities[82]. Memory and attention processes have an important role in enabling communication[91,92]. Becoming sensitive to one another's perspective can happen due to contextual effects, like when information is made available from priming and automatic recall, together with attention cueing[90]. When trying to mentalize, retrieval of memory traces that include or overlap with all kinds of information that is shared occurs[91]. Cues about what a person might already know about what she/he can see or hear (*e.g.*, conversational common ground, knowledge, local routines, *etc.*) might be accessible. How a person perceives reality, however, might be a less straightforward guess to make. A modulating role for such memories in mentalizing abilities has been suggested. When mentalizing, whole events (real or imagined), as well as episodic memories linked to the target person, are remembered and become (mentally) ingrained. Thus, the content and quality of imagination might play a central role in more or less adequate attributions of mental states [82].

However, using one's own theories of mind to infer others' intentions requires motivation and effort [90,93]. Experiments by Lin *et al*[93] showed that attention-demanding secondary tasks reduce people's ability to mentalize. Lower working memory capacity predicted less effective use of the theory of mind.

Thus, the everyday routine in clinical settings, what with the necessity of shiftwork, multi-tasking, as well as frequent interruptions, might negatively influence performance[94], learning, and accessibility of memory (including attitudes). Moreover, other skills not considered essential by financing bodies of healthcare providers may also fall by the wayside. Contemporary health finance policies might increase pressure to focus on higher-paying tasks, potentially incentivizing unfavorable behaviors. However, evidence for empathy and attitude in learning and for outcomes in healthcare already exists.

Future research into social cognition in health care should focus on the conditions that increase the likelihood that other perspectives are represented during conversations, counterbalance an egocentric perspective, and enhance behavior.

Experience-based training programs could address the gap between theoretical conceptions of the importance of empathy for self- and patient care, as well as improve mentalizing and emotional regulation, which is necessary for letting empathy guide social behavior. These interventions implement specific feedback mechanisms that are easy to establish in clinical contexts, such as peer-supervision, once the basic concept is taught[18]. Remembering, collecting, and using the information to predict what others think, feel, or might do depends on an individual's cognitive abilities, context, and disposition. Research into the mechanism of change revealed that change most likely happens when intense and enduring negative affect accumulates; thus, motivation to modify views first arises, followed by a systemic reorganization.

### *Limitation*

As the interviews were conducted in a semi-structured way, and open-ended questions were predominant, the number of questions varied between the interviews due to time constraints. Also, after 17 interviews, one additional question was added to the initial catalog of 15 questions. No question was asked in every interview. For the percentage of questions asked, see Figure 3. The number of questions asked ranged from 6 to 14 (mean = 11.30, SD = 1.79), with an average of 4.70 questions not asked. However, questions overlapped in terms of their subject, as the questionnaire aimed to investigate the topic in depth from different viewpoints.

Inductive category development as a way of qualitative content analysis has been questioned, because derived definitions do not appear to be functionally justified, and practical relevance has been doubted[95,96]. Alternative frameworks for category formation have been recommended, suggesting that coding decisions should be made in accordance with the individual study at hand. However, regarding the current investigation (explorative design), inductive category formation was adequate in minimizing the possible influence of preexisting assumptions.

One should also account for possible bias arising from all interviewers being female.

Finally, our sample size was somewhat small ($n$ = 33), as the approach was a hypothesis-generating one. Nevertheless, our sample might be quite representative, as the number of participants per sub-specialty was selected according to the distribution of medical sub-specialties in Austria. However, depending on circumstances (*e.g.*, clinical department differences) and socialization, conceptions of the importance of empathy and communication might vary.

## CONCLUSION

Our findings show that dimensions identified as being relevant to anamnesis-taking included expert knowledge-related skills, as well as soft skills, methodical, and environmental ones.

The analysis of interviews adds to the ongoing theoretical discussion of competency-based education in medicine.

## ARTICLE HIGHLIGHTS

### *Research background*

If a change should be facilitated - either in individual patients for a better health status, or society at large for overcoming difficult circumstances - understanding of minds, reflection and empathy is needed. These change processes with the mentioned ingredients should be assessed further for the long run.

### *Research motivation*

Knowing one's own mind to transform oneself is essential. Empathy is needed in the context of patient-centered care.

### *Research objectives*

To assess how medical students perform in their ability to provide an empathic medical history taking.

### *Research methods*

Interviews with experienced physicians/mentors.

### *Research results*

Differences between medical specialties are shown, but in general all physicians claim for a strengthening of empathy.

### *Research conclusions*

Concise structure and an empathic attitude are necessary for the understanding of minds in order to get the needed information for adequate clinical reasoning and clinical decision making.

### *Research perspectives*

Understanding of minds and mentality can be facilitated, trained and strengthened.

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## FOOTNOTES

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**Informed consent statement:** Participants were required to give informed consent to the study. No patients were enrolled in the study. Furthermore, the analysis used anonymous data that were obtained after each participant had agreed to the assessment by written consent.

**Conflict-of-interest statement:** We have no conflict of interest and no financial relationships to disclose.

**Data sharing statement:** Data is available on request.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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ORIGINAL ARTICLE

Observational Study

# Cross-sectional study of traumatic stress disorder in frontline nurses 6 mo after the outbreak of the COVID-19 in Wuhan

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## Abstract

*BACKGROUND*

Frontline nurses in Wuhan directly fighting severe acute respiratory syndrome coronavirus-2 diseases are at a high risk of infection and are extremely susceptible to psychological stress, especially due to the global coronavirus disease 2019 (COVID-19) pandemic. The psychological after-effects of this public health emergency on frontline nurses will last for years.

*AIM*

To assess factors influencing post-traumatic stress disorder (PTSD) among

frontline nurses in Wuhan 6 mo after the COVID-19 pandemic began.

***METHODS***

A total of 757 frontline nurses from five hospitals in Wuhan, China, participated in an online survey from July 27 to August 13, 2020. This cross-sectional online study used a demographic information questionnaire, the PTSD Checklist for the Diagnostic and Statistical Manual of Mental Disorders, the Connor-Davidson Resilience Scale, and the Patient Health Questionnaire-4. The chi-square test and logistic regression were used to analyze the association of demographics, COVID-19-related variables, and PTSD. Logistic regression was also conducted to investigate which variables were associated with PTSD outcomes.

***RESULTS***

A total of 13.5%, 24.3%, and 21.4% of the frontline nurses showed symptoms of PTSD, depression, and anxiety, respectively. The multivariate logistic regression analysis showed that the following factors were strongly associated with PTSD: Having a relative, friend, or colleague who died of COVID-19; experiencing stigma; or having psychological assistance needs, depressive symptoms or anxiety. Showing resilience and receiving praise after the COVID-19 outbreak were protective factors.

***CONCLUSION***

Frontline nurses still experienced PTSD (13.5%) six months after the COVID-19 outbreak began. Peer support, social support, official recognition, reward mechanisms, exercise, better sleep, and timely provision of information (such as vaccine research progress) by the government *via* social media, and adequate protective supplies could mitigate the level of PTSD among nurses responding to COVID-19. Stigmatization, depression, and anxiety might be associated with a greater risk of PTSD among nurses.

**Key Words:** Post-traumatic stress disorder; Frontline nurses; COVID-19; Mental health; Pandemic

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**Core Tip:** The mental health of frontline nurses in Wuhan has been significantly affected by the coronavirus disease (COVID-19). This study aims to evaluate the influencing factors of post-traumatic stress disorder (PTSD) among frontline nurses in Wuhan six months after the COVID-19 pandemic began and implement a mental health plan. The prevalence rates of PTSD, depression and anxiety among frontline nurses were 13.5%, 24.3%, and 21.4%, respectively. The risk factors for nurses to develop PTSD are the death of a relative, friend, or colleague from COVID-19, stigma, depression, and anxiety. Resilience and reward mechanisms are protective factors to prevent PTSD.

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## INTRODUCTION

A novel coronavirus disease (COVID-19) was first reported in December 2019 in Wuhan, China. The World Health Organization (WHO) Director-General announced that the COVID-19 outbreak was a public health emergency of international concern on 30 January 2020[1]. As of 14 August 2020, 20439814 confirmed cases and 744385 confirmed deaths had been reported by the WHO, and the disease eventually spread to more than 216 countries, areas, or territories[2]. Increasing demand for the care of COVID-19 patients and high morbidity and mortality continue to challenge the global health system.

Wuhan was considered a high-risk area for COVID-19. According to the daily report on COVID-19 statistics released by the National Health Commission of China, as of 24:00 on February 24, 2020, Wuhan had a total of 47071 confirmed cases and a total of 2043 deaths[3]. To efficiently stop the spread of COVID-19, medical staff fought the disease. However, there were a total of 3387 cases of COVID-19 infection among medical staff in mainland China. More than 90% of medical staff infections occurred in Hubei Province, mainly in Wuhan[4]. While rescuing lives, frontline medical staff witnessed the clinical

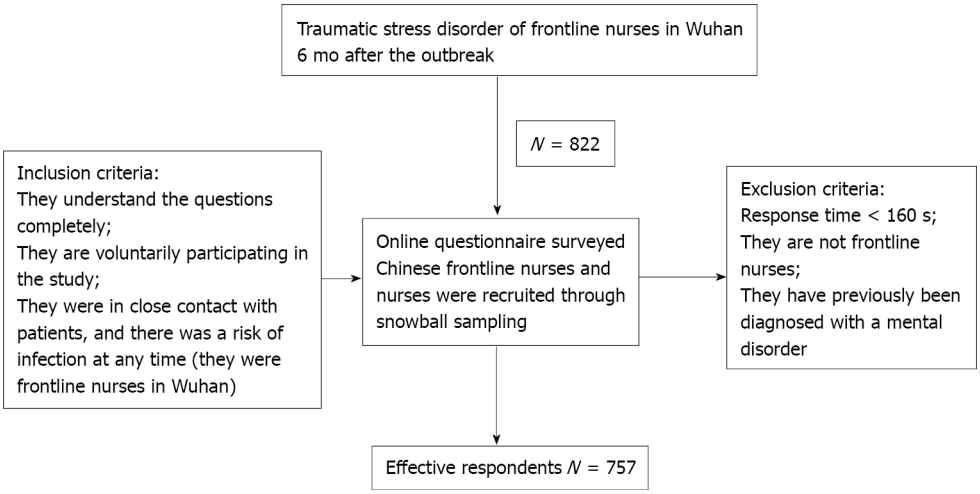


**Figure 1 The inclusion and exclusion criteria of the online questionnaire.**

reactions and deaths of numerous patients with severe cases of COVID-19.

An overwhelming workload, shortage of medical supplies, insufficient rest, high risk of infection, stigma, and fear of infection of family members or friends increase the risk of post-traumatic stress disorder (PTSD) among frontline nurses. PTSD[5,6] is a mental disorder characterized by intrusive thoughts, avoidance, cognitive and mood disturbances, and arousal symptoms that may be experienced after traumatic life events, such as threats of severe injury, death, war, sexual offenses, and terrible catastrophes.

Due to the COVID-19 pandemic, frontline nurses were considered susceptible to PTSD. Studies on the COVID-19 outbreak in China[7], Spain[8], Italy[9], Jordan[10], and the United States[11] have discussed how the battle against COVID-19 caused anxiety, depression, and PTSD symptoms among frontline nurses.

Studies on the impact of severe acute respiratory syndrome (SARS)[12], Middle East respiratory syndrome[13], and influenza A[14] found that one to two years after a disease outbreak, frontline nurses endured symptoms of anxiety, depression, and PTSD. However, there is little information available on the long-term impact of PTSD on frontline nurses who treated SARS patients during the COVID-19 outbreak.

This study aims to investigate the influencing factors of PTSD six months after the COVID-19 outbreak among frontline nurses who were exposed to COVID-19. It is imperative to provide mental health support for frontline nurses, and facilitate their psychological recovery from PTSD related to the COVID-19 pandemic.

## MATERIALS AND METHODS

### *Ethical considerations*

The study was reviewed and approved by the Ethics Committee of the Union Hospital affiliated to Tongji Medical College, Huazhong University of Science and Technology (Approval number 2020-0189). This study was conducted according to the principles of the Declaration of Helsinki.

### *Design*

The research team assessed the traumatic stress disorder of frontline nurses who worked in Wuhan during the outbreak through a cross-sectional survey using social media (such as WeChat and QQ) six months after the outbreak, from July 27 to August 13, 2020. Before starting the investigation, all participants had to give their informed consent, and the purpose of the study was explained. The participants could exit the survey at any time.

### *Participants*

The study recruited 822 first-line medical staff from six tertiary general hospitals. After those who met the exclusion criteria were removed, 92.1% (757 out of 822) of the staff were included in the statistical analyses. A total of 274 participants (36.2%) were from Zhongnan Hospital of Wuhan University, 149 (19.7%) were from Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 39 (5.2%) were from Wuhan Central Hospital, 150 (19.8%) were from Wuhan Jin Yin Tan Hospital (Wuhan Medical Treatment Center), 104 (13.7%) were from Wuhan Third Hospital, and 41 (5.4%) were from Renmin Hospital of Wuhan University. The participants worked in Wuhan during the

height of the pandemic from January to February 2020. The inclusion and exclusion criteria are presented in Figure 1. The demographics of the study participants are presented in Table 1.

### Demographic questionnaire

This questionnaire collected information on the participants' general characteristics, including age, sex, and job-related information, and COVID-related information.

### Post-traumatic stress disorder

The PTSD Checklist for the Diagnostic and Statistical Manual of Mental Disorders[15] was used to measure the post-traumatic stress disorder of frontline nurses in Wuhan six months after the outbreak. This scale has been widely and commonly used in previous studies[16]. The scale consists of 20 items scored on a Likert-type scale ranging from 0 = "not at all" to 4 = "extremely". The total scores range from 0 to 80, with higher scores indicating more severe symptoms (cutoff score ≥ 33). These statements are classified into four distinct domains: Re-experiencing (5 items, score 0 to 20); avoidance (2 items, score 0 to 8); negative alteration in cognition and mood (6 items, score 0 to 24) and arousal (7 items, 0 to 28).

### Resilience

The psychometric properties of the Connor-Davidson Resilience Scale (CD-RISC 10) are well documented. The CD-RISC 10[17], in its Chinese version[18], was used to assess psychological resilience, especially the ability to cope with adversity. The 10 self-report items are scored on a Likert-type scale from 0 = "not true at all" to 4 = "true nearly all the time". The total score ranges from 0 to 40, and higher scores indicate better resilience (cutoff score ≥ 30).

### Anxiety and depression

The Patient Health Questionnaire-4 (PHQ-4)[19], including the PHQ-2 and Generalized Anxiety Disorder-2 (GAD-2), were used to assess both depression and anxiety disorders, respectively. The Chinese versions[20] have been validated and widely used. The PHQ-2 and GAD-2 use two core criteria to assess the levels of major depressive disorder and anxiety, respectively. Each item is scored on a 4-point Likert-type scale from 0 = "not at all" to 3 = "nearly every day". The total score ranges from 0 to 6, and higher scores indicate greater levels of depression and anxiety (cutoff score ≥ 3).

### Statistical analysis

Data were analyzed using IBM SPSS version 21.0 (Chicago, IL, United States). Frequencies and percentages were calculated for the categorical data. The chi-square test was used to verify differences in the categorical variables between groups. Binary logistic regression analyses were used to explore the factors impacting post-traumatic stress, such as demographics, anxiety, depression, and resilience. The test level was $P = 0.05$; that is, a $P$-value of less than 0.05 was considered statistically significant.

## RESULTS

### Demographic characteristics

A total of 757 participants were included in this investigation. The mean age was 32.60 years (SD = 7.64). The mean working time was 10.16 years (SD = 8.28). The study sample consisted of 688 women (86.4%) and 69 men (13.6%). The demographics of the participants are presented in Table 1.

### Levels of PTSD, anxiety, and depression

The mean PTSD, resilience, depression, and anxiety scores were 17.74 ± 11.87, 25.29 ± 6.95, 1.75 ± 1.43, and 1.70 ± 1.43, respectively. A total of 13.5% of the sample met the symptom criteria for PTSD. The prevalence of depression was 24.3%, and 21.4% of the participants had anxiety symptoms. The proportion of frontline nurses in Wuhan enrolled in this survey who scored above the established cutoff for resilience was 28.7%.

### Factors associated with PTSD

Six items found significant differences between nurses with post-traumatic stress disorder, including having a relative, friend, or colleague who died of COVID-19, experiencing stigma, receiving praise, showing resilience, having depression symptoms, and having anxiety symptoms. No differences were observed between groups in sex, age, education, marital status, working years, or previous anti-epidemic experience (all $P < 0.05$) (Table 1).

Six items were significantly associated with PTSD among nurses, including having a relative, friend, or colleague who died of COVID-19, experiencing stigma, receiving praise, showing resilience, having depression symptoms, and having anxiety symptoms ($P < 0.05$). No differences were observed between groups in gender, age, marital status, education, working years, or previous anti-epidemic experience ($P$

> 0.05) (Table 1).

### Regression analyses of PTSD

As shown in Table 2, several variables were found to be associated with a higher risk of PTSD, such as having a relative, friend, or colleague who died of COVID-19 [odds ratio (OR): 2.226, $P < 0.01$], experiencing stigma (OR: 3.038, $P < 0.01$), not receiving praise (OR: 0.442, $P < 0.01$), lacking resilience (OR: 0.190, $P < 0.01$), having depressive symptoms (OR: 3.625, $P < 0.01$), and having anxiety symptoms (OR: 3.849, $P < 0.01$).

## DISCUSSION

### Key findings

This study found that six months after the COVID-19 outbreak began in Wuhan, China, the prevalence of PTSD, depression, and anxiety among frontline nurses were 13.5%, 24.3%, and 21.4%, respectively. The following factors were associated with a greater likelihood of having PTSD: Having a relative, friend, or colleague who died of COVID-19; experiencing stigma; having depression symptoms; and having anxiety symptoms. Showing resilience and receiving praise after the COVID-19 outbreak were helpful in prevent PTSD.

### The prevalence of PTSD

The incidence of PTSD among frontline nurses was lower at the time of the survey than at the initial stage of the COVID-19 outbreak (16.83%-71.5%)[21-25]. A possible reason might be that the nurses may have been under less psychological stress six months after the outbreak than they were during the initial period, which was also found in Cai *et al*[7]'s research.

### Factors influencing PTSD

It is important to note that the participants who had a relative, friend, or colleague who died of COVID-19 were more likely to report high levels of PTSD. In contrast, no differences in the history of personal infection were observed between those who did not have PTSD. This study highlights that exposure to high-risk work environments (such as directly caring for infected patients) was not the main determinant of adverse psychological outcomes. This result was also found 13 to 26 mo after the SARS outbreak[26] among medical staff at Toronto hospitals that treated SARS patients. A previous study showed[27] that during the SARS outbreak, the death of colleagues created a stressful atmosphere in the hospital. It is also possible that the death of a relative, friend, or colleague places a heavy psychological burden on nurses[28]. These trends may be explained by peer support promoting adaptive coping.

Stigmatization was found to be predictive of a high level of PTSD. Frontline nurses at hospitals are vulnerable to stigmatization, loneliness, and exclusion due to working in areas with the highest incidence of COVID-19. COVID-19-related fear may have led the nurses to be isolated from other individuals, which may also have had different effects on their social support. Experience of stigma can have long-term adverse effects on nurses' mental health. Such effects were examined by Liu *et al*[29], Zandifar *et al*[30], and Röhr *et al*[31].

The logistic regression analysis showed that the nurses who had received praise from government agencies were less likely to report high levels of PTSD. Frontline nurses who are officially recognized, which is common in Chinese society, have a strong sense of being protected and supported by organizations. Such recognition may play an important role in experiencing satisfaction through continued working in these settings. Previous studies[32,33] reported that people with severe PTSD symptoms performed better than those without PTSD symptoms in reward trials. In response to the ongoing psychological effects among nurses after the COVID-19 outbreak, official recognition and reward mechanisms appear to be needed.

Psychological resilience was a significant protective factor for PTSD among the frontline nurses six months after the COVID-19 outbreak. Lutha and Cicchetti[34] refers to an individual's ability to positively adjust after trauma and respond to adverse experiences. Psychological resilience research[35] during the COVID-19 epidemic showed that more frequent exposure to the outdoors and sunlight, more exercise, greater perceived social support, better sleep, and more frequent prayer may contribute to greater psychological resilience.

### Personal depression and anxiety contributed to adverse outcomes

One study[36] conducted in China during the COVID-19 outbreak showed that increased distress, decreased sleep quality and increased self-efficacy could cause anxiety among medical staff, which could affect their mental health. Making difficult ethical decisions regarding the distribution of medical supplies, the lack of personal equipment, and progress in COVID-19 vaccine research made medical staff particularly vulnerable to mental health problems. Therefore, reasonable rest time and shifts, a safe work environment, the satisfaction of basic needs, and the availability of information on vaccine

**Table 1 Socio-demographic characteristics and its subscales among study participants (*n* = 757)**

| Variables | Characteristics | Total *n* (%) | PTSD *n* (%) | | $\chi^2$ | *P* value |
|---|---|---|---|---|---|---|
| | | | No | Yes | | |
| Sex | Male | 69 (9.1) | 64 (8.5) | 5 (0.7) | 2.526 | 0.112 |
| | Female | 688 (90.9) | 591 (78.1) | 97 (12.8) | | |
| Age | < 25 | 132 (17.4) | 116 (15.3) | 16 (2.1) | 3.859 | 0.452 |
| | 26-30 | 232 (30.6) | 205 (27.1) | 27 (3.6) | | |
| | 31-35 | 183 (24.2) | 156 (20.6) | 27 (3.6) | | |
| | 36-40 | 88 (11.6) | 71 (9.4) | 17 (2.2) | | |
| | > 40 | 122 (16.1) | 107 (14.1) | 15 (2.0) | | |
| Marital status | Married | 492 (65.0) | 422 (55.7) | 70 (9.2) | 0.684 | 0.408 |
| | Single/Divorced/Other | 265 (35.0) | 233 (30.8) | 32 (42.2) | | |
| Education | Secondary education | 98 (12.9) | 82 (10.8) | 16 (2.1) | 0.842 | 0.656 |
| | Bachelor's degree | 585 (77.3) | 508 (67.1) | 77 (10.2) | | |
| | Postgraduate/Doctoral degree | 74 (9.8) | 65 (8.6) | 9 (1.2) | | |
| Working years | 0-2 | 114 (15.1) | 101 (13.3) | 13 (1.7) | 1.289 | 0.863 |
| | 3-5 | 148 (19.6) | 128 (16.9) | 20 (2.6) | | |
| | 6-10 | 219 (28.9) | 191 (25.2) | 28 (3.7) | | |
| | 11-20 | 178 (23.5) | 150 (19.8) | 28 (3.7) | | |
| | ≥ 20 | 98 (12.9) | 85 (11.2) | 13 (1.7) | | |
| Previous anti-epidemic experience | No | 694 (97.1) | 600 (79.3) | 94 (12.4) | 0.035 | 0.851 |
| | Yes | 63 (8.3) | 55 (7.3) | 8 (1.1) | | |
| Nurse infected by COVID-19 | No | 732 | 634 | 98 | 0.141 | 0.707 |
| | Yes | 25 | 21 | 4 | | |
| A relative, friend or colleague died of COVID-19 | No | 611 (80.7) | 542 (71.6) | 69 (9.1) | 12.929 | 0.000[b] |
| | Yes | 146 (19.3) | 113 (14.9) | 33 (4.4) | | |
| Experienced stigma | No | 596 (78.7) | 536 (70.8) | 60 (7.9) | 27.902 | 0.000[b] |
| | Yes | 161 (21.3) | 119 (15.7) | 42 (5.5) | | |
| Received praise | No | 504 (66.6) | 425 (56.1) | 79 (10.4) | 6.262 | 0.012[a] |
| | Yes | 253 (33.4) | 230 (30.4) | 23 (3.0) | | |
| Resilience (CD-RISC-10) | < 30 | 540 (71.3) | 442 (58.4) | 98 (12.9) | 35.297 | 0.000[b] |
| | ≥ 30 | 217 (28.7) | 213 (28.1) | 4 (0.5) | | |
| Depression (PHQ-2) | < 3 | 573 (75.7) | 541 (71.5) | 32 (4.2) | 125.861 | 0.000[b] |
| | ≥ 3 | 184 (24.3) | 114 (15.1) | 70 (9.2) | | |
| Anxiety (GAD-2) | < 3 | 595 (78.6) | 558 (73.7) | 37 (4.9) | 125.549 | 0.000[b] |
| | ≥ 3 | 162 (21.4) | 97 (12.8) | 65 (8.6) | | |

[a]*P* < 0.05.

[b]*P* < 0.01. PTSD: Posttraumatic stress disorder; COVID-19: Coronavirus disease 2019; CD-RISC-10: Connor-Davidson Resilience Scale; PHQ-2: Patient Health Questionnaire-2; GAD-2: Generalized Anxiety Disorder-2.

research progress may help reduce stress among nurses. Previous studies[37-39] also found that anxiety could lead to PTSD, exacerbated by the effects of a higher frequency of social media exposure. Notably, having up-to-date authoritative and true information about COVID-19 on social media may reduce the rate of PTSD.

**Table 2 Logistic regression analyses for posttraumatic stress disorder (*N* = 757)**

| | B | SE | Wald | Sig | Exp (B) | 95% Confidence interval | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower bound | Upper bound |
| A relative, friend or colleague died of COVID-19 (No) | 0.800 | 0.283 | 7.969 | 0.005 | 2.226 | 1.277 | 3.879 |
| Experienced stigma (No) | 1.111 | 0.270 | 16.974 | 0.000 | 3.038 | 1.791 | 5.154 |
| Received praised (No) | -0.816 | 0.288 | 8.042 | 0.005 | 0.442 | 0.252 | 0.777 |
| Resilience < 30 | -1.662 | 0.540 | 9.475 | 0.002 | 0.190 | 0.066 | 0.547 |
| Depression < 3 | 1.288 | 0.322 | 15.962 | 0.000 | 3.625 | 1.927 | 6.818 |
| Anxiety < 3 | 1.348 | 0.321 | 17.678 | 0.000 | 3.849 | 2.053 | 7.214 |
| Constant | -5.010 | 0.999 | 25.134 | 0.000 | 0.007 | | |

COVID-19: Coronavirus disease 2019.

### *Limitations*

Several limitations of this survey must be mentioned. First, since the COVID-19 pandemic has had a long-term negative psychological impact on nurses, longitudinal research should be conducted in the future. Second, the research may have been biased because the participants were not recruited randomly. Third, due to the endpoint of the study, the challenges and opportunities of vaccination remain unknown.

## CONCLUSION

Six months after the COVID-19 outbreak began, frontline nurses were still experiencing pandemic-related distress, which could lead to long-term PTSD. Our findings indicated that peer support, social support, exercise, better sleep, official recognition, and reward mechanisms should be prioritized to alleviate the negative psychological responses of nurses dealing with the pandemic. Our study further shows that the timely provision of information (such as vaccine research progress) by the government on social media and adequate protective supplies might mitigate the level of PTSD among nurses responding to COVID-19. Stigmatization, depression, and anxiety might be associated with a greater risk of PTSD among nurses.

## ARTICLE HIGHLIGHTS

### *Research background*

The worldwide spread of coronavirus disease 2019 (COVID-19) is an international public health emergency posing challenges for health care systems. The mental health of nurses was significantly affected by this crisis, and nurses played a crucial role in successfully fighting the COVID-19 pandemic.

### *Research motivation*

Few studies have focused on the risk of post-traumatic stress disorder (PTSD) among frontline nurses six months after the COVID-19 outbreak. Our research group aimed to investigate the prevalence of PTSD among nurses and the implementation of mental health programs.

### *Research objectives*

This study aimed to evaluate the factors associated with PTSD, determine what psychosocial support nurses need, and identify ways to reduce the level of PTSD among nurses responding to the COVID-19 pandemic in Wuhan, China.

### *Research methods*

A total of 757 frontline nurses from six tertiary general hospitals in Wuhan, China, were recruited. The structured questionnaire included a demographic information section, the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders, the Connor-Davidson Resilience Scale, the Patient Health Questionnaire-4, and COVID-19-related items. The cross-sectional survey was conducted from July 27 to August 13, 2020, *via* social media.

### *Research results*

This study found that six months after the COVID-19 outbreak in Wuhan, China, the prevalence of PTSD, depression, and anxiety among frontline nurses was 13.5%, 24.3%, and 21.4%, respectively. The following factors were associated with a greater likelihood of having PTSD: Having a relative, friend, or colleague who died of COVID-19; experiencing stigma; having depressive symptoms, and having anxiety symptoms. Showing resilience and receiving praise after the COVID-19 outbreak were helpful in preventing PTSD.

### *Research conclusions*

Frontline nurses still experienced long-term pandemic-related distress six months after the COVID-19 outbreak. Peer support, social support, official recognition, reward mechanisms, better sleep, exercise, and the timely provision of information (such as vaccine research progress) by the government on social media, and adequate protective supplies could mitigate the level of PTSD among nurses responding to COVID-19. Stigmatization, depression, and anxiety might be associated with a greater risk of PTSD among nurses.

### *Research perspectives*

Considering the long-term adverse effects of PTSD on frontline nurses, longitudinal studies should be conducted in the future. Additional research is needed to better understand whether the vaccine could mitigate the negative impact on the mental health of nurses and other populations.

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SYSTEMATIC REVIEWS

# Catatonia in older adults: A systematic review

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## Abstract

### *BACKGROUND*

Catatonia is a complex psychomotor syndrome that often goes unrecognized and untreated, even though its classification has evolved in recent years. Prompt and correct identification of catatonia allows for highly effective treatment and prevention of possible complications. The underrecognition of catatonia in older patients is also frequent, and research in this population is scarce.

### *AIM*

To conduct a systematic review of the literature on catatonia in older people to ascertain its clinical characteristics across settings.

### *METHODS*

Following the PRISMA guidelines, MEDLINE, EMBASE, and PsycINFO databases were searched from inception to December 2021, with a strategy aimed at identifying all articles published on catatonia in older adults. Titles and abstracts were scanned and selected independently by two authors. Papers investigating issues related to catatonia and/or catatonic symptoms in older people, with English abstracts available, were included. References of selected articles were

revised to identify other relevant studies.

*RESULTS*

In total, 1355 articles were retrieved. After removing duplicates, 879 remained. Of the 879 identified abstracts, 669 were excluded because they did not meet the inclusion criteria. A total of 210 articles underwent full text review, and 51 were eliminated for various reasons. Fourteen more articles were selected from the references. Overall, 173 articles were reviewed: 108 case reports, 35 case series, 11 prospective cohort studies, 6 case-control studies, 3 retrospective cohort studies and 10 reviews. We found several particular aspects of catatonia in this population. Catatonia in older patients is highly prevalent and tends to have a multifactorial etiology. Older patients, compared to younger patients, have a higher risk of developing catatonia with benzodiazepine (BZD) withdrawal, in bipolar disorder, and in the general hospital. Age, together with other risk factors, was significantly associated with the incidence of deep venous thrombosis, neuroleptic malignant syndrome poor outcome, other complications and mortality. Treatment with BZDs and electroconvulsive therapy is safe and effective. Prompt treatment of its cause is essential to ensure a good prognosis.

*CONCLUSION*

Catatonia in older patients is highly prevalent and tends to have a multifactorial etiology. The risk of developing catatonia in some settings and conditions, as well as of developing complications, is high in this population. Symptomatic treatment is safe and effective, and timely etiologic treatment is fundamental.

**Key Words:** Catatonia; Older adults; Etiology; Phenomenology; Prevalence; Treatment

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**Core Tip:** Catatonia in older people is underrecognized and undertreated, as demonstrated by the scarce bibliography published in this age group, in which the prevalence is high and the etiology usually multifactorial. Catatonia can frequently present together with delirium. General medical conditions and neurological disorders have a very important role in its etiology. Older people could have a higher risk of developing catatonia in bipolar disorder, the general hospital and with benzodiazepine (BZD) withdrawal. Also, they have a higher risk of developing complications secondary to this condition. BZDs and electroconvulsive therapy have been proven to be safe and effective symptomatic treatments, but the correct identification and treatment of the etiology are crucial for a full recovery.

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## INTRODUCTION

Catatonia is a psychomotor syndrome caused by physical illnesses, such as infections; endocrine, metabolic, and neurologic disorders; psychiatric conditions, mainly affective and psychotic; and medications and other substances[1]. The contemporary concept of catatonia has evolved significantly. The Diagnostic and Statistical Manual - Fifth Edition (DSM-5) classifies catatonia either as a specifier of all mental disorders, as secondary to a general medical condition (GMC), and as catatonia not otherwise specified for when the syndrome is identified but not yet their etiology[2]. Based on a review of the available evidence published in recent decades and considering their clinical utility and global applicability, the International Classification of Diseases - 11$^{th}$ Edition classifies catatonia as a new diagnostic group at the same hierarchical level as the other included disorders. This edition, approved in May 2019, considers that catatonia can be caused by mental disorders, psychoactive substances (including medications), and medical conditions. In the former, catatonia is valued with the symptom specifier within the category "psychomotor symptoms" and, in the other two cases, as a secondary presentation form[3]. In patients older than 18 years, catatonia is mostly associated with affective disorders[1]. Its early recognition is important, as it is a potentially deadly syndrome. However, it is highly treatable, usually responding to treatment of the cause and to short courses of benzodiazepines (BZDs) or electroconvulsive therapy (ECT)[4-7].

Catatonia is also underrecognized in older adults, something that in this population may lead to delayed treatment, misdiagnosis, adverse events, and even death[8,9]. Despite the increasing amount of research on catatonia, there have been few specific studies on older patients. This review aims to summarize the published literature on catatonia in older adults to provide up-to-date knowledge about this entity for clinicians working with this population.

## MATERIALS AND METHODS

This systematic review was conducted using the PRISMA method[10]. The MEDLINE, EMBASE, and PsycINFO databases were searched from inception through December 2021. The search strategy was as follows: CATATONIA/or catatoni*.af. and aged/or "aged, 80 and over"/or frail elderly/or (elder* or "old people" or geriatr* or senior* or aged or "over 65" or "over 80" or "65 year*" or "85 year*").ti,ab. Articles identified were imported into a standard reference manager, EndNote X7, and duplicate manuscripts were removed. Papers that investigated issues related to catatonia and/or catatonic symptoms in older people, with an English abstract available, were included. Titles and abstracts were scanned for relevance. Papers were selected according to the inclusion criteria by two authors independently (Jaimes-Albornoz W and Serra-Mestres J). Full texts were ordered in case of uncertainty to maximize sensitivity. References of selected articles were cross-checked to identify other potentially eligible studies. Case reports, case series, controlled studies, or review articles were eligible for inclusion in this review. The full texts of studies that passed the initial screening were reviewed and potentially excluded based on the same criteria. From this selection we only included Abstracts/Conference proceedings and letters to the editor that describe cases of catatonia whose clinical correlates have not been previously described. The literature search strategy is summarized in the flow chart presented in Figure 1. We also present all the clinical correlates of our catatonic patients in a psychogeriatric unit (Tables 1, 2 and 3). Information on patients diagnosed with dementia in this series has been published previously[11].

## RESULTS

In total, 173 articles were considered: 108 case reports, 35 case series (12 also carried out a systematic review of the literature), 11 prospective cohort studies, 6 case control studies, 3 retrospective cohort studies, and 10 reviews. All articles were reviewed and are summarized below.

### *Epidemiological aspects*

The prevalence of catatonia is largely dependent on its recognition, diagnostic criteria used, and setting. Although the general prevalence of catatonia is not fully known, it is considered to be between 5% and 20% among acute psychiatric patients; however, it varies according to the underlying or comorbid conditions[12]. A prevalence of 14%-71% has been described in mood disorders, 4%-67% in schizophrenia spectrum disorders, and between 4%-46% in GMCs[13]. A recent meta-analysis including 74 studies and 107304 individuals showed an overall pooled mean prevalence of catatonia of 9.2% among subjects diagnosed with a variety of psychiatric and medical conditions[13].

In the older population, the prevalence of catatonia also seems to vary depending on the setting and diagnostic criteria used. In liaison psychiatry services using the Bush Francis Catatonia Rating Scale (BFCRS) criteria, the prevalence of catatonia was 5.5%[14] and 8.9%[8]. Another study conducted in older patients in an acute inpatient general psychiatry ward reported a prevalence of 11.2% using the BFCRS and 6.1% using the DSM-5 criteria[15]. The prevalence was noted to be higher in acute psychogeriatric units in the United Kingdom (Table 1) and Spain[16], where the prevalence was 27% and 39.6% and 24.3% and 20.8%, respectively, using the BFCRS and DSM-5 criteria.

### *Pathophysiology*

The specific brain mechanisms underlying catatonia are still poorly understood. The model developed by Northoff *et al*[17,18], who hypothesized that catatonic symptoms are mainly associated with orbitofrontal-prefrontal/parietal cortical dysfunction ('top-down' model of catatonia), abnormal 'horizontal' cortical-cortical modulation, and basal ganglia-cortical dysfunction (a 'bottom-up' mechanism), is criticized because the results are inconsistent and have generally been limited to schizophrenic patients with catatonia[19]. Studies with structural and functional brain imaging[20], clinical observations made after lobotomies and frontal lobe lesions, and experiments carried out in animals[21] have described incompatible results with Northoff's theory[17,18]'s theory. We are still far from having an integrative pathophysiological model of catatonia resulting from clinical, structural, and functional abnormalities of such a different nature. In this regard, only two articles were found about older people with catatonia that used brain imaging. The first was in patients with bipolar disorder (BD) and major depressive disorder (MDD), employing functional near-infrared spectroscopy[22], and the other used SPECT in

**Table 1 Catatonia in a United Kingdom acute psychogeriatric ward**


| Abstract | |
|---|---|
| Aims | To determine the frequency and characteristics of catatonia in older people in a psychogeriatric ward |
| Methods | All patients admitted were screened for catatonia with the Bush-Francis Catatonia Screening Instrument over a period of 6 mo. Data was collected on sociodemographics, past medical/psychiatric/drug history, clinical findings, treatment, complications/outcome, and investigations. Treatment with lorazepam orally or intramuscularly was initiated in patients who fulfilled diagnostic criteria for catatonia |
| Results | 37 patients were admitted. Prevalence of catatonia was 27%, 10 out of 37 (Bush-Francis criteria) and 24.3%, 9 out of 37 (DSM-5 criteria). The 10 catatonic patients have a mean age of 75.8 years; range: 67-87; and 8 were female. 90% of these patients had a cardiovascular risk factors. The etiology was multifactorial in 50% of the cases. 6 patients had dementia. In 3 of them catatonia was associated with the use of neuroleptics, in 1 with neuroleptics and a urinary infection (she also had delirium), in another with major depression and in only one dementia was a possible etiology. 40% of the cases developed catatonia secondary to affective disorders and 10% to schizophrenia spectrum disorder. In the total sample there were 14 patients with dementia. The catatonia rate in these patients was 42.8% (6 of 14). 9 patients received treatment for catatonia with lorazepam, all of which achieved complete remission, 1 of the these was also treated with clonazepam. 1 patient was treated with sodium valproate and achieved a partial response. 3 patients developed complications secondary to catatonia. One had an elevated creatine kinase of 1083 IU/L, another a deep venous thrombosis, and the last one, hypokalemia |
| Conclusions | Catatonia is a very prevalent entity in the psychogeriatric ward. The etiology is usually multifactorial. This condition occurred frequently in patients admitted with dementia. Treatment with lorazepam is highly effective and safe |


DSM-5: Diagnostic and Statistical Manual - Fifth Edition.

**Table 2 History, antipsychotic exposure and current diagnoses in patients with catatonia in United Kingdom acute psychogeriatric ward**

| Age/sex | Medical history | Psychiatric history | Current acute medical diagnosis/antipsychotic exposure | Current acute psychiatric diagnosis |
|---|---|---|---|---|
| 67/F | Bowel obstruction resulting in perforation | Bipolar disorder | None | Bipolar disorder, current episode depressive severe without psychotic symptoms |
| 87/M | Hypertension; Hyperlipidemia; Lip carcinoma | Alzheimer's disease | None/(risperidone, quetiapine) | Late onset Alzheimer's disease |
| 76/F | Hypertension; DM2; Hyperlipidemia | Vascular dementia | None/quetiapine | Vascular dementia |
| 75/F | Ischemic heart disease; Irritable bowel syndrome; Hypothyroidism; Pulmonary fibrosis; Diveticulitis | RDD; Health anxiety; Dementia | None | Late onset Alzheimer's disease; RDD, current episode severe without psychotic symptoms |
| 71/F | Hyperlipidemia; Atrial fibrillation; Repeated urinary tract infections; Diverticulitis | RDD; Alcohol misuse; Alzheimer's disease | Urinary tract infection/(aripiprazole, olanzapine) | Young onset Alzheimer's disease; Delirium superimposed on dementia |
| 70/F | Hypertension; Osteoarthritis | RDD | None | RDD, current episode severe with psychotic symptoms |
| 74/F | Parkinson's disease; Glaucoma; Obesity | Schizoaffective disorder | None | Schizoaffective disorder not otherwise specified |
| 68/F | Hyperlipidemia | Young onset Alzheimer's disease | None/none | Young onset Alzheimer's disease |
| 85/M | Hypertension; DM2; Jaw osteomyelitis; Isquemic heart disease; Pacemaker | Mixed dementia | None/risperidone | Mixed dementia |
| 85/F | Hypertension; Atrial fibrillation; Breast cancer | Depression | None | Severe depressive episode without psychotic symptoms |

RDD: Recurrent depressive disorder; DM2: Type 2 diabetes mellitus.

older patients who developed catatonia as a result of late-onset schizophrenia[23]. Their conclusions were similar to those previously reported in adult patients.

It has also been suggested that catatonia could be a manifestation of intense anxiety and/or fear, resembling tonic immobility in animals, an evolutionary adaptive defense strategy to survive contact with predators attacking moving prey[24]. In humans, fear could also be caused by internal events and psychopathological experiences, such as hallucinations and delusions or anxiety/fear. This freezing would correspond to the immobility, stupor, catalepsy, and mutism observed in catatonia. Alternatively, catatonic excitement would be analogous to the 'fight-flight' response mediated by the

**Table 3 Catatonia signs frequency using Bush Francis Catatonia Rating Scale in older people**

| Catatonia signs | Country, clinical setting, (*n*: Patients) | | | | | Total (*n* = 79) | % |
|---|---|---|---|---|---|---|---|
| | Spain[5] CLS, (*n*: 10) | Australia[10] CLS, (*n*: 6) | United Kingdom[7] PW, (*n*: 10) | Hungary[11] APW, (*n*: 11) | Spain[12] PW, (*n*: 42) | | |
| Inmobility/stupor | 10 | 5 | 7 | 7 | 24 | 53 | 67.1 |
| Staring | 10 | 3 | 7 | 7 | 22 | 49 | 62.0 |
| Mutism | 8 | 2 | 7 | 4 | 18 | 39 | 49.5 |
| Negativism | 7 | 3 | 4 | 0 | 25 | 39 | 49.5 |
| Withdrawal | 8 | 3 | 4 | 3 | 18 | 36 | 45.6 |
| Rigidity | 9 | 4 | 6 | 2 | 15 | 36 | 45.6 |
| Excitement | 0 | 0 | 3 | 3 | 27 | 33 | 41.8 |
| Posturing | 7 | 4 | 5 | 6 | 8 | 30 | 37.9 |
| Verbigeration | 1 | 1 | 2 | 0 | 26 | 30 | 37.9 |
| Perseveration | 1 | 0 | 3 | 2 | 20 | 20 | 33.0 |
| Stereotipies | 4 | 1 | 4 | 2 | 15 | 26 | 33.0 |
| Autonomic abnormalities | 1 | 1 | 3 | 1 | 16 | 16 | 27.8 |
| Impulsivity | 1 | 0 | 2 | 1 | 15 | 19 | 24.0 |
| Automatic obedience | 1 | 1 | 3 | 1 | 16 | 22 | 21.5 |
| Combativeness | 2 | 0 | 4 | 0 | 14 | 20 | 20.4 |
| Ecophenomena | 6 | 1 | 2 | 0 | 5 | 14 | 17.7 |
| Ambitendency | 0 | 1 | 2 | 2 | 8 | 13 | 16.5 |
| Grasp reflex | 0 | 1 | 1 | 2 | 9 | 13 | 16.5 |
| Grimacing | 3 | 1 | 0 | 0 | 8 | 12 | 15.3 |
| Mitgehen | 3 | 0 | 0 | 5 | 1 | 9 | 11.4 |
| Gegenhalten | 3 | 0 | 3 | 2 | 0 | 8 | 10.2 |
| Waxi flexibility | 2 | 0 | 4 | 0 | 0 | 6 | 7.6 |
| Mannerism | 0 | 0 | 0 | 0 | 4 | 4 | 5.1 |

APW: Acute psychiatric ward; CLS: Consultation-Liaison service; PW: Psychogeriatric ward.

sympathetic nervous system. A recent study in older patients with MDD found that those with catatonia and with agitation had increased hair cortisol concentrations[25], a hormone associated with stress. Nevertheless, it has also been postulated that it is possible to differentiate between emotive and nonemotive subtypes of catatonia, suggesting that not all catatonia patients experience emotional distress[26]. This theory seems to be supported by the findings that catatonia in older adults is not always related to intense anxiety[27].

### *Phenomenology, clinical signs, and diagnosis of catatonia*

The clinical presentation of catatonia in older adults (frequency of catatonic signs and clinical types) is generally similar to that of younger patients. Table 3 shows the frequency of signs of catatonia evaluated with the BFCRS in the 5 prospective observational studies carried out in older people[8,11,14-16]. Two clinical types of catatonia have been consistently reported in both populations[1,28]. A hypokinetic variant (retarded-stuporous) is characterized by reduced movement or immobility, mutism, and withdrawal. This is most frequently observed in depressive disorders and GMCs. A hyperkinetic or excited variant, presenting with increased aimless motor activity (qualitatively different from the overactivity of pure mania, which is purposeful), confusion, and frequent autonomic dysfunction, is mostly observed during manic episodes and in delirious mania. It is noteworthy that both forms of catatonia can coexist in the same patient, occurring in quick succession[1].

A forgotten subtype of catatonia, also described in older people[29], is periodic catatonia. It is characterized by rapid onset, brief and recurrent episodes of catatonia with a longitudinal course. Prognosis is

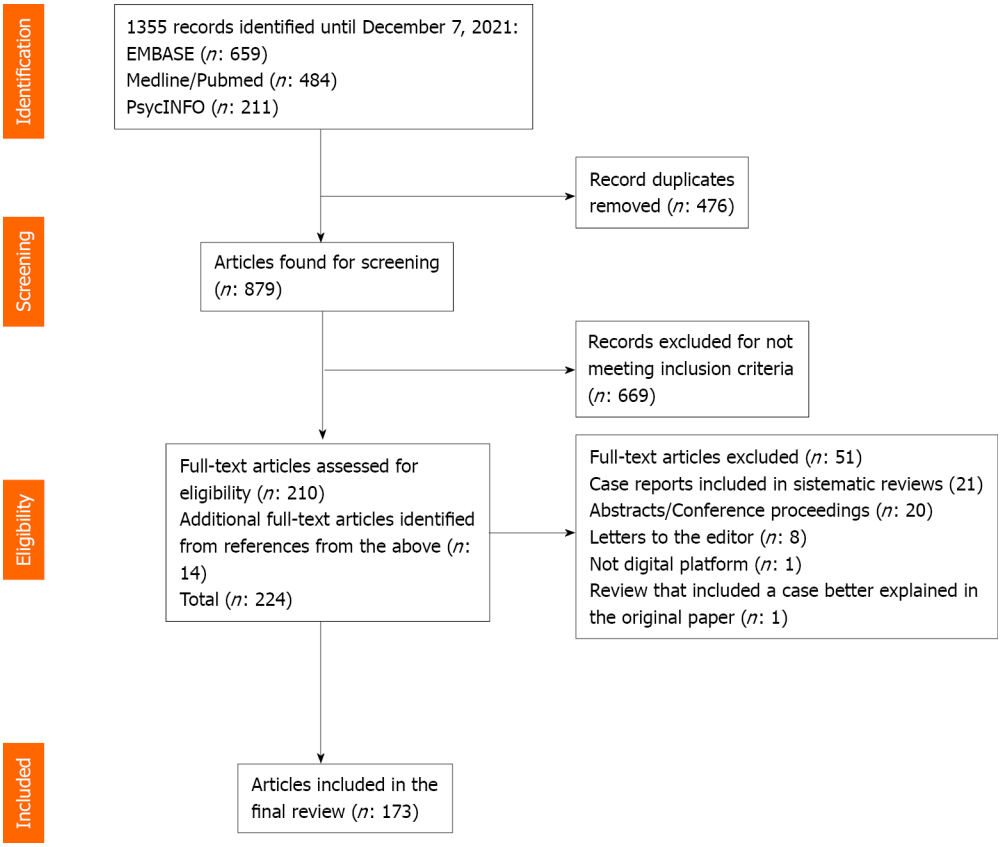


**Figure 1 PRISMA flow diagram.**

typically better than systematic catatonia, which is insidious and progressive. If it is properly identified can respond extremely well to ECT[29].

The assessment of catatonia requires careful observation during the clinical interview and the elicitation of specific signs during the neurological examination[28]. The routine use of validated rating scales is recommended to facilitate the identification of catatonic signs and the diagnosis of catatonia [30]. In adult patients, seven catatonia rating scales are available. The BFCRS is the most commonly used in research and clinical settings, including older people, because of its validity and reliability and its ease of administration[28,30]. It is also very sensitive, requiring only 2 out of 14 signs of the screening instrument to diagnose this condition[30]. The DMS-5 states that a diagnosis of catatonia can be made if there are at least three symptoms out of 12 presents at the time of assessment: Stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerisms, stereotypy, agitation, grimacing, echolalia and echopraxia[2].

The association of catatonia and delirium has been increasingly described[31,32]. Delirium is considered the most salient factor to predict a medical cause of catatonia[33]. Both share clinical features, lack specific laboratory findings and biomarkers and are diagnosed in similar clinical settings [32]. Delirium is a prominent clinical manifestation of malignant catatonia[34], delirious mania[35] , and neuroleptic malignant syndrome (NMS)[34,36]. Coexisting delirium was found in 30%[8] and 50%[14] of cases of older adults with catatonia in acute medical settings, in which the clinical presentation was generally in the retarded-stuporous form. This high prevalence decreases significantly in acute psychogeriatric wards, where delirium was described in 4.8%[16] and 10%[11] of catatonic cases. The differential diagnosis between catatonia and delirium is challenging, as both cause prominent psychomotor abnormalities. Delirium's classification predominantly relates to its motor aspects and is thus divided into hyperactive, hypoactive, and mixed forms[31]. There are also hypoactive and hyperactive forms of catatonia. Catatonia can be misdiagnosed as delirium and managed as such, and while delirium appears in the list of differential diagnoses of catatonia, the latter rarely figures into that of delirium[32]. Furthermore, unlike delirium, approximately 80% of catatonia cases of medical etiology are due to neurological disorders[33]. However, there are differences in their pharmacological management. The treatment of choice in catatonia, lorazepam, is rarely the treatment of choice in delirium, except when caused by BZD withdrawal. The most widely used symptomatic treatment of choice in delirium, antipsychotics, is generally to be avoided in the management of catatonia. Therefore, the ability of clinicians to ascertain a catatonic dimension in cases of delirium will facilitate selection of the appropriate treatment[31,32].

### *Course and prognosis of catatonia*

Catatonia in older people often presents acutely, but it can also have an insidious presentation. The duration can be transient or chronic, lasting for weeks, months or even years[37,38]. The total duration of illness could be significantly lower if the etiology is a GMC when compared with affective or psychotic disorders[38,39]. Acute catatonia has a good prognosis if it is diagnosed early, its symptoms and etiology are treated in a timely fashion, and the necessary measures are taken to prevent complications. If complications are already present, they are treated aggressively[28]. In organic catatonia, structural brain lesions may have a worse prognosis than metabolic causes[8,40]. Older patients in general hospitals with a longer duration of untreated catatonia may have a worse outcome in terms of rates of complications (40%) and even death (20%)[8].

Catatonia may develop a chronic or continuous course in some patients, mainly with chronic psychoses. In a study in chronically hospitalized older schizophrenic patients, catatonic symptoms were less common and less severe than in acute hospital patients, but the clinical pattern was similar[37]. According to the authors of the study, these findings suggest that catatonic phenomena may persist for years, a course described by Kahlbaum in several cases where catatonia persisted, in some patients, until their death[37].

### *Etiology-catatonia due to GMCs*

**Neurological disorders:** Dementia: Catatonia has been described in all dementia types, with reports in patients with Alzheimer's disease (AD)[41-43]; frontotemporal dementia (FTD)[44-49]; dementia with Lewy bodies (DLB)[50-55]; and other cases with mixed, vascular, or nonspecified dementia[56,57]. Two prospective studies in psychogeriatric units reported a high prevalence of catatonia in patients with dementia using DSM-5 criteria, at 35.3%[16] and 42.8%[11]. This prevalence was found to be lower in another study in a general psychiatric ward, which report a prevalence of 4.7% using the same criteria [15]. In this last series, almost three-quarters of the patients with catatonia had dementia; 28% of patients had associated depressive disorder, and 36% had a GMC[15], an association also present in most of the published dementia case reports.

Encephalitis: Encephalitis occurs more frequently in younger people; however, a few case reports in older patients have been found[58-62]. Among the patients with anti- N-methyl-D-aspartate (NMDA) receptor encephalitis[59-62], one also tested positive for herpes simplex virus[59]. In this population, in this type of encephalitis, until 17.4% patients could present with catatonia[63]. The remaining case reports of catatonia in older patients involved a patient with paraneoplastic encephalitis[58] and a patient with anti-Hu encephalitis[61]. Prior to catatonia onset, most cases presented with an array of psychopathologies, such as delusions[58-60], auditory hallucinations[60], visuotactile hallucinations [59], and mania[61]. The only exception was a case report of a patient with a history of anxiety who presented with parkinsonism[62].

Epilepsy: In this review, 12 older patients with catatonia in the context of epileptic activity were found. Most had nonconvulsive status epilepticus (NCSE)[61,64,65], one case had complex partial seizures secondary to viral encephalitis in a patient with BD[61], one case of frontal lobe epilepsy in a patient with dementia[66], and a patient with schizophrenia who developed clonic seizures[64]. Among NCSE patients, 4 cases were associated with the use of antidepressants (bupropion 75 mg/d[64], paroxetine 20 mg/d[67], sertraline 50 mg/d[67], mirtazapine 30 mg/d and sertraline 50 mg/d[67]) and 1 with paroxetine 7.5 mg/d and gabapentine 900 mg/d withdrawal[64]. Five had delirium[64,68], 1 had acute kidney injury[65], 4 had acute depressive symptoms[64], 3 had acute psychotic symptoms[64,68], 1 had mania and anti-Hu meningoencephalitis[61].

Cerebrovascular disease: There were articles reporting older patients who developed catatonia secondary to acute strokes[8,69-72] and past or chronic vascular changes[73,74]. No relation was found between lesion location and emergence of catatonia. Some of these cases had longstanding depression as well[71]. As to newer onset psychopathology, there were 1 case with delirium[69], and 2 patients with psychosis[70,71].

Parkinson's disease: Two papers found that catatonia could be differentiated by parallel ratings of parkinsonian symptoms and catatonia scales in older adult patients with schizophrenia[37] or depression[75]. In the Starkstein's study[75], apomorphine improved Parkinson's symptoms without affecting catatonic symptoms, thus supporting a biological basis for a distinction between the two conditions. Our review found 6 older patients with catatonia and Parkinson's disease[76-81]. The cases presented with diverse psychiatric conditions. For instance, one case had depression[81] and another case had depression and posttraumatic stress disorder[76]. All these patients developed symptoms, such as depression[78,79] and psychosis[76-80], prior to catatonia onset.

Other neurological disorders: Other neurological entities found in older patients with catatonia were epidural empyema[7], progressive supranuclear palsy[82], frontotemporal lobes atrophy[83], cerebral Whipple's disease[84], Creutzfeld-Jakob disease[85] and cerebral anoxia after a cardiac arrest[86].

**Metabolic, infectious, endocrine, nutritional and neoplastic disorders:** Some metabolic derangements can cause catatonia in older people. These include acute renal failure[15,52,87], heart failure[8,15], liver failure[15], post liver transplantation[88], dehydration[15], hypernatremia[87,89] and hyponatremia[90-93]. Infectious disorders associated with catatonia are acute[94-96] and chronic recurrent urinary tract

infection[97]; pneumonia[8,15,98] and coronavirus disease 2019[99-101]. Associated endocrine disorders are hyperparathyroidism[102,103], hypothyroidism[93,95], subclinical Cushing's syndrome[104], and hyperthyroidism due to Grave's disease[105]. Finally, pertaining to nutritional and neoplastic etiologies, only one case of cyanocobalamin deficiency[106] and another of a colon tumor have been described[15]. Most of these patients had a psychiatric history and developed catatonia secondary to a GMC or in association with drug withdrawal. None of these cases presented with acute psychopathology, with the exception of 4 cases that showed affective and/or psychotic symptoms secondary to the primary metabolic[93] and endocrine disorders[103,105,106].

### *Etiology-drugs and toxic substances*

**Antipsychotics:** Many cases of catatonia related to antipsychotic use in older patients have been published. Of these, there were patients that developed NMS associated with aripiprazole[107] haloperidol[108-113] and loxapine[114]. In addition, there are reports of catatonia induced by pipothiazine[115], quetiapine[11,116], and droperidol[117] and cases secondary to exposure to more than one antipsychotic: Haloperidol and trifluperazine[109], risperidone and quetiapine[11], aripiprazole and olanzapine[11], and risperidone, haloperidol and tiapride[8].

**Other drugs and toxic substances:** In total, eleven case reports were found of patients who developed catatonia after exposure to normal doses of a wide variety of drugs, such as phenelzine[118], allopurinol [119], prednisone[95] rivastigmine[41], donepezil[120], azithromycin[121], cefepime[122], amiodarone [123], methotrexate[124], tacro-limus[125] and imiquimod[126]. Eight out of 11 patients were female, one case had a stable BD prior to the index episode[125], another case had DLB[120] and another had AD[41]. None of them had current affective or psychotic psychopathology before exposure to the drug. One case presented with hyponatremia[126] and another with acute interstitial nephritis[122]. The others developed psychotic or depressive symptoms prior to, or simultaneously with, catatonia. There was also a catatonia case secondary to neurotoxicity reported by manganese[96] and another after deep brain stimulation successfully treated with lorazepam and right unilateral ECT[127].

**Catatonia secondary to drug withdrawal:** Descriptions of catatonia after the rapid tapering or abrupt discontinuation of BZDs after prolonged use have been published. These cases were related to nitrazepam[128], diazepam and alprazolam[128] , oxaze-pam and temazepam[128], clonazepam[128, 129], alprazolam[128], temazepam[128], diazepam[128], chlordiazepoxide[128] and lorazepam[130]. The doses of BZDs vary widely, but they are usually in the therapeutic range. The onset of withdrawal catatonia is 3-7 d after discontinuation, and the duration is 3-10 d. Also, it appears to present without electroencephalography abnormalities, such as diffuse slowing[128]. Moreover, there are sporadic reports of withdrawal catatonia secondary to antipsychotics and other psychotropics, such as clozapine [131], olanzapine[94], risperidone and olanzapine and chlorpromazine[56], haloperidol and cyamemazine[132], bromperidol and levomepromazine[133], amantadine[79], gabapentin[64,134], and lithium[94].

### *Etiology-catatonia secondary to psychiatric conditions*

**Affective disorders:** Studies in psychogeriatric units found a prevalence of affective disorders in catatonia of 40% (Table 1) and 42.8%[16]. In a psychiatric general inpatient service, catatonia was most prevalent among older patients with severe depression[75]. These patients had more severe cognitive impairment and more severe deficits in activities of daily living than depressed noncatatonic patients [75]. In a similar setting in Hungary, 28% of catatonic patients suffered from dementia associated with depressive disorder[15]. This relationship between the development of catatonia and organic conditions in patients with affective disorders has been replicated in most of the case reports or case series published[61,64,68,135].

Most case reports of catatonia in affective disorders have been published emphasizing the unusualness of the presentation (patient that can masquerade as Creutzfeld-Jakob disease[136]), the associated psychopathology (cases with nihilistic delusions suggestive of Cotard's syndrome[137,138]), or the comorbid conditions present (the affective cases described in the sections on catatonia secondary to GMCs or drug use/withdrawal).

**Schizophrenia spectrum disorders:** Reports of older patients with catatonia in psychotic disorders are sporadic. Cases of catatonia have been described in association with schizophrenia[139], psychotic disorder not otherwise specified[16], brief psychotic disorder[135] and schizoaffective disorder[11,15, 16]. In a study conducted in older adults with schizophrenia, a catatonia prevalence of 69% using BFCRS criteria was found[37]. In acute inpatient wards, schizophrenia spectrum disorders (SSD) is the third most frequent condition in catatonic older patients following affective disorders and those secondary to GMCs[11,16].

**Other disorders:** Catatonia has been reported in adjustment disorder[16,140], substance use disorder [16], conversion disorder[140,141], and posttraumatic stress disorder[142]. In one case report, there was a background of melancholia and a recent withdrawal of thioridazine; in another case report, the

adjustment disorder was diagnosed with depressed mood. In the remaining reports, psychiatric or organic comorbidities were not detailed. Table 4 shows all the etiologies associated with catatonia described above.

### *Treatment*

**BZDs:** BZDs are an effective treatment for catatonia in older adults in whom a full resolution is described within hours/days of treatment initiation[6]. Lorazepam is recommended as the first-line medication, and it is extensively reported to be highly effective, irrespective of the underlying cause[5,6,143,144]. Other BZDs, such as diazepam[128,145], midazolam[146,147], alprazolam[148], oxazepam [128], flunitrazepam[139], temazepam[128] and clorazepate[108], have also been described as useful in older people. This treatment should be maintained until the catatonia etiology is identified and appropriately treated[1,28]. In this review, the initial doses of lorazepam found ranged from 0.25 to 4 mg daily, with most patients receiving 1-2 mg. If catatonic symptoms respond partially to low doses of BZDs, titration to higher doses is recommended to achieve full symptom resolution[5,6]. During catatonic states, in this and in the other age groups, high BZD doses are typically well tolerated[6]. In older people, the associated risks are oversedation, respiratory depression, cognitive impairment, and falls[149]; therefore, monitoring is necessary. In the reviewed cases, doses ranged from 3-20 mg lorazepam/d. Lower response rates to BZDs have been described in patients with structural brain damage or with schizophrenia when compared with mood disorders or acute medical etiologies[5,6].

**ECT:** ECT should be a first-line treatment in patients with nonresponse or contraindication to BZDs, those who need a rapid response because of life-threatening conditions, or when malignant catatonia features are present[5,6,150]. Better response rates to treatment were found in catatonia related to mood disorders than in catatonia related to nonaffective psychosis[5,6,68]. Even so, ECT is one of the best treatments for catatonic schizophrenia, and this was also described in older patients by Suzuki *et al* [139], with excellent response rates in this group.

Among the older catatonic patients successfully treated with ECT, the etiology in most of them were mood disorders, followed by those secondary to non-affective psychosis. Less frequently the etiology was related to a GMC.

The number of sessions ranged from 2 to 25, but only 3 patients needed more than 15 sessions to respond. The mean number of sessions among all catatonic episodes was 10.33 sessions/episode. Exceptionally high initial seizure threshold in catatonic older patients treated with ECT has been reported[151].

The most common application frequencies during acute course ECT were 2 or 3 times a week. Most cases were treated with bifrontotemporal electrode placement and also, there has been reports of patients that received right unilateral ECT with a resolution of catatonia[152,153]. Furthermore, there is a report of a patient with catatonic schizophrenia who was treated by successful seizure induction by means of ECT, with electrodes applied bilaterally to the parietotemporal region after bifrontotemporal ECT failed to induce adequate seizures[154]. On the other hand, 3 articles described only a partial response to ECT in 3 older patients during a catatonic state after receiving 7-8 ECT sessions[8,78,155]. All these cases were associated with GMCs (cognitive impairment, Parkinson's disease, and manganese poisoning).

Two cases of catatonia refractory to ECT treatment have been reported. One on them was associated with encephalitis secondary to ovarian teratoma[58] and another one in a patient with depression and autistic spectrum disorder[151]. Continuation or maintenance ECT is recommended when relapse occurs despite pharmacological treatment and in patients with recurrence of catatonic symptoms when ECT is suspended[139]. Three cases were described with periodic relapses, but each new catatonic episode responded again to a course of ECT. Although there are no absolute contraindications for the use of ECT in older patients and it is considered a safe and well-tolerated treatment, medical risks must be evaluated individually[143,150]. There are case reports of catatonic patients with unstable or potentially unstable clinical conditions, such as a 95-year-old pacemaker user[156], full anticoagulation after pulmonary embolism[157], a 100-year-old patient with severe aortic stenosis[158], deep venous thrombosis[159]; that illustrates how, with the proper precautions, the benefits of ECT in such conditions might outweigh its risks.

ECT requires general anesthesia. Serious adverse effects related to ECT are extremely infrequent but include arrhythmia, seizures, or even death, although these have not been specifically reported in this population. Other mild adverse effects are considered transient, but they can be relevant in the older population, such as cognitive impairment, delirium, hypertension, increased risk of falls, or hypomania [150]. Cognitive impairment related to ECT is reported as transient, even in older patients, but limited cases of prolonged amnesia have also been described[160].

**Etiological treatment:** Early identification and treatment of etiological causes of catatonia are crucial, especially in this population[8,11,14]. Even in those patients with a previous history of psychiatric disorder, medical etiologies should always be considered because of the frequent simultaneous occurrence of both conditions[8,14,15,143]. Organic, toxic, and pharmacological conditions are common causes of catatonia and are overrepresented in the older population. In most cases of catatonia in this

**Table 4 Catatonia etiology in older people**

| Psychiatric disorders | General medical conditions | Drugs and toxic substances |
|---|---|---|
| Schizophrenia spectrum disorders: Schizophrenia; Schizoaffective disorder; Brief psychotic disorder; Psychosis not otherwise specified. Affective disorders: Major depressive disorder; Bipolar disorder. Others psychiatric disorders: Post-traumatic stress disorder; Conversive disorder; Adjustment disorder; Substance use disorder | Neurologic: Dementia: Alzheimer´s dementia; Frontotemporal dementia; Lewy bodies dementia; Mixed dementia; Organic dementia; Dementia not otherwise specified. Epilepsy. Cerebrovascular disease; Parkinson´s disease. Others: Cerebral anoxia; Creutzfeldt-Jakob's disease; Epidural empyema; Frontotemporal lobes atrophy; Cerebral Whipple's disease; Progressive supranuclear palsy. Metabolic: Acute renal failure; Heart failure; Liver failure; Post liver transplantation; Dehydration; Hyponatremia; Hypernatremia. Infectious: Urinary tract infection; Pneumonia; COVID-19. Endocrine: Hyperparathyroidism; Hypothyroidism; Hyperthyroidism. Others: Cyanocobalamin deficiency; Colon tumor | Drugs: Regular use: Antipsychotics: Haloperidol; Droperidol; Loxapine; Pipotiazine; Trifluoperazine; Tiapride; Aripiprazole; Risperidone; Quetiapine. Other drugs: Phenelzine; Allopurinol; Prednisone; Rivastigmine; Donepezil; Azithromycin; Cefepime; Amiodarone; Tacrolimus; Methotrexate; Imiquimod. Withdrawal: Benzodiazepines: Nitrazepam, diazepam, alprazolam, oxazepam, temazepam, clonazepam, chlordiazepoxide and lorazepam. Antipsychotics: Clozapine, olanzapine, risperidone, chlorpromazine, levomepromazine, bromperidol, haloperidol and cyamemazine. Others: Amantadine, lithium, gabapentine. Toxic substances: Manganese |

COVID-19: Coronavirus disease 2019.

literature search, remission occurred after specific catatonia symptomatic treatment was administered as well as treatment for the underlying medical condition[8,11,64,94]. Some reports noted remission of catatonia only when treating the underlying medical condition, without symptomatic treatment for catatonia[8,69,102,161]. Recent medication changes should be considered relevant because they highly suggest drug-induced catatonia. Suspension of the causal drug should be considered as part of the treatment, as in some patients, resolution of the catatonic state was only achieved with discontinuation of the drug[8,92,95], while others also needed con-comitant symptomatic catatonia treatment[8,95,109,162].

**Other treatments:** Zolpidem was broadly reported as an effective treatment for catatonia but with transient efficacy. In general, it was used as a diagnostic test because of its very short half-life when catatonia was suspected[108]. Other reports described the successful treatment of catatonic older patients with zolpidem alone or in combination with other treatments; thus, it could be considered an alternative treatment[45,49,58,104]. The NMDA receptor antagonists memantine and amantadine have also been reported as useful symptomatic treatments for catatonia, even in treatment-resistant patients [163]. Memantine doses ranged from 5-10 mg daily[163]. Amantadine was described as effective (doses ranging from 100-200 mg daily)[78,163]; however, nonresponsiveness was also reported[42,45,164,165]. Anticonvulsant drugs have been used as a catatonia treatment option in this population alone or in combination with partial or complete response. There are reports of valproate at doses ranging from 400-1250 mg daily[11,91,135,163], carbamazepine (100 mg/daily)[78], and topiramate[166]. Additionally, there are articles that described no response to valproate[91,163] or carbamazepine 600 mg/daily[167]. Dopaminergic drugs have also been postulated as potential treatments for catatonia due to the hypothesis that the dopaminergic system is involved in its pathophysiology. There are isolated reports of treatment with bromocriptine[112] and dopamine, the latter being used to treat hypotension during a catatonic state with full recovery[168]. The patient received bupropion as continuation treatment without relapse of catatonia. Also, there have been published a NMS cases which were treated satisfactorily with 25 ECT sessions and bupropion 300 mg/d[164] and with 11 ECT sessions and bromocriptine 15 mg/d[112]. Another article reported a case of successful treatment with methylphenidate in an older depressed patient with catatonic stupor who did not respond to lorazepam[169]. There are articles reporting anecdotal evidence of successful treatment of catatonia with propofol[170] , biperiden[171,172], olanzapine[162,173] and lithium[174]. Another article reported the on efficacy of tramadol in several consecutive catatonic episodes in an older patient with a diagnosis of schizoaffective disorder[132]. Finally, neuromodulation treatments, such as repetitive transcranial magnetic stimulation [111] and transcranial direct current stimulation[175], were also described as effective. The catatonia treatments used in older people are summarized in Table 5.

### *Prevention and treatment of adverse events*

Catatonic states can induce complications in relation to immobility, dehydration or inability to have oral intake, which are especially relevant in older patients. Some of these complications include deep vein thrombosis (DVT), pulmonary embolism, pressure ulcers, infections, acute renal injury, rhabdomyolysis, electrolyte distur-bances, pulmonary aspiration and secondary pneumonitis and/or pneumonia, or muscular contractures[143,165,176].

In a retrospective chart review, Ishida *et al*[176] concluded that age and the presence of risk factors for dynamic vascular patterns were significantly associated with the incidence of DVT. Patients older than 65 years had an odd ratio (OR) of 3.23, and younger patients had an OR of 1[176].

**Table 5 Catatonia treatments used in older people**

| 1º line | 2º line | 3º line |
|---|---|---|
| Benzodiazepines: Lorazepam; Diazepam; Midazolam; Alprazolam; Oxazepam; Flunitrazepam; Temazepam | Electroconvulsive therapy: Bifrontotemporal ECT; Right unilateral ECT; Acute ECT; Continuation ECT; Maintenance ECT | Drugs: Amantadine; Biperiden; Bupropion (as continuation treatment); Bromocriptine; Carbamazepine; Dopamine; Lithium; Memantine; Methylphenidate; Olanzapine; Propofol; Topiramate; Tramadol; Valproate; Zolpidem. Neuromodulation treatments: Repetitive Transcranial Magnetic Stimulation; Transcranial Direct Current Stimulation |

ECT: Electroconvulsive therapy.

Early identification and treatment of catatonia and its underlying cause are crucial to rapidly improve stupor and prevent all these complications[5,6,144]. Specific preventative measures include frequent vital sign checks, anticoagulation, postural changes, intravenous fluids, nasogastric feeding, and urinary catheterization[165]. Additionally, the progression to malignant catatonia with autonomic instability and hyperthermia is a life-threatening condition that should be watched.

## DISCUSSION

Catatonia in older people is an underrecognized entity and is consequently undertreated, as evidenced by the scarce literature found after a systematic search. The majority of articles are case reports or case series, with few prospective studies. However, a very interesting fact is evident: Most case descriptions show similar medical and psychiatry histories, clinical manifestations, etiologies, comorbidities and responses to treatment; clinical correlates that are very similar to those cases reported by prospective studies.

Catatonia in this population is highly prevalent, and the prevalence increases when the clinical setting studied is more specific (general hospital: 5.5%[14] and 8.9%[8]; general psychiatry unit: 11.2%[15]; psychogeriatric units: 27% (Table 1) and 39.6%[16]. Catatonia prevalence in younger patients in similar settings is lower: 1.6%[177], 1.8%[108] and 2.4%[8] in liaison services and approximately 10% in acute inpatient wards[13]. This suggests that older people may have a higher risk of developing catatonia than those under 65 years of age, as shown in Navarra's liaison psychiatry study, where their patients over 65 years were 3.95 times more likely to develop catatonia than their younger counterparts [8].

There is some evidence that supports the possibility that somatic and cognitive impairment have a significant role in the development of catatonia[16]. This could be related to the highest prevalence of dementia and medical disorders, such as cardiovascular risk factors (hypertension, type 2 diabetes mellitus, and dyslipidemia), in this population[178], which were present in most case reports described in the United Kingdom psychogeriatric ward (Table 1) and in all patients of the psychiatry liaison consultation studies[8,14] (the other 2 prospective studies did not specify these data). It has been considered whether dementia is a specific risk factor for developing catatonia. Takács *et al*[15], in a study in a general psychiatry ward, concluded that it was not a risk factor, as the prevalence of catatonia was not very different in their patients with dementia (4.7%) compared to the total study sample (6.1%). However, in studies on psychogeriatric wards, the prevalence was higher in patients with dementia (35.3%[16] and 42.8%[11]) than in the total number of patients [20.8%[16] and 24.3% (Table 1)]. This nonconcordance could be caused by differences in the clinical settings and leaves open the role of dementia as a risk factor for catatonia.

The clinical presentation of catatonia is quite similar to that of adults under 65 years of age. In general, the most frequent signs are the same (immobility, staring, mutism, negativism, withdrawal, rigidity and posturing)[5,12,38]. Unlike what happens in patients under 65 years of age, excitement (41.8%), verbigeration (37.9%), perseveration (33%) and autonomic abnormalities (27.8%) seem to also be very frequent. In older people, the high prevalence of dementia and cardiovascular risk factors could also explain this different profile. In all catatonia prospective studies, the assessment was undertaken in a systematic way using the BFCRS; notably, the low frequency of the catatonic signs considered DSM-5 diagnostic criteria [ecophenomena (17,7%), grimacing (15,3%), waxy flexibility (7,6%) and mannerism (5,1%)] and the high frequency of other catatonic signs included in the BFCRS and not the DSM-5 criteria [staring (62%), withdrawal (45,6%) rigidity (45,6%) and autonomic abnormalities (27,8%)] (Table 3). These results could suggest the need to review the very strict current diagnostic criteria and to take into account what was reported by Stuivenga *et al*[12], that giving a dimensional approach to catatonic signs could help improve diagnostic sensitivity. In older people, it may be better to use, in an initial assessment, the Bush Francis Catatonia Screening Instrument, which includes the above catatonic signs, to identify more patients susceptible to receiving potentially very effective treatment.

Catatonia and delirium co-occur relatively frequently in older people. Management could be a challenge for clinicians; however, if we follow a therapeutic and care algorithm, the chances of better

results are greater[32]. A systematic review on the issue recommended identifying and treating the etiology of both conditions, initially trying a challenge test with lorazepam; avoiding the use of high-potency neuroleptics; taking the necessary measures to prevent and treat complications; and if there is no response with lorazepam, considering the use of amantadine, memantine or topiramate. ECT is indicated in refractory or life-threatening cases[32].

The probability that catatonia in acute medical settings has a medical etiology or is related to drug use/withdrawal is greater than 50%. The prevalence of catatonia was strongly associated with age in the setting of critical illness[179]. This probability increases in critically ill elderly patients by up to 80%-100%[33]. These high rates of catatonia in clinical settings should lead us to consider that the etiology of catatonia is medical until proven otherwise, especially in older adults[33]. It has been frequently reported that the possible organic etiology of patients with catatonia tends to be overlooked, even more so if they have a psychiatric history because of a belief that the psychiatric disorder is the cause of catatonia[143,180].

In almost all dementia cases traced, these disorders were not the cause of catatonia; rather, they emerged as a consequence of the acute onset of psychopathology, GMCs, and/or due to the use of drugs, mainly neuroleptics. This occurred in 29 of 31 (93.5%) patients with dementia reported in observational prospective studies[8,11,14-16]. This does not appear to occur in FTD patients. Catatonia and FTD share a common pathophysiology, frontal lobe dysfunction, and similar symptoms (mutism, stupor, stereotypy, mannerisms, perseveration, negativism, echophenomena, and others[44], which are a central part of their diagnostic criteria[2,181]. This could cause catatonia to be even more underdiagnosed and therefore not adequately treated in this specific type of dementia. In FTD, catatonia should be suspected when the patient has a sudden and sustained increase in previous psychomotor symptoms or when the appearance of new catatonic symptoms is observed. In the rest of the reports of catatonia secondary to neurological disorders, GMCs and the use of drugs, something similar takes place. Catatonia occurs frequently when GMCs cause psychotic or depressive symptoms or when the latter appear as drug adverse effects and/or in patients with a psychiatric history of disorders of both spectra. In future studies, the systematic evaluation of the presence or absence of depressive or psychotic psychopathology in these patients will reveal their roles in the development of catatonia.

In general, in this population, antipsychotics can also increase the risk of NMS and can contribute to the development or worsening of catatonic symptoms[182,183]. Moreover, the NMS risk of poor outcome and mortality is associated with older age[184]. Some authors have recommended antipsychotic discontinuation during the acute phase of catatonia and to reinitiate treatment once catatonia is in remission[5,185]. Due to the risks concerning the safety of antipsychotics, their use in acute catatonia is generally not recommended in this population[185]. Caution should be the rule on prescribing, and the risk assessment should be individualized to each patient[6]. Catatonia can also appear after withdrawal from different types of drugs, mainly BZDs. The predominant subtype was stuporous catatonia with sporadic reports of catatonic excitement. Given that BZD withdrawal is more frequently associated with motor hyperactivity, excited catatonia may not be reported as such[128]. A significant number of these reports described a series of concurrent psychiatric and GMCs that could have played a role in the development of catatonia, mainly depression[128], dementia[57], pneumonia, and infectious exacerbation of chronic obstructive pulmonary disease[128]. Rosebush and Mazurek[186] suggest the possibility that older individuals may be more vulnerable to developing catatonia upon BZD withdrawal, particularly if the drug is rapidly tapered or abruptly discontinued in patients who have taken them for a long time.

In relation to catatonia secondary to psychiatric conditions, this syndrome is more frequently associated with mood disorders than with SSD, as occurs in patients between 18 and 65 years of age. In this population, mood disorders were associated with a 2.7-fold higher risk of developing catatonia compared to psychotic conditions[16]. Again, in patients with affective disorders, age could be a risk factor for developing catatonia. A naturalistic cohort study in BD patients showed that it could present more frequently in older people with catatonic features compared with younger people[187]. As in affective conditions, most of the reports of catatonia in SSD patients have acute psychotic and/or depressive psychopathology and various organic disorders. Although catatonia has been described in practically all the mental conditions of our classification systems, in older adults, cases published outside of affective and SSD disorders are anecdotal and probably due to lack of recognition.

General treatment recommendations on catatonia are derived from case reports or observational studies due to the lack of randomized controlled trials[188]. Despite a possible publication bias, usual treatments, such as BZDs and ECT, show excellent response rates and are considered effective in older adults[5,6,143,144]. Lorazepam is the most extensively used BZD, but other options (Table 5) were tested with good responses. ECT is considered the most successful treatment for catatonia. It is also a safe and effective option for treating catatonia in older patients, regardless of the etiology[5,6]. Some studies have suggested that ECT may be more effective in older patients than in other age groups[139]. It remains controversial whether ECT should be considered a first-line treatment in older patients when catatonia symptoms appear in the context of a MDD[150]. Faster and higher remission rates have been described with ECT in comparison with antidepressant medications. Therefore, it seems reasonable to consider ECT as a priority option if catatonia is present and the underlying condition is also responsive to ECT [150]. There are interesting descriptions of the response to catatonia treatment with other drugs;

however, we can consider these options as a third-line treatment because of the limited literature available on the matter (Table 5).

Our review has important limitations, the main one being that all the conclusions are based on the results of mostly case reports and few prospective studies. Publication bias may be present, and the heterogeneity of the prospective studies does not allow for qualitative analysis. The hypotheses presented here will have to be confirmed in prospective studies designed specifically for that purpose. However, the clinical correlates of all these cases significantly coincide with the results of prospective studies, regardless of the year or place of publication or etiology of catatonia. The most important strength is the summarizing of all the bibliographies on catatonia in older adults published since inception in the main medical databases until December 2021, using articles obtained through a systematic search following the PRISMA recommendations.

## CONCLUSION

Catatonia in older people is highly prevalent and is associated with affective disorders, GMCs, and SSDs in that order of frequency, although its etiology is frequently multifactorial. GMCs, mainly dementia and other neurologic disorders, have a significant role in the etiology, and this is sometimes overlooked. Older patients, compared to younger patients, have a higher risk of developing catatonia in BD, in psychiatric liaison services, and they may be more vulnerable to developing catatonia with BZD withdrawal. Age, together with other risk factors, was significantly associated with the incidence of DVT, NMS poor outcome, other complications and mortality. The response to symptomatic treatment with BZDs and ECT is very good and safe, and other effective options are also available. The simultaneous treatment of the etiology of catatonia is also fundamental. Specifically, designed prospective studies are needed to more accurately identify the clinical correlates of catatonia in older people.

## ARTICLE HIGHLIGHTS

### *Research background*

Catatonia in older people is an underrecognized and undertreated systemic medical syndrome despite having specific treatment that has shown great effectiveness. These patients are at increased susceptibility of developing potentially life-threatening complications.

### *Research motivation*

Systematic reviews on this topic have not been conducted. Similar previous reviews were not systematic, and since their publication, the number of papers in this regard has practically doubled. We considered that an update was necessary.

### *Research objectives*

This review aimed to synthesize all the published literature related to catatonia in older patients. This summary will provide up-to-date knowledge about this condition.

### *Research methods*

A comprehensive systematic review was conducted according to PRISMA recom-mendations. An extensive search strategy was developed, and the MEDLINE, EMBASE, and PsycINFO databases were searched. Screening was completed in duplicate. Papers that investigated issues related to catatonia and/or catatonic symptoms in older people with an English abstract available were included. Additionally, we provided all the clinical correlates of our series of catatonia in a psychogeriatric ward.

### *Research results*

In total, 173 articles were considered in this systematic review. Most of them were case reports and case series (143), and only 11 were prospective cohort studies. Catatonia in older people is highly prevalent, and in most cases, its etiology is multifactorial. Neurological disorders could play a very important role in catatonia development; in part, cardiovascular risk factors could explain this association. BZDs and ECT are very effective and well tolerated treatments.

### *Research conclusions*

This systematic review provides a comprehensive summary of catatonia in older people. These patients have a higher risk of developing catatonia than younger patients with BD in the general hospital and secondary to BZD withdrawal. Age is related, within other risk factors, to poor NMS prognosis and the development of complications.

### *Research perspectives*

The current review revealed that the number and quality of studies on this issue are scarce. Given the high morbidity of catatonia in older people, prompt identification and treatment are essential. Thus, further prospective research is warranted to more accurately identify all the clinical aspects of catatonia in older people.

## FOOTNOTES

**Author contributions:** Jaimes-Albornoz W and Serra-Mestres J designed this study and completed article screening, data extraction, analysis and interpretation as well as manuscript preparation; Isetta M prepared and wrote the methods section, acquired data and performed initial screening; Ruiz de Pellon-Santamaria A, Nizama-Vía A and Albajar I completed additional data extraction, analysis and interpretation and prepared and wrote manuscript subsections; all authors read and approved the final manuscript.

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SCIENTOMETRICS

# Burnout amongst radiologists: A bibliometric study from 1993 to 2020

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## Abstract

### *BACKGROUND*

Burnout amongst radiologists is common in many different institutions and is increasing day by day. To battle burnout, we have to address the root causes already recognized in published literature. Therefore, it is crucial to examine and discern important publications.

### *AIM*

To provide evidence-based data and trends related to burnout in radiologists so that researchers can work on it further and develop preventive strategies to overcome this problem.

### *METHODS*

Bibliometric analysis conducted by two independent reviewers separately used Scopus Library for data extraction by using medical subject heading and International Classification of Diseases keywords. Forty-nine articles were selected for analysis after an extensive scrutiny. Statistical Package for the Social Sciences version 20 was used for analysis. Pearson correlation coefficient, Kruskal Wallis test, and Mann-Whitney U test were applied.

### *RESULTS*

The most productive period with regards to the number of publications was between 2017 and 2019. A total of 160 authors contributed to the topic burnout among radiologists, with an average of 3.26 authors *per* paper. About 41.68% of the authors were female, whilst 35% of them were first authors. The co-citation analysis by author involved 188 cited authors, 13 of whom were cited at least 70 times. Only six out of forty-nine studies were funded by various government

institutions and non-governmental organizations.

*CONCLUSION*
Current analysis casts a spotlight on important trends being witnessed in regard to the mental health of radiologists, including lack of funding for mental health research, narrowing of female *vs* male citation gap, as well as authorship and citation trends.

**Key Words:** Bibliometric; Analysis; Burnout; Radiologist; Stress; Scientometrics

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**Core Tip:** Our analysis casts a spotlight on important trends being witnessed in regard to the mental health of radiologists. These include lack of funding for mental health research, narrowing of female *vs* male citation gap, as well as authorship and citation trends. By studying these patterns, we can understand key areas lacking in the current bulk of radiological research and subsequently address them to improve the long-term yield, variety, and impact of radiological studies.

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## INTRODUCTION

Burnout is a syndrome described in International Classification of Diseases 11th edition as a result of chronic workplace stress that has not been successfully managed. It is characterized by feelings of exhaustion, negativism, and reduced professional efficacy[1,2]. Burnout is a major problem that is affecting multiple specialties[3]. The Medscape National Physician Burnout and Depression Report of 2018 conducted a survey that involved 15000 physicians from different specialties. It revealed that 42% of physicians were burned out, 12% were feeling depressed, and 3% were clinically depressed[4]. According to National Physician Burnout and Suicide Report 2020, radiologists rank among the top five specialties most burned out. Diagnostic radiologists have a higher rate of burnout than the average for all physicians[5]. Several studies have shown burnout in both radiology physicians and radiology trainees[6,7].

Burnout amongst radiologists is common in many different institutions and is increasing day by day. Shanafelt *et al*[8] stated the prevalence of burnout among radiologists in the United States to be 61.4% ($n$ = 261) in 2014; a statistically significant increase from 47.7% ($n$ = 216) in 2011[8]. Burnout in radiologists is also common in Canada because of increased workload and employment constraints[9]. A study conducted in Saudi Arabia concluded that one-fourth of radiology residents have high burnout rates [10]. These high rates of burnout not only affect the physicians' well-being but also their patients and the healthcare system as a whole. It is associated with medical errors, lapses in patient safety, disruptive workplace behaviors, depression, and substance abuse[11]. People suffering from burnout are also at an increased risk of cardiovascular-related events, metabolic syndrome, systemic inflammation, and impaired immunity[12].

Essentially, bibliometric is the application of quantitative analysis and statistics to publications such as journal articles and their accompanying citation counts[13]. Analysis of the citation counts can reveal the most productive authors, countries, institutions, and journals within a particular research area[14]. The procedure is transparent, and results can be reproduced using the same method and are scalable. It serves the purpose of guiding limited resources to important research areas[14]. This research will provide evidence based data and trends related to burnout in radiologists so that researchers can work on it further and develop preventive strategies to overcome this problem.

## MATERIALS AND METHODS

### *Data extraction software*

Scopus Library was selected as the preferred library for data extraction because of its extensive coverage of articles from all over the globe, it is faster and operator friendly, and citation analysis is faster as compared with Web of Science, Google Scholar, and PubMed[15].

### Article selection

Only original articles were included in research to maintain authenticity of the paper. Reviews, editorials, reports, guidelines, and commentary were excluded. Articles written in English language were only included in the study. Only articles related to consultant radiologist and radiology trainees/postgraduates were selected for analysis. Articles related to radiology nurses, radiology technicians, and other helping staff were excluded in order to get an authentic estimation of burnout among radiology doctors. There was no limitation on the basis of time of publication of article.

### Keywords selection

The International Classification of Diseases 11$^{th}$ edition, medical subject heading, and review articles from various sources were used to form a final list of keywords. They were searched in abstract, article title, and keywords section of articles. Keywords include "burnout", "burnout syndrome", "stress", "mental stress", "strain", "mental strain", "overload", "exhaustion", "mental distress", "depersonalization", "companion fatigue", "emotional wellbeing", "job satisfaction", "radiologist", "radiology resident", "radiology trainee", "radiology postgraduate", "radiology post-graduate", "consultant radiologist", "radiology department", and "radiology fellow".

### Data extraction

Data were extracted in the month of March 2020 by two authors (MFHQ and MHA) separately and a final list of articles was prepared. A difference of 7.4% was identified between both the lists, which was resolved by consulting a third reviewer (DM). The final list of articles was composed by extensive vetting of articles through complete text reading of articles and determining its characters based on inclusion criteria. Forty-nine articles were selected for analysis. Data were extracted to Microsoft Excel from Scopus consisting of name of article, year of publication, number of citations, digital object identifier, affiliation of authors, country of origin of authors, journals, H-factor, and funding of study. Gender of authors was determined by searching for their profiles on official institutions sites. Impact factor was determined by Journal Citation Report 2019.

### Statistical analysis

Statistical Package for the Social Sciences (SPSS), version 20 (Armonk, NY, United States) was used for analysis. In order to determine association between impact factor of journals and citations, the Pearson correlation coefficient test was used. In order to determine impact of funding and citations, Kruskal Wallis test was applied. For association of gender with citations, Mann-Whitney U test was applied. $P < 0.05$ was considered as significant. Co-citation analysis was performed using Vos Viewer version 1.6.14.

## RESULTS

All the articles on burnout among radiologists with their total citation and digital object identifier are given Table 1 in descending order in reference to their year of publication. The mean number of citations for the article in Table 1 was 27, while the median was 10 (interquartile range = 18). When citations of all the articles were summed up, the sum was found to be 1328, of which 5.9% ($n = 76$) were self-citation. The number of citations *per* year ranged from one to 12 (Table 1).

Figure 1 shows the total number of citations *per* year, with the graph increasing rapidly after 2016. The most productive time period with regards to number of publications was between 2017 and 2019, in which 16 articles were published out of 49, as shown in Figure 2, while the least productive time period was before 1993, during which not a single article was published on burnout among radiologists.

### Top rated journals and institutions

All 49 articles were published in 29 journals belonging to different parts of the world; journals were ranked according to the greatest number of publications, which are shown in Table 2, along with their citations and impact factors. Impact factors of journals ranged from 0.32-15. Statistically significant association was found between number of publications and journal impact factor, with $P$ value of < 0.01, while journal impact factor and number of citations was also significant, with $P$ value of 0.02.

Harvard Medical School and Università Cattolica Del Sacro Cuore, Rome were the leading institutions, with more than five publications, respectively, followed by University of Washington, Seattle (four publications) and University of Texas MD Anderson Cancer Centre (three publications) (Supplementary Table 1).

### Top authors and their countries of origin

A total of 160 authors contributed to the topic burnout among radiologists, with an average of 3.26 authors *per* paper. Author *per* article ranged from 1 to 12. Nineteen out of 160 worked on more than one article, as shown in Table 3 along with their H-index and gender. In total, 41.68% of the authors were female, while 35% of them were first authors. Statistically significant association was found between

**Table 1 Articles with digital object identifier and number of citations**

| No | Article title | DOI | Number of citations |
|---|---|---|---|
| 1 | Burnout among Interventional Radiologists | 10.1016/j.jvir.2019.06.002 | 1 |
| 2 | Burnout in Canadian Radiology Residency: A National Assessment of Prevalence and Underlying Contributory Factors | 10.1177/0846537119885672 | 1 |
| 3 | Burnout in Academic Radiologists in the United States | 10.1016/j.acra.2019.12.029 | 1 |
| 4 | Radiologist Burnout According to Surveyed Radiology Practice Leaders | 10.1016/j.jacr.2019.07.008 | 5 |
| 5 | Burnout in Chairs of Academic Radiology Departments in the United States | 10.1016/j.acra.2018.12.006 | 3 |
| 6 | Association of Racial Bias with Burnout among Resident Physicians | 10.1001/jamanetworkopen.2019.7457 | 6 |
| 7 | Stressors contributing to burnout amongst paediatric radiologists: Results from a survey of the Society for Paediatric Radiology | 10.1007/s00247-019-04370-z | 3 |
| 8 | Prevalence of Burnout Among Paediatric Radiologists | 10.1016/j.jacr.2018.08.016 | 10 |
| 9 | Impact of work hours and sleep on well-being and burnout for physicians-in-training: The Resident Activity Tracker Evaluation Study | 10.1111/medu.13757 | 4 |
| 10 | Using Wellness Days to Mitigate Resident Burnout | 10.1016/j.jacr.2018.09.005 | 1 |
| 11 | Burnout Phenomenon and Its Predictors in Radiology Residents | 10.1016/j.acra.2019.09.024 | 0 |
| 12 | Non-radiation occupational hazards and health issues faced by radiologists-A cross-sectional study of Indian radiologists | 10.4103/ijri.IJRI_403_18 | 1 |
| 13 | Prevalence of Burnout Among Canadian Radiologists and Radiology Trainees | 10.1016/j.carj.2018.05.005 | 5 |
| 14 | Burnout: Job Resources and Job Demands Associated with Low Personal Accomplishment in United States Radiology Residents | 10.1016/j.acra.2017.12.002 | 14 |
| 15 | Burnout: Prevalence and associated factors among radiology residents in New England with comparison against United States resident physicians in other specialties | 10.2214/AJR.16.17541 | 30 |
| 16 | Emotional Wellness of Current Musculoskeletal Radiology Fellows | 10.1016/j.acra.2016.12.024 | 8 |
| 17 | Occupational burnout among radiographers, sonographers and radiologists in Australia and New Zealand: Findings from a national survey | 10.1111/1754-9485.12547 | 6 |
| 18 | Reading efficiency can be improved by minor modification of assigned duties; a pilot study on a small team of general radiologists | 10.1007/s11604-017-0629-8 | 4 |
| 19 | Prevalence of burnout among musculoskeletal radiologists | 10.1007/s00256-017-2578-9 | 22 |
| 20 | Burnout, stress and satisfaction among Australian and New Zealand radiation oncology trainees | 10.1111/1754-9485.12541 | 14 |
| 21 | 'You can't be a person and a doctor': The work-life balance of doctors in training – A qualitative study | 10.1136/bmjopen-2016-013897 | 26 |
| 22 | Factors associated with burnout among residents in a developing country | 10.1016/j.amsu.2016.01.090 | 17 |
| 23 | Evaluation of the effect of a 1-day interventional workshop on recovery from job stress for radiation therapists and oncology nurses: A randomised trial | 10.1111/1754-9485.12322 | 15 |
| 24 | Quality care, public perception and quick-fix service management: A Delphi study on stressors of hospital doctors in Ireland | 10.1136/bmjopen-2015-009564 | 8 |
| 25 | A study on the relationship between stress and fatigue and the musculoskeletal symptoms experienced by Korean radiation workers | 10.1589/jpts.27.427 | 4 |
| 26 | Stress, satisfaction and burnout amongst Australian and New Zealand radiation oncologists | 10.1111/1754-9485.12217 | 35 |
| 27 | Work-related stress, musculoskeletal disorder complaints, and stress symptoms among radiographers in the northern part of Jordan | 10.1016/j.jmir.2014.04.002 | 0 |
| 28 | Audit of the job satisfaction levels of the UK radiography and physics workforce in UK radiotherapy centres 2012 | 10.1259/bjr.20130742 | 12 |
| 29 | Association of work-related stress with depression and anxiety in radiologists | 10.1007/s11547-013-0355-y | 12 |
| 30 | Work stress and metabolic syndrome in radiologists: First evidence | 10.1007/s11547-013-0329-0 | 23 |
| 31 | Results of a Canadian study examining the prevalence and potential for developing compassion fatigue and burnout in radiation therapists | 10.1017/S1460396914000144 | 5 |

| | | | |
|---|---|---|---|
| 32 | Is there a gender gap in Italian radiology? A cross-sectional study | 10.1016/j.ejrad.2013.04.007 | 11 |
| 33 | The emotional wellness of radiology trainees: Prevalence and predictors of burnout | 10.1016/j.acra.2012.12.018 | 29 |
| 34 | The incidence of burnout or compassion fatigue in medical dosimetrists as a function of various stress and psychologic factors | 10.1016/j.meddos.2012.07.006 | 4 |
| 35 | Burnout in therapy radiographers in the UK | 10.1259/bjr/16840236 | 25 |
| 36 | Anxiety and depression in doctors undergoing postgraduate training courses at Armed Forces Postgraduate Medical Institute Rawalpindi | Not Available | 0 |
| 37 | The relevance of psychological support to medical resident and specializing in radiology and imaging diagnosis | 10.1590/S0100-39842011000200006 | 1 |
| 38 | An investigation into work related stressors on diagnostic radiographers in a local district hospital | 10.1016/j.radi.2009.09.005 | 11 |
| 39 | Satisfaction at work among radiologists | 10.1007/s11547-009-0461-z | 14 |
| 40 | Work stress, satisfaction and burnout in New Zealand radiologists: Comparison of public hospital and private practice in New Zealand: Radiology-Original article | 10.1111/j.1754-9485.2009.02063.x | 19 |
| 41 | Job stress and job satisfaction of physicians, radiographers, nurses and physicists working in radiotherapy: A multi-centre analysis by the DEGRO Quality of Life Work Group | 10.1186/1748-717X-4-6 | 71 |
| 42 | Occupational stress and its predictors in radiographers | 10.1016/j.radi.2006.09.008 | 14 |
| 43 | Work stress in radiologists. A pilot study | 10.1007/s11547-008-0259-4 | 35 |
| 44 | Repetitive Stress Symptoms in Radiology: Prevalence and Response to Ergonomic Interventions | 10.1016/j.jacr.2008.01.014 | 31 |
| 45 | The informational roles and psychological health of members of 10 oncology multidisciplinary teams in the UK | 10.1038/sj.bjc.6602816 | 66 |
| 46 | Satisfaction and stress factors in the radiologist's profession | Not Available | 5 |
| 47 | Job stress and satisfaction among clinical radiologists | 10.1053/crad.1999.0379 | 62 |
| 48 | Mental health of hospital consultants: The effects of stress and satisfaction at work | 10.1016/S0140-6736(96)90077-X | 628 |
| 49 | Job satisfaction in the medical imaging profession: alleviating the shortage of personnel | Not Available | 6 |

DOI: Digital object identifier; UK United Kingdom.

**Table 2 Top rated journals with number of publications, citations, and impact factor**

| No. | Journals | No of document | Citation | Impact factor |
|---|---|---|---|---|
| 1 | *Academic Radiology* | 6 | 55 | 2.0 |
| 2 | *Journal of Medical imaging and Radiation Oncology* | 5 | 89 | 1.2 |
| 3 | *Journal of the American College of Radiology* | 4 | 47 | 1.6 |
| 4 | *Radiologia Medica* | 4 | 84 | 1.8 |
| 5 | *BMJ Open* | 2 | 34 | 2.6 |
| 6 | *British Journal of Radiology* | 2 | 37 | 2.1 |
| 7 | *Canadian Association of Radiologist Journal* | 2 | 06 | 0.9 |
| 8 | *Radiography* | 2 | 25 | 0.7 |

female as first author and number of citations, with a *P* value of 0.03.

Authors belonged to 20 different countries of the world (Supplementary Table 2). United States was the leading country, with the greatest number of researchers, followed by United Kingdom, Italy, Australia, Canada and South Korea as shown in Table 4.

### *Co-citation analysis*

Co-citation analysis is important to understand if there is a subject similarity between two documents. Co-citation analysis by author shows the intellectual structure of scientific disciplines. When two authors are cited together in a third document, they are said to be co-cited. If two authors are cited together in more papers, the stronger the relationship, hence greater the co-citation strength and therefore, higher will be their probability to be logistically related in terms of substance and linguistics.

**Table 3 Top rated authors with number of articles and H-index**

| Author | Gender | Number of articles | H-index |
|---|---|---|---|
| Magnavita N | Female | 5 | 25 |
| Fileni A | Male | 4 | 13 |
| Mulcahy MJ | Male | 4 | 6 |
| Chew FS | Male | 3 | 26 |
| Ahmed FS | Male | 2 | 10 |
| Ayyala RS | Female | 2 | 04 |
| Bergamaschi A | Male | 2 | 31 |
| Ganeshan D | Male | 2 | 16 |
| Graham J | Female | 2 | 12 |
| Guenette JP | Male | 2 | 7 |
| Leung J | Male | 2 | 8 |
| Probst H | Female | 2 | 8 |
| Ramirez AJ | Female | 2 | 45 |
| Relyea-Chew A | Female | 2 | 13 |
| Richards MA | Male | 2 | 64 |
| Rioseco P | Female | 2 | 4 |
| Ruzal-Shapiro C | Female | 2 | 20 |
| Smith SE | Female | 2 | 14 |
| Taylor GA | Male | 2 | 48 |

**Table 4 Leading countries on the basis of origin of authors**

| Country/Territory | Number of author |
|---|---|
| United States | 18 |
| United Kingdom | 8 |
| Italy | 5 |
| Australia | 4 |
| Canada | 4 |
| South Korea | 2 |

The co-citation analysis by author involved 188 cited authors, 13 of whom were cited at least 70 times. The authors that were most cited included Schulze W, followed by Schlen S and Dormin C. Supplementary Figures 1 and 2 depict the network; the names of authors are shown by a circle. The importance of an author is indicated by the size of the circle, the distance between the labels signifies the relevance, the connection represents collaboration, and the same color indicates belonging to the same cluster.

### *Funding and its relationship with citations*

Only six out of forty-nine studies were funded by various government institutions and non-governmental organizations. Five of them yielded a positive result as compared to hypothesis. There was no significant relationship between funding and number of citations ($P$ = 0.69). Funding organization is shown in Table 5.

**Table 5 Funding organization for research**

| Funding organization | Frequency |
|---|---|
| National Institutes of Health | 2 |
| Mayo Clinic | 1 |
| National Cancer Institute | 1 |
| National Heart, Lung, and Blood Institute | 1 |
| University of Texas MD Anderson Cancer Centre | 1 |

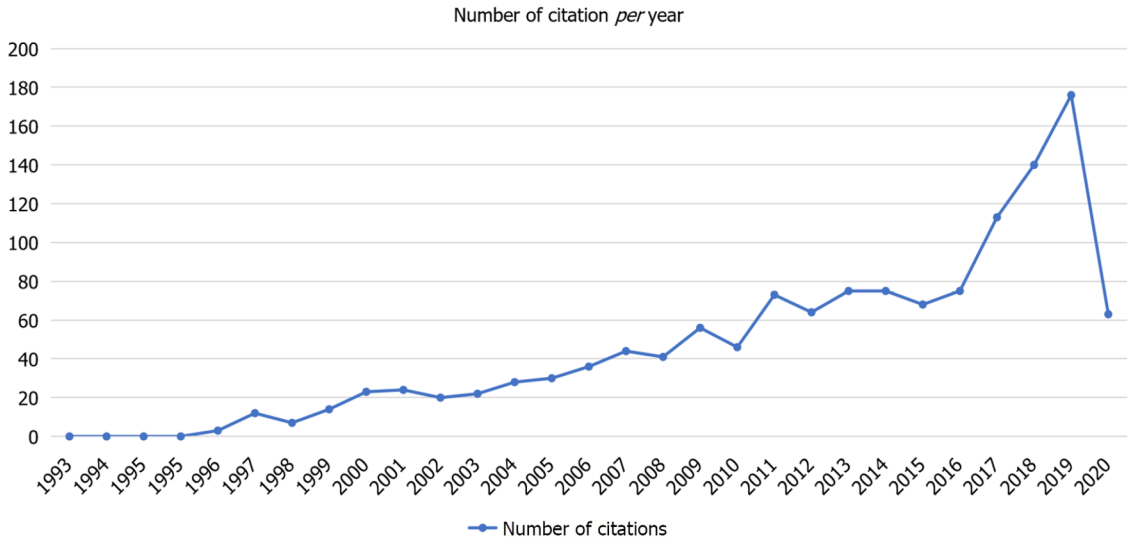


**Figure 1 Number of citations *per* year.**

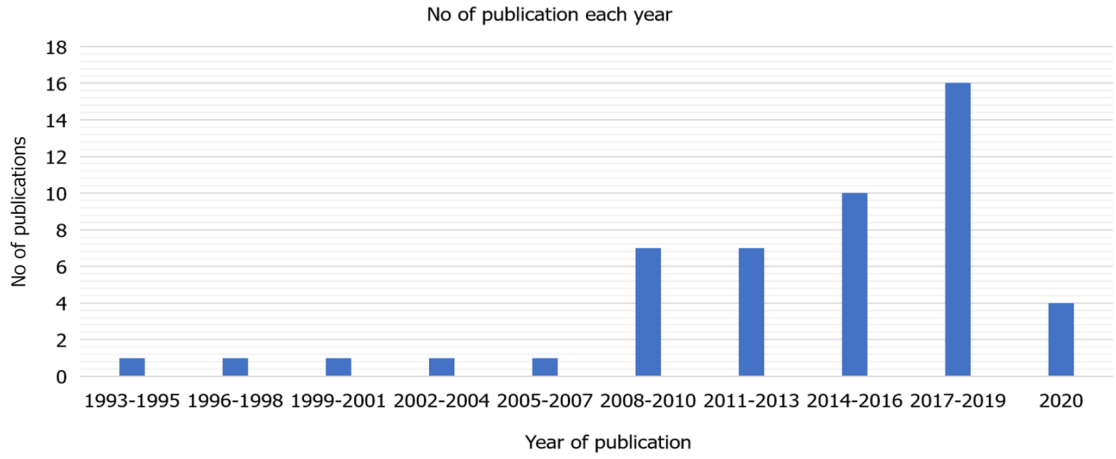


**Figure 2 Number of publications *per* year.**

## DISCUSSION

### *Year of publications of articles and citations*

Articles for most notable work burnout towards the field of radiology are listed in Table 1. The top cited source 'Mental health of hospital consultants: The effects of stress and satisfaction at work' was cited in 1996. The second most cited source 'Job stress and job satisfaction of physicians, radiographers, nurses and physicists working in radiotherapy: A multi-centre analysis by the DEGRO Quality of Life Work Group' was cited in 2009. The third most cited source was 'The informational roles and psychological health of members of 10 oncology multidisciplinary teams in the UK' was cited in 2005. This shows that there does not seem to be a particular trend amongst the most cited sources. They range from 1996-2009.

However, what can be noted is that the top cited sources show a more general picture in the trend of burnout. In other words, the top cited sources involve multiple disciplines and healthcare workers such as consultants in different fields and different health care workers in the field of radiology. This allows the articles to be cited by multiple authors in different fields. If radiology-specific studies are seen then the trend shows that the top cited articles, which include 'Stress, satisfaction and burnout amongst Australian and New Zealand radiation oncologists' and 'Burnout: Prevalence and associated factors among radiology residents in New England with comparison against United States resident physicians in other specialties', are sited in the year 2017.

As far as the trend, in the field of radiology, most of the citations in radiology peaked after 1979[16]. Furthermore, the trend of psychiatric disorders and neuroimaging increased after 1989, with most neuroimaging studies produced in 2007[17]. However, there are no particular bibliometric analyses produced for depression and burnout amongst healthcare workers. The trend in this particular research shows that studies on burnout started in 1993, but the bulk of studies involving burnout in radiologists were seen between 2017-2019.

### Top authors and their countries of origin

Table 2 shows that the top number of citations, which were ($n$ = 89) and ($n$ = 84), were seen in the journals the *Journal of Medical imaging* and *Radiation Oncology and Radiologia Medica*. These journals have lower impact factors compared to other journals such as *BMJ Open*. This refutes Bradford's law that states that most authors prefer publishing in core journals because straying from main articles reduces the impact of an article[18]. In other words, journals with more citations do not correlate with journals that have higher impact factors, specifically for the topic of burnout.

The impact of each author and their work is shown in Table 3. An observation to be made is that the number of articles does not correlate with an increased H-index. In fact, the authors with the highest H-index only have two articles published, whereas the author with five articles has a lower H-index than the top authors. The highest H-index was seen by author, Richard MA, with an H-index of 64. He has only published two articles. The author, Magnavita N has five articles published but has an H-index of 25. This is supported by an article that states that H-index is loosely related to the number of articles [19]. Rather, H-index is more closely associated with academic rank in certain fields[20]. Therefore, more articles do not correlate with high H-indexes in the topic of burnout in radiology.

The study shows that the majority of papers were published in the United States with a number of 18 authors. This trend seems to be the basic trend in many current and older studies in multiple fields[21]. A study by Tran *et al*[22] about depression and artificial intelligence showed the same trend that more papers were produced from the United States[22]. This trend happens because, according to an article on reviewer analysis, it seems that papers from the United States are reviewed and considered more highly than other papers from different countries[23].

Overall, 58.3% of the authors were males and 41.7% were female, and the proportion of female first authors (84.0%) was larger than the proportion of male first authors (82.3%). The differences in total authors could be attributed to the fact that, according to the World Health Organization, the number of male physicians on average worldwide generally outweighs their female counterparts[24]. However, the slightly higher proportion of female first authors indicates women are better at collaborating with their peers for research purposes. This could be due to their more egalitarian nature[25] and hence a more collaborative approach in the workforce. Our analysis found a significant association ($P$ = 0.03) between female first authors and number of citations, indicating that female first authors tended to be cited more than their male counterparts. This is in contrast to a prior study that reported low citations in primary female authors[26], which could indicate a possible narrowing of prior lack of female representation.

### Co-citation analysis

All of the articles in our top-cited list focused on the prevalence, causes, and prevention aspect of burnout. This was also demonstrated by the co-citation analysis by author. Co-citation creates clusters of research for the articles that are cited together. These clusters reveal which researchers all over the world are working on burnout among radiologists, and this research will have a substantial effect on the betterment of working environment and preventive strategies. Interestingly, the conclusions of these studies were consistent and help the reader to determine the burden of disease and its importance.

### Funding and its relationship with citations

Only 6 out of 49 studies were funded by various government institutions and non-governmental organizations. Five of them yielded a positive result as compared to the hypothesis. Our analysis shows that most research was privately funded/funded by non-government agencies, hence raising the ethical concerns about a possible conflict of interest in regards to reporting of results[27]. Moreover, we found no significant relationship between funding and the number of citations ($P$ = 0.69), which is in contrast to prior research that claimed grant sponsored articles to receive generally more citations and be published in higher quality journals[28].

It could also be concluded that government emphasis and subsequent funding on mental health research regarding radiologists remain small-scale despite adequate data showing significant burnout being noted in one-fourth of all radiologists[29], while another study noting only 19% of radiologists having mechanisms to address burnout[30].

### Limitations

Inherent limitations of bibliometric analysis should be considered, the first being technical problems: Spelling and name changes, progressive changes in the database, language biases, and problems with journal impact factor[31]. These limitations apply to our study as well; nevertheless we tried to alleviate their impact by choosing articles only from the Scopus database to ensure some degree of uniformity in method and use of citations. However, using solely Scopus predisposes us to the exclusion of influential studies present in other databases and the exclusion of any studies before 1996 due to the lack of complete citation information in the database before that year[32,33].

## CONCLUSION

Our analysis casts a spotlight on important trends being witnessed in regards to the mental health of radiologists. These include lack of funding for mental health research, narrowing of female *vs* male citation gap, as well as authorship and citation trends. By studying these patterns, we can understand key areas lacking in the current bulk of radiological research and subsequently address them to improve the long-term yield, variety, and impact of radiological studies.

## ARTICLE HIGHLIGHTS

### Research background

Burnout is an important topic in today's era, with many articles trying to figure out the causes and stressors in the medical field. As a health community, we need to collect all the data for burnout to first understand the prevalence in each area and then the causes for each area. Burnout among radiologists is common in many different institutions and is increasing.

### Research motivation

To battle burnout, we have to address the root causes already recognized in published literature. It is crucial to examine and discern important publications. This analysis will allow us to see which areas have collected data on the prevalence and causes of burnout. This analysis will also allow us to determine the missing areas from where we need data.

### Research objectives

The current study will provide evidence-based data and trends related to burnout in radiologists so that researchers can work on it further and develop preventive strategies to overcome this problem.

### Research methods

Bibliometric analysis was conducted using Scopus Library for data extraction by using Medical subject heading and International Classification of Diseases keywords. Forty-nine articles were selected for analysis after extensive scrutiny. Statistical Package for the Social Sciences, version 20 was used for analysis. Pearson correlation coefficient, Kruskal Wallis test, and Mann-Whitney U test were applied.

### Research results

The most productive time period with regards to the number of publications was between 2017 and 2019. A total of 160 authors contributed to the topic burnout among radiologists, with an average of 3.26 authors *per* paper. About 41.68% of the authors were female, while 35% of them were first authors. The co-citation analysis by the author involved 188 cited authors, 13 of whom were cited at least 70-times. Only six out of 49 studies were funded by government institutions and non-governmental organizations.

### Research conclusions

The current analysis casts a spotlight on important trends being witnessed in regards to the mental health of radiologists, including lack of funding for mental health research, narrowing of female *vs* male citation gap, as well as authorship and citation trends.

### *Research perspectives*

This analysis provides high yield information that will allow for the identification of additional areas of interest that need to be addressed and what information has high value. This information can be used in the long run to produce higher-quality papers.

## FOOTNOTES

**Author contributions:** Qureshi MFH designed the basic framework of study and contributed to data analysis and writing; Mohammad D, Shah SMA, Lakhani M, Shah M, Ayub MH, and Sadiq S prepared the initial draft and performed the literature research; all authors approved the final draft.

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*MINIREVIEWS*

# Neuroimmune crosstalk through brain-derived neurotrophic factor and its precursor pro-BDNF: New insights into mood disorders

Xiao-Pei Zhao, Hui Li, Ru-Ping Dai

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## Abstract

Mood disorders are the most common mental disorders, affecting approximately 350 million people globally. Recent studies have shown that neuroimmune interaction regulates mood disorders. Brain-derived neurotrophic factor (BDNF) and its precursor pro-BDNF, are involved in the neuroimmune crosstalk during the development of mood disorders. BDNF is implicated in the pathophysiology of psychiatric and neurological disorders especially in antidepressant pharmacotherapy. In this review, we describe the functions of BDNF/pro-BDNF signaling in the central nervous system in the context of mood disorders. In addition, we summarize the developments for BDNF and pro-BDNF functions in mood disorders. This review aims to provide new insights into the impact of neuroimmune interaction on mood disorders and reveal a new basis for further development of diagnostic targets and mood disorders.

**Key Words:** Brain-derived neurotrophic factor; pro-BDNF; Neural circuits; Neuroimmune; Mood disorders; Depression

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**Core Tip:** The neuroimmune crosstalk plays a crucial role in the regulation of mood disorders. Recent studies have shown that the brain-derived neurotrophic factor (BDNF) and its precursor pro-BDNF are cardinal regulators in the neuroimmune axis. However, the roles and potential mechanisms of BDNF/pro-BDNF signaling in the neuroimmune crosstalk in the context of mood disorders remain unexplored. In this review, we summarize recent studies on the role of BDNF/TrkB signaling and pro-BDNF/p75$^{NTR}$ signaling in the neuroimmune axis and how they influence the development of mood disorders.

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## INTRODUCTION

Mood disorders are complex diseases characterized by mood depression and anhedonia. Depressive episodes, manic episodes, bipolar disorder, as well as persistent mood disorders are the typical symptoms. In addition, mood disorders are among the most common mental disorders in the world and major contributors to the global burden of disease[1,2]. In Europe, for example, the current burden is greater than that from 10 years ago despite the availability of reasonably effective pharmacological and psychological interventions[3]. Moreover, the World Health Organization in 2008 ranked major depression as the third cause of the disease burden worldwide and predicted that the disease will rank first by 2030[4]. Furthermore, various studies have shown the impact of depression, anxiety and stress on different systems including the cardiovascular and immune systems[5]. However, the mechanisms and pathogenesis of the syndrome still remain unclear. Although antidepressants were previously used extensively in the treatment of mood disorders, current forms of treatment are largely suboptimal. It is therefore urgent and necessary to explore novel therapeutic targets for the treatment of mood disorders.

Several theories have been put forward to explain mood disorders, including the neural circuit hypothesis, neurotransmitter hypothesis, hypothalamus-pituitary-adrenal (HPA) axis dysfunction, neurotrophic hypothesis and cytokine hypothesis[1]. Among them, neurotrophins, particularly brain-derived neurotrophic factor (BDNF), are extensively studied for their role in mood disorders. Additionally, dysfunctions in BDNF and its precursor pro-BDNF in the central nervous system (CNS) are well known to play a critical role in the pathogenesis of mood disorders. However, it is still unclear whether peripheral BDNF can reflect changes in the levels of BDNF in the CNS. Moreover, recent studies have shown that there are changes in BDNF and pro-BDNF signaling in the immune cells of patients with depression[6]. Nonetheless, the exact mechanisms of BDNF/pro-BDNF in neuroimmune crosstalk are yet to be elucidated. The changes in BDNF/pro-BDNF signaling in the CNS and immune system suggest that this neurotrophin is a linker in neuroimmune crosstalk; an emerging topic that has gained popularity in the field of mood disorders.

## INTRACELLULAR PROCESSING AND SIGNALING OF BDNF AND PRO-BDNF

BDNF is the second identified member of the neurotrophin family and the most widely distributed neurotrophin in the CNS as well as the peripheral nervous system[7]. Previous studies have reported that BDNF is expressed in neurons, astrocytes, Schwann cells, fibroblasts and possibly, smooth muscle cells[8]. In addition, regulation of BDNF processing is governed by complex regulatory mechanisms at the transcriptional, translational and posttranslational levels of gene expression[9]. The human BDNF gene is located on chromosome 11, region p13-14 and spans 70 kb. The gene has a complex structure as it consists of 11 exons (I-IX, plus Vh and VIIIh) in the 5' end and nine functional promoters. The coding sequence resides in exon 9 and has eight upstream exons that encode promoters regulating regional and cell-type-specific expression[10]. Moreover, the BDNF protein is initially synthesized into pro-BDNF in the endoplasmic reticulum. Pro-BDNF is then subsequently cleaved by proconvertases/furin to generate either a 28-kDa truncated form (truncated BDNF) or the 13.5-kDa mature BDNF. Following this, the mature BDNF is stored in the dense-core vesicle and is secreted upon neuronal activation. Additionally, BDNF signaling plays a critical role in promoting neuronal survival, phenotypic differentiation, axonal and dendritic growth and synapse formation[11,12].

BDNF function is mediated by two receptor systems, namely, TrkB and $p75^{NTR}$ (pan 75 neurotrophin receptor)[13]. Extensive research has shown that BDNF binds to its high-affinity receptor TrkB, causing the autophosphorylation of TrkB, subsequently activating the mitogen-activated protein kinase pathway, phospholipase C-γ pathway, phosphatidylinositol 3-kinase pathway and other signaling pathways. Additionally, BDNF-TrkB signaling affects the survival, development and function of neurons. They also promotes the formation of the dendritic spine, provides a structural basis for synapse formation and improves the transmission efficiency of synapses[14].

As the intermediate during the synthesis of BDNF, pro-BDNF can also be secreted outside the cells in different sites of the CNS, such as the cerebral cortex, cerebellum, substantia nigra, amygdala and hypothamalus[8]. In addition, pro-BDNF can be cleaved extracellularly into mature or truncated BDNF by matrix metalloproteinases/plasmin[12]. Pro-BDNF can also bind to its high affinity receptor, $p75^{NTR}$ with its co-receptor sortilin and exert an effect opposite to the biological function of mature BDNF, including neuronal apoptosis, pruning of axons and dendrites and long-term depression[13-15].

Therefore, it is important to discuss the roles of these two proteins involved in mood disorders. Moreover, activation of TrkB and $p75^{NTR}$ promotes and suppresses the growth of the dendritic spine, respectively. Therefore, cleavage of pro-BDNF may represent a new mechanism that controls the direction of BDNF regulation, *i.e.*, synaptic potentiation or synaptic depression.

Several signaling pathways are activated following the binding of pro-neurotrophin to $p75^{NTR}$. These signaling pathways which summarized in Figure 1 are mediated by the interaction of $p75^{NTR}$ to its adaptor proteins, including tumor necrosis factor receptor-associated factor 6, the neurotrophin receptor-interacting factor, melanoma-associated antigen (MAGE), neurotrophin receptor p75 interacting MAGE homolog, Schwann cell factor 1, rho GDP dissociation inhibitor (RhoGDI) and other proteins[16]. Additionally, there are three major downstream pathways for $p75^{NTR}$ including nuclear factor (NF)- κB signaling, RhoGDI and the RhoA signaling, and Jun kinase signaling cascade. Notably, NF-κB is a transcription factor that can be activated by $p75^{NTR}$ but not *via* Trk receptors. Moreover, RIP2 was previously shown to link $p75^{NTR}$ to the NF-κB pathway[17]. Activation of NF-κB also contributes to the NGF-dependent survival of developing sensory neurons, oligodendrocytes and Schwann cells[18-21]. It mediates the NGF-dependent increase in the expression of the survival factor Bcl-xL and a survival pathway in PC12 cells[22]. RhoA causes the actin cytoskeleton to become rigid, which limits the mobility of the growth cone and inhibits neuronal elongation in the developing nervous system[23]. Recent evidence suggests that RhoA activity is regulated by the cytoplasmic domain of $p75^{NTR}$[24]. Furthermore, the unbound state of $p75^{NTR}$ associates with RhoGDI, which subsequently interacts with RhoA and activates RhoA signaling[25]. It was also shown that neurotrophins inhibit the association between RhoGDI and $p75^{NTR}$, thus suppressing the release of RhoA and promoting the elongation of the growth cone[26,27]. Additionally, pro-neurotrophin binds to $p75^{NTR}$ and activates the c-Jun N-terminal kinases (JNK) signaling pathway, causing apoptosis of developing neurons[28]. In contrast, TrkA can prevent $p75^{NTR}$-mediated apoptosis induced by the JNK pathway[29].

## ROLE OF BDNF/PRO-BDNF IN THE CNS IN DEPRESSION/BIPOLAR DISORDERS

The neurocircuits involved in regulating mood disorders include the hypothalamus, hippocampus, brain stem nuclei, temporal lobe, caudate, the anterior cingulate cortex (ACC), frontal cortex, basal forebrain, the extended amygdala, including the central nucleus of the amygdala (CeA) and medial nucleus of the amygdala (MeA), bed nucleus of the stria terminalis (BNST) and the shell of the nucleus accumbens (NAc)[11,30]. Clinical and experimental studies showed that depression may be driven by a dysregulated circuit function across multiple brain regions[31]. In addition, BDNF was also shown to be highly expressed in the cortex, hippocampus, limbic structures, cerebellum and the olfactory bulb[32]. Using specific antibodies against pro-BDNF, previous studies showed that pro-BDNF is widely and abundantly expressed throughout the adult brain. Moreover, experimental studies have shown that pro-BDNF, in different brain regions, regulates depressive behaviors. A previous study also reported that pro-BDNF is upregulated in the hippocampus, neocortex, the medial prefrontal cortex (PFC) and brainstem of individuals with a depression-like phenotype[33]. In contrast, there was a decrease in the expression of pro-BDNF in the NAc of rats with learned helplessness. These studies therefore suggest that the association of BDNF and pro-BDNF with the mood status is dependent on the specific location and the neural circuitry.

### *Hippocampus*

Existing evidence shows that the BDNF in the hippocampus plays an important role in the pathogenesis of depression[34]. First, previous studies reported that the expression of hippocampal BDNF declined in different depression models. For instance, chronic-stress-induced models of depression showed decreasing levels of BDNF in the hippocampus and antidepressant treatment upregulated the expression of BDNF and TrkB in the hippocampus of rats[35]. It was also shown that chronic unpredictable mild stress (CUMS) decreased the levels of BDNF in the hippocampus and PFC, but increased the levels of BDNF in the basolateral nucleus of the amygdala (BLA). On the contrary, the blood oxygen level-dependent (BOLD) activity was elevated in the hippocampus and PFC but reduced in the BLA after exposure to CUMS, indicating that the levels of BDNF were negatively correlated with BOLD activity in the WT CUMS-exposed mice[30]. Second, it was reported that various antidepressants can restore the downregulation of BDNF in the hippocampus. Notably, antidepressant drugs increased the expression of BDNF mRNA in the hippocampi of rats[36]. In addition, treatment with monoamine oxidase inhibitors increased the expression of BDNF in specific hippocampal subfields. Consistent with these results, it is reported that administration of leptin exerted antidepressant effects and increased the expression of BDNF in the hippocampus[37]. Third, it has been shown that impairment of hippocampal BDNF signaling produces certain depression-related behaviors and reduces the effect of the antidepressants[38]. Previous studies have shown that upregulating the levels of hippocampal BDNF produces antidepressant effects. In addition, it is reported that direct incorporation of BDNF in the hippocampus of rodents mimics antidepressant treatment[12]. Moreover, it was previously shown that peripheral administration of BDNF produces anxiolytic and antidepressant effects. Therefore, the

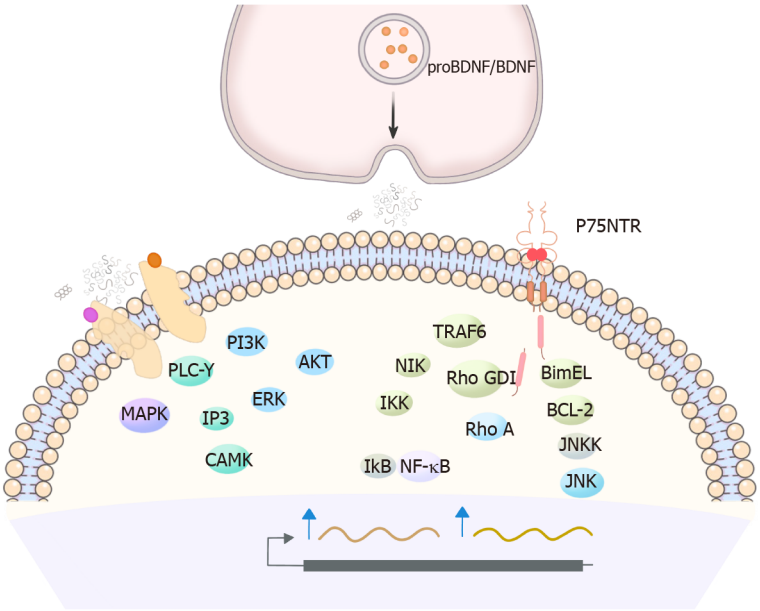


**Figure 1 Role of brain-derived neurotrophic factor and pro-BDNF in neuroimmune crosstalk in mood disorders.** Brain-derived neurotrophic factor (BDNF) or pro-BDNF can be stored in the dense-core vesicles and released upon neuronal activity. The released BDNF and pro-BDNF mainly bind to their high affinity receptors, TrkB and $p75^{NTR}$, respectively and mediate the downstream signaling pathways. BDNF-TrkB signaling leads to neuronal survival, development and long-term potentiation. In contrast, pro-BDNF-$p75^{NTR}$ signaling mediates neuronal apoptosis, axonal pruning and long-term depression. BDNF: Brain-derived neurotrophic factor; NF-κB: Nuclear factor-κB.

downregulation of BDNF in the hippocampus contributes to the pathogenesis of depression.

Several mechanisms have been proposed to underlie the role of hippocampal BDNF in depression. It is well known that BDNF/TrkB signaling activates the cAMP-response element binding protein (CREB) cascade and that antidepressant treatment upregulates the cAMP-CREB cascade in the hippocampus [39]. The activating cAMP-CREB signaling enhances the response to a tricyclic antidepressant. Therefore, downregulation of BDNF may inhibit downstream cAMP-CREB signaling and promote progression of mood disorders. In contrast, the inhibition of neurogenesis resulting from the reduced levels of BDNF may contribute to mood disorders, particularly depression. It is noteworthy that neurogenesis in adult animals is restricted to the subventricular zone of lateral ventricles and the dentate gyrus of the hippocampus. Furthermore, hippocampal neurogenesis is mediated by BDNF/TrkB signaling and is sensitive to a variety of environmental stimuli, including exercise, enrichment and antidepressant treatment[40]. It has also been shown that chronic antidepressant treatment increases neurogenesis in the hippocampus of adult rodents. Moreover, the effects of antidepressants on neurogenesis are dependent on intact BDNF signaling through TrkB[36]. According to a previous study, mice lacking TrkB in hippocampal neural progenitor cells failed to exhibit antidepressant-induced proliferation and neurogenesis[41].

It has also been shown that the levels of pro-BDNF and its receptors are increased in the hippocampus of rats with depression[42]. In addition, pro-BDNF negatively regulates dendritic complexity and depresses synaptic transmission in the hippocampus. There was an increase in the levels of hippocampal pro-BDNF in carioca high-conditioned freezing (a model of anxiety disorder) rats[43]. Additionally, injection of anti-pro-BDNF antibodies through the intracerebroventricular and intraperitoneal routes reverses the stress-induced depressive behavior[44]. In the major depressive disorder (MDD), reductions in the levels of pro-BDNF are seen in the right but not the left hippocampus, with no changes in the dentate gyrus[45]. Furthermore, exposure to the water maze increases the levels of the pro-BDNF protein in the dorsal hippocampus although the levels decrease in the ventral hippocampus. A recent study by our research group also demonstrated that pro-BDNF was upregulated in the hippocampus of rats with a depression-like or anxiety-like phenotype[44]. Moreover, intra-hippocampal injection of pro-BDNF antibodies attenuated the depression-like and anxiety-like behaviors, suggesting that pro-BDNF, in the hippocampus, is a common mediator of anxiety and depression[44].

### *Hypothalamus*

The hypothalamus is a vital neuroendocrine region that not only influences the neuroendocrine and immune systems but also is closely related to the pathogenesis of depression. Additionally, many preclinical and clinical studies have proven that certain depressive characteristics are associated with abnormities in the hypothalamus. For instance, neuroimaging and postmortem brain microscopy studies showed widespread anatomical changes, volume deficits and neuron pathological changes in the hypothalamus of individuals with depression[46]. It has also been shown that intracerebroven-

tricular administration of BDNF in rats leads to an increase in the activity of the HPA axis[47]. According to previous studies, BDNF in the hypotha-lamus can regulate glucose and energy metabolism by acting directly on the hypotha-lamus. Moreover, a decrease in the levels of BDNF in hypothalamic nuclei may result in anorexia in rats[48,49]. It has been reported that trans-resveratrol increases the expression of BDNF in the frontal cortex, hippocampus and hypothalamus of rats with stroke, suggesting that BDNF protects neurons against cerebral ischemia[50].

### PFC

The PFC is an important region of the brain that is involved in depression-like behavior. Previous studies reported that depressed suicide victims had low levels of BDNF in the hippocampus and PFC, especially in the ventromedial PFC[51]. Additionally, the antidepressant effects of ketamine were lost in mice lacking BDNF or TrkB or when the medial PFC was injected with anti-BDNF antibodies. Moreover, the chronic administration of different antidepressants such as escitalopram and fluoxetine is capable of increasing the levels of BDNF in the PFC of both rats and humans[52]. The mPFC-selective knockdown of BDNF showed diminished motivation but not impaired response-outcome learning[53].

### ACC

The ACC is located in the medial subregion of the frontal lobe and is part of a neural system involved in motivating or energizing behavior and hierarchical reinforcement learning. It has been shown that there is a decrease in BDNF signaling in the subequal ACC of individuals with MDD[54]. Additionally, the Chaihu Shugan Powder significantly improves depressive behavior by increasing the mRNA expression levels of BDNF and TrkB in the hippocampus, amygdala and frontal lobe[55]. It is also reported that treatment with anti-pro-BDNF antibodies in the ACC restores the CUMS-induced decrease in the levels of BDNF mRNA in the cortex and hippocampus[56].

### Midbrain

The midbrain, also known as the mesencephalon, is a region of the developing vertebrate brain that is composed of the tectum and tegmentum. The tectum makes up the rear portion of the midbrain and is composed of two paired rounded swellings, the superior and inferior colliculi. The tegmentum is located in front of the tectum. It consists of fiber tracts and three regions distinguished by their color, *i.e.*, the red nucleus, the periaqueductal gray (PAG) and the substantia nigra[57]. It has been shown that the BDNF and TrkB receptors are enriched in the dorsal PAG of the rat midbrain, which is considered to be a key structure in the pathophysiology of panic disorder. In addition, BDNF/TrkB signaling in the dorsal PAG is implicated in the beneficial effects of antidepressants in panic disorder[58,59]. Moreover, chronic infusion of BDNF into the midbrain is reported to increase the neurotransmission of 5-hydroxytryptamine (HT) and exert antidepressant effects in the learned helplessness and forced swim test depression models[60]. Moreover, direct administration of BDNF into the midbrain is sufficient to induce antidepressant-like behavior and neurogenesis[36]. A recent study also showed that BDNF-TrkB-mTORC1 signaling in the ventral PAG is required for sustained antidepressant effects[61].

## INTERACTION OF PRO-BDNF/BDNF WITH NEUROTRANSMITTERS IN MOOD DISORDERS

The monoamine hypothesis postulates that depression is primarily caused by imbalances in the neurotransmission of monoamines, namely dopamine (DA), serotonin (5-HT) or norepinephrine (NE)[62]. In addition, numerous studies have suggested that BDNF signaling is closely associated with changes in the 5-HT and DA systems during the development and neuroplasticity of mood dysfunction.

### 5-HT system

Distinct effects of BDNF on the 5-HT system have been identified in depression. Notably, 5-HT is produced in the raphe nuclei of the brain stem region then spreads to terminal regions throughout the brain including the hypothalamus, cortex, hippocampus and amygdala. It also regulates a wide repertoire of functions such as behavior, cognition and mood[12,34]. Previous studies conducted on preschoolers have revealed a correlation between BDNF and 5-HT polymorphisms during brain development. The studies have also shown high levels of cortisol that could be a cause of depression. Additionally, the local administration of BDNF into the main cluster of the cell bodies of serotonergic neurons in the dorsal raphe nuclei (DRN) is reported to increase the length of dendrites and alter the electrophysiological activity of 5-HT neurons[63].

Infusion with BDNF results in hyperinnervation of 5-HT axons at the site of infusion in either the cerebral cortex or hippocampus. Moreover, BDNF has a profound effect on the sprouting of either intact 5-HT or neurotoxin-lesioned neurons[62]. Reduced levels of BDNF in $BDNF^{+/-}$ mice also leads to decreased functional activity in the $5\text{-}HT_1A$ receptor in the hippocampus and deficient $5\text{-}HT_2A$ receptors in the PFC and DRN of the midbrain. In addition, BDNF/TrkB is an upstream regulator of the $5\text{-}HT_2A$

pathway[64]. It is also reported that hippocampal BDNF improves some specific behavioral impairments including anxiety and anhedonia in 5-$HT_4$R KO mice[65].

### Dopaminergic system

Depression is likely controlled by two interacting brain systems: the brain stress system HPA pathway and the brain reward system [ventral tegmental area-NAc (VTA-NAc) and VTA-PFC]. The VTA-NAc is the origin of dopaminergic neurons[12] and the dopaminergic VTA-NAc pathway is critical for reward and motivation. Notably, intrahippocampal infusion of BDNF produces antidepressant effects although it appears to play a prodepressive role in the VTA-NAc reward system. Additionally, many studies have shown that the levels of BDNF are increased in the VTA and NAc of depressed rats and mice although the levels are reduced in the hippocampus. Moreover, recent research has shown that intra-VTA injections of BDNF lead to an increase in depression-like behavior in rats as revealed by the forced swim test. It has also been shown that chronic neonatal stress not only leads to long-term changes in the expression of BDNF in the VTA, but also causes depression-like behavior in adults. In addition, the increased levels of BDNF seem to disinhibit the VTA DA neurons since knocking down BDNF in VTA prevents social-defeat-induced cross-sensitization to amphetamine. Furthermore, BDNF activity is closely associated with the excitability of VTA-DA neurons[66]. Chronic optogenetic phasic stimulation of VTA DA neurons increases the levels of NAc-BDNF and exacerbates social avoidance. Additionally, blocking BDNF-TrkB signaling in the NAc and VTA prevents aggravation of social avoidance. Therefore, BDNF signaling in the VTA-NAc pathway is required for the development of the susceptible phenotype induced by chronic social stress.

NAc is located in the basal forebrain, rostral to the preoptic areas. In addition, neurons in NAc integrate reward-related dopaminergic signals as well as glutamatergic input from the PFC, hippocampus, amygdala and hypothalamus[38,67]. In NAc, BDNF is expressed in dopaminergic and excitatory neurons projecting to NAc. TrkB is expressed in neurons expressing both the dopamine D1 and D2 receptors. Similar to VTA, it is reported that enhancing BDNF function in NAc can induce the behavioral changes associated with mood disorders, including anhedonia, anxiety and social interaction in rodents[38]. Moreover, inhibiting BDNF–TrkB signaling using dominant-negative TrkB-T1 in NAc, results in a dramatic antidepressant effect.

Moreover, previous research has enhanced basal dopaminergic and BDNF signaling to investigate their effects on behavioral changes. The results have shown significant comorbidity of substance dependence and depressive disorders[68]. However, the implication of pro-BDNF signaling in NAc on mood disorders is yet to be explored. Since the antidepressant effects on behavior despair are mediated by BDNF–TrkB signaling in the hippocampus, it is possible that pro-BDNF-$p75^{NTR}$ mechanisms are involved in the VTA-NAc-mediated anhedonic phenotype. Therefore, selective deletion of genes encoding receptor $p75^{NTR}$ in NAc may be helpful in explaining the specific role of pro-BDNF and mBDNF in depressive behaviors.

### Glutamatergic and γ-aminobutyric acid systems

Pharmacological, genetic and postmortem evidence strongly suggests the involvement of synaptic dysfunction in affective disorders. Importantly, disorders are associated with a broad range of altered glutamatergic and glutamatergic and γ-aminobutyric acid (GABAergic) neurometabolism[69].

It is noteworthy that decreased levels of GABA in the plasma, cerebrospinal fluid, prefrontal and occipital cortices and dorsal anterolateral PFC neurons have been reported in patients with MDD[70]. Additionally, the effect of BDNF on the plasticity of GABAergic neurons in the hippocampus has been widely investigated in neuropsychiatric disorders. Previous studies using transgenic mouse models have shown that the genes with a high level of BDNF dependency were *Cort*, *Vgf*, *Sst*, *Tac1* and *Npy*. Those with intermediate BDNF dependency were *Snap25* and *Gad2* (*Gad65*) and those with little or no BDNF dependency were *Gad1* (*GAD67*), *Pvalb*, *Rgs4*, *Slc6a1*, *Calb2* and *Gabra1*[71]. BDNF regulates transmission at glutamatergic and GABAergic synapses through both pre- and postsynaptic mechanisms. In addition, BDNF promotes the release of GABA and increases the expression of cell membrane GABAA-R through the presynaptic tyrosine receptor kinase B[72]. It is also reported that postsynaptic BDNF promotes the expression and synaptic insertion of glutamate receptors. A previous study on promoter IV mutant BDNF (BDNF-KIV) mice uncovered the suppression of GABAergic transmission and an aberrant plasticity in the mPFC. This suggests that decreased activity-dependent transcription of BDNF results in altering synaptic function[73].

Additionally, previous studies have found a higher hippocampal mRNA expression of the GABAA-R subunit in the right hemisphere of rats. Intra-PFC infusion with allopregnanolone is also able to increase the gene expression of the γ2 GABAA-R subunit and BDNF in the right hemisphere of the same infused area, while bilateral injection increases the expression of BDNF in the hippocampus and PFC[53]. Moreover, deletion of the serotonin transporter induces neuroplastic impairments mediated by BDNF signaling in the spine and reduces the levels of GABAergic markers in both adulthood and during development[74]. Furthermore, the application of BDNF in the neocortical layer 2/3 rapidly suppresses GABAergic transmission through the release of endocannabinoids from the postsynaptic pyramidal cells, which act in a retrograde manner to suppress the release of presynaptic transmitters[75].

Several studies have shown that BDNF can also modulate the release and function of glutamatergic neurons. For example, a previous study showed that there was a decrease in the levels of the N-methyl-D-aspartate (NMDA) receptor and GABAergic transmission in $BDNF^{Met/Met}$ mice in which the processing of BDNF was impaired[41]. It is also reported that BDNF-dependent synaptic plasticity is involved in the antidepressant effect of low-dose ketamine, a noncompetitive antagonist of the NMDA receptor. According to a previous study, ketamine enhances BDNF signaling and augments plasticity at excitatory synapses[76]. In addition, activation of TrkB modulates presynaptic glutamate release in hippocampus[77]. Overall, these studies strongly suggest the critical role of BDNF-dependent synaptic activity in the regulation of affective behaviors.

## BDNF/PRO-BDNF AS MEDIATORS OF NEUROIMMUNE CROSSTALK IN MOOD DISORDERS

More recent studies have been conducted to explore the neuroimmune crosstalk in mood disorders[78]. The crosstalk includes the communication between the nervous and immune systems, the effects of neuroendocrine hormones on the immune system, the innervation of lymphoid organs and the regulatory effects of cytokines on the HPA axis[79]. In addition, it is reported that microglia (resident immune cells in the CNS) as well as astrocytes can secrete some soluble agents such as chemokines, cytokines and neurotrophic factors to regulate immune responses in the CNS, and are implicated in the pathogenesis of mood disorders. Moreover, the levels of pro-BDNF/BDNF in the blood or mononuclear cells are associated with mood disorders, suggesting that peripheral pro-BDNF/BDNF can be diagnostic markers of mood disorders.

Neurotrophins, inflammatory mediators and oxidative stress are three well studied circulating diagnostic markers of mood disorders[80,81]. BDNF can also be used to indicate the efficacy of psychotropics. However, it is still debatable whether the levels of blood BDNF reflect the brain BDNF levels. In clinical studies, ELISA or western-blotting-based measurements of BDNF protein levels in body fluids or tissue samples are considered as potential proxies of brain function and associated diseases. Most clinical studies measure the levels of peripheral BDNF in saliva, serum, plasma, platelets and whole blood. The results show that peripheral blood BDNF appears to be a good indicator of brain BDNF levels. Additional studies have also corroborated that the levels of BDNF in whole blood and plasma are associated with the BDNF levels in the hippocampus[82].

A meta-analysis has shown that the levels of peripheral BDNF are equally reduced in patients with manic and depressive episodes[83]. In addition, previous studies have shown that there is a decrease in the levels of circulating BDNF in older and adolescent bipolar disorder patients in a euthymic state[84-86]. Moreover, a preliminary study showed that patients with bipolar mania had lower levels of the BDNF protein and mRNA, compared to healthy controls[87]. However, these findings were not consistent across all the studies. For instance, a previous study reported that the levels of mature BDNF and the ratio BDNF/proBDNF were significantly higher in patients with BD[88]. It was shown that pediatric bipolar patients had significantly higher levels of BDNF mRNA after eight weeks of treatment [89]. Moreover, a recent study reported that BD patients responsive to lithium had normal levels of serum BDNF[90]. Further research also revealed that lithium and valproic acid selectively activate the promoter IV of BDNF and trigger the respective downstream targets in neurons[91].

Pro-BDNF and its receptors, $p75^{NTR}$ and sortilin are upregulated in the serum of female patients with depression and positively correlated with depression scores[92]. Furthermore, the increased levels of pro-BDNF in the serum of patients with depression is reversed by long-term antidepressant treatment. It has been reported that the serum levels of BDNF in mood-stabilized bipolar disorder patients are significantly higher than those in healthy controls[93]. The serum levels of pro-BDNF in bipolar disorder patients are significantly lower than those in controls. These studies suggest that pro-BDNF/BDNF is closely related to the pathophysiology of bipolar disorder. However, further studies are required to explore how peripheral pro-BDNF/BDNF affects the pathogenesis of bipolar disorder.

Despite the close correlation between the levels of blood BDNF and various mood disorders, it is still unclear whether BDNF is able to cross the blood-brain barrier. While some studies argue that BDNF cannot directly traverse the blood-brain barrier, others indicate that BDNF is able to be transported[94,95]. Moreover, a number of studies have reported on additional problems related to the poor half-life and rapid degradation of BDNF[94,95]. More importantly, BDNF and pro-BDNF are enriched in human platelets but are undetectable in mice because the *BDNF* gene is not expressed in mouse megakaryocytes[96]. Therefore, it may be unrealistic to compare the peripheral BDNF levels in the mouse models of mood disorders with those of patients. Beyond the serum or plasma, peripheral BDNF/TrkB or pro-BDNF/$p75^{NTR}$ can be derived from immune cells.

## BDNF/TRKB AND PRO-BDNF/P75$^{NTR}$ SIGNALING DERIVED FROM IMMUNE CELLS IN MOOD DISORDERS

The hypotheses that inflammatory processes contribute to brain-related pathologies such as depressive disorders, has gained popularity particularly because of the activation of immune responses. Might it be possible that some immune cells such as nonspecific leukocytes and lymphocytes produce neurotransmitters and neuropeptides? Notably, immune mediators often interact with neurotransmitter receptors and also modulate neural pathways[97]. In turn, neuropeptides trigger the release of proinflammatory mediators that may amplify or facilitate inflammation by enhancing vasodilation, blood flow, vascular leakiness and leukocyte trafficking to sites of inflammation.

Similarly, BDNF and TrkB are expressed and released from microglia/monocytes, T and B cells. The released BDNF is in turn believed to exert neurotrophic effects[98]. In the CNS, BDNF and TrkB are expressed in the microglia which are the resident macrophages within the brain parenchyma[2]. When the microglia are activated, they can induce $Ca^{2+}$-response elements then bind to CREB and the calcium-responsive factor to mediate BDNF transcription[99,100]. Additionally, the released BDNF from the microglia can bind to TrkB and this has been implicated in neuropathic pain. However, it is still unclear what role the BDNF in the microglia plays in mood disorders and this requires to be studied further.

In addition, more recent studies have shown that pro-BDNF and p75$^{NTR}$ are also expressed in monocytes, T and B cells and are upregulated in the different immune-mediated inflammatory cells (Figure 2)[101-103]. Previous research on septic mice also showed that pro-BDNF signaling contributes to the development of cognitive dysfunctions by interfering with the functions of immune cells[104]. Moreover, additional studies have shown that pro-BDNF and p75$^{NTR}$ are upregulated in patients with multiple sclerosis as well as in mouse models and this contributes to the dysfunction of immune cells, mediated by pro-BDNF-p75$^{NTR}$-NF-κB signaling[105]. Our recent study showed that increased expression of proBDNF in M2-like monocytes may be highly associated with proinflammatory responses in the type-A aortic dissection disease[106]. Therefore, use of monoclonal antibodies against pro-BDNF may be a promising treatment to modulate the perturbed immune functions in the immune-mediated inflammatory diseases[105].

It is also reported that there is an increase in the levels of pro-BDNF, p75$^{NTR}$ and sortilin in the peripheral blood mononuclear cells of patients with depression and this is associated with the severity of disease[92]. In addition, both pro-BDNF and p75$^{NTR}$ are significantly upregulated in the lymphocytes of MDD subjects[92]. An early study reported that systemic administration of anti-pro-BDNF antibodies attenuated the depression-like behavior in rats. Given that it is hard for antibodies to reach the brain through the intact blood–brain barrier, it is likely that the therapeutic effect of systemic treatment with anti-pro-BDNF antibodies may be realized by neutralizing the peripheral pro-BDNF. Furthermore, a recent study by our research group showed that there was an increase in the levels of pro-BDNF and p75$^{NTR}$ in the CD11b$^{+}$ monocytes and macrophages in the intestinal laminar propria of mice under CUMS-induced depression[107].

Upregulation of pro-BDNF/p75$^{NTR}$ in monocytes/macrophage is closely related to the activation of proinflammatory cytokines and gastrointestinal immobility. Our recent study showed that treatment with fluoxetine can inhibit upregulation of pro-BDNF/p75$^{NTR}$, cytokine activation and attenuate gastrointestinal immobility[107]. These results therefore indicate that pro-BDNF/p75 signaling may be involved in the gut-brain axis during depression. We also used a lipopolysaccharide-induced model of cognitive dysfunction in mice to show that there was an increase in the levels of pro-BDNF/p75$^{NTR}$ in CD4$^{+}$ T lymphocytes in the meninges. There was also an increase in the levels of the tumor necrosis factor-, interleukin (IL)-1, IL-6 and interferon-. Additionally, systemic administration but not the intracerebroventricular injection of anti-pro-BDNF antibodies attenuated cognitive dysfunction and inhibited the activation of proinflammatory cytokines[108]. A recent study also revealed that pro-BDNF and p75$^{NTR}$ in monocytes played a role in neuroinflammation after chronic infection[109]. Therefore, pro-BDNF/p75$^{NTR}$ signaling derived from immune cells may act as the inflammatory mediators to promote the interaction of neuroimmune during the development of depression or cognitive dysfunction.

## CONCLUSION

BDNF/TrkB and pro-BDNF/p75$^{NTR}$ signaling pathways are widely expressed in different regions of brain. BDNF signaling exert different effects on mood disorders. In contrast, pro-BDNF/p75$^{NTR}$ signaling in CNS mainly promotes the development of mood disorders, such as depression and anxiety. Low levels of BDNF in circulation are negatively correlated with disease severity of depression. It should be noted, however, that BDNF is enriched in platelets and can be detected in human samples whereas BDNF is undetectable in the serum or platelets from mouse. This difference may limit the application of findings about BDNF/pro-BDNF signaling in mice to clinical practice. In contrast, pro-BDNF/p75$^{NTR}$ signaling in immune cells is upregulated in patients with depression or depressive mice. Further studies should investigate the roles of pro-BDNF/p75$^{NTR}$ in the neuroimmune crosstalk during the pathogenesis of mood disorders.

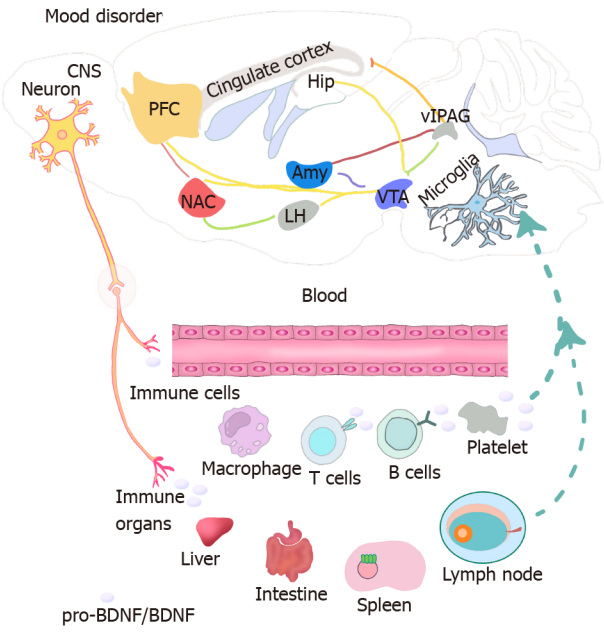


**Figure 2 Intracellular signaling of pro-BDNF/brain-derived neurotrophic factor in the nervous system.** Decreased levels of brain-derived neurotrophic factor (BDNF) are observed in most of the brain regions and contribute to the pathogenesis of mood disorders by interacting with different neurotransmitters. Pro-BDNF signaling is increased in the hippocampus and is implicated in anxiety-like behavior and depression. Moreover, there is an increase in pro-BDNF signaling in immune cells and this is correlated with disease activity in depression. Upregulated pro-BDNF signaling in immune cells may promote disease progression probably through interfering with the function of immune cells or directly acting on the neurons after being released from the microglia. Central nervous system dysfunction during mood disorders may also affect the immune functions and induce gastrointestinal immobility. CNS: Central nervous system; PFC: Prefrontal cortex; NAC: Nucleus accumbens; VTA: Ventral tegmental area; BDNF: Brain-derived neurotrophic factor; LH: Lateral hypothalamus.

## FOOTNOTES

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*MINIREVIEWS*

# Digital phenotyping in depression diagnostics: Integrating psychiatric and engineering perspectives

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## Abstract

Depression is a serious medical condition and is a leading cause of disability worldwide. Current depression diagnostics and assessment has significant limitations due to heterogeneity of clinical presentations, lack of objective assessments, and assessments that rely on patients' perceptions, memory, and recall. Digital phenotyping (DP), especially assessments conducted using mobile health technologies, has the potential to greatly improve accuracy of depression diagnostics by generating objectively measurable endophenotypes. DP includes two primary sources of digital data generated using ecological momentary assessments (EMA), assessments conducted in real-time, in subjects' natural environment. This includes active EMA, data that require active input by the subject, and passive EMA or passive sensing, data passively and automatically collected from subjects' personal digital devices. The raw data is then analyzed using machine learning algorithms to identify behavioral patterns that correlate with patients' clinical status. Preliminary investigations have also shown that linguistic and behavioral clues from social media data and data extracted from the electronic medical records can be used to predict depression status. These other sources of data and recent advances in telepsychiatry can further enhance DP of the depressed patients. Success of DP endeavors depends on critical contributions from both psychiatric and engineering disciplines. The current review integrates important perspectives from both disciplines and discusses parameters for successful interdisciplinary collaborations. A clinically-relevant model for incorporating DP in clinical setting is presented. This model, based on investigations conducted by our group, delineates development of a depression predic-

tion system and its integration in clinical setting to enhance depression diagnostics and inform the clinical decision making process. Benefits, challenges, and opportunities pertaining to clinical integration of DP of depression diagnostics are discussed from interdisciplinary perspectives.

**Key Words:** Digital phenotyping; Depression; Ecological momentary assessment; Telepsychiatry; Passive sensing; Smart phone

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**Core Tip:** There are systematic/quantitative reviews and meta-analyses of digital phenotyping (DP) in depression available in literature. These reviews are primarily published by engineering groups and provide limited psychiatric perspective, especially clinical relevance and clinical integration. The current review presents an overview of digital phenotyping of depression diagnostics and assessment from both psychiatric and engineering perspective. The overview includes major advances in the field of DP of depression diagnostics, including active and passive ecological momentary assessment, DP using data from social media, and DP using data from electronic medical records. We briefly discuss investigations conducted by our group and present a model for clinical integration of DP informed by those investigations conducted by our group. Finally, we discuss benefits, challenges, and opportunities pertaining to clinical integration of DP of depression diagnostics from an interdisciplinary perspective.

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## INTRODUCTION

Major depressive disorder (MDD) is a common, serious, and debilitating illness affecting all ages; children and adolescents, adults, and elderly[1]. It affects more than 264 million people worldwide and is associated with significant morbidity, increased mortality due to high suicide risk, diminished functioning, and poor quality of life[1,2].

In 2017, the worldwide prevalence of MDD was estimated to be at 4.4% globally[2]. The lifetime risk of depression was much higher (15%-18%)[2]. Consistent with this high risk, in terms of disease burden, MDD represented the third highest cause of Years Lived with Disability (YLD) globally[3]. In the United Sates (US), MDD accounted for 3.7% of all US adjusted disability years with significant economic burden and societal costs[4,5]. The National Survey on Drug and Health (NSDUH) conducted in 2017 found that an estimated 17.3 million or 7.1% of US adults have experienced at least one major depressive episode[4].

Similar to other fields of medicine, there has been a strong impetus in psychiatry to personalize depression assessment and treatment[6,7]. However, despite decades of research, few clinically relevant biomarkers, genetic variations or clinical characteristics have been identified that can aid in depression diagnosis and treatment[6,7]. Advances in digital technologies provide an exciting opportunity to personalize depression care[8]. Smart phones with their digital sensors and increasingly advanced computing capabilities have the potential to serve as "human sensors" by capturing granular changes in behavioral patterns[8,9]. Electronic medical records can gather large amounts of data across multiple disciplines of medicine, generate personalized patient reports, and seamlessly transfer data between large health care systems. Telepsychiatry can help us reach patients in real-time and conduct assessments in their natural settings. Integration and application of these technologies has the potential to significantly advance and personalize depression care.

Several recent systematic reviews of digital technologies and their application in depression care are available in literature[9-12]. These reviews are focused on either clinical or engineering/technical aspects of digital phenotyping technologies in depression care[9-12]. The objective of the current review is to integrate, evaluate, and synthesize evidence-informed literature from both clinical and engineering perspectives. The goal is to present a clinically-relevant, evidence informed review beneficial to clinicians, engineers, and researchers from diverse disciplines. Another goal is to help advance multidisciplinary collaborations with clear clinical objectives. We will summarize gaps, challenges, and opportunities from clinical, engineering, and legal perspectives. Finally, informed by investigations conducted by our research group[13-16], we will present a model for integration of digital phenotyping technologies in clinical setting to improve depression care.

## DEPRESSION DIAGNOSIS AND ASSESSMENT: CURRENT STANDARD OF CARE

MDD is a heterogeneous disorder with potentially diverse and multifactorial presentations[17,18]. Decades of research has shown that depression is the result of a complex interplay between genetic and environmental vulnerabilities initiating a cascade of neurobiological changes in diverse bodily systems [19,20]. Diagnosis of MDD includes confirmation of symptomatic threshold, patient distress, and functional impairment as a result of depression symptoms[21]. Diagnosis also involves ruling out medical, psychiatric, and substance use disorders that may present with depression symptomatology [21]. Two major taxonomies available for diagnosing depressive disorders include American Psychiatric Association's The Diagnostic and Statistical Manual of Mental Disorders (5$^{th}$ edition; [DSM-5]) and World Health Organization's The International Statistical Classification of Diseases and Related Health Problems (11$^{th}$ edition; [ICD-11])[21,22]. Diagnostic criteria for MDD are same in both classifications. Depression is characterized by two primary symptoms; depressed mood and loss of pleasure or interest lasting at least 2 weeks[21,22]. To meet the threshold for a Major Depressive Episode (MDE), these core symptoms should be accompanied by at least four more symptoms (for a total of at least five) as noted in Table 1[21,22]. Additionally, significant distress and measurable negative impact on functioning are required for a depression diagnosis (Table 1)[21,22]). Symptoms of depression can be grouped into three major categories; psychological or emotional, neurovegetative, and neurocognitive (Figure 1)[23]. Psychological symptoms are primarily subjective in nature *i.e.,* they depend on a patient's experience and their perception of these symptoms. It can be argued that psychological symptoms (*e.g.,* anhedonia/Lack of interest or pleasure) have behavioral consequences and lead to a change in functioning. Neurovegetative and neurocognitive symptoms are objective in nature and have measurable behavioral manifestations with subsequent impact on functioning. Patient reporting of subjective symptoms is inherently based on their experience and perception of these symptoms. This subjective vs. objective nature of depression symptoms with discussion of their direct or indirect behavioral manifestation and impact on functioning is critical to digital phenotyping in depression diagnostics. This distinction has a direct clinical relevance for application of digital phenotyping diagnostics in real-world clinical settings.

Patient self-rated and clinician-rated depression questionnaires are frequently used in screening and diagnosis of MDD[24,25]. Commonly used patient self-rated instruments include the 9-item Patient Health Questionnaire (PHQ-9), the Beck Depression Inventory (BDI), the 16-item Quick Inventory of Depression Symptomatology-Self Rated (QIDS16-SR), and the Center for Epidemiologic Studies Depression Scale (CES-D)[24,26]. In real world clinical settings, self-rated instruments are used more frequently than clinician-administered instruments as they are easier to administer and demand fewer resources[27]. These instruments also play a critical role in the continuum of depression care and help personalize patient care.

### *Limitations of current depression diagnosis and assessment*

The DSM of Mental Disorders (DSM-5) endeavors to categorize psychiatric symptomatology into specific disorders[21]. Despite evidence supporting such categorization, DSM-based diagnosis of depression remains subjective, as it relies upon patient report, clinician observation, and clinical judgment. In real world settings, clinicians struggle with the limitations of DSM-based diagnosis due to heterogeneity of patient presentations not fully captured by DSM criteria[28]. Limitations of DSM-based depression diagnosis and assessment are further exacerbated by challenges in clinical setting such as brief (15 to 20 minutes) patient visits with limited time for clinical assessments, and complexity of patient presentations with multiple comorbidities[29]. Administration of depression rating scales can add some objectivity to clinical assessments. However, evidence indicates that few clinicians use rating scales in their clinical practice[30]. This is due to several reasons, including lack of adequate resources to administer such scales[30]. Furthermore, the rating scales rely on a patient's memory and capture a narrow spectrum of a patient's overall mental state[31]. A major DSM criterion for depression diagnosis is two weeks of persistent symptomatology[21]. Evidence suggests that patient reports during clinical encounters may be largely influenced by their symptoms during the days leading up to the clinical encounter[31]. Due to their reliance on patient recall, clinical assessments may fail to fully capture the severity of the neurovegetative and neurocognitive symptoms of depression (*e.g.,* fatigue, sleep disturbances, concentration)[31,32]. Current clinical assessments also fail to capture functional impact of depression, a core criterion (criterion B) for depression diagnosis[31,33]. These assessments provide a cross-sectional evaluation of a patient's mental state as they are administered infrequently, usually every 4 to 6 weeks during the patient's clinic visit.

## DIGITAL PHENOTYPING IN DEPRESSION

Digital Phenotyping is defined as "moment-to-moment quantification of the individual-level human phenotype in situ using data collected from personal digital devices"[34,35]. DP has the potential to greatly improve the accuracy of depression diagnosis and assessment by adding much needed

**Table 1 Summary of major depressive disorder criteria**

| Five (or more) of the following symptoms present for at least 2 wk period |
|---|
| Depressed mood |
| Anhedonia *i.e.,* diminished interest or pleasure |
| Weight loss or weight gain |
| Sleep disturbances (insomnia or hypersomnia) |
| Psychomotor agitation or retardation |
| Fatigue |
| Feelings of worthlessness or excessive inappropriate guilt |
| Cognitive difficulties |
| Suicidal thoughts and/or behaviors |
| *Other Criteria:* |
| Symptoms cause clinically significant distress or functional impairment |
| Symptoms are not better explained by other psychiatric or medical diagnosis |

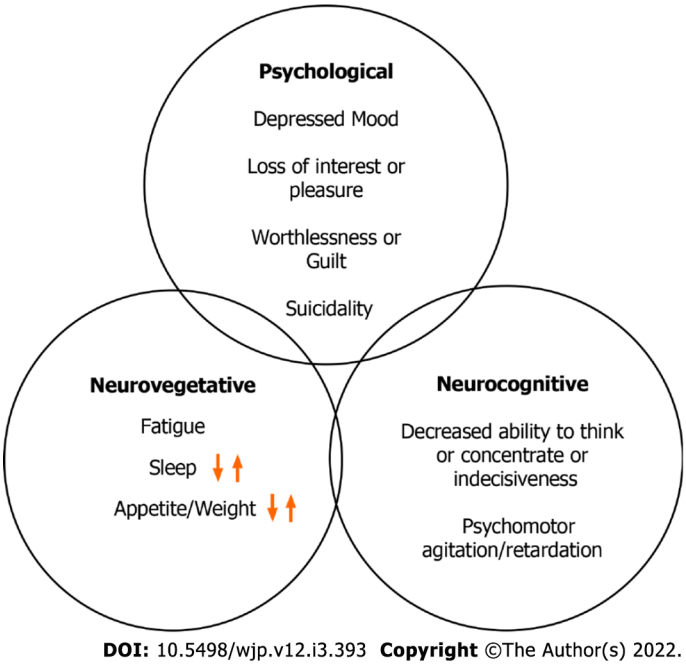


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**Figure 1 Depression symptomatology.**

objectivity to the process. By generating objectively measurable endophenotypes, it can serve as a behavioral biomarker to personalize depression care[34,35]. The generated phenotype provides an ecological and continuous representation of a patient's physical, emotional, behavioral, social, and cognitive activities in real-time[35,36]. At present, DP relies on two primary sources of data, active and passive data, generated by Ecological Momentary Assessments (EMA) conducted using personal digital devices. Active EMA consist of data reported directly by the user, and passive EMA consists of data automatically collected from digital devices and platforms[9,11,37]. The digital devices that currently serve as DP sources include smart phones, wearable sensors, and data collected from human-computer interactions[9,37]. DP in depression diagnostics involves a multistep process[38,39]. The first step involves obtaining signals from the digital devices to generate raw data. Once the data is collected, the goal is to find patterns that correlate with patient's clinical status. This step involves use of machine learning algorithms to find predictive behavioral features from the raw data sets. The final step is to integrate the features and electronic self-reports (active EMA) to generate an ecological, continuous, and personalized digital phenotype of the patients that can enhance depression diagnostics and assessment in clinical setting[38,39].

## ECOLOGICAL MOMENTARY ASSESSMENT IN DEPRESSION DIAGNOSTICS

EMA involve repeated sampling of an individual's behaviors and experiences in real-time, in the person's natural environment[40]. EMA conducted digitally as part of DP in depression diagnostics strives to minimize recall bias seen with assessments conducted in clinical settings[9,11]. In addition, it seeks to maximize ecological validity and allows the investigation of processes that influence behavior in real world settings[9,11]. As mentioned earlier, EMA can be categorized into active and passive EMA [9,11]. Any data or assessments that need active input by participants falls under Active EMA (*e.g.*, electronic assessments using depression questionnaires). Passive EMA includes any data or assessments collected passively (*i.e.*, without participant's active input)[9,11].

Table 2 delineates depression symptomatology and major categories of active and passive EMA used to measure these symptoms. 'Subjective symptoms' such as depressed mood, guilt/negative beliefs, and suicidality can be primarily measured using active EMA such as depression questionnaires. 'Subjective symptoms with direct behavioral manifestations' such as anhedonia and concentration difficulties can be measured using both active and passive EMA. Similarly, both active and passive EMA measurements play an important role in evaluation of 'objective symptoms with subjective patient experiences' such as psychomotor agitation or retardation and appetite. Finally, 'objective symptoms with direct behavioral manifestations' such as fatigue and sleep are primarily measured using passive EMA. As shown in Figure 2, active EMA such as self-report questionnaires can be used to measure depression symptoms, distress due to these symptoms, and their impact on functioning, while passive EMA can significantly contribute to the assessments of objective behavioral manifestations such as neurovegetative symptoms and impact on functioning.

### *Active EMA*

In active EMA, patients are prompted to enter information into their electronic devices at specific time intervals based on the type of assessment conducted[9,11]. A variety of standardized and non-standardized questionnaires can be used, allowing researchers to collect a varied amount of information from patients in real-time, in their natural environments[9,11].

Standardized assessments used in active EMA are generally self-report and self-administered questionnaires[9,11]. These assessments are validated to assess symptoms of depression[9,11]. Some examples of standardized assessments that have been used in EMA studies include: Patient Health Questionnaire (PHQ-9), Hamilton Depression Rating Scale (HDRS), Quick Inventory of Depressive Symptomatology (QIDS), and Beck Depression Inventory (BDI)[9,11]. While these depression assessment questionnaires are the same as those conducted in-person during a clinic visit, the major difference is that the active EMA are conducted in real-time, in participants' natural environment, and can be conducted more frequently to minimize recall bias[9,11]. Active EMA can be used for screening or to guide treatments based on depression status[41]. When used with passive EMA (passive sensing), they are frequently used as 'ground truth' to develop machine learning models[11,14]. In mobile health (mHealth) studies, these are administered at baseline and then at specific intervals (*e.g.*, PHQ-9 administered bi-weekly, QIDS administered weekly)[13,14].

Non-standardized assessments used in active EMA usually lack validation studies supporting their use in depression diagnosis or monitoring. However, they may provide important clinical information and leverage mHealth technology to conduct brief assessments in real-time and in the patients' natural environment[11,13]. Examples include general questions about mood, anxiety, sleep time and quality, medication adherence, medication tolerability, and physical activity[11,13]. Information gathered using these assessments can be combined with passive EMA data to improve detection of depressive symptomatology[11,14]. For example, studies have shown negative correlation between self-reported mood and the amount of time the phone screen was on and the percentage of social and entertainment apps used by the participant[11]. These assessments can be used for daily monitoring of symptoms[11,13]. The frequency of their administration varies between studies depending on the assessment and the study objective[11,13].

Several studies have highlighted the issue of recall bias with self-report depression questionnaires conducted every 4 to 6 week during patients' clinic visits[9,11]. Evidence indicates that patients with depression tend to judge their symptoms to be more severe or remember negative experiences more prominently when asked to recall them retrospectively[9,42]. Active EMA *via* mobile devices allows the collection of information in real-time, minimizing recall bias[9,11,42]. Obtaining this information in real-time also allows clinicians to put variations of mood in patients' situational and social context. This may reveal subtle patterns of emotional expression that would otherwise be missed by traditional depression assessments[43]. Daily monitoring of mood may improve patients' insight in their illness and allows them to become active participants in their treatment[11,43]. This may help them recognize patterns in their mood changes or negative feelings, triggers that lead to these changes, and help them examine if their coping strategies were effective[43]. Active EMA can also be used to monitor suicidal ideation, a critical aspect in depression management. One study found that 58% of their participants logged suicidal ideation during EMA assessment but denied it on retrospective review[44].

**Table 2 Depression symptoms, ecological momentary assessment active, and ecological momentary assessment passive**

| Depression symptoms |
|---|
| Depressed mood. anhedonia |
| Fatigue, sleep disturbances (insomnia or hypersomnia) |
| Psychomotor agitation or retardation, cognitive difficulties |
| Appetite problems |
| Guilt/negative beliefs |
| Suicidal thoughts/behaviors |
| EMA active |
| Standardized assessments |
| Self-report depression questionnaires (*e.g.*, PHQ-9) |
| Non-standardized assessments |
| Daily mood, anxiety, sleep ratings |
| Acoustic and paralinguistic information with audio sampling *e.g.*, voice intonation |
| EMA passive (behavioral feature categories, features, and sensors used) |
| Physical activity and sleep |
| Activity time-accelerometer |
| Inactivity-accelerometer, GPS |
| Distance-accelerometer, GPS |
| Movement duration and speed-GPS |
| Sleep duration, latency, efficiency-fitbit, accelerometer |
| Location |
| Home stay-GPS |
| Location clusters and variance-GPS |
| Entropy-GPS |
| Circadian rhythm-GPS |
| Social communication |
| Call duration/frequency, missed calls, number of conversations-call log |
| Sms text (incoming and outgoing)-sms text message log |
| Device |
| Social media engagement, social media app usage |
| Screen active duration and frequency |
| Social media engagement duration/frequency-app usage |
| Response time notification |
| Computer-keyboard interactions |

EMA: Ecological momentary assessment; GPS: Global positioning system; PHQ-9: Patient Health Questionnaire-9.

Active EMA includes alternate ways to assess affect and cognition using samples collected from patients[45]. Analyses of acoustic samples have identified acoustic cues that can predict individuals' emotions and affective state[46]. This includes features such as prosodic features, spectral-based features, and glottal features[46].

### *Passive EMA*

Passive sensing using smart phones and wearables can capture multiple dimensions of human behavior. Studies conducted in patients with depression have provided preliminary evidence of feasibility and efficacy of using passive sensing data for clinical inferences[9-11]. Passive sensing can capture and

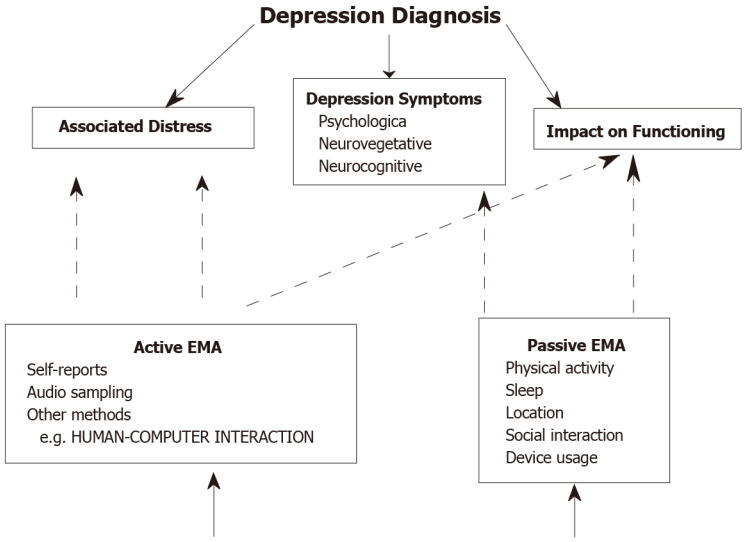


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**Figure 2 Depression diagnosis and ecological momentary assessment.**

monitor behavioral correlates of all three clusters of depression symptomatology: psychological, neurovegetative, and neurocognitive. However, it is especially useful to capture the neurovegetative and neurocognitive symptoms (*e.g.*, fatigue, sleep, concentration), as these symptoms have direct impact on behavior and functioning[13,14]. Several studies have shown consistent and statistically significant correlations between objective behavioral features collected *via* mobile phones and wearable devices and depressive symptomatology[9,10,14].

The process of passive sensing involves collecting raw and continuous data from multiple sensors present in mobile phones and wearable devices such as a Fitbit[13,14]. These include sensors such as the accelerometer, Global Positioning System sensor (GPS), light sensor, and microphone[9,10]. Data is also gathered on device analytics such as call logs, Short Message Service (SMS) texting patterns, and device activity[9,10]. Behavioral features are extracted from the raw data. The features are expected to capture behaviors, such as location clusters captured by GPS reflecting the number of locations visited by the individual. In patients with depression, behavioral features capture changes in behavior as a reflection of depression status and severity. The features are grouped into specific categories as correlates of depression symptomatology (*e.g.*, reduced activity and decreased number of locations visited by the individual may be reflective of anhedonia and fatigue)[9,10].

Table 2 describes categories of behavioral features, their correlates in depression symptomatology, and features that have shown consistent and statistically significant correlations with depression symptoms[9,10]. In studies conducted in non-clinical samples, features *home stay (more time at home)* and *screen active duration (longer phone usage*) showed consistent positive correlations with depression symptomatology[9,10]. In the same sample, features that showed consistent negative correlations with depression symptoms include *amount of vigorous activity, location variance, and distance covered*[9,10]. In clinical samples, features that showed consistent positive correlations with mood symptoms include *screen active duration* and *incoming call frequency and duration* (amount of time spent by the individual on incoming calls)[9,10]. Features that showed consistent negative correlations with depression symptoms in clinical samples include the *amount of visible cell towers* (reflecting mobility), *SMS text messages received*, and *outgoing call frequency and duration*[9,10]. Recently, our group developed techniques to identify Internet usage sessions (*i.e.*, time periods when a user is online)[15]. A novel set of features were extracted based on usage sessions from the Internet traffic meta-data[15]. Machine learning models developed using these features were successfully able to predict depression status of the participants [15].

In addition to the analyses of acoustic samples provided by patients, passively gathered acoustics samples (from patients' digital devices) have also been used to predict patients' affective state[45]. Studies have shown that participants' affective state and cognitive traits can be predicted using alternate methods, such as language analyses and human-computer interactions[45,47].

### *Challenges and limitations of active and passive EMA*

For both active and passive EMA, the degree of patients' technical knowledge can be a critical factor affecting compliance. Technical problems and inappropriate operating systems have been cited as among the most common reasons for participant drop out in EMA studies[41,42]. For active EMA, this may include technical issues with data entry and uploading of data. For passive EMA, it usually

involves uploading of passive sensory data to the servers[41,42].

Assessments conducted in active EMA can become inconvenient and burdensome for participants [11]. This can lead to non-compliance. Studies have found that patient compliance with assessments decreases with time depending on their content and frequency of administration[9,11]. The need for active data entry may deter patients from adopting active EMA[37]. The standardized assessments administered electronically on a weekly or bi-weekly basis (*e.g.*, PHQ-9) can be conducted more frequently than in-office settings but still suffer from a similar recall-bias due to the duration they cover [9,11,42]. Although, one might argue that this recall bias is much less compared to their administration in office settings (usually every 4-6 week) due the higher frequency of their electronic administration. From a research perspective, daily mood monitoring can serve as a type of intervention, confounding the study design. Studies have shown that daily symptom recording, without any other direct treatment/intervention, improved symptoms of depression[11].

For passive EMA, other major technological challenges include battery drainage concerns reported by participants due to passive sensing on their mobile devices[48,49]. Studies have reported lack of sensor precision affecting data analyses (*e.g.*, inaccurate location data)[48,49]. Another major issue is missing sensory data[15,50,51]. As an example, the energy management system on a phone may turn off GPS when the battery level is low. In addition, it is well known that GPS does not perform well in certain common environments (*e.g.*, indoors), where it either fails to collect data or collects data with large errors[15]. Other challenges include heterogeneous data collection from different sensing devices[52, 53]. As an example, because of the different operating systems and the specific sensors used by Android and iOS, the two predominant smart phone platforms, the methods of data collection on these two platforms differ substantially. Consequently, the behavioral parameters derived from the different sources of sensing data exhibit significant differences[52,53]. The large volume of collected data may present a challenge for secure storage, statistical analysis, and clinical application[48]. Other technological challenges include data security and privacy, in particular, when the data needs to be shared with clinician's office[13,48].

Depression questionnaires and clinical interviews are used as 'ground truth' to find correlations with passive sensory data and to develop machine learning models[9,10]. A major limitation of this approach is the fact that the 'ground truth' (*i.e.*, the questionnaires and interviews) is still subjective. This may change over time as we gather larger amounts of data leading to better machine learning models based on passive sensory data. However, what if there is a significant discrepancy between active EMA (*i.e.*, patients' perception of their symptoms) and passive EMA (*i.e.*, objective behavioral data gathered by sensors on their mobile devices and analyzed using machine learning models)? In clinical settings, such a discrepancy may pose a challenge for clinicians with their decision-making process.

### *Privacy, legal, and ethical challenges*

Digital phenotyping technologies have the potential to revolutionize mental health research and clinical care. However, they also present ethical, legal, privacy, and regulatory challenges[54]. A key initial consideration when developing and subsequently implementing digital depression assessment technologies is that of consent and, specifically, of informed consent, a key bioethics principal[55]. Participants agreeing to digital phenotyping in research or clinical settings should understand the risks and benefits of any monitoring hardware or software, or of any subsequent intervention. Ethical constituents of informed consent include sharing information with the patient, assessing decisional capacity of the patient, and examining a patient's voluntarism[56]. For many of these technologies, a clinician must assess a participant's understanding of the scope and granularity of data being collected. Since there is a broad range of technology literacy in the general public and few participants will have a full understanding of the data they are sharing or of its potential uses, the informed aspect of informed consent is ever more crucial[55,57]. One must also ensure that participants understand that consent is an ongoing process and can be withdrawn at any time.

Data privacy and protection are also key issues. When acquiring data, there must be adequate encryption to ensure data is securely transmitted from the source (*e.g.*, a smartphone) to a storage device (*e.g.*, servers). Once data is collected, there must be clear guidelines as to who can access this data and for what purpose. Storing data then becomes one of the biggest issues due to the scope and nature of data that is collected. Even with safeguards in place, data breaches are common in healthcare settings [55,57]. Another salient feature of data is that of ownership. Key questions to consider that largely remain unanswered are: Who owns the data created? What can be done with the data in the future? Who can profit from the data? As data collection moves from requiring user input (active EMA) to collecting passive data (passive EMA), the security and privacy challenge of bystanders, who do not provide consent, comes into play[57].

Once the ethical, security, and privacy concerns are managed, those who implement the various mHealth modalities must consider their liability. Liability can stem from failure to act on information ( *e.g.*, suicidal ideation), errors that stem from malfunction of apps, misunderstanding or misinterpretation of information by patients[58]. In the studies by our group[13,14], a study clinician is on call at all times to act on suicidal ideation that is entered into the study app when participants completed their weekly depression questionnaires. When these apps evolve to use more passive data and are ultimately predictive, what happens when the software predicts there is a risk of suicide? When must a clinician

act? At what level would the risk of suicide have to be for the information to be actionable? Moving forward, these issues must be carefully addressed, both from patient safety and provider liability perspectives.

## INTEGRATING ACTIVE AND PASSIVE EMA

Depression symptomatology includes both subjective and objective symptoms. Psychological symptoms such as depressed mood, guilt and negative beliefs, and suicidality are subjective in nature (*i.e.*, these symptoms depend on patients' subjective experience and perception of their status). Assessment of these symptoms requires clinical interview and/or use of depression questionnaires. Similarly, patient's *distress* due to depression (criterion B), a required criterion, is also subjective and requires clinical assessment. Active EMA may be necessary to fully evaluate these subjective symptoms and criteria. One may argue that behavioral and functional consequences of these symptoms can be captured using passive EMA, providing a more comprehensive assessment of these symptoms.

Neurovegetative and neurocognitive symptoms such as fatigue, sleep disturbances, psychomotor agitation/retardation, and concentration difficulties are objective symptoms with direct behavioral manifestations. Active EMA using interview and depression questionnaires may provide assessment of these symptoms based on patient perception of these symptoms but may fail to capture the actual behavioral manifestations. Similarly, *functional impairment*, another essential criterion (criterion B) for depression diagnosis, can be more fully captured using passive EMA. Similar to the subjective symptoms, patients' own assessment and perception of their status assessed using clinical interview and depression questionnaires (active EMA) can provide a more comprehensive assessment of objective symptoms. In summary, at present time, utilization of both active and passive EMA may be necessary to generate a more comprehensive digital phenotype of the patient[13].

### *LifeRhythm: Integration of active and passive EMA to predict depression symptomatology*

Our group, in a 4-year project funded by the National Science Foundation, demonstrated successful prediction of depression symptomatology integrating active and passive EMA (Figure 3). The *LifeRhythm* project involved a two-phase study conducted in college age participants with depression, in comparison with a control group without depression diagnosis[14-16,52]. In Phase I of the project, a smart phone application, *LifeRhythm*, was developed to passively collect sensory data (location, activity, social interaction) for both Android and iOS, the two predominant smartphone platforms. Feature extraction techniques were developed to extract behavioral features from the sensory data as correlates of depression symptomatology and machine-learning models were developed to predict self-report depression questionnaire scores and depression status. These techniques and prediction models were then validated and refined in Phase II of the study. In Phase II, wristbands (Fitbit devices) were added to the sensory diagnostics for characterizing specific behavioral features (*e.g.*, sleep disturbances and activity level). A total of 182 participants were recruited in this two-phase study and were followed over an 8 month study period. Three sets of data were collected during participant's study participation: sensory data collected by the *LifeRhythm* app (EMA passive), self-report depression questionnaire completed electronically by the participant every two weeks (EMA active), and clinical assessments conducted by a study clinician. Study findings demonstrated that passive sensory data (EMA passive) predicted self-report depression scores and depression status per clinical interview conducted by the study clinician[14-16,52]. Notably, integration of passive sensing (EMA passive) and self-report depression scores (EMA active) showed better prediction power compared to passive or active EMA alone.

### *DepWatch: Integrating active and passive EMA in clinical setting to predict treatment response*

At present, we are investigating development of a depression prediction system, *DepWatch*, and its integration in clinical setting to inform the clinical decision making process (Figure 4). This 4-year project, funded by the National Institute of Mental Health, builds on the findings and insights gained from the *LifeRhythm* project[13]. It includes two study phases. The objective of Phase I is to develop machine learning models to predict response or lack of response to antidepressant treatment, when patients meeting a specific threshold for depression symptoms undergo adjustments to their antidepressant medication regimen. Similar to the *LifeRhythm* project, passive sensory data (EMA passive) is collected using the app developed by our team for both Android and iOS platforms. Active EMA conducted electronically include daily self-report mood and anxiety ratings, weekly self-report depression questionnaire, weekly self-report medication safety and tolerability assessments, and other clinical information collected at baseline. Participants also undergo monthly clinical assessments conducted by a study clinician to assess their depression status and their response/non-response to antidepressant treatment compared to their baseline status. A total of 250 participants meeting a specific threshold for depression severity and starting or adjusting antidepressant treatment are currently being enrolled in the Phase I. Machine learning models will be developed using passive and active EMA data. *DepWatch*, an automatic data collection, analytic, and prediction system will be developed based on the

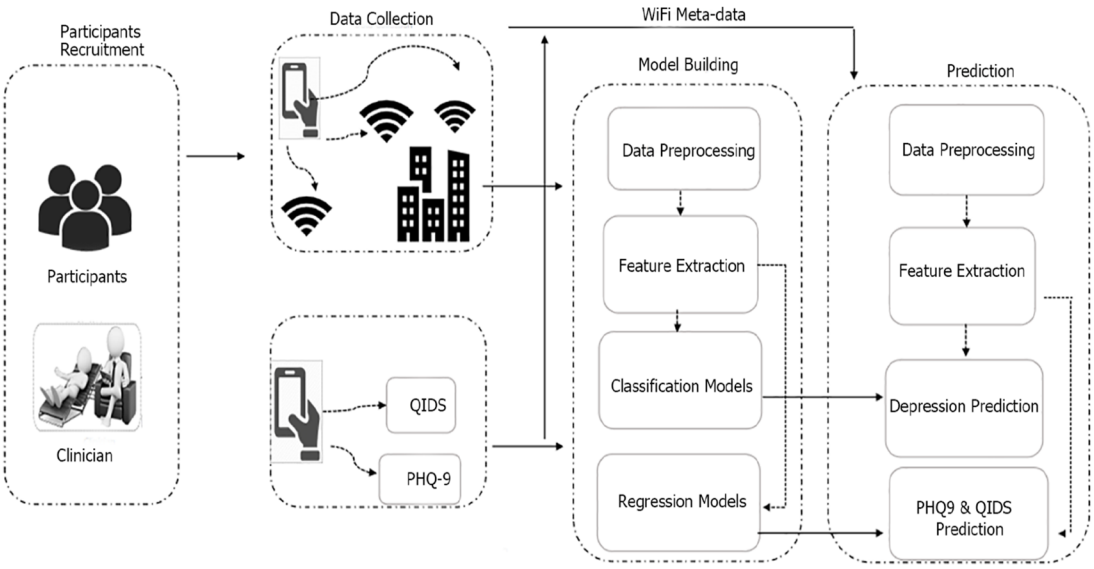


**Figure 3 *LifeRhythm*: Integration of active and passive ecological momentary assessment to predict depression.** Adapted from Ware *et al*[86] with permission from the Association for Computing Machinery (ACM) Citation: Ware S, Yue C, Morillo R, Lu J, Shang C, Kamath J, Bamis A, Bi J, Russell A, Wang B. Large-scale Automatic Depression Screening Using Meta-data from WiFi Infrastructure. *Proceedings of the ACM on Interactive, Mobile, Wearable and Ubiquitous Technologies* 2018; 2: 1-27. Copyright © The Association for Computing Machinery (ACM).

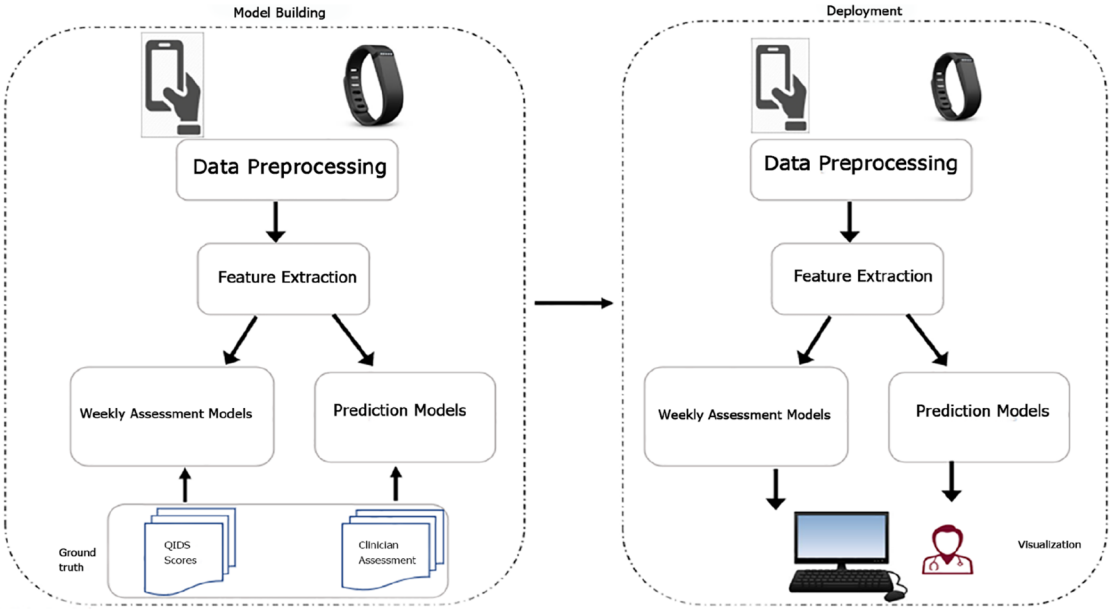


**Figure 4 *DepWatch*: Integrating active and passive ecological momentary assessment in clinical setting.** Adapted from Kamath *et al*[13] an open access article distributed under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/) with permission from the J Psychiatr Brain Sci (JPBS). Citation: Kamath J, Bi J, Russell A, Wang B. Grant Report on SCH: Personalized Depression Treatment Supported by Mobile Sensor Analytics. *J Psychiatr Brain Sci* 2020; 5: e200010. Copyright © The J Psychiatr Brain Sci (JPBS).

machine learning algorithms developed in Phase I and other relevant clinical information. In Phase II, the *DepWatch* prediction system will be investigated for its usefulness and applications as a clinical support system in the real-world clinical setting, compared to standard of care. Three clinicians will use *DepWatch* to support their clinical decision making process for their patients. A total of 128 participants under care of the three participating clinicians will be enrolled in Phase II[13].

## PREDICTING DEPRESSION STATUS USING OTHER DIGITAL TOOLS

### *Predicting depression status using social media*

Preliminary investigations are exploring behavioral and linguistic cues from social media data to predict depression status. Data can be extracted from a variety of social platforms including popular sites such as Twitter, Facebook, Instagram, and Reddit[59,60]. These investigations have used several variables/features of interest in social media data that may predict depression status. These include Language analyses (*e.g.*, length, characteristics of the posts), Emotion and Cognition analyses (*e.g.*, affect and intensity of posts reflecting anxiety or anger), Behavior analyses (*e.g.*, posting frequency, interaction with others on the platform), Demographics analyses (*e.g.*, age, gender inferred using computational techniques), and Image analysis (*e.g.*, visual information from the images posted)[59]. Machine learning and statistical modeling are applied to the extracted data to develop and validate algorithms to predict depression status[59,60]. At present, the major limitation of this promising area of research includes the "ground truth" definition of depression and the methods used to identify and operationalize depression status[59]. Some studies have demonstrated strong construct validity by using evidence-based and clinically-relevant practices to define depression (*e.g.*, use of depression questionnaire or use of ICD-10 diagnostic codes)[59,61]. Despite these current limitations, data mining from social media has a promising future in digital phenotyping. This innovative tool, in conjunction with EMA, can be used to augment digital phenotyping in depression diagnostics.

### *Predicting depression status using EMR*

Digital phenotyping of depression status can be enhanced by using extracted data from EMRs[60,62]. Studies conducted to date have primarily utilized features (extracted from EMR) interdependent with depression diagnosis to predict clinical depression. Such features include depression billing codes, medication information, and structured and unstructured notes containing explicit diagnostic information. Computational methods, such as natural language processing (NLP), have been developed to extract data from narrative clinical notes in EMR. NPL is an automated method of extracting and processing text into meaningful concepts based on a set of rules[63]. Recent studies have used non-psychiatric features in EMR and have applied machine learning approaches to the extracted data to predict depression status[62]. These EMR data extraction techniques can be used in conjunction with EMA to improve depression diagnostics as part of digital phenotyping strategy.

## TELEPSYCHIATRY

The use of teleconferencing technology in psychiatry dates back to the 1950s, when the Nebraska Psychiatric Institute started using teleconferencing to provide group therapy, consultation-liaison services, and medical student training[64]. Initial research focused mainly on increasing access to care in remote geographical areas and comparing the efficacy of video visits with in-person visits[65]. Growth of telepsychiatry was slow and patchy until recently. This was primarily due to technological challenges and usability issues, lack of willingness among healthcare professionals to modify well-established routines (*e.g.*, face to face interactions), lack of financial resources, and lack of organizational innovation [66,67]. For decades, telepsychiatry was considered effective and feasible, but not desirable.

With the COVID-19 pandemic of 2020, there was a paradigm shift. The personnel and financial barriers to the use of telepsychiatry were removed overnight, and practices across the United States transitioned to telehealth. The number of telehealth visits increased by 50% over the first quarter of 2020, compared with the same period in 2019[68].

The efficacy of telepsychiatry has been well established over the past few decades[69,70]. Multiple reviews have analyzed studies of various telepsychiatry outcomes, including feasibility, adherence, clinical outcomes, and cost. One review of 22 controlled studies concluded that telepsychiatry could adequately perform all functions of management of mental illness, including monitoring, surveillance, mental health promotion, mental illness prevention, and biopsychosocial treatment programs, more efficiently and as well as or more effectively than in-person care[71]. Other reviews have reported similar results[72,73].

### *Telepsychiatry: Challenges and opportunities*

Challenges of widespread, successful adoption of telepsychiatry practice can be divided into systemic challenges and personnel challenges. Systemic challenges include federal and state licensure and reimbursement policies that restrict the use of telepsychiatry, platform and internet bandwidth issues, availability of leadership support, and the "digital divide", which describes a lack of reliable device/internet access in underserved populations. Personnel challenges include a lack of clinician training and support, fear of technology amongst both patients and providers, physical and cognitive disabilities that limit the use of technology, patient safety issues, and provider concern that telepsychiatry does not provide the same range and depth of data that is provided in an in-person encounter [74,75].

One way to address this concern about the lack of personal interaction with the patient is to integrate EMA and DP based approaches with telepsychiatry visits. Incorporating both passive and active EMA data with the information available to the clinician might not only address the concern about the availability of "real time" patient data to the clinician, it may also augment and improve the clinician's ability to accurately assess the neurovegetative symptoms of depression such as sleep and activity. In a study by Moore *et al*, sixty-seven older adults completed paper-and-pencil measures of mindfulness, depression, and anxiety along with two weeks of identical items reported during ambulatory monitoring *via* EMA before and after participation in a randomized trial of Mindfulness-Based Stress Reduction (MBSR). EMA measures of depression substantially outperformed paper-and-pencil measures with the same items[76].

Passive and active EMA may improve the clinician's ability to predict and diagnose depression in underdiagnosed subgroups such as older adults[77]. Incorporating active EMA approaches more frequently may allow clinicians to increase engagement with an isolated, depressed patient. Combining EMA with telepsychiatry may improve access to care for patients with anergia/amotivation, and offers the opportunity to provide rapid interventions based on activity data[78].

## CLINICAL INTEGRATION OF DIGITAL PHENOTYPING

The therapeutic alliance between patients and their provider is the cornerstone of depression care. It is well established that a strong therapeutic relationship is a robust predictor for treatment response across all therapeutic interventions, including pharmacological interventions[79]. The current model of clinical care has a significant negative impact on this therapeutic relationship due to brief medication management visits, fragmentation of care, limited contact between patients and their clinicians, and lack of meaningful monitoring in between patients' clinic visits. One of the objectives of integrating DP into clinical care is to enhance the therapeutic relationship between patients and their providers[80]. A digital connection between patients and their providers and monitoring *via* active and passive EMA in between patients' clinic visits can reinforce the therapeutic relationship[80]. The other major objective of using DP is to improve accuracy and clinical relevance of diagnostic assessment. As noted earlier, depression assessment should evaluate three major areas: depression symptoms, patient distress, and impact on functioning. Current clinical assessment focuses primarily on patient symptoms and distress. Digital data can enhance assessment of symptoms and distress (*e.g.*, use of active EMA in-between visits). More importantly, digital data, specifically passive EMA, can greatly enhance clinical assessments by providing objective data on behavioral consequences of symptoms/distress with its impact on functioning. As shown in Figure 5, DP and other digital tools can be incorporated into clinical practice at multiple stages of depression diagnostics and management. Initial patient evaluation (in-person) can be improved using patient specific data gathered from EMR using machine learning algorithms. Active and passive EMA can provide continuous monitoring in between patient visits and inform patient-provider discussion and assessment during in-person or virtual visits. These digital and in-person interactions between patients and their providers can increase patients' engagement in their care and support shared decision-making. Use of virtual telepsychiatry visits interspersed by in-person visits can help increase frequency of patient-provider contact, further strengthening the therapeutic relationship.

## MACHINE LEARNING AND FUTURE OF DIGITAL PHENOTYPING

Current diagnostic systems, DSM-5 and ICD-11, were originally conceived using careful observations of symptoms by expert clinicians[21]. These taxonomies are useful for grouping individuals into broad diagnostic categories but it is becoming increasingly evident that the diagnostic categories lack neurobiological validity as well as clinical predictability[81]. It is also becoming evident that these diagnostic categories are spectrum disorders with heterogeneous clinical presentations and diverse underlying etiological and pathophysiological factors[81]. The current 'best-possible' evidence-informed treatment choices are successful only in limited number of patients partially due to this heterogeneity of clinical presentations with diverse underlying pathophysiology[82]. To address this critical gap, the National Institute of Mental Health (NIMH) launched a research initiative called the Research Domain Criteria (RDoC) project[83]. The RDoC initiative, a translational program, intends to synergistically integrate self-reports, neuropsychological tests, brain measurements, and genetic profiles to create precision medicine in psychiatry[83]. Machine learning approaches offer a rich set of tools towards achieving the goal of endophenotype modelling proposed by the RDoC initiative[84]. Machine learning models developed for the field of psychiatry are typically supervised machine learning models that employ a two-step process: training and testing. The collected data is divided into training and testing datasets. A learning algorithm is first fitted on the training dataset to train the model. The 'trained' model is then empirically evaluated by testing it on the testing dataset[84]. This two-step approach is consistent with the 'precision psychiatry' objectives of the RDoC initiative[83,84]. Data gathered from diverse

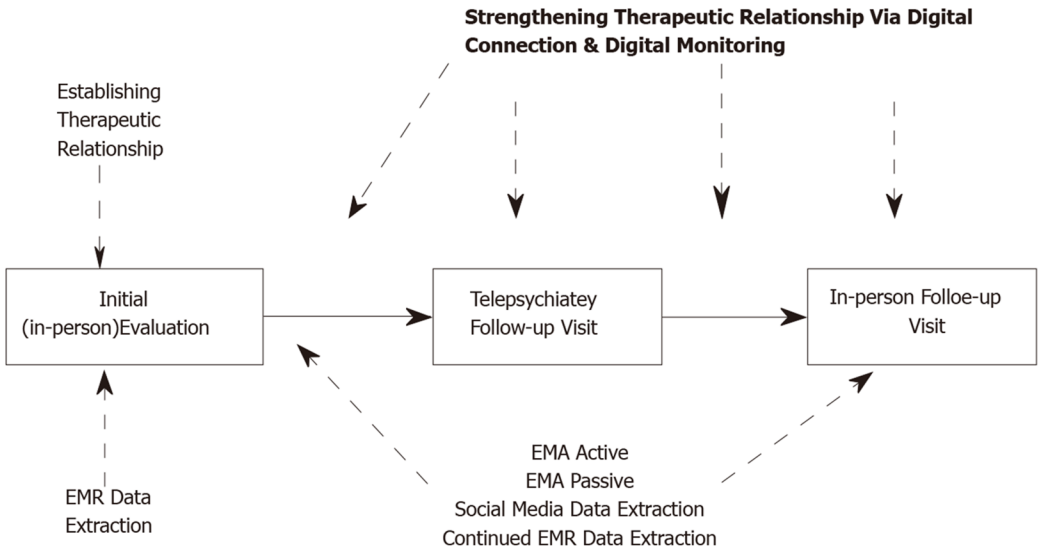


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**Figure 5 Hybrid clinical care model: Integration of in-person and digital care.** EMA: Ecological momentray assessment; EMR: Electronic medical record.

retrospective and prospective datasets (*e.g.*, genetic profiles, neuroimaging, EMR, active and passive EMA data) can be integrated and analyzed using machine learning approaches to generate objectively measurable and clinically predictable endophenotypes. The models generated can then be validated in a new set of patients to predict clinical outcomes including treatment outcomes. The machine learning approaches can translate complex discoveries into clinically relevant predictions bringing us closer to the goal of precision psychiatry.

## CONCLUSION

If we are to fulfill the promise of DP in depression diagnostics, it is critical that teams of psychiatric and engineering researchers work together to address the numerous challenges we have described. All investigations and digital tools under development should be scrutinized for their clinical relevance and real-world applicability. Investigations in the field of DP, to date, are spearheaded primarily by engineers with limited involvement of psychiatric researchers. This is problematic because, at present, clinical acumen of psychiatric clinicians play a central role in depression diagnosis, assessment, and management. The purportedly objective measures (*e.g.*, depression questionnaires) are important tools, yet remain subjective in nature and play a limited secondary role in clinical settings. The field of DP needs to draw upon the experience and expertise of psychiatric clinicians as 'ground truth' combined with depression questionnaires. It is essential to include psychiatric investigators who have background and expertise in clinical care and clinical research into the research team. A major role of clinical investigators as part of the research team would be to assess clinical relevance of digital tools under development compared to the standard of clinical care.

Once the digital tools show promise in predicting depression status as assessed by the 'ground truth' (clinical judgment and depression questionnaires), the next step would be to challenge the subjectivity of the 'ground truth' by focusing on a different, objectively measurable outcome. As noted earlier, depression questionnaires and clinician interview are fundamentally subjective as they rely on patients' memory/perception and on clinicians' clinical judgment. In comparison, change in functioning with its behavioral manifestations may be a better and a more objective 'ground truth'. In clinical setting, change in functioning is considered an important marker of depression status as it reflects depression symptoms, distress, and is associated with objective behavioral consequences. Furthermore, change in functioning with its behavioral consequences can be quantified objectively using DP tools. In the past decade, depression research has been striving towards 'remission' as an outcome[85,86]. This goal of achieving remission is directly related to patients' functional improvement. DP may provide us with objective tools to measure both remission and functional improvement.

In conclusion, we live in a time when most of the global population carry smart phones in their pockets and broadband access is rapidly increasing even in remote areas. DP based on smart phones and other digital tools can significantly enhance depression diagnostics. Objective continuous measurement of behavioral manifestations of depression using patients' own devices can provide clinically useful markers. Such 'behavioral biomarkers' can be used to refine diagnostic processes and

management. These objective markers (passive EMA) combined with assessments conducted in patients' milieu (active EMA) and strengthened therapeutic relationship and monitoring due to continuous digital connection between patients and their providers can help us move closer to the goal of personalized and patient-centered care.

## FOOTNOTES

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ORIGINAL ARTICLE

Basic Study

# Magnesium-L-threonate exhibited a neuroprotective effect against oxidative stress damage in HT22 cells and Alzheimer's disease mouse model

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## Abstract

***BACKGROUND***

Oxidative stress results in the production of excess reactive oxygen species (ROS) and triggers hippocampal neuronal damage as well as occupies a key role in the pathological mechanisms of neurodegenerative disorders such as Alzheimer's disease (AD). A recent study confirmed that magnesium had an inhibitory effect against oxidative stress-related malondialdehyde *in vitro*. However, whether Magnesium-L-threonate (MgT) is capable of suppressing oxidative stress damage in amyloid β $(Aβ)_{25-35}$-treated HT22 cells and the AD mouse model still remains to be investigated.

***AIM***

To explore the neuroprotective effect of MgT against oxidative stress injury *in vitro* and *in vivo*, and investigate the mechanism.

***METHODS***

$A\beta_{25-35}$-induced HT22 cells were preconditioned with MgT for 12 h. APPswe/PS1dE9 (APP/PS1) mice were orally administered with MgT daily for 3 mo. After MgT treatment, the viability of $A\beta_{25-35}$-treated HT22 cells was determined *via* conducting cell counting kit-8 test and the cognition of APP/PS1 mice was measured through the Morris Water Maze. Flow cytometry experiments were applied to assess the ROS levels of HT22 cells and measure the apoptosis rate of HT22 cells or hippocampal neurons. Expression of B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X (Bax), hypoxia-inducible factor (HIF)-1α, NADPH oxidase (NOX) 4, $A\beta_{1-42}$ and phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) pathway proteins was quantified by Western blot.

***RESULTS***

*In vitro* data confirmed that $A\beta_{25-35}$-induced HT22 cells had a significantly lower cell viability, higher ROS level and higher apoptosis rates compared with those of control cells (all $P < 0.001$). MgT prevented the $A\beta_{25-35}$-triggered oxidative stress damage by elevating viability and decreasing ROS formation and apoptosis of HT22 cells (all $P < 0.001$). APP/PS1 mice exhibited worse cognitive performance and higher apoptosis rate of hippocampal neurons than wild-type (WT) mice (all $P < 0.01$). Meanwhile, significant higher expression of $A\beta_{1-42}$ and NOX4 proteins was detected in APP/PS1 mice than those of WT mice (both $P < 0.01$). MgT also ameliorated the cognitive deficit, suppressed the apoptosis of hippocampal neuron and downregulated the expression of $A\beta_{1-42}$ and NOX4 proteins in APP/PS1 mouse (all $P < 0.05$). Moreover, MgT intervention significantly downregulated HIF-1α and Bax, upregulated Bcl-2 and activated the PI3K/Akt pathway both *in vitro* and *in vivo* (all $P < 0.05$).

***CONCLUSION***

MgT exhibits neuroprotective effects against oxidative stress and hippocampal neuronal apoptosis in $A\beta_{25-35}$-treated HT22 cells and APP/PS1 mice.

**Key Words:** Alzheimer's disease; Magnesium; Neuroprotective effect; Oxidative stress; Hippocampal; Neuronal apoptosis

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**Core Tip:** The dysfunction of oxidative stress is considered to stimulate the production of reactive oxygen species and induce hippocampal neuron damage which are the significant hallmarks of neurodegenerative diseases such as Alzheimer's disease. Recent studies have explored the *in vitro* anti-malondialdehyde effect of magnesium. However, the potential neuroprotective effect of Magnesium-L-threonate (MgT) against oxidative stress remains to be explored. Our study demonstrated that MgT exhibited neuroprotective effects on suppressing oxidative stress and hippocampal neuronal apoptosis *in vitro* and *in vivo*, suggesting the promising therapeutic potential of MgT in oxidative stress-associated neurodegenerative disorders.

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## INTRODUCTION

As a progressive neurodegenerative disease, Alzheimer's disease (AD) occupies most cases of dementia, and it is clinically characterized by the deterioration of cognitive ability and brings a massive burden on AD patients' survival quality and social medical cost[1]. Although the pathological mechanism of AD is still incompletely elucidated, it was reported that oxidative stress occupied a key role in the pathogenic mechanism of this disease[2]. Numerous researches indicated that oxidative stress was a vital issue during the development of the neurodegenerative diseases, including AD, amyotrophic lateral sclerosis and so on. Oxidative stress could also accelerate amyloid β (Aβ) aggregation and induce neuronal

apoptosis in the brain tissues, especially in the hippocampus[3-7]. Hence, the exploration of antioxidative stress agents suggests a promising therapeutic option for achieving a neuroprotective effect against neurodegenerative diseases associated with hippocampal neuronal damage.

Magnesium is one of the essential cations in the intracellular environment and is only second to potassium in concentration. Magnesium is involved in the synthesis of many enzymes that are important in various biological processes[8]. The concentration of brain magnesium is decreased in AD patients when compared with control subjects[9]. Based on this finding, recent research has assessed the application of the novel magnesium compound Magnesium-L-threonate (MgT), which increases brain magnesium concentration after oral administration, for ameliorating AD-associated pathological changes[10-12]. Although MgT exhibits a protective effect against synaptic damage in an AD mouse model[11], its effects on oxidative stress and hippocampal neuronal damage remain unexplored. It has been recently confirmed that magnesium has an inhibitory effect against oxidative-stress-related malondialdehyde (MDA) *in vitro*[13,14]; therefore, it has become of interest to investigate whether MgT is capable of suppressing oxidative stress damage *in vivo*. Therefore, this research explored the potential protective effects of MgT against oxidative stress and neuronal injury in $A\beta_{25-35}$-treated HT22 cells and in APPswe/PS1dE9 (APP/PS1) mouse hippocampus.

*For the in vitro* experiment, in order to evaluate the capacity of MgT against $A\beta_{25-35}$-triggered oxidative stress and neuronal damage and explore the related mechanism, HT22 cell was chosen as the cell model, and it is well known as the immortalized murine hippocampal neuron[15]. We also explored the *in vivo* potential neuroprotective effects of MgT against oxidative stress, Aβ production and hippocampal neuronal damage in APP/PS1 mouse, a typical animal model of AD[16].

## MATERIALS AND METHODS

### Experimental materials

MgT was acquired from Macklin (Shanghai, China); $A\beta_{25-35}$ was purchased from MedChemExpress LLC (New Jersey, USA); The cell counting kit-8 (CCK-8) detection kit was provided from APExBIO Technology LLC (Houston, USA); A fluorescein isothiocyanate-annexin V/propidium iodide apoptosis agent was obtained from BD (New Jersey, USA); A reactive oxygen species (ROS) testing kit was supplied from Beyotime Biotechnology (Shanghai, China); The antibodies were purchased from Cell Signaling Technology (Danvers, USA), BioLegend (San Diego, USA) and Abcam (Cambridge, USA); The rest of experimental materials were bought from Thermo Fisher Scientific (Waltham, USA), CWBIO (Beijing, China) and Gibco (New York, USA).

### HT22 cell culture and drug administration

Based on the previously described method, HT22 cell culture and differentiation procedures were carried out[17,18]. Briefly, HT22 cell was cultured in the normal cell culture medium and then differentiated in N2 supplement-containing neurobasal medium for 1 d prior to drug administrations. According to the previous research[19], when it was exposed to 40 μmol/L $A\beta_{25-35}$ for 1 d, the viability of HT22 cell would significantly decrease. Therefore, this study chose 40 μmol/L as the appropriate concentration of $A\beta_{25-35}$ administration. Before $A\beta_{25-35}$ treatment, the dilution of $A\beta_{25-35}$ was carried out by using sterile saline and then it was kept at 37°C for 7 d for peptide pre-aging, as reported previously [19]. In order to investigate whether MgT could be applied to inhibit the oxidative stress damage triggered by $A\beta_{25-35}$ administration, HT22 cell was preconditioned with or without 50 μmol/L MgT for 12 h prior to be processed with 40 μmol/L $A\beta_{25-35}$ for 1 d.

### Cell viability detection

The viability was assessed *via* the CCK-8 experiment for HT22 cell exposed to $A\beta_{25-35}$ and MgT. Briefly, after different drug treatments for the three groups, each well of HT22 cells was incubated with 10 μL CCK-8 and the absorbance value was acquired at 450 nm by using an absorbance reader (California, USA).

### Quantitative assessment of ROS production

Total intracellular ROS generation was detected using an oxidation-sensitive fluorogenic dichlorodihydro-fluorescein diacetate (DCFH-DA) probe and further quantified with flow cytometry, as described previously[20]. Briefly, after drug administration, HT22 cells were washed and reacted with 10 μmol/L DCFH-DA probe during this experiment procedure. The cell samples were collected and finally detected using the flow cytometer (BD, USA). The percentages of DCFH-DA labeled cells represented the intracellular ROS level.

### Mice and drug administrations

APP/PS1 male mice and wild-type (WT) litter-mate male mice were acquired from the Nanjing Biomedical Research Institute of Nanjing University (Nanjing, China). The animal experiment received

the approbation from the local animal ethical and welfare committee. All protocols were designed to minimize discomfort or pain to the mice. The mice were housed in a specific-pathogen-free environment (23 ± 1 °C, 12 h/12 h light/dark, 50% humidity) with free access to water and food.

In the animal experiment procedure, 6-mo-old mice weighing 33-35 g were set as three groups (three mice per group): MgT-treated APP/PS1 mice (registered as 'TG + MgT group'), control APP/PS1 mice (TG group) and control WT mice (WT group). MgT-treated mice received daily administration of MgT (910 mg/kg/d) *via* drinking water for 3 mo on the basis of the previously described method[11]. The remaining mice (TG and WT groups) were treated with drinking water. After drug treatment, mice were used for the Morris Water Maze test and then killed under deep anesthesia (intraperitoneal injection, 150 mg/kg pentobarbital sodium) to collect the hippocampal tissues for further biochemical investigations.

### Morris water maze test

All mice were behaviorally tested for cognitive ability using the Morris water maze after 3 mo of treatments with or without MgT, as previously described[1]. At the beginning, each mouse was pretrained in this water maze with the visible platform for 1 d. Subsequently, all mice received the hidden platform training for 5 d (4 trails per day, 90 s per trial). For each trail, the mice were released from four starting quadrant positions in a different order and swam for 90 s. If the exploration time of mouse was less than 90 s, the trails would stop and the time to find the hidden platform was recognized as escape latency. If the mouse missed the setting time, it would be guided to arrive in the platform and the escape latency of 90 s was recorded. For each mouse, before the statistical analysis was carried out, the escape latencies of four trails were averaged. Finally, the platform was taken out and the mice were tested on a 90 s probe test at 24 h after the hidden platform training. After each trail, mice should be dried with a clean towel and put on an electric blanket to keep their body warm. For each mouse, the latency to arrive in the removed platform, the percentage of the time spent in the target quadrant (the quadrant where the platform was previously settled) and the number of times crossed the target position (the previous location of the platform) were measured during the probe test.

### Apoptosis detection

A fluorescein isothiocyanate-annexin V/propidium iodide testing agent was utilized to measure the apoptosis rate of HT22 cells. After drug administration, HT22 cells were washed, trypsin digested and incubated with this testing agent before flow cytometry. The allophycocyanin-annexin V/propidium iodide kit was also applied to assess the apoptosis rate of hippocampal neurons. After isolation of the hippocampal tissue, a single cell suspension was prepared, stained with anti-NeuN antibody, followed by appropriate Alexa-Fluor-488-conjugated secondary antibody, and finally detected with this kit for flow cytometric examination.

### Western blotting

The proteins in HT22 cells or hippocampal tissue were quantified, probed with a series of specific primary antibodies and visualized with a Digital Imaging machine (Gel Logic, Rochester, New York, USA). The relative protein density was quantified as previously described[21]. The involved primary antibodies were diluted to 1:1000, except for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (1:2000).

### Statistical analysis

Significance was measured using one-way analysis of variance with Fisher's least significant difference tests for multiple comparison using Prism 6 software (Graphpad, San Diego, CA, USA). For each group, data were shown as mean ± SE and $P < 0.05$ indicated significant differences.

## RESULTS

### MgT attenuated cytotoxicity in the $A\beta_{25-35}$-treated HT22 cell

As demonstrated in Figure 1, $A\beta_{25-35}$-exposed cells showed obvious lower cell viability than control cells ($P < 0.001$). Compared with $A\beta_{25-35}$-exposed cells, the viability of MgT-$A\beta_{25-35}$-exposed cells was obviously elevated ($P < 0.001$). Thus, all data of the CCK8 test illustrated that the pretreatment with MgT inhibited the cytotoxicity in the $A\beta_{25-35}$-exposed HT22 cell model.

### MgT suppressed ROS generation and hypoxia-inducible factor-1α overexpression in $A\beta_{25-35}$-treated HT22 cell

Intracellular ROS level measured by the DCFH-DA test exhibited an obvious increase in $A\beta_{25-35}$-administrated cells *vs* control cells ($P < 0.001$). Compared with $A\beta_{25-35}$-treated cells, the ROS level was remarkably decreased in MgT-$A\beta_{25-35}$-treated cells ($P < 0.001$) (Figure 2A and B). As indicated in Figure 2C and D, hypoxia-inducible factor (HIF)-1α protein expression was increased in the $A\beta_{25-35}$-

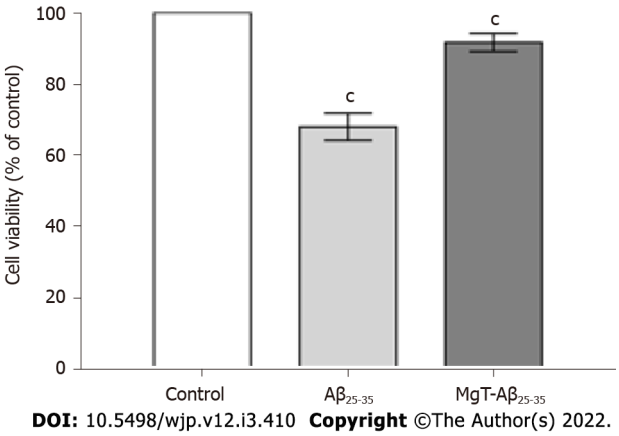


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**Figure 1 Magnesium-L-threonate administration inhibited the cytotoxicity in the amyloid $\beta_{25-35}$-administrated HT22 cells.** $n = 3$. $^{c}P < 0.001$ *vs* former group. Aβ: Amyloid β; MgT: Magnesium-L-threonate.

exposed HT22 cells ($P < 0.001$), which was effectively downregulated by MgT treatment ($P < 0.01$).

### *MgT inhibited the apoptosis and regulated the expression of apoptotic-related proteins in the $A\beta_{25-35}$-treated HT22 cell*

The effects of MgT treatment in regulating apoptosis and apoptotic-associated proteins expression were also measured, aiming to further assess the neuroprotective effect of MgT against neuronal damage in the $A\beta_{25-35}$-treated HT22 cell. As displayed in Figure 3A and B, $A\beta_{25-35}$-administrated group owned a higher apoptosis rate of HT22 cells than control group ($P < 0.001$), and the apoptosis rate was obviously reduced after MgT intervention ($P < 0.001$). What's more, the $A\beta_{25-35}$-administrated group had a lower B-cell lymphoma 2 (Bcl-2) protein (an anti-apoptotic molecule[22]) expression level and a higher Bcl-2-associated X (Bax) protein (a pro-apoptotic molecule[23]) expression level than control group (both $P < 0.001$), while MgT treatment effectively promoted Bcl-2 expression ($P < 0.001$) and blocked Bax expression ($P < 0.01$) (Figure 3C-E).

### *MgT restored downregulated phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) signaling pathway in $A\beta_{25-35}$-exposed HT22 cell*

The effects of MgT administration on regulating PI3K/Akt pathway, which was a classical pathway related to cell apoptosis[24], were also detected. As shown in Figure 4, $A\beta_{25-35}$-exposed cells showed lower ratios of phosphorylated (p)-PI3K/PI3K and p-Akt/Akt than control cells (both $P < 0.001$). After MgT administration, these two ratios were significantly upregulated (both $P < 0.001$).

### *MgT ameliorated impaired cognition of AD mouse*

The behavioral performance was recorded with the Morris water maze method to assess the effect of MgT intervention against memory deficit in AD mouse. Compared with WT group, TG group exhibited prolonged escape latency, while the escape latency was shortened in the TG + MgT group *vs* TG group (Figure 5A). The number of platform crossings and the percentage of target quadrant exploration time were significantly decreased in the TG group *vs* WT group (both $P < 0.01$), while these two cognitive scores were increased after MgT administration (crossings, $P < 0.01$; target quadrant exploration time; $P < 0.05$) (Figure 5B–D). The TG group had a longer latency to locate the removed platform than WT group ($P < 0.001$), and the latency was shorter in the TG + MgT group *vs* TG group ($P < 0.01$) (Figure 5E). Nevertheless, no obvious differences regarding the swimming speed and body weight were discovered among all groups (Figure 5F and G).

### *MgT suppressed hippocampal $A\beta_{1-42}$, HIF-1α and NADPH oxidase (NOX)4 protein expression in AD mouse*

Compared with WT group, elevated expression of HIF-1α, NOX4 (a reliable marker of oxidative stress [25,26]) and $A\beta_{1-42}$ proteins was seen in the TG group (HIF-1α and $A\beta_{1-42}$, $P < 0.001$; NOX4, $P < 0.01$), while these indexes were all decreased in the TG + MgT group *vs* TG group (all $P < 0.01$) (Figure 6).

### *MgT prevented hippocampal neuronal apoptosis and regulated apoptosis-associated protein expression in AD mouse*

The effects of MgT administration in ameliorating neuronal apoptosis and regulating the expression of apoptotic-associated proteins were also examined to further demonstrate the neuroprotective effect of MgT on APP/PS1 mouse hippocampus. As listed in Figure 7A and B, the apoptosis rate of hippocampal

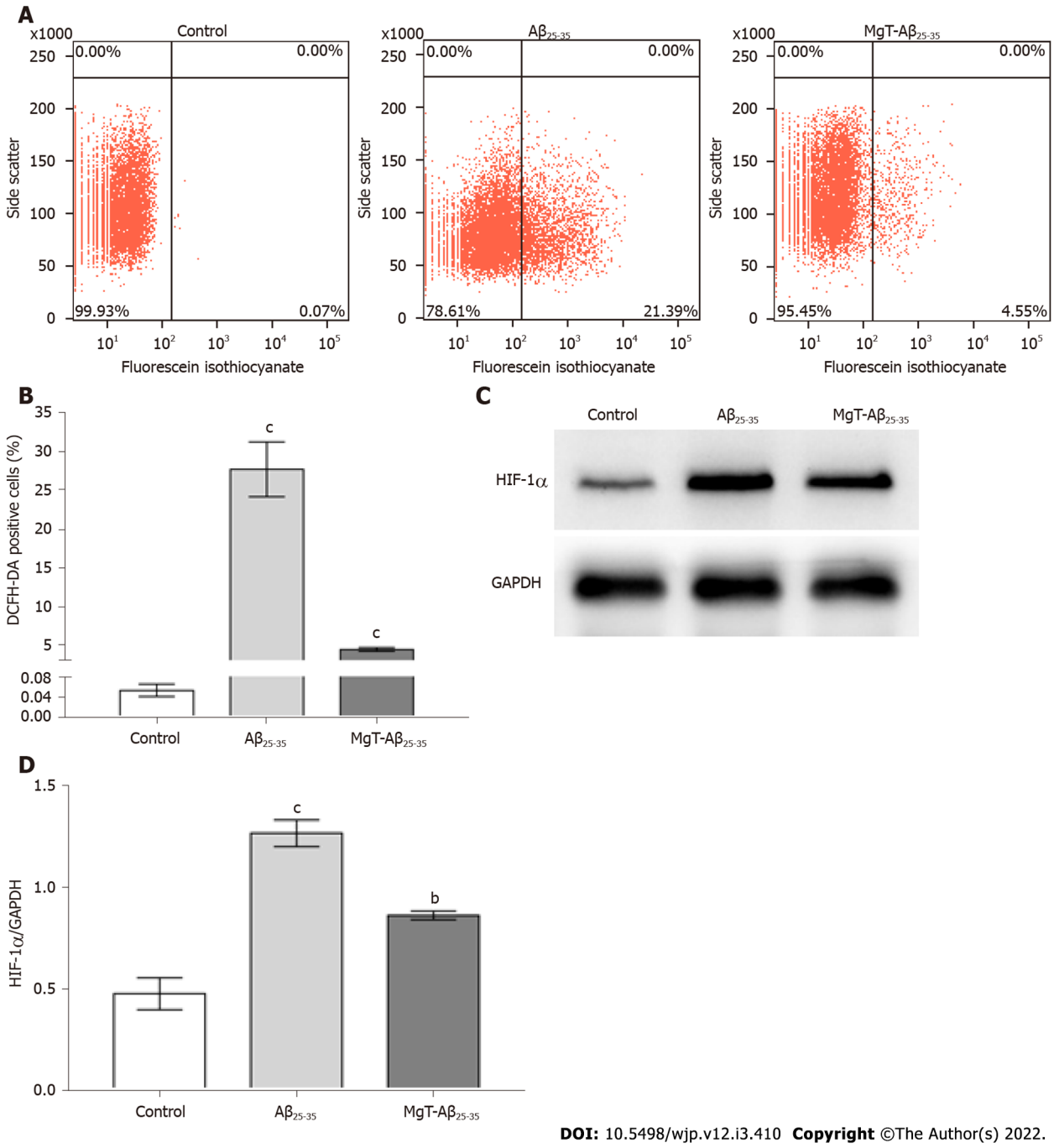


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**Figure 2 Magnesium-L-threonate treatment suppressed the elevated reactive oxygen species level and hypoxia-inducible factor-1α protein expression in the amyloid $\beta_{25-35}$-exposed HT22 cells.** A, B: The percentages of dichloro-dihydro-fluorescein diacetate positive cells of each group; C: Protein band images of hypoxia-inducible factor (HIF)-1α and glyceraldehyde-3-phosphate dehydrogenase of each group; D: The HIF-1α protein expression level of each group. $n = 3$. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ *vs* former group. Aβ: Amyloid β; MgT: Magnesium-L-threonate; HIF: hypoxia-inducible factor; DCFH-DA: dichloro-dihydro-fluorescein diacetate; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

neuron was elevated in the TG group *vs* WT group ($P < 0.01$), while TG + MgT group had a significant lower apoptosis rate than TG group ($P < 0.01$). Moreover, the downregulation of Bcl-2 expression and the upregulation of Bax expression were noticed in TG group *vs* WT group (both $P < 0.001$), while MgT treatment promoted Bcl-2 expression ($P < 0.01$) and suppressed Bax expression ($P < 0.001$) (Figure 7C-E).

### *MgT activated the PI3K/Akt pathway in AD mouse*

The effect of MgT administration on the PI3K/Akt pathway was also detected in the *in vivo* experiment of this study. As shown in Figure 8, p-PI3K/PI3K and p-Akt/Akt ratios were reduced in TG group *vs* WT group (both $P < 0.001$), while these two ratios were obviously elevated after MgT administration (p-PI3K/PI3K ratio, $P < 0.05$; p-Akt/Akt ratio, $P < 0.001$).

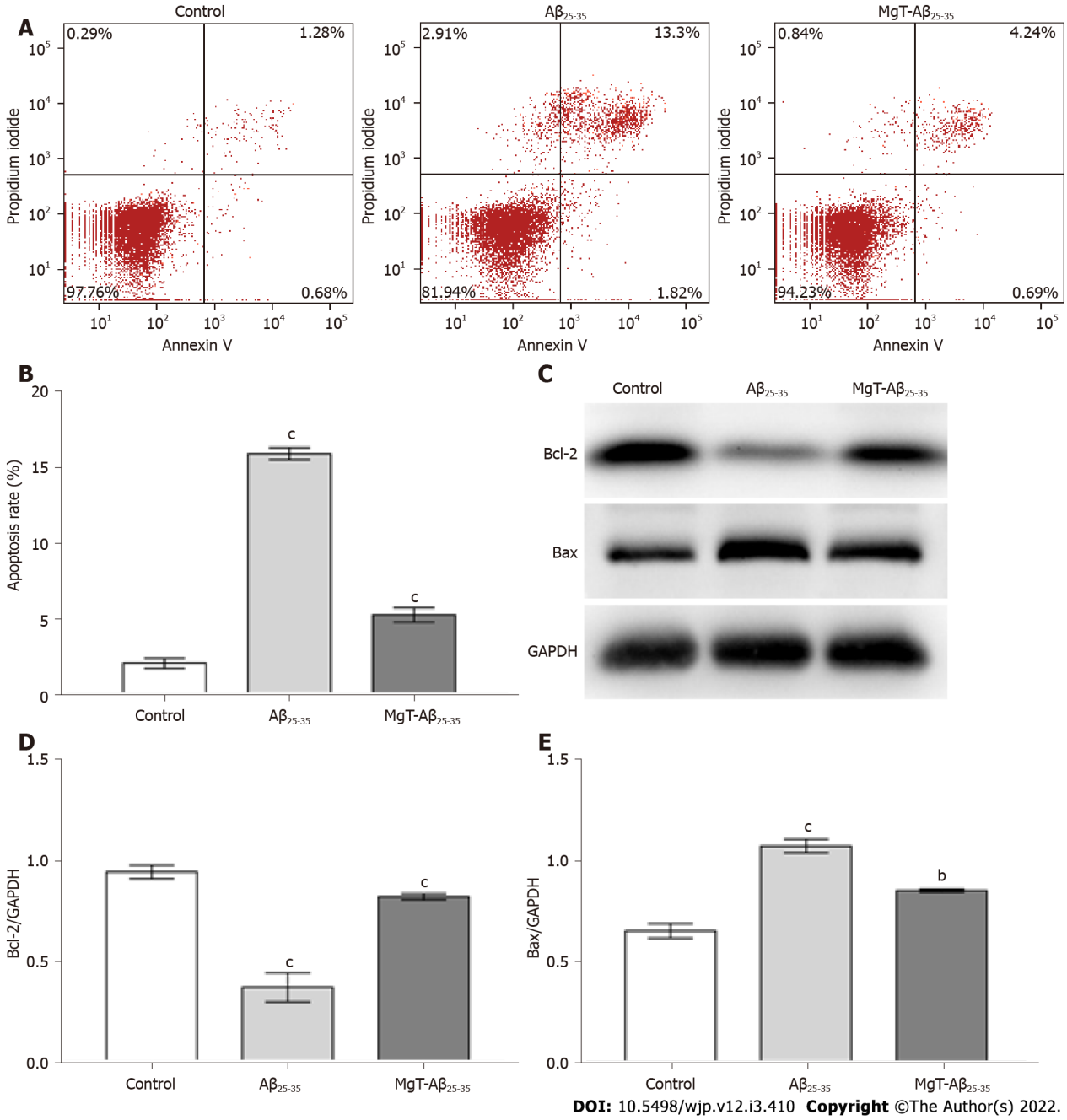


**Figure 3 Magnesium-L-threonate administration prevented the apoptosis and regulated the apoptotic-associated proteins expression in the amyloid $\beta_{25-35}$-administrated HT22 cells.** A, B: The apoptosis rate of each group; C: Protein band images of B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X (Bax) and glyceraldehyde-3-phosphate dehydrogenase in each group; D: The Bcl-2 protein expression level of each group; E: The Bax protein expression level of each group. $n = 3$. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ *vs* former group. Aβ: Amyloid β; MgT: Magnesium-L-threonate; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2-associated X; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

## DISCUSSION

It was demonstrated that oxidative stress could trigger neuronal damage in the hippocampus tissues of the brain, which is the vital pathological mechanism of neurodegenerative diseases, including AD[27]. Recently, the findings of the *in vitro* study certified that extracellular magnesium concentration could act as a regulator that effectively influenced the level of MDA, a pathological marker closely associated with oxidative stress damage[13,14]. Several researches indicated that MgT could elevate the level of brain magnesium *via* oral administration[10,12]. Therefore, this research attempted to validate the effects of MgT against oxidative stress and neuronal damage in the $A\beta_{25-35}$-treated HT22 cell and the hippocampus of APP/PS1 mouse, and investigated the involved mechanism.

Growing evidences have proved that during the pathological progression of neurogenerative disease, such as AD, abnormal oxidative stress resulted in the generation of ROS and hippocampal neuronal apoptosis thus leading to the deterioration of brain function[27,28]. The *in vitro* experiment part of this

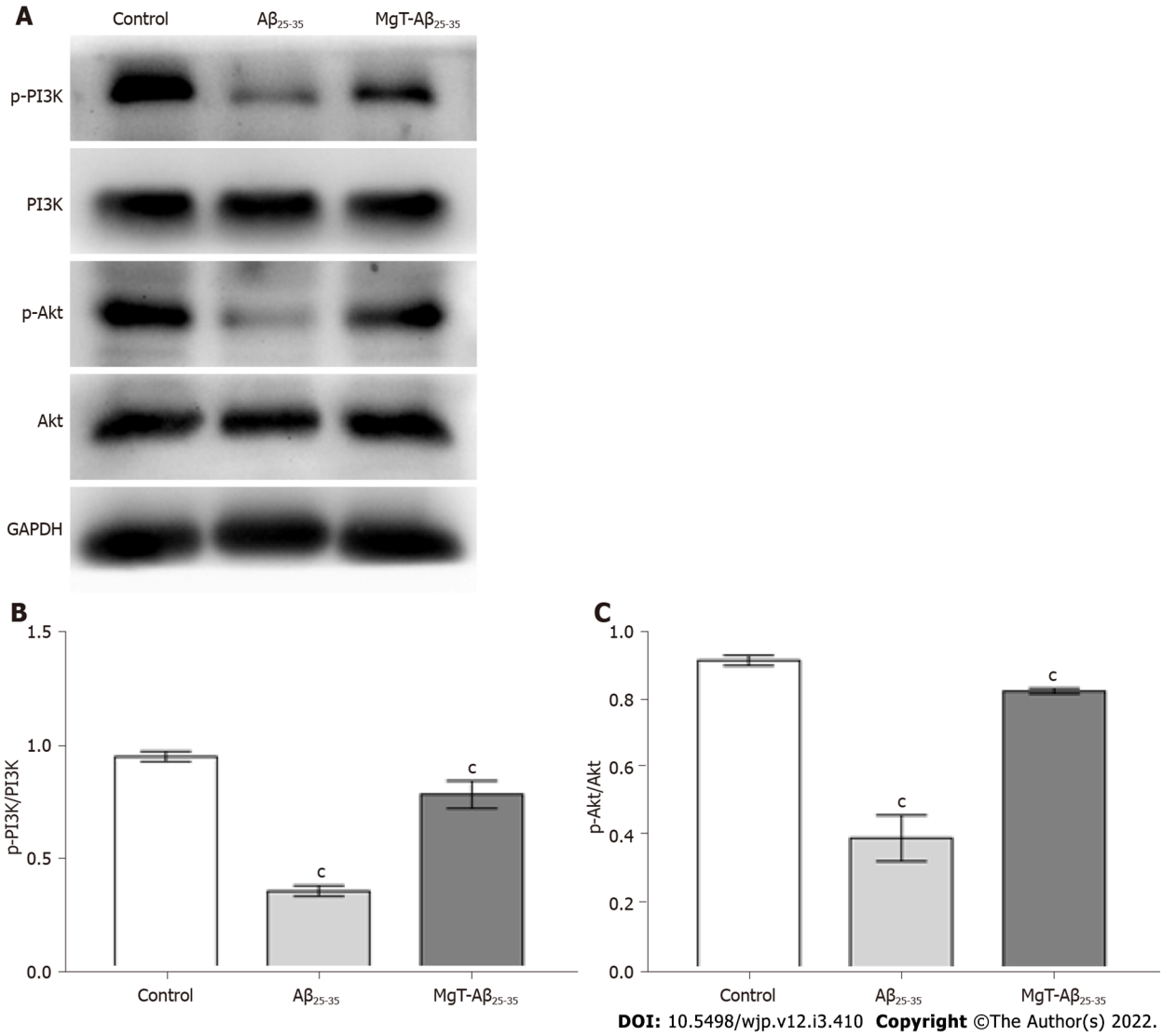


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**Figure 4 Magnesium-L-threonate treatment suppressed the downregulation of phosphatidylinositol-3-kinase/protein kinase B pathway in the amyloid $\beta_{25-35}$-exposed HT22 cells.** A: Protein band images of phosphorylated (p)-phosphatidylinositol-3-kinase (PI3K), PI3K, p-protein kinase B (Akt), Akt and glyceraldehyde-3-phosphate dehydrogenase of each group; B: The p-PI3K/PI3K ratio of each group; C: The p-Akt/Akt ratio of each group. $n = 3$. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ *vs* former group. Aβ: Amyloid β; MgT: Magnesium-L-threonate; PI3K: phosphatidylinositol-3-kinase; Akt: protein kinase B; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

study, oxidative stress, was detected by assessing the ROS level and cell apoptosis was detected by measuring the apoptosis rate and quantifying the expression of apoptosis-associated proteins. The *in vitro* data revealed that MgT remarkably blocked the oxidative stressors $A\beta_{25-35}$-induced[28] oxidative damage and apoptosis in the HT22 cells as proved by the elevation of cell viability, the reduction of ROS generation, the decrease of apoptosis rate and Bax expression, and the upregulation of Bcl-2 expression after MgT administration. In line with these *in vitro* results, the *in vivo* data confirmed the suppressive effect of MgT treatment against oxidative stress-triggered hippocampal neuronal damage *via* downregulating the expression level of the oxidative stress marker NOX4 protein and inhibiting the apoptosis of the hippocampal neuron in the AD mouse model. Additionally, it has been confirmed that the increased ROS induced by oxidative stress can lead to abnormal production of Aβ which can worsen the pathological process of AD[29]. In our *in vivo* study, the measurement of $A\beta_{1-42}$ expression by western blotting confirmed the inhibitory effect of MgT against Aβ production in the AD mouse model.

Numerous researches verified the key role of HIF-1α in the mediation of oxygen homeostasis within the cellular environment. A close relationship was discovered between HIF-1α level and oxygen balance: HIF-1α level remained low under the physiological situation while it was significantly elevated under the hypoxia condition[30,31]. Moreover, recent study revealed that the high glucose-triggered oxidative stress accelerated Aβ aggregation *via* the regulation of the ROS/HIF-1α mechanism *in vitro*, which supported a strong relationship between ROS and HIF-1α, and that the crosstalk between the two could deteriorate the Aβ production under abnormal oxidative stress condition[32]. Another research also indicated the crosstalk between HIF-1α and ROS in RAW 264.7 cell model[33]. Therefore, the effect

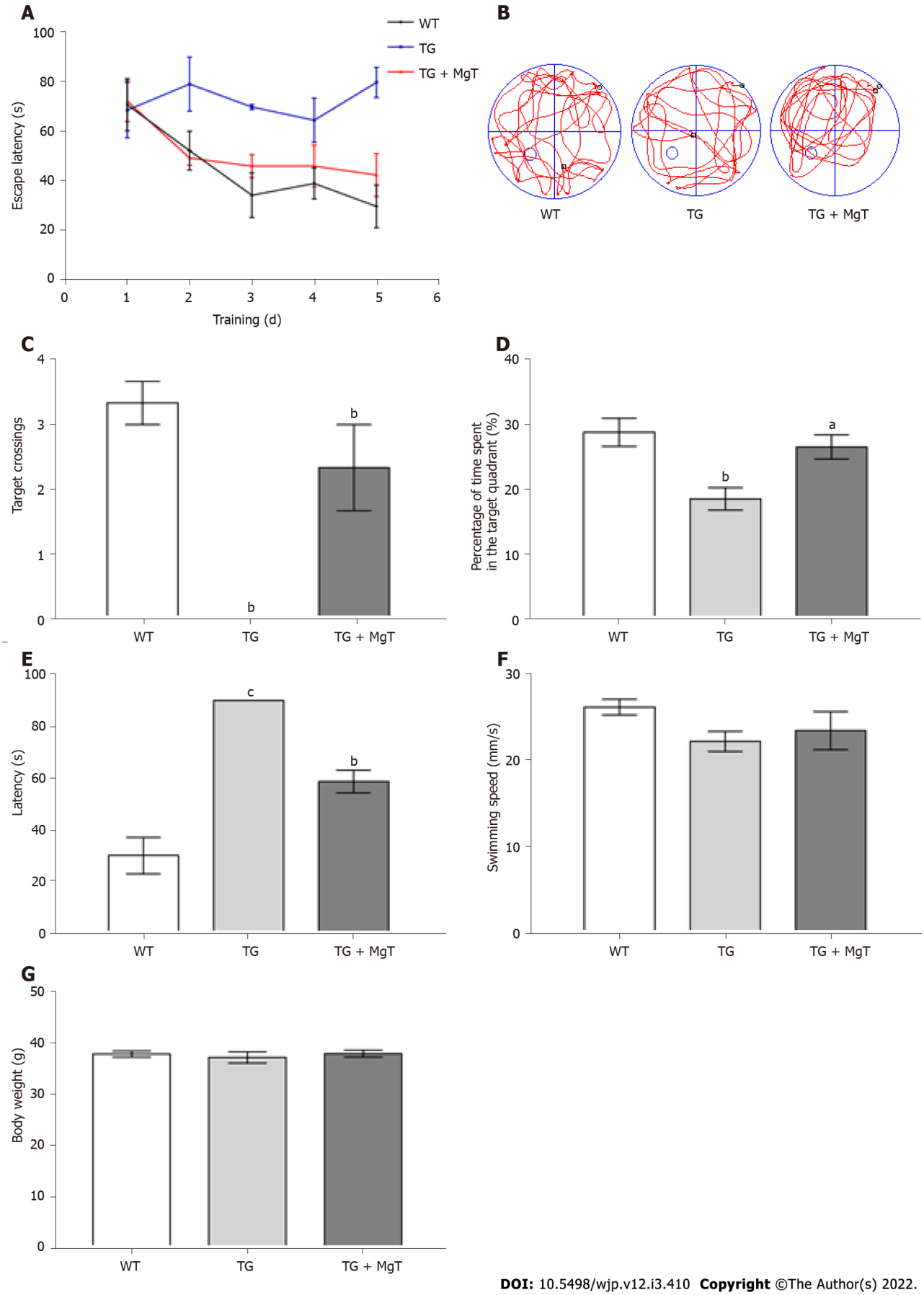


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**Figure 5 Magnesium-L-threonate administration prevented the memory deficit of APPswe/PS1dE9 mouse.** A: The escape latency of each group; B: The swimming track explored the removed platform of each group; C: The number of platform crossings of each group; D: The percentage of the time spent in the

target quadrant of each group; E: The latency located the removed platform of each group; F: The swimming speed of each group; G: The body weight of each group. $n = 3$. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ *vs* former group. MgT: Magnesium-L-threonate; TG: APPswe/PS1dE9 mice group; WT: Wild-type mice group.

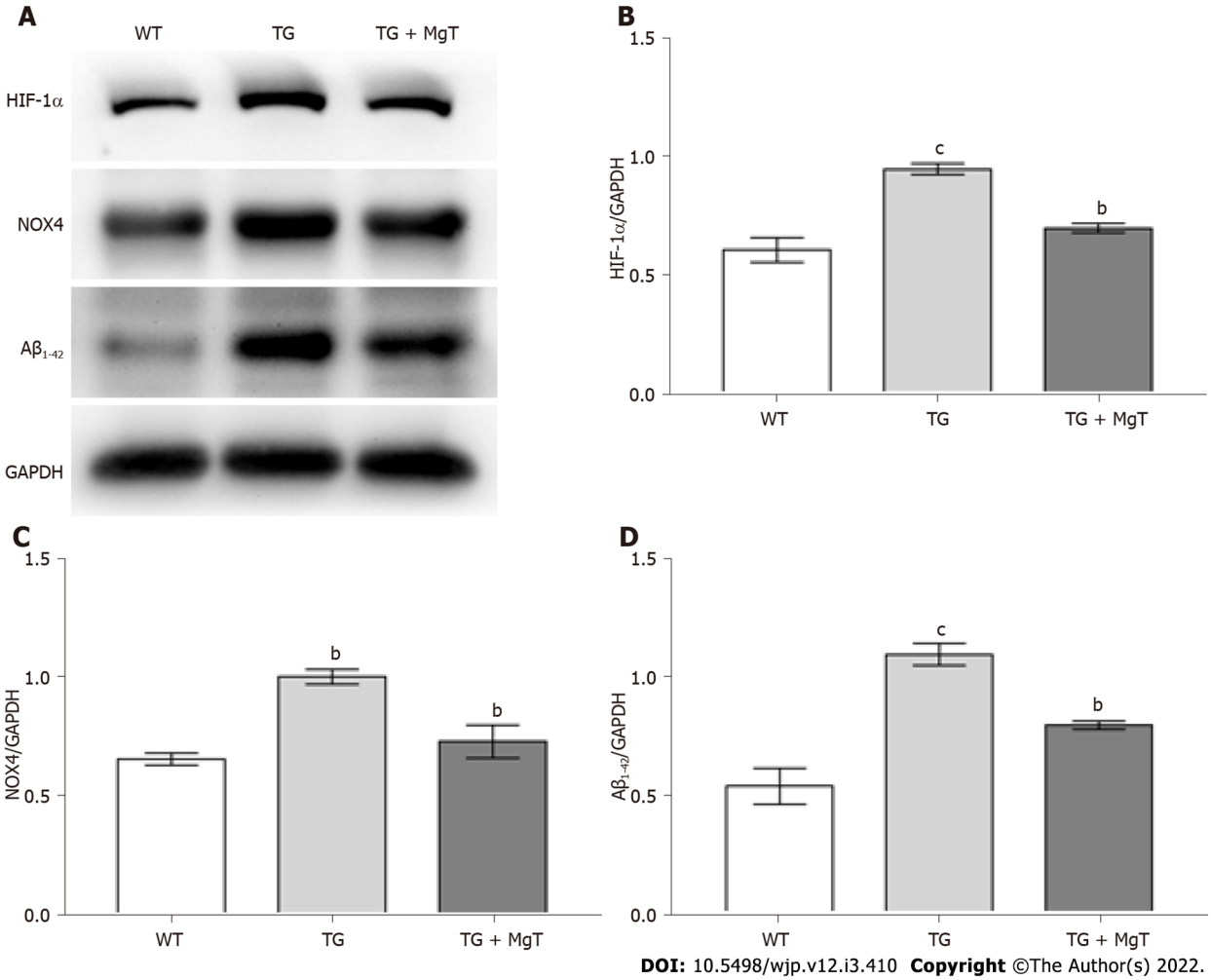


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**Figure 6 Magnesium-L-threonate treatment prevented the upregulation of amyloid $\beta_{1-42}$, hypoxia-inducible factor-1α and NADPH oxidase 4 proteins in APPswe/PS1dE9 mouse hippocampus.** A: Protein band images of hypoxia-inducible factor (HIF)-1α, NADPH oxidase (NOX) 4, amyloid β $(Aβ)_{1-42}$ and glyceraldehyde-3-phosphate dehydrogenase of each group; B: The HIF-1α protein expression of each group; C: The NOX4 protein expression of each group; D: The $Aβ_{1-42}$ protein expression of each group. $n = 3$. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ *vs* former group. MgT: Magnesium-L-threonate; TG: APPswe/PS1dE9 mice group; WT: Wild-type mice group; Aβ: Amyloid β; HIF: hypoxia-inducible factor; NOX: NADPH oxidase; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

of MgT administration on HIF-1α expression was also investigated. The observations from *in vivo* and *in vitro* investigations indicated that MgT significantly suppressed the HIF-1α overexpression in $Aβ_{25-35}$-treated HT22 cells and APP/PS1 mice.

PI3K/Akt pathway is an important cellular pathway occupying a pivotal role in the mediation of cell apoptosis[34]. A recent study demonstrated that Rotundifuran-induced ROS production could lead to cell apoptosis *via* suppressing the PI3K/Akt pathway in the cervical cancer cell model[35]. Another study also showed that inhibition of apoptosis was correlated with the ROS-mediated PI3K/Akt pathway in a streptozotocin-treated INS-1 cell model[24]. Based on the above findings, dysregulation of the PI3K/Akt signaling pathway supports the relationship between oxidative stress and apoptosis. The present experimental procedure also detected the effect of MgT administration on the PI3K/Akt pathway. According to the results from Western blotting, the PI3K/Akt pathways were downregulated in $Aβ_{25-35}$-administrated HT22 cells and APP/PS1 mice, which were restored by MgT administration.

In light of the findings that MgT administration exhibited neuroprotective effects against oxidative stress and hippocampal neuronal apoptosis in this AD mouse model, which were the vital pathological mechanisms underlying the cognitive deficit of AD[3,36], the cognitive ability of MgT-treated APP/PS1 mouse was measured. In this experiment, the results acquired from the Morris water maze test confirmed that MgT treatment ameliorated the cognitive deficit in this AD animal model, but the further mechanism underlying the memory protective effect of MgT needs to be further investigated.

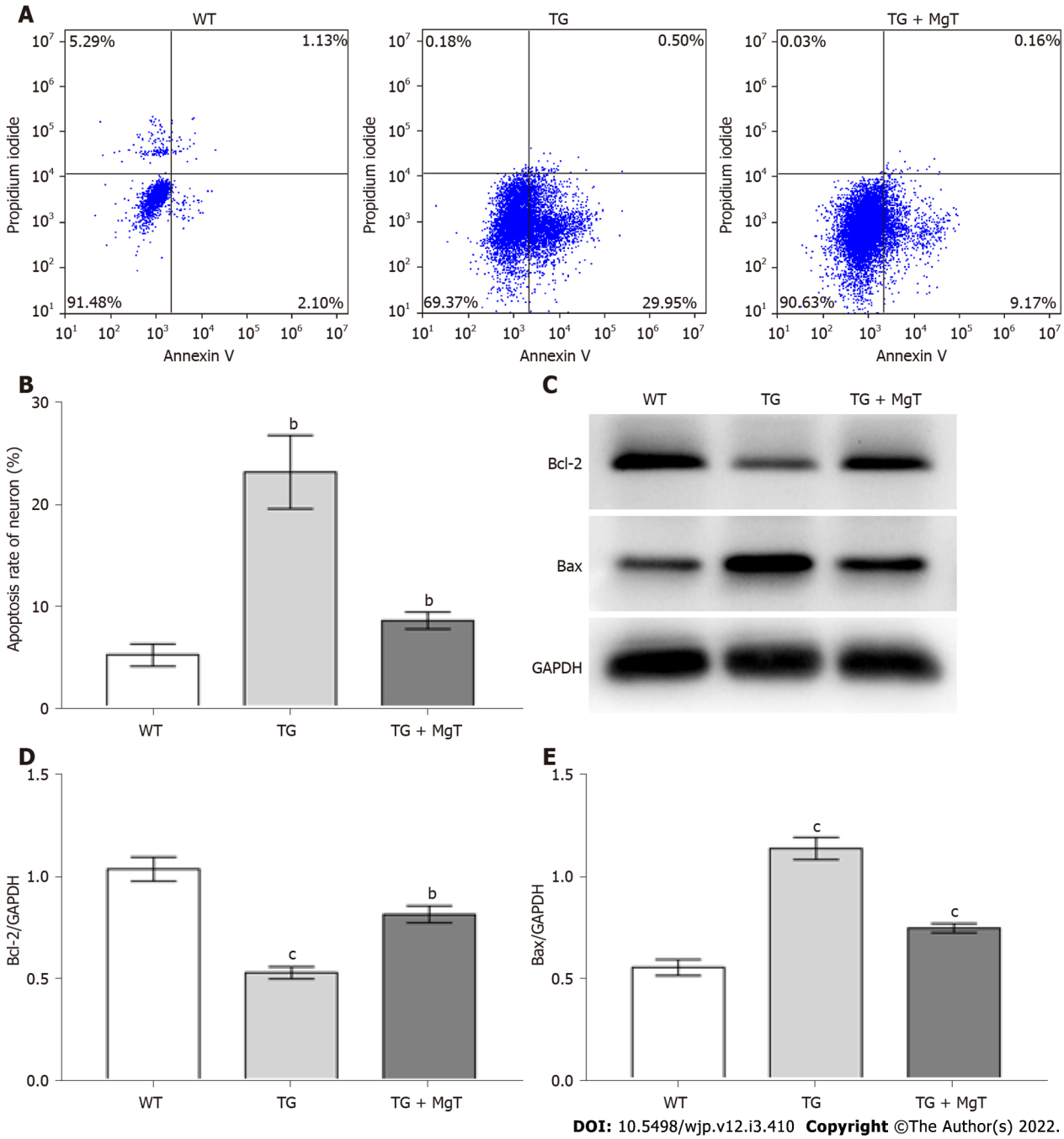


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**Figure 7 Magnesium-L-threonate administration regulated the neuronal apoptosis and mediated the expression of apoptotic-related proteins in APPswe/PS1dE9 mouse hippocampus.** A, B: The apoptosis rate of hippocampal neuron of each group; C: Protein band images of B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X (Bax) and glyceraldehyde-3-phosphate dehydrogenase of each group; D: The Bcl-2 protein expression level of each group; E: The Bax protein expression level of each group. $n = 3$. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ *vs* former group. MgT: Magnesium-L-threonate; TG: APPswe/PS1dE9 mice group; WT: Wild-type mice group; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2-associated X; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

There are several limitations in this experiment. In this study, APP/PS1 mice were applied as the animal model of AD. Although this animal model was a typical and common model of AD and it could be employed to mimic the cognitive impairment and pathological changes of AD[16], it might not reflect all types of this disease. Therefore, it is necessary to conduct further explorations to validate the above-mentioned effects of MgT on other types of Alzheimer's disease, animal models of other neurodegenerative diseases and clinical trials.

## CONCLUSION

It can be demonstrated in this study that MgT intervention has neuroprotective effects against oxidative

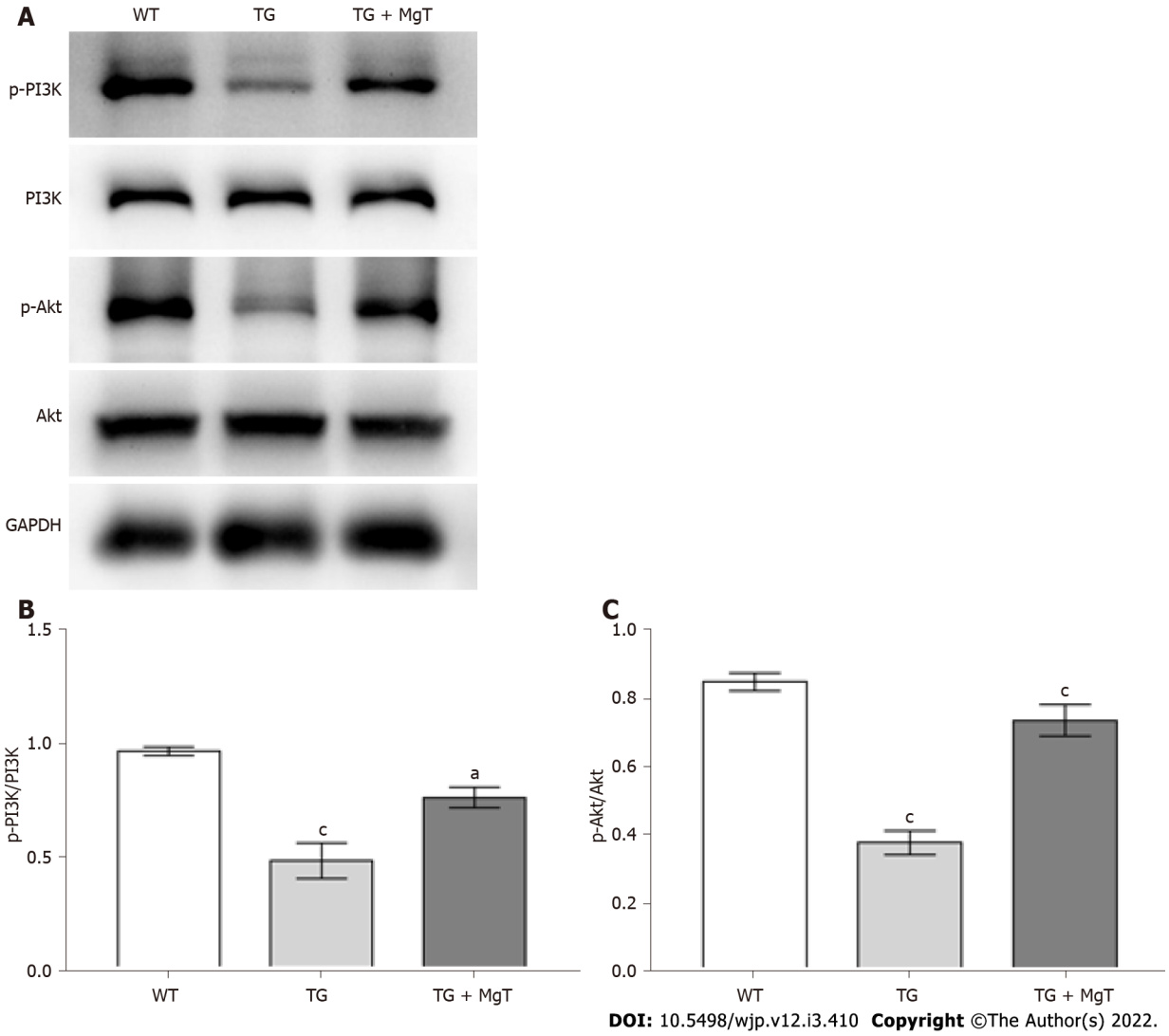


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**Figure 8 Magnesium-L-threonate treatment activated the phosphatidylinositol-3-kinase/protein kinase B pathway in APPswe/PS1dE9 mouse hippocampus.** A: Protein band images of phosphorylated (p)-phosphatidylinositol-3-kinase (PI3K), PI3K, p-protein kinase B (Akt), Akt and glyceraldehyde-3-phosphate dehydrogenase of each group; B: The p-PI3K/PI3K ratio of each group; C: The p-Akt/Akt ratio of each group. $n = 3$. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ *vs* former group. MgT: Magnesium-L-threonate; PI3K: phosphatidylinositol-3-kinase; Akt: protein kinase B; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; WT: Wild-type mice group; TG: APPswe/PS1dE9 mice group.

stress and hippocampal neuronal damage in $A\beta_{25-35}$-treated HT22 cells and AD mouse model. Our study suggests a promising therapeutic agent for the amelioration of oxidative stress and hippocampal neuronal damage-associated neurodegenerative disorders.

## ARTICLE HIGHLIGHTS

### *Research background*

The increasing prevalence of Alzheimer's disease (AD) in the elderly population has posed a huge financial and medical burden on the society. Effective methods to block the progression of the cognitive deterioration in AD patients are urgently required. As oxidative stress accounts for a pivotal role in the pathological mechanism of neurodegenerative diseases, including AD, anti-oxidative stress treatments may provide a promising therapeutic direction. Recent study had explored the anti-malondialdehyde effect of magnesium *in vitro*, however the potential anti-oxidative stress damage effect of Magnesium-L-threonate (MgT) still remains to be verified.

### *Research motivation*

This research investigated the suppressive effect of MgT against oxidative stress injury, thus developing a therapeutic reference basis for the future explorations.

### *Research objectives*

This research aimed to determine the neuroprotective effect of MgT against oxidative stress damage and explore the related mechanism which may bring a research foundation for the feasibility of MgT.

### *Research methods*

As the cell and animal models, amyloid β $(Aβ)_{25-35}$-treated HT22 cells and APPswe/PS1dE9 (APP/PS1) mice were treated with MgT administration. After the MgT administration, cell counting kit-8 detection was applied to analysis the viability of HT22 cells and the Morris Water Maze test was used to record the cognition of APP/PS1 mice. Reactive oxygen species (ROS) production of HT22 cells and cell apoptosis of both models were all quantified by using the flow cytometry assay. The expression of hypoxia-inducible factor (HIF)-1α, NADPH oxidase (NOX) 4, $Aβ_{1-42}$, B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X (Bax) and phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) pathway proteins was quantified by Western blotting.

### *Research results*

MgT effectively suppressed the HT22 cellular injury triggered by $Aβ_{25-35}$-induced oxidative stress by elevating the viability, blocking the ROS formation and downregulating HIF-1α. MgT significantly ameliorated the impaired cognitive performance of APP/PS1 mouse and inhibited the upregulation of $Aβ_{1-42}$, NOX4 and HIF-1α protein expression. In addition, MgT obviously suppressed the cell apoptosis, regulated apoptotic-related proteins and upregulated the PI3K/Akt pathway in both models. In future research, further explorations are required to confirm the above-mentioned effects of MgT in more disease models.

### *Research conclusions*

This study demonstrates the protective effect of MgT against oxidative stress injury in $Aβ_{25-35}$-treated HT22 cells and APP/PS1 mice.

### *Research perspectives*

This study provides a promising therapeutic agent to ameliorate the oxidative stress damage-associated neurodegenerative diseases. More investigations to demonstrate this effect of MgT on other types of Alzheimer's disease, *in vivo* models of other neurodegenerative diseases and clinical experiments are required in further research.

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## FOOTNOTES

**Author contributions:** Xiong Y and Ruan YT contributed to designing this study, collecting samples, carrying out experiments and writing the manuscript; Zhao J, Yang YW, Chen LP and Mai YR contributed to collecting samples and revising the manuscript; Yu Q, Cao ZY, Liu FF and Liao W contributed to analyzing the data and revising the manuscript; Liu J had full access to all of the data in the study, and took responsibility for the integrity of the data and the accuracy of the data analysis; all authors have approved the final article.

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**Conflict-of-interest statement:** All authors declare no conflicts of interest.

**Data sharing statement:** No additional data are available.

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ORIGINAL ARTICLE

Observational Study

# Clinical high-risk criteria of psychosis in 8–17-year-old community subjects and inpatients not suspected of developing psychosis

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## Abstract

*BACKGROUND*

In children and adolescents compared to adults, clinical high-risk of psychosis (CHR) criteria and symptoms are more prevalent but less psychosis-predictive and less clinically relevant. Based on high rates of non-converters to psychosis, especially in children and adolescents, it was suggested that CHR criteria were: (1) Pluripotential; (2) A transdiagnostic risk factor; and (3) Simply a severity marker of mental disorders rather than specifically psychosis-predictive. If any of these three alternative explanatory models were true, their prevalence should differ between persons with and without mental disorders, and their severity should be associated with functional impairment as a measure of severity.

***AIM***

To compare the prevalence and severity of CHR criteria/symptoms in children and adolescents of the community and inpatients.

***METHODS***

In the mainly cross-sectional examinations, 8–17-year-old community subjects ($n$ = 233) randomly chosen from the population register of the Swiss Canton Bern, and inpatients ($n$ = 306) with primary diagnosis of attention-deficit/hyperactivity disorder ($n$ = 86), eating disorder ($n$ = 97), anxiety including obsessive–compulsive disorder ($n$ = 94), or autism spectrum disorder ($n$ = 29), not clinically suspected to develop psychosis, were examined for CHR symptoms/criteria. Positive items of the Structured Interview for Psychosis-Risk Syndromes (SIPS) were used to assess the symptomatic ultra-high-risk criteria, and the Schizophrenia Proneness Instrument, Child and Youth version (SPI-CY) was used to assess the 14 basic symptoms relevant to basic symptom criteria. We examined group differences in frequency and severity of CHR symptoms/criteria using $\chi^2$ tests and nonparametric tests with Cramer's V and Rosenthal's $r$ as effect sizes, and their association with functioning using correlation analyses.

***RESULTS***

The 7.3% prevalence rate of CHR criteria in community subjects did not differ significantly from the 9.5% rate in inpatients. Frequency and severity of CHR criteria never differed between the community and the four inpatient groups, while the frequency and severity of CHR symptoms differed only minimally. Group differences were found in only four CHR symptoms: *suspiciousness/persecutory ideas* of the SIPS [$\chi^2$ (4) = 9.425; $P$ = 0.051, Cramer's V = 0.132; and $Z$ = -4.281, $P$ < 0.001; Rosenthal's $r$ = 0.184], and *thought pressure* [$\chi^2$ (4) = 11.019; $P$ = 0.026, Cramer's V = 0.143; and $Z$ = -2.639, $P$ = 0.008; Rosenthal's $r$ = 0.114], *derealization* [$\chi^2$ (4) = 32.380; $P$ < 0.001, Cramer's V = 0.245; and $Z$ = -3.924, $P$ < 0.001; Rosenthal's $r$ = 0.169] and *visual perception disturbances* [$\chi^2$ (4) = 10.652; $P$ = 0.031, Cramer's V = 0.141; and $Z$ = -2.822, $P$ = 0.005; Rosenthal's $r$ = 0.122] of the SPI-CY. These were consistent with a transdiagnostic risk factor or dimension, *i.e.*, displayed higher frequency and severity in inpatients, in particular in those with eating, anxiety/obsessive–compulsive and autism spectrum disorders. Low functioning, however, was at most weakly related to the severity of CHR criteria/symptoms, with the highest correlation yielded for *suspiciousness/persecutory ideas* (Kendall's tau = -0.172, $P$ < 0.001).

***CONCLUSION***

The lack of systematic differences between inpatients and community subjects does not support suggestions that CHR criteria/symptoms are pluripotential or transdiagnostic syndromes, or merely markers of symptom severity.

**Key Words:** Psychotic disorders; Risk assessment; Minors; Community; Inpatients; Psychosocial functioning

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**Core tip:** Clinical high-risk of psychosis (CHR) criteria and symptoms are more prevalent but less psychosis-predictive and clinically relevant in minors compared to adults, and, therefore, alternatively proposed as pluripotential, transdiagnostic risk factors, or severity markers of mental disorders. If any of these explanatory models were true, their prevalence should differ between 8–17-year-old community subjects ($n$ = 233) and inpatients ($n$ = 306), included in our study, and their severity should be associated with psychosocial functioning. Yet, CHR criteria and symptoms hardly differed between groups and were at most weakly associated with functioning. Consequently, our study did not support any alternative explanatory model of CHR criteria.

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## INTRODUCTION

### *Delays in treatment of beginning or first psychosis in children and adolescents*

Psychotic disorders are severe mental disorders with often chronic course that incur high costs and burden to both society and affected patients[1-4]. Since the 1980s, multiple retrospective studies reported an association of a negative outcome of first-episode psychosis with a longer duration of untreated – or rather, inadequately treated – first-episode psychosis, as well as with untreated illness, *i.e.*, the untreated duration of both the initial prodrome and first-episode psychosis[5-8]. These negative effects of the duration of untreated psychosis or of untreated illness also occurred when patients had sought professional help for mental problems early but were not recognized as suffering from psychotic symptoms or a developing psychotic disorder[9]. Consequently, patients were treated for other, apparently more predominant complaints, frequently depressive or anxiety disorders[9]. Such delays in providing adequate treatment were further prolonged when the psychosis and/or the prodrome had an early onset in childhood and adolescence, that is, before age of 18 years[5,10,11]. This possibly explains the assumed inherent more negative course of early-onset compared to adult-onset psychoses[11]. Potential explanations of the longer duration of untreated psychosis and of untreated illness in children and adolescents with a psychotic disorder include the masking of the emergence of a psychotic disorder by other comorbid conditions such as substance abuse, depressive and anxiety syndromes, and a higher risk to overlook positive symptoms – especially if parents and primary care providers assume that the adolescents' symptoms are the expression of a sort of adolescent crisis[11-13]. Additionally, insufficient awareness and training of the general and mental health network (pediatricians, general physicians, school psychologists, and child and adolescent psychiatrists) might result in failures to adequately and routinely assess psychotic symptomatology in adolescents[12]. Finally, the greater frequency of insidious-onset illness trajectories[10-12] may further impede a timely detection. Thus, it was concluded that children and adolescents with developing, or already manifest, psychotic disorders would require specific early detection strategies to reduce duration of untreated psychosis and of untreated illness, in order to improve long-term outcomes[12,13].

### *Early detection of psychosis – the clinical high-risk approach*

Based on findings regarding the negative effects of extended duration of untreated psychosis and of untreated illness, and the need to specifically intervene earlier in the course of illness, clinical high-risk for psychosis (CHR) criteria were gradually developed and initially validated in adult patient samples within the 1990s[14-17].

The two dominant current CHR approaches are the ultra-high-risk (UHR) approach developed to detect psychosis in the year before the onset of the first episode[16,17] and the basic symptom approach developed to detect signs of emerging psychosis as early as possible[14,15,18]. The UHR approach (Table 1) consists of three criteria, of which only the attenuated psychotic symptoms (APS) syndrome and the brief intermittent psychotic symptoms (BIPS) syndrome demonstrated sufficient psychosis-predictive validity in meta-analyses[19,20]. The third criterion, combining genetic risk and functional deterioration, was not uniquely related to an elevated psychosis risk[19,20].

The basic symptom approach (Table 1) consists of two partly symptomatically overlapping criteria: Cognitive Disturbances (COGDIS) and Cognitive–Perceptive Basic Symptoms (COPER), of which COPER thus far did not demonstrate sufficient evidence in terms of sufficient number of studies[19].

Consequently, within the framework of the Guidance Project of the European Psychiatric Association (EPA), the APS and BIPS syndromes of the UHR approach and COGDIS of the basic symptom approach (henceforth: EPA criteria) were recommended for alternative use in the early detection of psychosis in the clinic[19]. While both the UHR and the basic symptom approach – irrespective of each other – performed equally well in predicting conversion to psychosis within 6 months to 2 years, at which time they were associated with a conversion rate of 20%–30%, the basic symptom criteria were associated with significantly higher conversion rates at longer observation times compared to the UHR criteria[19].

In clinical samples, however, CHR criteria were associated with a significantly lower risk of conversion to psychosis in children and adolescents compared to adults[19,21]. Furthermore, in the community, children and adolescents reported CHR symptoms and criteria more frequently compared to adults[22,23]. These findings suggested that APS and BIPS may be less clinically relevant below the age threshold of 16 years, while perceptual and cognitive basic symptoms may be less clinically relevant below the age threshold of 18 and 23 years, respectively [22,23].

Taken together, these findings emphasize a need to account for developmental aspects in the early detection of psychosis[12,13] and to improve the specificity of the CHR approach by adding other predictors, for example, in a stepwise manner[24].

### *Alternative explanatory models of clinical high-risk states*

In light of the moderate conversion rates and an undisputed need for further improvement of CHR criteria as well as the reported various nonpsychotic outcomes of CHR patients[25,26], it was also argued that CHR criteria, in particular the APS and BIPS syndromes, would not be specific to the development of psychosis[27-30]. Rather, it was argued that these would represent a pluripotent

**Table 1 Clinical high-risk criteria: (1) Ultra-high risk criteria in the definition of the criteria of psychosis-risk syndromes of the structured interview for Psychosis-Risk Syndromes, Structured Interview for Psychosis-Risk Syndromes[43] and (2) the basic symptom criteria in the definition of the Schizophrenia Proneness Instrument, Child and Youth version[44]**

| (1) Ultra-high risk criteria |
|---|
| **Brief intermittent psychotic symptom (BIPS) syndrome** |
| At least 1 of the following SIPS positive items scored 6 "severe and psychotic" |
| P1 Unusual thought content/delusional ideas |
| P2 Suspiciousness/persecutory ideas |
| P3 Grandiose ideas |
| P4 Perceptual abnormalities/hallucinations |
| P5 Disorganized communication |
| Symptoms reached a psychotic level of intensity in the past 3 mo |
| Present for at least several minutes per day at a frequency of at least once per month but less than required for rating of a conversion to psychosis, *i.e.*, less than at least 1 h per day at an average frequency of 4 d/wk over 1 mo |
| **Attenuated positive symptom (APS) syndrome** |
| At least 1 of the 5 SIPS positive items (see above) scored 3 "moderate" to 5 "severe but not psychotic" |
| Symptoms have begun within the past year or currently rate one or more scale points higher compared to 12 mo ago |
| Symptoms have occurred at an average frequency of at least once per week in the past month |
| **Genetic risk and functional deterioration syndrome** |
| Patient meets criteria for schizotypal personality disorder according to SIPS |
| Patient has first-degree relative with a psychotic disorder |
| Patient has experienced at least 30% drop in the Global Assessment of Functioning score over the last month compared to 12 mo ago |
| [1 and 3] or [2 and 3] or all are met |
| **(2) Basic symptom criteria** |
| A general requirement for basic symptoms is that they deviate from what is considered the 'normal' self and, thus, have not always been present in the same severity |
| **Cognitive–perceptive basic symptoms (COPER)** |
| At least 1 of the following basic symptoms scored 3 "weekly occurrences" to 6 "daily occurrences" within the past 3 mo: thought interference; thought perseveration; thought pressure; thought blockages[1]; disturbance of receptive speech; decreased ability to discriminate between ideas and perception, fantasy and true memories; unstable ideas of reference; derealization; visual perception disturbances (excl. hypersensitivity to light or blurred vision); acoustic perception disturbances (excl. hypersensitivity to sounds); first occurrence ≥ 12 mo ago |
| **Cognitive disturbances (COGDIS)** |
| At least 2 of the following basic symptoms scored 3 "weekly occurrences" to 6 "daily occurrences" within the past 3 mo: inability to divide attention; thought interference; thought pressure; thought blockages[1]; disturbance of receptive speech; disturbance of expressive speech; unstable ideas of reference; disturbances of abstract thinking[1]; captivation of attention by details of the visual field |

[1]Assessable only from age of 13 yr onwards.

syndrome[27,28], a transdiagnostic risk factor[29], a transdiagnostic dimension of psychopathology[30], or merely a marker for the severity of nonpsychotic states[30]. Despite them frequently being used in synonym[29], pluripotential and transdiagnostic relate to different concepts.

Being derived from biology and initially applied to (embryonic) cells, pluripotent is defined as "not fixed as to potential development", and used to describe precursor cells that are only found in early embryonic states[31]. Thus, translated to psychiatric disorders, a pluripotential syndrome would be the first diagnostically neutral stage of potentially more severe psychopathology, which only later would acquire a degree of diagnostic specificity[27,28]. In this case, similar to embryonic pluripotent cells, a CHR state would completely transform into another disorder in that it would not be recognizable anymore. Examples are APS that will not be detectable once they have been transformed into frank psychotic symptoms, *i.e.*, after the conversion to psychosis.

In contrast, transdiagnostic risk factors would be distributed across the community and would be present in various disorders, in which they would still be assessable, and mediate the association between environmental exposures and disorders[32]. Similarly, a transdiagnostic dimension of psychopathology may be present in various disorders but not at all or only in very mild subclinical forms in the

community outside states of mental ill health. In these cases, CHR symptoms would develop in the wake of other mental problems.

Lastly, a severity marker of psychopathology would be generally present in mental disorders, in which it would be most pronounced or frequent in those with severe mental disorders and/or most functional impairment due to their mental problems. Furthermore, it would be more frequent in acute states of illness compared to (partly) remitted states. In this case, CHR symptoms and criteria should be increasingly present with declining functioning.

Mental problems in childhood and adolescence often lack continuity into adulthood[33] and specificity for mental disorders[34], and frequently present as insidious onset of disorders, initially with mild forms of mental problems[12,35]. Consequently, children and adolescents represent an excellent age group to study the nature of symptoms and syndromes, such as CHR symptoms and criteria[36], and in particular, to study which of the three alternative models best fits the data.

### Study aims

The aim of this study was to examine which of these alternative explanatory models of CHR criteria and symptoms – pluripotential syndrome, transdiagnostic risk factor/dimension, and severity marker – best fits the data of an age group in which CHR criteria and symptoms are likely the least psychosis-specific [19,21]. To that end, we cross-sectionally studied the frequency of CHR criteria and symptoms in an 8–17-year-old randomly recruited sample of the Swiss community and in 8–17-year-old inpatients whose main diagnosis was a disorder that, earlier, had been longitudinally associated with an elevated risk to develop psychosis in adulthood[36,37] (Supplementary Table 1). The three alternative explanatory models were associated with in the following differential premises: (1) In the case of the CHR criteria and symptoms acting as a pluripotential syndrome, these should not be detectable after the onset of severe mental disorder, *i.e.*, after their transformation in a diagnostically specific disorder in the inpatient group. Rather, CHR criteria and symptoms should still be detectable as a potential precursor state in the community subjects of that roughly a third must be expected to develop a mental disorder in their lifetime[39]. Consequently, if CHR criteria and symptoms would be more frequent in community subjects compared to inpatients, then they are likely pluripotential; (2) In the case of CHR criteria and symptoms representing a transdiagnostic risk factor or dimension, they would be expected to accumulate in the extreme range of persons with mental disorders. Thus, if CHR criteria and symptoms would be more frequent in the inpatients compared to community subjects, then they likely represent a transdiagnostic risk factor or dimension; and (3) Lastly, in the case of CHR criteria and symptoms being a severity marker of psychopathology, they should be associated with illness severity and, relatedly, the degree of functional impairment. Consequently, if CHR criteria and symptoms would show a significant negative correlation with functioning, then they likely represent a severity marker of psychopathology.

## MATERIALS AND METHODS

### Sample description

We recruited the samples as part of the multicenter naturalistic 'Bi-national Evaluation of At-Risk Symptoms in children and adolescents' (BEARS-Kid) study between September 2013 and December 2017. Recruitment of inpatients took place at the Child and Adolescent Psychiatric Departments of the Universities of Bern, Switzerland, Zurich, Switzerland, and Cologne, Germany; recruitment of community subjects was exclusively carried out in Bern. General inclusion criteria were: age between 8.0 and 17.9 years, and sufficient language skills in German or English. General exclusion criteria were: past or present diagnosis of a psychotic disorder; current antipsychotic medication; a clinical indication of an IQ ≤ 70; presence of disturbance due to the direct physiological effects of a general medical condition or of substance use; and clinical suspicion of an emerging psychosis and, consequently, consultation of the local early detection service. Because co-occurrence of mental disorders is rather the rule than the exception in patients with mental disorders, in clinical as well as in community samples [40,41], we did not use (co-) morbidities with mental disorders as an exclusion criterion in either the inpatient and community sample in order not to limit representativeness.

For the recruitment of a representative community sample, the Agency for Informatics and Organization of the Canton Bern randomly drew a sample (including addresses) stratified for age and sex from the population register of the city of Bern and its urban hinterland (approximately 200 000 residents). Subsequently, we searched directories and the Internet for telephone numbers. The availability of a working telephone number served as an eligibility criterion in this group. We established first contact by an information letter, personally addressing each potential participant and his/her parents. Next, we contacted parents and/or their children by telephone, informed them in detail, and asked them to give written informed consent and assent. In children below age 16.0 years, we contacted parents first. Nine hundred and eighty persons were drawn from the register, for 176 of them, we could not ascertain a working telephone number, and 41 persons were drawn twice. Of the remaining 763 persons, 234 agreed to participate, yet one person later on withdrew consent. A total of 353 did not agree to participate, mainly for lack of interest (35.6%) or time (35.9%). We excluded 52

persons because they had reached 18 years old by the time contact was made (53.9%), had moved away from the greater Bern area (32.7%), or lacked the ability to participate in the study for language or physical health reasons (13.5%). With 124 persons, all attempts (at least 40) to reach them on the telephone remained fruitless. Thus, according to the standard definitions of the American Association for Public Opinion Research[42], the contact rate was 82.7%, the cooperation rate was 39.9%, the refusal rate was 49.2%, and the response rate was 32.6%.

The inpatient sample was recruited in all three participating centers during their inpatient stay or during their subsequent day clinic stay; seven inpatients (2.3%) had been strongly advised to undergo inpatient treatment but had refused. For inclusion, the main diagnosis according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders, DMS-IV[38] had to be one for which Rubino *et al* [37] had reported at least a 2.5 times increased prevalence of subsequent schizophrenia (Supplementary Table S1): attention deficit hyperactivity disorder (ADHD) (inattentive, hyperactive and impulsive subtype); anxiety disorders (social and severe specific phobia, mainly school phobia); obsessive–compulsive disorder; and eating disorder (anorexia and bulimia nervosa). Additionally, we included patients with Asperger's syndrome, which had not been considered by Rubino *et al*[37] but has been recognized explicitly as a developmental disorder with an increased risk of psychotic episodes in young adulthood in DSM-IV[38]. We recruited 539 inpatients, 97 with eating disorders, 86 with ADHD, 94 with anxiety and obsessive–compulsive disorders, and 29 with Asperger's syndrome.

We followed up 423 subjects (78.5%) after 1 year; 243 inpatients, 23 (9.5%) with a CHR criterion at baseline; and 180 community subjects, 15 (8.3%) with a CHR criterion at baseline. A total of 331 subjects (61.4%) participated in the 2-year follow-up; 189 inpatients, 16 (8.5%) with a CHR criterion at baseline, and 142 community subjects, 10 (7.0%) with a CHR criterion at baseline.

### *Clinical high-risk assessments*

We used well-established semistructured interview assessments to assess CHR criteria and symptoms, which had demonstrated good inter-rater reliability in trained raters[43-45]. The Structured Interview for Psychosis-Risk Syndromes (SIPS)[43], including a revised version of the Global Assessment of Functioning scale, was carried out for the evaluation of the five APS and BIPS (Table 1) as well as the genetic risk and functional decline criterion of the UHR criteria in the SIPS definition of the Criteria of Psychosis-Risk Syndromes (COPS) (Table 1). The five criteria-relevant positive items of the SIPS are syndromally rated for psychopathological severity on a seven-point Likert scale, ranging from 0 (not present) to 6 (severe and psychotic). In doing so, APS are defined by any SIPS positive item with a score between 3 and 5, and BIPS by any SIPS positive item with a score of 6. We rated a SIPS-positive item as present when its score was 3–6. We calculated the sum score of the five positive items across all scores (0–6) as a severity estimate of symptomatic UHR criteria.

We used the Schizophrenia Proneness Instrument, Child and Youth version, SPI-CY[44,45] for the evaluation of the 14 basic symptoms included in COPER and COGDIS (Table 2). Basic symptoms were rated for their severity according to their frequency of occurrence on a seven-point Likert scale, ranging from 0 (not present) to 6 (present daily). We rated basic symptoms as present when their score was 1–6. We calculated the sum scores of the nine basic symptoms included in COGDIS and of the 10 basic symptoms included in COPER as a severity estimate of COGDIS and COPER, respectively.

Basic symptoms included in COPER and COGDIS differ from APS/BIPS as defined by a score of 3 on the SIPS-positive items by the more immediate insight into basic symptoms that results from the lack of externalization or of their consideration of possibly being meaningful, and from the immediate control of these[14,15,44,45]. Thus, other than in attenuated hallucinations or illusions (SIPS positive item P4), which are at least briefly perceived as true perceptions of existence, real stimuli [43], in perceptual basic symptoms, the misperceived real object or sound is not considered as a true change of the stimulus for even a split-second[44]. Rather, the insight into the pathological nature of the misperceptions of features of a real object or sound is immediate and complete, and thus, contrary to APS, perceptual basic symptoms are not puzzling to the degree that they are considered to indicate a meaningful change in the surroundings[43], apart from a change in one's own mental processes[44]. With this, perceptual basic symptoms rate 1–2 in the SIPS positive item P4, *i.e.*, as sensitivity or perceptual changes that are noticed but not considered to be significant in terms of what is going on in the world[43]. Furthermore, cognitive basic symptoms are not related to thought content and, consequently, are not rated as any unusual thought content or attenuated delusional idea on SIPS positive items P1–P3. Additionally, for their immediate recognition as unusual, commonly brief disruptions in normal thought processing[44], cognitive basic symptoms rarely impair the individual's own way of structuring and verbally presenting thoughts in terms of *conceptual disorganization* (SIPS positive item P5), *i.e.*, by talking about irrelevant topics or going off track to a degree that is unusual to the individual[43]. Moreover, the basic symptoms *derealization* and *unstable idea of reference* are only "as if" feelings with full reality testing and no (temporary) consideration as realistic ideas or of meaningfulness[44]; thus, they differ from attenuated nihilistic ideas or attenuated ideas of reference that are scored at APS-level in the SIPS positive item P1 – or in P2, if the idea of reference has a paranoid touch[43]. Finally, *impaired discrimination between ideas and perception* in terms of basic symptoms always occurs with real stimuli or memories of real events that are briefly considered as possible phantasies[44]; thus, it does not even briefly introduce unusual ideas as required for an attenuated delusion[43] and, for this reason, also rates

**Table 2 Sociodemographic and clinical characteristics of the sample (*n* = 539)**

| | Inpatients (*n* = 306) | Community subjects (*n* = 233) | Statistics; effect size |
|---|---|---|---|
| Age: mean ± SD (Median) | 14.4 ± 2.5 (14.9) | 13.0 ± 2.9 (12.9) | U = 26032.5, $^{c}P < 0.001$: $r = 0.231$ |
| Sex: *n* (%) male | 133 (43.5) | 102 (43.8) | $\chi^2_{(1)} = 0.013$, $P = 0.908$; V = 0.005 |
| Migration background[1]: *n* (%) | 52 (17.0) | 64 (27.5) | $\chi^2_{(1)} = 8.593$, $^{b}P = 0.003$; V = 0.126 |
| Graduated from school: *n* (%) | 28 (9.2) | 15 (6.4) | $\chi^2_{(1)} = 1.326$, $P = 0.250$; V = 0.050 |
| Current school class (*n* = 491): mean ± SD | 7.5 ± 2.5 (8) | 6.2 ± 2.6 (6) | U = 20894.5, $^{c}P < 0.001$; $r = 0.253$ |
| Family history of psychotic disorder: *n* (%) | 4 (1.3) | 1 (0.4) | $\chi^2_{(1)} = 1.105$, $P_{exact} = 0.396$, V = 0.045 |
| Any lifetime nonpsychotic axis-I disorder[2]: *n* (%) | 306 (100) | 22 (9.4) | $\chi^2_{(1)} = 455.368$, $^{c}P < 0.001$; V = 0.919 |
| Any present nonpsychotic axis-I disorder[2]: *n* (%) | 306 (100) | 13 (5.6) | $\chi^2_{(1)} = 488.187$, $^{c}P < 0.001$; V = 0.952 |
| Number present axis-I disorders[2]: mean ± SD (Median) | 1.5 ± 0.7 (1) | 0.1 ± 0.3 (0) | U = 1499.5, $^{c}P < 0.001$; $r = 0.883$ |
| Any present depressive disorder: *n* (%) | 55 (18.0) | 0 | $\chi^2_{(1)} = 46.638$, $^{c}P < 0.001$; V = 0.294 |
| Any present manic episode[3]: *n* (%) | 0 | 1 (0.4) | $\chi^2_{(1)} = 1.316$, $P = 0.251$; V = 0.049 |
| Any present anxiety disorder[2]: *n* (%) | 68 (22.2) | 2 (0.9) | $\chi^2_{(1)} = 53.426$, $^{c}P < 0.001$; V = 0.315 |
| Any present obsessive–compulsive disorder: *n* (%) | 35 (11.4) | 1 (0.4) | $\chi^2_{(1)} = 25.720$, $^{c}P < 0.001$; V = 0.218 |
| Any present adjustment disorder: *n* (%) | 3 (1.0) | 0 | $\chi^2_{(1)} = 2.297$, $P = 0.262$; V = 0.065 |
| Any present eating disorder: *n* (%) | 98 (32.0) | 0 | $\chi^2_{(1)} = 91.203$, $^{c}P < 0.001$; V = 0.411 |
| Any present somatoform disorder: *n* (%) | 4 (1.3) | 0 | $\chi^2_{(1)} = 3.069$, $P = 0.137$; V = 0.075 |
| Any present substance use disorder: *n* (%) | 4 (1.3) | 2 (0.9) | $\chi^2_{(1)} = 0.242$, $P = 0.623$; V = 0.021 |
| Any present tic disorder: *n* (%) | 9 (2.9) | 0 | $\chi^2_{(1)} = 6.969$, $^{b}P = 0.008$; V = 0.114 |
| Any present attention deficit hyperactivity disorder: *n* (%) | 103 (33.7) | 7 (3.0) | $\chi^2_{(1)} = 76.532$, $^{c}P < 0.001$; V = 0.377 |
| Any present conduct disorder: *n* (%) | 18 (5.9) | 2 (0.9) | $\chi^2_{(1)} = 9.345$, $^{b}P = 0.002$; V = 0.132 |
| Any present developmental disorder: *n* (%) | 31 (10.1) | 0 | $\chi^2_{(1)} = 25.045$, $^{c}P < 0.001$; V = 0.216 |
| Global Assessment of Functioning score (0-100): mean ± SD (Median) | 52.3 ± 8.8 (53) | 81.0 ± 10.0 (85) | U = 1516.0, $^{c}P < 0.001$; $r = 0.819$ |
| SOFAS (0-100): mean ± SD (Median) | 60.0 ± 11.0 (60) | 84.3 ± 7.9 (88) | U = 3001.5, $^{c}P < 0.001$; $r = 0.786$ |

[1]defined by first or second nationality other than the country of residence;
[2]does not include simple specific phobias of objects with little functional relevance but includes severe specific phobias such as school phobia;
[3]no participant met criteria of a bipolar disorder at baseline. SOFAS: Social and Occupational Functioning Assessment Scale[42]. V: Cramer's V; *r*: Rosenthal's *r*: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

at most 2 on the SIPS positive item P1.

### *Assessments of mental disorders and functioning*

We used the Mini-International Neuropsychiatric Interview for Children and Adolescents, M.I.N.I. KID [46] for the assessment of past and present mental disorders according to the DSM-IV, including past and present affective or nonaffective psychotic disorders that served as exclusion criterion. The M.I.N.I. KID had demonstrated good construct validity with other interview assessments of DSM-IV disorders and expert diagnoses as well as good inter-rater and test–retest reliability[46].

We estimated symptom-independent current and highest-within-last-12-mo global levels of psychosocial functioning using the Social and Occupational Functioning Assessment Scale (SOFAS) of DSM-IV[38]. We used SOFAS scores to define functioning in the analyses of the correlation between severity of mental disorders and CHR symptoms and criteria.

### Assessment procedure and quality assurance

We conducted the baseline assessments of inpatients in the clinic, and community participants could choose between being assessed in the clinic or at their homes, mostly choosing the latter. Thus, we could not blind raters to the group assignment. Therefore, in order to avoid systematic assessment bias due to this nonblinding of groups, interviewers were restricted to the assessment of either the inpatient or the community sample. Interviewers were clinical psychologists who had received an intensive training for about 3 months, especially in the semistructured context-dependent personalized assessment of CHR symptoms and mental disorders, in order to achieve a ≥ 95% concordance rate with the trainers (in all instances the first or the last author). Only when an interviewer had achieved this level of agreement with the experts, they were allowed to conduct interviews independently. We had chosen the concordance rate over Cohen's kappa, because kappa is dependent on the prevalence of an event[47] and tends to decrease when a response/event is rare or very frequent. Thus, because low prevalence rates were expected for the community sample in particular, we chose the concordance rate to define the minimum inter-rater reliability[48,49]. In the training, we paid close attention not only to the validity and reliability of positive ratings but also to those of negative ratings, *i.e.*, to not jump to a negative rating at the first negation of a symptom. Weekly supervision of symptom ratings performed by the first or last author further ensured excellent, valid and reliable data quality across centers.

At 1- and 2-year follow-ups, we interviewed participants for CHR symptoms and criteria as well as conversion to psychosis using the SPI-CY, SIPS and psychoses section of the M.I.N.I. KID. Potential conversions were also discussed in the weekly supervisions.

### Data analysis

We used SPSS version 24 for all analyses that the first and last author, both trained in biostatistics, conducted. We compared frequency rates of CHR symptoms and criteria between groups by $\chi^2$ test or Fisher's exact tests in case of expected cell frequencies below $n = 5$ in 2 × 2 tables. Standardized residuals were used to detect significantly deviating cell frequencies of standardized residuals ≥ |1.96|; the effect size was calculated using Cramer's V.

We compared the severity of the ordinal CHR symptoms and criteria as well as the ordinal level of functioning as assessed with the SOFAS, which were all non-normally distributed (Kolmogorov–Smirnov test: all $P < 0.001$), between groups using Kruskal–Wallis with post-hoc Mann–Whitney *U* tests; the effect size of the Mann–Whitney *U* tests was calculated using Rosenthal's r.

We analyzed the correlations between severity of CHR symptoms and criteria, and functioning using Kendall's tau, which controls for tied pairs, and, additionally, using partial correlation analyses with group as the control variable.

To not decrease the sensitivity to detect group differences and, thus, to support one of the alternative explanatory models of the CHR state, we did not adjust for multiple testing. Although such an adjustment of the alpha level would have greatly reduced the type I error, *i.e.*, the false rejection of a true null hypothesis, the detection of meaningful small to moderate group differences would have become unlikely[50]. Thus, in light of this, the nonadjustment of alpha was regarded as a more conservative testing of the alternative models. Additionally, testing for group differences in CHR criteria and symptoms independently (weak testing criterion[50]), the power of the study, the ability to correctly reject a false null hypothesis assuming group equality, can be assumed to be independent of the multiple testing[50]. At a given alpha of 0.05, a sample size of $n = 539$ in two or five groups, and an assumed small to medium effect of 0.2, G*Power version 3.1. estimated the power of the different group comparisons of frequency or severity of CHR criteria and symptoms between 0.911 and 0.997.

## RESULTS

### Group characteristics

Inpatients and community subjects did not differ in distribution of sex, family history of psychotic disorder, or number of those already graduated from school (Table 2). However, inpatients were slightly older and, when still at school, attended a higher school class. Furthermore, we detected a small effect of migration background with higher frequency in the community sample. Unsurprisingly, we detected strong group effects for clinical variables, demonstrating that, compared to community subjects, inpatients suffered more frequently from mental disorders and had a lower level of functioning (Table 2).

### Group differences in frequency of CHR symptoms and criteria

Neither inpatients nor community subjects reported any BIPS. Furthermore, the genetic risk and functional decline syndrome was rare and only occurred in two inpatients, without reaching a level of significance (Table 3). Also, we detected only at most weak and nonsignificant group effects with respect to all other single or combined CHR criteria, which, overall, were reported by < 10% of both samples (Table 3). In doing so, the most frequent CHR criterion was COPER (Table 3). We found similar

**Table 3 Frequency of clinical high-risk criteria in the two groups (*n* = 539)**

| | Inpatients (*n* = 306) | Community subjects (*n* = 233) | $\chi^2$ test; Cramer's V |
|---|---|---|---|
| BIPS syndrome: *n* (%) | 0 | 0 | -- |
| APS syndrome: *n* (%) | 7 (2.3) | 5 (2.1) | $\chi^2_{(1)} = 0.012$; $P = 0.912$, V = 0.005 |
| Genetic risk and functional decline syndrome: *n* (%) | 2 (0.6) | 0 | $\chi^2_{(1)} = 1.529$; $P_{exact} = 0.508$, V = 0.053 |
| COGDIS: *n* (%) | 10 (3.3) | 4 (1.7) | $\chi^2_{(1)} = 1.258$; $P = 0.262$, V = 0.048 |
| COPER: *n* (%) | 21 (6.9) | 10 (4.3) | $\chi^2_{(1)} = 1.613$; $P = 0.204$, V = 0.055 |
| Any 1 of 5 CHR criteria: *n* (%) | 29 (9.5) | 17 (7.3) | $\chi^2_{(1)} = 0.806$; $P = 0.369$, V = 0.039 |
| Any 1 of 3 EPA criteria: *n* (%) | 15 (4.9) | 9 (3.9) | $\chi^2_{(1)} = 0.336$; $P = 0.562$, V = 0.025 |
| No CHR criterion: *n* (%) | 277 (90.5) | 216 (92.7) | $\chi^2_{(7)} = 5.676$; $P = 0.578$, V = 0.103 |
| Only genetic risk and functional decline: *n* (%) | 2 (0.7) | 0 | |
| Only COPER: *n* (%) | 12 (3.9) | 8 (3.4) | |
| Only COGDIS: *n* (%) | 2 (0.7) | 2 (0.9) | |
| COPER and COGDIS: *n* (%) | 6 (2.0) | 2 (0.9) | |
| Only APS: *n* (%) | 4 (1.3) | 5 (2.1) | |
| APS and COPER: *n* (%) | 1 (0.3) | 0 | |
| APS, COPER and COGDIS: *n* (%) | 2 (0.7) | 0 | |

BIPS: Brief intermittent psychotic symptoms; APS: Attenuated psychotic symptoms; COGDIS: Cognitive Disturbances; COPER: Cognitive–Perceptive Basic Symptoms; EPA: European Psychiatric Association. V: Cramer's V: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

results when we compared frequencies of CHR criteria across the different inpatient groups and community subjects (Table 4); thus, these results did not indicate that CHR criteria were especially associated with any of the four diagnostic categories.

Between inpatients and community subjects, we detected differences of weak effect size with respect to CHR symptoms for only three basic symptoms, two of them only included in COPER (Supplementary Table 2): (1) *Pressure of thought* (8.5% in inpatients vs 3.0% in community subjects; Cramer's V = 0.113, yet, all standardized residuals < |1.96|); (2) *Derealization* (11.4% in inpatients *vs* 2.6% in community subjects; Cramer's V = 0.165, both standardized residuals of symptom present > |1.96|), and (3) *Visual perception disturbances* (11.4% in inpatients *vs* 4.7% in community subjects; Cramer's V = 0.119, standardized residuals of symptom present in community subjects > |1.96|).

When we considered the different diagnostic categories, we found some additional, yet unsystematic group differences - often only at single cell level in terms of a significant standardized residual (Tables 5 and 6). The strongest, near moderate group effect yielded for *derealization*, which showed an increased prevalence in eating disorders, and anxiety and obsessive-compulsive disorders, and a decreased prevalence in community subjects (Table 5). All other effect sizes of group comparisons with at least one significant standardized residual of any cell were only small (Tables 5 and 6). *Visual perception disturbances* were again significantly less frequent in community subjects (Table 5). *Thought pressure* and *impaired discrimination between ideas and true memories, and phantasy* were only more prevalent in anxiety and obsessive-compulsive disorders, *thought interference* and *captivation of attention* in Asperger's syndrome, and *unstable ideas of reference* in eating disorders (Table 5). With regard to APS, *unusual thought content / delusional ideas* (SIPS positive item P1) were most frequent in anxiety and obsessive-compulsive disorders (Table 6), which was mainly due to frequent report of *thought insertion* and *broadcasting* as well as *unusual, somatic* and *nihilistic ideas* at attenuated level. Furthermore, patients with Asperger's syndrome most frequently reported *suspiciousness/persecutory ideas* (SIPS positive item P2), mainly attenuated *ideas of being redlined* or *observed* (Table 6). Of all CHR symptoms, both inpatients and community subjects most frequently reported *perceptual abnormalities/hallucinations* (SIPS positive item P4) (Table 6).

### Group differences in severity of CHR symptoms and criteria

The severity of CHR criteria and symptoms hardly differed between inpatients and community subjects (Table 7). Only the sum score of the ten basic symptoms of COPER, the single basic symptoms *thought pressure*, *derealization* and *visual perception disturbances* as well as the SIPS positive item *suspiciousness/persecutory ideas* (P2) were significantly more severe in inpatients (Table 7). Again, more indications of

**Table 4 Frequency of clinical high-risk criteria in the four diagnostic subsamples and the community sample (*n* = 539)**

| | ED (*n* = 97) | ADHD (*n* = 86) | AnxD and OCD (*n* = 94) | ASS (*n* = 29) | Community subjects (*n* = 233) | $\chi^2$ test; Cramer's V |
|---|---|---|---|---|---|---|
| APS syndrome: *n* (%) | 4 (4.1) | 0 | 3 (3.2) | 0 | 5 (2.1) | $\chi^2_{(4)} = 4.632$; $P = 0.327$, V = 0.093 |
| Genetic risk and functional decline syndrome: *n* (%) | 0 | 1 (1.2) | 1 (1.1) | 0 | 0 | $\chi^2_{(4)} = 4.016$; $P = 0.404$, V = 0.086 |
| COGDIS: *n* (%) | 4 (4.1) | 2 (2.3) | 4 (4.3) | 0 | 4 (1.7) | $\chi^2_{(4)} = 3.427$; $P = 0.489$, V = 0.080 |
| COPER: *n* (%) | 9 (9.3) | 3 (3.5) | 8 (8.5) | 1 (3.4) | 10 (4.3) | $\chi^2_{(4)} = 5.558$; $P = 0.235$, V = 0.102 |
| Any 1 of 5 CHR criteria: *n* (%) | 11 (11.3) | 5 (5.8) | 12 (12.8) | 1 (3.4) | 17 (7.3) | $\chi^2_{(4)} = 5.369$; $P = 0.252$, V = 0.100 |
| Any 1 of 3 EPA criteria: *n* (%) | 7 (7.2) | 2 (2.3) | 6 (6.4) | 0 | 9 (3.9) | $\chi^2_{(4)} = 5.022$; $P = 0.285$, V = 0.097 |
| No CHR criterion: *n* (%) | 86 (88.7) | 81 (94.2)[1] | 82 (87.2) | 28 (96.6) | 216 (92.7) | $\chi^2_{(28)} = 20.675$; $P = 0.839$, V = 0.098 |
| Only genetic risk and functional decline: *n* (%) | 0 | 1 (1.2) | 1 (1.1) | 0 | 0 | |
| Only COPER: *n* (%) | 4 (4.1) | 2 (2.3) | 5 (5.3) | 1 (3.4) | 8 (3.4) [1] | |
| Only COGDIS: *n* (%) | 0 | 1 (1.2) [1] | 1 (1.1) | 0 | 2 (0.9) | |
| COPER and COGDIS: *n* (%) | 3 (3.1) | 1 (1.2) | 2 (2.1) | 0 | 2 (0.9) | |
| Only APS: *n* (%) | 2 (2.1) | 0 | 2 (2.1) | 0 | 5 (2.1) | |
| APS and COPER: *n* (%) | 1 (1.0) | 0 | 0 | 0 | 0 | |
| APS, COPER and COGDIS: *n* (%) | 1 (1.0) | 0 | 1 (1.1)[1] | 0 | 0 | |

[1]Indicates that 1 subject of this category converted to psychosis within 2 years. No brief intermittent psychotic symptoms (BIPS) criteria met. ED: Eating disorder; ADHD: attention-deficit hyperactivity disorder; AnxD and OCD: anxiety disorder, including obsessive-compulsive disorder; ASS: Asperger's syndrome; APS: attenuated psychotic symptoms; COGDIS: Cognitive Disturbances; COPER: Cognitive-Perceptive Basic Symptoms: EPA: European Psychiatric Association; CHR: Clinical high-risk. V: Cramer's V: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

group differences were globally indicated when diagnostic groups were analyzed separately in Kruskal–Wallis tests (Table 8). The sum scores of SIPS positive items and of the basic symptoms of COPER, the basic symptoms *captivation of attention by details of the visual field*, *thought pressure*, *derealization* and *visual perception disturbances* as well as the SIPS positive items *unusual thought content/delusional ideas* (P1) and *suspiciousness/persecutory ideas* (P2) significantly differed between groups (Table 8). Mann–Whitney tests of these variables (Supplementary Table 3) revealed that the severity of the basic symptoms of COPER was higher in eating disorders than in both ADHD and community subjects, higher in anxiety and obsessive–compulsive disorders than in ADHD and community subjects, and more pronounced in Asperger's syndrome compared to community subjects. The severity scores of the five SIPS positive items and of *unusual thought content/delusional ideas* (P1) were significantly higher in anxiety and obsessive-compulsive disorders compared to eating disorders, ADHD and community subjects. *Captivation of attention by details of the visual field* was significantly more pronounced in Asperger's syndrome compared to eating disorders, but less pronounced in Asperger's syndrome compared to ADHD; furthermore, it was more severe in anxiety and obsessive–compulsive disorders compared to community subjects. *Thought pressure* only differed between eating disorders and community subjects, with higher score in the former. Severity ratings of *derealization* were higher in eating disorders than in community subjects, and higher in anxiety and obsessive-compulsive disorders compared to both ADHD and community subjects. *Visual perception disturbances* scored higher in eating disorders, anxiety and obsessive–compulsive disorders, and Asperger's syndrome than in community subjects. Finally, ratings of *suspiciousness/persecutory ideas* (SIPS positive item P2) were higher in eating disorders than in community subjects, higher in anxiety and obsessive–compulsive disorders compared to community subjects as well as to ADHD, in which it was higher than in Asperger's syndrome; further, they were more severe in Asperger's syndrome compared to community subjects.

**Table 5 Frequency of criteria-relevant basic symptoms in the four diagnostic subsamples and the community sample (*n* = 539)**

| | ED (*n* = 97) | ADHD (*n* = 86) | AnxD and OCD (*n* = 94) | ASS (*n* = 29) | Community subjects (*n* = 233) | $\chi^2$ test; Cramer's V |
|---|---|---|---|---|---|---|
| Inability to divide attention: *n* (%) | 1 (1.0) | 0 | 2 (2.1) | 0 | 0 | $\chi^2_{(4)} = 6.534$; $P = 0.163$, V = 0.101 |
| Captivation of attention: *n* (%) | 0 | 0 | 1 (1.1) | **2 (6.9)** | 4 (1.7) | $\chi^2_{(4)} = 9.855$; [a]$P = 0.043$, V = 0.135 |
| Disturbance of abstract thinking[1]: *n* (%) | 0 | 0 | 0 | 0 | 2 (1.3) | $\chi^2_{(4)} = 3.129$; $P = 0.536$, V = 0.088 |
| Disturbance of expressive speech: *n* (%) | 5 (5.2) | 3 (3.5) | 5 (5.3) | 2 (6.9) | 15 (5.6) | $\chi^2_{(4)} = 0.752$; $P = 0.945$, V = 0.037 |
| Disturbance of receptive speech: *n* (%) | 1 (1.0) | 1 (1.2) | 3 (3.2) | 0 | 1 (0.4) | $\chi^2_{(4)} = 5.013$; $P = 0.286$, V = 0.096 |
| Thought interference: *n* (%) | 2 (2.0) | 1 (1.2) | 3 (3.2) | **3 (10.3)** | 5 (2.1) | $\chi^2_{(4)} = 8.009$; $P = 0.091$, V = 0.122 |
| Thought blockages[1]: *n* (%) | 9 (10.0) | 5 (11.1) | 8 (9.2) | 2 (9.1) | 13 (8.3) | $\chi^2_{(4)} = 0.403$; $P = 0.982$, V = 0.032 |
| Thought pressure: *n* (%) | 8 (8.2) | 4 (4.7) | **11 (11.7)** | 3 (10.3) | 7 (3.0) | $\chi^2_{(4)} = 11.019$; [a]$P = 0.026$, V = 0.143 |
| Unstable ideas of reference: *n* (%) | **3 (3.1)** | 0 | 1 (1.1) | 0 | 1 (0.4) | $\chi^2_{(4)} = 6.673$; $P = 0.154$, V = 0.111 |
| Thought perseveration: *n* (%) | 0 | 2 (2.3) | 3 (3.2) | 1 (3.4) | 3 (1.3) | $\chi^2_{(4)} = 3.964$; $P = 0.411$, V = 0.086 |
| Impaired discrimination between true memories and phantasy: *n* (%) | 1 (1.0) | 1 (1.2) | **6 (6.4)** | 0 | 7 (3.0) | $\chi^2_{(4)} = 7.310$; $P = 0.120$, V = 0.116 |
| Derealization: *n* (%) | **17 (17.5)** | 2 (2.3) | **14 (14.9)** | 2 (6.9) | **6 (2.6)** | $\chi^2_{(4)} = 32.380$; [c]$P < 0.001$, V = 0.245 |
| Visual perception disturbances: *n* (%) | 13 (13.4) | 7 (8.1) | 10 (10.6) | 5 (17.2) | **11 (4.7)** | $\chi^2_{(4)} = 10.652$; [a]$P = 0.031$, V = 0.141 |
| Acoustic perception disturbances: *n* (%) | 12 (12.4) | 6 (7.1) | 10 (10.6) | 2 (6.9) | 17 (7.3) | $\chi^2_{(4)} = 3.063$; $P = 0.547$, V = 0.075 |

[1]Assessable only from age of 13 years onwards, thus only calculated on *n* = 404. ED: Eating disorder; ADHD: Attention-deficit hyperactivity disorder; AnxD and OCD: anxiety disorder, including obsessive-compulsive disorder; ASS: Asperger's syndrome. In **bold**, cells with standardized residuals ≥ |1.96|. This equals significant deviation from the expected cell frequency. V: Cramer's V: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

### *Association of functioning with CHR symptoms and criteria*

In both bivariate and partial correlation analyses, correlations between functioning and severity of CHR criteria and symptoms were at most of small effect size.

In simple bivariate correlation analyses between functioning, *i.e.*, SOFAS scores, and severity of CHR criteria and symptoms, we detected few significant correlations of small effect size with the sum score of COPER (tau = -0.140, $P < 0.001$), the sum score of SIPS positive items (tau = -0.113, $P < 0.001$), the SIPS positive items *suspiciousness/persecutory ideas* (P2: tau = -0.172, $P < 0.001$), *perceptual abnormalities/hallucinations* (P4; tau = -0.112, $P = 0.001$), and *disorganized communication* (P5; tau = -0.076, $P = 0.034$) as well as the basic symptoms *thought pressure* (tau = -0.078, $P = 0.028$), *derealization* (tau = -0.116, $P = 0.001$), and visual (tau = -0.096, $P = 0.007$) and *acoustic perception disturbances* (tau = -0.073, $P = 0.040$). All of these four basic symptoms are part of COPER; only *thought pressure* is also part of COGDIS. For the severity of COGDIS and other CHR symptoms, the correlations with functioning were between tau = -0.065 ($P = 0.056$) for *thought interference* and tau = 0.018 ($P = 0.614$) for *disturbances of abstract thinking*.

When group was controlled for in partial correlation analyses, the correlations between functioning and the sum score of COPER ($r = -0.087$, $P = 0.044$), the sum score of SIPS positive items ($r = -0.164$, $P < 0.001$), the SIPS positive items *suspiciousness/persecutory ideas* (P2; $r = -0.120$, $P = 0.005$), *perceptual abnormalities/hallucinations* (P4; $r = -0.165$, $P < 0.001$), and *disorganized communication* (P5; $r = -0.126$, $P = 0.003$) remained, and in the case of SIPS items, became even slightly more pronounced. Contrary to this, none of the single basic symptoms with a significant correlation with functioning in bivariate analyses was again significant when group was controlled for. Rather, *thought inference* ($r = -0.102$, $P = 0.019$) and *disturbances of expressive speech* ($r = -0.094$, $P = 0.030$) became significant. The remaining correlations with functioning were between $r = -0.078$ ($P = 0.071$) for *acoustic perception disturbances* and $r = 0.019$ ($P =$

**Table 6 Frequency of brief intermittent and attenuated psychotic symptoms in the four diagnostic subsamples and the community sample (*n* = 539)**

| | ED (*n* = 97) | ADHD (*n* = 86) | AnxD and OCD (*n* = 94) | ASS (*n* = 29) | Community subjects (*n* = 233) | $\chi^2$ test; Cramer's V |
|---|---|---|---|---|---|---|
| P1: Unusual thought content/delusional ideas: *n*(%) | 6 (6.2) | 4 (4.7) | **14 (14.9)**[1] | 4 (13.8) | 13 (5.6) | $\chi^2_{(4)} = 11.391$; [a]$P = 0.023$, V = 0.145 |
| P2: Suspiciousness/persecutory ideas: *n*(%) | 2 (2.1) | 1 (1.2) | 4 (4.3) | **3 (10.3)**[2] | 4 (1.7) | $\chi^2_{(4)} = 9.425$; $P = 0.051$, V = 0.132 |
| P3: Grandiose ideas: *n*(%) | 0 | 0 | 0 | 0 | 1 (0.4) | $\chi^2_{(4)} = 1.316$; $P = 0.859$, V = 0.049 |
| P4: Perceptual abnormalities/hallucinations: *n*(%) | 14 (14.2) | 20 (23.3) | 22 (23.4) | 8 (27.6) | 54 (23.2) | $\chi^2_{(4)} = 4.150$; $P = 0.368$, V = 0.088 |
| P5: Disorganized communication: *n*(%) | 0 | 0 | 0 | 0 | 1 (0.4) | $\chi^2_{(4)} = 1.316$; $P = 0.859$, V = 0.049 |

[1]most frequent in AnxD and OCD: thought insertion and broadcasting; unusual, somatic and nihilistic idea;
[2]most frequent in ASS: ideas of being redlined or observed (common rating). In **bold**, cells with standard residuals ≥ |1.96|. This equals a significant deviation (less or more) from the expected cell frequency. ED: Eating disorder; ADHD: Attention-deficit hyperactivity disorder; AnxD and OCD: Anxiety disorder, including obsessive-compulsive disorder; ASS: Asperger's syndrome. V: Cramer's V: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

0.666) for *thought perseveration*.

### *Conversion to psychosis*

Altogether, four had developed a psychosis within 2 years (*i.e.*, 0.7% of the whole sample and 1.2% of the 2-year follow-up sample). Only one of the converters had not met a CHR criterion at baseline (Table 4). Three conversions had occurred in the inpatient sample, including the one without CHR criteria at baseline, and one in the community subjects (Table 4), in a female without any mental disorder at baseline. Thus, with regard to the total baseline sample ($n$ = 539), the 2-year conversion rate in subjects without CHR criteria was 0.2% and the 2-year conversion rate in subjects with CHR criteria was 6.5% ($\chi^2_{(1)} = 22.807$, Fisher's exact $P = 0.002$; Cramer's V = 0.206). With regard to the 2-year follow-up sample ($n$ = 331), these numbers were 0.3% and 11.5% ($\chi^2_{(1)} = 25.220$, Fisher's exact $P = 0.002$; Cramer's V = 0.276).

## DISCUSSION

In light of the relevant nonconversion rates in CHR samples, in particular in UHR samples[19,20], and their various outcomes[25,26], it has been suggested that CHR criteria might better be regarded as a pluripotent syndrome, or a transdiagnostic risk or severity marker[27-30]. If either of these were true, relevant and systematic differences in the frequency and severity of CHR criteria and symptoms between patients with severe mental illness requiring inpatient treatment and community subjects should be present. We examined this in two child and adolescent samples of the BEARS-Kid study with respect to both the UHR and the basic symptom approach.

We had chosen this age group because higher nonconversion rates compared to adult samples were reported for this group[19,21], and because CHR symptoms and criteria were shown to be more prevalent and less clinically relevant in children and adolescents[22,23,51-53]. Consequently, we expected that CHR symptoms and criteria would most likely show characteristics indicative of a pluripotent syndrome, of a transdiagnostic risk factor or of a severity marker in this age group.

### *Age and the CHR state*

Both community and clinical studies on the effect of age on CHR symptoms and criteria indicated an age threshold around age of 16 years for APS and BIPS, with perceptual APS/BIPS being more prevalent below this age and all APS/BIPS being less clinically relevant[22,23,51,53]. For perceptual and cognitive basic symptoms, the age thresholds for prevalence and clinical significance were around age of 18 and 23 years, respectively[23,52]. Thus, all participants were at an age below the threshold suggested for basic symptoms, while the suggested age threshold for APS/BIPS was within the age range of our sample. Consequently, the observed group difference in age could have biased the overall older inpatient group towards reporting a lower number of APS/BIPS compared to the younger community sample; consequently, hiding relevant group effects. Therefore, were repeated the analyses of APS/BIPS in the age group below the suggested age threshold; *i.e.*, with 8- to 15-year-old ( Supplementary Tables 4–6), which led to comparable results.

**Table 7 Severity of clinical high-risk criteria and symptoms (mean SD, median) in inpatients and the community sample (*n* = 539)**

| | Inpatients (*n* = 306) | Community subjects (*n* = 233) | Mann–Whitney U; Rosenthal's r |
|---|---|---|---|
| Sum score of SIPS positive items | 2.5 ± 2.5, 2 | 2.1 ± 2.3, 1 | $Z$ = -1.852, $P$ = 0.064; $r$ = 0.080 |
| Sum score of 9 basic symptoms of COGDIS | 0.8 ± 2.5, 0 | 0.4 ± 1.2, 0 | $Z$ = -1.125, $P$ = 0.260, $r$ = 0.048 |
| Sum score of 10 basic symptoms of COPER | 1.6 ± 3.6, 0 | 0.6 ± 1.7, 0 | $Z$ = -3.852, [c]$P$ < 0.001; $r$ = 0.166 |
| P1: Unusual thought content / delusional ideas | 0.9 ± 1.0, 1 | 0.8 ± 0.9, 1 | $Z$ = -1.341, $P$ = 0.180; $r$ = 0.058 |
| P2: Suspiciousness / persecutory ideas | 0.4 ± 0.8, 0 | 0.2 ± 0.6, 0 | $Z$ = -4.281, [c]$P$ < 0.001; $r$ = 0.184 |
| P3: Grandiose ideas | 0.1 ± 0.3, 0 | 0.1 ± 0.4, 0 | $Z$ = -0.426, $P$ = 0.670; $r$ = 0.018 |
| P4: Perceptual abnormalities / hallucinations | 1.0 ± 1.4, 0 | 1.0 ± 1.2, 0 | $Z$ = -1.119, $P$ = 0.263; $r$ = 0.048 |
| P5: Disorganized communication | 0.1 ± 0.3, 0 | 0.1 ± 0.3, 0 | $Z$ = -0.397, $P$ = 0.691; $r$ = 0.017 |
| Inability to divide attention | 0.1 ± 0.5, 0 | 0 | $Z$ = -1.514, $P$ = 0.130; $r$ = 0.065 |
| Captivation of attention | 0.0 ± 0.2, 0 | 0.0 ± 0.3, 0 | $Z$ = -0.757, $P$ = 0.449; $r$ = 0.033 |
| Disturbance of expressive speech | 0.2 ± 0.8, 0 | 0.1 ± 0.4, 0 | $Z$ = -0.268, $P$ = 0.789; $r$ = 0.012 |
| Disturbance of abstract thinking[1] | 0 | 0.0 ± 0.1, 0 | $Z$ = -1.622, $P$ = 0.105; $r$ = 0.070 |
| Thought interference | 0.1 ± 0.6, 0 | 0.1 ± 0.4, 0 | $Z$ = -0.591, $P$ = 0.555; $r$ = 0.025 |
| Thought blockages[1] | 0.2 ± 0.8, 0 | 0.1 ± 0.6, 0 | $Z$ = -1.044, $P$ = 0.297; $r$ = 0.045 |
| Thought pressure | 0.2 ± 0.9, 0 | 0.1 ± 0.5, 0 | $Z$ = -2.639, [b]$P$ = 0.008; $r$ = 0.114 |
| Disturbance of receptive speech | 0.0 ± 0.3, 0 | 0.0 ± 0.1, 0 | $Z$ = -1.324, $P$ = 0.185; $r$ = 0.057 |
| Unstable ideas of reference | 0.0 ± 0.2, 0 | 0.0 ± 0.2, 0 | $Z$ = -1.046, $P$ = 0.296; $r$ = 0.045 |
| Impaired discrimination between ideas/true memories and phantasy | 0.1 ± 0.6, 0 | 0.0 ± 0.3, 0 | $Z$ = -0.230, $P$ = 0.818; $r$ = 0.010 |
| Thought perseveration | 0.0 ± 0.3, 0 | 0.0 ± 0.2, 0 | $Z$ = -0.607, $P$ = 0.544; $r$ = 0.026 |
| Derealization | 0.4 ± 1,1, 0 | 0.0 ± 0.2, 0 | $Z$ = -3.924, [c]$P$ < 0.001.; $r$ = 0.169 |
| Visual perception disturbances | 0.3 ± 1.1, 0 | 0.1 ± 0.4, 0 | $Z$ = -2.822, [b]$P$ = 0.005; $r$ = 0.122 |
| Acoustic perception disturbances | 0.2 ± 0.9, 0 | 0.2 ± 0.8, 0 | $Z$ = -1.014, $P$ = 0.311; $r$ = 0.044 |

[1]Assessable only from age of 13 years onwards, thus only calculated on n = 404.
*r*: Rosenthal's *r*: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

Compared to adult samples, group differences indicative of a potential pluripotent or transdiagnostic nature of CHR symptoms and criteria should be even more obvious in children and adolescents below these age thresholds. Yet, overall, our results revealed only few group differences of small effect size in frequency and severity of CHR symptoms and no group differences in frequency of CHR criteria. Additionally, at most weak associations were found between CHR symptoms or sum scores of symptoms with level of psychosocial functioning as a proxy measure of severity of mental ill health.

### *The CHR state as a pluripotent syndrome*

Being derived from biology and commonly applied to describe a property of cells, pluripotent (from "pluri": several, and "potent": being able) describes the property of immature or stem cells that are capable of giving rise to several different cell types, into which they transform[31,54]. When extended to psychiatry, a pluripotential syndrome would be the first, diagnostically indistinct expression of any developing more severe psychopathology, which only later may acquire a degree of diagnostic specificity[27,28]. In doing so, similar to pluripotent cells, a pluripotent mental state would be completely absorbed in the final, manifest mental state or disorder. Thus, if they were pluripotent, CHR criteria and symptoms would no longer be detectable in patients with manifest mental disorders; *i.e.*, after their transformation into a diagnostically specific disorder. Yet, they might already be detectable in healthy persons who might be at risk of developing a mental disorder in future, such as children and adolescents of the community, of whom a third can be expected to develop a mental disorder in their lifetime[39]. Thus, from a pluripotent point of view, we expected a higher rate of CHR criteria and symptoms in community subjects compared to inpatients.

**Table 8 Severity of clinical high-risk criteria and symptoms (mean ± SD, median) in the four diagnostic subsamples and the community sample (N = 539)**

| | ED (n = 97) | ADHD (n = 86) | AnxD and OCD (n = 94) | ASS (n = 29) | Community subjects (*n* = 233) | Kruskal–Wallis (results of *post hoc* Mann–Whitney tests) |
|---|---|---|---|---|---|---|
| Sum score of SIPS positive items | 2.1 ± 2.4, 1 | 2.0 ± 2.1, 1 | 3.1 ± 2.6, 2 | 3.3 ± 3.3, 2 | 2.1 ± 2.3, 1 | $\chi^2_{(4)} = 18.866$, $^cP = 0.001$ (AnxD and OCD>ED = ADHD = GPS) |
| Sum score of COGDIS | 0.8 ± 2.1, 0 | 0.5 ± 1.7, 0 | 1.2 ± 3.5, 0 | 0.7 ± 1.7, 0 | 0.4 ± 1.2, 0 | $\chi^2_{(4)} = 7.692$, $P = 0.104$ |
| Sum score of COPER | 1.8 ± 3.6, 0 | 1.1 ± 3.3, 0 | 2.2 ± 4.2, 0 | 1.1 ± 1.7, 0 | 0.6 ± 1.7, 0 | $\chi^2_{(4)} = 26.988$, $^cP < 0.001$ (ED = AnxD and OCD = ASS > GPS; AnxD and OCD = ED > ADHD) |
| P1: Unusual thought content | 0.8 ± 0.9, 1 | 0.7 ± 0.9, 1 | 1.2 ± 1.1, 1 | 1.2 ± 1.3, 1 | 0.8 ± 0.9, 1 | $\chi^2_{(4)} = 12.397$, $^aP = 0.015$ (AnxD and OCD > ED = ADHD = GPS) |
| P2: Suspiciousness/persecutory ideas | 0.4 ± 0.8, 0 | 0.2 ± 0.6, 0 | 0.5 ± 0.9, 0 | 0.7 ± 1.1, 0 | 0.2 ± 0.6, 0 | $\chi^2_{(4)} = 30.502$, $^cP < 0.001$ (ASS = AnxD and OCD = ED > GPS; AnxD and OCD = ASS > ADHD) |
| P3: Grandiose ideas | 0.1 ± 0.3, 0 | 0.1 ± 0.2, 0 | 0.2 ± 0.5, 0 | 0.1 ± 0.3, 0 | 0.1 ± 0.4, 0 | $\chi^2_{(4)} = 4.029$, $P = 0.402$ |
| P4: Perceptual abnormalities | 0.8 ± 1.3, 0 | 1.0 ± 1.5, 0 | 1.2 ± 1.4, 1 | 1.3 ± 1.6, 1 | 1.0 ± 1.2, 0 | $\chi^2_{(4)} = 6.391$, $P = 0.172$ |
| P5: Disorganized communication | 0.0 ± 0.2, 0 | 0.0 ± 0.2, 0 | 0.1 ± 0.4, 0 | 0.1 ± 0.3, 0 | 0.1 ± 0.3, 0 | $\chi^2_{(4)} = 3.129$, $P = 0.539$ |
| Inability to divide attention | 0.0 ± 0.4, 0 | 0 | 0.1 ± 0.9, 0 | 0 | 0 | $\chi^2_{(4)} = 6.537$, $P = 0.163$ |
| Captivation of attention | 0 | 0 | 0.0 ± 0.2, 0 | 0.1 ± 0.4, 0 | 0.0 ± 0.3, 0 | $\chi^2_{(4)} = 9.749$, $^aP = 0.045$ (ASS > ED = ADHD) |
| Disturbance of expressive speech | 0.2 ± 0.9, 0 | 0.1 ± 0.6, 0 | 0.2 ± 1.0, 0 | 0.1 ± 0.4, 0 | 0.1 ± 0.4, 0 | $\chi^2_{(4)} = 0.675$, $P = 0.954$ |
| Disturbance of abstract thinking[1] | 0 | 0 | 0 | 0 | 0.0 ± 0.1, 0 | $\chi^2_{(4)} = 2.632$, $P = 0.621$ |
| Thought interference | 0.1 ± 0.5, 0 | 0.1 ± 0.5, 0 | 0.1 ± 0.6, 0 | 0.3 ± 1.0, 0 | 0.1 ± 0.4, 0 | $\chi^2_{(4)} = 7.912$, $P = 0.095$ |
| Thought blockages[1] | 0.2 ± 0.8, 0 | 0.2 ± 0.9, 0 | 0.3 ± 1.0, 0 | 0.1 ± 0.4, 0 | 0.1 ± 0.6, 0 | $\chi^2_{(4)} = 2.048$, $P = 0.727$ |
| Thought pressure | 0.3 ± 0.9, 0 | 0.1 ± 0.6, 0 | 0.4 ± 1.2, 0 | 0.1 ± 0.4, 0 | 0.1 ± 0.5, 0 | $\chi^2_{(4)} = 10.944$, $^aP = 0.027$ (ED = AnxD and OCD > GPS) |
| Disturbance of receptive speech | 0.0 ± 0.1, 0 | 0.0 ± 0.2, 0 | 0.1 ± 0.5, 0 | 0 | 0.0 ± 0.07, 0 | $\chi^2_{(4)} = 5.047$, $P = 0.283$ |
| Unstable ideas of reference | 0.1 ± 0.3, 0 | 0 | 0.0 ± 0.1, 0 | 0 | 0.0 ± 0.2, 0 | $\chi^2_{(4)} = 6.643$, $P = 0.156$ |
| Impaired discrimination between | 0.0 ± 0.3, 0 | 0.1 ± 0.7, 0 | 0.2 ± 0.7, 0 | 0 | 0.0 ± 0.3, 0 | $\chi^2_{(4)} = 7.344$, $P = 0.119$ |
| Thought perseveration | 0 | 0.1 ± 0.4, 0 | 0.1 ± 0.4, 0 | 0.0 ± 0.1, 0 | 0.0 ± 0.2, 0 | $\chi^2_{(4)} = 3.954$, $P = 0.412$ |
| Derealization | 0.4 ± 1.1, 0 | 0.1 ± 0.7, 0 | 0.6 ± 1.5, 0 | 0.2 ± 0.7, 0 | 0.0 ± 0.2, 0 | $\chi^2_{(4)} = 32.930$, $^cP < 0.001$ (ED = AnxD and OCD > ADHD = GPS) |
| Visual perception disturbances | 0.4 ± 1.2, 0 | 0.3 ± 1.2, 0 | 0.3 ± 1.0, 0 | 0.3 ± 0.7, 0 | 0.1 ± 0.4, 0 | $\chi^2_{(4)} = 10.764$, $^aP = 0.029$ (ED = AnxD and OCD = ASS > GPS) |
| Acoustic perception disturbances | 0.3 ± 1.0, 0 | 0.2 ± 0.7, 0 | 0.3 ± 1.0, 0 | 0.1 ± 0.3, 0 | 0.2 ± 0.8, 0 | $\chi^2_{(4)} = 3.227$, $P = 0.521$ |

[1]assessable only from age of 13 years onwards, thus only calculated on *n* = 404. ED: Eating disorder; ADHD: Attention-deficit hyperactivity disorder; AnxD and OCD: Anxiety disorder, including obsessive-compulsive disorder; ASS: Asperger's syndrome; GPS: community subjects.

Contrary to this expectation, we found no global pattern of differences in CHR criteria between inpatients and community subjects, and the four group differences in the prevalence of CHR symptoms; *i.e.*, in *suspiciousness/persecutory ideas*, *thought pressure*, *derealization* and *visual perception disturbances*, pointed towards a slightly higher rather than lower prevalence in inpatients. This lack of support for

assuming pluripotency of the UHR criteria specifically, is in line with results of the longitudinal data of two North American CHR studies[55]. Comparing outcome of help-seeking patients with and without UHR criteria, these studies detected no group differences in rates of new emergence of nonpsychotic disorders, thus not supporting diagnostic pluripotency of the UHR states[55]. Furthermore, the authors noted that the persistence of the generally frequent baseline comorbidities to UHR states would not qualify as support for assuming pluripotency of UHR states, even when only the UHR state is remitted at baseline[55]. Indeed, the above definition of a pluripotent state would rule out the concurrent presence of both the pluripotent state and its assumed outcome.

The missing empirical support for regarding the CHR state as a pluripotent syndrome is somewhat unsurprising in light of the frequent indistinct use of the term pluripotential for states that were equaled to earliest, unspecific mental states of mental disorders[31]. Yet, in models of developing psychosis, these earliest and unspecific states are commonly distinguished from the more specific CHR states[10,18,56]. Then again, pluripotent states or trajectories have been equated to transdiagnostic ones[30] despite their considerably differing assumptions with regard to the course of their constituting symptoms – transformation and, thus, forever vanishing of pluripotential states and symptoms *versus* maintenance or even increase of transdiagnostic symptoms.

### *The CHR state as a general transdiagnostic risk factor*

In contrast to a pluripotent state, a transdiagnostic risk factor as well as a transdiagnostic dimension of psychopathology would still be present in various mental disorders[32], while they would be present in the community to a clearly lesser degree or not at all outside states of mental ill health. Thus, if CHR criteria and symptoms would represent a transdiagnostic risk factor or a transdiagnostic psychopathological dimension, they should accumulate in the extreme range of persons with mental disorders and, hence, should be more frequent or severe in inpatients compared to community subjects. Indeed, a large body of research indicates that so-called psychotic-like experiences, commonly assessed by self-report questionnaires or fully-standardized lay-person interviews, can be measured in the community, in which they are linked to the presence of non-psychotic disorder, particularly common mental disorder [28,57]. Thus, it was argued that psychotic-like experiences are transdiagnostic phenomena that, among others, also predict greater illness severity[57].

In our analyses, these assumptions were not supported for CHR criteria. The prevalence rates of CHR criteria did not differ between the community subjects (7.3%) and the inpatient sample (8.2%). Yet, both rates were higher than the 2.4% rate of clinician-assessed CHR criteria in young adults of the community aged 16–40 years[58]. In line with earlier findings[22,23], this indicates an effect of age across broader age ranges but not within children and adolescents. This lack of support for a transdiagnostic model of CHR criteria is likely related to the differences in assessments and definition. Studies on psychotic-like experiences commonly do not use CHR instruments for the assessment of APS/BIPS by trained clinicians in semi-structured interviews, which makes such psychotic-like experiences a poor and invalid proxy of APS that overestimates the presence of APS by far[59-62]. Furthermore, studies on psychotic-like experiences commonly disregard the onset/worsening and frequency requirements of CHR criteria[62] (Table 1).

With regard to CHR symptoms and irrespective of these additional requirements, we found some group differences in frequency and severity, in particular with respect to the severity of some single CHR symptoms. Yet, these findings were mostly unsystematically and randomly distributed, except for the UHR-relevant APS *suspiciousness/persecutory ideas*, the two COPER-relevant basic symptoms *derealization* and *visual perception disturbances*, and the COPER- and COGDIS-relevant basic symptom *thought pressure*. These four CHR symptoms were more frequent and severe in inpatients, in particular in eating disorders, and anxiety and obsessive–compulsive disorders; additionally, the paranoid APS was more frequent and severe in autism-spectrum disorder. Thus, they may be the most likely candidates of all CHR symptoms for transdiagnostic risk factors or a transdiagnostic psychopathological dimension.

*Suspiciousness/persecutory ideas* (P2) of the SIPS in terms of APS/BIPS include symptoms ranging from a general lack of trust in and suspiciousness of others, as well as vague ideas of threat or that others do not mean well to more concrete ideas of being followed, observed or in danger and paranoid ideas of reference[43]. Their severity can range from ideas still being doubted to various degrees and not significantly impeding behavior, to holding these ideas with absolute conviction, resulting in significant impact on behavior[43]. Social fears related to one's own possibly inadequate or embarrassing behavior (but not to the negative intentions of others) were not scored here. In adolescents, ideas of reference that exclusively involved peers and the idea that they might think or talk badly about the patient/subject were also not rated, as the critical comparison with peers is a common phenomenon in adolescents' identity formation and, consequently, as these ideas are possibly related to lower levels of self-esteem [63,64].

In our study, the paranoid APS was most frequent and severe in anxiety, obsessive–compulsive, and in autism-spectrum disorders. This is in line with reports that paranoia is not specific to psychosis but occurs in a wide range of disorders[65] and also frequently in community samples of adolescents[65,66]. In particular, paranoia was significantly positively associated with anxiety but not autistic symptoms, and negatively associated with symptoms of ADHD[63]. The latter is also in line with our finding that none of the ADHD patients reported paranoid APS. Other studies have linked autistic traits

and psychotic-like experiences, including paranoia, in the adult community[67] and reported similarly high levels of paranoia in psychotic and autism-spectrum disorders[68]. In contrast to psychotic disorders in which paranoia was based upon victimization, suspicion, and threat of harm, in autism-spectrum disorders, paranoia was based less upon these but more so upon social cynicism[68]. Yet, certain (developing) personality accentuations or disorders that involve paranoia and suspiciousness, in particular paranoid, schizotypal and borderline personality[69,70], might have contributed our findings. However, for the ongoing personality development in this age group, we had not assessed these in our study on children and adolescents.

Of the basic symptoms, *thought pressure* that is part of both COPER and COGDIS was more frequent and severe in inpatients, particularly in anxiety and obsessive–compulsive disorders. *Thought pressure* involves the subjective occurrence of a great number of thematically unrelated and often unrecognized, fragmented thoughts whose (dis)appearance is hard to control[44]. Thereby, *thought pressure* is distinct from intrusive thoughts of obsessive–compulsive disorder that involve a certain topic. Furthermore, in their assessment, the occurrence within states of extreme emotional arousal, such as in panic attacks, has to be excluded[44]. Thus, this finding is not explained by phenomenological similarities between *thought pressure* and cognitive symptoms in anxiety and obsessive–compulsive disorders. Yet, these similar cognitive symptoms might signal a general liability to difficulties in suppressing irrelevant or inadequate thoughts that, as suggested for intrusive thoughts, might be related to altered functional connectivity in the temporal gyri[71]. More qualitative and basic research into the link between *thought pressure* and anxiety and obsessive–compulsive disorders is clearly needed.

*Visual perception disturbances* include various, often fleeting misperceptions of real visible objects including oneself and other persons that are immediately recognized as false perceptions, and are not even for a split-second considered as changes in the outside world[44]. As with all basic symptoms, they have to have started at a certain point in life[44] and thus, contrary to schizotypy-related perceptual aberrations, have no trait characteristic[15,72,73]. Furthermore, they must be unrelated to a somatic condition or substance use[44]. As outlined above in the section "Assessments", they rate on the SIPS below the APS-relevant range with a score of 2[43,44,73]. Examples of *visual perception disturbances* include changes in the perception of the color or color intensity of objects, in the perception and estimation of the size of, or distance to objects, and in the shape of objects, as well as perceptions that resemble floaters or flashes of light in the vision as known, for example, from auras of migraine, retinal detachment or optic neuritis[44]. Therefore, they are different from unformed attenuated or frank visual hallucinations that are not perceived as "in the eye" but are located – at least initially – in the outside world[43,73]. Despite being a part of COPER, *visual perception disturbances* were found to be on the periphery of a network of symptoms of psychosis in an adult patient sample[74]. Such a peripheral position was also found for the depression items of the SIPS and of the Positive And Negative Syndrome Scale[75], though at the opposite side of the network, likely indicating that these symptoms are less specific to psychosis. Thus, *visual perception disturbances* that longitudinally had been significantly linked to the development of psychosis in adults[14] might be a more general expression of severe mental problems in childhood and early adolescence. This view is supported by reports that visual hallucinations were more frequent in children and adolescents with psychosis compared to adult psychosis patients[76], and that attenuated and transient hallucinations as well as perceptual disturbances were more frequent and less clinically relevant in children and adolescents[22,23], who likely grow out of them over time due to progressing neurocognitive and brain maturation[52].

*Derealization* is defined by an alienation from the surrounding and/or the experience of the external environment as unfamiliar, with other people appearing as if only acting a role and the world appearing as if being two-dimensional or a stage set in the presence of knowledge of its reality[44]. It often co-occurs with more frequent depersonalization experiences; and together, they might form a syndrome in itself[77-79]. Both are part of the definition of panic disorders[77,78] and are therefore not rated as basic symptoms when exclusively occurring within a panic attack. Thus, as in *thought pressure*, our finding of increased *derealization* in anxiety and obsessive–compulsive disorders is not explained by this phenomenological overlap. Yet, as personality disorders had not been assessed in this study, we did not exclude their possible occurrence as part of a developing Borderline or schizotypal personality accentuation or disorder[78]. *Depersonalization* and, to a lesser degree, *derealization* are frequent phenomena in the general population with higher rates in psychiatric patients, in particular those with affective and anxiety disorders[77,78]. *Derealization* and *depersonalization* might have partly different neurobiological underpinnings[80]; and only *derealization* was found to be predictive of future psychosis and, thus included into COPER[14]. However, in line with our current findings, studies reported that both *derealization* and *depersonalization* might be responses to strong emotions, such as embarrassment, or might be attempts at coping, in particular in affective and anxiety disorders[81]. Additionally, one study on bulimia reported a link between threatening stimuli and dissociative states, in particular derealization, in which it was assumed to fulfill a similar function as binge eating itself; *i.e.*, lowering awareness of generalized threat and negative self-esteem[82]. Thus, the increased prevalence and severity of *derealization* in patients with eating disorders, and anxiety and obsessive–compulsive disorders might be related to their propensity to perceive high emotional arousal, especially threat.

*Derealization* and *visual perception disturbances* are only part of the basic symptom criterion COPER (Table 1) that is likely less specific but more sensitive compared to COGDIS[15]. Although not more frequent, our analyses revealed that COPER was more severe in inpatients, in particular those with eating disorders, and anxiety and obsessive–compulsive disorders. Therefore, the inclusion of *derealization* and *visual perception disturbances* in COPER in addition to that of *thought pressure* might have conveyed the higher severity, though not frequency of COPER in inpatients, in particular in eating, autism-spectrum, and anxiety and obsessive–compulsive disorders.

### *The CHR state as a general transdiagnostic severity marker*

A transdiagnostic severity marker of psychopathology would be expected to be generally present in mental disorders and to be most pronounced in those with severe mental disorders and, relatedly, in those with most severe functional impairment due to their mental problems. Thus, the severity and likelihood of presence of CHR criteria and symptoms would be expected to significantly increase with decreasing psychosocial functioning as a proxy measure of illness severity. As already discussed, CHR symptoms and criteria differed only to a minimal degree in their prevalence between inpatients and community subjects, in whom they were also rare. They hardly exceeded 10% in inpatients, except for *derealization* and *visual perception disturbances* (both 11.4%) and *perceptual abnormalities/hallucinations* (P4) that were present in 20.9% of inpatients but also in 23.4% of community subjects. Furthermore, CHR symptoms and criteria demonstrated an association with psychosocial functioning, the proxy severity measure. However, this association was, at most, of small effect size even when becoming significant. This finding indicates that CHR criteria and symptoms would be poor transdiagnostic severity markers of mental problems; at least when psychosocial functioning is used as a proxy measure.

With regard to basic symptoms, only COPER became significant in both bivariate and partial group-controlled correlation analyses, showing a small maximum effect of Tau = -0.140. Significant single basic symptoms differed between the two types of analyses. In doing so, *thought pressure*, *derealization*, and *visual* and *acoustic perception disturbances* became significant in bivariate, and *thought inference* and *disturbances of expressive speech* became significant in partial analyses, in no case exceeding tau = -0.116. Of these six symptoms, all but *disturbances of expressive speech* are part of COPER, while only *thought pressure* and *interference* as well as *disturbances of expressive speech* are part of COGDIS. Since *thought pressure*, *derealization*, and *visual perception disturbances* showed significant group differences, this strong group effect may mostly explain their association with functioning in bivariate correlation that, consequently, was strongly reduced in partial correlations.

Results on the APS syndrome and single APS were more consistent. In both bivariate and partial correlation analyses, the sum score of SIPS positive items as well as the single SIPS positive items *suspiciousness/persecutory ideas* (P2), *perceptual abnormalities/hallucinations* (P4), and *disorganized communication* (P5) were significantly negatively correlated with psychosocial functioning. Yet, as in basic symptoms, these correlations were only of weak effect size and did not exceed $r$ = -0.165 (respectively $r$ = -0.201 in 8–15-year-olds) in *perceptual abnormalities/hallucinations* (P4). This is in line with a recent community study, whose $n$ = 211 participants had been 11-13 years old at baseline[84]. Authors reported an association between psychotic experiences assessed with the Schedule for Affective Disorders and Schizophrenia for School-aged Children (K-SADS[83]) and poorer functioning[84]. Furthermore, $n$ = 86 (40.8%) and $n$ = 56 (26.5%) participated in the first and second follow-up at age 14–16 years and 17–21 years, respectively[84]. Participants with psychotic experiences at baseline had persistently poorer global functioning throughout adolescence and into early adulthood. As in our cross-sectional results, this effect was above and beyond what was explained by presence of a mental disorder, suggesting an underlying vulnerability which extends beyond diagnosable mental disorder [84]. Unfortunately, the authors did not report effect sizes and did not distinguish between the different psychotic experiences. Therefore, it remains unclear if these associations were also of only small effect size and if they were mainly driven by similar (attenuated) psychotic symptoms.

In our study, only the comparably frequent and, (regarding content) heterogeneous SIPS positive item *unusual thought content/delusional ideas* and the extremely rare SIPS positive item *grandiose ideas* were not significantly related to functioning. *Unusual thought content/delusional ideas* (P1) includes all but paranoid and grandiose ideas[43]. Thus, it is probable that the included unusual ideas differ in their association with functioning; e.g., that attenuated *Ich-Störungen* may more strongly impair functioning than magical thinking. For this reason, future studies should examine single attenuated delusional ideas differentially to further determine which APS might or might not have the potential of a transdiagnostic severity marker. Similarly, a more differential examination is needed for *perceptual abnormalities/hallucinations* (P4) that involves different sensory modalities, as these were differentially, though inconsistently related to conversion to psychosis in UHR samples[85-87].

The lack of strong correlations between CHR symptoms and criteria, and functioning might be perceived as challenging the notion that these possess clinical relevance. However, symptoms are generally defined by a departure from normal function – not necessarily psychosocial function – or feeling, which is apparent to the patient, reflecting the presence of an unusual state or of a disease[38]. Thus, functional impairment is not always a prerequisite even for some psychotic disorders, such delusional disorders that, according to the DSM[38], do not have to lead to functional impairment *per se*. Moreover, in ICD-10 (and the future ICD-11), functional impairment is not a requirement for any

psychotic disorder[88]. Furthermore, in the SIPS and their anchor points for severity ratings of the positive items[43], a rating of 3 (or lower) does not require an impact on functioning, while a rating of 4 requires only potential and partial impact on functioning; a significant impact on functioning is only required for severe APS of score 5 or BIPS score of 6. Yet, ratings of 5 were rare, occurring in only 13 instances, and ratings of 6 never occurred. Rather, ratings of 3 dominated in those with APS: 68.3% scored 3 on P1, 85.7% on P2 and 66.1% on P4; and the single case of APS on P3 and P5, respectively, had a rating of 3 each. Additionally, other than in the current version of Comprehensive Assessment of At-Risk Mental States, the APS syndrome of the SIPS does not require a significant functional decline or impairment[19]. Thus, the lack of an association with functional impairment does not limit the qualification of CHR symptoms and criteria as symptoms or syndromes.

As for the basic symptoms, affected persons can commonly cope with these mostly fleeting experiences (e.g., by increased willpower or concentration) for as long as their number or frequency does not exceed their coping capacities, and for as long as the employed coping strategies are not maladaptive (such as social withdrawal or other avoidance strategies)[44,52,89]. Thus, for their subjective perception as not normal, basic symptoms may induce distress and worries about one's own mental health[52,89] but not necessarily impairment in psychosocial functioning. Consequently, functional impairment is not a general prerequisite for symptoms or syndromes, in particular in the prevention of disorders that, within psychiatry, also aims for the prevention of functional impairment [90]. In light of this, making functional impairment an obligatory requirement of CHR criteria was explicitly discouraged in recent recommendations for diagnosing a CHR state within the framework of the EPA Guidance project[19].

### *The CHR state as a precursor state of psychoses*

Four subjects developed psychosis within 2 years; *i.e.*, 0.7% of the whole sample ($n$ = 539) and 1.2% of the 2-year follow-up sample ($n$ = 331). These numbers are higher than the reported annual incidence rate in the community of this age of 0.1%[91]. Conversions to psychosis mainly occurred in inpatients, of whom 1.0% converted to psychosis compared to just 0.4% in the community sample. Three quarters of the few conversion-to-psychoses cases occurred in the inpatient sample, in which also the non-CHR-related conversion occurred, and three quarters of converters had met CHR criteria at baseline. Thus, with conversion rates between 6.5% across all CHR subjects at baseline, and 11.5% for CHR subjects with a 2-year follow-up, the 2-year conversion rates within CHR subjects were within the range of pooled conversions rates reported for child and adolescent CHR samples of early detection services of 9.5%[19]. At this, our conversion rates were slightly higher than the 3-year conversion rates reported for 16–40-year-olds of the community that were 4.7% for all five CHR criteria and 11.1% for the three EPA criteria[92].

Of note, the effect sizes of the association of CHR criteria at baseline with subsequent conversion to psychosis were the highest of all reported effect sizes, approaching a moderate effect size in case of the two-year follow-up sample (Cramer's V = 0.276).

### *Strengths and limitations*

Our study has several strengths and limitations. Clear strengths include the large sample size, the CHR assessment with well-established instruments, and the thorough training in and supervision of the assessment of CHR symptoms and criteria in order to minimize rater and center effects, and to maximize interrater reliability. Furthermore, in order to reduce a potential systematic assessment bias due to the impossible blinding of raters to groups, the inpatient and community sample was assessed by different interviewers. Another strength is the inclusion of a severely ill inpatient sample with main disorders that had been reported to be related to an increased prevalence of schizophrenia in adulthood [37] (Supplementary Table 1). Thus, our inpatient sample – in theory – was biased towards reporting increased rates of CHR symptoms and, consequently, towards revealing any transdiagnostic nature of CHR criteria and symptoms.

Limitations to our study are the mainly cross-sectional nature and the nonassessment of nonpsychotic mental disorders at follow-up. This would have allowed us to compare conversion rates to psychosis with conversion to, or persistence of other mental disorders, and would have allowed us to study the relationship of different mental disorders to the course of CHR criteria and symptoms.

The conduction of multiple analyses and the related nonadjustment for multiple testing might have been another possible limitation. Yet, as discussed already in the section "Data analysis", because all of our hypotheses assumed group differences, the type I error (alpha), *i.e.*, the rejection of a true null hypothesis, would have be become less likely, if we had corrected the alpha-level for multiple comparisons. However, even without correction for multiple testing, the null hypothesis was rarely rejected; this resulted in the main conclusion of a lack of a general group difference. This main conclusion would not have changed, had we corrected the alpha-level for multiple comparison and, consequently, had detected even fewer (and likely no) group differences. In light of this, the nonadjustment of the type I error can be regarded as the more conservative testing of the overall hypotheses assuming group differences. Additionally, the high power of the study, the ability to correctly reject a false null hypothesis assuming group equality, must be assumed to be uncompromised by the current nonadjusted analyses[50]. Thus, any adjustment for multiple testing would not have led

to a different conclusion. Furthermore, the conduction of multiple analyses had offered the advantage to detect any possibly robust pattern indicative of any one of the three examined alternative explanatory models of CHR states and symptoms.

## CONCLUSION

Overall, our results did not support the general predications that CHR criteria and symptoms would represent a pluripotent syndrome[27,28], a transdiagnostic risk factor[33], a transdiagnostic dimension of psychopathology[30], or even merely a marker for the severity of nonpsychotic states[30]. To that end, our data gave no support for a general diagnostic pluripotency of CHR symptoms and criteria that exceeds their undoubted and frequently demonstrated pluripotency for psychosis outcomes[55]. Furthermore, for lack of any clinically relevant, *i.e.*, at least moderate correlation with functioning, there was also no sufficient support for CHR symptoms and criteria as general severity markers of psychopathology. Indications of some transdiagnostic risk factors or dimension status with respect to eating, autism-spectrum, and anxiety and obsessive–compulsive disorders, however, were found for four CHR symptoms, two of them exclusive to COPER: *suspiciousness/persecutory ideas* (P2), *thought pressure*, *derealization* and *visual perception disturbances*. The fact that these indications did not extend to any CHR criterion highlights the importance of the additional requirements of CHR criteria on onset/worsening and occurrence for their potential specificity for the psychosis-spectrum. Indeed, with regard to the CHR criteria, we found the strongest, nearly moderate effect for their association with subsequent psychosis. This association, however, seems not strong enough to conclusively explain their role in children and adolescents by their psychosis-predictive potential.

Overall, our results more clearly indicate what CHR symptoms and criteria are *not* rather than *what* they are. Our results may support the view that CHR criteria should be regarded as a self-contained disorder or syndrome, similar to the proposition of the attenuated psychosis syndrome in DSM-5[93]. To evaluate this assumption, future community studies evaluating the effect of CHR criteria on help seeking and mental wellbeing are needed. If persons meeting CHR criteria generally suffer from their CHR symptoms, seek help for them, and/or experience disturbances in psychosocial functioning irrespective of, or in addition to, the effects of any other potential comorbid mental disorder, then CHR criteria would fulfil general criteria for mental disorders (defined as a clinically significant behavioral or psychological syndrome associated with disability and/or severe distress); and consequently, the assumption of a CHR Syndrome would be supported. Thus, further research on CHR symptoms and criteria, and their cause and meaning in children and adolescents is needed to better understand their significance in this age group, and to detect factors that convey their higher clinical relevance in adulthood.

## ARTICLE HIGHLIGHTS

### *Research background*

Many patients with clinical high-risk of psychosis (CHR) criteria do not develop psychosis, in particular if they are still in their childhood and adolescence. Therefore, CHR criteria were suggested to be not a risk indicator of psychosis development but (1) A pluripotential syndrome that will transform itself into all kinds of mental disorder; (2) A transdiagnostic risk factor from that all kind of different disorders develop; or (3) Simply a severity marker of mental disorders.

### *Research motivation*

The simple nonconversion to psychosis and the persistence or new-occurrence rate of nonpsychotic mental disorders in CHR samples, however, do not allow for the conclusion of any of the three alternative explanatory models, which might explain why they are often proposed interchangeably. Thus, to gain more insight into the nature of CHR symptoms and criteria, we examined the differential implications that each of these models has on the occurrence of CHR criteria and symptoms and their association with a proxy measure of illness severity in patients with severe mental disorders; *i.e.*, inpatients and community subjects. We expected that any pattern of group differences indicative of one of the alternative explanatory models should become particularly apparent in a child and adolescent sample, as CHR symptoms and criteria were reported to be more frequent but less clinically relevant and less associated with psychosis in children and adolescents compared to adults.

### *Research objectives*

Following a propositional logic approach, we examined which of the three alternative explanatory models of CHR criteria and symptoms would best fit our data. The three alternative explanatory models were associated with the following differential premises with respect to the data: (1) If CHR criteria and symptoms are more frequent in community subjects compared to inpatients, then they are likely

pluripotential. This has been assumed because a pluripotent syndrome would have transformed into a mental disorder and, thus, not be present in inpatients, but in a community sample wherein a proportion can be expected to develop a mental disorder in future; (2) If CHR criteria and symptoms are more frequent in inpatients compared to community subjects, then they likely represent a transdiagnostic risk factor or dimension. This has been assumed because they would aggregate in persons with mental illness; and (3) If CHR criteria and symptoms show a clinically relevant, significant negative correlation with functioning as a proxy measure of illness severity, then they likely represent a severity marker of psychopathology.

### Research methods

As part of the Bi-national Evaluation of At-Risk Symptoms in children and adolescents (BEARS-Kid) study, we cross-sectionally examined the frequency and severity of CHR criteria and symptoms in an 8–17-year-old randomly recruited sample of the Swiss community ($n$ = 233) and in 8–17-year-old inpatients ($n$ = 306) whose main diagnosis was a disorder that, earlier, had been associated with an elevated risk for psychosis in adulthood (obsessive compulsive and anxiety, attention deficit, eating, and autism-spectrum disorder) using $\chi^2$ and nonparametric analyses. Furthermore, the associations between psychosocial functioning, and CHR criteria and symptoms were analyzed with bivariate and partial correlation analyses, the latter controlling for group membership. CHR criteria and symptoms according to the ultra-high risk and the basic symptom approach were assessed in clinical interviews by trained psychologists using the Structured Interview for Psychosis-Risk Syndromes (SIPS) and the Schizophrenia Proneness Instrument, Child and Youth version (SPI-CY). Furthermore, we followed up 78.5% of the participants after 1 year, and 61.4% after 2 years past baseline for a conversion to psychosis.

### Research results

The 7.3% prevalence rate of CHR criteria in community subjects did not differ significantly from the 9.5% rate in inpatients. Frequency and severity of CHR criteria never differed between the community and the four inpatient groups. The frequency and severity of CHR symptoms differed between the community and the four inpatient groups only in four CHR symptoms: *suspiciousness/persecutory ideas* of the SIPS as well as tho*ught pressure*, *derealization* and *visual perception disturbances* of the SPI-CY. The persistent pattern of these differences was consistent with a transdiagnostic risk factor or dimension; *i.e.*, these symptoms were more frequent and severe in inpatients, in particular in those with eating, anxiety/obsessive–compulsive and autism-spectrum disorders. Furthermore, low functioning was – if at all – at most weakly related to the severity of CHR criteria and symptoms; the highest, yet weak correlation was for *suspiciousness/persecutory ideas*. Four participants had developed a psychotic disorder within two years past baseline. In doing so, the 2-year conversion rate in participants with CHR criteria was 11.5% and, the comparison of the conversion rate in participants with and without CHR criteria at baseline exhibited the highest, near moderate effect size of all comparisons.

### Research conclusions

This study was the first to systematically study alternative explanatory models for current CHR states, which propose that CHR criteria and symptoms would represent a pluripotent syndrome, a transdiagnostic risk factor or dimension, or even merely a marker for the severity of any mental disorder. The general lack of systematic differences in the frequency and severity of CHR criteria and symptoms between inpatients and community subjects, and the lack of a sufficiently strong association between functioning, and CHR criteria and symptoms did not support any of these alternative explanatory models. Rather, the strongest, though still only moderate effect was found for the association of CHR criteria and the subsequent development of a psychotic disorder within two years. This association, however, appears not strong enough to conclusively explain the role of CHR criteria and symptoms in children and adolescents by their psychosis-predictive potential. Thus, overall, our results more clearly indicate what CHR symptoms and criteria are *not* rather than indicating *what* they are.

Only four CHR symptoms – *suspiciousness/persecutory ideas* of the SIPS, and *thought pressure*, *derealization* and *visual perception disturbances* of the SPI-CY – exhibited a pattern of group differences indicative of a transdiagnostic risk factor, in particular with respect to eating, autism-spectrum, and anxiety and obsessive–compulsive disorders. Thus, their inclusion and definition in current CHR criteria should be critically examined in future studies.

### Research perspectives

Our results add to the growing support of the view that CHR criteria should be regarded as a self-contained disorder or syndrome. To more fully test this assumption, future community studies should evaluate the effect of CHR criteria on help seeking and mental wellbeing. If persons meeting CHR criteria generally suffer from their CHR symptoms, seek help for them, and/or experience disturbances in psychosocial functioning irrespective of, or in addition to, the effects of any other potential comorbid mental disorder, CHR criteria would fulfil general criteria for mental disorders in terms of a CHR Syndrome. Thus, further research on CHR symptoms and criteria, and their cause and meaning in children and adolescents is needed to better understand their significance in this age group, and to

detect factors that convey their higher clinical relevance in adulthood.

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## FOOTNOTES

**Author contributions:** Schultze-Lutter F and Schimmelmann BG designed the study; Walger P, Franscini M, Traber-Walker N, Flückiger R and Michel C were involved in the acquisition of data; Schultze-Lutter F and Michel C analyzed and interpreted the data for the work and drafted the first version of this work; all authors revised the article critically for important intellectual content, and agreed to the submitted version.

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ORIGINAL ARTICLE

Observational Study

# Spectrum of neuropsychiatric symptoms in chronic post-stroke aphasia

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## Abstract

### *BACKGROUND*

Neuropsychiatric symptoms (NPS) have been insufficiently examined in persons with aphasia (PWA) because most previous studies exclude participants with language and communication disorders.

### *AIM*

To report a two-part study consisting of a literature review and an observational study on NPS in post-stroke aphasia.

### *METHODS*

Study 1 reviewed articles obtained from PubMed, PsycINFO, Google Scholar and Cochrane databases after cross-referencing key words of post-stroke aphasia to NPS and disorders. Study 2 examined language deficits and activities of daily

living in 20 PWA (median age: 58, range: 28-65 years; 13 men) with the Western Aphasia Battery-Revised and the Barthel Index, respectively. Informants of these 20 PWA were proxy-evaluated with the Neuropsychiatric Inventory and domain-specific scales, including the Stroke Aphasia Depression Questionnaire-10 item version and the Starkstein Apathy Scale. In addition, an adapted version of the Hospital Anxiety and Depression Scale was directly administered to the PWA themselves. This observational study is based on the baseline assessment of an intervention clinical trial (EudraCT: 2017-002858-36; ClinicalTrials.gov identifier: NCT04134416).

***RESULTS***

The literature review revealed a broad spectrum of NPS in PWA, including depression, anxiety, apathy, agitation/aggression, eating and sleep disorders, psychosis, and hypomania/mania. These findings alert to the need for improving assessment and treatment approaches of NPS taking into consideration their frequent occurrence in PWA. Study 2 showed that the 20 participants had mild- to-moderate aphasia severity and were functionally independent. A wide range of comorbid NPS was found in the post-stroke aphasic population (median number of NPS: 5, range: 1-8). The majority of PWA (75%) had depressive symptoms, followed by agitation/aggression (70%), irritability (70%), anxiety (65%) and appetite/eating symptoms (65%). Half of them also presented symptoms of apathy, whereas euphoria and psychotic symptoms were rare (5%). Domain-specific scales revealed that 45% of participants had apathy and 30% were diagnosed with depression and anxiety.

***CONCLUSION***

Concurrent NPS are frequent in the chronic period of post-stroke aphasia. Therefore, further research on reliable and valid assessment tools and treatment for this aphasic population is strongly warranted.

**Key Words:** Aphasia; Stroke; Neuropsychiatric symptoms; Anxiety; Apathy; Depression

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**Core Tip:** The literature on neuropsychiatric disorders in persons with aphasia (PWA) is limited, given that this population is usually excluded from neuropsychiatric evaluations. This article provides a state-of-art analysis on the prevalence, nature, pathophysiology, assessment, and treatment of neuropsychiatric symptoms (NPS) in PWA. We also report findings from a proof-of-concept observational study that included 20 PWA after chronic left hemisphere lesions which identified a spectrum of NPS, primarily depression, irritability, agitation, anxiety, and apathy.

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## INTRODUCTION

Aphasia, defined as the partial or complete loss of language caused by brain damage is one of the most frequent and devastating sequelae of stroke[1-3]. In fact, about 21% to 38% of acute stroke individuals have aphasia[1] and 25% to 50% of them still show residual language and communication deficits in the chronic period[4]. Before focusing on neuropsychiatric symptoms (NPS) associated with post-stroke aphasia (PSA), below we present a brief overview on the impact of aphasia in the acute and chronic stroke periods as well as the traditional and emerging evaluation approaches used to classify language deficits and to implements adequate therapies.

### *Overview on PSA*

PSA may be associated with worse outcomes in acute/subacute (onset to week 12), chronic (week 13-week 52) and very chronic (week 53 onwards) periods than strokes unassociated with aphasia[5,6]. This is the consequence of the increased length of hospital stay and inpatient medical complications, including those caused by the neurological disability itself. The course of aphasia during the sub-acute and chronic stroke periods may also be complicated by reduced functional independence, longer stays

in rehabilitation settings, reduced adherence to aphasia therapy, particularly in older people, and poorer quality of life and activities of daily living[1,5,6].

Stroke lesions causing aphasia usually affect the left hemisphere (dominant for language in most right handed individuals) in the distribution of the middle cerebral artery territory with damage to the perisylvian language core and its subcortical structures (basal ganglia, internal capsule and white matter). The resulting syndromes are chiefly characterized by impaired repetition in the context of impaired spontaneous speech, and variable deficits in auditory comprehension and naming. These syndromes are known as the "classical" or "perisylvian" aphasias (Broca's, Wernicke's, conduction and global) which roughly account for 80% of all cases and have poorer prognosis than other types of aphasias[7]. The rest of post-stroke aphasic syndromes, representing 20% of all cases, are associated with infarctions in arterial "borderzone" vascular territories (*i.e.*, the junction between anterior and middle cerebral arteries). These aphasias (motor, sensory and mixed transcorticals and anomic) are characterized by preserved repetition and echolalia with variable deficits in other language domains (spontaneous speech, comprehension and naming) and usually have better long-term prognosis than perisylvian aphasias[8]. Whereas infarctions account for around 80% of cases, hemorrhages are less frequent[1]. The clinical profile of acute and chronic PSA is heterogeneous with a variable degree of involvement of phonology, semantics, fluency and connected speech production. Traditional classifications of aphasia dichotomically separate syndromes (*e.g.*, Broca's, Wernicke's, transcortical) on the basis of differences in surface language deficits (fluent/nonfluent speech, impaired/preserved comprehension). In spite of this coarse division, the syndrome-based approach (*e.g.*, Broca's aphasia) is still retained in clinical practice to predict prognosis, manage recovery in acute clinical settings, and inform patients and relatives[1]. However, using this approach the aphasia profile in more than a quarter of stroke patients is unclassifiable and there is no clear-cut correspondence between lesion location and aphasia profile particularly in chronic cases. Even more important is that clinical labels (*e.g.*, Broca's aphasia) provide little information on the underlying language and cognitive deficits and knowing the status of these deficits is crucial to select adequate model-based therapies. Therefore, since understanding the neural mechanisms underpinning language processing is important for diagnosis and treatment, current accounts use data-driven approaches for aphasia classification and lesion-based predictions of recovery[9,10]. Moreover, it is well known that persons with aphasia (PWA) have an increased incidence of NPS compared to patients with other chronic diseases[2,11], greatly influencing rehabilitation responses, quality of life, and long-term functional outcomes[12-15]. In general, NPS are a frequent and challenging consequence of stroke, derived from the crossroad of lesion-related brain factors and psychological distress related to the event and its functional impact in daily life[16,17]. Several comprehensive reviews dealing with NPS in post-stroke patients have been reported[18-22] and a recent original study evaluating 518 non-aphasic stroke patients found that half of the sample presented at least one NPS based on Neuropsychiatric Inventory (NPI)[23,24]. However, one relevant limitation of the above studies is that they exclude aphasic participants due to the inherent linguistic-assessment difficulties[25-29]. The aims of the present study were thus twofold. In study 1 the objective was to carry out a narrative review on NPS in PSA, covering data of prevalence, risk factors, assessment tools, pathophysiology, and treatment options. Study 2 reports original data from 20 PWA in the chronic phase after suffering a left hemisphere lesion who were evaluated with the NPI and domain-specific psychiatric scales to examine the frequency and severity of NPS.

## MATERIALS AND METHODS

### *Study 1: Literature review*

**Search strategy:** The authors conducted a literature search on Medline/PubMed, PsycINFO, Google Scholar and Cochrane databases from inception to June 2021. Key search terms for NPS or disorders were cross-referenced to PSA. The following terms were included: "aphasia" or "PSA" or "acquired language impairment" or "acquired language disorder" or "post-stroke linguistic disorder" or "post-stroke linguistic impairment" AND "neuropsychiatric*" or "neuropsychiatry" "psychy*" or "neurobehav*" or "behavio[u]r*" or "emotion*" or "mood" or "affect*" or "depression" or "depressive" or "dysthym*" or "distress" or "apathy" or "apathetic" or "motivat*" or "drive" or "indifferen*" or "anxiety" or "anxious*" or "stress" or "phobia" or "fear" "catastrophic reaction" or "disinhibit*" or "impulsiv*" or "agitat*" or "aggress*" or "anger" or "irritab*" or "psycho*" or "hallucination" or "delusion" or "delusive" or "prodrom* or "sleep" or "appetite" or "eating" or "elation" or "pathological laugh*" or "euphoria" or "mania" or "bipolar" or "quality of life". Articles including the terms "stroke" or "post-stroke" or "cerebrovascular" AND "neuropsychy*" or "neurobehav*" or "emotion" or "depression" were also screened for aphasia terms within its full text and considered for inclusion. This search strategy was analogous to other published reviews on post-stroke depression[30,31].

Titles, abstracts, and full texts were reviewed by 2 independent observers (MB and LE) to assess inclusion criteria and read the selected articles for final incorporation. In addition, references of all

selected articles were searched for studies that could also meet inclusion criteria. Possible investigator divergences were compared and resolved through discussion. A third observer (GD) was available for an appeal if disagreements existed. Studies were included if: (1) Participants had a clear assessment of aphasia and presented a single or multiple NPS or disorders; (2) NPS or disorders were assessed with validated scales or through clearly defined criteria; (3) participants were adults (*i.e.*, 18 years or older); (4) participants were only affected by cerebrovascular lesions; and (5) articles were written in English.

This narrative review prioritized manuscripts in the following order: (1) Meta-analysis or systematic reviews; (2) randomized clinical trials; (3) cohort studies; and (4) case-reports. When only case-reports were retrieved, articles including neuroimaging measures were prioritized. Studies including participants with pre-stroke neurodegenerative (*e.g.*, primary progressive aphasia, dementia) or premorbid psychiatric disorders that would make differential diagnoses difficult were excluded from the search.

### *Study 2: A proof-of-concept study of neuropsychiatric symptoms in chronic post-stroke aphasia*

**Study design and subject selection:** The focus of this study was the assessment of the frequency of NPS at baseline of an intervention trial in PWA after stroke (EudraCT:2017-002858-36; ClinicalTrials.gov identifier: NCT04134416). The study included 20 chronic PWA (median age of participants: 58, range: 28-65 years; 13 men) evaluated at the Unit of Cognitive Neurology and Aphasia at the University of Malaga, Spain. A consecutive series of participants meeting the following criteria were included: (1) Age between 18 and 70 years; (2) right handedness (80 points in the Edinburgh handedness inventory)[32]; (3) Spanish as native language; (4) left-hemisphere stroke lesions; and (5) diagnosis of aphasia established by a score in the aphasia quotient (AQ) of the Western Aphasia Battery-Revised (WAB-R) ≤ 93.8 points[33]. Exclusion criteria were: (1) Dysarthria without aphasia; (2) bilateral lesions; (3) increased risk of a new stroke or unstable neurological condition (*e.g.*, transient ischemic attacks); (4) history of pre-stroke dementia and/or psychiatric disorders (schizophrenia, major depression, bipolar disorder, anxiety disorders); (5) alcohol and substance use or abuse; or (6) coexistence of aphasia with post-stroke dementia. Table 1 shows the demographic and clinical characteristics of the group. Participants with aphasia also underwent comprehensive neurological, neuropsychological, and neuroradiological assessments. Participants who were taking psychotropic drugs (antidepressants or tranquillizers) and/or antiepileptics were not excluded, but all prescribed medications were maintained stable during the study. Written informed consent was obtained from all participants and informants after providing detailed descriptions of the study. None of the participants or informants refused to take part in the investigation. The study was performed in accordance with the Declaration of Helsinki and approved by the Ethical Research of Drugs Committee Provincial of Malaga, Spain and the Spanish Drug and Healthcare Products Agency.

**Functional evaluation:** The Barthel Index was employed to measure the degree of assistance required by each person on 10 items of mobility and self-care regarding activities of daily living. A higher score (maximum: 100 points) reflects a better competence to function independently[34].

**Language evaluation:** The type and severity of aphasia were evaluated with the WAB-R[33]. The profile of aphasia was made according to the taxonomic criteria of the WAB-R and aphasia severity was rated according to the scoring of the AQ of WAB-R. Lower AQ scores indicate more severe aphasia.

**Multidomain neuropsychiatric evaluation:** Relatives in close contact with participants were interviewed using the NPI[24]. Although this semi-structured interview was originally developed to evaluate the spectrum of NPS in patients with dementia, its use has later been expanded to assess people with stroke and other neurological conditions[23,35-37]. The NPI assesses the frequency and severity of psychological and behavioral symptoms grouped into 12 categories: delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, appetite, and sleep/nighttime disturbances. The questions pertain to changes in the patient's behavior since the onset of the stroke and, if so, whether the altered behavior was present during the last month. For the purpose of this study, the presence of symptoms was determined by the number of patients with scores > 0 in the respective symptom[23]. Frequency scores range from 1 to 4 (where 1= occasionally, less than once per week; 4 = very frequently, once, or more per day or continuously). Severity scores range from 1 to 3 (where 1 = mild, 2 = moderate, 3 = severe). Each domain´s final composite score is the product of the frequency times the severity, with a maximum score of 12 points.

**Domain-specific neuropsychiatric evaluation:** Since the NPI does not provide specific cut-off scores for neuropsychiatric diagnoses, domain-specific scales that specifically assessed depression, anxiety, and apathy disorders were also used. These scales were selected because all of them have previously been used in patients with stroke[38-40]. After data interpretation, neuropsychiatric diagnoses were blindly assessed by an expert behavioral neurologist who was blinded to the outcome goals of this study.

**Hospital Anxiety and Depression Scale:** The Hospital anxiety and depression scale (HADS) is a 14-item instrument evaluating both anxiety and depression (seven items for each subscale)[39]. For each

**Table 1 Demographic and clinical characteristics of persons with aphasia**

| Patient | Sex/handedness | Age (yr) | Education (yr) | Stroke duration (mo) | Barthel index[1] | Lesion volume ($cm^3$) | Aphasia type[2] | Antidepressants |
|---|---|---|---|---|---|---|---|---|
| 1 | F/R | 50 | 12 | 80 | 80 | 113.33 | Conduction | Sertraline |
| 2 | M/R | 61 | 14 | 103 | 90 | 163.02 | Broca | Citalopram |
| 3 | M/R | 49 | 17 | 61 | 90 | 210.38 | Broca | No |
| 4 | M/R | 42 | 11 | 45 | 100 | 99.31 | Anomic | Citalopram |
| 5 | M/R | 63 | 8 | 11 | 85 | 23.16 | Conduction | No |
| 6 | F/R | 58 | 12 | 126 | 95 | 188.76 | Anomic | No |
| 7 | M/R | 60 | 12 | 45 | 60 | 44.96 | Anomic | No |
| 8 | M/R | 54 | 14 | 44 | 90 | 66.97 | Anomic | No |
| 9 | M/R | 51 | 13 | 7 | 80 | 225.69 | Anomic | Amitriptyline |
| 10 | M/R | 54 | 10 | 19 | 90 | 282.59 | Wernicke | No |
| 11 | F/R | 58 | 15 | 66 | 95 | 98.84 | Broca | No |
| 12 | F/R | 61 | 12 | 17 | 45 | 4.47 | Anomic | Sertraline |
| 13 | M/R | 32 | 18 | 10 | 100 | 34.01 | Wernicke | Sertraline |
| 14 | M/R | 49 | 8 | 13 | 80 | 17.45 | Anomic | No |
| 15 | F/R | 28 | 8 | 6 | 100 | 51.26 | Anomic | No |
| 16 | F/R | 65 | 17 | 13 | 100 | 26.10 | Wernicke | No |
| 17 | M/R | 64 | 17 | 120 | 100 | 157.58 | Anomic | No |
| 18 | F/R | 65 | 17 | 13 | 75 | 158.25 | Broca | No |
| 19 | M/R | 58 | 8 | 17 | 100 | 69.66 | Wernicke | No |
| 20 | M/R | 63 | 17 | 10 | 100 | 50.43 | Wernicke | Fluoxetine |
| Median | | 58 | 12.5 | 18 | 90 | 84.25 | | |

[1]Barthel Index measures participant´s independence in activities of daily living;
[2]Type of aphasia was obtained from fluency, comprehension, and repetition subtest of the Western Aphasia Battery-Revised.
F: Female; M: Male; R: Right-handed.

statement, the participant chooses one of four responses (*e.g.*, 'definitely as much', 'not quite as much', 'only a little', 'hardly at all')[39]. Scores for each subscale range from 0 to 21 points and a cut-off scores of 8 points are used for each scale. In the present study, the HADS was directly administered to the PWA. To overcome comprehension deficits of participants, each question together with the alternative responses were printed in large font letters on individual pages and the items were read aloud by the examiner who then scored a reliable answer. Cronbach's alpha for HADS-Anxiety varies from 0.68-0.93 and for HADS-Depression from 0.67-0.90[41].

**Starkstein Apathy Scale:** This scale was developed to assess apathy in patients with neurological diseases including stroke[40,42]. Informants of the participants were requested to answer the Starkstein Apathy Scale (SAS)'s 14 items, each of which scores on a 0–3 scale[40]. The cut-off score of the SAS is 14 (maximum score 42) and higher scores indicate more severe apathy. The scale has an excellent Cronbach's α of 0.939[43].

**Stroke Aphasia Depression Questionnaire:** The stroke aphasia depression questionnaire (SADQ)-10 was developed to assess depressed mood in patients with aphasia[38]. It contains 10 items answered on a 0-3 scale by the principal informant on behalf of the PWA. The cut-off score of the SADQ-10 is 14 points (maximum score 30)[44]. Participants are classified as having depression when they score ≥ 14 points[38], or classified with subthreshold depression[45] when the SADQ-10 score is ≥ 6[46]. The questionnaire has an excellent internal consistency, with a Cronbach's alpha of 0.80 and split-half reliability of $r = 0.81$[44].

### Statistical analysis

We computed descriptive statistics for demographic and clinical data. In addition, non-parametrical two-tailed Spearman's correlations on NPI scores and domain-specific instruments (AS, HADS and SAQ21) were performed. Statistical analysis regarding the number of NPS based on demographic and clinical variables were obtained with non-parametric independent samples Mann-Whitney U test and Kruskal-Wallis test. All statistical tests were two-tailed, and the significance threshold was set at $P < 0.05$. Analyses were carried out using SPSS v.21 and JASP (2020) software.

### Lesion overlap

For the purpose of the current study, only $T_1$-weighted magnetic resonance images (MRI) were acquired at the baseline assessment to delineate the lesion of each participant with aphasia. The MRI sequence was acquired on a 3-T MRI scanner (Philips Intera, Amsterdam, The Netherlands), Release 3.2.3.4, with a MASTER gradient system (nominal maximum gradient strength = 30 mT/m, maximum slew rate = 150 mT/m/ms), equipped with a six-channel Philips SENSE head coil. Lesions were manually drawn in native space by DL-B and MJT-P, who were blind to all clinical data outcomes at the moment of the lesion delineation. Lesion maps were drawn by using Mricron software[47] on a slice-by-slice basis. Lesion overlap maps were created as follow: first, individual lesion maps and $T_1$-weighted images were reoriented according to the anterior commisure. To achieve optimal normalization of the lesions and the $T_1$-weighted images, cost function masking was applied during the preprocessing[48]. $T_1$-weighted images after masking out individual lesions were segmented into different tissues and the resulting parameters were used to normalize both the $T_1$-weighted images and the lesion masks to Montreal Neurological Institute space. Normalized lesion masks were smoothed with a 3 mm FWHM kernel and binarised. The overlap of the resulting binarised masks was performed with ImCalc. All these processing steps were performed with SPM12 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/software/spm12).

## RESULTS

### Study 1: Literature review

One hundred fourteen articles covering PSA and NPS (disorders) were included in this narrative review. The studied publications focused primarily on assessment/diagnosis of depression and anxiety ($n$ = 34/29.8%) and on intervention approaches ($n$ = 24/20.5%). Few articles covered prevalence data of NPS in PWA ($n$ = 6/5.2%), risk factors ($n$ = 5/4.2%) or pathophysiological mechanisms ($n$ = 7/6.1%). Over half of all articles covered depression ($n$ = 60/52.6%), 21 articles (18.4%) examined anxiety, and 12 articles (10.5%) referred to quality of life in PWA. Systematic reviews and meta-analysis accounted for 16.6% of all included articles ($n$ = 19). Below, we present the synthesis of published data on depression, anxiety, apathy, agitation/aggression, mania, and psychosis.

**Depression:** The co-occurrence of stroke and aphasia is a stressful life event resulting in mood alterations and depression[11]. In fact, post-stroke depression has been identified as one of the most frequent and long-term sequela of PWA[11,26,49,50]. The disorder is categorized in the diagnostic and statistical manual for mental disorder-fifth edition (DSM-5) as "mood disorders due to another medical condition" such as stroke with depressive features, major depressive-like episode, or mixed-mood features (simultaneous depression and manic features)[30,51]. A diagnosis of major depression includes depressed mood and/or anhedonia/Loss of interest alongside four other symptoms (weight loss/gain, insomnia/hypersomnia, psychomotor agitation/retardation, fatigue, feelings of worthlessness, diminished concentration, and suicidal ideation) lasting for two or more weeks, and having an impact on daily functioning[51].

Depressive symptoms are associated with communication impairments following stroke, but the prevalence of depression in PWA is seldomly reported[26,28,45,52]. However, if any NPS are reported in PWA it is usually depression. Prevalence of this disorder ranges from 52%[53] to 62%[54] of PWA one year post-stroke, and this incidence is higher than in the overall stroke population[53-56]. As for risk factors, the presence of aphasia augments the chance of developing depressive symptoms[21,29,53,54]. Moreover, depressive symptoms may account for a significant variance in functional communication after acquired aphasia[57] and persons with Broca's aphasia (non-fluent verbal production with mild impairment in comprehension) are almost 9 times more likely to suffer depression compared to Wernicke's patients (fluent speech with impaired auditory and reading comprehension)[58]. Regarding aphasia evolution, Herrmann *et al*[59] compared single left-sided acute to chronic PWA and depression and found no significant between-group differences on depression sum-scores, age, sex, or severity of hemiparesis. On the other hand, Kauhanen *et al*[60] stated that aphasia increases the risk of developing depression in the chronic phase of stroke (> 6 mo of evolution)[60].

In the absence of suitable biological markers, the assessment and diagnosis of depression must rely on the results of clinical evaluations and psychometric testing[61]. To date, only a handful of instruments for the assessment of clinical depression in PWA have been proposed[26,62,63]. Among the

most common are the SADQ-21 and its shortened version (SADQ-10)[38], the Aphasic Depression Rating Scale[64], the Signs of Depression scale[65], or the Depression Intensity Scale Circles[66]. Non-verbal measurements, such as the Dynamic Visual Analogue Mood Scale[67] represent an important step forward in assessing mood in people with language impairments[68] while objective acoustic measures related to affective state change in the speech of PWA are also being developed[69]. On the other hand, the ROMA consensus statements highlight the general health questionnaire-12 for the assessment of emotional wellbeing in PWA[70] In addition, in PWA showing mild deficits in auditory comprehension, it is feasible to use well-known testing scales (*e.g.*, Beck Depression Inventory, the Hamilton Depression Rating Scale or the HADS[27,71-73]).

Causal factors of depression after stroke are probably multifactorial. Alterations in monoamine neurotransmitter systems, higher levels of glutamate in the synaptic cleft, hypothalamic–pituitary–adrenal axis abnormalities, anomalous neurotrophic responses, and an excess of proinflammatory cytokines have all been linked to the pathogenesis of depression after stroke[26,31,74]. The idea that the risk of depression after stroke is influenced by lesion location is still controversial[75]. The hypothesis was first proposed over 30 years ago by Robinson's group reporting that left-hemisphere strokes, especially in frontal region, were associated with depressive disorders[76,77]. Many replication studies have been carried out since then, but results remain inconclusive. Systematic reviews performed by Carson *et al*[78] and Wei *et al*[79] found no support for a higher frequency of depression in frontal left-hemisphere stroke lesions. As Wei *et al*[79] discuss, most patients with severe aphasia are excluded from studies, and the frequency of depression in left-hemisphere patients may be underestimated. However, a multivariate lesion-symptom mapping study found a significant association between the severity of depression scores and lesions affecting the left dorsolateral prefrontal cortex in 39 PWA and chronic stroke[80]. Therefore, a coherent explanatory model, able to integrate the underlying pathophysiological mechanisms of depression in PWA, still remains to be formulated.

Therapeutic interventions to alleviate depression in PWA are still scarce[81]. In fact, less than one percent of PWA receive direct treatment for psychological distress[82]. In a systematic review of rehabilitation interventions for the prevention and treatment of depression in PWA Baker *et al*[83] highlight that PWA with mild depression may benefit from psychosocial-type treatments, whereas no evidence was found for the treatment of moderate to severe depression. A systematic review by Wray *et al*[84] for self-management interventions (*i.e.*, decision-making, problem solving, goal setting) could also not clarify whether these approaches were suitable for PWA, especially with moderate or severe aphasia. More recent reports show that the employment of two weeks of Intensive Language-Action Therapy has proven effective in reducing not only language deficits but also low mood in persons with fluent and non-fluent aphasias[71,85]. This is in line with Baker *et al*[83]'s statement, who suggested that treatment strategies for the improvement of physical, cognitive and communication functions can have a beneficial effect on both rehabilitation and depression outcomes in PWA. A randomized controlled trial for PWA, comparing behavioral therapy and usual care with a usual care control, showed significant improvement of affective symptomatology in the experimental group at three and six months post-intervention[86]. The development of solution-focused psychotherapy approaches, in addition to behavioral activation therapies, specifically tailored for PWA are also under way[82,87,88]. No studies have been published about the pharmacological treatment of depressed PWA. Neuromodulation techniques, such as transcranial direct current stimulation or repetitive transcranial magnetic stimulation have shown promise for the treatment of depression in PWA[89-91].

**Anxiety:** Adult anxiety comprises a class of conditions that includes generalized anxiety disorder, panic disorder, and phobias[51,92]. In the context of PWA, the DSM-5 classifies these conditions as anxiety disorders due to another medical condition[51] and clinical criteria are disproportionate fear, apprehension of danger, restlessness and day-to-day distress[93-95]. PWA regularly report feeling anxious when employing language to communicate[96]. In some patients, anxiety during language testing can escalate quickly to frustration, transient bursts of tears, eventually leading to requests of interrupting testing (catastrophic reactions)[97-99]. Such reactions are usually associated to non-fluent aphasias due to anterior left-hemisphere or basal ganglia lesions[100,101]. It is noteworthy that anxiety has received comparatively less attention in PWA than depression[94,101]. Impairments in the ability to communicate is one the most significant sources of stress for PWA[102,103]. To date, the prevalence of anxiety among PWA is estimated to be around 44%, in contrast to the 18%-25% of stroke survivors without language disorders[94,104,105]. Schöttke *et al*[106] however, find a slightly lower prevalence of both anxiety (29%) and depression (38%) in acute PWA and people with post-stroke anomia. As for risk factors, Pompon *et al*[107] indicates that PWA are at higher risk for experiencing chronic stress, which, in turn, is associated with increases in depression and anxiety.

Cahana-Amitay and colleagues (2011) coined the term "linguistic anxiety", to describe a person in whom the deliberate, laborious production of language precipitates the apprehension of committing an error, with the anticipation of linguistic failure serving as the trigger[96,108]. Even in mild aphasia, language-based anxiety can interfere with task performance[108]. Indeed, stress reactivity is considerably higher during linguistic in comparison to non-linguistic tasks[55,94,103] and higher anxiety and stress responses are related to non-fluent aphasias[96,102]. PWA also show heightened physiological arousal and anxiety scores in general compared to stroke patients without aphasia[94,109].

Post-stroke anxiety is assessed *via* questionnaires and/or clinical interviews and PWA are ordinarily excluded from anxiety evaluations[94,104] as scales to assess post-stroke anxiety in aphasia have not yet been developed and validated[104]. Usually, modified versions of the Behavioural Outcomes of Anxiety Scale[110], the HADS[39], the Generalized Anxiety Disorder-7[111], or the Burden of Stroke Scale[112] are employed to rate anxiety in PWA. In addition, the NPI can be proxy-administered[35].

One potential psychological mechanism underlying linguistic anxiety is the overfocus on the language testing (area of worry), coupled with reduced attentional functions. The patient's fixation on his/her impaired language performance reduces the ability to follow language assignments, which is signaled by heightened physiological stress responses such as heart rate and skin conductance[96,108]. Premorbid personality traits (self-demand attitude, perfectionism) may also favor the emergence of anxiety in PWA[103]. The pathophysiological mechanisms involved in post-stroke anxiety in PWA remain unknown as there are few studies that explore the physiological stress responses in PWA during language examination[96]. An extended cortical and subcortical network was proposed to be involved in the regulation of stress and anxiety responses, including the reticular system of the brainstem, limbic structures (amygdala), and the frontal lobe, activating both the autonomic nervous system and the hypothalamus-pituitary-adrenal axis[96,108]. However, a recent meta-analysis studying post-stroke anxiety and lesion location found no strong associations[104]. Recently, Ryan *et al*[113] reported a systematic review of non-pharmacological treatment interventions for anxiety in PWA. The authors did find 10 studies (5 randomized controlled studies) and none of them showed significant improvement of anxiety outcomes in PWA[113]. Torres-Prioris *et al*[103], stressed the usefulness of including adequately trained laypersons/carers in the evaluation and treatment of PWA to overlook the "white coat" effect. Affected individuals usually show reduced anxiety levels towards familiar people in both evaluation and rehabilitation[103]. A beneficial role of the β-blocker agent propranolol in naming has been suggested[114,115]. It is possible that this agent improves anomia by exerting its anxiolytic effects[115, 116].

**Apathy:** Apathy is defined as a multidimensional syndrome of diminished goal-directed behavior, emotion and cognition resulting in a loss of initiative, decreased interaction with their environment, and interest in social life[117-119]. However, the DMS-5 does not categorize apathy as an independent mental illness but as an incipient symptom in other psychiatric and neurocognitive disorders (*e.g.*, energy loss in major depressive disorder)[51]. The prevalence of apathy in PWA is currently unknown as a previous meta-analysis covering post-stroke apathy could not provide any specific data for the aphasic population[120]. However, Kennedy *et al*[121] evaluated 19 acute PWA with the Apathy Inventory-Clinical Scale[122] and found that 53% of the sample was apathetic[121]. In fact, during the acute post-stroke phase, aphasia correlates with apathy severity and PWA are also less likely to show resolution of such motivation deficits[121]. Apathy is usually proxy-assessed through the SAS[40], the Apathy Evaluation Scale[123], the Apathy Inventory-Clinical Scale[122] or the Dimensional Apathy Scale[124] in addition to the NPI[24]. Actigraphy records from an unaffected arm may serve to measure poststroke apathy in PWA, but should not be used alone[125]. Crucial brain structures for motivated behavior in healthy people include fronto-striatal circuits (including the nucleus accumbens), the dorsal anterior cingulate and the orbitofrontal cortex[126,127]. On the other hand, Starkstein *et al*[128] recently reviewed the neuroimaging literature and found that lesions of the basal ganglia are the most common correlates of apathy in stroke. However, no studies have specifically evaluated the neuroimaging correlates of apathy in PWA. In addition, there is a lack of high-quality evidence to guide management of post-stroke apathy[117,120,129] and only one case report described the improvement of apathy and behavioral disinhibition with transcranial direct current stimulation combined with speech-language therapy in patient with severe non-fluent aphasia[91]. The recent Canadian Stroke Best Practice Recommendations specifically endorses to offer nonpharmacological interventions, such as exercise and music therapy, to stroke patients with marked apathy (with or without clinical depression), but not special recommendation were given for PWA[130]. Ideally, treatment would begin soon after stroke, as apathy limits the patients' ability to participate in the intensive rehabilitation programs.

**Agitation and aggression:** Agitation, inability to control anger and aggression are observed symptoms in PWA[22,36,131]. Anger represents an emotional reaction, whereas aggressiveness is understood as the subsequent behavioral reaction[132]. As everyday functional communication is reduced in PWA, they can become frustrated, less tolerant and irritable, getting easily angry regarding trivial matters [133]. The study of aggression in PWA has traditionally been difficult, and only few articles have been published[132,134-137]. However, it seems that aphasia is associated with higher levels of anger, as well as loneliness and social isolation[131,132]. Angelelli *et al*[36] observed three times more risk of agitation in PWA and four times more risk of being irritable than those with normal language. Another study evaluating anger in acute stroke patients found that 31% of participants with aphasia ($n$ = 26) were irritable and aggressive[134]. A more recent study, evaluating anger in acute stroke, found that half of PWA ($n$ = 26) and 10 dysarthric participants ($n$ = 44) displayed anger[135]. On studying mild post-stroke aphasia, Choi-Kwon *et al*[138] found that lesion location was not related to anger. However, participants with moderate to severe aphasia were excluded, thus biasing the results. There are no validated questionnaires for the assessment of anger in PWA. Instruments employed to evaluate anger in non-aphasic population include the state-trait anger expression inventory-2 or the modified Spielberger trait

anger scale[139]. In addition, there are no studies targeting the pathophysiology or treatment of agitation and irritability in PWA.

**Hypomania/mania:** Elevated mood, hypomania and mania are seldomly reported in PWA, except in aphasic patients with posterior left hemisphere strokes[140]. Mania is defined as an abnormally and persistently raised expansive or irritable mood, thought and speech acceleration, lack of insight, overactivity, and social disinhibition[141]. In the context of PWA, the DSM-5 classifies these conditions as bipolar and related disorders due to another medical condition[51]. In a study conducted by Signers *et al*[140], one-fifth of participants with chronic fluent aphasia and posterior left hemisphere lesions were elated (a state of extreme happiness or excitement[142]) and unaware of their language impairment[140]. By contrast, elation has not been described among patients with non-fluent aphasia [143], except in a case of mixed transcortical aphasia associated with hypermusia, musicophilia, and compulsive whistling[144]. It seems that mania after left hemisphere damage is rare and according to the sparse published information it is difficult to describe its demographic, clinical and prognostic characteristics[141]. To date, only case reports have been published on mania in PWA[145-147]. These studies suggest that the onset of mania may be delayed up to two years post-stroke[148]. Manic states following stroke are often difficult to treat as brain damage and comorbidities enhance adverse effects and impair efficacy of some antimanic agents[149]. Case reports of post-stroke mania in non-aphasic stroke patients have found lithium, anticonvulsant mood stabilizers (valproate or carbamazepine), atypical antipsychotic drugs (olanzapine, aripiprazole, risperidone), clonazepam and clonidine to be effective[150,151]. However, there are no studies of treatment of hypomania and mania in PWA.

**Psychosis: Delusions and hallucinations:** Post-stroke psychosis involves the presence of delusions and/or hallucinations[152]. Within the context of PWA, the DSM-5 classifies this conditions as psychotic disorder due to another medical condition[51]. The development of psychosis is considered to be among the most devastating post-stroke syndromes[153]. Delusions in PWA are not rare. Shehata *et al*[55] evaluated 30 PWA and 31 non-aphasic stroke patients with the Eysenck Personality Questionnaire and found that psychosis was more prominent in PWA. Another study found that 28 PWA out of 61 chronic participants developed delusions, being mostly of persecutory nature[140]. The symptoms were found to be more common with posterior left hemisphere lesions[140], particularly in patients with Wernicke´s aphasia[154], who are more paranoid and aggressive[19,155,156] than patients with anterior lesions who instead may become more frustrated and depressed[133,140]. A detailed language evaluation of Wernicke's aphasia is desirable because characterization of speech and language deficits can be misinterpreted as psychotic speech disorder[157-159]. Potential explanations for this relationship may include auditory comprehension deficits with misinterpretation of information, in addition to anosognosia for aphasia and psychosis. Up to now, the pathophysiological mechanisms underlying psychosis in PWA are unknown, in part, because these patients are excluded from stroke studies on NPS[25,152]. Treatment approaches for psychosis in PWA are also not currently known. Antipsychotic medication is the main treatment for stroke patients[152] as poststroke and primary psychosis may likely reflect a common mechanism[152,160] but further research is strongly needed for PWA.

### *Study 2: A proof-of-concept study of neuropsychiatric symptoms in chronic post-stroke aphasia*

**Demographic and clinical data:** Demographic and clinical data of participants are shown in Table 1. The Barthel Index indicated that most PWA were functionally independent, with a median score of 90 points (range: 45-100). Only one participant (subject 12) with anomic aphasia and a dense right hemiparesis showed high dependency regarding activities of daily living (Barthel Index: 45 points). All participants were in the chronic phase of stroke evolution with a median duration of 18 mo (range: 7-126). Results indicate that 9 patients were diagnosed with anomic aphasia (77.3 ± 6.2 points on the AQ of WAB-R), 5 with Wernicke´s (55.4 ± 15.9 points), 4 with Broca´s (55.7 ± 9.2 points) and 2 with conduction aphasia (64.8 ± 14.9 points). Table 2 displays the number and composite score of NPS in our sample based on the NPI. As can be seen, there was a significant presence of comorbid NPS. In fact, all 20 participants were rated by their informants as exhibiting more than one NPS, except in one participant (subject 15), a female of 28 years of age with mild aphasia, who only showed a high NPI score in changes in appetite/eating behavior. On average, each PWA yielded a median number of 5 NPS (range: 1-8), with a mean composite score of 2 points (range: 1-6), indicating symptoms of mild severity in the chronic phase of stroke evolution.

Based on the result of the NPI, the majority of PWA (75%) had depressive symptoms, followed by agitation and irritability (70%), anxiety and appetite/eating disorders (65%). Half of the sample also showed symptoms of apathy, while sleep disturbances were also relatively frequent (40%). Euphoria and psychotic disorders were rare. The most severe symptoms were apathy, depression, anxiety, agitation, and irritability (see Table 2). Regarding sexes, women had a median number of 6 NPS while men presented 5 NPS. Mann-Whitney U tests showed that there were no statistically significant sex differences concerning the number of NPS ($P$ = 0.841). Antidepressants were taken by 7 patients. Median results showed that participants taking antidepressants were rated with a relatively similar number of NPS (6) compared to the participants without antidepressant intake (5), ($P$ = 0.496). When analyzing the median number of NPS based on aphasia type, participants with Broca´s aphasia

**Table 2 Incidence and composite score of neuropsychiatric symptoms based on the domain-general neuropsychiatric inventory evaluation**

| NPI symptom | No. of PWA with NPS (max. 20) | Percentage of PWA with NPS (%) | Composite NPI score[1] |
|---|---|---|---|
| Depression | 15 | 75 | 4 |
| Irritability | 14 | 70 | 2 |
| Agitation | 14 | 70 | 2 |
| Anxiety | 13 | 65 | 2.5 |
| Appetite/eating disorders | 13 | 65 | 1 |
| Apathy | 10 | 50 | 4.5 |
| Disinhibition | 9 | 45 | 1 |
| Sleep/nighttime disturbances | 8 | 40 | 1.5 |
| Euphoria | 1 | 5 | 2 |
| Aberrant motor behavior | 1 | 5 | 2 |
| Hallucinations | 1 | 5 | 1 |
| Delusions | 0 | 0 | 0 |

[1]Neuropsychiatric inventory scores were calculated based on positive cases.

Incidence of symptom was determined by the number of persons with aphasia with frequency scores of > 0 of the respective symptom. PWA: Persons with aphasia; NPI: Neuropsychiatric Inventory; NPS: Neuropsychiatric symptoms.

presented the highest number of symptoms (6.5) followed by anomic participants (5), conduction aphasia (4.5) and Wernicke´s aphasia (3). However, non-parametric Kruskal-Wallis test showed no statistically significant differences ($P$ = 0.508).

Specific-domain scales revealed that 30% of PWA were above the cut-off score for depression and anxiety (based on the SADQ-10, HADS-anxiety), 40% of patients were diagnosed with subthreshold depression (SADQ-10)[45,85] and 45% of participants had apathy (SAS) (see Table 3). However, percentages of diagnosis of the proxy-administered SADQ-10 stands in contrast to HADS-Depression results. Average scores of these domain-specific scales point into mild disorder severity. There were significant correlations between two domain-specific scales (SADQ-10 and SAS) and the most frequently reported NPI domains (e.g., depression, anxiety, apathy, agitation, and irritability) (see Table 4). No significant correlations were found between both neuropsychiatric scales (NPS and domain-specific scales) and aphasia severity (measured with the AQ of WAB-R), fluency, comprehension, or repetition scores.

**Lesion size and location:** The MRIs of participants showed a wide range of lesion volumes (Table 1). Lesion location showed that the maximum areas of overlap comprised regions of the long and the anterior segments of the arcuate fasciculus, the insula and the putamen in the left hemisphere. Involvement of different sectors of the left anterior cingulate gyrus were seen in six participants. The overlay of lesions is shown in Figure 1.

## DISCUSSION

### *Study 2: A proof-of-concept study of neuropsychiatric symptoms in chronic post-stroke aphasia*

Results of study 2 show that our participants presented mild-to-moderate aphasia severity and were functionally independent. We found a spectrum of comorbid NPS in all but one participant with mild anomic aphasia. On average PWA had a median number of 5 NPS (range: 1-8). The most frequent symptoms were depression, irritability, agitation/aggression, and anxiety, followed by appetite/eating disorders, apathy, and sleep disorders, whereas euphoria, delusions/hallucinations were rare. Apathy and depressive symptoms were rated as the most severe by their caregivers, followed by anxiety and agitation. There were no statistically significant differences regarding the number of NPS based on sex, antidepressant intake or aphasia type. When employing domain-specific scales that provide cut-off scores for diagnoses, 30% of participants had mild anxiety and depression, 45% showed subthreshold depression and 45% of participants had mild-to-moderate apathy.

The prevalence of depressive and anxiety symptoms based on the NPI was higher than the frequency of these disorders using the SADQ-10 and HADS. As mentioned, the NPI is an informant-based questionnaire developed to screen for the presence of symptoms, but not to establish diagnoses of

**Table 3 Incidence and median score of neuropsychiatric diagnoses based on domain-specific scales**

| Domain-specific scale (range) | No. of PWA with diagnoses | Percentage of PWA with diagnosis (%) | Median score (range) |
|---|---|---|---|
| SADQ-10, depression (0-30) | 6 | 30 | 15 (14-19) |
| SADQ-10, subthreshold depression (0-30) | 9 | 45 | 14 (13-19) |
| SAS, apathy (0-42) | 9 | 45 | 12 (1-35) |
| HADS, anxiety (0-21) | 6 | 30 | 5 (0-12) |
| HADS, depression (0-21) | 3 | 15 | 5.5 (1-14) |

PWA: Persons with aphasia; SADQ-10: Stroke Aphasic Depression Questionnaire-version 10; SAS: Starkstein Apathy Scale; HADS: Hospital Anxiety and Depression Scale.

**Table 4 Correlations between neuropsychiatric inventory-subdomains and domain-specific scales**

| Domain-specific scale | NPI-subdomains | Spearman correlation (rs) |
|---|---|---|
| SADQ-10 | NPI-depression | 0.67, $P < 0.001$[a] |
| | NPI-anxiety | 0.60, $P < 0.005$[a] |
| | NPI-apathy | 0.43, $P = 0.540$ |
| | NPI-agitation | 0.60, $P < 0.005$[a] |
| | NPI-irritability | 0.63, $P < 0.003$[a] |
| HADS | NPI-depression | 0.38, $P = 0.820$ |
| | NPI-anxiety | 0.27, $P = 0.240$ |
| | NPI-apathy | 0.27, $P = 0.243$ |
| | NPI-agitation | 0.14, $P = 0.540$ |
| | NPI-irritability | 0.11, $P = 0.620$ |
| SAS | NPI-depression | 0.50, $P < 0.023$[b] |
| | NPI-anxiety | 0.30, $P = 0.192$ |
| | NPI-apathy | 0.58, $P < 0.006$[a] |
| | NPI-agitation | 0.18, $P = 0.440$ |
| | NPI-irritability | 0.09, $P = 0.700$ |

[a]$P < 0.01$;
[b]$P < 0.05$.
NPI: Neuropsychiatric Inventory; SADQ-10: Stroke Aphasic Depression Questionnaire-version 10; SAS: Starkstein Apathy Scale; HADS: Hospital Anxiety and Depression Scale.

mental disorders. Thus, we expected to find a higher number of symptoms with the NPI in contrast to domain-specific scales. Results revealed a higher percentage of depression with the SADQ-10 than with the HADS, therefore showing a low level of congruency between these proxy and self-rated measures. Correlation analyses between NPI subdomains and domain-specific scales showed that the SADQ-10 correlated with a higher number NPI subdomains (depression, anxiety, irritability, and agitation) than the HADS (no associations found). The SAS, on the other hand, showed a significant correlation with NPI subdomains of apathy and depression. In general, it seems that proxy-rated neuropsychiatric instruments (*e.g.*, SADQ-10) are more sensitive to evaluate PWA than directly considering aphasic individuals themselves (*e.g.*, HADS) because of cognitive or communication problems. In support of these findings, outcome differences between proxy-based and directly administered instruments have also been described in other studies regarding PWA[161]. Moreover, family members have generally been found to be reliable informants in areas of emotions, daily activities, well-being, and overall quality of life[162]. In fact, Bourgeois *et al*[21] advise physicians to give credence to caregivers' testimonies about the behavior of PWA. Nevertheless, the opinion of informants should not jeopardize the autonomy and self-determination of PWA[163]. In general, more studies regarding the reliability and validity of neuropsychiatric proxy and self-measured instruments in PWA are strongly needed. Lastly, we found a lack of correlation between neuropsychiatric assessment tools (NPI and domain-

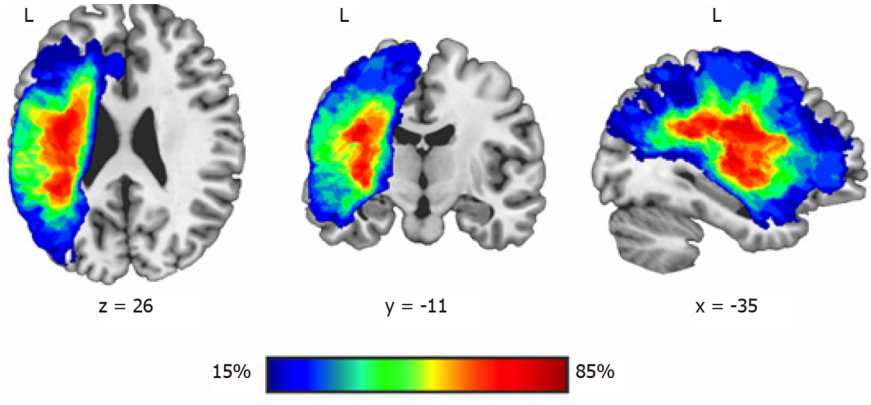


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**Figure 1 Lesion overlap map from the 20 participants overlaid on a brain template in Montreal Neurological Institute standard space.** The maximum lesion overlap (red color) (85%, *n* = 17) involved regions comprising the left arcuate fasciculus (long and the anterior segments), the insula and the putamen. Different sectors of the left anterior cingulate gyrus were involved in six participants. L: left.

specific scales) and WAB-R. These results align with findings from another study showing no correlations between WAB-R and depression scores based on the SADQ-21 in PWA and chronic left hemisphere strokes[80].

Structural MRIs in our sample showed a wide range of lesion volumes. There was a predominant involvement of the left perisylvian language core and lesion overlap analysis showed that the region corresponding to the arcuate fasciculus, insula and putamen were affected in 17 participants (85%). The insular cortex together with the striatum and the anterior cingulate gyrus (affected in 6 participants) are intrinsic components of the Salience Network[164]. The Salience Network is composed of two major hubs, anterior insula and dorsal anterior cingulate cortex. It also included three interconnected subcortical hubs: amygdala, ventral striatum, and substantia nigra/ventral tegmental area[165]. This network, among others, contributes to complex brain functions such as communication, social behavior, and self-awareness, by means of integrating of sensory, emotional, and cognitive information[164,165]. Damage to the left Salience Network in our sample may have impaired self-regulation of cognition, behavior, emotion and autonomic arousal favoring the emergence of an array of NPS[164]. Moreover, lesions in the left arcuate fasciculus have been associated with affective symptoms and somatic depressive complaints[166] and preliminary findings show that the lesion load in the left arcuate fasciculus correlates with naming improvement in PWA treated with antidepressants[167]. In any case, the role of the arcuate fasciculus in the NPS of PWA requires further analysis.

Some limitations to the current study should be acknowledged. First, this was a relatively small sample including people with chronic PSA of mild to moderate severity, so that it is not representative of all PWA and stroke. Another limitation is that we only used three domain-specific scales, whereas the NPI assesses twelve NPS. Nevertheless, we have evaluated the three most prevalent neuropsychiatric disorders already found in stroke patients without aphasia. In any case, future studies may include further domain-specific scales targeting other neuropsychiatric disorders. A longitudinal study to evaluate the evolution of NPS from the acute to the chronic phase of stroke survivors is also warranted.

## CONCLUSION

### *Study 1: Literature review*

We did find that NPS in PWA are insufficiently investigated. Prevalence of NPS in PWA is unknown, hindering the development of assessment tools and treatment strategies. If reported, most researchers and clinicians tend to focus mostly on diagnosing depression to the extent that there are no reports on symptoms of disinhibition, aberrant motor behavior, appetite-eating disorders, or sleep disturbances, already identified in non-aphasic stroke patients using the NPI. In addition, no pharmacological randomized controlled trials have been published for the reviewed symptoms in PWA. Pharmacotherapy, neuromodulation and behavioral therapies have only been implemented for depression and/or anxiety. Therefore, further research on the prevalence, assessment, pathophysiology, and treatment of NPS in PSA is strongly needed.

### *General conclusions and directions for further research*

The comorbidity of NPS in patients with chronic PSA is very frequent and seems to exceed the prevalence data reported in the non-aphasic stroke population. Therefore, more studies are necessary as NPS are still underdiagnosed in chronic PSA. Our study 1 shows the paucity of reports dealing with

NPS diagnosis, assessment, and treatment in PWA. In our study 2, we found high comorbidity of NPS among a small sample of PWA. Findings from study 2 suggest that the NPI may be used as a screening instrument and this assessment can be complemented with domain-specific psychiatric scales. Further aims must attempt to develop structured interviews and guidelines for the diagnosis, treatment, or prevention of comorbid NPS in PWA.

Many important questions regarding the neuropsychiatric spectrum in PWA remain unanswered or unaddressed. What is the frequency of NPS in acute aphasic stroke patients? Which are the best psychometric instruments to evaluate NPS? What is the best combination of self-rated and proxy-based measures depending on the severity of language impairment (production and/or comprehension deficits)? Which are the most important demographic variables that affect the occurrence of NPS in PWA? How do premorbid psychiatric conditions affect the occurrence and clinical phenomenology of NPS and language deficits after stroke? Is there any relationship between anosognosia for aphasia and NPS (hypomania/mania, psychosis)? How do NPS evolve or remit spontaneously? Are psychopharmacological agents including cognitive enhancing drugs useful? What kind of behavioral therapies should be applied for NPS in PWA? Does aphasia therapy positively influence psychiatric outcomes? Does the treatment of one NPS affect the outcome and comorbidity of other symptoms? Should biological treatments be prioritized over behavioral approaches, or should they be combined?

## ARTICLE HIGHLIGHTS

### *Research background*

Aphasia due to stroke is associated with worse outcomes than in non-aphasic stroke patients. Worse outcomes in post-stroke aphasia often result from the co-occurrence of neuropsychiatric symptoms (NPS) and disorders.

### *Research motivation*

Persons with aphasia (PWA) are frequently excluded from studies on stroke related NPS because of their language and communication deficits. The exclusion of PWA and stroke hinders obtaining relevant information on prevalence, diagnosis, associated deficits (cognitive impairment, functional disability), assessment, neurobiological mechanisms, and treatment of NPS in this population.

### *Research objectives*

We report a two-part study consisting of a literature review on NPS (study 1) and an observational study on NPS in chronic post-stroke aphasia (study 2).

### *Research methods*

In study 1, we reviewed the databases after cross-referencing key words of post-stroke aphasia to NPS and disorders. In study 2, we evaluated aphasic deficits, activities of daily living and a spectrum of NPS and disorders using well-validated scales in 20 persons with chronic mild-to-moderate post-stroke aphasia associated with left hemisphere strokes. NPS were evaluated with the 12 symptom domains of the Neuropsychiatric Inventory and with three domain-specific scales for depression, anxiety, and apathy.

### *Research results*

The literature review performed in study 1 revealed a spectrum of NPS in PSA including depression, anxiety, apathy, agitation/aggression, psychosis, and hypomania/mania. This broad spectrum of NPS was also found in observational study 2, since all but one PWA has more than one NPS (median number of NPS: 5, range: 1-8).

### *Research conclusions*

A spectrum of NPS is highly prevalent in chronic PSA. Therefore, future comprehensive evaluations of NPS using multidomain and domain-specific scales will enable a better characterization of this broad spectrum favoring the design and implementation of adequate therapies.

### *Research perspectives*

Since the spectrum of NPS in PWA and stroke is an underexplored research area, there are still many pending issues to be addressed. Essential areas of inquiry include knowing the incidence in acute and chronic stroke periods, risk factors (family and personal history of psychiatric disorders), clinical features, assessment instruments devised to test language and communication impaired patients, impact on quality of life, neurobiological correlates, short- and long-term outcomes, and response to psychological and biological interventions.

## FOOTNOTES

**Author contributions:** Dávila G, Berthier ML, Edelkraut L, López-Barroso D and Torres-Prioris MJ were involved in the acquisition of the original data; Dávila G, Berthier ML and Edelkraut L conceived and designed the manuscript; D ávila G, Berthier ML and Edelkraut L reviewed the literature; López-Barroso D, Torres-Prioris MJ, Aloisi J, Starkstein SE and Jorge RE analyzed the language and neuropsychiatric original data; López-Barroso D and Torres-Prioris MJ analyzed neuroimaging data and created the figure; Dávila G, Berthier ML, López-Barroso D, Torres-Prioris MJ, Starkstein SE, Jorge RE and Edelkraut L wrote the manuscript; all authors gave final approval of the current version of the article to be published.

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ORIGINAL ARTICLE

Observational Study

# Studying the relationship between clinical features and mental health among late-onset myasthenia gravis patients

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## Abstract

***BACKGROUND***

Mental disorders are common comorbidities among individuals with neurological diseases, and the prevalence of depressive and anxiety-related symptoms in newly referred patients at neurology outpatient clinics is high. There have been few studies on the mental health of patients with late-onset myasthenia gravis (MG).

***AIM***

To examine the relationship between clinical features and the mental health symptoms within late-onset MG patients.

***METHODS***

A total of 105 patients diagnosed with MG were recruited consecutively from a neuromuscular outpatient clinic between December 2020 and February 2021. Patients were classified into two groups: early-onset MG (age at onset < 50 years, $n$ = 63) and late-onset MG (age at onset ≥ 50 years, $n$ = 42). Social demographic data and information about marital status, education level, clinical symptoms, serum antibody levels, and therapies used were collected for all participants. Participants were also evaluated using the Myasthenia Gravis Composite scale, the Myasthenia Gravis Activities of Daily Living scale, the Myasthenia Gravis Quality of Life 15 (MG-QOL-15) questionnaire, the 17-item version of the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A). The relationship between clinical features and mental health in late-onset MG patients was examined using multivariate logistic regression analyses.

*RESULTS*

Late-onset MG patients were more prone to dyspnea, had higher levels of serum anti-acetylcholine receptor antibodies, and higher total scores on the MG-QOL-15, HAM-D, and HAM-A questionnaires, than early-onset MG patients had ($P < 0.05$). Among those with late-onset MG, female patients had higher total HAM-D and HAM-A scores than male patients had ($P < 0.05$). High scores on the QOL-15 questionnaire were associated with higher incidences of anxiety and depression, and the association was found to be independent after adjusting for confounding risk factors. In the late-onset subgroup, the areas under the receiver operating characteristic curves for the MG-QOL-15 score-based diagnostic accuracy for anxiety and depression state were 0.816 ($P = 0.001$) and 0.983 ($P < 0.001$), respectively.

*CONCLUSION*

Higher MG-QOL-15 scores were a risk factor for anxiety and depression in late-onset MG, and women with late-onset MG were more likely to have anxiety and depression than men were.

**Key Words:** Mental health; Late-onset myasthenia gravis; Anxiety; Depression

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**Core tip:** Mental disorders are the common comorbidities among myasthenia gravis (MG) patients in older age. In this study, we found that female patients with late-onset MG were more susceptible to anxiety and depression than their male counterparts, and that higher scores on the Myasthenia Gravis Quality of Life 15 questionnaire were an independent risk factor for anxiety and depression in patients with late-onset MG. This is the first report detailing the relationship between clinical features and mental health in the subgroup of MG patients with late disease onset.

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## INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder that is mainly caused by autoantibodies binding to nicotinic acetylcholine receptors (AChRs) at muscle endplates, and is characterized by skeletal muscle fatigability and weakness[1,2]. MG is also associated with emotional, cognitive, and behavioral symptoms[3].

Mental disorders are the most common comorbidities among individuals with neurological diseases, and the prevalence of depressive and anxiety-related symptoms in newly referred patients at neurology outpatient clinics is high[4]. MG is an autoimmune disease that can lead to disability. The global prevalence of MG is roughly 40-180 cases per 1 million individuals[5]. However, there are limited data on the relationship between mental disorders and MG, especially in patients with late-onset forms of the disease. Furthermore, because myasthenic symptoms of MG may overlap with somatic symptoms of depression and anxiety[6], such as fatigue or shortness of breath, which are also common in mental disorders, and facial weakness and blepharoptosis generally convey an impression of depression and apathy[7], comorbidities accompanied by mental and myasthenic symptoms may be misdiagnosed, thus the need to focus on both mental and physical therapies has been highlighted[8,9].

Mental disorders have often been reported; the incidence is up to 59% of MG patients, with depression being the most common disorder, followed by anxiety and hypochondria[10]. The unpredictable progression, chronic course and long-term treatment for MG can lead to limitations and reductions in quality of life (QOL)[11-13], which were found to predispose to psychological stress[7]. There is a questionnaire specifically aimed at assessing QOL among MG patients (Myasthenia Gravis Quality of Life 15-item (MG-QOL-15) scale, including 15 test items that address MG-specific social functioning and uses five response options, based on which QOL can be effectively rated[14,15]. The measures of MG-QOL-15 try to capture patients' appraisal of and satisfaction with their current level of functioning compared to what they perceive to be possible or ideal, and higher scores on the MG-QOL-15 questionnaire were indicative of more severe clinical cases to some extent[13].

Longer disease duration, severity of disease, and MG-induced respiratory failure may contribute to the increased rates of depression[16,17]. Compromised swallowing and communication abilities, unpredictable and fluctuating nature of respiratory dysfunction suggests concerning risk factors for

developing anxiety among MG patients[7,16-18]. Fewer work restrictions could be protective factors for developing mental disorders in the limited observational studies[19]. Late-onset MG occurring in older adults is more difficult to manage mainly because of the multiple comorbidities[20,21] and MG with late disease onset is on the rise in recent years[22]. Due to the frequent occurrence of comorbidities in older people that might be confused with MG symptoms[23], awareness of the occurrence of mental disorders in older age groups of MG is needed for earlier intervention and thus a better outcome. To this end, this cross-sectional study aimed to investigate the relationship between clinical features and mental health in patients with late-onset MG.

## MATERIALS AND METHODS

### Study design and participants

This cross-sectional study was conducted in The First Affiliated Hospital of the Sun Yat-sen University, in Guangzhou, China. A total of 105 patients diagnosed with MG were recruited consecutively from a neuromuscular outpatient clinic between December 2020 and February 2021. Clinical data were collected, and scores on clinical scales were procured through face-to-face evaluations with professional neurologists. This study was approved by the Ethics Committee of The First Affiliated Hospital of the Sun Yat-sen University. We obtained informed consent from all patients prior to the scale-based clinical examinations.

### Inclusion and exclusion criteria

All participants were diagnosed with MG according to international consensus-based guidelines[24]. This study included patients who met the following criteria: (1) Diagnosed with MG; (2) aged ≥ 16 years; and (3) ability to fully cooperate during clinical scale-based evaluations. Patients were excluded if they: (1) Were under treatment with antianxiety and/or antidepressant drugs; and (2) had incomplete data.

### Clinical data and scales

We collected data on sociodemographic characteristics, inducing factors, comorbidities, specific clinical features (*i.e.*, disease duration, Myasthenia Gravis Foundation of America Classification, symptoms at first evaluation, and mental status), details of serum antibodies levels [*i.e.*, levels of anti-AChR/muscle-specific tyrosine kinase (MuSK) antibodies], and immunotherapy history. Patients were independently examined using the Myasthenia Gravis Composite (MGC) scale, the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale, the MG-QOL-15 questionnaire, the 17-item version of the Hamilton Depression Rating Scale (HAM-D), and the Hamilton Anxiety Rating Scale (HAM-A) by two neurologists (both of whom were qualified to perform these evaluations).

The MGC scale[25] is composed of 10 items that measure symptoms and signs of MG, with a maximum score of 50 points, the reliability coefficient of the MGC scale was 98%, indicating excellent test-retest reliability. The MG-ADL scale[26] is composed of eight questions, aims to assess disability of ocular (2 items), bulbar (3 items), respiratory (1 item), and limb (2 items), with each response graded from 0 (normal) to 3 (most severe), and the total score ranges from 0 to 24, reliability coefficient was 93.7%. The MG-QOL-15 consists of 15 items: mobility (9 items), symptoms (3 items), general contentment (1 item), and emotional well-being (2 items)[27], with each response graded from 0 (not at all) to 4 (very much), and total scores of up to 60 points, the Chinese MG-QOL-15 had excellent internal consistency (Cronbach's $\alpha = 0.928$). Higher scores on MGC, MG-ADL, or MG-QOL-15 scales were indicative of more severe clinical cases. The HAM-A and HAM-D scales consist of 14 and 17 items, respectively, and are used to measure mental health symptoms[28,29]. The total scores are 56 (for the HAM-A) and 53 (for the HAM-D), and total HAM-A scores were classified as no (< 7), potential (7-13), assured (14-29), and severe (> 29) anxiety. Total HAM-D scores were classified as no (< 7), potential (7-17), assured (17-24), and severe (> 24) depression, the Cronbach's coefficient of them was > 0.8, indicating good internal consistency. The above questionnaires and scales were administered in the Chinese language, and are all reliable, valid, and widely used[30-33].

### Groups

Participants were categorized into the following subgroups according to their age at disease onset[34]: early-onset MG (age at onset < 50 years, $n = 63$) and late-onset MG (age at onset ≥ 50 years, $n = 42$). HAM-A scores ≥ 7 and HAM-A scores < 7 were considered to be indicative of anxiety and nonanxiety states, while HAM-D scores ≥ 7 and HAM-D scores < 7 were classified to be depressive and nondepressive states, respectively[35,36]. Patients were considered seropositive for anti-AChR antibodies if their titers were > 0.45 nmol/L on ELISA. They were deemed seropositive for anti-MuSK antibodies if their titers were > 0.05 nmol/L on a radioimmunoassay. All test reagents were purchased from RSR Ltd. (Cardiff, United Kingdom.

### Statistical analysis

Statistical analyses were performed using SPSS version 25 software (IBM, Chicago, United States) and GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA). Categorical data were presented as counts and percentages, and were analyzed using Fisher's exact test or $\chi^2$ test. Numerical data were presented as medians and interquartile ranges (partial distribution), and compared using the Mann-Whitney *U* test. Correlations were estimated with Pearson or Spearman correlation coefficients. Clinical determinants of anxiety and depression were used in multivariate logistic regression analyses, while gender, age at onset, body mass index (BMI), anti-AChR antibody levels, and MG-QOL15 scores were considered confounding risk factors. Receiver operating characteristic (ROC) curves were drawn to evaluate the value of MG-QOL-15 scores for diagnosing anxiety and depression. Significance was accepted if *P* values were < 0.05, and are denoted as $^{a}P < 0.05$, $^{b}P < 0.01$, and $^{c}P < 0.001$.

## RESULTS

### Baseline characteristics

Patients with late-onset MG (age at onset ≥ 50 years) accounted for 40.0% ($n$ = 42) of the 105 patients, and those with early-onset MG (age < 50 years) accounted for 60.0% ($n$ = 63). Among the patients with late-onset MG, 45.24% were women, and 54.76% were men. Among the early-onset MG patients, 58.73% were women, and 41.27% were men.

The medians (interquartile ranges) of HAM-A scores were 5 (5.5) in early-onset patients and 8.5 (7.5) in late-onset patients. These scores were significantly different between the two groups ($P$ < 0.001; Figure 1A). The HAM-D scores were 7 (8) and 10.5 (7.75) in early-onset and late-onset patient groups, respectively, and there was a significant difference between the two groups ($P$ = 0.018; Figure 1B). There were also significant differences in BMI, disease duration, dyspnea symptoms, anti-AChR antibody levels, and MG-QOL-15 scores between the two groups ($P$ < 0.05). HAM-A and HAM-D scores were significantly higher in female patients with late-onset MG than in those with early-onset MG ($P$ < 0.001 and $P$ = 0.001, respectively), but no significant differences were observed when only male patients were considered in these analyses ($P$ = 0.192 and $P$ = 0.731, respectively; Figure 2A and B). Baseline characteristics of the early-onset and late-onset groups are shown in Table 1.

### Correlation between clinical features and age at onset, assessed using Pearson or Spearman correlation analysis

There was a positive correlation between age at onset and BMI ($r$ = 0.41, $P$ < 0.001), anti-AChR antibody levels ($r$ = 0.31, $P$ = 0.001), MG-QOL-15 scores ($r$ = 0.32, $P$ = 0.001), HAM-A scores ($r$ = 0.41, $P$ < 0.001), and HAM-D scores ($r$ = 0.26, $P$ = 0.007). However, there was a negative correlation between age at onset and disease duration ($r$ = 0.59, $P$ < 0.001). Correlations between all clinical features and age at onset are detailed in Table 2.

### Clinical determinants of anxiety and depression in MG patients, measured using logistic analysis

Based on results from univariate analyses as well as previous literature[14-19], variables that may be relevant for mental health outcomes (gender, age at onset, BMI, anti-AChR antibody levels, and MG-QOL-15 scores) were included in a logistic regression model. No multicollinearity amongst the variables was found (variance inflation ranged from 1.072 to 1.536; tolerance ranged from 0.651 to 0.933) (Supplementary Table 1).

When the incidence of anxiety and depression were included as independent variables in the logistic analysis, they were associated with age at onset and MG-QOL-15 when other confounders were not considered. However, only MG-QOL15 scores were found to be independently associated with an increased risk of anxiety [odds ratio (OR) 1.10, 95%CI 1.04-1.15, $P$ < 0.001) after adjusting for possible confounds (including gender, age at onset, BMI, and anti-AChR antibody levels). MG-QOL-15 scores were also significantly associated with the incidence of depression in MG patients (OR 1.20, 95%CI: 1.10-1.30, $P$ < 0.001) (Table 3).

### Diagnostic value of MG-QOL15 scores for examining mental health in late-onset MG patients

When multivariate analysis was performed after adjusting for related confounds, MG-QOL-15 scores were found to be independent risk factors for anxiety and depression. In patients with late-onset MG, the median (interquartile ranges) MG-QOL-15 scores in the nonanxiety and anxiety groups were 8 (10.5) and 20 (17), respectively, and there were significant differences between the two groups ($P$ < 0.001). Similarly, MG-QOL-15 scores were significantly different between the depression and nondepression groups ($P$ < 0.001; Supplementary Figures 1A and 2A). We also examined whether MG-QOL-15 scores could help to diagnose or predict anxiety/depression state in late-onset MG patients using ROC curves [the larger the area under the ROC curve (AUC), the higher the diagnostic accuracy], and the smallest point that maximizes the value of (sensitivity + specificity  1) is calculated as the cut-off value, which would lead to the maximum degree of classification for anxiety/depression state. In our study, the AUC

**Table 1 Comparison between early-onset and late-onset groups**

| | Total patients (*n* = 105) | Early-onset (*n* = 63) | Late-onset (*n* = 42) | *P* value |
|---|---|---|---|---|
| Gender (*n*, %)[1] | | | | |
| Male | 49 (46.67) | 26 (41.27) | 23 (54.76) | |
| Female | 56 (53.34) | 37 (58.73) | 19 (45.24) | 0.231 |
| Marital status (*n*, %)[2] | | | | |
| Married | 63 (60.0) | 33 (52.38) | 30 (71.43) | 0.067 |
| Single (unmarried/divorced/widowed) | 42 (40.0) | 30 (47.62) | 12 (28.57) | |
| Education (*n*, %)[2] | | | | |
| Primary school and below | 26 (24.76) | 12 (19.05) | 14 (33.33) | 0.073 |
| Secondary school | 44 (41.90) | 25 (39.68) | 19 (45.24) | |
| College and above | 35 (33.33) | 26 (41.27) | 9 (21.43) | |
| Career change due to illness (*n*, %)[2] | | | | 0.955 |
| No change | 69 (65.71) | 41 (65.08) | 28 (66.67) | |
| Leave of absence | 24 (22.86) | 15 (23.81) | 9 (21.43) | |
| Transfer/unemployment | 12 (11.43) | 7 (11.11) | 5 (11.90) | |
| BMI (kg/m$^2$)[3] | 21.71 (5.77) | 20.51 (4.21) | 24.36 (4.53) | < 0.001[c] |
| Disease duration (mo)[3] | 5.00(12.21) | 7.00(13.34) | 4.00(8.50) | 0.016[a] |
| MGFA classification at evaluating (*n*, %)[1] | | | | |
| I | 28 (26.67) | 21 (33.33) | 7 (16.67) | |
| II | 40 (38.10) | 22 (34.92) | 18 (42.86) | |
| III | 31 (29.52) | 16 (25.40) | 15 (35.71) | |
| IV | 6 (5.71) | 4 (6.35) | 2 (4.76) | 0.255 |
| Thymectomy (*n*, %)[2] | 44 (41.90) | 28 (44.44) | 16 (38.10) | 0.551 |
| Comorbidities (*n*, %)[2] | 49 (46.67) | 32 (50.79) | 17 (40.48) | 0.299 |
| Inducing factor (*n*, %)[1] | | | | |
| Respiratory infection | 12 (11.43) | 6 (9.52) | 6 (14.29) | |
| Overfatigue | 3 (2.86) | 1 (1.59) | 2 (4.76) | |
| No triggers | 90 (85.71) | 56 (88.89) | 34 (80.95) | 0.470 |
| Clinical features | | | | |
| Onset symptom | | | | |
| Blepharoptosis (*n*, %)[2] | 97 (92.38) | 59 (93.65) | 38 (90.48) | 0.711 |
| Dysphagia (*n*, %)[2] | 50 (47.62) | 29 (46.03) | 21 (50.00) | 0.842 |
| Limb muscle weakness (*n*, %)[2] | 55 (52.38) | 31 (49.21) | 24 (57.14) | 0.550 |
| Dyspnea (*n*, %)[2] | 15 (14.29) | 5 (7.94) | 10 (23.81) | 0.043[a] |
| Serum antibody (nmol/L) [3] | | | | |
| Anti-AChR Ab | 9.54 (25.98) | 3.11 (17.98) | 17.51 (27.45) | 0.002[b] |
| Anti-MuSK Ab | 0 (1.13) | 0.31 (2.17) | 0 (0) | 0.098 |
| Seronegative (*n*, %)[2] | 16 (15.24) | 11 (17.46) | 5 (11.90) | 0.582 |
| Immunotherapy at evaluating | | | | |
| Glucocorticoids (*n*, %)[2] | 76 (72.38) | 49 (77.78) | 27 (64.29) | 0.181 |
| Azathioprine (*n*, %)[2] | 31 (29.52) | 19 (30.16) | 12 (28.57) | 0.861 |
| Tacrolimus (*n*, %)[2] | 8 (7.62) | 3 (4.76) | 5 (11.90) | 0.262 |

| | | | | |
|---|---|---|---|---|
| Leflunomide (*n*, %)[2] | 22 (20.95) | 13 (20.63) | 9 (21.43) | 0.922 |
| No immunotherapy (*n*, %)[2] | 53 (50.48) | 32 (50.79) | 21 (50.00) | 0.936 |
| Neuropsychological scales | | | | |
| MGC[3] | 6.00 (6.50) | 6.00 (6.00) | 7.00 (7.00) | 0.103 |
| ADL[3] | 3.00 (3.00) | 3.00 (4.00) | 3.00 (2.00) | 0.960 |
| QOL-15[3] | 14.00 (15.00) | 12.00 (13.50) | 16.00 (20.00) | 0.027[a] |
| HAM-A[3] | 6.00 (7.00) | 5.00 (5.50) | 8.50 (7.50) | < 0.001[c] |
| HAM-D[3] | 8.00 (7.00) | 7.00 (8.00) | 10.50 (7.75) | 0.018[a] |

[1]*n* (%), Fisher's exact test.
[2]*n* (%), Pearson's $\chi^2$ test.
[3]Median (25%Q, 75%Q), Mann-Whitney *U* test.
[a]*P* < 0.05.
[b]*P* < 0.01.
[c]*P* < 0.001.
BMI: Body mass index; ADL: Activities of daily living scale; MGC: Myasthenia Gravis Composite scale; MG-QOL-15: Myasthenia Gravis Quality of Life 15 questionnaire; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale.

**Table 2 Correlation between clinical features and age at onset**

| Clinical features | Correlation | 95%CI | *t* | *P* value |
|---|---|---|---|---|
| Disease duration | -0.59 | -0.70, -0.446 | -7.370 | < 0.001[c] |
| BMI | 0.41 | 0.233, 0.555 | 4.520 | < 0.001[c] |
| Anti-AChR Ab | 0.31 | 0.128, 0.475 | 3.335 | 0.001[b] |
| QOL-15 | 0.32 | 0.133, 0.479 | 3.383 | 0.001[b] |
| HAM-A | 0.41 | 0.236, 0.557 | 4.548 | < 0.001[c] |
| HAM-D | 0.26 | 0.074, 0.432 | 2.759 | 0.007[b] |

[a]*P* < 0.05.
[b]*P* < 0.01.
[c]*P* < 0.001.
BMI: Body mass index; MG-QOL-15: Myasthenia Gravis Quality of Life 15 questionnaire; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale.

for MG-QOL-15 scores at a cut-off value of 14.5 in the anxiety group was 0.816 ($P$ = 0.001), and the sensitivity-specificity was 75.86% and 84.62%, respectively (Supplementary Figure 1B). The AUC for MG-QOL-15 scores at a cut-off value of 14.5 in the depression group was 0.983 ($P$ < 0.001), and the sensitivity-specificity were 70.59% and 100%, respectively (Supplementary Figure 2B).

## DISCUSSION

In the current study, late-onset MG patients had higher total scores on the MG-QOL-15, HAM-A, and HAM-D scales compared with early-onset group MG patients, and there was a positive linear correlation between age at onset and MG-QOL-15 scores, HAM-A scores, and HAM-D scores. These results support the idea that late-onset MG is correlated with more severe impairments to patients' QOL and mental state. MG has previously been demonstrated to affect QOL, as well as mental and physical health[37]. Factors that influence QOL in MG include trouble with eyesight, skeletal muscle weakness, activity limitations, and unhealthy mental state[38,39]. MG-QOL-15 scales have also previously been applied to assess MG-related dysfunction[40]. Several studies reported that MG-QOL-15 scores in MG patients are highly and positively correlated with scores on the HAM-A and HAM-D scales[38,41,42]. These findings supported the notion that low QOL correlates with poor mental health in MG patients.

We also found that female patients with late-onset MG were more susceptible to anxiety and depression. It is important to examine what factors are related to the mental health of patients with late-onset MG and why there are sex-related differences. The prevalence of depression and anxiety is higher among women than men. This difference in mental disorders is the result of a complex interplay

**Table 3 Multivariate logistic model of the clinical determinants of anxiety/depression in myasthenia gravis patients**

| Variables | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| Anxiety | | | | |
| Gender | 0.96 (0.45-2.07) | 0.917 | 0.65 (0.25-1.68) | 0.372 |
| Age at onset | 1.04 (1.02-1.07) | 0.002[b] | 1.02 (0.99-1.05) | 0.305 |
| Disease duration | 0.93 (0.88-0.98) | 0.070 | 0.97 (0.90-1.04) | 0.414 |
| BMI | 1.10 (0.99-1.23) | 0.075 | 1.05 (0.92-1.21) | 0.485 |
| Anti-AChR Ab | 1.02 (1.00-1.05) | 0.092 | 1.02 (0.99-1.05) | 0.274 |
| QOL-15 | 1.10 (1.05-1.16) | < 0.001[c] | 1.10 (1.04-1.15) | < 0.001[c] |
| Depression | | | | |
| Gender | 0.82 (0.36-1.82) | 0.636 | 0.56 (0.19-1.64) | 0.293 |
| Age at onset | 1.03 (1.00-1.06) | 0.022[a] | 1.03 (0.99-1.06) | 0.162 |
| Disease duration | 0.98 (0.93-1.03) | 0.418 | 1.06 (0.98-1.15) | 0.172 |
| BMI | 1.05 (0.93-1.17) | 0.440 | 0.97 (0.83-1.13) | 0.678 |
| Anti-AChR Ab | 1.10 (0.99-1.04) | 0.387 | 1.01 (0.97-1.05) | 0.582 |
| QOL-15 | 1.19 (1.10-1.28) | < 0.001[c] | 1.20 (1.10-1.30) | < 0.001[c] |

[a]*P* < 0.05.
[b]*P* < 0.01.
[c]*P* < 0.001.
Model 1: Unadjusted; Model 2: Adjusted for possible confounders including gender, age at onset, body mass index, and anti-acetylcholine receptor antibody. BMI: Body mass index; QOL-15: Myasthenia Gravis Quality of Life 15 questionnaire; OR = exp (β).

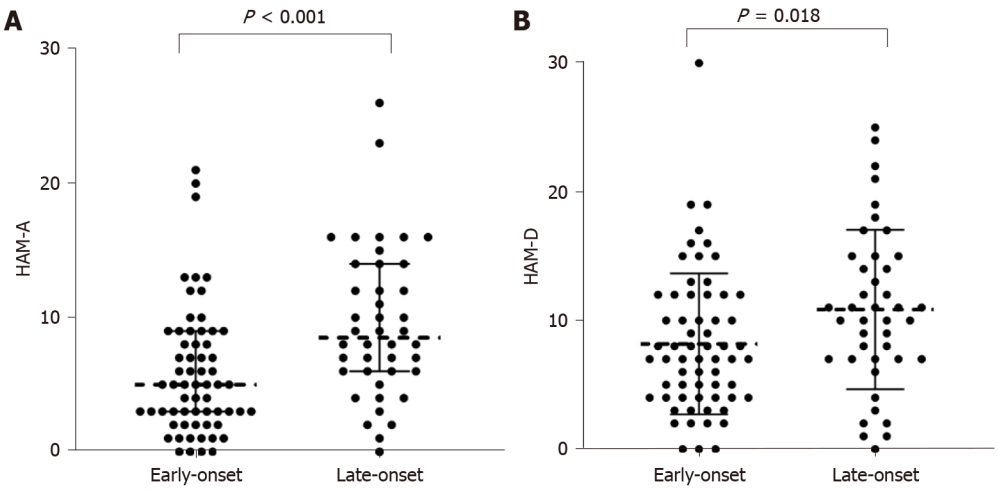


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**Figure 1 Hamilton anxiety rating and the Hamilton depression rating scores according to age of onset.** A: The median (interquartile range) of Hamilton anxiety rating (HAM-A scale scores in early-onset and late-onset groups were 5 (5.5) and 8.5 (7.5), respectively. The HAM-A scale score was significantly higher in the late-onset group than early-onset group (*P* < 0.001); B: The Hamilton depression rating (HAM-D) score levels in early-onset and late-onset groups were 7 (8) and 10.5 (7.75), respectively. The HAM-D scale score was significantly higher in the late-onset group than early-onset group (*P* = 0.018). *P* value was calculated using Mann-Whitney *U* test.

between genetic, hormonal and psychosocial factors[43-45]. Some studies have shown that women rather than men carrying the SS genotype of serotonin transporter gene-linked promoter region (5-HTTLPR) more easily develop depressive symptoms under a negative environment[46,47]. Female patients with MG tend to have more severe cases of the disease, and may also be affected by hormonal changes associated with menstruation, pregnancy, and/or postpartum fluctuations in hormone levels [48-50]. Previous studies have reported that the use of glucocorticoids is associated with changes in

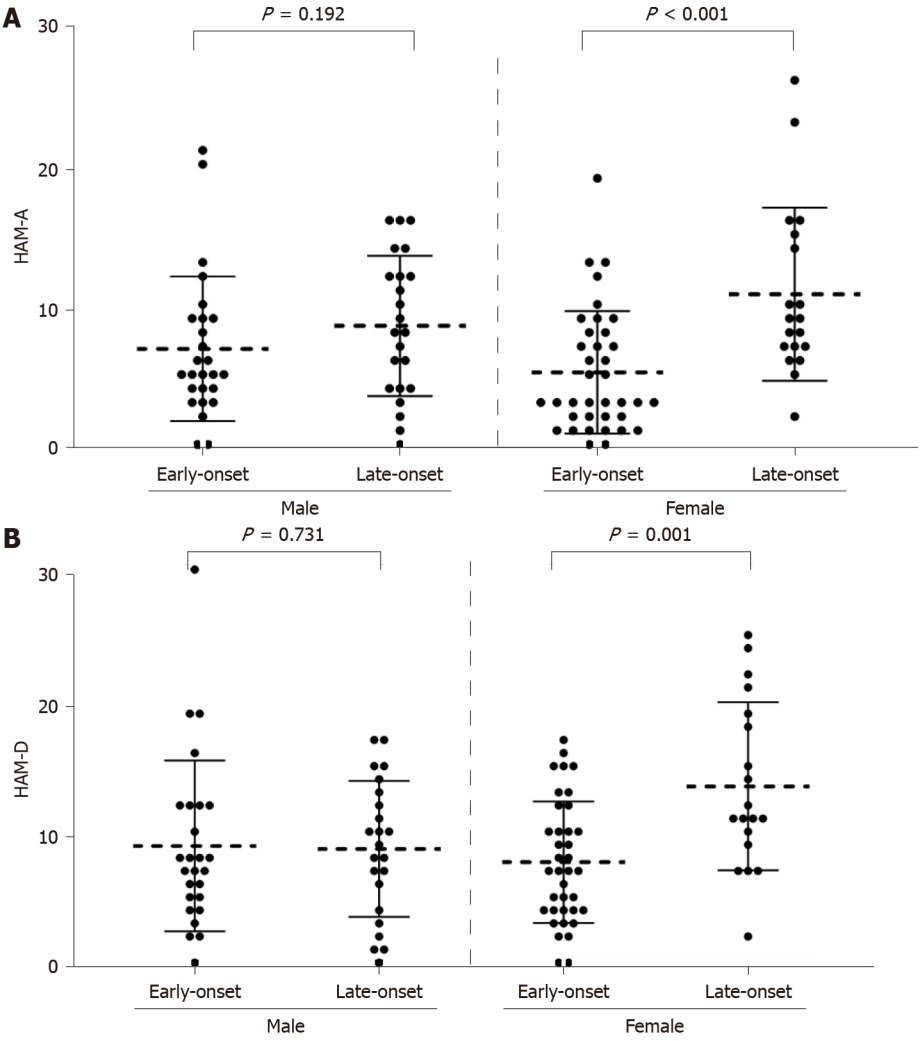


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**Figure 2 Hamilton anxiety rating and the Hamilton depression rating scores according to age of onset and sex.** A: The median (interquartile range) of Hamilton anxiety rating (HAM-A scale levels in late-onset groups were 3 (6), and 9 (8), respectively, and HAM-A scale scores were significantly higher in late-onset group than early-onset group in women ($P < 0.001$); B: The Hamilton depression rating (HAM-D) score levels in early-onset and late-onset groups were 7 (7) and 11 (10), respectively, and HAM-D scale score was significantly higher in late-onset group than early-onset group in women ($P = 0.001$). There were no significant differences in men for both HAM-A and HAM-D scale scores. *P* value was calculated using Mann-Whitney *U* test.

physical appearances, leading to conditions such as moon face and/or central obesity, which may have greater negative sociopsychological effects on women with MG than men. Moreover, some patients with late-onset MG do not have positive responses to medication, and some are intolerant to treatment, which can result in refractory conditions[51]. Female patients with late-onset MG may endure the adverse effects of comorbidities longer than their male counterparts, which would contribute to poorer QOL[52]. These factors could explain why female MG patients had higher susceptibility to anxiety and depression than male patients.

Our study showed that MG-QOL-15 scores were independently associated with an increased risk of anxiety and depression when gender, age at onset, BMI, and anti-AChR antibody levels were adjusted for in a multivariate analysis. We found that the ORs (95%CIs) of MG-QOL-15 scores for the anxiety and depression groups were 1.10 (1.04-1.15, $P < 0.001$) and 1.20 (1.10-1.30, $P < 0.001$), respectively, indicating that under the same conditions of gender, age at onset, and other factors, the odds of anxiety state increased by 10% and depression state increased by 20% for each increase in MG-QOL-15 scores, and high MG-QOL-15 scores were indeed a risk factor for anxiety/depression state. Previous studies have demonstrated that lower perceived QOL is highly correlated with mental impairment in MG patients[9,53,54]. In late-onset groups, the areas under the ROC curves for MG-QOL-15 scores at a cutoff value of 14.5 in the anxiety and depression groups were 0.816 and 0.983, respectively, which suggested that MG-QOL-15 scores had good diagnostic accuracy for the mental disorders, at least among late-onset MG patients. Our data revealed that MG-QOL-15 score cutoff of 14.5 could be a good indicator for poor mental health in need of attention among late-onset MG patients. Further research is needed for fine-tuning this threshold.

Some research has also reported that patients with MG who received thymectomy or proper immunosuppressive therapy had improved physical health and decreased disability symptoms, which indirectly improved mental health[55,56]. However, our study found that the rate of thymectomy and immunosuppressive treatment was comparable between early-onset and late-onset groups, but that late-onset MG patients had significantly higher levels of serum anti-AChR antibodies and were more prone to dyspnea. The proportion of overweight patients in the late-onset group was greater than that in the early-onset group. This pattern could be related to older age, which contributes to reductions in physical activity and possibly susceptibility to the adverse effects of glucocorticoids[57]. Compared to early-onset MG patients, higher anti-AChR antibody titers were reported in late-onset MG patients[57,58], which may partly be due to immune dysregulation, including age-related decreases in immunocompetence and increases in the production of autoantibodies[59,60]. Bulbar[23] and ocular symptoms [61] have been previously reported to be more common in late-onset MG patients. However, we found no differences in extraocular or limb muscle involvement between the two groups. Genetic factors may influence these results, since a similar study that reported a higher occurrence of ocular symptoms in late-onset patients also reported a higher proportion of women in the late-onset group[62].

There were some limitations to our study. First, limits in our sampling method make it difficult to draw firm conclusions. Second, our study had a prospective design, so further follow-up and particularly studies that include healthy control groups are needed to validate the results. However, our study had some advantages. For example, all included patients were enrolled from the same neuromuscular outpatient clinic. Thus, they received prompt and high-quality clinical scale evaluations that were performed by well-qualified and trained professionals, which ensured the integrity and authenticity of the data.

## CONCLUSION

Our research showed that female patients with late-onset MG were more susceptible to anxiety and depression than their male counterparts, and that higher MG-QOL-15 scores were an independent risk factor for anxiety and depression in patients with late-onset MG. To our knowledge, this is the first report detailing the relationship between MG-QOL-15 scores and mental health in the subgroup of MG patients with late disease onset. Thus, this association warrants further exploration in future research.

## ARTICLE HIGHLIGHTS

### *Research background*

The prevalence of depressive and anxiety-related symptoms in newly referred patients at neurology outpatient clinics is high, and mental state of myasthenia gravis (MG) patients were seldom assessed by mental scales routinely, so little is known about the exact relationship between MG and mental disorders that often accompany it.

### *Research motivation*

Due to the frequent occurrence of comorbidities in older people that might be confused with MG symptoms, awareness of mental disorders in older age groups of MG is needed for earlier intervention and thus a better outcome. In the present, there have been few studies on the mental health of patients with late-onset MG, so we conducted this study to assess the related factors for developing mental disorders in the subgroup of MG patients.

### *Research objectives*

This study aimed to investigate the relationship between clinical features and mental health in patients with late-onset MG, in addition to treating physical symptoms, attention should also be paid to mental disorders in late-onset MG patients.

### *Research methods*

A total of 105 patients diagnosed with MG were recruited consecutively from a neuromuscular outpatient clinic between December 2020 and February 2021 in our hospital. Clinical data including sociodemographic, neurological and mental information were collected, and scores on clinical scales were procured through face-to-face evaluations with professional neurologists. The relationship between clinical features and mental health in late-onset MG patients was examined using multivariate logistic regression analyses.

### *Research results*

Late-onset MG patients had higher total scores on the MG Quality of Life 15 (MG-QOL-15) quest-

ionnaire, the 17-item version of the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A) compared with early-onset group MG patients. Female patients had higher total HAM-D and HAM-A scores than male patients among late-onset MG ($P < 0.05$), and high scores on the MG-QOL-15 questionnaire were independently associated with higher incidences of anxiety and depression. In late-onset groups, the areas under the receiver operating characteristic curves for MG-QOL-15 scores at a cutoff value of 14.5 in the anxiety and depression groups were 0.816 and 0.983, respectively.

### *Research conclusions*

We found that female patients with late-onset MG were more susceptible to anxiety and depression than their male counterparts, and that higher MG-QOL-15 scores were an independent risk factor for anxiety and depression in patients with late-onset MG. An MG-QOL-15 score cutoff of 14.5 could be a good indicator for poor mental health in need of attention among late-onset MG patients.

### *Research perspectives*

In the future, we will seek to determine protective factors against developing mental disorders among late-onset MG. Further follow-up and particularly studies that include healthy control groups are needed to validate the results.

## FOOTNOTES

**Author contributions:** Liu WB was the guarantor and contributed to the conception of the study; Yu L and Qiu L participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; Ran H, Ma Q, Lu YR revised the article critically for important intellectual content.

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**Informed consent statement:** All study participants provided informed written consent prior to the scale-based clinical examinations.

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.

**Data sharing statement:** No additional data are available.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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ORIGINAL ARTICLE

Observational Study

# Childhood maltreatment and suicide ideation: A possible mediation of social support

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## Abstract

### *BACKGROUND*

Existing literature suggests a positive link between childhood maltreatment (CM) and suicide ideation (SI). Nevertheless, whether social support significantly mediates this association remains unknown.

### *AIM*

To investigate whether social support significantly mediates the association between CM and SI.

### *METHODS*

In this cross-sectional study of 4732 adolescents from southwest China, we intended to discuss the association between CM and multiple types of SI. In addition, the mediation of major types of social support in this association was also investigated. A self-administrated questionnaire was used to collect the data. A series of multivariate logistic regression models were employed to estimate the association between different types of CM, social support, and SI. The possible mediation of social support in the association between CM and SI was assessed using the path model.

### *RESULTS*

Based on the cutoffs for subscales of Childhood Trauma Questionnaire, 928 (19.61%), 1269 (26.82%), 595 (12.57%), 2337 (49.39%), and 3067 (64.81%) respondents reported physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect, respectively. Among all the social sources, parental support presented as a significant mediator in the association between emotional

maltreatment, both abuse and neglect, and all three types of SI: 1-wk, 1-year, and lifetime. Parental social support mediated 5.31% and 29.23%, 4.80% and 24.50%, and 7.04% and 44.42% of the overall emotional abuse-SI and emotional neglect-SI associations, respectively.

***CONCLUSION***

Our findings suggest that improving parental social support might be effective in preventing suicidal risk related to childhood emotional maltreatment in adolescents.

**Key Words:** Adolescent; Childhood maltreatment; Suicide ideation; Mediation; Social support

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**Core Tip:** Childhood maltreatment (CM) is associated with suicide ideation (SI). In the current study, we investigated the mediating role of social support in the association between CM and SI in a large sample (4732) of Chinese children and adolescents. Our results revealed a strong association between emotional CM and SI. In addition, only parental social support has been presented as a significant mediator in the association between emotional maltreatment and SI. The current study highlighted the intervention relevance of parental social support in emotional CM associated with suicidal risk. Rebuilding the parent-child relationship may be a promising way in preventing emotional CM-related suicide.

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## INTRODUCTION

Suicide represents a serious threat worldwide and has become the second leading cause of death among adolescents[1]. The theory of suicidality defines suicidal behavior as a continuous process that begins from suicide ideation (SI) and ends at completed suicide[2]. It has been estimated that more than 1.5 million individuals died of suicide worldwide in 2020[3]. A meta-analysis including 686672 children and adolescents across the world has estimated the lifetime and 1-year suicide prevalence rates in children and adolescents between 1989 and 2018 were 18.0% and 14.2%, respectively[4]. In China, according to a large sample cross-sectional study, about 32% of children and adolescents reported SI[5]. SI stands as a relevant indicator of acute suicidal risk because it generally leads to suicidal attempts during the 1$^{st}$ year of the ideation[6,7]. Thus, effective intervention on SI can be a plausible strategy to reduce suicidal risk.

Childhood maltreatment (CM) is an adverse life event that immediately influences the mental health of the children and may compromise their long-term physical and psychological health[7-9]. Normally, CM can be categorized into: physical abuse (PA), emotional abuse (EA), sexual abuse (SA), physical neglect (PN), and emotional neglect (EN)[10]. In China, the estimated prevalence rates of CM were 26.6%, 19.6%, 8.7%, and 26.0% for PA, EA, SA, PN, and EN in 2015[11]. A recent meta-analysis reported a high prevalence rate of CM among Chinese primary and middle school students (PA: 20%, EA: 30%, SA: 12%, PN: 47%, EN: 44%)[12]. It has been reported that CM has a lasting negative influence on the mental health of the victims[13,14]. Children who had been exposed to any kind of CM may present several emotional and behavioral problems such as depression symptoms, anxiety, impulsivity, social isolation, misconduct, aggressivity, delinquency, and hyperactivity[14]. These problems may lead to SI according to the Stress-Diathesis Theory of Suicidality[15]. Additionally, Li *et al*[16] disclosed that CM history increased the risk of major depressive disorder, an intimate risk factor of SI. From this perspective, a positive connection between CM and SI should exist.

Interpersonal psychological theory of suicidal behavior believes that isolation increases the desire to commit suicide[17]. Perceived social support protects against isolation. Malecki *et al*[18] defined social support as getting supportive behavior that boosts individual functioning or buffers them from negative outcomes. Social support comes from different sources; therefore, disparities may exist in the associations between different sources of social support and SI. Numerous studies have found that social support from family and friends was negatively associated with SI[19]. However, Hetrick *et al*[20] found that neither of them showed a significant relationship with suicidal behavior in a clinical sample of young adolescents diagnosed with depressive disorder. More recently, a large cross-sectional study reported that social support from relatives, friends, and parents were all negatively associated with SI among 2899 Chinese rural left-behind children; however, social support from teachers was insignificant

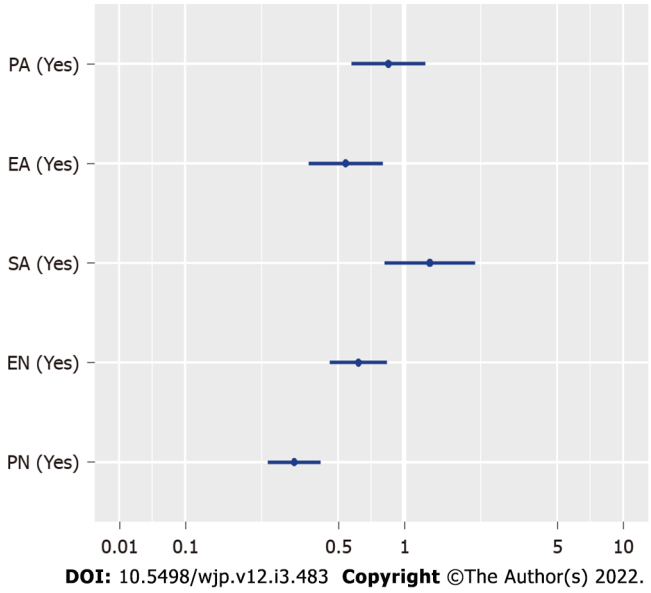

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**Figure 1 Adjusted odds ratios with 95%CIs for the associations between different childhood abuse and parental social support.** ORs: Odds ratios; EA: Emotional abuse; EN: Emotional neglect; PA: Physical abuse; PN: Physical neglect; SA: Sexual abuse.

[21]. All the existing literature in the field suggests that social support may play a buffering role in SI and suicidal behaviors among youngsters. Nevertheless, controversies remain to be further investigated, especially for different sources of social support.

Moreover, studies have suggested a positive and reciprocal association between CM and social support. On one hand, CM may generate social isolation, behavior disorder, and harmful interaction, which may cause decreased social support[18]. On the other hand, lower social support was also associated with the occurrence of CM[22]. In psychological research, moderation and mediation are two important concepts to understand the association between two variables of study interest. The mediation model assumes that there is a third variable, which sits in the association path between the two variables. In contrast, the moderation model specifies that a third variable modifies the strength of the association between the two variables[23]. Combine all existing evidence together, it is reasonable to suspect that social support may play a mediation role in the association between CM and SI. With this regard, in the current study, we aim to investigate this hypothesis by using a large population-representative sample of Chinese children and adolescents. We put forward the assumption that social support significantly mediates the association between CM and SI. In addition, social support of different sources showed discordant mediation in this association.

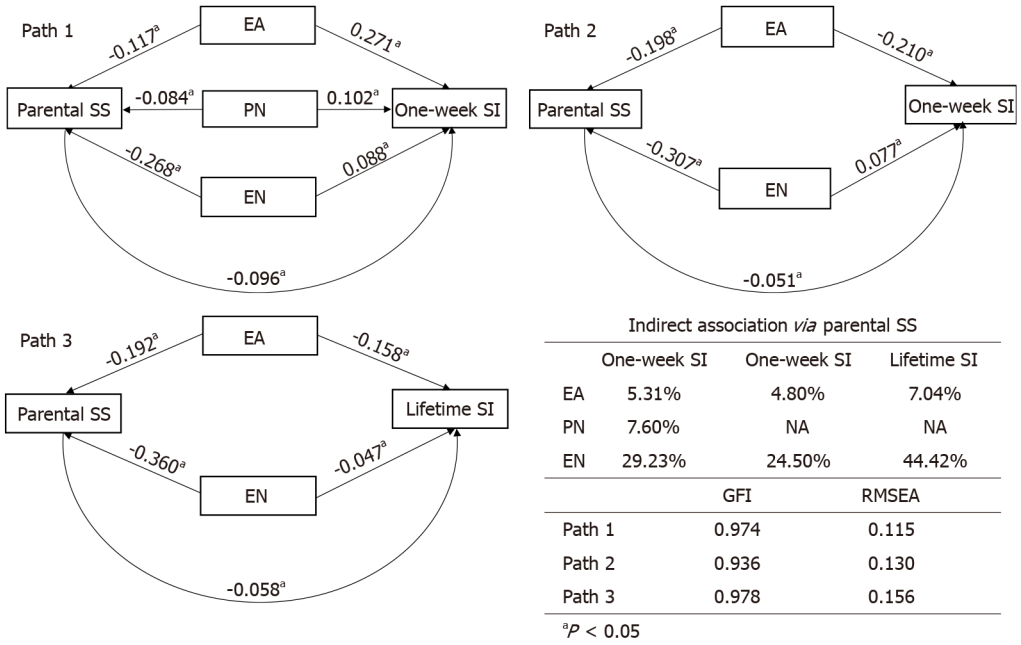
## MATERIALS AND METHODS

### *Participants*

We implemented a sampling survey in Kaiyuan, southwestern China Yunnan province between October 19 and November 3, 2020. A two-stage simple random cluster sampling method with probability proportionate to sample size design was used to determine study participants. In the first stage, among all primary, junior high, and senior high schools in Kaiyuan, 19 were randomly selected; in the second stage, based on the required sample size, several classes (4-6) within the chosen school were selected. All eligible students within the chosen class were preliminarily included. Students were further excluded if they were: (1) Aged below 10 years or above 18 years; (2) Reported serious mental or physical illnesses; (3) Had difficulties in hearing or speaking; and (4) Refused to participate. Before the survey, the study protocol was reviewed and approved by the Ethics Committee of Kunming Medical University.

### *Measures*

After written informed consents from the legal guardians were provided, a self-administered questionnaire survey was conducted in each sampling school. The quality of the finished questionnaire was checked on the site immediately by pretrained quality control personnel, who were either graduate students who majored in psychology or public health or health professionals recruited locally. The questionnaire was comprehensive and self-developed and contained the following sections: general characteristics, CM, perceived social support, SI, resilience, sexual harassment behavior, depression, and anxiety, *etc.* Except for the general characteristics, all the information was measured by using well-




Indirect association *via* parental SS

| | One-week SI | One-week SI | Lifetime SI |
|---|---|---|---|
| EA | 5.31% | 4.80% | 7.04% |
| PN | 7.60% | NA | NA |
| EN | 29.23% | 24.50% | 44.42% |

| | GFI | RMSEA |
|---|---|---|
| Path 1 | 0.974 | 0.115 |
| Path 2 | 0.936 | 0.130 |
| Path 3 | 0.978 | 0.156 |

$^aP < 0.05$

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**Figure 2 Path models and fitting results for direct and indirect associations between childhood maltreatment and different types of suicide ideation with the mediation of parent social support.** EA: Emotional abuse; EN: Emotional neglect; GFI: Goodness-of-fit index; NA: Not available; PN: Physical neglect; RMSEA: Root mean square error of approximation; SI: Suicide ideation; SS: Social support.

established instruments.

**CM:** The 28-item Childhood Trauma Questionnaire (CTQ) Short form represents one of the best self-report tools that retrospectively screens for five types of CM (PA, EA, SA, PN, EN)[10]. Each item uses a 5-point Likert style rating: never (1 point), occasionally (2 points), sometimes (3 points), frequently (4 points), and always (5 points). The whole questionnaire can be divided into 5 dimensions; each dimension contains five separate questions and measures one specific type of CM. Therefore, the score of each dimension varies from 5 to 25 points, and the total score of CTQ-Short form ranges from 25 to 125. The cutoffs of 8, 9, 6, 8, and 10 for PA, EA, SA, PN, and EA, respectively, were recommended[24]. In this study, we have followed the same cutoffs to dichotomize different types of CM. The Chinese version of CTQ presented a good internal consistency (Cronbach's α: 0.78-0.90) and test-retest reliability (Kappa: 0.79-0.88)[25]. The Cronbach α of CTQ in the current study was 0.84 (bootstrap 95%CI: 0.84-0.85).

**Perceived social support:** In the current study, we used the Chinese version of Child and Adolescent Social Support Scale (CASSS) for perceived social support[18]. The 40-item CASSS is a well-validated instrument that measures perceived social support from four sources: parents, teachers, classmates, and close friends. Each source includes 10 items with 5 responses that can be assigned a score from 1 (never) to 5 (always). Consequently, the combined score for every source ranges from 5 to 50 points. In the current study, we dichotomized different sources of social support by using the medians. The Cronbach α of CASSS in the current study was 0.92 (bootstrap 95%CI: 0.92-0.93).

**SI:** One-week and lifetime SI were assessed using the Chinese version of the Beck Scale for Suicide Ideation (BSSI). BSSI represents one of the best self-report inventories designed to evaluate the intensity of suicide thoughts and intentions. It is composed of 19 items, each graded from 0 to 2 by intensity. A higher total score of BSSI indicates more severe SI[26]. The Cronbach α of the BSSI in the current study was 0.88 (bootstrap 95%CI: 0.87-0.88). One-year SI was determined using a single question: how many times in the past year have you seriously considered ending your life? The responses include: never (0 times), rarely (only once), sometimes (twice), often (3-4 times), and very often (5 times or more). Participants who reported considered ending their own lives at least once were deemed positive.

**Depression and anxiety:** Depression and anxiety were examined using the Chinese version of The Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety Disorder-7 (GAD-7). PHQ-9 includes 9 questions scored from 0 to 3 based on the intensity of the symptom asked[27]. A recent study recommended a cutoff of 10 or above to screen for major depression whatever the age[28]. In this study, we adopted a threshold of 12 (the median of PHQ-9) to dichotomize study subjects. The Cronbach α of PHQ-9 in the current study was 0.88 (bootstrap 95%CI: 0.88-0.89). For GAD-7, a cutoff score between 7 and 10 can be used to efficiently screen for anxiety[29]. In our study, we used a cutoff of 9 following the

median of the combined score. The Cronbach α of GAD-7 in the current study was 0.91 (bootstrap 95%CI: 0.90-0.91).

### Statistical analysis

We performed a descriptive analysis to feature the main characteristics of the participants. The results of the multivariate binary logistic regression models led us to path analysis to determine the direct association between CM and SI, together with their possible indirect association meditated by different sources of social support. Associated factors of SI, childhood abuse, and social support identified from the multivariate logistic regression models were simultaneously incorporated into the hypothesized path model to control for possible confounding. We performed data analysis using the R software (Version 4.0.4). Considering the unequal probability sampling method used in this study, we mainly used the "survey" package to perform descriptive, univariate, and multivariate analyses. Path analysis was executed using the "lavaan" package.

## RESULTS

### Major characteristics of the participants

The main characteristics of our study subjects have been summarized in Table 1. Initially, 4858 eligible students were surveyed. Among them, 4732 with complete required information were included in our final analysis. Based on the cutoffs for subscales of CTQ, 928 (19.61%), 1269 (26.82%), 595 (12.57%), 2337 (49.39%), and 3067 (64.81%) were PA, EA, SA, PN and EN victims, respectively. The medians for different dimensions of CASSS were 37 [interquartile range (IQR): 9] for parent's support, 42 (IQR: 8) for teacher's support, 37 (IQR: 9) for classmate's support, and 39 (IQR: 9) for close friend's support. The prevalence rates of 1-wk, 1-year, and lifetime SI were 26.85% (95%CI: 24.30%-30.00%), 34.99% (95%CI: 30.60%-40.00%), and 55.69% (95%CI: 51.50%-60.00%), respectively.

### Associations between CM, social support, and SI

We have used a series of binary univariate logistic regression models to screen for possible influencing factors of different types of SI. Based on the univariate analysis results, a group of multivariate logistic regression was further fitted, and the results were collectively displayed in Table 2. After adjusting for potential covariates, especially depression and anxiety, different types of CM, EA, PN, and EN were consistently associated with elevated odds ratios (ORs) of 1-wk, 1-year, and lifetime SI. For social support of different sources, only the support from parents was inversely associated with SI. Adjusted ORs for 1-wk, 1-year, and lifetime SI were 0.67 (95%CI: 0.55-0.83), 0.64 (95%CI: 0.53-0.77), and 0.63 (95%CI: 0.52-0.77), respectively.

We further analyzed the adjusted associations between CM and parental social support. For all five types of child abuse, EA, PN, and EN were prominently and inversely related to parental social support (Figure 1).

### Path analysis

Based on the aforementioned analytical results, we proposed three different path models to illustrate the direct associations between CM and SI, together with their possible indirect associations mediated by parental social support. Standardized path coefficients, together with their statistical test results and model fitting indexes were jointly illustrated in Figure 2. Goodness-of-fit index and root mean square error of approximation indicated ideal model fitting for all three path models. The fitting results revealed that parental social support presented as a significant mediator in the association between emotional maltreatment, both abuse and neglect, and all three types of SI: 1-wk, 1-year, and lifetime. Parental social support mediated 5.31% and 29.23%, 4.80% and 24.50%, and 7.04% and 44.42% of the overall EA-SI and EN-SI associations, respectively.

## DISCUSSION

The current study investigated the association between CM and SI by using a large representative sample of 4732 Chinese children and adolescents. Particularly, we estimated the possible mediation of social support in this association. Our analysis results were in general supportive of the hypotheses: social support could be a prominent mediator in the association between CM and SI. In addition, different sources of social support discordantly mediated the associations between different types of CM and SI. These findings may suggest that to reduce suicidal risk among youngsters who have experienced CM, rebuilding or consolidating social support might be an effective strategy.

We found that among all types of CM, only EN and EA showed a strong association with SI. Previous studies in a Chinese adolescent population also reported a prominent association between EN, EA, and

**Table 1 General characteristics of study participants**

| Characteristic | mean ± SD[1]/median (IQR)[2] | *n* (%) |
|---|---|---|
| Age | 13.46 ± 1.95[1] | |
| Mother's age | 39.00 ± 5.76[1] | |
| Male sex | | 2359 (49.85) |
| Ethnicity | | |
| Han majority | | 1312 (27.73) |
| Minorities | | 3420 (72.27) |
| Grade | | |
| Primary school | | 1617 (34.17) |
| Junior high school | | 2544 (53.76) |
| Senior high school | | 571 (12.07) |
| Residence | | |
| Urban | | 1581 (33.41) |
| Rural | | 3151 (66.59) |
| Childhood maltreatment | | |
| Physical abuse (yes) | | 928 (19.61) |
| Emotional abuse (yes) | | 1269 (26.82) |
| Sexual abuse (yes) | | 595 (12.57) |
| Physical neglect (yes) | | 2337 (49.39) |
| Emotional neglect (yes) | | 3067 (64.81) |
| Boarding students (yes) | | 2373 (50.14) |
| Single child (yes) | | 1061 (22.42) |
| Living situation | | |
| With both parents | | 3272 (69.15) |
| With single parent | | 618 (13.06) |
| With others | | 1460 (17.79) |
| Perceived social support (CASS score) | | |
| Parents | 37 (9)[2] | |
| Teachers | 42 (8)[2] | |
| Classmates | 37 (9)[2] | |
| Close friends | 39 (9)[2] | |
| Suicide ideation (yes) | | |
| 1-wk | | 1271 (26.85) |
| 1-yr | | 1656 (34.99) |
| Lifetime | | 2639 (55.69) |
| Depression (PQH ≥ 12) | | 2488 (52.57) |
| Anxiety (GAD-7 ≥ 9) | | 2413 (50.99) |

[1]mean ± SD.
[2]Median (interquartile range).
IQR: Interquartile range; CASS: Child and Adolescent Social Support; PQH: Patient Health Questionnaire; GAD-7: Generalized Anxiety Disorder-7.

**Table 2 Multivariate logistic regression results for associated factors of different suicide ideation**

| Covariates | 1-wk SI | | 1-yr SI | | Lifetime SI | |
|---|---|---|---|---|---|---|
| | Multivariate 1 | Multivariate 2 | Multivariate 1 | Multivariate 2 | Multivariate 1 | Multivariate 2 |
| Sex (Ref: Male): Female | 1.49 (1.31-1.66) | 1.36 (1.20-1.55) | 2.08 (1.75-2.47) | 1.41 (1.12-1.77) | 1.70 (1.42-2.03) | 1.41 (1.12-1.77) |
| Age: + 1 yr | | | 1.01 (0.93-1.10) | 0.87 (0.79-0.96) | 0.95 (0.88-1.03) | 0.87 (0.81-0.95) |
| Ethnicity (Ref: Han majority): Minorities | | | 0.93 (0.76-1.10) | 1.07 (0.92-1.24) | | |
| Grade (Ref: Primary school) | | | | | | |
| Junior high School | | | 1.14 (0.75-1.72) | 1.17 (0.87-1.57) | 1.31 (0.99-1.73) | 1.13 (0.84-1.52) |
| Senior high school | | | 0.83 (0.50-1.38) | 0.80 (0.49-1.29) | 1.18 (0.79-1.75) | 0.74 (0.44-1.25) |
| Residence (Ref: Urban): Rural | 1.19 (1.03-1.37) | 1.20 (0.99-1.44) | 0.90 (0.73-1.11) | 1.39 (1.10-1.76) | | |
| Boarding students (Ref: No): Yes | | | 0.70 (0.56-0.88) | 0.72 (0.55-0.92) | | |
| Single child (Ref: No): Yes | | | 1.03 (0.92-1.16) | 0.69 (0.54-0.88) | | |
| Childhood abuse (Ref: No) | | | | | | |
| PA: Yes | 1.39 (1.17-1.65) | | 1.09 (0.86-1.38) | | 1.32 (1.04-1.68) | |
| EA: Yes | 1.99 (1.77-2.26) | | 2.79 (2.19-3.56) | | 2.08 (1.66-2.60) | |
| SA: Yes | 1.50 (1.20-1.87) | | 1.07 (0.79-1.43) | | 1.16 (0.85-1.59) | |
| PN: Yes | 1.54 (1.33-1.77) | | 1.30 (1.06-1.59) | | 1.25 (1.07-1.47) | |
| EN: Yes | 2.28 (1.94-2.67) | | 1.63 (1.36-1.97) | | 1.47 (1.29-1.68) | |
| Perceived social support (CASS) | | | | | | |
| Parent support (Ref: < 37): ≥ 37 | | 0.66 (0.55-0.83) | | 0.63 (0.52-0.77) | | 0.63 (0.52-0.77) |
| Teacher support (Ref : < 42): ≥ 42 | | 0.94 (0.77-1.12) | | 0.97 (0.82-1.14) | | 0.97 (0.83-1.14) |
| Classmate support (Ref : < 37): ≥ 37 | | 0.88 (0.77-1.00) | | 0.91 (0.73-1.14) | | 0.90 (0.72-1.13) |
| Close friend support (Ref : < 39): ≥ 39 | | 0.80 (0.69-0.93) | | 0.80 (0.64-1.00) | | 0.80 (0.64-1.00) |
| Depression (Ref PQH < 12): Yes | 1.15 (0.90-1.48) | 1.35 (1.06-1.72) | 2.94 (2.15-4.03) | 1.88 (1.32-2.68) | 2.12 (1.65-2.73) | 1.86 (1.31-2.64) |
| Anxiety (Ref: GAD-7 < 9): Yes | 1.75 (1.46-2.08) | 2.06 (1.72-2.48) | 1.85 (1.35-2.54) | 1.98 (1.62-2.43) | 2.23 (1.84-2.69) | 1.99 (1.61-2.46) |

CASS: Child and Adolescent Social Support; EA: Emotional abuse; EN: Emotional neglect; GAD-7: Generalized Anxiety Disorder-7; PA: Physical abuse; PN: Physical neglect; PQH: Patient Health Questionnaire; SA: Sexual abuse; SI: Suicide ideation.

SI[30,31]. EA and EN are related to a range of poor mental health outcomes[32,33]. Although physical and sexual CM have also been linked to SI, a longitudinal study has found that emotional maltreatment was the strongest predictor of SI[34]. Emotional maltreatment has been found to be a strong predictor of internal psychopathology development and may interrupt the psychosocial well-being during children's growth. Thus, it represents a source of lifetime depression[35]. A meta-analysis revealed that emotional maltreatment was strongly associated with major depression in an adolescent population [36]. These findings highlight the important role of emotional abuse in adolescent suicidal risk.

An important finding of our study is that among all sources of social support only parental social support presented as a significant mediator in the association between emotional maltreatment and SI. This finding is consistent with some previous studies, which have proven that parental support buffered the harmful effect of past stressful events on mental health among adolescents[36,37]. Moreover, some studies have revealed that social support from parents is a principal mediator in the association between depression and SI[37,38]. Parents exert an important impact during adolescence mainly through emotional assistance and positive relationships[39]. Studies have shown a protective effect of parental social support as the pivotal factor in the stress-buffering model[40,41]. Under this situation, supportive parents may protect adolescents against mental disorders even if they have been exposed to a stressful environment. Therefore, intervention measures concentrating on improving or rebuilding the parent-child relationship could be effective in reducing emotional maltreatment associated with suicidal risk

among youngsters.

Another interesting finding would be that although parental social support presented as a statistically significant mediator in their associations with SI for both EA and EN, the proportion of parental social support mediation was several folds higher in EN-SI association than in EA-SI association. As the two major types of CM, neglect and abuse have disparate influences on children: in the context of neglect, children could grow up with a lower level of belongingness and acceptance[24], whereas EA victims have experienced an insecure attachment relationship with their parents[42]. Many studies have shown that insecurely attached children are at an elevated risk of mental health problems[43]. In a newly published meta-analysis, the authors concluded that insecure attachment may be a predictor of depression among children and adolescents[44]. Considering the fact that depression is the single strongest risk factor of suicide, it is possible that for emotionally abused adolescents the EA-SI association is in essence the association between depression, which originated from insecure attachment and SI. As adolescent depression is hard to intervene directly, the consolidation of parental social support can only exhibit a very limited effect. Therefore, for adolescents who had experienced childhood emotional maltreatment, when implementing parental social support intervention measures to antagonize suicide risk, priority should be given to neglect victims.

The current study emphasized the role of parental social support in emotional maltreatment associated with suicide risk among Chinese adolescents. Family-based interventions, like family therapy [45] and attachment-based family therapy (ABFT)[46], probably can be used to restore and improve secure parent-child relationships. Prior studies on Chinese adolescents have proven that family therapy can effectively decrease depression symptoms and increase parental social support[47,48]. Meanwhile, the efficacy of attachment-based family therapy in reducing depressive symptoms and SI has also been documented in adolescents[49].

Some limitations of the current study should be noticed. First, our study did not investigate the source of CM in the sample. Second, our analysis was based on cross-sectional data. Therefore, causal inference cannot be reached, and the mediation we identified should be further corroborated by longitudinal studies. Third, all information was collected by self-reporting measures, which are prone to information bias. Finally, the extrapolation of study results to the general adolescent population in China should be made cautiously since our study sample was drawn from a localized region in southwest China.

## CONCLUSION

The current findings provide support for the previous studies regarding the strong relationship between CM and SI. Moreover, a prominent mediation of parental social support has been identified in the association between emotional CM and SI. Our major findings highlight the promising and intervenable role of parental support in antagonizing emotional CM associated with suicide risk. For emotionally maltreated children and adolescents, rebuilding the parent-child relationship might be effective in suicide prevention.

## ARTICLE HIGHLIGHTS

### *Research background*

Suicide represents a major public health problem among the child and adolescent populations worldwide. Suicide ideation (SI) is the percussor of suicidal behavior. In China, over 32% of children and adolescents have reported SI. Adverse lifetime events such as childhood maltreatment (CM) increase the risk of SI. Meanwhile, social support protects against SI. Thus, a pathway between CM and SI *via* social support may exist.

### *Research motivation*

Although the mediation of social support in the association between CM and SI seems plausible, this hypothesis has not been discussed. The motivation of our study is to investigate the mediation role of social support.

### *Research objectives*

To investigate whether social support significantly mediates the association between CM and SI.

### *Research methods*

A large representative sample of 4732 adolescents from southwest China Yunnan province was surveyed. CM was defined into five types according to the 28-items Childhood Trauma Questionnaire (CTQ) Short-form: physical abuse (PA), emotional abuse (EA), sexual abuse (SA), physical neglect (PN),

and emotional neglect (EN). The Chinese version of the Beck Scale for Suicide Ideation, the Child and Adolescent Social Support Scale, the Patient Health Questionnaire, and the 7-item anxiety scale were used to measure suicide ideation, social support, depression, and anxiety, respectively. We performed logistic regression and path analysis to evaluate the mediation of social support.

### *Research results*

The prevalence rates of 1-wk, 1-year, and lifetime SI were 26.85% (95%CI: 24.30%-30.00%), 34.99% (95%CI: 30.60%-40.00%), and 55.69% (95%CI: 51.50%-60.00%), respectively. In addition, based on the cutoffs for subscales of CTQ, 928 (19.61%), 1269 (26.82%), 595 (12.57%), 2337 (49.39%), and 3067 (64.81%) were PA, EA, SA, PN and EN victims. According to the multivariate logistic regression, EA, PN and EN were consistently associated with SI. In addition, parental social support was inversely associated with SI. Following the multivariate analysis results, we performed path analysis. Parent social support presented as a significant mediator in the associations between emotional maltreatment (EA and EN) and SI.

### *Research conclusions*

The current study suggests that parental social support may be considered as a potential mediator in the relationship between CM and SI. Intervention to rebuild the parent-child relationship may help to intervene CM-associated suicide risk.

### *Research perspectives*

Future longitudinal studies are needed to verify the mediation of parental social support in the association between CM and SI.

## FOOTNOTES

**Author contributions:** Ahouanse RD and Chang W contributed equally as joint first authors; Xiao YY designed the study; Ahouanse RD, Chang W, Ran HL, Fang D, Che YS, Deng WH, Wang SF, Peng JW, and Chen L collected and verified the data; Ahouanse RD and Xiao YY performed data analysis; Ahouanse RD and Chang W drafted the manuscript; Xiao YY provided critical revision of the manuscript for important intellectual content; all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

# Personality traits and self-harm behaviors among Chinese children and adolescents: The mediating effect of psychological resilience

Xue-Yang Jiao, Chuan-Zhi Xu, Ying Chen, Qing-Lan Peng, Hai-Liang Ran, Yu-San Che, Die Fang, Jun-Wei Peng, Lin Chen, Si-Fan Wang, Yuan-Yuan Xiao

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## Abstract

### *BACKGROUND*

Previous studies have shown that personality traits are associated with self-harm (SH) in adolescents. However, the role of resilience in this association remains unclear. Our research aims to explore the hypothesized mediation effect of resilience in the relationship between personality traits and SH in Chinese children and adolescents.

### *AIM*

To evaluate resilience as a mediator of the association between personality traits and SH.

### *METHODS*

A population-based cross-sectional survey involving 4471 children and adolescents in Yunnan province in southwestern China was carried out. Relevant data were collected by self-reporting questionnaires. Univariate and multivariate logistic regression models were employed to identify associated factors of SH. A path model was used to assess the mediation effect of resilience with respect to personality traits and SH association.

### *RESULTS*

Among the 4471 subjects, 1795 reported SH, with a prevalence of 40.1% (95%CI: 34.4%-46.0%). All dimensions of personality traits were significantly associated with SH prevalence. Resilience significantly mediated the associations between three dimensions of personality (extroversion, neuroticism, psychoticism) and SH, accounting for 21.5%, 4.53%, and 9.65%, respectively, of the total associations. Among all dimensions of resilience, only emotional regulation played a significant mediation role.

*CONCLUSION*
The results of the study suggest that improving emotion regulation ability might be effective in preventing personality-associated SH among Chinese children and adolescents.

**Key Words:** Adolescents; Emotion regulation; Mediation; Personality traits; Resilience; Self-harm

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**Core Tip:** In children and adolescents, personality traits are closely related to self-harm (SH) behaviors. In this cross-sectional study of 4471 Chinese children and adolescents, we detected a significant role of resilience in the association between personality traits and SH. Further, among all dimensions of resilience, only emotion regulation mediated the association between personality and SH. Improving emotion regulation ability could reduce the occurrence of SH in Chinese children and adolescents.

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## INTRODUCTION

Self-harm (SH) refers to the behavior of harming one's own body with or without the intention of suicide[1]. SH is a global health concern. Among all age groups, the highest risk of SH has been reported in the adolescent population, and the lifetime prevalence of SH in non-Western countries was found to be higher than that in Western countries[2]. A meta-analysis found that the prevalence of SH among Chinese adolescents has reached 22.37%[3]. SH is the most prominent risk factor of future suicide[4]. Considering the high prevalence of SH among adolescents, together with the intimate relationship between SH and suicide, proactively preventing SH can be an effective way to reduce suicidal risk among teenagers.

Identifying the influencing factors of SH is crucial for SH prevention. In recent years, the positive link between poor mental health and SH has been repeatedly reported in adolescent populations: Impulsivity, anger dysregulation, and low self-esteem are the identified risk factors for SH in adolescents[5,6]. Personality traits are also significantly associated with adolescent SH. A study on Norwegian adolescents found that neuroticism was a risk factor that contributed to SH in youth[7]. Similarly, among Italian middle school students, those with more impulsive and aggressive personalities were more likely to report SH[8]. A domestic study in Chinese college students suggested that, those with higher extraversion scores (E scores) in the Eysenck personality questionnaire were at higher risk of SH[9]. In addition, a cross-sectional study with a large sample size showed that susceptible personality traits were significantly related to SH consciousness[10].

As a long-lasting and stable feature of an individual, personality is hard to intervene directly. Therefore, exploring modifiable factors which lie along the pathway between personality and SH would be more practicable in preventing personality-associated SH among adolescents. In recent years, some studies have found that mental resilience plays a beneficial role in protecting adolescents from SH[11-13]. Psychological resilience refers to the ability of an individual to adjust to changes when experiencing a traumatic, or negative, or frustrating event[14]. Many studies have shown that personality traits are significantly associated with resilience: For instance, extroversion, conscientiousness, and openness have been shown to be positively correlated with resilience, whereas emotionality has shown a negative association[15,16]. All of these findings suggest that resilience may play a mediating role in the association between personality traits and SH; however, this hypothesis has never been thoroughly investigated.

Aiming to address this shortcoming, the current study used a large representative sample of Chinese children and adolescents to examine the relationship between personality traits and SH, and more importantly, the possible mediation effect of resilience on personality-associated SH.

## MATERIALS AND METHODS

### Study design

The data used for analysis in this study were obtained from the Mental Health Survey of Children and Adolescents in Kaiyuan. A cross-sectional survey was carried out in Kaiyuan, Yunnan province in southwest China, from October 27 to November 4, 2020. The survey used a population-based two-stage simple random cluster sampling method with probability proportionate to sample size (PPS) design. It was carried out in two stages: In stage one, eight primary schools, nine junior high schools and two senior high schools were randomly selected from all schools in Kaiyuan; in stage two, 3–4 classes were randomly selected from each chosen school, and all students within the chosen classes who met the inclusion criteria were included.

Based on the literature, we set a conservative SH prevalence of 20%, and an acceptable error rate of 2% was determined. According to the simple random sampling sample size calculation method, we reached a preliminary required sample size of 1600. Considering that the sampling error in the cluster samples would inevitably be higher than that in random samples, we used a design effect of '2' to further adjust for the required sample size, and the final calculated sample size was 3200.

In this study, except for personality, SH, and resilience, we also measured suicide ideation among the respondents. Since children under the age of 10 cannot fully understand the definition and consequences of suicide[17], we only included adolescents aged 10 years old and above. Subjects were further excluded if at least one of the following exclusion criteria was satisfied: (1) Unable to complete the questionnaire due to severe psychological or physical illnesses; (2) Having a speech disorder, communication disorder or reading comprehension disorder; and (3) Refused to participate. Before the survey, the written informed consent of the respondents was obtained from their legal guardians. In addition, when the survey was underway, verbal consent was also obtained from the respondents themselves.

The study protocol was reviewed and approved by the Ethics Review Board of Kunming Medical University, No. KMMU2020MEC047.

### Measurements

A structured questionnaire was used to collect information from the participants. This questionnaire mainly measures demographics, personality traits, anxiety and depression, SH behaviors, psychological resilience, suicide ideation, and parenting styles. The demographics section consisted of factual questions, and validated instruments were used for all of the other sections. In the current study, we used the following sections to perform the data analysis: General characteristics, SH behavior, psychological resilience, personality traits, depression, and anxiety.

SH behaviors: The modified version of the Adolescents Self-Harm Scale (MASHS) developed by Feng [18] was used to measure lifetime SH behaviors[18]. The MASHS includes 18 items measuring frequency (never, 1 time; 2–4 times, 5 times and above) and severity (non-observable, mild, moderate, severe, devastating) of the 18 most common SH behaviors in Chinese adolescents.

Personality traits: The children's version of the Eysenck Personality Questionnaire developed by Eysenck and other researchers in 1975 was used to assess personality traits[19]. The questionnaire consists of 88 items, divided into four subscales: Neuroticism (N); psychoticism (P); E; lie (L). The first three scales represent the three dimensions of the personality structure and are independent of each other. The L scale is a measure of effectiveness and represents the personality traits related to false trust. Each question is scored '1' or '0', and finally converted into a normal standard T score. For the L scale, a T score greater than 61.5 was taken to indicate a lack of authenticity. The T scores for N, P, and E scales were collectively used to classify subjects into five levels. E (extraversion) was divided into: Typical introversion ($T \leq 38.5$), introversion ($38.5 < T \leq 43.3$), extraversion intermediate ($43.3 < T \leq 56.7$), extroversion ($56.7 < T \leq 61.5$), and typical extroversion ($T > 61.5$). N was divided into: Typical non-neuroticism ($T \leq 38.5$), non-neuroticism ($38.5 < T \leq 43.3$), neuroticism intermediate ($43.3 < T \leq 56.7$), neuroticism ($56.7 < T \leq 61.5$), and typical neuroticism ($T > 61.5$). P was divided into: Typical non-psychoticism ($T \leq 38.5$), non-psychoticism ($38.5 < T \leq 43.3$), psychoticism intermediate ($43.3 < T \leq 56.7$), psychoticism ($56.7 < T \leq 61.5$), and typical psychoticism ($T > 61.5$)[9,20]. The Cronbach's α was 0.891 (Bootstrap 95%CI: 0.886-0.896).

Depression and anxiety: The Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7) were used to assess the subjects' experience of depression and anxiety in the past two weeks. There are nine items on the PHQ-9, which correspond to the nine diagnostic criteria for depression (interest in doing things, mood fluctuations, sleep quality, vitality, appetite, self-evaluation, concentration on things, speed of movement, thoughts of suicide)[21]. The GAD-7 contains seven items, which measure nervousness, anxiety, uncontrollable worry, excessive worry, inability to relax, inability to sit still, irritability, and ominous premonition[22]. Each item on the PHQ-9 and GAD-7 is divided into four levels by severity of the scenario: Not at all (0 point), several days (1 point), more than half of the days (2 points), almost every day (3 points). A higher combined score was taken to indicate more severe symptoms of depression or anxiety[23]. The Cronbach's α for the PHQ-9 and GAD-7 were 0.883 (Bootstrap 95%CI: 0.874-0.890) and 0.909 (Bootstrap 95%CI: 0.902-0.915).

Resilience: The Resilience Scale for Chinese Adolescents (RSCA) compiled by Hu and Gan[24] was used. It contains 27 items, including two dimensions of personal strength and support. The personal strength dimension is divided into three factors: Goal concentration, emotion regulation, and positive perception. The support dimension is divided into two factors: Family support and interpersonal assistance. The questionnaire is scored using a five-point scale (1-totally disagree, 2-disagree, 3-not sure, 4-agree, 5-totally agree), with a higher total score representing a higher level of mental resilience[24]. The Cronbach's α was 0.846 (Bootstrap 95%CI: 0.837-0.855).

### Statistical analysis

We used the R software (Version 4.0.3, The R Foundation for Statistical Computing, Vienna, Austria) to perform the statistical analysis, and the "Survey" package has been mainly used to adjust for unequal sampling probability. Descriptive statistics are presented to describe the general characteristics of the survey subjects, t tests, chi-squared tests, and rank-based non-parametric tests were carried out to compare the differences between subgroups as appropriate to variable type. Univariate and multivariate binary unconditional logistic regression models were used to explore the crude and adjusted associations between personality traits and SH (prevalence, repetition, severity). A series of path models were fitted to examine psychological resilience as a mediator of the associations between personality and SH prevalence, SH severity, and SH repetition. Except for the univariate logistic regression models which adopted a lower significance level of 0.10 to screen for possible covariates, the significance level for all of the other statistical analyses was set as 0.05 (two-tailed).

## RESULTS

### General characteristics

A total of 4780 children and adolescents met the inclusion criteria, of whom 57 were excluded because of incomplete information. A further 252 respondents were defined as untrustworthy because their EPQ-L scores were greater than 61.5. In the end, 4471 subjects were included in the analysis, and the effective response rate was 93.5%. Among all analyzed participants, 1795 reported SH behaviors, accounting for 40.1% (95%CI: 34.4%-46.0%). In respect to the general characteristics listed in Table 1, except for sex and ethnicity, statistically significant differences were found between respondents who self-harmed and those who did not SH. The T sores for the E, N, and P dimensions of personality traits were also different between the two groups. Compared with SH subjects, subjects who did not SH reported a consistently higher level of resilience, either in general, or on the five specific dimensions.

### Associated factors of SH

Based on univariate logistic regression analysis, age, gender, grade, anxiety, depression, resilience, and all of the personality trait dimensions (extraversion, neuroticism, psychoticism) were included into the subsequent multivariate logistic regression models: Model 1 represented the adjusted associations between the three dimensions of personality traits and SH; Model 2 revealed the adjusted association between resilience and SH; in Model 3, personality traits and resilience were simultaneously incorporated into the model, and the results indicated that typical introverted personality types (E ≤ 38.5) were associated with an increased risk of SH (OR = 1.46, 95%CI: 1.14-1.87), whereas a more stable mood (a lower N score) (OR = 0.19, 95%CI: 0.13-0.26) and a lower psychotic score ($P$ ≤ 56.7) (OR = 0.29, 95%CI: 0.17-0.51) were associated with a decreased risk of SH (Table 2).

### Mediation of resilience

Based on the results of the multivariate logistic regression models, we constructed a possible path model to illustrate resilience as a mediator of the associations between the three personality trait dimensions and SH prevalence. The analytical results showed that the mediation effect of resilience for all of the three personality trait dimensions was significant: The standardized path coefficients were -0.0301 (0.494 × -0.061), 0.0225 (-0.369 × -0.061), and 0.0145 (-0.238 × -0.061), which accounted for 21.5%, 4.53%, and 9.65% of the total associations, respectively (Figure 1). We further dissected this association based on the five dimensions of resilience. The path model suggested that among the three significant dimensions of resilience identified by a prior multivariate logistic regression model (the results are summarized in Supplementary Table 1), only emotion regulation was identified as a prominent mediator (Figure 2).

We intended to further analyze the possible mediation effect of emotion regulation in terms of the associations between personality traits and SH repetition, as well as SH severity. However, the preliminary multivariate analysis revealed that the adjusted associations between emotion regulation and SH repetition/severity were all insignificant (Supplementary Table 2); thus, the suspected mediation effect was not found.

**Table 1 General features of 4471 adolescents, Kaiyuan, Yunnan, China, 2020**

| Features | Total (*n* = 4471) | SH (*n* = 1795) | Non-SH (*n* = 2676) | Test statistic | *P* value |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Age (X bar ± S) | 13.01 (0.40) | 13.42 (0.34) | 12.73 (0.43) | -11.99[1] | 0.01 |
| Sex, *n*, (%): Boys | 2184 (48.8) | 824 (45.9) | 1360 (50.8) | 3.17[2] | 0.09 |
| Ethnicity, *n*, (%) | | | | 0.37[2] | 0.67 |
| Han | 1242 (27.8) | 504 (28.1) | 738 (27.6) | | |
| Yi | 1788 (40.0) | 693 (38.6) | 1095 (40.9) | | |
| Others | 1441 (32.2) | 598 (33.3) | 843 (31.5) | | |
| Grade, *n*, (%) | | | | 32.24[2] | 0.01 |
| Primary school | 1472 (32.9) | 374 (20.8) | 1098 (41.0) | | |
| Junior high school | 2442 (54.6) | 1157 (64.5) | 1285 (48.0) | | |
| Senior high school | 557 (12.5) | 264 (14.7) | 293 (10.9) | | |
| Mental health | | | | | |
| Depression, *n*, (%): Yes (PHQ9 ≥ 10) | 501 (11.2) | 411 (22.9) | 90 (3.4) | 176.27[2] | 0.01 |
| Anxiety, *n*, (%): Yes (GAD7 ≥ 7) | 778 (17.4) | 570 (31.8) | 208 (7.8) | 244.43[2] | 0.01 |
| Personality traits | | | | | |
| EPQ-E, *n*, (%) | | | | 3.54[3] | 0.01 |
| Typical extroversion: Score E > 61.5 | 1024 (22.9) | 357 (19.9) | 667 (24.9) | | |
| Extroversion: 56.7 < score E ≤ 61.5 | 740 (16.6) | 270 (15.0) | 470 (17.6) | | |
| Intermediate: 43.3 < score E ≤ 56.7 | 1825 (40.8) | 763 (42.5) | 1062 (39.7) | | |
| Introversion: 38.5 < score E ≤ 43.3 | 419 (9.4) | 191 (10.6) | 228 (8.5) | | |
| Typical introversion: score E ≤ 38.5 | 463 (10.4) | 214 (11.9) | 249 (9.3) | | |
| EPQ-N, *n*, (%) | | | | -18.10[3] | 0.01 |
| Typical neuroticism: Score N > 61.5 | 646 (14.4) | 510 (28.4) | 136 (5.1) | | |
| Neuroticism: 56.7 < score N ≤ 61.5 | 323 (7.2) | 197 (11.0) | 126 (4.7) | | |
| Intermediate: 43.3 < score N ≤ 56.7 | 1227 (27.4) | 574 (32.0) | 653 (24.4) | | |
| Non-neuroticism: 38.5 < score N ≤ 43.3 N ≤ 43.3 | 552 (12.3) | 189 (10.5) | 363 (13.6) | | |
| Typical non-neuroticism: Score N ≤ 38.5 NN ≤ 38.5 | 1723 (38.5) | 325 (18.1) | 1398 (52.2) | | |
| EPQ-P, *n*, (%) | | | | -11.02[3] | 0.01 |
| Typical psychoticism: score P > 61.5 | 422 (9.4) | 289 (16.1) | 133 (5.0) | | |
| Psychoticism: 56.7 < score P ≤ 61.5 | 518 (11.6) | 308 (17.2) | 210 (7.8) | | |
| Intermediate: 43.3 < score P ≤ 56.7 | 2335 (52.2) | 967 (53.9) | 1368 (51.1) | | |
| Non-psychoticism: 38.5 < score P ≤ 43.3 | 1026 (22.9) | 211 (11.8) | 815 (30.5) | | |
| Typical non-psychoticism: Score P ≤ 38.5 | 170 (3.8) | 20 (1.1) | 150 (5.6) | | |
| Resilience (Median, IQR) | | | | | |
| Combined score | 89 (19) | 84 (16) | 93 (20) | -15.98[3] | 0.01 |
| Goal concentration | 17 (6) | 16 (6) | 18 (6) | -11.17[3] | 0.01 |
| Emotion regulation | 20 (7) | 18 (7) | 21 (6) | -13.26[3] | 0.01 |
| Positive perception | 14 (5) | 13 (5) | 14 (5) | -2.68[3] | 0.02 |
| Family support | 21 (6) | 19 (5) | 22 (5) | -10.27[3] | 0.01 |
| Interpersonal assistance | 20 (6) | 18 (6) | 21 (6) | -10.93[3] | 0.01 |

[1]*t* test.
[2]Chi-squared test.
[3]Wilcoxon rank-sum test.
SH: Self-harm; E: Extraversion; N: Neuroticism; P: Psychoticism.

## DISCUSSION

In the current study, we discussed the relationship between personality traits and SH in a large representative sample of Chinese children and adolescents. The analysis of the results showed that all personality trait dimensions were significantly related to the prevalence of SH after adjusting for other covariates. Resilience played a noticeable mediating role in terms of the associations between different dimensions of personality (E, N, P) and SH, accounting for 21.5%, 4.53%, and 9.65% of the total associations, respectively. Further analysis revealed that, for different dimensions of resilience, only emotion regulation was identified as a prominent mediator in this association. The current study could provide valuable evidence for personality-associated SH prevention in children and adolescents.

A high lifetime prevalence of SH (40.1%) was found in our study sample, and this prevalence was much higher than that previously reported. For example, two previously published meta-analysis papers found a lifetime SH prevalence of 13.7% (95%CI: 11.0%-17.0%) and 16.9% (95%CI: 15.1%-18.9%) among children and adolescents globally[2,25]. Another meta-analysis found that the prevalence of SH among Chinese adolescents was 22.37%[3], which is comparable to our previous study involving children and adolescents who were randomly chosen from another city (Lincang) of Yunnan province, with a reported lifetime prevalence of SH of 47%[12]. These prominent differences in the lifetime prevalence of SH can likely be attributed to heterogeneity in SH instruments and definitions, which prevent a direct comparison of the studies involving different children and adolescent populations.

An important finding of our study is that personality traits were significantly associated with SH prevalence: Higher E scores were correlated with lower SH odds, whereas higher N and P scores were associated with an increased risk of SH. These associations were well supported by existing literature. First of all, introverts may find it more difficult to integrate into society, although no pertinent studies have been published to elaborate upon the influence of introversion on SH, and a higher risk of future suicide has been reported among introverted college students[26]. The positive association that was identified in the current study between neuroticism and SH is in line with the results published by Hafferty *et al*[27]. Another meta-analysis on neuroticism and suicide ideation showed that neuroticism was also a significant risk factor for suicide ideation and is of great significance for suicide prevention [28]. The positive connection between psychoticism and SH can also be justified. Studies have found that high psychoticism individuals exhibited higher levels of impulsivity and aggressiveness, which are known risk factors for SH[29,30].

The path analysis results indicated that resilience was a significant mediator of the association between all personality trait dimensions and SH. In general, resilience is related to positive personality traits such as optimism, persistence, cooperation, maturity, and responsibility[31]. A study on American college students also found that neuroticism in personality traits was negatively correlated with resilience, while conscientiousness and extroversion were positively correlated with resilience[16,32]. In addition, existing studies have shown that resilience has a protective effect on the occurrence of SH in adolescents, and adolescents with higher levels of resilience were less likely to develop SH[11]. In the relationship between personality and SH, resilience-mediated associations accounted for over one-fifth (21.5%) of the total association for the extraversion dimension, which was the highest among all of the three dimensions. This finding probably suggests that, for introverted children and adolescents, building up resilience might be an effective way to prevent personality-related SH.

Resilience is a composite definition. Our further analysis revealed that, among the five dimensions of resilience, only emotion regulation was a significant mediator of the association between personality traits and SH. Emotion regulation refers to the ability to respond to the ongoing demands of experience with a range of emotions in a socially tolerable manner[33]. A newly published study found that poor emotion regulation was an important cause of SH[34]. In addition, a retrospective study has also indicated that there were differences in the ability to control emotions among individuals with different personalities[35]. Therefore, among all dimensions of resilience, improving emotion regulation ability could be regarded as the priority in antagonizing personality-associated SH among children and adolescents. Currently, some effective intervention methods in improving emotion regulation ability have already been proposed. Since SH has a high prevalence in children and adolescents, group-based therapy should be prioritized when considering interventions. Acceptance-based emotion regulation group therapy had a good effect on improving emotion regulation ability and reducing SH: It focuses on controlling behavior when emotions are present, rather than controlling emotions themselves[36-38]. Domestic studies have also shown that acceptance-commitment therapy has a positive effect on the acceptance of bad emotions and feelings, as well as on the rational use of emotion regulation strategies in patients with bipolar disorder[39]. Moreover, although studies on emotion regulation intervention strategies were also published recently in China, they mainly focused on clinical populations, such as

**Table 2 Univariate and multivariate logistic regression fitting results for associated factors of self-harm**

| Variable | Univariate model; Crude OR (90%CI) | Multivariate model 1; Adjusted OR (95%CI) | Multivariate model 2; Adjusted OR (95%CI) | Multivariate model 3; Adjusted OR (95%CI) |
|---|---|---|---|---|
| Age: +1 yr | 1.20 (1.14-1.27) | 1.00 (0.93-1.08) | 1.03 (0.95-1.11) | 1.01 (0.94-1.09) |
| Sex (Ref: Boys): Girls | 1.22 (1.01-1.46) | 0.98 (0.75-1.28) | 1.09 (0.89-1.34) | 0.98 (0.76-1.27) |
| Grade (Ref: Primary school) | | | | |
| Junior high school | 2.64 (2.11-3.31) | 1.81 (1.23-2.67) | 2.18 (1.49-3.19) | 1.82 (1.24-2.69) |
| Senior high school | 2.65 (2.01-3.48) | 1.43 (0.89-2.30) | 2.12 (1.29-3.49) | 1.51 (0.93-2.46) |
| Depression (Ref: PHQ9 < 10): PHQ9 ≥ 10 | 8.53 (6.29-11.59) | 2.21 (1.49-3.27) | 3.30 (2.56-4.82) | 2.18 (1.47-3.23) |
| Anxiety (Ref: GAD7 < 7): GAD7 ≥ 7 | 5.52 (4.55-6.69) | 1.43 (1.14-1.78) | 2.28 (1.84-2.83) | 1.37 (1.10-1.70) |
| Personality traits | | | | |
| EPQ-E (Ref: Typical extroversion, score E > 61.5) | | | | |
| Extroversion (56.7 < score E ≤ 61.5) | 1.07 (0.94-1.22) | 1.10 (0.90-1.34) | | 1.05 (0.85-1.29) |
| Intermediate (43.3 < score E ≤ 56.7) | 1.34 (1.16-1.55) | 1.29 (1.06-1.57) | | 1.13 (0.92-1.40) |
| Introversion (38.5 < score E ≤ 43.3) | 1.57 (1.26-1.95) | 1.50 (1.17-1.91) | | 1.21 (0.94-1.54) |
| Typical introversion (score E ≤ 38.5) | 1.61 (1.26-2.04) | 1.90 (1.41-2.56) | | 1.46 (1.14-1.87) |
| EPQ-N (Ref: Typical neuroticism, score N > 61.5) | | | | |
| Neuroticism (56.7 < score N ≤ 61.5) | 0.42 (0.33-0.52) | 0.63 (0.45-0.88) | | 0.64 (0.45-0.91) |
| Intermediate (43.3 < score N ≤ 56.7) | 0.23 (0.20-0.27) | 0.45 (0.34-0.60) | | 0.50 (0.37-0.67) |
| Non-neuroticism (38.5 < score N ≤ 43.3) | 0.14 (0.11-0.18) | 0.31 (0.21-0.46) | | 0.36 (0.24-0.54) |
| Typical non-neuroticism (score N ≤ 38.5) | 0.06 (0.05-0.08) | 0.16 (0.11-0.22) | | 0.19 (0.13-0.26) |
| EPQ-P (Ref: Typical psychoticism, score P > 61.5) | | | | |
| Psychoticism (56.7 < score P ≤ 61.5) | 0.67 (0.51-0.90) | 0.83 (0.61-1.13) | | 0.86 (0.62-1.19) |
| Intermediate (43.3 < score P ≤ 56.7) | 0.33 (0.24-0.44) | 0.66 (0.47-0.93) | | 0.73 (0.51-1.03) |
| Non-psychoticism (38.5 < score P ≤ 43.3) | 0.12 (0.09-0.17) | 0.36 (0.26-0.50) | | 0.42 (0.30-0.58) |
| Typical non-psychoticism (score P ≤ 38.5) | 0.06 (0.04-0.09) | 0.25 (0.14-0.42) | | 0.29 (0.17-0.51) |
| Resilience (Ref: RSCA < 89): RSCA ≥ 89 | 0.32 (0.27-0.36) | | 0.42 (0.36-0.50) | 0.63 (0.52-0.77) |

SH: Self-harm; E: Extraversion; N: Neuroticism; P: Psychoticism; RSCA: Resilience Scale for Chinese Adolescents.

depressed teenagers[40]. Therefore, the usefulness and effectiveness of available emotion regulation intervention methods for the general child and adolescent population in China are yet to be corroborated.

The major advantages of the current research are that it involved a large population-based representative sample of Chinese children and adolescents, and the study design and implementation were scientific and rigorous. However, two limitations should be noted. First, due to the cross-sectional design, causal inferences were impossible. Second, the entire study sample was chosen from a single

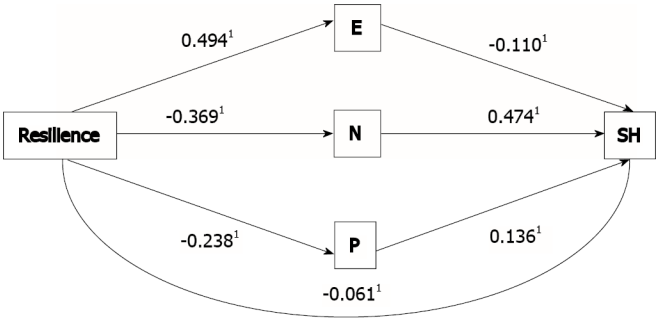


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**Figure 1 The path model of resilience, personality traits, and self-harm.** [1]Statistically significant. SH: Self-harm.

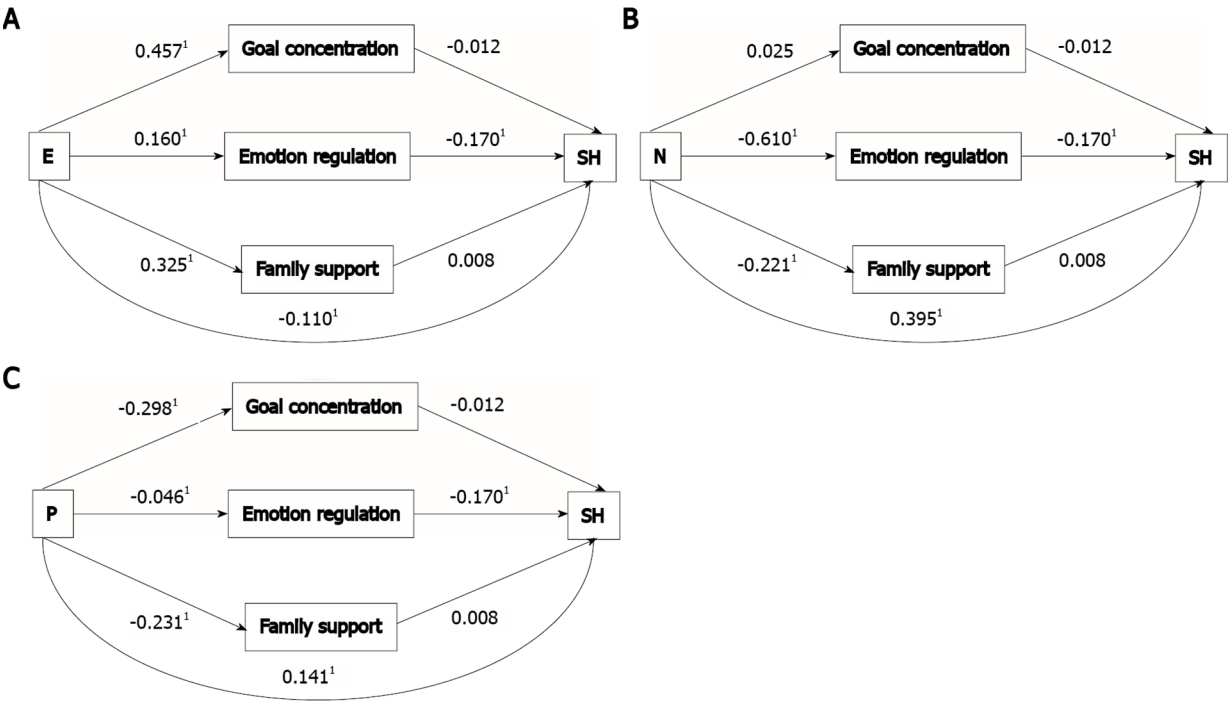


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**Figure 2 The path model of different dimensions of resilience, personality traits, and self-harm.** A: The mediation of resilience in personality traits E and self-harm (SH); B: The mediation of resilience in N and SH; C: The mediation of resilience in P and SH. [1]Statistically significant. SH: Self-harm; E: Extraversion; N: Neuroticism; P: Psychoticism.

province in southwest China; therefore, the results cannot be generalized to the entire Chinese child and adolescent population.

## CONCLUSION

In this cross-sectional study, we discussed the relationship between personality traits and SH in a large sample of Chinese children and adolescents. More importantly, we thoroughly examined the mediating role of resilience in this relationship. We found that personality traits were significantly associated with SH, and resilience was identified as a prominent mediator. Further analysis revealed that, for all the dimensions of resilience, emotion regulation was the only noticeable mediator. The major findings of our study are of significance in preventing seemingly unchangeable personality-associated SH among children and adolescents: For introverted individuals, interventions that focus on reinforcing resilience might be a promising strategy. This hypothesis should be further corroborated by future intervention studies.

## ARTICLE HIGHLIGHTS

### *Research background*

Children and adolescents are at increased risk of self-harm (SH), an established indicator of future suicide. Published studies support a positive relationship between personality traits and SH. There is a possibility that resilience may play a mediating role in the association between personality traits and SH; however, this hypothesis has never been thoroughly investigated.

### *Research motivation*

The current study aimed to provide valuable evidence for identifying personality traits that are associated with SH in children and adolescents.

### *Research objectives*

To investigate resilience as a mediator of the association between personality traits and SH among a large representative sample of Chinese children and adolescents.

### *Research methods*

We surveyed 4780 children and adolescents from Kaiyuan City, Honghe Prefecture, Yunnan province, China. The children's version of the Eysenck Personality Questionnaire was used to assess the personality traits. The Chinese Youth psychological resilience scale was used to measure the level of resilience. The revised version of the Adolescent Self-harm Scale was used to measure the lifetime prevalence of SH among the survey subjects. We used univariate and multivariate logistic regression models and path analysis to evaluate resilience as a mediator.

### *Research results*

Among the 4471 subjects included into the final analysis, the prevalence of SH was 40.1% (95%CI: 34.4%-46.0%). For different dimensions of personality traits, higher E-dimension scores and lower N- and P-dimension scores were associated with a lower SH prevalence. Resilience was identified as an obvious mediator of the associations between the three dimensions of personality and SH, accounting for 21.5%, 4.53%, and 9.65%, respectively, of the total associations. In addition, we found that, among the five dimensions of resilience, only emotion regulation was identified as a significant mediator.

### *Research conclusions*

According to the current research results, we found that resilience was a significant mediator of the association between personality traits and SH, especially the dimension of emotion regulation. Intervention measures which aim to improve resilience may be effective in preventing personality traits that are associated with SH in Chinese children and adolescents.

### *Research perspectives*

Future interventional studies are warranted to further corroborate our major findings.

## FOOTNOTES

**Author contributions:** Xiao YY conceived the study; Jiao XY, Xu CZ, Chen Y, Peng QL, Ran HL, Che YS, Fang D, Peng JW, Chen L, and Wang SF collected, verified, and analyzed the data; Jiao XY and Xu CZ drafted the manuscript; all authors provided critical revision of the manuscript for important intellectual content.

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ORIGINAL ARTICLE

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# Trends in suicide by hanging, strangulation, and suffocation in Serbia, 1991-2020: A joinpoint regression and age-period-cohort analysis

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## Abstract

***BACKGROUND***

Hanging is one of the most commonly used methods for suicide in both sexes worldwide. In a number of countries, hanging mortality has increased over the last decades. Nevertheless, there is a scarcity of studies that have explored the patterns and trends for mortality of suicide by hanging on global, regional and national levels, as most evaluations are limited to certain populations.

***AIM***

To assess the trends of suicide mortality by hanging, strangulation, and suffocation in Serbia, from 1991 to 2020.

***METHODS***

This nationwide study, with epidemiological descriptive study design, was carried out based on official data. The age-standardized rates (ASRs, expressed *per* 100000 persons) were calculated by direct standardization, using the World Standard Population. Mortality trends from suicide by hanging were assessed using the joinpoint regression analysis: The average annual percent change (AAPC) with the corresponding 95% confidence interval (95%CI) was calculated. Age-period-cohort analysis was performed to address the possible underlying reasons for the observed suicide trends.

***RESULTS***

Over the 30-year period studied, there were 24340 deaths by hanging (17750 males and 6590 females) in Serbia. In 2020, the ASR of deaths by hanging was 4.5 *per* 100000 persons in both sexes together (7.6 in males *vs* 1.7 in females). The trends of suicide mortality by hanging decreased significantly between 1991 and 2020 in

both males (AAPC = -1.7% *per* year; 95%CI: -2.0 to -1.4) and females (AAPC = - 3.5% *per* year; 95%CI: -3.9 to -3.1). Mortality rates of suicide by hanging had a continuously decreasing tendency in both sexes together in all age groups: The only exception was among males in 40-49 age group, with an increasing trend of suicide by hanging from 1991 to 2011 (by +0.3% *per* year).

*CONCLUSION*

The trends in suicide mortality by hanging have been decreasing in Serbia in the last three decades in both sexes, but this was more pronounced in women than in men. Despite the decreasing trends observed in mortality of suicide by hanging, further research is needed for better clarification of trends and help in suicide prevention in the future.

**Key Words:** Suicide; Hanging; Mortality; Trends; Joinpoint analysis

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**Core Tip:** Although scarce, previous research showed disparities in mortality trends of suicide by hanging across the world. The mortality trends of suicide by hanging decreased significantly in Serbia in the last three decades in both sexes together, but it was more pronounced in women than in men. In 2020, the age-standardized rate of mortality by hanging was 4.5 *per* 100000 persons in both sexes together (7.6 in males *vs* 1.7 in females), the male-to-female ratio was almost 5. Further research will allow a clarification of trends and help in a more effective suicide prevention.

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## INTRODUCTION

Suicide is a complex global public health issue[1-3]. According to the World Health Organization (WHO) 2000-2019 estimates, almost 800000 people die every year due to suicide across the world[4]. Previous research revealed that hanging was the predominant method of suicide in both sexes in most countries in the last decades[5,6]. Spicer and Miller[7] indicated that hanging, following firearms and drowning, was the most lethal method of suicide, while poisoning and cutting were the least lethal methods.

According to a systematic review and meta-analysis, the most common method of suicide in the Eastern Mediterranean Region of WHO was hanging (with a share of 39.7%, 95%CI: 26.8–52.7)[8]. Also, in almost all countries in Eastern Europe[4] and South Asia[9] hanging was the preferred method of suicide. During a 10-year period from 2004 to 2013 in India, poisoning as a method of suicide has declined in both genders aged 15-29 years, while hanging became the preferred method[10]. Based on the WHO mortality database, between 2000 and 2015 among 58 countries the age-standardized mortality rates of suicide by hanging among persons aged 15-64 were the highest both in males and females in Lithuania, while the highest rates among persons aged 65 years and older were both in males and females in Serbia[5]. The 20-year study (1997-2016) that examined suicides in South Africa, showed that mortality rates due to hanging increased by 3.9% *per* year in males and by 3.0% *per* year in females [11]. Similarly, over a period of 44 years (1969-2012) both sexes in Norway showed an upward trend for suicide by hanging, with a notably significant increase in men aged 15–24 years[12].

Previous studies[13-16] indicated that suicide rates were the highest among males, elderly, single individuals, those with less schooling, family disintegration, unemployment, poverty, living in rural areas, with mental illness (especially alcohol misuse). Some authors indicated that males more frequently use highly lethal methods of suicide, such as hanging or firearms, in comparison to females [17]. In people with substance use disorders in Norway, the most common cause of death in males was hanging, while in females it was poisoning[18]. A study of the effects of Greece's economic crisis during the years 2011 and 2012 recorded the strengthened seasonality of suicides, while a noteworthy suicide risk was revealed for males, persons aged 45 years or more and for suicides by hanging[19].

The 2030 Agenda for Sustainable Development adopted by the United Nations in 2015 includes a target to reduce suicide mortality by one third by 2030, and to promote mental health and wellbeing [20]. The coronavirus disease 2019 (COVID-19) pandemic has drastically changed social and daily life: Lockdown, business restrictions, school closures, social distancing policies in order to prevent the spread of the coronavirus infection, and possible delays in diagnoses of mental and other illnesses led to

increased mental stress globally, but how it is affecting the burden of suicide is not yet clear[21,22]. Nevertheless, there is a scarcity of studies that have explored the trends for mortality of suicide by hanging on global, regional and national levels, as most evaluations are limited to some populations[3,5,6].

Serbia is a country in southeastern Europe where the previous three decades marked its socio-political landscape from the end of the last to the beginning of this century, representing a time-frame of civil wars and global crisis; in addition to 1991-1999 civil wars, the break-up of Yugoslavia, influx of arrivals of more than a million refugees, devastating impact of the United Nations-imposed economic sanctions (1992-1995), a 78-d NATO's bombing in 1999, political changes and transition to democracy in 2000, and global financial crisis in 2008. As the result of dramatic socio-economic changes, the population of Serbia has experienced significant health problems[23,24]. This study aimed to evaluate the direction and magnitude of the national trends in mortality of suicide by hanging in Serbia from 1991 to 2020, with special emphasis on age, period and cohort effects.

## MATERIALS AND METHODS

### Study design

For this nationwide research, with epidemiological descriptive study design, we used data of annual underlying mortality causes in Serbia to describe mortality trends of suicide by hanging for the period 1991–2020.

### Data sources

Official death certification data for suicide by hanging, strangulation and suffocation were obtained from the Statistical Office of the Republic of Serbia (unpublished data).

During the calendar period considered, different revisions of the international classification of diseases (ICD) were used in Serbia: From 1990 to 1996 data about the main cause of death were classified by 9$^{th}$ Revision (ICD-9), and since 1997 the data processing of mortality statistics is based on 10$^{th}$ Revision (ICD-10). Mortality data of suicide by hanging, strangulation and suffocation were covered by site code E953 by ICD-9[25] and code X70 based on ICD-10[26]. In this study, term "suicide by hanging" includes deaths from suicide by hanging, strangulation and suffocation. Besides this, "suicides" include deaths from self-inflicted injury or intentional self-harm, but not those that are of undetermined intent. In Serbia, according to the WHO guidelines, the definition of the underlying cause of death includes a disease or injury that has started a series of diseases or an injury that has triggered a series of disease states that directly led to death.

Death registration and certification of cause of death in Serbia is conducted by an authorized physician in a health care organization, a coroner, or a forensic physician. The procedure is consistent throughout the whole country and comprises several levels of control and verification by another trained medical doctor or specialist. The procedures of death certification and registration in Serbia are coordinated by the Ministry of Health and the Ministry of Internal Affairs. The standard practice with unnatural deaths is that the investigating judge orders an autopsy, including toxicological analyses. All data files are confidential. The completeness of the Serbian mortality database was 98% in 2000[27]. Also, the WHO evaluated national mortality data in Serbia as medium quality, based on criteria such as completeness reporting of > 90% and ill-defined causes and injury deaths with undetermined intent appear on < 10% of registrations[28].

Estimates of the resident population, based on the official censuses (1991, 2002 and 2011 censuses), were obtained from the same Serbian national statistical database. This study comprised the whole population of Serbia (approximately 7 million inhabitants). During the study period, as a consequence of wars in the former Yugoslavia during the 1990s, Serbia had the largest populations (nearly 1000000 persons) of refugees (from the former Socialist Federal Republic of Yugoslavia) and internally displaced persons (from Kosovo & Metohia), and ranked among the top countries in the world by the number of refugees[29]. During the following decades, after the wars in the former Yugoslavia, Serbia remained at the top of the list of European countries in terms of forced migration, as well as one of the five countries in the world facing a prolonged refugee crisis[30]. The last census in 2011 showed there are nearly 300000 forced migrants living in Serbia, equaling 3.9% of the total population. Data for refugees were included in the Serbian population in the present study and could not be set aside as a special contingent.

### Statistical analysis

In this study, two types of death rates (expressed *per* 100000 persons) of suicide by hanging in Serbia were calculated: Specific (age- and sex-specific) and age-standardized. The age-standardized rates (ASRs) were calculated by the direct standardization method, using the World standard population[31] as a reference population.

The temporal trends for mortality of suicide by hanging were assessed using the joinpoint regression analysis (Joinpoint regression software, Version 4.5.0.1–June 2017, available through the Surveillance Research Program of the United States National Cancer Institute), proposed by Kim *et al*[32]. Joinpoint regression analysis was used to identify point(s), the so-called "joinpoints", where a significant change (increases or decreases) in the linear slope of the trend occurred, and to estimate annual percent change (APC) based on the trend within each segment[32]. Finally, the average annual percent change (AAPC) over the entire considered period was calculated; for each annual percent estimate, the corresponding 95% confidence interval (95%CI) was determined[33]. Due to difficulties in computing with small numbers (small number of cases reported in youngest age group), we restricted the analysis to the age group 10 years and over. Disparities in suicide mortality trends according to age and sex were tested by using a comparability test[34]. The objective of the comparability test was to designate whether the two regression mean functions were identical (test of coincidence) or parallel (test of parallelism). A $P$ value of < 0.05 was considered statistically significant. In determining the direction of temporal trends, the terms "significant increase" or "significant decrease" were used, in order to signify that the slope of the trend was statistically significant ($P$ < 0.05, on the basis of the statistical significance of the AAPC compared to zero). For non-statistically significant trends ($P$ > 0.05, while AAPC with a 95%CI overlapping with zero), the terms "non-statistically significant increase" (for AAPC > 0.5%), and "non-statistically significant decrease" (for AAPC < -0.5%) were used, while the term "stable" was used for AAPC between -0.5% and 0.5%.

The age-period-cohort analysis was performed to examine the effects of age, period, and birth cohort on the observed temporal trends using the United States NCI web-based statistical tool, according to the method proposed by Rosenberg *et al*[35]. The parameters of the age-period-cohort analysis included longitudinal age curves (indicated the fitted longitudinal age-specific rates in the reference cohort, adjusted for period deviations), the period rate ratios (represent variations in mortality rates over time associated with all age groups simultaneously), the cohort rate ratios (associated with changes in mortality rates across groups of individuals with the same birth years, that is, for successive age groups in successive time periods), and local drifts (represent the annual percentage changes for each age group, generated from log-linear regressions) with net drift (represents the average annual percentage change in mortality *per* year of birth). Due to difficulties in computing due to unstable mortality rates, we omitted < 10 and 80+ age groups from the age-period-cohort analysis. The significance test used was a 1-df Wald test. Values of $P$ less than 0.05 were considered statistically significant.

### *Ethics statement*

This study is approved by the Ethics Committee of the Faculty of Medical Sciences, University of Kragujevac (No. 01-14321).

## RESULTS

In the period 1991-2020, a total of 24340 (17750 males and 6590 females) deaths of suicide by hanging in Serbia were reported (Table 1). The overall average annual ASR was 7.0 *per* 100000 in both sexes together (ranging from 9.1 *per* 100000 in 1991 to 4.5 *per* 100000 in 2020). The average annual ASR was 11.1 *per* 100000 in men and 3.3 *per* 100000 in women. Suicide by hanging was about 3.7 times more common in males than females in Serbia.

Trend for mortality of suicide by hanging was decreasing significantly in both sexes together by -2.1% yearly (95%CI: -2.4 to -1.8), from 1991 to onwards (Figure 1A and Table 2). Overall mortality of suicide by hanging peaked at 9.2 *per* 100000 in 1993, and declined thereafter to 4.5 *per* 100000 in 2020. Joinpoint regression analysis identified one joinpoint (in 2012), with consequent two trends: Both periods showed significantly decreasing trends, firstly with APC of -1.6% (95%CI: -1.9 to -1.2) and then with APC of -4.1% (95%CI: -5.6 to -2.6).

Suicide death rates by hanging increased with age both in males and females (Tables 2 and 3). In both sexes, suicide mortality rates were almost four times higher in people aged 70 or older than in people under 70. Age-specific suicide mortality rates in males were two times higher than rates in females in people under 70 and almost three times higher in people aged 70 or older. Suicide mortality rates were decreasing significantly in all age groups in both sexes from 1991 to 2020: The only exception was for males in age group 40-49, with an unfavorable trend of suicide mortality by hanging in 1991-2011 period, with APC = +0.3% *per* year (95%CI: -0.9 to +1.4). According to comparability test, mortality trends of suicide by hanging by age were parallel ($P$ > 0.05) both in males and females.

Suicide mortality rates by hanging in males decreased from 14.1 *per* 100000 in 1991 to 7.6 *per* 100000 in the last year observed; AAPC = -1.7%, 95%CI: -2.0 to -1.4 (Figure 1B and Table 3). Joinpoint analyses of suicide mortality by hanging in males identified one joinpoint in the year 2012, with two trends: Both trends were decreasing significantly, with APC of -1.2% (95%CI: -1.6 to -0.9) and -3.7% (95%CI: -5.2 to -2.3). In females, suicide mortality rates by hanging decreased from 5.4 *per* 100000 in 1993 to 1.7 *per* 100000 in the last year observed. Trend of suicide mortality by hanging in females decreased significantly from 1991 to 2020 (AAPC = -3.5%, 95%CI: -3.9 to -3.1). According to the comparability test,

**Table 1 Suicide mortality by hanging/strangulation/suffocation in Serbia, 1991-2020; number of cases and age standardized rate *per* 100000 (using World standard population)**

| Year | All | | Males | | Females | |
|---|---|---|---|---|---|---|
| | Number | ASR | Number | ASR | Number | ASR |
| 1991 | 978 | 9.1 | 690 | 14.1 | 288 | 4.7 |
| 1992 | 1010 | 9.1 | 697 | 13.7 | 313 | 5.0 |
| 1993 | 1033 | 9.2 | 690 | 13.6 | 343 | 5.4 |
| 1994 | 948 | 8.5 | 679 | 13.3 | 269 | 4.3 |
| 1995 | 830 | 7.4 | 588 | 11.4 | 242 | 4.0 |
| 1996 | 909 | 8.3 | 638 | 12.6 | 271 | 4.5 |
| 1997 | 907 | 8.1 | 649 | 12.6 | 258 | 4.0 |
| 1998 | 857 | 7.6 | 594 | 11.6 | 263 | 4.2 |
| 1999 | 947 | 8.2 | 661 | 12.7 | 286 | 4.3 |
| 2000 | 919 | 7.7 | 646 | 12.1 | 273 | 3.9 |
| 2001 | 860 | 7.4 | 605 | 11.4 | 255 | 3.9 |
| 2002 | 876 | 7.4 | 644 | 12.0 | 232 | 3.3 |
| 2003 | 807 | 6.9 | 600 | 11.5 | 207 | 2.9 |
| 2004 | 836 | 7.1 | 623 | 11.6 | 213 | 3.2 |
| 2005 | 856 | 6.9 | 609 | 11.0 | 247 | 3.2 |
| 2006 | 881 | 7.3 | 640 | 11.7 | 241 | 3.3 |
| 2007 | 841 | 7.0 | 609 | 11.1 | 232 | 3.3 |
| 2008 | 804 | 6.9 | 572 | 10.6 | 232 | 3.4 |
| 2009 | 836 | 7.1 | 630 | 11.6 | 206 | 3.1 |
| 2010 | 745 | 5.9 | 562 | 9.7 | 183 | 2.4 |
| 2011 | 818 | 6.8 | 603 | 10.9 | 215 | 3.1 |
| 2012 | 807 | 6.7 | 616 | 11.1 | 191 | 2.7 |
| 2013 | 734 | 6.1 | 562 | 10.1 | 172 | 2.5 |
| 2014 | 720 | 5.9 | 558 | 9.9 | 162 | 2.2 |
| 2015 | 646 | 5.4 | 501 | 9.0 | 145 | 2.1 |
| 2016 | 603 | 5.2 | 451 | 8.4 | 152 | 2.2 |
| 2017 | 614 | 5.1 | 481 | 8.7 | 133 | 1.9 |
| 2018 | 586 | 4.8 | 466 | 8.2 | 120 | 1.7 |
| 2019 | 586 | 5.1 | 453 | 8.5 | 133 | 1.9 |
| 2020 | 546 | 4.5 | 433 | 7.6 | 113 | 1.7 |
| Overall | 24340 | 7.0 | 17750 | 11.1 | 6590 | 3.3 |

ASR: Age-standardized rate.

trends of suicide mortality by hanging in men and women were not parallel and not coincident ($P < 0.05$).

The risk of death from suicide by hanging increased continuously with age in both sexes together (Figure 2). The net drift was -1.8% (95%CI: -2.3 to -1.3) *per* year, and the curves of local drift values were under 0 in all age groups, with a few non-significant exceptions in the youngest age groups. Period rate ratios were significantly declining over the whole period studied, particularly after 2013. Cohort rate ratios showed significantly downward patterns, but these tendencies slowed down in recent cohorts, particularly for those born in 1951-1980 birth cohorts and after 1996. Results of Wald tests showed that the relative risk for suicide by hanging in Serbia had statistically significant ($P < 0.05$) cohort and period

**Table 2 Joinpoint regression analysis[1] of suicide mortality by hanging/strangulation/suffocation in both sexes in Serbia, by age, 1991-2020**

| Age[2] | Year 1991 | | Year 2020 | | Number of joinpoints | AAPC | Lower 95%CI | Upper 95%CI |
|---|---|---|---|---|---|---|---|---|
| | No of cases | rates | No of cases | rates | | | | |
| Age-specific rates[3] | | | | | | | | |
| 10-19 | 9 | 0.9 | 4 | 0.6 | 0 | - 2.7[1] | -4.4 | -1.1 |
| 20-29 | 56 | 5.8 | 20 | 2.5 | 0 | - 1.5[1] | -2.4 | -0.6 |
| 30-39 | 101 | 8.4 | 45 | 4.7 | 0 | - 1.2[1] | -1.8 | -0.6 |
| 40-49 | 133 | 14.1 | 69 | 7.1 | 0 | - 1.5[1] | -2.2 | -0.8 |
| 50-59 | 190 | 17.5 | 100 | 10.8 | 0 | - 1.4[1] | -1.8 | -1.1 |
| 60-69 | 219 | 23.7 | 123 | 12.4 | 0 | - 2.8[1] | -3.1 | -2.4 |
| 70-79 | 161 | 48.6 | 107 | 18.5 | 0 | - 3.5[1] | -4.1 | -2.9 |
| 80+ | 109 | 76.5 | 78 | 24.5 | 0 | - 3.4[1] | -3.9 | -3.0 |
| Age-standardized rates[3] | | | | | | | | |
| All ages | 978 | 9.1 | 546 | 4.5 | 1 | -2.1[1] | -2.4 | -1.8 |

[1]Statistically significant trend.
[2]Joinpoint results are not shown for the subgroups aged < 10 yr, because during the observed period, a total of 2 cases of suicide by hanging/strangulation/suffocation deaths occurred in both sexes.
[3]*Per* 100000 people.
AAPC: Average annual percentage change; CI: Confidence interval.

effects, as well as the net drift and local drifts.

In Serbia in both males and females, the risk of death from suicide by hanging increased by age (Table 4). The period effects have showed a downward pattern since 2013 in males, while continuously decreasing in females. The risk of deaths by hanging decreased, in general, with birth cohort in both sexes in Serbia, with stable cohort effects for men and women born between 1946 and 1966. The local drift values were under zero in all age groups in both genders, while an insignificant value was observed in age groups < 50 in males and < 30 in females (data not shown). The net drift was −1.4% (95%CI: −1.9 to −0.9) in males, and in females it was −3.7% (95%CI: −5.1 to −2.2). The Wald test showed statistically significant period and cohort effects for both genders, as well as net drift, but the local drifts were not statistically significant ($P > 0.05$).

## DISCUSSION

This study described mortality trends of suicide by hanging in Serbia over a 30-year period from 1991 to 2020. Male predominance in suicide rates by hanging was showed. Trends of suicide mortality by hanging have been decreasing in both sexes and all age groups, but it was more pronounced in women than in men. Furthermore, this population-based analysis revealed significant period and birth-cohort effects in mortality of suicide by hanging.

Unfortunately, national-level data on the suicide by hanging are quite limited[36]. In the WHO mortality database, only about one third of the WHO Member States reported data on methods of suicide, and that was mostly highly developed countries[5,36]. The data on global suicides mortality by hanging are much clearer for high-income countries, which account for 50% of all suicides by hanging in the world. Hanging was a common method of suicide in Europe between 1970 and 2009: Its prevalence in Poland was the highest, comprising 90% of all suicides, with the very high (7:1) male-to-female rate ratio[37], while lower prevalence of suicides by hanging with sex differentials was reported in Estonia [38], Germany[39], Austria[40], and Finland[41]. The earlier study on suicide-related mortality in Serbia indicated that hanging accounted for 61.2% of all suicides in the 1991-2014 period, with a 3:1 male-to-female rate ratio[24]. However, data on mortality rates of suicide by hanging at the national level are still very sparse.

This manuscript indicates an annual ASR of suicide by hanging of 4.5 *per* 100000 population in Serbia in 2020 (7.6 for males and 1.7 for females). In Canada in 2018 an ASR of hanging of 9.6 was recorded in males and 3.0 in females[42]. In Australia, from 1986 to 2005, ASR of hanging was 7.33 in males and 1.47 in females, with increasing trends[43]. In India in 2014, ASR of suicide by hanging was 6.1 among males and 2.6 among females[44]. Based on the WHO mortality database, among 58 countries in 2015, ASR of

**Table 3 Joinpoint analysis: Trends[1] in age-specific suicide mortality rates (*per* 100000) by hanging/strangulation/suffocation in Serbia, by sexes, 1991-2020**

| Age[2] | Males | | Females | |
|---|---|---|---|---|
| | Period | APC (95%CI) | Period | APC (95%CI) |
| 10-19 | 1991-2020 | -2.8[1] (-4.4 to -1.0) | [3] | |
| 20-29 | 1991-2020 | -1.2[1] (-2.1 to -0.3) | [3] | |
| 30-39 | 1991-2014 | -0.1 (-1.0 to +0.7) | 1991-2020 | -2.2[1] (-3.3 to -1.1) |
| | 2014-2020 | -7.7[1] (-13.5 to -1.5) | | |
| | Full period[4] | -1.1[1] (-1.7 to -0.4) | | |
| 40-49 | 1991-2011 | +0.3 (-0.9 to +1.4) | 1991-2020 | -3.2[1] (-4.4 to -2.1) |
| | 2011-2020 | -4.9[1] (-8.5 to -1.1) | | |
| | Full period | -1.0[1] (-1.7 to -0.2) | | |
| 50-59 | 1991-2020 | -0.8[1] (-1.3 to -0.4) | 1991-2020 | -3.2[1] (-4.0 to -2.5) |
| 60-69 | 1991-2020 | -2.3[1] (-2.8 to -1.8) | 1991-2008 | -2.2[1] (-3.8 to -0.6) |
| | | | 2008-2020 | -7.6[1] (-10.1 to -5.0) |
| | | | Full period | -4.3[1] (-5.1 to -3.5) |
| 70-79 | 1991-2020 | -3.1[1] (-3.6 to -2.5) | 1991-2020 | -4.7[1] (-5.5 to -3.9) |
| 80+ | 1991-2020 | -3.2[1] (-3.7 to -2.7) | 1991-2020 | -3.8[1] (-4.9 to -2.8) |
| All ages | 1991-2012 | -1.2[1] (-1.6 to -0.9) | 1991-2020 | -3.5[1] (-3.9 to -3.1) |
| | 2012-2020 | -3.7[1] (-5.2 to -2.3) | | |
| | Full period | -1.7[1] (-2.0 to -1.4) | | |

[1]Statistically significant trend.
[2]Joinpoint results are not shown for the subgroups aged < 10 yr, because during the observed period, a total of 1 case of suicide by hanging/strangulation/suffocation deaths occurred in men and 1 case in women.
[3]Incalculable: Joinpoint results are not shown because fewer than 10 cases of suicide by hanging/strangulation/suffocation occurred in each of the decennium in any year.
[4]For full period presented average annual percent change.
APC: Annual percent change; CI: Confidence interval.

suicide by hanging among persons aged 15-44 was the highest both in males and females in Guyana (73.4 and 24.4, respectively), among persons aged 45-64 it was the highest in males in Lithuania (88.1) and in females in Belgium (18.0), while among persons aged 65 years and older rates were the highest in Republic of Korea (106.0 and 32.2, respectively)[5]. Variations in suicide rates can be attributed to many different factors, such as social, economic, personal factors, mental health[45,46]. Numerous studies confirmed association between unemployment rates and suicide rates by hanging[47]. In many countries (like Lithuania and other Eastern European countries, Brazil, the United States of America), mortality rates of suicide were linked to alcohol consumption[46,48,49]. The Serbian National health surveys (2000, 2006, 2013, 2019)[50] reported a lower prevalence of risk factors such as alcohol use and substance abuse in population of Serbia compared to most of the neighbouring countries and other countries in Europe[51]. Also, variations in mortality by hanging can be partly interpreted as the effects of availability of lethal methods, suicide prevention efforts, mental health diagnosis and treatment availability[52,53]. In India, more developed states with higher agricultural employment and higher literacy reported higher rates of suicide by hanging[44]. Although it is always a question whether the differences in suicide mortality rates are real or reflect variations in data quality worldwide, suicide by hanging is less likely to be misclassified as unintentional or undetermined death unlike other suicide methods[6].

Study about suicide mortality by hanging in 58 countries reported higher suicide mortality in males compared with females[5]. Similar to other countries, mortality rates of suicide by hanging were considerably higher (3.7:1) in men compared to women in Serbia, which might be because of the differences in alcohol use, substance abuse, mental health, marital status or unemployment between males and females. The 2019 Serbian National Health Survey determined that, in the last 12 months, 1.7% of Serbian population (3.2% of men and 0.3% of women) at least once a week drank risky on a single occasion of drinking (equivalent to 60 g of pure ethanol or more)[50]. Every month, 18.3% of men and

**Table 4 Age, period, and cohort effects on suicide mortality by hanging/strangulation/suffocation in Serbia, by sexes, 1991-2020**

| Group | | Males | | Females | |
|---|---|---|---|---|---|
| | | Effect | 95%CI | Effect | 95%CI |
| Age | 10-14 | 1.7 | 0.9–3.1 | 0.8 | 0.2–3.1 |
| | 15-19 | 4.4 | 3.0–6.4 | 1.6 | 0.7–3.6 |
| | 20-24 | 8.4 | 6.3–11.3 | 2.9 | 1.6–5.2 |
| | 25-29 | 9.3 | 7.1–12.1 | 3.1 | 1.8–5.2 |
| | 30-34 | 10.8 | 8.7–13.5 | 3.7 | 2.5–5.5 |
| | 35-39 | 12.7 | 10.5–15.4 | 4.2 | 2.9–5.9 |
| | 40-44 | 15.3 | 12.9–18.2 | 4.2 | 3.1–5.9 |
| | 45-49 | 17.4 | 14.8–20.5 | 5.1 | 3.7–6.9 |
| | 50-54 | 21.1 | 17.1–23.7 | 5.2 | 3.8–7.1 |
| | 55-59 | 21.5 | 17.3–24.3 | 5.2 | 3.7–7.1 |
| | 60-64 | 21.4 | 17.7–25.8 | 5.2 | 3.7–7.3 |
| | 65-69 | 21.2 | 17.3–25.9 | 5.3 | 3.7–7.6 |
| | 70-74 | 25.1 | 20.3–31.0 | 5.5 | 3.8–8.0 |
| | 75-79 | 30.8 | 24.5–38.5 | 5.7 | 3.9–8.4 |
| Period | 1991-1995 | 1.1 | 0.9–1.2 | 1.3 | 1.1–1.7 |
| | 1996-2000 | 1.0 | 0.9–1.2 | 1.2 | 1.0–1.5 |
| | 2001-2005 | 1.0 | 1.0–1.0 | 1.0 | 1.0–1.0 |
| | 2006-2010 | 1.0 | 0.9–1.1 | 0.9 | 0.7–1.1 |
| | 2011-2015 | 0.9 | 0.8–1.0 | 0.7 | 0.5–0.9 |
| | 2016-2020 | 0.7 | 0.6–0.8 | 0.5 | 0.4–0.7 |
| Cohort | 1916–1920 | 2.9 | 2.0–4.3 | 6.4 | 3.6–11.3 |
| | 1921–1925 | 2.2 | 1.7–2.9 | 4.5 | 2.9–7.0 |
| | 1926–1930 | 1.9 | 1.5–2.4 | 3.3 | 2.2–4.9 |
| | 1931–1935 | 1.7 | 1.4–2.1 | 2.7 | 1.9–3.9 |
| | 1936–1940 | 1.4 | 1.2–1.7 | 2.3 | 1.6–3.3 |
| | 1941–1945 | 1.2 | 1.0–1.5 | 1.9 | 1.3–2.6 |
| | 1946–1950 | 1.1 | 0.9–1.3 | 1.4 | 1.0–2.0 |
| | 1951–1955 | 1.1 | 0.9–1.3 | 1.1 | 0.8–1.5 |
| | 1956–1960 | 1.1 | 0.9–1.3 | 1.1 | 0.8–1.6 |
| | 1961–1965 | 1.0 | 1.0–1.0 | 1.0 | 1.0–1.0 |
| | 1966–1970 | 0.9 | 0.8–1.1 | 0.8 | 0.5–1.2 |
| | 1971–1975 | 0.9 | 0.8–1.2 | 0.6 | 0.4–0.9 |
| | 1976–1980 | 0.9 | 0.7–1.1 | 0.7 | 0.4–1.1 |
| | 1981–1985 | 0.9 | 0.7–1.2 | 0.6 | 0.4–1.0 |
| | 1986–1990 | 0.8 | 0.6–1.1 | 0.4 | 0.2–0.8 |
| | 1991–1995 | 0.7 | 0.4–1.0 | 0.5 | 0.2–1.1 |
| | 1996–2000 | 0.7 | 0.4–1.1 | 0.2 | 0.1–1.0 |
| | 2001–2005 | 0.6 | 0.3–1.5 | 0.1 | 0.0–4.7 |
| | 2006–2010 | 0.4 | 0.0–2.9 | 0.1 | 0.0–49.4 |

Wald Chi-square tests for estimable functions, *P* value

| | | |
|---|---|---|
| Net drift | < 0.000 | < 0.000 |
| All period rate ratios | < 0.000 | < 0.000 |
| All cohort rate ratios | < 0.000 | < 0.000 |
| All local drifts | 0.092 | 0.897 |

CI: Confidence interval.

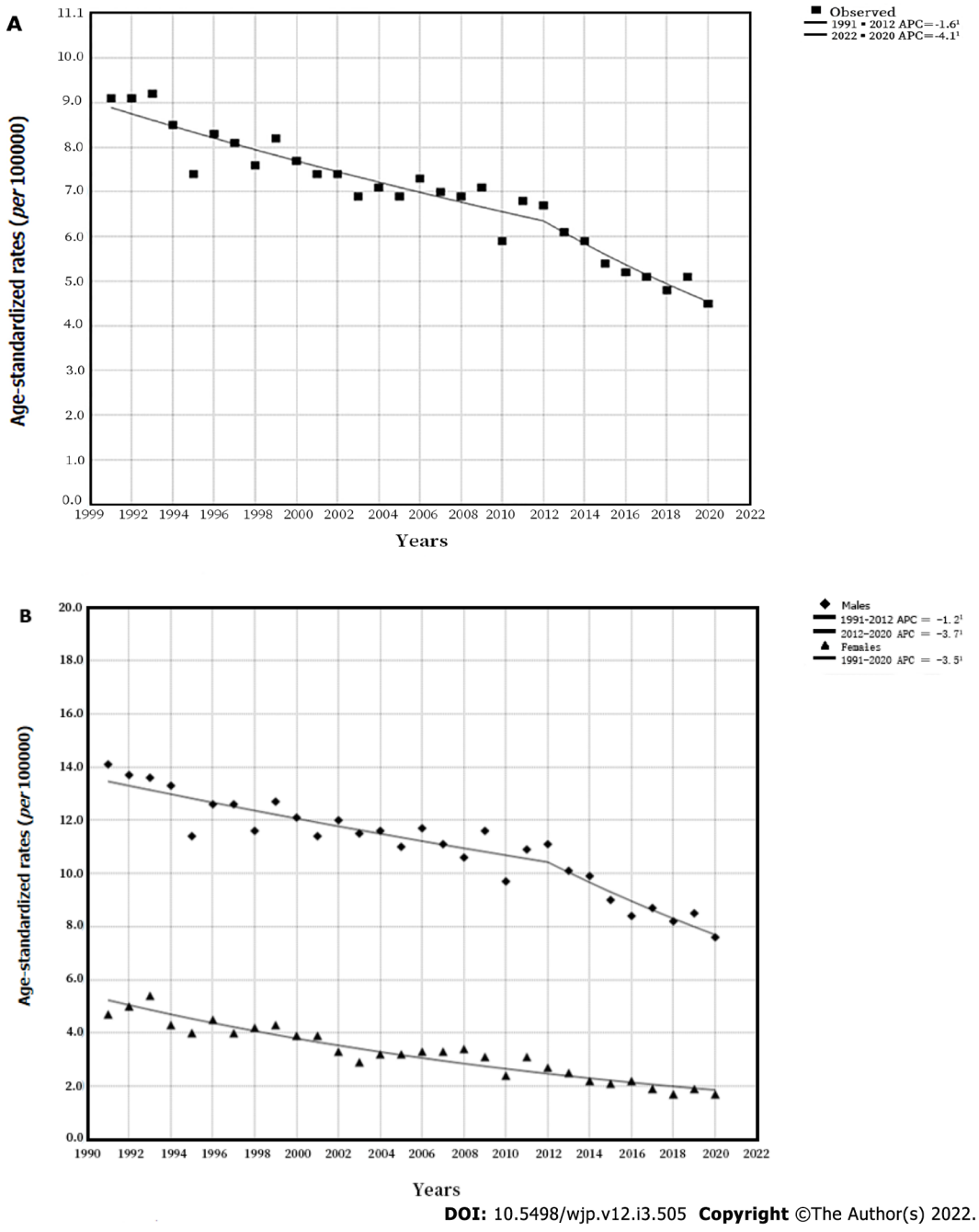


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**Figure 1 Trend in suicide mortality by hanging/strangulation/suffocation in Serbia, 1991-2020.** A: Joinpoint regression analysis; all: 1 Joinpoint; final selected model: 1 Joinpoint; B: By sex, 1991-2020; joinpoint analysis; Males: 1 Joinpoint *vs* Females: 0 Joinpoints. Final selected model: Males-1 Joinpoint, Females-0 Joinpoints. Rejected parallelism. [1]Indicates that the APC is significantly different from zero at the alpha = 0.05 level. APC: Average percentage change.

4.5% of women drank risky on a single occasion, which is a lower percentage than the European Union average[50,51]. By contrast, Serbian female population reported significantly more often the use of sedatives, sleep aids and painkillers (24.5%, 14.6%, and 44.8%, respectively) than males (11.3%, 10.4%, and 36.1%, respectively). Similar to the population in Europe, symptoms of depression were observed

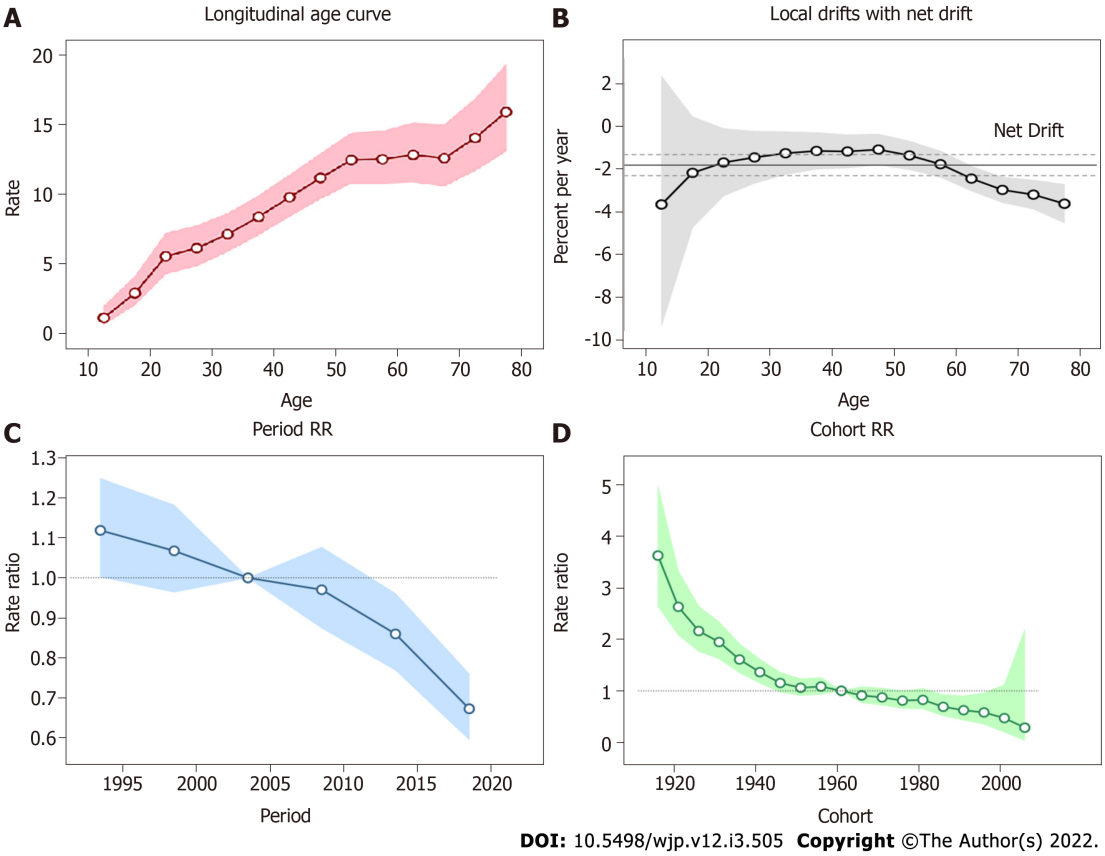


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**Figure 2 Legend: Suicide mortality by hanging/strangulation/suffocation in Serbia, by sexes, 1991-2020: An age-period-cohort analysis.** A: Longitudinal age curve of suicide by hanging mortality rates (*per* 100000 people) and 95% confidence intervals (the area colored in pink); B: Local drift value: age group-specific annual percent change (%) and 95% confidence intervals (the area colored in grey); C: Period effects for the suicide by hanging mortality rates and 95% confidence intervals (the area colored in blue); D: Cohort effects for the suicide by hanging mortality rates and 95% confidence intervals (the area colored in green). RR: Rate ratio.

more often in females (2.8%) than in males (1.5%) in Serbia in 2019. Similar to almost all countries in Eastern and Central Europe, poor social support was recorded in 15.4% of the population in Serbia, most often among residents with lower level of education, lower household income, who live in suburban settlements and the elderly[50,51].

In Serbia, mortality pattern of suicide by hanging was characterized by an initial decrease (by -1.6% *per* year) and followed by a sharp decline (by -4.1% *per* year) since 2012 (less pronounced declines observed in eldest men than in women during the study, although trends in males were parallel with trend in overall). In 2020 in Serbia, irrespective of more accelerated decreasing mortality trends of suicide by hanging in males in comparison to females in the recent decade, male-to-female rate ratio was almost 5:1, in relation to the beginning of the observed period when it was 3:1. Apart from Serbia, in both sexes together in those aged 15–65 years and above, decreasing rates of suicide by hanging have also been observed in Finland, Hungary and Switzerland from 2000 to 2015[5]. By contrast, significantly increasing death rates of suicide by hanging have been observed in some countries; for instance, in Canada by +1.1% *per* year from 1981 to 2018 for both sexes together[42], among Australians aged 10–24 years between 2004 and 2014[54], in the United States of America by +52% for all ages combined from 2000 to 2010[52], in Mexico by +11.89% from 2003 to 2012[55], in England and Wales over three decades [45], in South Korea[5,56]. Both sexes experienced an upward trend for suicide by hanging from 1969 to 2012 in Norway (by +1.5% *per* year in males and by +2.7% in females), with a particularly significant increase in 15–24 year old males[12]. The observed suicide mortality increase between 2000 and 2015 ( *e.g.*, the Republic of Korea and the United States of America) could be explained by various factors, including financial crisis, increased unemployment and easy access to highly lethal methods such as hanging[5,45]. Also, the observed increase in suicide by hanging could possibly be explained by substitution with other methods, primarily of suicide by firearms or by poisoning, thanks to stricter gun control, control of pesticide use, prescription of drugs, *etc.*[57-60]. Significant differences in suicide mortality by sexes could be explained by different prevalence of the main risk factors (such as mental disorders, alcohol and drug abuse)[5]. Gender differences regarding suicidal behavior, also known as the "gender paradox of suicidal behavior", include several factors that have a gender-dependent impact on suicidal behavior, such as stressful life events, socio-demographical factors, socio-economical factors, sexual abuse, psychiatric (co)morbidity, attitude towards antidepressant treatment, choice of suicide

methods[17]. The 2019 Serbian National Health Survey recorded depressive symptoms in 2.1% of Serbian population, which is a decrease compared to 2013 (4.1%)[50]. Also, 49.3% of Serbian population consumed alcohol: 3.1% drank every day, which is lower than in 2013 (4.7%) and 2006 (3.4%). Although different revisions of the ICD were used in Serbia, from 1991 to 1996 and from 1997 to 2000, this could not have notably affected some of the trend changes observed during the period observed, both because the changes would be reflected in trends in both sexes and because the incidence of symptoms and insufficiently defined conditions in the structure of general mortality has not changed significantly[61]. Besides this, the implementation of national guidelines for suicide prevention only in some countries might, at least partly, explain the observed differences in suicide mortality rates and trends in the world [62].

Mortality from suicide by hanging in Serbia has been declining since 1991 in all age groups in both genders. The risk of death of suicide by hanging declined continuously in every subsequent birth cohort since 1916. In contrast, the earlier study on suicide-related mortality in Serbia showed non-significant declining mortality trends of suicide by hanging in males aged 20-59 in 1991-2014 period[24]. An increasing excess suicide rate in men was observed in Poland between 1970 and 2009, and the suicide rate peaked at ages 40-54 years[37]. In Canada, between 1981 and 2018, there was an increasing trend in suicide by hanging for both males and females aged 10-64, and a decreasing suicide trend at ages 65+ years[42]. In the United States of America, between 2000 and 2010, trends in suicide by hanging/suffocation increased for ages 15-69, and decreased at ages 70+ years[52]. In Japanese aged 15 or above, in 1990–2011, the trend for suicide by hanging in males increased by +2.4% *per* year, while in females it remained flat[61].

However, Serbia saw a non-significant increase in mortality of suicide by hanging in males aged 40-49 from 1991 to 2011. The possible explanations for this unfavorable trend during this period in males include the devastating effects of civil wars, the economic and political sanctions, the collapse of the economy, the hyperinflation of the national currency, the notable drop in general living standard, the poor quality of health services (shortage of drugs, medical equipment, together with a large number of wounded individuals, decreasing hospitalization rates, particularly for people aged ≥ 60 years), the influx of more than a million refugees and social disintegration all generated circumstances where suicide prevention and management presented a significant challenge in medical practice[63,64]. The autopsy protocols of all 44 suicides committed by war veterans in the capital Belgrade over the 1991-2000 period showed that 27.3% of veterans had posttraumatic stress disorder, 9.1% had major depression and 6.8% had schizophrenia, while most suicides (84.1%) were committed by recruits of the Yugoslav National Army who spent 3-8 mo in the zone of war operations[65]. Contrary, among migrants of the Balkan wars in Sweden during the 1991-2001 Balkan wars, in comparison to other European migrants in Sweden during the same period, the risk of death from somatic diseases and psychiatric disorders, particularly post-traumatic stress disorder, was elevated, while the risk of suicide was reduced[66]. The reason for decreased risk of suicide in migrants from the Balkan wars could possibly be because those people were not having mental health problems, maintained a high drive for survival despite adversity, and also had increased surveillance, such as more frequent health check-ups in Sweden.

But, the decline in the rates of deaths by hanging is not fully explained. Differences in the classification of causes of death and in postmortem examinations exist across countries[67]. Registration of autopsies in Serbia began in 2006, with stable autopsy rate of about 2% of all deaths from 2006 to 2015, so it is unlikely that this affected the coding of mortality from suicide by hanging[51]. Furthermore, some level of underreporting might exist[68,69]. International comparisons are also complicated by methodological differences between studies: *i.e.* some studies considering trends of suicide mortality, but not all, in analysis comprised code ICD-10 X70 together with the undetermined death (particularly codes ICD-10 Y20, Y87.0)[1-3,5,6]. However, the authors consider that the changes in trends of suicide mortality could not be explained by underreporting or misclassification alone[70].

The COVID-19 pandemic has brought other circumstances detrimental to mental health that were not seen during the economic downturns, such as fears of virus infection, social distancing, isolation at home and quarantine. Some authors indicated that quarantine was associated with negative psychological effects, such as symptoms of post-traumatic stress, depression and anxiety, observed in China and Canada during the 2003 outbreak of severe acute respiratory syndrome (SARS)[71,72]. In the context of COVID-19-related consequences, suicide prevention that must include joint measures such as financial provisions and social support programs, as well as timely access to mental healthcare and optimal treatment for mental disorders is urgently needed[73].

The changes in trends in suicide by hanging require attention from health authorities and indicate a need for innovations in approaches to suicide prevention. In order to take the right action, the understanding of the scale of the problem is critical for prevention. Recognizing changes in methods of suicide is important because preventive measures aimed toward this growing problem across certain countries are necessary (*e.g.* improving mental health literacy, less availability of the method, such as in certain hospitalized or incarcerated individuals, correctional facilities *etc.*). Further research is needed in order to allow a much better clarification of suicide trends and help in a more effective prevention of suicide by hanging[45,62].

### *Strengths and limitations*

To the best of our knowledge, this is the first report which quantifies national mortality trends of suicide by hanging in Serbia from the year 1991 through 2020. Another strength is that it covers the whole population of Serbia using mortality data which is evaluated as medium quality based on the WHO criteria[28], with trends analyzed by both joinpoint and age-period-cohort analysis. Thus, the satisfactory reliability and validity of mortality statistics of suicide in Serbia enable international comparison. However, there were several limitations in this study. Of course, the question of data quality always exists due to a possibility of underreporting or misclassification of suicide. Although a longer study period might provide a more accurate assessment of mortality time trends, no data were available for a longer period in Serbia. There are no separate data on mortality among population of refugees and internally displaced persons, which might confound the pattern of suicide mortality in Serbia. Also, age-period-cohort analysis has inherent limitations (such as ecological fallacy or collinearity among age, period, and cohort effects). Besides this, although this study was population-based and could not investigate individual factors that contributed to the changes in trends of suicide mortality, this is a nationwide study that suggests strong period and birth cohort effects as determinants of changes in suicide by hanging in Serbia.

## CONCLUSION

The trends in suicide mortality by hanging have been decreasing in Serbia in the last three decades in both sexes, but this was more pronounced in women than in men. Despite the decreasing trends observed in mortality of suicide by hanging, further research is needed for better clarification of trends and help in suicide prevention in the future.

## ARTICLE HIGHLIGHTS

### *Research background*

Hanging is one of the most commonly used methods for suicide in both sexes worldwide.

### *Research motivation*

Although scarce, previous research showed disparities in mortality trends of suicide by hanging across the world.

### *Research objectives*

The aim of this manuscript was to assess the trends of suicide mortality by hanging in Serbia, from 1991 to 2020.

### *Research methods*

This population-based study was based on official data. The age-standardized rates (ASRs, expressed *per* 100000 persons) were calculated by direct standardization, using the World Standard Population. Mortality trends from suicide by hanging were assessed using the joinpoint regression analysis: The average annual percent change (AAPC) with the corresponding 95% confidence interval (95%CI) was calculated. In order to address the possible underlying reasons for observed suicide trends, an age-period-cohort analysis was performed.

### *Research results*

Over the 30-year period studied, there were 24340 deaths by hanging (17750 males and 6590 females) in Serbia. In 2020, the ASR of deaths by hanging was 4.5 *per* 100000 persons in both sexes together (7.6 in males *vs* 1.7 in females). The trends of suicide mortality by hanging decreased significantly between 1991 and 2020 in both males (AAPC = -1.7% *per* year; 95%CI: -2.0 to -1.4) and females (AAPC = -3.5% *per* year; 95%CI: -3.9 to -3.1). The suicide by hanging rate was found to increase with increasing age in both sexes. Mortality rates of suicide by hanging had a continuously decreasing tendency in both sexes together in all age groups: The only exception was among males in 40-49 age group, with an increasing trend of suicide by hanging from 1991 to 2011 (by +0.3% *per* year).

### *Research conclusions*

The trends in suicide mortality by hanging have been decreasing in Serbia in the last three decades in both sexes, but this was more pronounced in women than in men.

### *Research perspectives*

Further research will allow a clarification of trends and help in a more effective suicide prevention.

## FOOTNOTES

**Author contributions:** All authors equally contributed to this paper with conception and design of the study, data acquisition and analysis, drafting and critical revision and editing, and approval of the final version.

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ORIGINAL ARTICLE

Prospective Study

# Trajectories of response in schizophrenia-spectrum disorders: A one-year prospective cohort study of antipsychotic effectiveness

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## Abstract

*BACKGROUND*

Antipsychotic drugs remain the mainstay of schizophrenia treatment; however, their effectiveness has been questioned, and it is not possible to predict the response to a specific antipsychotic drug in an individual patient. Thus, it is important to compare the effectiveness of the various antipsychotics and search for possible response predictors.

*AIM*

To investigate the effectiveness of antipsychotic drugs, we examined response trajectories and predictors for belonging to different trajectory groups.

*METHODS*

The Bergen-Stavanger-Innsbruck-Trondheim (BeSt InTro) trial compared the effectiveness of three atypical antipsychotics-amisulpride, aripiprazole, and

olanzapine-in a prospective, semirandomized, rater-blind, head-to-head design. Adult participants with a schizophrenia spectrum disorder diagnosis, according to international classification of diseases, Tenth Revision (ICD-10) F20–29, were included. Participants were followed for a period of 12 mo, with assessments at baseline; after one, three and six weeks; and after three, six, nine and 12 mo. A latent class mixed model was fitted to our data. The three-trajectory model based on the Positive and Negative Syndrome Scale (PANSS) total score reduction was found to have adequate fit, and the study drugs, as well as various demographic and clinical parameters, were tested as predictors for belonging to the different trajectory groups.

***RESULTS***

Overall, 144 participants were included, and 41% completed the 12-mo study period. The largest trajectory group, consisting of 74% of participants, showed a PANSS total score reduction of 59% from baseline to 12 mo (Good response group). A trajectory group comprising 13% of participants had their PANSS total score reduced by 82.5% at 12 mo (Strong response group), while the last response trajectory group comprising 13% of the participants had a PANSS total score reduction of 13.6% (Slight response group). The largest part of the total reduction for the Good and Strong response groups occurred at six weeks of treatment, amounting to 45% and 48% reductions from baseline, respectively. The use of amisulpride predicted belonging to the Strong response group, while unemployment, depression, and negative psychotic symptoms at baseline increased the chance of belonging to the Slight response group, indicating a poor response to antipsychotic drug treatment.

***CONCLUSION***

Most of the participants (87%) had a good outcome after one year. Amisulpride users, more often than aripiprazole and olanzapine users, belonged to the response trajectory group with a strong response.

**Key Words:** Schizophrenia; Response; Trajectories; Treatment; Antipsychotic drugs

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**Core Tip:** In this clinical trial of the three atypical antipsychotics amisulpride, aripiprazole, and olanzapine, we identified three trajectory groups of responses at the one-year follow-up. The majority of the study participants (87%) followed a trajectory of a good or strong response to antipsychotic drugs, while 13% showed a poor response. The use of amisulpride predicted belonging to the Strong response group. This antipsychotic should therefore be used more often in clinical practice. Unemployment, depression, and negative psychotic symptoms at baseline predicted nonresponse to antipsychotic drugs.

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## INTRODUCTION

Antipsychotic drugs remain one of the most effective interventions for patients with schizophrenia-spectrum disorders[1], as recommended by the guidelines for schizophrenia treatment[2,3]. The choice of antipsychotic drug is based on its efficacy and side-effect profile, the patient's personal history of previous response to antipsychotics, and the clinician's experience with different types of antipsychotics [2,4]. Several studies exist on the efficacy of the various antipsychotic drugs in both multiple-episode and first-episode schizophrenia, including pairwise and network meta-analyses, which conclude that antipsychotic drugs are generally more efficacious than placebo[1,5,6]. However, the long-term use of antipsychotic drugs has been criticized because of the associated severe side effects, including brain structural changes[7] and metabolic abnormalities[8]. Moreover, a study showed that nonmedicated patients with schizophrenia performed better after the first three years of illness[9]. Many studies support, however, the effect of antipsychotic drugs on both symptom improvement and social function, as well as on the risk of hospitalization, mortality, and suicidality[10-12]. These results apply both to first-episode and multiple-episode treatment-resistant schizophrenia.

There are various ways to describe the effects of antipsychotic drug treatment on patients with schizophrenia. Important parameters include medication adherence and side effects, symptom improvement, and illness relapse. Clinicians and researchers in the field of schizophrenia frequently use the terms "treatment response", "symptom remission", and "recovery". However, not all of these concepts have been clearly defined, and it is of high importance to agree on their definitions and rating methods to enhance the quality of clinical practice and research in schizophrenia. The first step in the progress of schizophrenia treatment is the response to antipsychotic drugs, which provides an amelioration of mostly positive psychotic symptoms and helps patients maintain stability. The second step is the remission of symptoms, where a prolonged improvement of key schizophrenia symptoms can be seen. The last and most difficult stage to achieve is recovery, where the patient enjoys functional and social autonomy, with no symptoms of schizophrenia or mild symptoms over a long period.

There remains a lack of consensus on the definition of standardized response criteria. Researchers have used different criteria based on the reduction of the Positive and Negative Syndrome Scale (PANSS)[13] total score and the Brief Psychiatric Rating Scale (BPRS)[14] score from baseline[15,16]. Various cutoffs have been used in clinical trials, from at least 20% to 30%, 40%, or 50% of the baseline score. Another issue is the clinical significance of the measured response, and researchers have proposed solving this problem by linking the PANSS and BPRS scores to Clinical Global Impression (CGI) scales[17]. They concluded that it is useful to apply both PANSS and CGI, as they measure different dimensions, and that it is possible to link PANSS scores to CGI scores. For example, the importance of a 20% reduction in PANSS score varies from the perspective of treating refractory patients *vs* acutely ill, nonrefractory patients[18,19]. In a study of response to antipsychotics in drug-naive patients with schizophrenia, 71% responded to second-generation antipsychotics at the one-year follow-up, with a 50% drop in baseline PANSS total score[20]. A shorter duration of untreated psychosis, compliance with medication treatment, and alcohol and other substance use were important predictors influencing response but not remission.

The course of schizophrenia is highly heterogeneous, and it has not yet been possible to predict which patient will respond adequately to which antipsychotic drug. An important aim of current research is to define predictors of medication response. A novel way to examine response is to define trajectories that describe the timeframe of symptom change. Trajectories also provide better information about the course of schizophrenia than dichotomized measures of success or failure of treatment, as the latter does not capture the complexity of treatment response.

### Aims of the study

In our study, the Bergen-Stavanger-Innsbruck-Trondheim (BeSt InTro) study, we compared the efficacy of three antipsychotic drugs-amisulpride, aripiprazole, and olanzapine-after a 12-mo follow-up[21]. The primary aim of this study was to define trajectories for the pooled 12-mo response to treatment with three different antipsychotic drugs. We then wanted to identify possible predictors for belonging to a certain response trajectory in the studied cohort.

## MATERIALS AND METHODS

### Design and duration

This cohort study included participants in the BeSt InTro study, a 12-mo prospective, randomized, rater-blind, head-to-head comparison of amisulpride, aripiprazole, and olanzapine[21]. Each participant was randomized to a sequence of the examined antipsychotic drugs, for example amisulpride-olanzapine-aripiprazole or aripiprazole-amisulpride-olanzapine. The patient was offered the first drug in the randomized sequence, and this drug was the basis of the intention-to-treat (ITT) analyses. If the first drug could not be used because of previous inefficacy or tolerability issues, the patient was offered the next drug in the randomized sequence. The drug that was actually chosen was the basis of the preprotocol (PP) analyses.

Participants were followed over a period of 12 mo, and the assessment points were at baseline and then after one week, three weeks, six weeks, three months, six months, nine months, and 12 mo. The study medications were administered as oral tablets, and the dosing intervals were 50–1200 mg/d for amisulpride, 5–30 mg/d for aripiprazole, and 2.5–20 mg/d for olanzapine.

The participating study centers were in Bergen, Trondheim, and Stavanger in Norway in collaboration with the Schizophrenia Research Group in Innsbruck, Austria.

### Study population

The inclusion criteria were 18 years of age or more and a diagnosis within the schizophrenia spectrum according to International Classification of Diseases, Tenth Revision (ICD-10) diagnoses F20–29. Participants should also have symptoms of ongoing psychosis as determined by a score of four or more on at least one of the following PANSS items: P1 (delusions), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution), or G9 (unusual thought content).

Exclusion criteria were the inability to understand the native language, organic psychosis due to limbic encephalitis, pregnancy or breastfeeding, hypersensitivity to the active substance or any of the excipients of the study drugs, prolactin-dependent tumors, pheochromocytoma, lactation, combination with medications that could induce torsade de pointes, and patients with known risk of narrow-angle glaucoma.

Patients' clinical condition and capability of providing informed consent were confirmed by their attending physician or psychiatrist. All patients entering the study provided written informed consent. More information about randomization and concomitant medications can be found in the BeSt InTro primary outcome publication[21].

### Outcome measures

The primary outcome measure was the change in PANSS total score during the one-year follow-up, which corresponded to the minimum recommended time of maintenance antipsychotic drug therapy after an acute psychotic episode in patients with schizophrenia[22,23]. To compute the percentage reduction in PANSS, we subtracted 30 points, as this is the minimum score possible. To calculate response rates, we used the following formula: [(PANSS baseline-30)-(PANSS followup-30)] × 100/(PANSS baseline-30)[15].

We used the Structured Clinical Interview for the PANSS. All investigators conducting assessments were trained and calibrated by the PANSS Institute (https://panss.org/) until satisfactory interrater reliability was achieved.

Other outcome measures included the Calgary Depression Scale for Schizophrenia (CDSS), the CGI-Severity of Illness scale (CGI-S), and the Global Assessment of Functioning scale (GAF) as the average of GAF function and GAF symptom scale score[24].

### Data analyses/statistical methods

A latent class mixed model (LCMM) with PANSS total score as a dependent variable, time as an independent fixed variable, and subject as a random intercept was fit to our data. The model fitting was performed in R using the LCMM package[25]. Models with a different number of latent classes and with the time variable on different functional forms were investigated. The Bayesian information criterion (BIC) and entropy were used to select the best model. Lower BIC and higher entropy values indicate a better model fit. Differences between the latent classes obtained by the LCMM model were examined. The model with three latent classes and with time represented as visit number best fit the data. We labeled the three different response groups as "Strong response group", "Good response group" and "Slight response group". Comparisons between response groups were performed by analyzing categorical and continuous variables with the use of chi-square tests and one-way ANOVAs in IBM SPSS Statistics (version 24). In the case of significant ANOVA tests, post hoc pairwise analyses were performed using Tukey's test. In the antipsychotic drug use comparison among response groups, we divided the patients according to the ITT method, and post hoc pairwise analyses were conducted using Fisher's test.

The data were also analyzed by splitting the patients into two groups: The Good and Strong response groups were merged into the "Response group", and the Slight response group was labeled the "Nonresponse group".

### Ethics and monitoring

The study was approved in Norway by the Regional Committees for Medical and Health Research Ethics and the Norwegian Medicines Agency and in Austria by the Ethical Committee of the Medical University of Innsbruck and the Austrian Federal Office for Safety in Health Care (BASG).

The Department of Research and Development in Haukeland University Hospital conducted clinical monitoring according to the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) in Norway; in Austria, this was performed by the Clinical Trial Centre at the Medical University of Innsbruck.

## RESULTS

### Subjects

Between October 20, 2011 and December 30, 2016, 359 participants were assessed for eligibility, and 144 were included and randomized to one of the study drugs. In total, 215 patients were excluded (107 did not meet the inclusion criteria, 82 declined to participate, and 26 for other reasons). Fifty-nine participants (41%) completed the 12-mo study period. The demographic and clinical characteristics for each response trajectory group are presented in Table 1.

In the cases of missing data, the total number of patients with data available for analysis was as follows: White: 134; Living alone: 137; Employed: 136; Smokers: 127; Alcohol abuse/dependence: 135; Drug abuse/dependence: 136; DUP: 65; Years of education: 127; GAF: 143; CDSS: 135.

**Table 1 Baseline demographic and clinical characteristics in response trajectory analyses (mean ± SD)**

| | Strong response group (*n* = 19) | Good response group (*n* = 106) | Slight response group (*n* = 19) | Total (*n* = 144) | *P* value (3 groups) | *P* value (2 groups) |
|---|---|---|---|---|---|---|
| | *n* (%) | *n* (%) | *n* (%) | *n* (%) | | |
| Men | 13 (68.4) | 70 (66) | 10 (52.6) | 93 (64.6) | 0.495 | 0.242 |
| White | 14 (87.5) | 87 (87.9) | 17 (89.5) | 118 (88.1) | 0.978 | 0.837 |
| Living alone | 7 (38.9) | 48 (48) | 6 (31.6) | 61 (44.5) | 0.640 | 0.418 |
| Employed | 3 (17.6) | 32 (32) | 1 (5.3) | 36 (26.5) | 0.036 | 0.024 |
| Smokers | 13 (81.2) | 58 (61.1) | 13 (81.2) | 84 (66.1) | 0.113 | 0.172 |
| Alcohol abuse/dependence | 2 (13.3) | 8 (7.9) | 3 (15.8) | 13 (9.6) | 0.496 | 0.326 |
| Drug abuse/dependence | 4 (26.7) | 19 (18.6) | 4 (21.1) | 27 (19.9) | 0.759 | 0.888 |
| AP-naive | 5 (26.3) | 45 (42.4) | 6 (31.6) | 56 (38.9) | 0.323 | 0.483 |
| Antipsychotic drug | | | | | 0.046 | 0.023 |
| Amisulpride | 9 (47.4) | 34 (32.1) | 1 (5.3) | 44 (30.6) | | |
| Aripiprazole | 4 (21.1) | 37 (34.9) | 7 (36.8) | 48 (33.3) | | |
| Olanzapine | 6 (31.6) | 35 (33) | 11 (57.9) | 52 (36.1) | | |
| Diagnosis | | | | | 0.226 | 0.428 |
| Schizophrenia F20 | 15 (78.9) | 56 (52.8) | 13 (68.4) | 84 (58.3) | | |
| Schizotypal F21 | 0 (0) | 1 (0.9) | 1 (5.3) | 2 (1.4) | | |
| Delusional disorder F22 | 1 (5.3) | 18 (17) | 2 (10.5) | 21 (14.6) | | |
| Acute and transient F23 | 2 (10.5) | 16 (15.1) | 0 (0) | 21 (14.6) | | |
| Schizo-affective F25 | 1 (5.3) | 7 (6.6) | 2 (10.5) | 10 (6.9) | | |
| Other nonorganic F28 | 0 (0) | 1 (0.9) | 0 (0) | 1 (0.7) | | |
| Unspecified nonorganic F29 | 0 (0) | 7 (6.6) | 1 (5.3) | 8 (5.5) | | |
| Age | 31.7 (12.3) | 31.3 (12.7) | 33.5 (13.9) | 31.7 (12.7) | 0.798 | 0.508 |
| DUP | | | | | | |
| Mean weeks | 114 (207) | 101.7 (261.6) | 119 (163.1) | 105.1 (244.2) | 0.979 | 0.875 |
| Median weeks | 6 | 25 | 40 | 21 | 0.332 | 0.966 |
| Duration of AP treatment (weeks) | 21.1 (19.3) | 19.8 (20.9) | 16.2 (14.5) | 19.5 (19.9) | 0.716 | 0.436 |
| Years of education | 11.0 (1.6) | 12.6 (2.9) | 11.6 (2.3) | 12.2 (2.7) | 0.047 | 0.303 |
| CGI-S | 5.8 (0.6) | 4.8 (0.8) | 5.3 (0.7) | 5.0 (0.8) | < 0.001 | 0.061 |
| GAF | 30.6 (10.7) | 37.4 (8.7) | 32.2 (8.0) | 35.8 (9.3) | 0.002 | 0.068 |
| CDSS | 8.1 (6.4) | 6.0 (4.8) | 9.0 (4.9) | 6.7 (5.1) | 0.035 | 0.038 |
| PANSS total | 94.7 (12.2) | 72.3 (12.1) | 85.4 (15.6) | 78.4 (15.9) | < 0.001 | 0.023 |
| PANSS positive | 25.4 (5.2) | 19.8 (4) | 22.2 (4.1) | 21.2 (4.8) | < 0.001 | 0.123 |
| PANSS negative | 20.8 (6.2) | 16.2 (5.2) | 21.4 (6.1) | 17.8 (6.1) | < 0.001 | 0.006 |
| PANSS general | 48.4 (6.3) | 36.3 (6.6) | 41.8 (9) | 39.4 (8.6) | < 0.001 | 0.172 |

Chi-square and ANOVAs were used. For the antipsychotic parameter, Fisher's test was used.

Smokers: Daily tobacco smokers; AP-naïve: No previous exposure to antipsychotic drugs; DUP: Duration of Untreated Psychosis; CGI-S: Clinical Global Impression severity of illness scale; GAF: Global Assessment of Functioning scale-split version, average of GAF function and GAF symptom scale score; CDSS: The Calgary Depression Scale for Schizophrenia total score; PANSS: Positive and Negative Syndrome Scale.

The number of patients with data available for analysis for DUP by group was as follows: Strong response group: 8; Good response group: 50; Slight response group: 7.

### *Trajectories of response*

In total, participants had an average PANSS total score of 78.4 points at baseline, which was reduced by 56% after one year. In our three-trajectory model (Figure 1), a large group of patients ($n$ = 106, 74%) (Good response group) had a 54% reduction in PANSS total score over the first 26 wk of follow-up and maintained it after one year, with a 59% total reduction (Table 2). The second group of patients ($n$ = 19, 13%) showed the fastest response, with a 17% reduction after one week of antipsychotic treatment, and had the largest reduction in PANSS total score among the three groups, with 82.5% at one year (Strong response group). These two groups showed similar improvement of PANSS total score until the six-week follow-up (Good response group: 45% reduction, Strong response group: 48% reduction). However, after this, the Good response group had only a 15% further reduction until the one-year follow-up. In contrast, the Strong response group continued to show remarkable improvement until one year, with a 34% further reduction after the six-week follow-up. The third group of patients ($n$ = 19, 13%) followed a trajectory of poor improvement, with a 13.6% reduction in PANSS total score over the one-year study period (Slight response group). The course of the PANSS total score in this group was quite stable throughout the entire follow-up period.

Patients in the three groups had different baseline average PANSS total scores. Patients in the Strong response group had the highest average PANSS total score (99.7 points), while patients in the Good response group had the lowest (73.3 points). The end point estimates, however, were quite similar, with the Strong response group ending at 42.2 points and the Good response group ending at 47.6 points. Patients in the Slight response group had an average PANSS total score of 86.1 at baseline but had a substantially higher PANSS total score than patients in both the other two groups at the six-week follow-up and until the end of the one-year follow-up (78.5 points).

### *Predictors of response*

In our three-trajectory model and after conducting post hoc pairwise analyses, we did not find significant differences among the trajectory groups regarding years of education or CDSS score at baseline. Having a regular job was significantly more common among patients in the Good response group than in the Slight response group after the pairwise analyses. In post hoc pairwise analyses for the GAF score at baseline, patients in the Strong response group had significantly lower GAF scores than patients in the Good response group. For the CGI-S score, patients in the Good response group had a significantly lower score at baseline than patients in both other response groups. As expected, because the grouping was based on the PANSS total score data, the PANSS total, PANSS positive, and PANSS general average scores at baseline were significantly different in all the post hoc pairwise comparisons between response groups. Patients in the Strong response group had higher PANSS total, PANSS positive and PANSS general average scores at baseline than patients in both the other response groups. For the PANSS negative score, we found significant differences between the Good response and the Strong response group and between the Good response and the Slight response group. Patients in the Slight response group had the highest PANSS negative average score at baseline, while patients in the Good response group had the lowest.

When the Strong and Slight response groups were compared in the antipsychotic drug post hoc analyses, we found significantly more patients who used amisulpride in the Strong response group (47.4% *vs* 5.3%). The proportion of Slight response patients in each medication group was as follows: 1/44 for amisulpride, 7/48 for aripiprazole and 11/52 for olanzapine. When these proportions were compared pairwise, we did not find a significant difference between olanzapine and aripiprazole or between amisulpride and aripiprazole. There was a statistically significant difference between olanzapine and amisulpride (*i.e.*, a significantly higher proportion of Slight response participants in the olanzapine group than in the amisulpride group).

In the comparison between the Response and Nonresponse groups, there was a significant difference regarding employment status: More patients in the Response group had a regular job at baseline. The CDSS score at baseline was significantly higher in the Nonresponse group than in the Response group. The Nonresponse group had higher average scores in both PANSS total-86.1 *vs* 77.3 points-and PANSS negative-21.4 *vs* 17.3 points-at baseline. There was a significantly higher proportion of patients who used amisulpride in the Response group than in the Nonresponse group-43/125 compared to 1/18.

## DISCUSSION

The key finding of our study is that 87% of participants followed a trajectory of good or strong response to antipsychotic drugs. This provides additional strong evidence of the efficacy of antipsychotic drugs, corresponding to current research and treatment guidelines for schizophrenia[1-3,5,6]. The largest group of patients, the Good response trajectory group, showed a 54% reduction in PANSS total score at the one-year follow-up. This percentage can be regarded as a good response to schizophrenia treatment, as

**Table 2 Response measured as Positive and Negative Syndrome Scale total score improvement from baseline**

| | Baseline PANSS total score | 1 wk[1] | 3 wk[1] | 6 wk[1] | 12 wk[1] | 26 wk[1] | 39 wk[1] | 52 wk[1] |
|---|---|---|---|---|---|---|---|---|
| Strong response group | 99.7 | 12.0 (17.2%) | 26.6 (38.2%) | 33.5 (48.1%) | 42.4 (60.8%) | 48.3 (69.3%) | 56.7 (81.3%) | 57.5 (82.5%) |
| Good response group | 73.3 | 10.2 (23.5%) | 16.3 (37.6%) | 19.3 (44.7%) | 19.8 (45.8%) | 23.4 (54%) | 25.8 (59.6%) | 25.7 (59.4%) |
| Slight response group | 86.1 | 3.5 (6.2%) | 9.0 (16%) | 1.5 (2.7%) | 6.4 (11.3%) | 1.7 (3%) | 7.5 (13.4%) | 7.6 (13.6%) |
| Total | 78.4 | 9.9 (20.5%) | 16.7 (34.5%) | 18.4 (38%) | 20.7 (42.6%) | 22.1 (45.6%) | 26.4 (54.4%) | 27.2 (56.2%) |

[1]PANSS total baseline–PANSS total follow-up point. PANSS: Positive and Negative Syndrome Scale; %: Percentage of improvement from baseline score.

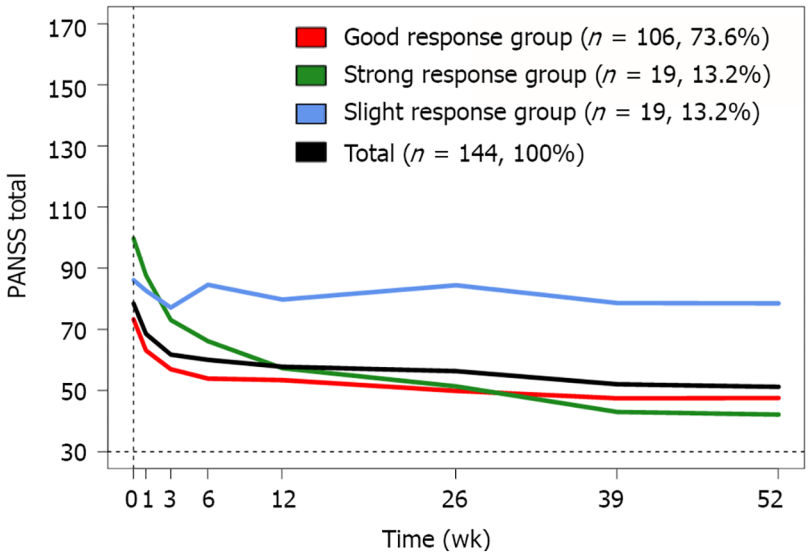


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**Figure 1 Response trajectories.**

a cutoff of 20%, 30%, 40%, or 50% reduction in PANSS total score has been used in clinical studies[15]. The PANSS total change of 54% corresponds to a CGI-I (improvement scale) of "much improved"[19]. The Slight response group in our study included both antipsychotic-naive patients and patients with previous exposure to antipsychotics. We know from previous research that a group of patients (approximately 13%-25%) will not respond adequately after a trial of an antipsychotic drug in their first episode of psychosis[26-28], while approximately 30% of those with chronic schizophrenia will be regarded as treatment-resistant after two failed trials with antipsychotics[29].

Another key finding of this study is the importance of response in the first six weeks of treatment, which seems to predict further response to the antipsychotic drug. Participants in the Slight response group did not show any further improvement after the first six weeks of treatment. Both the current Norwegian guidelines and the National Institute for Health and Care Excellence (NICE) guidelines suggest a trial with medication at an optimum dosage for four to six weeks[2,30]. The Maudsley guidelines propose an assessment of the adjusted dosage over two to three weeks and an antipsychotic switch if there is no effect during this period. If a partial response is detected, the clinician should continue for at least four weeks before abandoning this treatment[3]. Our data could suggest that patients without a reduction in the PANSS total score of 30% from baseline to six weeks in treatment with nonclozapine antipsychotic drugs seldom achieve sufficient response, and switching to another antipsychotic drug should be considered. On the other hand, the results from the OPTiMiSE study, a multicenter three-phase switching study in first-episode schizophrenia, concluded that switching antipsychotics did not improve clinical outcomes in patients who had not reached symptomatic remission after their first antipsychotic trial compared to continuing treatment[31]. The authors suggested an algorithm of treatment with a single antipsychotic drug for up to 10 wk, followed by the use of clozapine in patients who did not reach symptomatic remission.

There were significant differences in the distribution of the examined antipsychotic drugs among the three response groups, and our findings indicate more favorable results for amisulpride. Interestingly, amisulpride is less frequently used than aripiprazole and olanzapine. In Norway, the use of amisulpride remained stable from 2014 to 2018, and in 2018, amisulpride was used 30 times less frequently than olanzapine and 9 times less frequently than aripiprazole[32]. In the United States, amisulpride is

registered for the treatment and prevention of postoperative nausea and vomiting[33] but not for schizophrenia treatment. Hence, one of the most effective drugs is not available for antipsychotic treatment. This is a strong reminder that different prescribing cultures among countries regarding the choice of drugs for schizophrenia treatment exist[4,34] and underlines the need for evidence-based clinical practice in schizophrenia treatment.

We found three variables that predicted nonresponse: Unemployment, depression, and negative psychotic symptoms. Previous studies have suggested that there may be a correlation between employment status and other types of outcomes. The causal direction, however, remains unclear[35,36]. In our study, we found that patients in the Slight response group had a significantly lower percentage of employment, both in the two-group and three-group analyses. Of the 36 participants with paid work at baseline, 35 belonged to the Response group and only one to the Nonresponse group, showing a strong predictive value of having paid work for a good symptom outcome over the 12-mo follow-up. We also found a higher level of symptoms of depression at baseline in the Nonresponse group. This corresponds with previous studies showing that depression in schizophrenia is common and associated with negative outcomes[37]. The Slight response group had the highest PANSS negative average score at baseline in both the two-group and three-group analyses. Negative psychotic symptoms are difficult to treat with the available antipsychotic drugs, which stresses the need for new therapeutic agents in schizophrenia treatment[38].

### *Strengths and limitations*

Our study (BeSt InTro) is the first head-to-head comparison of amisulpride, aripiprazole and olanzapine in a randomized, pragmatic efficacy trial. This direct comparison of these agents provides some clear advantages compared to network meta-analyses. Moreover, our study was industry-independent and rater-blind. Another strength of the study was the frequent follow-up points, particularly in the first weeks of treatment, which are quite important, as demonstrated above. Our follow-up was relatively long (12 mo), which gave an advantage compared to other response studies that examined shorter periods with antipsychotic drugs. Finally, we used well-validated instruments to describe our main parameters, such as PANSS, CGI and CDSS.

Our study has also some limitations. First, there was no placebo control; therefore, we must interpret our results with caution. Second, there was a drop-out rate of 59%, which is comparable to that found in other large randomized antipsychotic drug trials, such as the CATIE study (74% before 18 mo)[39] and the EUFEST study (41.6% before 12 mo)[40]. Furthermore, further analyses of attrition indicated that the sample after 52 wk was representative of the sample at baseline. Finally, some of our participants entered the study having tried other antipsychotic(s) previously, while the rest were antipsychotic-naive. This could have brought some bias into the interpretation of our results. Last, the vast majority of the included patients were white Europeans (88%). Our results are therefore not generalizable to all human populations.

## CONCLUSION

In summary, the vast majority of our study participants had a very good outcome during the 12-mo course. The response to antipsychotic drugs after the first six weeks of treatment predicted a further course during the first year, and the use of amisulpride indicated a better response. An antipsychotic switch should be considered in patients with inadequate response (less than 30% reduction in PANSS total from baseline) after six weeks of treatment. Unemployment, depression, and negative psychotic symptoms at baseline predicted nonresponse.

## ARTICLE HIGHLIGHTS

### *Research background*

It is important to compare the effectiveness of various antipsychotic agents in the treatment of schizophrenia. The Bergen-Stavanger-Innsbruck-Trondheim (BeSt InTro) study directly compared three antipsychotics (amisulpride, aripiprazole and olanzapine) in patients with schizophrenia-spectrum disorders between October 20, 2011 and December 30, 2016. The inclusion and follow-up of the patients are now completed, and the main findings have been published. In this substudy, we examined response trajectories and possible predictors for belonging to the different response groups.

### *Research motivation*

Schizophrenia is a serious illness with a heterogeneous course. Pharmacological treatment with antipsychotic drugs remains the cornerstone in the treatment of schizophrenia, yet it is not possible to predict its effect on individual patients. Finding predictors of medication response can enhance the quality of schizophrenia treatment and the development of more personalized medicine.

### *Research objectives*

The main objective of this substudy was to define response trajectories after a one-year follow-up for patients randomized to the three studied antipsychotics. The secondary objective was to define predictors of belonging to the different response trajectories. After realizing these objectives, we could present some suggestions for better clinical practice. We could also suggest further research on switching antipsychotics and on factors that predicted nonresponse, such as unemployment, depression, and negative psychotic symptoms.

### *Research methods*

Our study was a cohort study with data from a clinical trial of three antipsychotics in a prospective, randomized, rater-blind design. We defined response trajectories by fitting a latent class mixed model with Positive and Negative Syndrome Scale (PANSS) total as a dependent variable, time as an independent fixed variable, and subject as a random intercept to our data. We used the Bayesian information criterion and entropy to select the best model, and the model with three latent classes and with time represented as visit number best fit the data. Response trajectories provide a better picture of the course of symptoms over time and are a relatively novel way of examining response in schizophrenia.

### *Research results*

The finding that 87% of the participants had a good or strong response to antipsychotic treatment adds to the research evidence about the general effectiveness of antipsychotic drugs. The response after the first six weeks of treatment seems to indicate further response to antipsychotics. The results indicate the need for further research on switching antipsychotics in incomplete responders to avoid delays in treatment and to enhance the quality of treatment.

### *Research conclusions*

Antipsychotic treatment has a good effect in a vast majority of schizophrenia-spectrum patients enrolled in a randomized drug trial. Furthermore, the six-week response seemed to predict the effects through the one-year follow-up. This can indicate an antipsychotic switch in patients without a reduction in the PANSS total score of 30% from baseline to six weeks in treatment with nonclozapine antipsychotics. Another important conclusion is the favorable results for amisulpride in comparison to aripiprazole and olanzapine, which could encourage more frequent use of this drug in schizophrenia treatment.

### *Research perspectives*

Future research on schizophrenia treatment should be designed to develop more personalized medicine through the identification of response predictors.

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## FOOTNOTES

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LETTER TO THE EDITOR

# Therapeutic use of melatonin in schizophrenia-more than meets the eye!

Ahmed Naguy

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## Abstract

Adjunctive melatonin use in schizophrenia, as supported by a modicum of evidence, has multiple transcending chronobiotic actions, including fixing concurrent sleep problems to bona fide augmentative antipsychotic actions, mitigating the risk of tardive dyskinesias, curbing the drastic metabolic syndrome and ultimately providing neuroprotective actions. Its use is rather an art than science!

**Key Words:** Melatonin; Schizophrenia; Chronobiotic; Neuroprotectant; Antipsychotic; Tardive dyskinesia; Metabolic syndrome

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**Core Tip:** Adjuventia melatonin use in schizophrenia is strongly recommended, although it is supported by a modicum of evidence. Its use has multiple transcending chronobiotic actions, rectifying sleep disturbance in schizophrenia to bona fide augmentative antipsychotic actions, mitigating the risk of relentless tardive dyskinesias, curbing the drastic cardio-metabolic syndrome and ultimately providing neuroprotective actions in the face of the neuroprogressive course of schizophrenia.

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## TO THE EDITOR

In a recent issue of the *World J Psychiatry*, Duan *et al*[1] conducted an interesting systematic review of melatonin use for schizophrenia. They concluded that add-on melatonin can help with sleep, might curtail metabolic risk and possibly mitigate tardive dyskinesia in patients with schizophrenia. We completely agree with authors, and we[2] have previously published on melatonin adjuventia in patients with bipolar mood disorders as well. Herein, we will try to expand a bit more on the therapeutic potential of melatonin in schizophrenia.

Sleep and circadian rhythm disturbances, as high as 80%, lie at the core of the etiopathogenesis of schizophrenia, as supported by both human studies and preclinical evidence in animal (mice) models with genetic mutations pertinent to schizophrenia[3]. Wide heterogeneity in phenotypes has been demonstrated. This includes, among other things, severe circadian misalignment, phase advances and delays, non-24 h rhythms that were not entrained by the light/dark cycle and disturbed sleep/wake cycle, perhaps reflecting the heterogeneity of the disease itself.

Melatonin secretion is reduced in schizophrenia. Therefore, it follows that melatonin (N-acetyl 5-methoxytryptamine) use addresses a core pathophysiology central to schizophrenia, beyond being a mere sleeping aid.

Moreover, it has been shown that melatonin might augment anti-psychotic efficacy by virtue of anti-inflammatory and anti-oxidant actions. Melatonin impacts tryptophan catabolic pathways *via* its effect on stress response and cortisol secretion, and this might impact cortex associated cognition, amygdala associated affect and striatal motivational processing. Melatonin in schizophrenia has been demonstrated to serve both as a biologic marker and as a treatment adjunct[4].

Melatonin mitigates risk of tardive dyskinesia, akin to similar use of vitamin E, given that melatonin is 6-10 times more potent than vitamin E. Moreover, it curbs metabolic syndrome. Mechanistically, melatonin regulates the photo-neuroendocrine axis. It has complex interactions with leptin, improves insulin resistance, and possesses cardio-protective actions.

Schizophrenia relapses are typified with neuroprogression leading to subcortical atrophy, ventriculomegaly and further white matter loss. This is chiefly mediated through microglial activation, neuroinflammation and oxidative/nitrosative stress. Mitochondrial dysfunction due to deficiency of the antioxidant glutathione also contributes[5]. Taken together, these findings make case for a role for melatonin in neuroprotection, owing to its anti-apoptotic actions and its regulation of adult hippocampal neurogenesis.

Quo Vadis? melatonin use in schizophrenia, as supported by a modicum of evidence base, has multiple transcending chronobiotic actions, including bona fide antipsychotic actions, mitigation of tardive dyskinesia, curbing metabolic syndrome and ultimately providing neuroprotective actions. Its use is rather an art than science!

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LETTER TO THE EDITOR

# Does COVID-19 increase the risk of neuropsychiatric sequelae? Evidence from a mendelian randomization approach

Alfonsina Tirozzi, Federica Santonastaso, Giovanni de Gaetano, Licia Iacoviello, Alessandro Gialluisi

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## Abstract

Observational studies based on electronic health records (EHR) report an increased risk of neurological/neuropsychiatric sequelae for patients who have had coronavirus disease 2019 (COVID-19). However, these studies may suffer from biases such as unmeasured confounding, residual reverse causality, or lack of precision in EHR-based diagnoses. To rule out these biases, we tested causal links between COVID-19 and different potential neurological/neuropsychiatric sequelae through a two-sample Mendelian randomization analysis of summary statistics from large Genome-Wide Association Scans of susceptibility to COVID-19 and different neurological and neuropsychiatric disorders, including major depression, anxiety, schizophrenia, stroke, Parkinson's and Alzheimer's diseases. We found robust evidence suggesting that COVID-19 – notably the hospitalized and most severe forms – carries an increased risk of neuropsychiatric sequelae, particularly Alzheimer's disease, and to a lesser extent anxiety disorder. In line with a large longitudinal EHR-based study, this evidence was stronger for more severe COVID-19 forms. These results call for a targeted screening strategy to tackle the post-COVID neuropsychiatric pandemic.

**Key Words:** COVID-19; Sars-CoV-2; Neurological disorders; Neuropsychiatric disorders; Alzheimer's disease; Anxiety; Mendelian randomization

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**Core Tip:** Inspired by suggestive findings of an increased incident risk of neurological and neuropsychiatric sequelae in people who have had coronavirus disease 2019 (COVID-19), we carried out a two-sample Mendelian randomization analysis to further investigate causality links and build evidence free of biases such as unmeasured confounding, residual reverse causality or lack of precision in electronic health record-based diagnoses. This analysis – typically applied to genetic associations from large genomic studies on the diseases of interest – indicated that the most severe forms of COVID-19 increased the risk of Alzheimer's disease and anxiety, further supporting the findings of large observational studies.

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## TO THE EDITOR

During the ongoing coronavirus disease 2019 (COVID-19) pandemic, increasing attention is being paid to the long-term sequelae of the acute disease, particularly neurological and neuropsychiatric[1,2]. A recent retrospective analysis in more than 236000 COVID-19 survivors reported a significant increase of neurological/psychiatric outcomes in the six months after diagnosis, particularly for those treated in hospital, in an intensive care unit, and those who suffered encephalopathy[3]. The risk of first diagnosis of such sequelae, which included dementia, cerebrovascular, psychotic, mood and anxiety disorders, was almost double in those with COVID-19 compared to patients who suffered other types of viral influenza or respiratory infections, suggesting a specific contribution of Sars-CoV-2 infection to these sequelae[3]. This observational study was based on electronic health records, which unavoidably lack the precision of neurological/neuropsychiatric diagnoses, and may be subject to unmeasured confounding or residual reverse causality biases; in fact, most of the reported disorders are themselves risk factors for COVID-19 infection, and their milder forms may go undetected.

To overcome these limitations and provide independent evidence of the observations, we carried out a two-sample Mendelian randomization (MR) analysis to test whether susceptibility to COVID-19 could predispose to an increase in the risk of different psychiatric/neurodegenerative disorders, including major depression, anxiety, schizophrenia, stroke, Parkinson's and Alzheimer's diseases, as already suggested in the literature[2,3].

We employed summary statistics from large Genome-Wide Association Studies (GWAS) on COVID-19 susceptibility and all the disorders tested, through the MR-Base web app, or the equivalent R package TwoSampleMR v 0.5.6[4] when up-to-date summary statistics were not available in the MR-Base[5]. Since we detected no violation of the balanced horizontal pleiotropy assumption, we used Inverse variance weighted regression to model the relation between effects on exposure and outcome for each of the genetic instrumental variants (IVs). We selected the variants showing genome-wide significant associations with (COVID-19) exposure[6] ($P < 5 \times 10^{-8}$), removed palindromic variants, applied Linkage Disequilibrium (LD) clumping ($r^2$ cutoff 0.1 and clumping window 1000 kb), and retained only the variants that were also tested in the "outcome" study, resulting in 17-23 variants for each analysis.

MR analyses were repeated, testing variants associated with three different COVID-19 exposures, namely all (112612), hospitalized (24274) and severe cases (8779; namely, patients who required respiratory support, or whose death was related to COVID-19)[6], compared to population controls (> 1 million, see https://www.covid19hg.org/results/r6/).

This analysis indicated a significant causal link between severe and hospitalized COVID-19 and the risk of Alzheimer's disease and anxiety disorder (AD) (Figure 1), which survived Bonferroni correction for six different outcome conditions ($\alpha = 8.3 \times 10^{-3}$).

This evidence is closely aligned with that from a large observational study[3], where patients who were hospitalized and required intensive care had a steeper increase in incident neuropsychiatric sequelae in the six months after infection. However, the increases observed here in Alzheimer (1%-3%) and anxiety risk (0.5%-1%) were considerably smaller than those reported by Taquet *et al*[3], although measures of incident and prevalent risk and the different design and setting of the studies mean they are not directly comparable. This might be explained by the typically low effect size of the common variants detected in GWAS and used in MR analysis, and by the type of comparison in the original study on COVID-19[6], where population controls can include a number of undetected cases, reducing the power of the comparison.

Our analysis presents some limitations. First, the use of summary statistics from a meta-analysis of diverse ancestries may introduce a population stratification bias. Although no data based only on

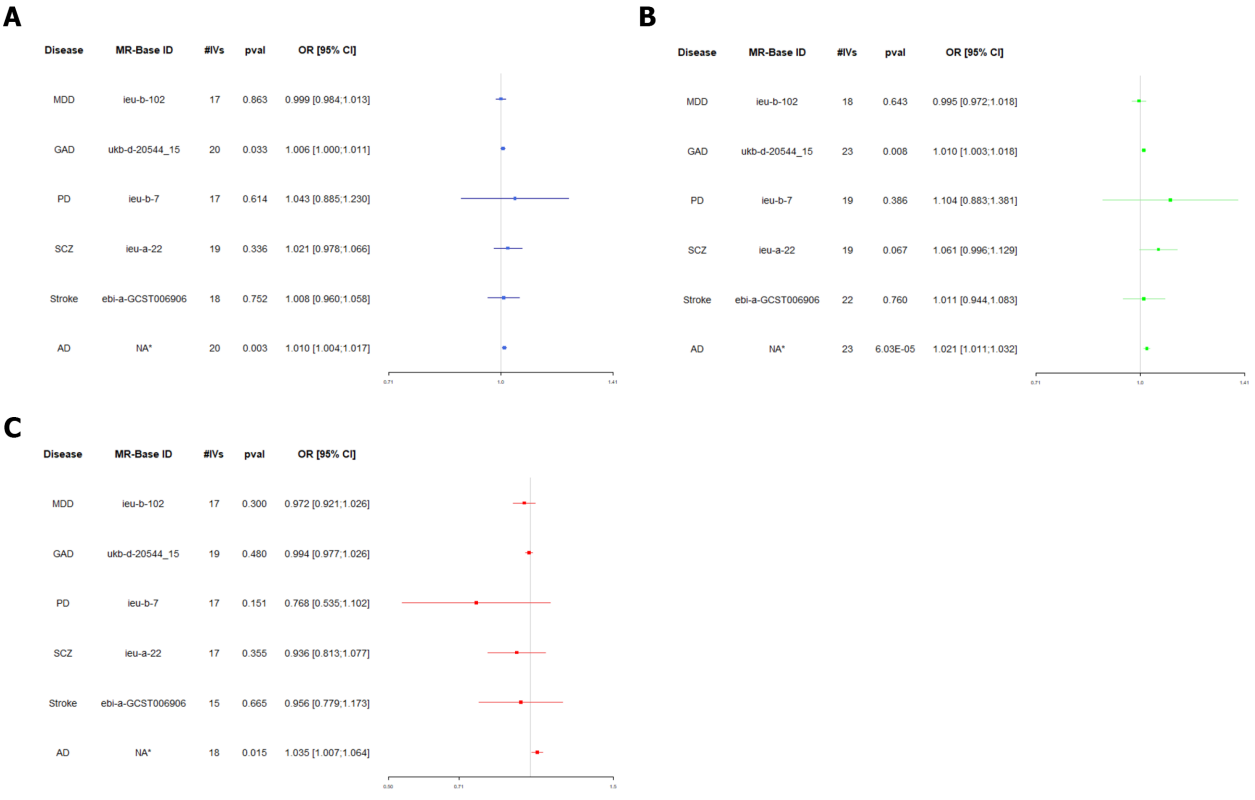


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**Figure 1 Mendelian randomization analysis testing (A) severe, (B) hospitalized and (C) all Covid-19 forms against the risk of neuropsychiatric/neurological disorders.** Odds ratios with 95% confidence intervals and *P* value from Mendelian randomization analyses are reported for each disorder tested as outcome against the three forms of coronavirus disease 2019 tested as exposure, with the number of instrumental variants (#IVs) analyzed. MR: Mendelian randomization; AD: Alzheimer's disease; GAD: Generalized anxiety disorder; OR: Odds ratios; CI: Confidence interval; NA: Not available. *Not available on MR-Base (see Data Availability statement or [5] for details).

European samples are available for the COVID-19 GWAS round 6 meta-analysis, we carried out a sensitivity analysis with the round 5 (European) meta-analysis results. This provided significant evidence of causality between hospitalized COVID-19 forms and increased AD risk (by 1.8%, $P < 0.05$), while only a trend of association was observed for increased AD risk *vs* the other COVID-19 exposures (Table 1). No significant evidence of causality was found for anxiety, although severe COVID-19 slightly increased the risk of GAD by 0.6% ($P = 0.09$). Overall, effect sizes between MR analysis using round 6 and round 5 (only EUR) data were very similar, corroborating the bounty of our main analysis. The lack of significance in most of the sensitivity MR analyses may be due to the notably smaller number of IVs used (from 3 to 10), implied by the smaller sample size and lower power of the round 5 meta-analysis. Therefore, caution is suggested in interpreting these data and further analyses are needed based on larger datasets, of European ancestry.

Second, partial sample overlap between the studies analyzed may introduce a type I error inflation bias which, however, does not apply to case-control outcomes when risk factor IVs are tested only in control participants[7]. While we do know the exact prevalence of Alzheimer and anxiety cases in the COVID-19 GWAS, the relatively low prevalence of these disorders in the general population (especially AD) suggests the real bias introduced by sample overlap may be very close to zero.

Last, although converging epidemiological and genetic evidence supports a causal effect of COVID-19 infection on neuropsychiatric/neurodegenerative disorders, the exact molecular mechanisms of this relationship remain to be clarified. The most convincing hypotheses so far involve the neurotropic action of the virus, dysregulation of the inflammatory response and of the vascular system, which in turn promote mechanisms that can affect mental health, like alteration of the blood-brain barrier and neuro-inflammation[2,8,9]. While deeper functional analyses will help clarify these aspects, the evidence presented here underlines the need for a targeted screening strategy to tackle the neuropsychiatric effects.

**Table 1 Mendelian randomization analysis testing (A) severe, (B) hospitalized and (C) all COVID-19 forms against Alzheimer and anxiety risk in European ancestry**

| Disease | MR-Base ID | #IVs | *P* value | OR [95%CI] |
|---|---|---|---|---|
| **(A)** | | | | |
| AD | NA[1] | 8 | 0.193 | 1.006 [0.998; 1.014] |
| GAD | ukb-d-20544_15 | 5 | 0.090 | 1.006 [0.998; 1.014] |
| **(B)** | | | | |
| AD | NA[1] | 3 | 0.047 | 1.018 [1.000; 1.036] |
| GAD | ukb-d-20544_15 | 3 | 0.250 | 1.010 [0.994; 1.026] |
| **(C)** | | | | |
| AD | NA[1] | 10 | 0.169 | 1.014 [0.994; 1.034] |
| GAD | ukb-d-20544_15 | 5 | 0.580 | 1.006 [0.985; 1.028] |

[1]Not available on MR-Base (see Data Availability statement or [5] for details).
Odds ratios with 95% confidence intervals and *P* value from Mendelian randomization analyses are reported for each disorder tested as outcome against the three forms of coronavirus disease 2019 tested as exposure, with the number of instrumental variants (#IVs) analyzed. MR: Mendelian randomization; AD: Alzheimer's disease; GAD: Generalized anxiety disorder; OR: Odds ratios; CI: Confidence interval; NA: Not available.

## FOOTNOTES

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*REVIEW*

# Abnormal synaptic plasticity and impaired cognition in schizophrenia

Xiu-Lin Wu, Qiu-Jin Yan, Fan Zhu

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## Abstract

Schizophrenia (SCZ) is a severe mental illness that affects several brain domains with relation to cognition and behaviour. SCZ symptoms are typically classified into three categories, namely, positive, negative, and cognitive. The etiology of SCZ is thought to be multifactorial and poorly understood. Accumulating evidence has indicated abnormal synaptic plasticity and cognitive impairments in SCZ. Synaptic plasticity is thought to be induced at appropriate synapses during memory formation and has a critical role in the cognitive symptoms of SCZ. Many factors, including synaptic structure changes, aberrant expression of plasticity-related genes, and abnormal synaptic transmission, may influence synaptic plasticity and play vital roles in SCZ. In this article, we briefly summarize the morphology of the synapse, the neurobiology of synaptic plasticity, and the role of synaptic plasticity, and review potential mechanisms underlying abnormal synaptic plasticity in SCZ. These abnormalities involve dendritic spines, postsynaptic density, and long-term potentiation-like plasticity. We also focus on cognitive dysfunction, which reflects impaired connectivity in SCZ. Additionally, the potential targets for the treatment of SCZ are discussed in this article. Therefore, understanding abnormal synaptic plasticity and impaired cognition in SCZ has an essential role in drug therapy.

**Key Words:** Schizophrenia; Synaptic plasticity; Synaptic structure; Synaptic transmission; Cognitive dysfunction; Abnormality

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**Core Tip:** Schizophrenia (SCZ) is a severe mental illness that affects several domains of cognition and behaviour. SCZ symptoms are typically classified into three categories, namely, positive, negative, and cognitive. The etiology of SCZ is thought to be multifactorial and poorly understood. Accumulating evidence has indicated abnormal synaptic plasticity and cognitive impairments in SCZ. This article will briefly review abnormalities in synaptic plasticity, including synaptic structure, synaptic plasticity-related genes, neuroplasticity, synaptic transmission, and cognitive dysfunction in SCZ.

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## INTRODUCTION

Schizophrenia (SCZ) is a chronic, dangerous psychiatric disorder that affects about 1% of people worldwide. Typically, SCZ, occurring in late adolescence or early adulthood, often results in lifetime disability if not effectively controlled. The symptoms of SCZ are generally grouped into three categories, addressed as follows: Positive symptoms (auditory hallucinations and persecutory delusions), negative symptoms (social withdrawal, self-neglect, loss of motivation and initiative, emotional blunting, and paucity of speech), and cognitive symptoms (problems with attention, certain types of memory, and executive functions)[1]. There are numerous hypotheses postulated to elaborate the pathophysiology of SCZ, including the neurodevelopmental hypothesis and synaptic hypothesis. The synaptic hypothesis involves abnormal synaptic transmission and impaired synaptic plasticity.

Synaptic plasticity consists of structural plasticity and functional plasticity. Various evidence discloses abnormal structural and functional plasticity in the pathogenesis of SCZ. Postmortem studies in the brain of SCZ patients point out that there is a significant decrease in the density of dendritic spines (DSs) and the size of postsynaptic density (PSD) in SCZ compared to healthy controls[2,3]. Similarly, functional imaging has revealed that the expression levels of synaptic structure related genes have changed in SCZ[4,5]. Change in morphology or distribution of synaptic structure is related to synaptic plasticity and contributes to SCZ. Additionally, a mouse model of SCZ induced by MK801 also proves that abnormal structural and functional plasticity can constitute to the etiology of SCZ. MK-801-induced mice display the disruption of long-term potentiation (LTP) and change of excitatory postsynaptic potential[6,7]. Furthermore, LTP-like plasticity deficits may result in impairments of learning and memory[8,9].

Abnormal synaptic plasticity might lead to cognitive impairments, including deficits in learning and memory, attention, and social cognition, in SCZ[9,10]. Cognitive impairments refer to aberrant functional connectivity or transmission. Cognitive deficit is an early warning sign of SCZ and contributes to poor functional outcomes[11]. Conventional antipsychotic drugs targeted by dopamine receptors have beneficial effects on positive symptoms but offer minimal benefit for negative symptoms or cognitive symptoms[12]. Therefore, in-depth research on abnormal synaptic plasticity and impaired cognition in SCZ could help understand the underlying mechanism of SCZ and find new drugs to treat it.

This review will focus on recent advances in the understanding of impaired synaptic plasticity and cognitive dysfunction, including changes in synaptic structure, synaptic plasticity-related genes, dysregulation of synaptic transmission, and disconnection, in SCZ, as well as the potential targets for SCZ.

## MORPHOLOGY OF THE SYNAPSE

The synapse is a structure that allows a neuron (or nerve cell) to communicate electrical or chemical signals to another neuron or other target effector cell. There are three common types of synapses, respectively called axodendritic, axosomatic, and axoaxonic (Figure 1). In the mammalian brain, neuronal signals are transmitted by two fundamental types of synapses: The electrical synapse and the chemical synapse[13]. A classical chemical synapse is composed of three main parts: (1) The presynaptic components, enclosing neurotransmitter-filled synaptic vesicles (SVs) and proteins (SNARE complex, Munc13, and Munc18) which promote SV recruitment and neurotransmitters release[14]; (2) The postsynaptic components, containing specific receptors and proteins including scaffolding proteins, neurotransmitter receptors, enzymes, and cytoskeletal components, which receive and transmit signals and regulate the synaptic plasticity[15]; and (3) The synaptic cleft, physical space between the presynaptic and postsynaptic terminals which is 10-20 nm, also called synaptic gap (Figure 1D)[16].

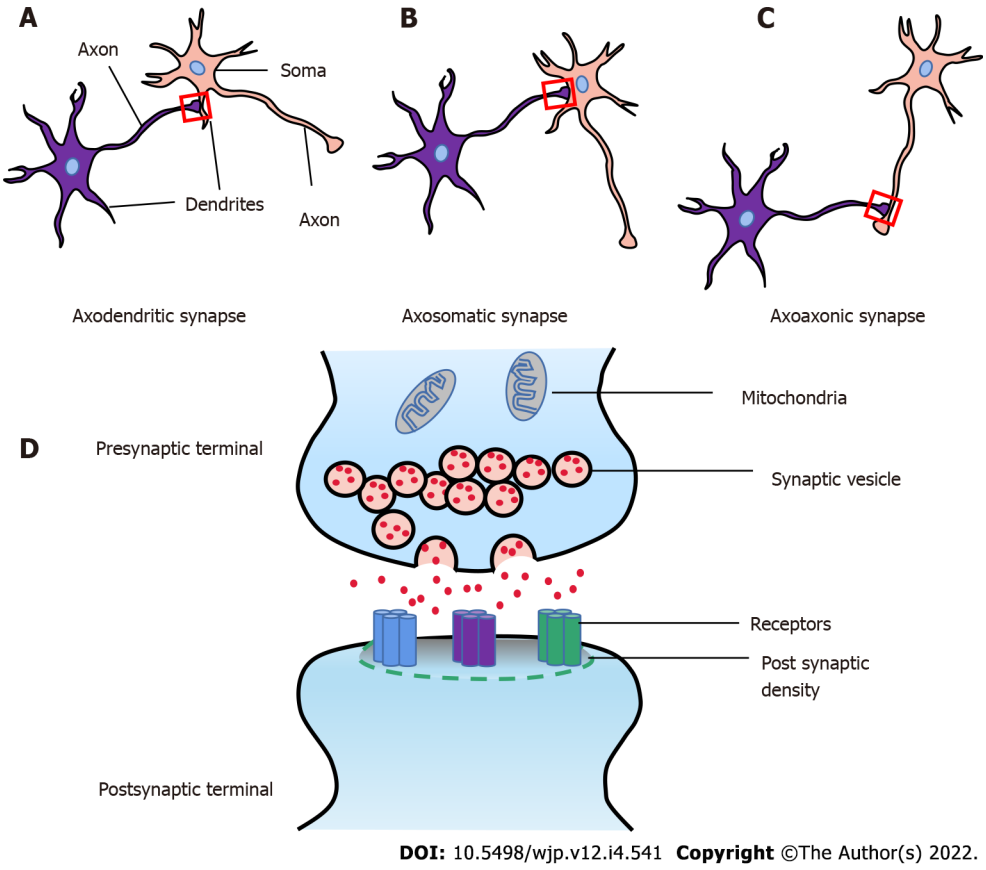


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**Figure 1 Types of synapse and structure of a classical chemical synapse.** A: Axodendritic synapse; B: Axosomatic synapse; C: Axoaxonic synapse; D: Structure of a classical chemical synapse. A typical chemical synapse usually consists of three parts: (1) Presynaptic membrane including clusters of neurotransmitter-filled synaptic vesicles, mitochondria, and so on; (2) Postsynaptic membrane including neurotransmitter-specific receptors; and (3) Synaptic cleft.

Furthermore, the surface where the presynaptic component and the postsynaptic component are connected is usually called the synaptic interface. It is determined by the width of the synaptic cleft, length of the synaptic active zone, the thickness of PSDs, and curvature of the synaptic interface[17-19]. Changes of synaptic interface closely relate to synaptic function.

*In vivo* imaging studies have shown that the decreased density of DSs may be a loss of synapse[20]. Spines have a critical role in synaptic transmission. The reduced spines directly correlate with the loss of synaptic function[21,22]. Many factors, including specific gene expression, signal transduction, and new synapse formation, can change synapse level. The total number of synapses is controlled by forming new synapses and pruning old or inappropriate synapses, and finally contributes to synaptic plasticity and memory consolidation[23].

## NEUROBIOLOGY OF SYNAPTIC PLASTICITY

Synaptic plasticity (also called synaptic strengths) is the ability of neurons to modify synaptic strength in response to external stimuli. During this process, the structure and function of the synapse are highly dynamic.

Structurally, synaptic plasticity is characterized by the insertion or retention of neurotransmitter receptors, especially AMPAR, into the postsynaptic membrane. Many factors, including the size of DS, the pool of SVs, the areas of active zone, and the PSD, may influence synaptic plasticity[24-26]. Functionally, LTP and long-term depression (LTD) are two forms of synaptic plasticity. There are usually two LTP types, namely, NMDA receptor-dependent LTP and mossy fibre LTP (a cAMP-dependent presynaptic form of plasticity)[27]. The activation of NMDA receptors and increased calcium ($Ca^{2+}$) concentration are essential for the induction of NMDA receptor-dependent LTP[28,29]. Noteworthy, the spine $Ca^{2+}$ signal is required to trigger LTP[30,31]. Thus, calcium/calmodulin-dependent protein kinase II (CaMKII) has an important role in NMDA receptor-dependent LTP. Besides, various kinases, including protein kinase C, the mitogen-activated protein kinase, and the tyrosine kinase Src, have been implicated in LTP induction[32-34]. Interestingly, some forms of LTP can only maintain 30-60 min, but some can last a very long time, from several hours to days, even for many weeks. The possibilities for the longer-term maintenance of LTP is involved in synaptic structural

remodeling, increased spines size, and enlargement of PSD[35,36].

In summary, synaptic structure, AMPAR trafficking, and DS dynamics are critical for the maintenance of synaptic plasticity.

## ROLE OF SYNAPTIC PLASTICITY

### *Synaptic plasticity in learning and memory*

The formation of memory involves four processes: Encoding, storing, consolidating, and retrieving information. Learning is viewed as the acquisition or encoding of the information to memory. The core hypothesis of synaptic plasticity and memory is as follows: Activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation, and is both necessary and sufficient for the information storage underlying the type of memory mediated by the brain area in which plasticity is observed[37].

Changing the strength of synaptic connections is a prime process underlying learning and memory formation. Accumulative studies suggest that synaptic plasticity is necessary for learning and memory. The induction of synaptic plasticity requires NMDAR activation. NMDAR1 knockdown mice show deficit in spatial memory in the hippocampus[38]. Besides, synaptic plasticity may contribute to declarative and relational memory[39], sequence learning[40], motor learning[41,42], and perceptual learning at sensory cortex synapses[43]. The traditional view is that fast learning requires more robust synaptic changes[44]. However, some studies suggest that weak synaptic plasticity can support fast learning[45]. Synaptic plasticity has a requisite role in learning and memory across many regions of the brain.

### *Synaptic plasticity in brain maturation*

Human brain maturation is a complex, dynamic, and lifelong process. Billions of cells proliferate, migrate, and maturate during early development, which leads to a brain with billions of neurons at birth, finally forming connections. As children become teenagers, the brain dynamically strengthens or weakens connections in response to environmental input[46]. Simultaneously, neural maturity is increased with age across various brain regions, including primary sensory, motor, associative learning, and cognition function[47]. The prefrontal cortex (PFC) is the last brain region to mature and can mediate executive function such as goal planning, working memory, and guided behavior[48].

Post-mortem studies suggest that the synaptic densities increase rapidly in the visual and auditory cortices, with a maximum of near 3 mo followed by pruning until the age of 12 years[49]. However, synaptic density in the PFC reaches the maximum during childhood, up to 150-200 percent of its adult level. Interestingly, synaptic elimination lasts to mid-adolescence in the PFC[50]. Furthermore, evidence shows that synaptic strength is reduced in the developing brain because it presents synaptic pruning [51]. The specialized and functionally-connected neural circuits accompany regional changes. Additionally, changes in brain volume occur in SCZ. Several reports suggest reducing cerebral cortical volume at premature birth compared to infants born at term[52]. Similarly, there are linearly decreased cortical gray matter and increased white matter across ages 4 years to 12 years[53,54]. In a word, the change of synaptic strength has an influential role in brain maturation and maintenance of a functional neuronal circuit.

## IMPAIRED SYNAPTIC PLASTICITY IN SCZ

### *Abnormal structural plasticity in SCZ*

Synaptic plasticity is mediated by structural changes (elongation, contraction, and shape changes) of DSs. DSs are tiny, actin-rich protrusions from the dendritic shaft of various types of neurons. Most of the excitatory synapses are on DSs. Postmortem studies suggest that the density of DSs is reduced in brain tissue of individuals with SCZ, including the neocortex (especially in layer deep 3) and hippocampus, while it may be increased in the dorsal striatum[3,55,56]. Moreover, reduced number of spines and decreased length of basilar dendrites have been observed in SCZ[3]. Deficits in DSs may contribute to the impairment of synaptic plasticity in SCZ.

DSs possess specialized subdomains, including PSD, scaffolding proteins, signal transduction molecules, ion channels, and cytoskeleton components. Under the electron microscope, PSD appears as a regular, dense band about 25 nm to 50 nm thick in the postsynaptic membrane. PSD has essentially different roles in the process of LTP formation[57]. Postmortem study demonstrates a drastic reduction of PSD in the nucleus accumbens in SCZ, especially in asymmetric synapse[2]. The alteration of the synaptic ultrastructure may result from overstimulation of the excitatory synapse. Thus, the alteration of PSD may contribute to SCZ.

### *Impaired LTP-like plasticity in SCZ*

LTP and LTD are two primary forms for studying synaptic plasticity. Many factors, including transmitter release and NMDAR function, can affect LTP[58,59]. The dopaminergic or serotonergic systems can also modulate LTP. Impaired LTP and LTD-like plasticity have been reported in SCZ[60,61].

Evidence has shown altered LTP-like plasticity in SCZ compared to healthy subjects[61,62]. Furthermore, NMDAR antagonists (phencyclidine, MK801, and ketamine) can induce SCZ-like symptoms in healthy individuals[63,64]. Studies reveal NMDAR hypofunction in SCZ[65]. Those changes are involved in excitation and inhibition imbalance, controlled by excitatory neurotransmission glutamate and inhibitory neurotransmission gamma-aminobutyric acid (GABA). Electrophysiological recordings reveal that MK801 treatment can significantly suppress the frequency of miniature excitatory postsynaptic current/miniature inhibitory postsynaptic current ratio of layer (L) 2/3 PNs[66]. Neurogranin, a calmodulin-binding protein, modulates LTP in the hippocampus. The lower level of neurogranin results in hypo-phosphorylation of NMDAR subunit NR2A and finally contributes to NMDAR current decay[67]. Maybe, NMDAR hypofunction accounts for the lack of associative LTP-like plasticity in patients with SCZ.

$Ca^{2+}$ entry is another crucial factor for the induction of LTP-like plasticity. The voltage-gated calcium channel is critical for mediating intracellular $Ca^{2+}$ entry, especially the $Ca_v1.2$ or $Ca_v1.3$ channel. Clinical findings reveal the alteration of intracellular calcium homeostasis in SCZ[68]. Calcium concentration level increases in the cerebrospinal fluid (CSF) of patients with SCZ when acute psychotic symptoms are in remission[69]. It means a positive correlation between SCZ and calcium dysregulation. Therefore, dysregulation of calcium concentration is responsible for changing neuronal excitability and LTP-like plasticity.

### *Aberrant plasticity-related genes in SCZ*

Gene expression studies, including microarray, have discovered the aberrant expression of synaptic plasticity-related genes in SCZ, such as GAP43 and PSD95. GAP43 is a phosphoprotein of the presynaptic membrane that regulates the growth state of axon terminals. Several postmortem studies show reduced GAP43 levels in the frontal cortex and the hippocampus of patients with SCZ[70,71]. What's more, PSD95 is the most abundant protein in the postsynaptic membrane. Postmortem studies show decreased PSD95 protein and mRNA expression levels in SCZ[72,73]. Interestingly, PSD95 can directly interact with ARC or IL1RAPL1 to regulate spine density and function[74,75]. Besides, TAOK2 kinase could directly phosphorylate Septin7 to regulate PSD95 stability and DS maturation[76]. The PSD proteins can directly reflect the number of synapses.

Additionally, some genes regulate the development and function of neuronal synapses. KIF3B, a member of the kinesin superfamily proteins, supports the NR2A/APC complex transport. Its dysfunction relates to SCZ[77]. The dynamic regulation of NR2A and NR2B is critical to the function of NMDAR, which has a substantial role in regulating synaptic plasticity. Besides, CaMKII, ARP2/3, Arc, and PI4KA affect NMDAR function and mediate $Ca^{2+}$ entry[78]. A recent study reports that an envelope protein encoded by human endogenous retrovirus type W (also called syncytin-1) regulates $Ca^{2+}$ entry *via* activating the TRPC3 channel[79], indicating that syncytin-1 may also regulate the development and function of neuronal synapses. Intriguingly, our results show that syncytin-1 can increase the expression of BDNF and IL-6 in SCZ[80,81]. BDNF, an essential member of the nerve growth factor family, regulates synapse formation and contributes to impaired plasticity in SCZ[82]. These data predict that syncytin-1 may participate in the regulation of synaptic plasticity.

In summary, abnormality of synapse morphology, LTP-like plasticity, and synaptic plasticity-related genes may contribute to the pathogenesis of SCZ.

## DYSCONNECTION IN SCZ

The hypothesis of dysconnectivity gives two inconsistent explanations: (1) Robust connectivity: The synapse has not been cleared in time in the process of neural system development; and (2) Weak connectivity: Synaptic connectivity decreases and is responsible for the processing information in the brain involving multi brain regions[83,84]. Impaired connectivity is a failure of proper functional integration within the brain, and the connection between different neuron systems influences the functional integration[85]. Effective and functional connectivity plays a prominent role in brain function. Functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magnetic resonance imaging (MRI), computer-assisted tomography, and magnetic resonance spectroscopy have been used to study brain structure or function.

With the development of brain imaging technology, impaired connectivity has been observed in SCZ. Evidence suggests that prefrontal-limbic cortices are hyperconnected with the mediodorsal thalamus and ventral parts of the striatum and pallidum by fMRI[86]. Impaired connectivity correlates with cognitive impairments. Additionally, PET reveals that SCZ involves dysfunction of a widely distributed cortico-thalamic circuitry[87].

Moreover, an MRI study shows reduced synaptic connectivity in SCZ[88]. These reductions are widespread in the left fronto-parietal network, lateral and medial visual network, motor network, default mode network, and auditory network. Reduced synaptic connectivity is also present in the first episode of psychosis but appears to progress throughout the disorder[89]. The reduction of synaptic connectivity may disturb brain development, including myelogenesis and synaptic pruning or disruption of maturation of inhibitory neural networks such as GABAergic interneurons[90-93]. Maybe, reduced synaptic connectivity involves impaired γ synchronization and increased excitation/inhibition ratio[94]. In conclusion, impaired connectivity found in the brain of patients with SCZ is related to the cognitive dysfunction in SCZ.

## COGNITIVE DYSFUNCTION IN SCZ

Since the "dementia praecox" was proposed, cognitive dysfunction had received extensive attention and research in SCZ. It is until 1970s that Gallhofer proposed cognitive symptoms as the third symptoms of SCZ. Cognitive impairments are in the first episode of SCZ[95]. Those deficits include the speed of processing, attention vigilance, working memory, verbal learning, visual learning, reasoning problem solving, and social cognitive[96]. Kudo *et al*[97] report that increased MMP-9 levels are associated with cognitive impairments in SCZ. High concentrations of S100B correlates with memory impairments, and the variants of S100B may lead to poor performance in patients with SCZ[98,99].

Cognitive deficits may impair global functioning or contribute to poor functional outcomes in SCZ [11]. A four-year follow-up study shows that first-episode SCZ with severe cognitive impairments has no social functioning improvement, even after therapy[100]. Besides, the function and structure of frontal-limbic brain regions have a meaningful role in functional outcome in SCZ[101]. Conventional antipsychotic drug treatment has minimal benefits on cognitive symptoms in SCZ, and even some may impair certain aspects of cognition, such as attention, short-term memory, and learning. However, second-generation (atypical) antipsychotics, such as clozapine, improve several cognitive function domains, especially attention and verbal fluency in SCZ[102-104]. In summary, cognitive deficits are core symptoms of SCZ and result in severe disability.

## CASCADE OF NEUROTRANSMITTER AND CIRCUIT DYSFUNCTION IN SCZ

SCZ is currently considered as a polygenic and multifactorial disorder, involving abnormality of synaptic function and neurotransmission, including dopaminergic pathway, serotoninergic pathway, glutamatergic pathway, GABAergic pathway, cholinergic pathway, and other neurotransmitter pathways, such as norepinephrine (NE) and neurosteroids.

### *Dopaminergic pathway*

Typically, the dopaminergic pathway consists of dopamine synthesis, release, and reuptake. It can activate the downstream signal cascades, which play a critical role in synaptic plasticity (Figure 2A). Dopamine is synthesized from tyrosine through two steps: (1) Tyrosine hydroxylase catalyzes the tyrosine to L-DOPA by hydroxylation; and (2) L-DOPA is converted to dopamine by DOPA decarboxylase[105,106]. Dopamine can be stored into SVs, transported to the presynaptic membrane by the vesicular monoamine transporter 2, and finally released to the synaptic cleft[107]. There are five subtypes of dopamine receptors (DRD1, DRD2, DRD3, DRD4, and DRD5) known to mediate dopaminergic physiological functions. Dopamine receptors, especially DRD2, can couple to Gαi/o protein and modulate the PI3K-Akt signal pathway[108,109]. The PI3K-Akt signal pathway has a critical role in cell survival, proliferation, differentiation, glucose metabolism, and gene transcription[110].

Dopaminergic dysfunction has a prominent role in the development of symptoms of SCZ. High dopamine levels in SCZ support this hypothesis[111]. Postmortem studies have suggested a hyperactive dopaminergic system in SCZ, compared to healthy controls[112]. Nowadays, most antipsychotic drugs target dopamine receptors to block dopamine transmission. Notably, DRD2 is considered as the primary target for antipsychotics to alleviate positive symptoms. Moreover, dopamine transporter and vesicular monoamine transporter are decreased in SCZ. However, increased expression of monoamine oxidase A appears to occur in the substantia nigra of patients with SCZ[113].

### *Serotonergic pathway*

Brain 5-HT plays a crucial role in affect and mood control, memory, reward, and modulation of developmental, physiological, and behavioral processes[114-116]. Typically, 5-HT synthesis needs two enzymes: Tryptophan hydroxylase and DOPA decarboxylase. After synthesizing, 5-HT can be transported into SVs and release to the synaptic cleft. Some 5-HT directly binds to its receptors (HTR1A, HTR1B, HTR2A, HTR4, and HTR6), activates downstream signaling pathways to trigger ion channels, and regulates synaptic plasticity (Figure 2B).

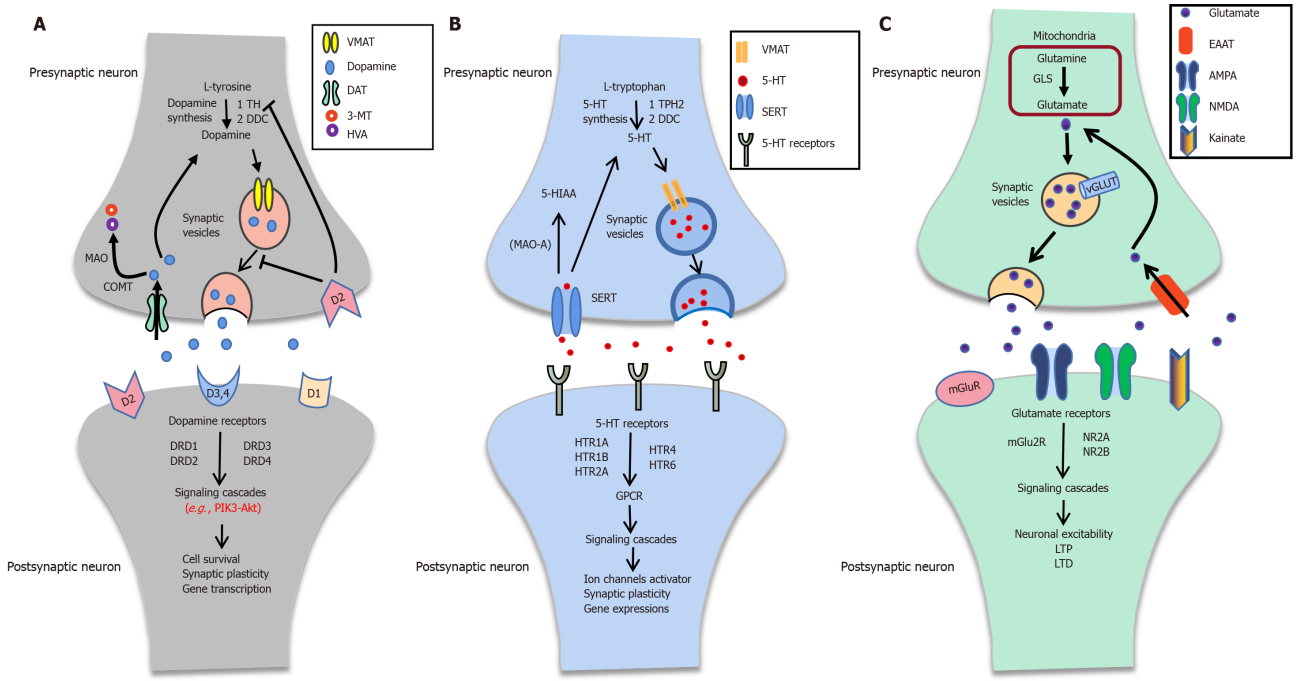


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**Figure 2 Neurotransmission in dopaminergic, serotonergic, and glutamatergic neurons.** Each pathway step is supplemented with associated genes according to KEGG. A: Dopaminergic pathway. Dopamine is synthesized from tyrosine through two steps: (1) Tyrosine hydroxylase catalyzes the tyrosine to L-DOPA by hydroxylation; and (2) L-DOPA converts to dopamine by DOPA decarboxylase (DDC). Dopamine can be stored into synaptic vesicles by the vesicular monoamine transporters and release to the synaptic cleft. Dopamine as a neurotransmitter, can directly bind to its receptor to activate downstream signaling cascades and influence cell survival, synaptic plasticity, and gene transcription. Besides, dopamine also can be transported back to the presynaptic membrane by the DAT and eliminated. DRD2, an auto-receptor, can inhibit the release of dopamine in the presynaptic membrane; B: Serotoninergic (5-HTergic) pathway. The synthesis of 5-HT needs two enzymes: Tryptophan hydroxylase and DDC. After synthesizing, 5-HT can be transported into synaptic vesicles and release to the synaptic cleft. Some of the 5-HT directly binds to its receptors (*e.g.*, HTR1A, HTR1B, HTR2A, HTR4, and HTR6), activates downstream signaling pathway to activate ion channels, and influences synaptic plasticity and gene expressions, and others are re-uptaken into the presynaptic membrane by the serotonin transporter; C: Glutamatergic pathway. Glutamate is converted from glutamine by phosphate-activated glutaminase in mitochondria and packaged into synaptic vesicles by vesicular glutamate transporters. Sequentially, the glutamate is released to the synaptic cleft and binds to the glutamate receptors, and then activates the downstream pathway or is repacked into presynaptic membrane by excitatory amino acid transporters. Signaling cascade activation might lead to the change of neural excitability and finally has effects on long-term potentiation or long-term depression. MAO: Monoamine oxidase; COMT: Catechol O-methyltransferase; 3-MT: 3-Methoxytyramine; HVA: Homovanillic acid; 5-HIAA: 5-Hydroxy indole acetic acid; EAATs: Excitatory amino acid transporters; 5-HT: Serotonin or 5-hydroxytryptamine; GPCR: G protein-coupled receptor; GLS: Glutaminase; NMDA: N-methyl-D-aspartate receptor; AMPA: α-Amino-3hydroxy-5methyl-4-isox-azolepropionic acid; mGluR: Metabotropic glutamate receptor; LTP: Long-term potentiation; LTD: Long-term depression.

Alteration of serotonin transmission has been implicated in the processes of SCZ. Tryptophan hydroxylase 2 (TPH2), a rate-limiting enzyme for serotonin synthesis, is selectively expressed in the raphe serotonergic neurons[117]. Postmortem studies and single nucleotide polymorphism (SNP) studies show a significant association of TPH2 with SCZ in Han Chinese[118,119]. Additionally, the expression level of SERT (5-HT transporter, also named 5-HTT) is reduced in the frontal cortex of subjects with SCZ[120]. Recently, a SNP meta-analysis shows a strong association between SERT polymorphism and SCZ[121]. Indeed, the 5-HT receptor has an outstanding role in 5-HT transmission. 5-HT1A agonist can directly bind to atypical antipsychotic drugs (AAPDs) to treat cognitive impairments associated with SCZ[122-124]. Maybe as a compensatory mechanism, the expression of serotonin 1A is increased or maybe due to the beneficial effects of AAPDs in SCZ, the 5-HT1A receptor is activated.

### *Glutamatergic pathway*

Glutamate is the principal excitatory neurotransmitter in the central nervous system. Notedly, glutamate is converted from glutamine by phosphate-activated glutaminase in mitochondria and packaged into SVs by vesicular glutamate transporters (VGLUTs). Sequentially, the glutamate releases to the synaptic cleft. It then activates the downstream pathway or is re-uptaken into the presynaptic membrane by excitatory amino acid transporter after binding to the glutamate receptors (Figure 2C). Besides, the cystine/glutamate antiporter system $x_c^-$, which might exchange cystine for glutamate in a 1:1 ratio, has a vital role in releasing glutamate[125]. The "glutamate hypothesis" was first proposed by Kim *et al*[126]. They found that glutamate levels were decreased compared to healthy controls in CSF with SCZ[126]. The glutamatergic hypothesis of SCZ is based on the NMDAR hypofunction and the abnormality of glutamate transmission in SCZ.

Postmortem brain study shows a decreased expression level of VGLUT1 in the hippocampus of patients with SCZ[127]. However, VGLUT2 protein levels are increased in the inferior temporal gyrus (ITG) of SCZ[128]. The loss of VGLUT activity eliminates vesicular release and glutamatergic neurotransmission and regulates presynaptic quantal size or synaptic plasticity[129]. Postmortem studies have also revealed an increase in EAAT1 and EAAT2 transcripts in Brodmann's area (BA) 10 of subjects with SCZ, but not BA46[130]. Similar results have a relatively high agreement in the thalamus and cerebellar vermis[131,132]. These results indicate that EAAT is involved in glutamate reuptake in SCZ. Furthermore, evidence shows that mRNA expression levels of SLC3A2 and SLC7A11, two system $x_c^-$ subunit genes, are decreased in peripheral white blood cells of SCZ patients compared to healthy controls. Abnormality of system $x_c^-$ is involved in glutamatergic neurotransmission[125]. NMDAR-mediated glutamate transmission has been implicated in cognitive execution in the nucleus accumbens of SCZ[133]. Changes in the mRNA and protein levels of NMDAR subunits have been described in SCZ [134]. Suppressed NMDAR signaling through Src kinase may facilitate presynaptic glutamate release during synaptic activity[135]. In addition, the D-amino acid oxidase activator (DAOA, also called G72) protein, which has an important role in modulating NMDAR signaling, has a strong association with SCZ[136,137]. Those results indicate that alteration of glutamatergic transmission has a meaningful role in SCZ.

### *GABAergic pathway*

Reduced GABAergic neurotransmission is in support of the 'GABA hypothesis' for SCZ[138]. RNA-Seq analysis reveals the disruption of GABA metabolite levels in SCZ[139]. Moreover, postmortem studies suggest that subjects with SCZ have lower mRNA and protein levels of synthetic enzyme GAD67 compared to healthy controls[140]. Lower expression of GAD67 may be a consequence of a deficiency of the immediate early gene Zif268, suggesting a potential mechanistic basis for altered cortical GABA synthesis and impaired cognition in SCZ[141]. GAD67 promoter methylation levels are associated with the SCZ-risk SNP rs3749034 and with the expression of GAD25 in the dorsolateral prefrontal cortex (DLPFC). Alternative splicing of GAD67 may contribute to GABA dysfunction in SCZ[142]. Similarly, the immunoreactivity of GAT1, a protein responsible for the reuptake of GABA, is decreased in SCZ [143]. Furthermore, GAD1 knockout rats exhibit SCZ-related phenotypes, such as cognitive impairments in spatial reference and working memory in the hippocampus[144]. A PET study using [$^{11}$C] Ro154513 has reported differential expression of GABA-A receptors in SCZ[145]. Therefore, the synthesis and reuptake of GABA are lower in SCZ. These abnormalities of GABAergic neurotransmission are related to cognitive impairments in SCZ.

### *Cholinergic pathway*

Acetylcholine has a vital role in cognitive and behavioural/psychological function. Pharmacologic studies show that central cholinergic activity profoundly affects the storage and retrieval of information in memory. The choline acetyltransferase, a cholinergic function marker, is correlated with the severity of cognitive impairments in the parietal cortex of schizophrenic patients[146]. Furthermore, cholinesterase inhibitors (donepezil or rivastigmine) have positive effects on cognitive dysfunction in SCZ[147, 148]. These inhibitions increase the synaptic concentration of acetylcholine and finally enhance and prolong acetylcholine action on muscarinic and nicotinic receptors in the postsynaptic membrane.

SCZ patients show decreased α4β2 nicotinic acetylcholine receptors (nAChR)[149]. However, the α7 nAChR level is increased in the DLPFC of SCZ patients[150]. Besides, functional polymorphisms of the α7 nAChR have shown genetic linkage in SCZ[151]. Muscarinic receptors, also called the metabotropic muscarinic acetylcholine receptors, have five subtypes (M1-M5 receptors), encoded by the CHRM1-5 genes. Postmortem studies suggest lower CHRM1 levels in the cortex of patients with SCZ[152]. The loss of cortical CHRM1 may be regulated by miR-107 in SCZ[153]. What's more, CHRM1 is involved in memory processes, and blockade of hippocampal CHRM1 demonstrates a deficit in working memory [154]. Together, these results suggest that alterations in the cholinergic pathway may contribute to a breakdown in cholinergic homeostasis and have a key role in the pathophysiology of SCZ, particularly the cognitive impairments.

### *Other neurotransmitter pathways*

Other neurotransmitter pathways, such as NE and neurosteroids, have also been implicated in the cognitive dysfunction of SCZ.

NE is a significant neuromodulator of brain function and neural gain. NE exerts its effects through noradrenergic receptors (α1, α2, and β). The alteration of noradrenergic neurotransmission has been studied for years. It is a consensus that patients with SCZ have higher NE levels than the control group [155,156]. Furthermore, α2-adrenergic receptor antagonist idazoxan has antipsychotic efficacy in the treatment of SCZ, especially the anxiety or depression symptoms[157]. It may be associated with the increased output of DA.

Additionally, the abnormality of neurosteroid transmission also has a crucial role in the pathobiology and symptomatology of SCZ[158]. Both the levels of progesterone and allopregnanolone (ALLO) are decremented in SCZ in a postmortem study[159,160]. Studies suggest that ALLO enhances NMDA

receptor neurotransmission by interaction with σ1 receptors in SCZ[161,162]. What's more, decreased levels of ALLO may modulate GABAergic transmission in the brain and finally lead to impairments of GABAergic function in SCZ[163].

## POTENTIAL TARGETS FOR TREATMENT OF SCZ

Most antipsychotic drugs target serotonin-dopamine receptors or serotonin-glutamate receptors, suggesting disarranged neurotransmitter interaction. Newer AAPDs, such as clozapine, olanzapine, and risperidone, have been developed because of their significant effects on dopaminergic receptor subtypes and serotonergic receptors[164]. Interestingly, co-immunoprecipitation studies verify that HTR2A and DRD2 physically interact in HEK293 cells. Furthermore, shreds of evidence reveal that HTR2A and mGlu2 receptors can assemble into a functional heteromeric complex to modulate each other's function [165,166]. The expression of HTR2A is required for phosphorylation of mGlu2R at serine 843 and promotes mGlu2R-modulate G i/o signaling[167]. Therefore, there are potential antipsychotic drugs by targeting HTR2A, DRD2, and mGlu2R. DRD3 was found to be associated with SCZ in a case-control study[168]. Several pharmaceutical studies suggest that DRD1/5 agonists have potential therapeutic effects in SCZ by improving cognitive or negative symptoms[169,170]. What's more, HTR4/6 agonists can improve cognitive symptoms in SCZ. HTR4/6 may be a promising target for treatment of cognitive dysfunction in SCZ[171]. Additionally, sarcosine (a competitive inhibitor of the type 1 glycine transporter) and D-amino acid oxidase (DAAO or DAO) inhibitor can improve the clinical symptoms in SCZ patients. Therefore, glycine transporter and DAO may offer potential therapeutic targets for SCZ [172,173].

There are many other potential targets for the treatment of SCZ. Accumulated pieces of evidence have revealed various susceptibility genes in SCZ, including STAB2, GRIN1, GRIN2A, ARC, BDNF, NRGN, syncytin-1, and others[67,81,174]. Interestingly, many of those genes appear to be related to the control of synaptic plasticity and cognitive impairments in SCZ. BDNF plays a principal role in regulating synaptic organization, neurotransmitter synthesis, and the maintenance of synaptic plasticity[175]. Data from our lab provide evidence that syncytin-1 can regulate the expression of BDNF and DISC1. Furthermore, GNbAC1, a monoclonal antibody targeting syncytin-1, has been implicated in the treatment of multiple sclerosis and type 1 diabetes[176,177]. Thus, syncytin-1 is a promising therapeutic target for SCZ in the future.

## CONCLUSION

Accumulated shreds of evidence indicate that changes in the morphology of synapses have a vital role in the incidence of SCZ. The potential role of synapse in SCZ appears much more complicated. In conclusion, the synapse can be involved in three aspects as follows: (1) The change of synaptic plasticity (*e.g.*, change in the dendrite spines, PSD, and alteration in LTP and LTD); (2) The abnormalities in neurotransmission (*e.g.*, dopaminergic transmission, serotoninergic transmission, and glutamatergic transmission); and (3) The impairment of cognition (*e.g.*, disconnection).

Impaired synaptic plasticity contributes to cognitive dysfunction in SCZ. These dysfunctions include abnormal brain connectivity and functional outcomes. With the development of brain imaging technology, research on cognitive impairments should do not focus on a single gene or brain regions but on neural circuits or brain networks to study the underlying mechanism in SCZ. SCZ is a complex disease, and there are still no available antipsychotic drugs to treat all symptoms of SCZ or accompany little side effects. Finding potential antipsychotic drug targets will help identify and develop novel therapeutic agents with fewer side effects.

## FOOTNOTES

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*REVIEW*

# Anorexia nervosa: Outpatient treatment and medical management

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## Abstract

Anorexia nervosa (AN) is a disabling, costly and potentially deadly illness. Treatment failure and relapse are common after completing treatment, and a substantial proportion of patients develop severe and enduring AN. The time from AN debut to the treatment initiation is normally unreasonably long. Over the past 20 years there has been empirical support for the efficacy of several treatments for AN. Moreover, outpatient treatment with family-based therapy or individual psychotherapy is associated with good outcomes for a substantial proportion of patients. Early intervention improves outcomes and should be a priority for all patients. Outpatient treatment is usually the best format for early intervention, and it has been demonstrated that even patients with severe or extreme AN can be treated as outpatients if they are medically stable. Inpatient care is more disruptive, more costly, and usually has a longer waiting list than does outpatient care. The decision as to whether to proceed with outpatient treatment or to transfer the patient for inpatient therapy may be difficult. The core aim of this opinion review is to provide the knowledge base needed for performing safe outpatient treatment of AN. The scientific essentials for outpatient treatment are described, including how to assess and manage the medical risks of AN and how to decide when transition to inpatient care is indicated. The following aspects are discussed: early intervention, outpatient treatment of AN, including outpatient psychotherapy for severe and extreme AN, how to determine when outpatient treatment is safe, and when transfer to inpatient healthcare is indicated. Emerging treatments, ethical issues and outstanding research questions are also addressed.

**Key Words:** Anorexia nervosa; Outpatient treatment; Medical management; Outpatient psychotherapy; Inpatient healthcare

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**Core Tip:** Outpatient psychotherapy is the mainstay of treatment of anorexia nervosa. Both early intervention and healthcare for severe and enduring anorexia nervosa are mainly performed in outpatient clinics. Even in severe and extreme anorexia nervosa outpatient psychotherapy is an alternative to inpatient treatment when the patient is medically stable. Medical management is essential for safe outpatient therapy. In this opinion review essentials in outpatient healthcare and medical management are discussed. Emerging therapies and outstanding research issues are addressed.

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## INTRODUCTION

Anorexia nervosa (AN) is characterized by starvation, malnutrition, fear of weight gain and/or a disturbed body image, and severe dietary restriction or other weight-loss behaviors (*e.g.*, purging, excessive physical activity). There are two subtypes of this condition: binge eating with purging (or only purging), and food restricting only[1,2]. Patients usually have a low body mass index (BMI), but some patients with rapid weight loss have a clinical picture of AN with a BMI within the normal range[3]. In addition, cognitive and emotional functioning are often markedly disturbed[4,5]. The prognosis is poor for a substantial proportion of patients[6], and mortality rates are high[7]. The comparative efficacy of available treatments is described in recent systematic reviews and meta-analyses[1,4]. The core aim of the present opinion review is to present an overview of the scientific essentials for AN outpatient treatment, including how to assess and manage the medical risks of AN, and how to decide when transition to inpatient care is indicated. Emerging therapies and outstanding research questions are addressed.

## DIFFERENTIAL DIAGNOSIS

The diagnostic criteria for AN in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) are provided in Table 1[2]. Diagnosing AN is usually straightforward, although sometimes the use of additional informants such as parents is necessary[4].

Inflammatory bowel disease (Crohn's disease or ulcerative colitis), malignancies, thyrotoxicosis and diabetes can present a clinical picture similar to AN. In rare cases AN can be mimicked by a cerebral tumor including pituitary adenoma[4]. Patients with severe depression can experience weight loss due to loss of appetite or a belief that they do not deserve food. A patient with schizophrenia might avoid food due to various delusions[4]. Avoidant/restrictive food-intake disorder (ARFID) was initially regarded as a disorder of childhood, but is now regarded as an age-neutral disorder[4]. Core symptoms are food avoidance or restriction (volume or variety), together with weight loss or faltering growth, nutritional deficiencies, dependence on nutritional supplements for sufficient intake, and/or psychosocial impairment[4]. Although patients with ARFID do not present with the concerns about weight and body shape typically associated with AN[8], they are susceptible to the same medical complications[4,9].

## EPIDEMIOLOGY

Approximately 92% of individuals affected by AN are female[10], but all genders, sexual orientations and ethnicities are affected[11]. The most common age of onset is 15-25 years[12]. The age of onset appears to be decreasing[6,13,14]. The incidence is low in children aged 4-11 years, but it increases significantly with age above 11 years[6]. The restricting subtype of AN is associated with earlier onset and greater likelihood of crossover to the binge-eating/purging subtype[15]. Onset after the age of 30 years is rare[13,16].

The estimated prevalence of AN among young females is 0.3%[13,17], and it affects up to 4% of females and 0.2% of males during their lifetime[17,18].

Time-trend data suggest that the incidence of AN in Europe increased from the 1930s to the 1970s. This might have been due to improvements in the detection rate of persons with AN, but it might also reflect a true increase. In the 1960s another beauty ideal became more widely adopted, as represented by very thin models such as the supermodel Twiggy. It appears that the incidence of AN in Europe was

**Table 1 Diagnostic criteria, subtypes and severity of anorexia nervosa**

| Diagnostic variable | |
|---|---|
| Diagnostic criteria | (1) Restriction of energy intake relative to requirements in anorexia nervosa leads to significantly low body weight for the patient´s age, sex, developmental trajectory and physical health. Significantly low weight is defined as a weight that is less than the minimal normal weight or (in children and adolescents) less than the minimum expected weight; (2) Intense fear of gaining weight or of becoming fat, or persistent behaviour that interferes with weight gain, even though the patient has a significantly low weight; and (3) Disturbance in the way in which one´s body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight |
| Subtype designation | Restricting subtype: During the past 3 mo, the patient has not engaged in recurrent episodes of binge-eating or purging behaviour (*i.e.* self-induced vomiting or the misuse of laxatives, diuretics or enemas). Weight loss is primarily through dieting, fasting or excessive exercise, or all of these methods; Binge-eating/purging subtype: During the past 3 mo, the patient has engaged in recurrent episodes of binge-eating or purging behaviour (*i.e.*, self-induced vomiting or the misuse of laxatives, diuretics or enemas) |
| Current severity | Mildly severe low body weight is defined as BMI > 17.00 kg/m$^2$; Moderately severe low body weight is defined as a BMI of 16.00-16.99 kg/m$^2$; Severe low body weight is defined as a BMI of 15.00-15.99 kg/m$^2$; Extremely severe low body weight is defined as BMI < 15.00 kg/m$^2$[1,2] |

All three diagnostic criteria are required for the diagnosis anorexia nervosa. BMI: Body mass index.

stable from 1970 into the 21$^{st}$ century[19], but the global incidence of AN appears to be increasing, particularly in Asia and the Middle East[20,21]. However, the incidence of AN remains low in Africa and among African American females in the USA, in Latin America, and among Hispanics/Latinos in the USA[19]. These observations may reflect both genetic and cultural etiological factors. A large-scale national health survey in South Africa revealed that despite a high mean BMI of 29.0 kg/m$^2$, more black African females were happy with their current weight and fewer attempted to lose weight, compared with females of other ethnicities[19,22]. A study involving the Caribbean Island of Curacao found no cases of AN among the mainly black population, while the incidence in the white population was similar to that in the United States and the Netherlands. That study was performed when the cultural influence of North America and Europe was increasing with the development of an affluent minority and relatively poor majority[23]. Studies involving Hispanics/Latinos in the United States found that they had fewer concerns about weight gain than did their non-Hispanic white peers, leading to fewer cases of AN[24]. This seems to be related to a body ideal of a "curvier" shape and higher body weight compared with the ideals in Western countries[25,26]. Case series of males with AN in Western societies indicate that they display many of the same characteristics and clinical course as females with AN[27]. AN in males has been reported in non-Western societies, but few cross-cultural data are available on the incidence and prevalence of AN among males[28,29].

## RISK FACTORS AND DEVELOPMENT

The etiology of AN is complex and involves genetic and neurobiological factors[30], and a range of psychological risk factors has been identified, such as childhood anxiety disorders, trauma (*e.g.*, sexual assault, physical abuse, neglect), early feeding problems, temperamental traits such as inhibition, perfectionism and harm avoidance[31]. In addition, living in a society in which a high value is placed on thinness, including occupations that require a lean physique and perfectionism (*e.g.*, sports and modelling), seems to be associated with an increased risk of AN[1,32-34]. Genetic studies indicate that genes coding for metabolic factors seem to play an important role in the development and maintenance of AN. The aspects of AN as a metabo-psychiatric disorder are further discussed in the section below on emerging therapies and outstanding research issues.

Most AN patients report that they started losing weight by voluntary dieting, but in some patients the weight loss is caused by depression, trauma, excessive exercise, a gastrointestinal disorder or protracted infection. If the initial weight loss is voluntary, the patient usually has a positive experience during the first mo. However, over time they will find it increasingly difficult to eat normally, and a normal meal can induce discomfort, anxiety or even panic reactions. The patient gradually becomes preoccupied with body weight and body shape. Negative experiences from trying to eat normally lead patients to eating too little. Food intake is further decreased in times of stress, and even everyday stressful experiences may induce a further reduction in food intake. Thus, patients enter a vicious cycle of reduced food intake with increasing overvaluation of shape and weight, and further reduction of food intake. Treatment becomes more difficult when these psychological maintaining mechanisms are established. The vicious cycle appears to include both psychological and somatic factors that are closely related to nutritional status (see Figure 1).

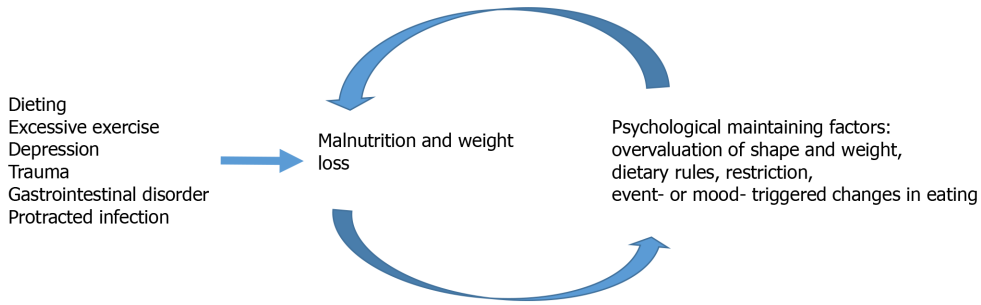


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**Figure 1 Illustration of how anorexia nervosa may develop in most patients.** Dieting, excessive exercise, depression, trauma, gastrointestinal disorder or protracted infection induce weight loss and malnutrition. In susceptible individuals the malnutrition causes the development of maintaining psychological mechanisms, which in turn decrease food intake and increase malnutrition. The malnourished patients enter a vicious cycle of reduced food intake with increasing overvaluation of shape and weight, they often establish dietary rules in order to decrease food intake and restrict their food intake. Everyday stressful experiences may induce event - or mood triggered further reduction in food intake.

## PRIMARY PREVENTION

Research into the primary prevention of eating disorders (EDs) is in its early stages. A meta-analysis[35] concluded that there are promising strategies for universal prevention (targeting whole populations) as well as the selective prevention of EDs (targeting individuals showing specified risk factors), but not for indicated prevention (early detection and intervention for individuals with symptoms below the diagnostic level of EDs). However, most studies were found to have a high risk of bias, which demonstrates the methodological challenges of this research. The picture is even more complicated when looking specifically at AN. Stice *et al*[36] reviewed known risk factors to target in preventive interventions. They highlighted the challenge that risk factors predicting other EDs (body dissatisfaction, negative affect, thin-ideal internalization, perceived pressure for thinness, dieting and family support deficits) do not consistently predict AN. Existing prevention programs tend to target these risk factors, and therefore they might be less effective in preventing AN. The only risk factor that spans the full spectrum of EDs, including AN, is impaired psychosocial functioning. An additional risk factor for AN is low BMI. This situation prompted Stice *et al*[36] to argue that AN-specific preventive strategies should target psychosocial functioning and healthy weight gain. However, previous universal prevention programs have demonstrated little or no effect on the prevalence of AN. A long-term effectiveness study of a school-based primary prevention program for AN in Germany found an effect on body self-esteem but not on disordered eating. However, that study exhibited implementation difficulties, including problems with maintaining the sample size[37]. Primary prevention in smaller populations with a high risk of an ED seems to exert some effects. An intervention designed to prevent the onset of EDs among adolescent athletes through a 1-year intervention program prevented the onset of EDs and reduced symptoms associated with EDs relative to assessment-only control athletes. However, the small number of ED patients in that study prevented a subgroup analysis of the effect on the prevalence of AN[36,38].

A recent study reviewed the evidence for the early detection of individuals fulfilling diagnostic criteria, which is an aspect of secondary prevention[39]. Those authors found evidence that educational interventions targeting professionals (*e.g.*, from medical, educational or sports environments) are somewhat effective. The case for early detection is very strong, since many studies have demonstrated that the risk of severe and enduring anorexia nervosa (SE-AN) increases with the duration of untreated illness[40]. Until more evidence on primary prevention of AN is available, it seems prudent to focus efforts and healthcare costs on early detection and ease of access to treatment.

## PROGNOSIS AND MORTALITY

Rates of recovery from AN at 1- to 2-year follow-ups with the best available treatments lie in the range of 13-50% across age groups[41,42]. Among the patients who complete psychotherapy the relapse rates are ranging from 9% to 52%, with most studies finding rates higher than 25%[43]. The average duration of illness with AN is about 6 years[12]. The long-term course is heterogeneous, with 20-year longitudinal studies finding that 30%-60% of patients will experience full remission, while 20% will have enduring illness and the remainder will have residual symptoms[43,44].

In a meta-analysis of 36 studies published between 1966 and 2010, the standardized mortality ratio for patients with AN (the percentage of observed deaths among patients with AN divided by the percentage of expected deaths in the population of origin) was 5.9[7]. One in five individuals with AN

who died had committed suicide[7]. However, these data were often derived from patients admitted to hospitals, and early intervention and active engagement might have reduced the prevalence, need for hospitalization and mortality[4,14]. No mortality was observed in a cohort of 51 patients with AN recruited from all individuals born in 1985 in Gothenburg, Sweden who were followed for 30 years[45]. Although these observations were made in a small cohort of young patients, they might indicate that early intervention and structured follow-up are associated with low mortality.

## COMORBIDITIES

Both psychiatric and somatic comorbidities are common in AN. The most common psychiatric comorbidities are mood and anxiety disorders, obsessive-compulsive disorders, personality disorders, substance-use disorders and neurodevelopmental disorders such as autism spectrum disorder or attention-deficit hyperactivity disorder[4]. Comorbid disorders tend to worsen the prognosis of AN because they interfere with treatment response[46-49]. Suicidal behaviors and ideation are markedly increased in patients with ED[50,51]. Type 1 diabetes is sometimes a challenging comorbidity, since the omission of insulin in order to lose weight can induce severe complications, including recurring ketoacidosis and rapid development of neurological, retinal and renal complications, and is associated with a significantly increased mortality rate compared with AN without type 1 diabetes[52].

## THE CLINICAL INTERVIEW AND THE PHYSICAL ASSESSMENT

Since most patients with AN should be treated as outpatients, the assessment should determine whether outpatient treatment is safe. A clinical interview is essential for risk assessment. Ascertaining the duration and severity of the patient's ED may help to identify likely complications. Assessment of nutrition should include information about the intake of bread and similar thiamine-containing nutrients, the intake of meat and fish and other zinc-containing nutrients, and whether the patient has a varied or monotonous diet with the associated risk of multiple deficiencies[53,54]. Information about physical capacity compared with friends or relatives of the same age should be obtained. The clinical interview should also assess whether the patient has excessive exercise, vomiting and use of laxatives or other medications, including those that aim to increase metabolism (*e.g.*, thyroxine), or herbs or other substances that may have metabolic or diuretic effects[55].

The presence of purging behaviors is sometimes difficult to assess, and corroborative sources of data should be obtained whenever possible. Information about past eating disorder treatment including previously diagnosed complications is also valuable[50]. Anamnestic information regarding attacks of dizziness, syncope, or near-syncope warrants the acquisition of more detailed anamnestic information about possible arrythmia and other causes of the attacks such as hypoglycemia or hypotension. Information regarding exercise (especially excessive exercise), vomiting or other purging activity, pulse rate during or before the attack, and data on altered medication can shed light on possible underlying mechanisms. In particular, recent onset of symptoms suggestive of cardiac arrythmia is important because refeeding might alter the electrolyte balance and further worsen unstable arrythmia. Chest pain and attacks of dyspnea could be related to pneumothorax or cardiovascular disease. The malnutrition in AN is associated with pulmonary changes that may predispose to spontaneous pneumothorax[56]. Patients with severe or extreme AN may have several potentially lethal complications, and these patients should be assessed by a physician with experience in extreme AN before outpatient treatment is commenced.

A physical examination should be performed in a sufficiently warm room and undressing should be performed gradually and respectfully to allow examination of the chest with auscultation of lungs and heart, including searching for systolic murmur in the left axilla that indicates mitral-valve insufficiency. Gentle palpation of the abdomen can give valuable information on the location of any abdominal pain, and whether the pain is referred. Palpation and percussion can reveal distension of the GI tract and other parts of abdomen including tendency to gastric retention. Arms and legs should be examined to assess the peripheral circulation, dehydration, peripheral oedema and pitting. Balance can be assessed by asking the patient to stand on one foot, and simple tests of coordination can reveal the risks of falling and fractures. Problems with coordination and balance can be related to malnutrition-induced cerebellar dysfunction or proximal myopathy, which is a common problem in severe malnutrition. This myopathy can be significantly increased during refeeding and can be associated with increased risk of falling[34].

It might be difficult to measure the blood pressure properly due to thin arms, but in patients with symptoms of orthostatic hypotension, valuable information can be revealed by using a blood-pressure cuff for children. Palpation of the pulse can give information about the heart rate, pulse pressure and dehydration, and the tendency for severe hypotension, which causes a very thin pulse wave with relative tachycardia[57]. Resting tachycardia is unusual and may be indicative of a superimposed infection or other complication[58]. The usual signs of infection (fever and elevated white blood cell count) may not be present in AN. A lower threshold to evaluate for an infection should be followed[57].

Examination of the teeth can reveal erosions, indicating possible vomiting with risk of electrolyte disturbances[59].

Blood tests in AN (especially restricting AN) can be normal or close to normal even when the patient is at risk of lethal arrythmia or other severe complications of treatment. Therefore, using blood tests alone without comparing with the clinical picture is not adequate for risk assessment. Assessment of patients with extreme AN (BMI < 15 kg/m$^2$) should be performed in collaboration with a physician with experience in extreme AN as this group of patients may have a large number of complications[57,60].

## TREATMENT

Outpatient psychotherapy is the mainstay of treatment for AN, as it is less costly and disruptive than other, more intensive levels of care[61,62]. A proportion of patients will need inpatient psychotherapy or supportive care. Research data to guide choices among types of psychotherapy for outpatient and inpatient treatment are limited and disputed[1]. AN remains difficult to manage since patients are often challenging to engage, and outcomes are often poor, even in those who agree to commence treatment [61]. However, over the past 20 years there has been empiric support for the efficacy of several treatments, mainly in the outpatient setting, and thanks to an improved understanding of the psychological mechanisms that maintain them, manualized treatments for children, adolescents and adults with AN have been developed.

The decision regarding whether to proceed with outpatient treatment or to transfer a patient for inpatient therapy may be difficult, especially in non-specialist or general psychiatry settings. The feasibility of outpatient psychotherapy requires containment of concerns regarding the short- and long-term somatic consequences of malnutrition and monitoring of medical safety needs. The patient's medical and psychiatric stability, AN severity, age and duration of illness must be considered during treatment decision-making[34]. Psychopharmacological medications are generally ineffective for promoting weight gain, reducing AN-related depressive symptoms or preventing relapse in AN[1]. However, there is some preliminary evidence for the use of atypical antipsychotics for adolescents to support the acute phase of renourishment[63]. Overall, medication plays a very limited role in the treatment of AN[1,64-66].

Early intervention improves outcomes, and so the rapid commencement of specialized treatment for EDs is essential[4,67,68]. The duration of untreated AN before treatment initiation varies, but multiple studies have found that adults and adolescents had AN for a mean of 30 mo before treatment was initiated[4]. The First Episode Rapid Early Intervention for Eating Disorders (FREED) study found that the duration of untreated AN in patients aged 16-25 years could be significantly reduced by implementing an early intervention service model and care pathway for young adults with EDs[69]. In addition, the proportion of patients taking up treatment was significantly higher among FREED patients than among those who received treatment as usual (TAU)[69].

### *Treatment of children and adolescents*

Family-based treatment (FBT) is the most empirically supported intervention for children and adolescents with AN[4,29,70,71]. In general, FBT does not align with a particular therapeutic approach, but instead integrates techniques from a variety of schools of psychotherapy, including systemic, strategic, narrative and structural types of family therapy[72]. The overall philosophy of FBT is to empower parents to help their child to overcome a disease that is beyond his/her own control. The family is viewed as a resource and the child or adolescent with AN is seen as embedded in the family and temporarily regressed, and parental involvement in therapy plays a pivotal role in treatment success[72].

Six randomized, controlled trials (RCTs) have assessed the efficacy of manualized FBTs for AN in adolescents. Manualized FBTs have been compared with a single individual therapy (*i.e.* adolescent-focused therapy) in only one RCT. In that trial, FBT was not significantly more efficacious than was adolescent-focused therapy at the end of treatment, but it was more effective for facilitating full remission at follow-up[61,73]. The findings of a Cochrane review suggest that the evidence favoring family-based interventions over standard treatment or other psychological approaches is not robust [74]. This opinion has been criticized partly because studies of questionable validity were not excluded from the Cochrane review and because the study had inadequate statistical power[75]. FBT is recommended in several clinical guidelines[29,62,76] on the basis of evidence of remission rate, faster weight gain and less reliance on the young patient's own motivation and ability to change their symptomatic behaviors.

Several modifications of standard FBT have been tested. One of these is Parent-Focused Family Therapy, a type of FBT in which most sessions only involve the parents. According to one high-quality RCT, this modality is as effective as traditional FBT, where the family is seen together[29,77]. Another modality of family therapy that has been adapted to treat AN is multifamily therapy, which draws on the conceptual principles of FBT, applying them to groups of typically five to seven families in extended whole-day sessions, initially over four consecutive days. The presence of other families and the intensity

of the contact creates a powerful treatment context wherein families learn from each other, share their experiences and gain multiple perspectives on the problems they face. The group context also helps to reduce the sense of isolation and stigmatization that is often experienced by families living with an ED [78]. Another high-quality RCT compared systemic family therapy with FBT and found no significant differences in remission rates; however, the rate of weight gain was greater and the need for hospitalization was significantly lower in the FBT group[79].

While parental involvement is effective and often necessary to bring about changes in children and adolescents with AN, it does come at a considerable cost for the families. Parents may find the task of renourishment in the face of strong emotional reactions from their child daunting[80,81], and the intensive care required may be an economic burden for parents since it may require them to take time off from work. Regardless of which mode of FBT is chosen, monitoring of the patient's somatic condition is necessary in order for parents to know that their child is safe while they struggle to learn how to manage, for example meal support, and for the family therapist to support the agency of the parents. Furthermore, although parents receiving FBT are supported to rely on their own experience when making feeding choices, they may need dietary advice on how to increase the energy density of the meals they provide to affected children. Consequently, easy access to multidisciplinary support helps parents and therapists to provide effective outpatient psychotherapy. It is important that all team members, *e.g.*, the physician in charge of somatic assessment, understand the principles of parent empowerment, as described by Katzman *et al*[82].

### Treatment of adults

Data to guide choices among types of psychotherapy for adults remain inadequate and disputed[1]. The guideline from the National Institute for Health and Care Excellence (NICE) on the recognition and treatment of EDs recommends that the first-line treatments for adults consist of structured individual therapies that focus on EDs, including individual cognitive behavior therapy (CBT) with an eating disorder focus (CBT-ED), Maudsley Model of Anorexia Nervosa Treatment for Adults or Specialist Supportive Clinical Management (SSCM) (36). These therapies have been evaluated in large-scale trials, which have revealed little or no difference in efficacy between them[4,83-86]. All of these therapies lead to considerable improvements in body weight and reductions in AN symptoms[4]. CBT-ED is the most widely used manualized individual psychotherapy for adult patients, with enhanced CBT for EDs (CBT-E) as described by Fairburn probably being the most widely disseminated CBT-ED for AN[87].

### Family based treatment or individual psychotherapy for adolescents?

The most common age of onset of EDs is in adolescence and young adulthood, but the clinical services for adolescents and adults are separate in some countries[4]. This means that patients and their families are often obliged to change treatments when the adolescent patient is transferred to adult services[61]. The choice of treatment should be related to the needs of the patients and their families. For adolescents, FBT is the current leading empirically supported intervention for AN[4,62]. NICE has recently recommended the use of CBT-ED in children and young people when family therapy is unacceptable, contraindicated or ineffective[62]. This recommendation was supported by promising results demonstrated by the application of CBT-E adapted for adolescents with EDs[72]. A recent systematic review found that outpatient CBT-E was well accepted by adolescent patients with AN; it was completed by about two-thirds of participants and produced improvements in eating-disorder psychopathology and general psychopathology, and remission from AN was achieved by about 50% of patients at the 12-mo follow-up[88].

Some of the differences and similarities of FBT *vs* individual psychotherapy were discussed in a recent conceptual comparison of FBT and CBT-E[72]. Briefly, parental involvement in FBT is vitally important for the ultimate success of the treatment. In CBT-E, parental involvement is useful but not essential[72], with their role being simply to support the implementation of the one-to-one treatment. Both types of treatment address adolescent development, but in FBT the adolescent is not viewed as being in control of his/her behavior (*i.e.* the ED is considered to be controlling the adolescent). This is corrected in the first phase of the treatment by improving the parental control over eating[72]. In CBT-E, the adolescent is helped to learn how to control his/her behavior, and parents may help and support the adolescent in taking control[72]. In FBT, the adolescent is initially not actively involved and plays a more passive role, although their role becomes more active in the second and third phases of the treatment, while in CBT-E the adolescent is encouraged from the beginning to become actively involved in the treatment[72]. CBT-E for adolescents does not use directives or coercive procedures. The patients are never asked to work on issues that they do not consider to be a problem, as that would tend to increase their resistance to change. The key strategy of CBT-E is to create a formulation of the main mechanisms maintaining their individual eating problems, and actively involve the patient in the decision to address them, including their low weight. If they do not reach the conclusion that they have a problem to address, the treatment cannot begin or must be suspended.

A lack of insight and motivation for change in the young person is one of the main reasons why FBT is often preferred by both healthcare services and parents. However, most adolescents are able to reach the conclusion that they have a problem to address if they are introduced to CBT-E by a trained psychotherapist[61,72,89]. Once the patient is engaged in the process of change, their personal eating-disorder

psychopathology (outlined in the formulation) is addressed *via* a flexible series of sequential cognitive behavioral procedures and strategies, integrated with progressive patient education[61]. Despite several differences, the general strategy that is common to FBT and CBT-E is to address the maintaining mechanism of the eating-disorder psychopathology, especially undereating, as opposed to exploring any potential causes of the eating-disorder psychopathology. Both treatments take an agnostic view of the cause of the illness; that is, no assumptions are made about the potential origins of EDs[72].

### Evidence-based treatment

Some clinical services still do not provide patients with evidence-based psychological treatments, or else they rely on therapists who deviate from the established protocols. The dissemination of FBT, CBT-E and other evidence-based treatments needs to be promoted. Web-centered training programs designed to enable simultaneous training of large numbers of therapists in different countries is a potential solution[61].

### Severe and extreme anorexia nervosa

In DSM-5, severe AN is defined as AN with a BMI of 15.00-15.99 kg/m$^2$, while extreme AN is defined as a BMI < 15.00 kg/m$^2$ (see Table 1)[2]. Most of the studies on outpatient treatment of AN have included patients with mild or moderate AN. However, some studies have shown that outpatient treatment can be a valid alternative to inpatient treatment in cases of severe or extreme AN if the patient is medically stable[83,90,91]. Outpatient treatment must be safe, otherwise concerns regarding the medical risks will become the focus, rendering psychotherapy difficult or impossible to perform. When a patient is medically stable there is no significant risk of dangerous complications during therapy. These issues are discussed in more detail below in the section on medical management and in the treatment section.

In a case series of 30 patients aged ≥ 17 years with a mean BMI of 15.1 kg/m$^2$ (range 12.82-15.99) at baseline, 66% completed outpatient CBT-E and demonstrated both considerable weight gain and reduced psychopathology at the end of treatment[90]. Among the 20 patients who completed the treatment, 11 (55%) were classified as having a "full response", corresponding to BMI ≥ 18.5 kg/m$^2$ combined with a global score on the Eating Disorder Examination Questionnaire (EDE-Q) of less than 1 SD above the community mean[87]. Moreover, among the 9 patients with BMI < 18.5 kg/m$^2$, 7 (35%) had a BMI that was classified as being of mild severity (≥ 17.0 kg/m$^2$ according to the DSM-5) and 2 (10%) had a BMI of moderate severity (16.00-16.99 kg/m$^2$), while no patient was classified as having severe or extreme AN. Changes remained stable at the 1-year follow-up, and no severe complications were observed in the study[90]. These findings indicate that outpatient CBT-E is a valid alternative to inpatient treatment for severe and extreme AN when the patient is medically stable.

### SE-AN

A substantial subgroup of patients with AN develop SE-AN[92]. This is currently a rather ill-defined patient population. SE-AN is characterized by: (1) A persistent state of dietary restriction, underweight and overvaluation of weight/shape with functional impairment; (2) Duration longer than 3 years; and (3) Exposure to at least two appropriately delivered evidence-based treatments[41,93]. It is difficult to define what an appropriate treatment is, and a duration of longer than 3 years is very common among patients with AN. In addition, the criteria for recovery from AN remain unclear, so this population is potentially very large. In a 22-year follow-up study of 246 patients with AN and bulimia nervosa, the patients were assessed at 9 years and at 22-25 years after inclusion. Approximately half of those with AN who had not recovered by 9 years progressed to recovery by the 22-year follow-up[94]. These findings argue against the implementation of palliative care for individuals with SE-AN. At present only one formal RCT has been published on the treatment of patients with SE-AN. In that study, 63 patients with an AN duration of at least 7 years were randomized to receive either CBT or SSCM, both adapted for the treatment of SE-AN and both in an outpatient setting. A very low attrition rate was observed, and small effects on the BMI and quality of life were detected in both treatment groups[95]. Raykos *et al*[96] compared illness severity and duration with outcome among 134 patients with SE-AN who received CBT-E in an outpatient setting and found that the illness severity and duration had no effect on outcome. In an inpatient study by Calugi and colleagues, 66 adult patients were divided into groups according to their illness duration: ≤ 7 or > 7 years. All patients received inpatient intensive CBT-E as described by Dalle Grave[97], and the two groups showed similar improvements in BMI and eating-disorder symptoms at the end of treatment and at the 12-mo follow-up[98]. Thus, there appears to be either a weak or no association between AN duration and the effect of treatment among patients with SE-AN[99]. Although the findings of several studies indicate that these patients can benefit from psychotherapy, many with SE-AN are not provided with a treatment program when they seek care[41]. Their presence in an eating-disorder unit can exert complicated effects on the milieu, with a significant proportion of SE-AN patients reporting having experienced coercive efforts to increase their body weight[41]. The poor understanding and paucity of treatments for SE-AN has been described as a crisis in the field of EDs[41].

### *Hypophosphataemia*

During the first weeks of refeeding the patient's blood levels of phosphate may drop significantly with an increased risk of cardiac arrhythmia. If not treated promptly in a patient with severe or extreme AN, critical hypophosphatemia may quickly ensue, which can lead to cardiac arrythmia, refeeding syndrome with heart failure, respiratory failure and central nervous system symptoms[50,100]. The clinical interview should include efforts to detect the risk of a sudden intake of large amounts of food, as part of binge-eating/purging AN. The BMI at the start of treatment and the food intake during the preceding 10 d indicate risk of significant hypophosphatemia during the first weeks of refeeding[101, 102]. Gradual increase of food intake during the first weeks of treatment significantly decreases the risk of significant hypophosphatemia. The AN-related inhibition of food intake will usually cause slow increase in the food intake in outpatient treatment. Mild hypophosphatemia can be treated with oral supplements, while significant hypophosphatemia is treated with intravenous phosphate. Patients with AN and a significant risk of severe hypophosphatemia should be treated as inpatient during the first weeks of refeeding.

### *Hypokalemia*

Loss of potassium is usually caused by vomiting or other purging, but significant hypokalemia may also be seen as part of a refeeding reaction caused by increased insulin release induced by food intake. The insulin induces an intracellular flux of potassium with concomitant hypokalemia. Hypokalemia is associated with risk of cardiac arrythmia. Potassium intake the last hours before blood sampling may result in falsely increased potassium readings. Moderate hypokalemia is treated with oral supplements, while severe hypokalemia is treated with intravenous infusion. Patients with recurrent hypokalemia would usually not be regarded as sufficiently stable for outpatient therapy, partly because refeeding can exacerbate the condition[103].

### *Alkalosis*

In purging, gastric acids are lost and alkalosis may be the consequence. Venous base excess can provide valuable information about alkalosis due to purging. As acid-base disturbances tend to develop before hypokalemia, venous base measurements may be more sensitive to purging than are blood levels of potassium. Alkalosis usually resolves rapidly when purging has stopped and the patient is rehydrated [103].

### *Hypoglycemia*

Significant hypoglycemia is a common problem in AN, both for the restricting and binge-eating/purging subtypes. The main symptoms are dizziness or feeling of weakness, sometimes related to physical activity or after consuming sugar-containing nutritious drinks. If sugar is absorbed quickly it may induce hyperglycemia with concomitant insulin release and hypoglycemia[104]. Severe hypoglycemia is associated with an increased risk of arrythmia. Hypoglycemia usually resolves with refeeding and is not usually a problem when normal weight is re-established. Symptomatic hypoglycemia in patients with severe or extreme AN is usually not compatible with safe outpatient psychotherapy[34,105].

### *Hyponatremia*

Isolated moderate hyponatremia is usually of little or no clinical importance, but severe hyponatremia warrants more detailed assessment and careful inpatient treatment[106].

### *Decreased glomerular filtration rate*

The glomerular filtration rate may decline over time[1,107]. Impaired renal function is frequently overlooked by physicians. Clinicians should consider collecting 24-h urine and calculate creatinine clearance to correctly assess renal function in patients with SE-AN[108].

### *Low blood counts and anemia*

Blood count often reveals leucopenia, granulocytopenia and mild thrombocytopenia. These low blood counts are usually moderate, have no clinical significance and typically resolve with refeeding. In rare cases extreme granulocytopenia or extreme thrombocytopenia indicate the need for inpatient care to manage risk of infection or bleeding[109,110]. Moderate anemia is common. It may be normocytic or macrocytic, even though vitamin B12 and folate may be normal[34]. Sometimes iron supplement is necessary, but the condition typically resolves with refeeding.

### *Vitamin deficiencies*

Several vitamin deficiencies are common in AN. Specifically, deficiencies in fat-soluble vitamins such as vitamin D are common[111]. Routine supplementation with age-appropriate oral multi-vitamin and multi-mineral supplement is recommended[62]. Usually, vitamin D and calcium would be included in these supplements.

Patients with a low intake of bread or other grain products may be at risk of developing thiamine deficiency. Severe thiamine deficiency can be fatal. Patients with suspected thiamine deficiency should be advised to take oral supplements or injections[112,113].

### Mineral deficiencies

Magnesium deficiency in AN is usually related to reduced intake, but laxatives and diuretics may also cause magnesium deficiency[102]. Deficiency may cause fatigue, muscle cramps, mental problems, cardiac arrythmia and osteoporosis[114]. Mild or suspected deficiency is treated with oral supplements [102]. Deficiency in zinc may cause depressive symptoms, reduced height growth and lack of appetite. Patients with low intakes of fish and meat should take an oral multi-mineral supplement containing zinc[115].

### Elevated liver enzymes

Elevated aminotransferases are common in patients with AN. A mild increase in aminotransferases during the initial weeks of refeeding should not cause alarm or slow down the rate of refeeding[116]. While the liver enzyme values in AN can reach severe levels, a supervised increase in food intake and return to a healthy body weight usually rapidly leads to normalization of elevated aminotransferases caused by starvation and refeeding[116].

### Electrocardiogram alterations

Sinus bradycardia, which is sometimes associated with orthostatic hypotension, is often observed in patients with severe or extreme AN[34]. An electrocardiogram (ECG) with corrected QT (QTc) interval measurement is usually performed to assess risk of arrythmia. When detected, a prolonged QTc interval is usually a consequence of QT- usage of interval-prolonging medications or electrolyte disturbances [117]. Most ECG abnormalities respond to adjustment of medication and electrolytes and most do not need further investigation[4].

Generally, if the clinical and biochemical assessment suggests a significant risk of arrythmia, inpatient assessment and medical stabilization is necessary before refeeding is commenced.

### Osteoporosis

This serious complication affects up to 50% of patients with AN and can be associated with a life-long elevated fracture risk and the debility that ensues with spinal vertebral compression fractures, among other conditions[118]. Measuring bone mineral density is indicated if the patient has had AN for more than 1 year or amenorrhea for more than 9 or 12 mo[34]. Bone densitometry should be conducted every 2 years during the active phase of AN[34]. Bone mineral density is usually expressed as the T-score, which compares the measured score with that of healthy young adults.

Patients with AN and a T-score of -1.5 to -2.5 (osteopenia) should be advised to focus on weight restoration, and adequate vitamin D and calcium intake[119]. A T-score of less than -2.5 indicates that the patient has osteoporosis. In addition to weight restoration with resumption of normal menses, supplementation with calcium, vitamin D or bisphosphonates is often considered. Only a few studies support the utility of bisphosphonates in AN, but their usage seems to reduce the risk of future spine and hip fractures[119]. However, there are significant safety concerns regarding the use of bisphosphonates, including fetal malformation in pregnant females who are exposed to them[119]. Some studies support the use of transdermal estrogen therapy in patients with AN and osteoporosis. Several RCTs have demonstrated that oral contraceptives are not effective in the treatment of osteoporosis in patients with AN[119].

### Inpatient treatment

Patients who have an ED that cannot be managed safely in the outpatient setting or do not respond sufficiently to outpatient treatment are usually advised to enter hospital as a day patient or receive residential or inpatient care. Two main groups of patients are usually transferred to inpatient care: (1) Those who need inpatient psychotherapy in order to gain weight or to stabilize purging[97]; and (2) those who are unable to benefit from inpatient psychotherapy but are in need of supportive care, usually due to medical complications or suicide risk. Some guidelines also recommend inpatient treatment in cases with a BMI of < 15 kg/m$^2$[1,120]. However, BMI alone may be of limited value as a criterion for inpatient care[83,90,91].

Various inpatient treatments for children and adolescents have been developed. In one study a family-based inpatient program was used to treat 57 patients during the period 2008-2014, and 37 patients consented to take part in a follow-up study[121]. The average length of hospital stay was 20.6 ± 13.6 wk. The average time between discharge and follow-up was 4.5 ± 1.8 years. A total of 65% of the participants had achieved a normal body weight (BMI ≥ 18.5 kg/m$^2$) and were classified as "weight recovered" at follow-up. These findings indicate that adolescents who are unable to benefit sufficiently from FBT in the outpatient setting may benefit from a family-based inpatient program.

If outpatient treatment of an adolescent or an adult has revealed stable engagement in therapy, but the patient has been unable to obtain sufficient weight gain, inpatient intensive treatment should be considered. For example, a patient who starts outpatient CBT-E for AN but is unable to achieve sufficient weight gain can enter inpatient intensive CBT-E[122,123]. These programs usually last 13 wk. During inpatient treatment, CBT-E is used to help the patient to address their psychological maintaining mechanisms while normal weight is re-established. Transfer to day-patient care or directly to outpatient CBT-E enables the patient to meet everyday challenges without returning to eating-disorder behaviors [122]. According to a recent review intensive CBT-E for the inpatient treatment of adolescents with AN was particularly effective, with approximately 80% of patients achieving normal weight by the 12 mo follow-up[88]. These studies suggest that outcome could be improved if outpatient and inpatient treatments are applying similar psychotherapeutical methods.

Indications for hospitalization for supportive care are usually risk of arrythmia, profound hypotension or dehydration, severe electrolyte abnormalities or risk of suicide. In intensely ill patients who are unable to benefit from outpatient or inpatient psychotherapy a multidisciplinary treatment team could be the best alternative. Treatment is designed by the different team members in regular meetings. The influence of specialists of pediatrics, internal medicine or intensive care medicine can be adapted to the need of the patient[50].

The available findings on inpatient treatment of AN, which mainly come from observational cohort studies, indicate that in a large percentage of patients inpatient treatment is associated with weight restoration and improvements in eating-disorder psychopathology. But unfortunately many patients experience relapse after discharge[61,124]. Studies have indicated that 30%-50% of patients need to be rehospitalized in the first years following discharge[125].

### *Relapse prevention*

Relapse prevention forms part of most psychotherapies, both inpatient and outpatient treatments. But relapse after the end of treatment remains a significant challenge. The usual strategy adopted for addressing relapse after inpatient treatment has been to provide some type of post-hospitalization treatment. Preliminary evidence, which remains to be validated, suggests that CBT is beneficial for patients with AN[61,126] as relapse prevention. One large trial tested Internet-based CBT added to TAU *vs* TAU alone in the post-hospitalization treatment phase in 258 females[127]. CBT completers had greater improvements in BMI compared with those who received TAU only. These findings indicate that the relapse-prevention effect of CBT can be delivered *via* the Internet.

## MEDICAL MANAGEMENT

The medical complications of AN affect all organs and systems, and are generally due to weight loss, malnutrition and purging behaviors[106,128].

### *Purging*

Most patients with AN have the restricting subtype, but a significant proportion has binge-eating/purging AN with self-induced vomiting or the misuse of laxatives, diuretics or enemas (see Table 1). A study of laxative use among adolescents with AN found a prevalence of 12%[129]**.** Taking high doses of laxatives is associated with electrolyte disturbances, dehydration and secondary hyperaldosteronism, which can be most challenging during therapy due to the accumulation of water with significant weight gain and oedema[103]. This is usually addressed during psychotherapy[87]. In order to avoid sudden fluid retention with unacceptable weight gain, laxatives should be gradually decreased over a period of 1-2 wk. During the last week, the patient should start taking stool softeners such as lactulose to reduce the tendency for constipation[103]. If the patient is taking extreme doses of laxatives and has very high blood levels of aldosterone, inpatient treatment during the laxative discontinuation may be indicated. However, laxative discontinuation is usually achieved in the outpatient setting[87]. Vomiting is addressed as part of outpatient psychotherapy[87]. Due to loss of acid and potassium, acid-base disturbances and hypokalemia may occur. Hypokalemia is associated with significant risk of cardiac arrhythmia. Severe hypokalemia is an emergency and is treated with inpatient intravenous infusion of potassium[60].

### *Excessive exercise*

Varying degrees of excessive exercise are common in AN. A French study[130] found that more than half (54%) of eating-disorder patients exercised for at least 6 h/wk. However, only a small minority of patients (5%) reported vigorous, compulsive exercise for at least 6 h/wk[18,130]. Excessive exercise is associated with increased risk of fractures[131]. Excessive exercise is sometimes used to compensate for specific episodes of perceived or actual overeating and can be regarded as being related to purging. However, a significant number of patients report that exercise is mainly used to regulate mood[132]. As it is a maintaining factor of the ED, excessive exercise is addressed in the psychotherapy[87].

### *Outpatient medical management*

Most of the medical complications associated with AN can be resolved to a normal status with weight restoration and nutritional rehabilitation. However, some complications can be fatal if not diagnosed and treated adequately and some other complications may persist and cause reduced quality of life (growth retardation, osteoporosis and renal insufficiency). The medical evaluation is aiming at detecting comorbidity and complications. As part of the comorbidity assessment and differential diagnostic considerations tests to detect coeliac disease (*e.g.*, transglutaminase antibodies), thyroid disease (blood levels of thyroxin and thyroid stimulating hormone) and prolactinoma (blood prolactin) are usually performed.

Many patients with AN experience pain in different parts of the body. Pain in the back can be related to minor fractures in the spinal column, which are usually compression fractures. Fractures induced by minimal trauma can significantly impair the quality of life. Attacks of chest pain could indicate pneumothorax or rib fractures, which sometimes occur with minimal trauma.

Gastrointestinal (GI) complaints are especially frequent in AN, with more than 90% of patients reporting GI complaints including postprandial fullness, early satiety, abdominal distention, pain, nausea and obstipation[50,133-135]. These symptoms sometimes increase after food intake and may inhibit attempts to eat sufficiently. Potential reasons for these problems other than AN should be assessed before initiating therapy. If no specific gastrointestinal disorder is diagnosed the symptoms may be regarded as secondary to the ED. Management of the symptoms should be discussed with the patient as part of the psychotherapy[134,136].

There is an increased risk of sudden cardiac death related to malnutrition in AN[50]. Assessment of the risk of sudden cardiac death is essential when determining which patients should receive inpatient medical stabilization prior to commencement of outpatient treatment. This evaluation requires detailed medical, psychiatric, and nutritional assessments, a physical examination, and laboratory testing as described in the treatment section.

A comprehensive account of medical management is outside the scope of this review but is available in the Management of Really Sick Patients with Anorexia Nervosa (MARSIPAN)[60] and Junior MARSIPAN guideline[137]. The scientific background for basic risk assessment and medical management of the most important medical complications relevant for outpatient treatment are discussed in the clinical interview and the physical assessment section and in the treatment section.

## ETHICAL ISSUES

A small proportion of patients do not appreciate the severity of their illness, even when they are in a life-threatening situation, which may interfere with their ability to make decisions about life-saving treatment[4]. In countries where compulsory care is possible, an important ethical dilemma may emerge: how many times should compulsory care be provided, and for how long should it be continued?

Those who have been in compulsory care several times sometimes need multidisciplinary treatment to survive their exacerbations. The costs for the patients, their families and the healthcare providers are significant, and sometimes patients or their healthcare providers want to discuss the possibility of ending multidisciplinary healthcare. This would raise several ethical questions. What is the prognosis if multidisciplinary treatment is continued and what quality of life can be expected? This ethical problem is growing with our increasing knowledge around how to assess medical risks and manage life-threatening complications. Patients with life-threatening AN can survive for several decades if they are brought to healthcare centers before they are at a terminal stage with irreversible life-threatening complications. The 22-year follow-up study of Eddy and colleagues found that a significant subpopulation of the patients who had not recovered by 9 years had recovered by 22 years[94]. There are insufficient data to enable a conclusion to be drawn on the probability of recovery after 20 years of SE-AN. In addition, patients with SE-AN can improve their quality of life by weight gain[138,139].

The stakeholders involved when a process towards ending treatment commences need to be determined. Yager[140] suggested that different stakeholders should be involved, including the patients and their families, healthcare providers (the entire treatment team as well as the institutional administrators and their boards), payers and policymakers. There is also a need to determine who is going to make a decision and at what level such decisions should be made[140,141]. Our poor understanding of SE-AN and the paucity of available treatments AN makes this ethical issue even more complicated[41].

## EMERGING THERAPIES AND OUTSTANDING RESEARCH ISSUES

### *AN as a metabo-psychiatric disorder*

The Psychiatric Genomic Consortium was established in 2007 to conduct meta- and mega-analyses of genome-wide genomic data related to psychiatric disorders. The Eating Disorders Workgroup has been

a part of this consortium since 2013. Members of this workgroup have performed genome-wide association studies, which have revealed strong associations between AN and insulin sensitivity, low BMI-adjusted fasting serum insulin and several other metabolic markers[30]. The increase in insulin sensitivity was greater than what could be explained by low BMI. The authors of that report suggested that it is time for a reconceptualization of AN and that it should be regarded as a metabo-psychiatric disorder[30,142].

Several other studies support the reconceptualization of AN towards regarding it as a metabo-psychiatric disorder. Our brain and gut are linked through humoral and bidirectional neural connections that allow fast and complex interactions *via* the brain-gut axis[143]. Several studies indicate that decreased food intake may alter the normal interactions in the brain-gut axis, thereby enhancing the maintenance of AN[142]. GI hormones and gut microbiota may be essential participants in the regulation of the brain gut axis. Several GI hormones are released by food intake and may participate in the development of the maintaining mechanisms in AN[144]. Some of them have been shown to induce anxiety and panic attacks in animals and humans when administered in supraphysiological doses, and in susceptible patients[145-147]. Ghrelin is a peptide hormone synthesized in the enteroendocrine cells of the stomach. It is released by calorie restriction and stress to stimulate appetite and increase food intake. Food intake increases ghrelin levels in healthy individuals, whereas in AN patients it is followed by decreased levels of ghrelin. Clinical trials of the novel ghrelin receptor agonist RM-131 in the treatment of AN are currently being performed[148].

### *Microbiota in AN*

The gut microbiota influences the extraction of energy from food and body weight gain, as well as appetite, gut permeability, inflammation and complex psychological behaviors such as depression or anxiety, all of which may play roles in the development and maintenance of AN. Nutrition is one of the main factors that influence the gut microbiota. Starvation has a substantial impact on the gut microbiota [149], inducing cell death in several fast-growing bacteria, while allowing the proliferation of slowly growing bacteria and bacteria that are able to feed on indigestible fiber or the mucin layer along the gut wall. Thus, food restriction might exert its maintaining effects on AN by affecting the gut microbiota [150,151].

The malnutrition-related alterations in the gut content also induce several metabolic effects, partly mediated by short-chain fatty acids (SCFAs) produced by the gut bacteria[152]. The pathways of SCFA production are relatively well understood, with major products being acetate, propionate and butyrate [153]. Acetate production pathways are widely distributed among bacterial groups, whereas pathways for the production of propionate and butyrate appear more highly conserved and substrate-specific. It has been proposed that an elevated colonic production of SCFA could stimulate numerous hormonal and neural signals at different tissue sites that would cumulatively suppress the energy intake[154]. There is emerging evidence that the anorexigenic hormone peptide YY (PYY) plays a role in the pathogenesis of AN[155]. PYY is produced mainly in the colon, where SCFAs are produced at high levels through the fermentation of fiber by the gut microbiota[156]. SCFAs strongly stimulate the production of PYY in human enteroendocrine L-cells in the gut wall[152].

Microbiota-modulating strategies may be promising determinants of the healing process and the outcome of AN[149]. Nutritional interventions, including supplements that have the potential to influence the gut microbiota, are important research targets when developing future AN therapies, especially for patients who are unable to normalize their gut microbiota by a sufficient food intake during psychotherapy. Fecal microbiota transplantation (FMT) has been associated with significant improvement in diseases such as irritable bowel syndrome[157,158]. FMT involves transplanting the entire fecal microenvironment, including SCFAs and other substances with potential effects on food intake and brain-gut interactions[159]. The first case reports on FMT in patients with SE-AN found weight gain in one patient, but no effect on BMI in another[160,161]. Data from the ongoing pilot study "Fecal Microbiota Transplantation (FMT) in the treatment of SE-AN"[162] may provide valuable information on feasibility of FMT in patients with SE-AN. Future studies should clarify whether interventions aimed at establishing normal brain-gut interactions can reduce dropout and relapse rates among patients with AN. Tools to assess and describe the responses mediated through the brain-gut axis, including clinical, biochemical and radiological methods like functional magnetic resonance imaging[163], should be further developed. Such approaches would allow interactions between the brain and gut in AN and the possibility of treatment with brain-gut modulation to be assessed.

### *Other emerging therapies*

Other emerging therapies focus on direct effects on the brain in regulating food intake and the cognitive alterations related to AN. Transcranial direct-current stimulation is a method for directly modulating the excitability of cortical regions using small electrical currents. A pilot study that applied this method to the left dorsolateral prefrontal cortex in seven patients with AN found that the procedure was well tolerated, and was associated with modest short-term improvements in scores on eating scales in five of the patients[148]. Another non-invasive technique, repetitive transcranial magnetic stimulation, was investigated in ten patients with AN, which revealed that a single session of repetitive transcranial magnetic stimulation was well tolerated and improved feelings of fullness and anxiety[148].

Deep brain stimulation is another neuromodulatory technique that is currently under investigation for the treatment of AN[148]. It is a surgical procedure that involves the implantation of stimulating electrodes into key brain structures that are believed to drive the pathological activity associated with AN[148]. One study applied continuous stimulation of the subcallosal cingulate for 1 year to 16 patients with SE-AN, which increased BMI from 13.8 to 17.3 kg/m$^2$[164]. However, these findings in studies of neuromodulatory techniques might be driven by a placebo effect as well as an increased motivation of patients to engage in TAU[4,165,166].

Learning models suggest that exposure-like therapy could be effective in AN. Exposure interventions to AN-related stimuli (*e.g.*, food, body) have been tested in small trials of patients with AN[4,167,168]. Virtual-reality environments have also been used to manage food-related or body-related fears in small trials including patients with AN[4,169].

Current research activity in the field of EDs is inadequate given the cost of the problem, since 8- to 10-times more research funding is provided for depression and psychosis[4]. Several projects have aimed at producing research priorities for AN. The Canadian Eating Disorder Priority Partnership was established to identify and prioritize the ten top research priorities for females aged at least 15 years with AN, by incorporating equal input from those with lived experience, families, and healthcare professionals. Their conclusions were published 2020[170]. The top priorities identified were related to "treatment gaps" and the need for "more surveillance data". Furthermore, a panel consisting of Australian members of the Australian and New Zealand Academy for Eating Disorders and the National Collaboration for Eating Disorders in Australia[171] were invited to take part in a survey on how important it was that each of 29 research areas received funding. The 291 responders were eating-disorder specialists, consumers/carers or affiliates (clinicians and researchers not specializing in EDs, along with participants from the industry). The top-three-ranked priorities for research funding were "accessible evidence-based treatments", "origins of EDs" and "early detection and intervention". Within these domains, the following research areas all received very high ratings: "early intervention at all critical risk periods", "what to do when first line treatments don't work", "enhancing existing eating-disorder treatments", "accessible services" and "early detection"[171].

These surveys support research on "early detection and intervention", including those that aim to decrease the time from the onset of AN to the initiation of evidence-based treatment.

Studies on the transition to adult psychiatric services ("treatment gaps") will be valuable, including those designed to determine how to ensure that the patient accepts transfer to another therapist, who will sometimes apply a different treatment approach. Comparisons of different models of organization including studies on the co-localization of adolescent and adult treatment services could be part of this research. Long term effects of outpatient *vs* inpatient therapy should be assessed. If a substantially larger proportion of the patients may be treated as outpatients, the problems related to coordinating outpatient and inpatient therapy can be reduced.

Studies on the effects of implementing treatment standards and therapist training suitable for therapists in decentralized treatment units may inform decisions around how to make services for early intervention more accessible.

National quality-assurance registries for EDs are being established in several countries[172], which can provide surveillance data and detect possible regional inequalities in healthcare. Studies on early intervention with optimally implemented, effective evidence-based methods would be of great value. How non-completion rates can be decreased is another essential research question to address ("enhancing existing eating-disorder treatments"). Establishing standards for practice and training appears to be of value for standardizing care and enhancing existing eating-disorder treatments[173].

In line with the aim of "enhancing existing ED treatments", several adaptations to FBT have been published in order to enhance effectiveness[174]. Still, outstanding dilemmas need research attention. Especially, FBT places a heavy task on parents, and it may be impossible for some families to mobilize for a variety of reasons, *e.g.*, other mental illnesses. Mental health services need guidance on how to support these families so the young person can stay home and yet receive the necessary day-by-day support. This is especially crucial in cases where the young person does not have the motivation and/or ability to initiate behavioral change that is needed to succeed in CBT-ED.

In light of the moderate success rates across all psychotherapeutic treatment for AN, two types of research might improve outcomes. First, information is needed on what works for whom, in order to choose more personalized modes of treatment. Second, research on how to maximize the effect of non-specific factors in therapy, *e.g.*, therapeutic alliance, may provide avenues for better outcomes in the future. One example of a service development that aims to adapt specific aspects of treatment to individual needs is the "PEACE pathway" which targets individuals with AN and autism spectrum disorders[175].

Turning to the medical management of AN, the mechanisms underlying sudden death in these patients warrant further research, since data are lacking regarding the cardiac rhythm at the end of life. The most significant other knowledge gaps include the management of bone mineral density, and the GI problems in AN, as well as electrolyte regulation, mechanisms of kidney damage and refeeding syndrome[176].

Despite the significant progress that has been made in the understanding of the medical complications of AN, considerable work remains to be done. There are both research and treatment gaps, and bridging them will ultimately improve the medical treatment outcomes of patients suffering from AN [176].

Defining the diagnostic criteria is probably the most important first step in SE-AN research. In addition, the criteria for recovery from AN will help delineate the population and help to define the aims of healthcare for SE-AN. Progress in understanding how to manage the medical complications of this illness has provided the potential to significantly increase the quality of life and life expectancy in this patient population. Some of the emerging strategies might improve the results of psychotherapy, including treatment aiming at reducing attrition, relapse and thereby decreasing recruitment to the SE-AN population. Early intervention with evidence-based therapy including engagement of the large population of patients with SE-AN who is not seeking healthcare will perhaps be the most important prophylactic intervention to reduce the number of patients with SE-AN.

## CONCLUSION

Outcome of AN is unacceptably poor. However, the last decades have brought several effective psychotherapies for children, adolescents and adults. For many reasons, outpatient treatment is preferable. Inpatient treatment is needed in cases of acute medical risk, severe suicidal risk and when weight gain is not obtained in outpatient treatment in spite of engagement in therapy. Due to progress in understanding of the medical complications of AN more patients can safely be treated as outpatients. The implementation of effective psychotherapies and safe outpatient medical management are valuable tools for improvement of healthcare in AN.

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MINIREVIEWS

# Effects of antiseizure medications on alternative psychosis and strategies for their application

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## Abstract

Forced normalization (FN) is a unique phenomenon that is often seen in the treatment of epilepsy. FN is characterized by abnormal mental behavior and disordered emotions in epilepsy patients despite a significantly improved electroencephalogram and successful seizure control; the occurrence of FN seriously affects patients' quality of life. The causes of FN include antiseizure medications (ASMs), epilepsy surgery and vagus nerve stimulation, with ASMs being the most common cause. However, with the timely reduction or discontinuation of ASMs and the use of antipsychotic drugs, the overall prognosis is good. Here, we perform an extensive review of the literature pertaining to FN, including its epidemiology, possible mechanisms, clinical features, treatment and prognosis.

**Key Words:** Forced normalization; Antiseizure medications; Neurotransmitter; Antipsychotic drugs; Electroshock

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**Core Tip:** Forced normalization (FN) is often seen in the treatment of epilepsy. FN is characterized by abnormal behavior and disordered emotions in epilepsy patients despite a significantly improved electroencephalogram and successful seizure control; the occurrence of FN seriously affects patients' quality of life. However, with timely recognition and treatment, the overall prognosis is good.

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## INTRODUCTION

Alternative psychosis is also known as forced normalization (FN). This phenomenon is characterized by abnormal mental behavior and disordered emotions after the seizures of active epilepsy patients are controlled and their electroencephalograms (EEGs) have significantly improved. FN is unique to the pharmacotherapy of epilepsy and often leads to the failure of epilepsy treatment. Although FN is still an entity with uncertain pathophysiology, it has received extensive clinical attention in recent years, and significant progress has been made regarding its pathogenesis and treatment strategies[1-5]. Recently, Calle-López *et al*[5] conducted a study on 193 FN episodes and found that the causes included antiseizure medications (ASMs), epilepsy surgery and vagus nerve stimulation (VNS), with ASMs being the most common cause. This article aims to describe the clinical features and possible mechanisms of FN induced by ASMs and to explore strategies for its treatment.

## HISTORICAL EVOLUTION OF FN

FN was first described by Landolt[6] in the 1950s. They noticed that after active epilepsy was well controlled and the EEG signals returned more or less to normal, the patients developed episodic behavioral abnormalities and mood disorders. They could not reasonably explain this clinical phenomenon and thought it might be a unique phenomenon in epilepsy patients. In 1965, De Jorio *et al*[7] summarized the clinical manifestations of this "Landolt FN". At the same time, Tellenbach[8] published a study on the electrophysiological characteristics of Landolt FN and began to explore its possible mechanism; since then, this unique phenomenon in the treatment of epilepsy has received more extensive attention.

The first discovery regarding the cause of FN was the influence of a type of herbal ingredient. Later, with the widespread use of ethosuximide (ESM) in clinical practice, it was found that the number of patients with FN gradually increased[9]. In 2005, Clemens[10] reported that FN could be caused by lamotrigine (LTG). There were also reports of FN caused by valproic acid (VPA), phenytoin (PHT), and zonisamide (ZNS)[4,5,9]. In recent years, studies on the relationships between FN and ASMs have focused more on levetiracetam (LEV)[11,12]. In 2018, Esang *et al*[12] systematically discussed the clinical features and treatment strategies for FN and explored its relationship with ASMs, which made the clinical diagnosis and treatment of FN more rational.

## EPIDEMIOLOGICAL CHARACTERISTICS OF FN

Carazo Barrios *et al*[3] found that 10 patients met the criteria for FN in a cohort analysis of 4468 patients with epilepsy; Wolf *et al*[13] reported that the prevalence of FN in epilepsy patients was 7.8%. Calle-López *et al*[5] used the MEDLINE, Embase, Cochrane and Scielo databases to collect clinical data, electrophysiological characteristics and imaging data of patients with FN for a systematic analysis. They found that 48.5% of cases of FN were caused by ASMs, 31.8% by epileptic surgery, and 13.6% by VNS.

## PATHOGENESIS OF FN

The pathogenesis of FN is unclear and lacks a solid experimental basis. It is difficult to establish a suitable animal model. Therefore, the current understanding and various hypotheses regarding the mechanism of FN are mainly based on the observation of responses to three clinical treatments: Epilepsy surgery, VNS and ASMs[3,9,14-17].

Human behavioral changes associated with FN are related to the midbrain limbic system, which has a wide range of connections with the cortex. After surgical removal of brain tissue from patients with epilepsy, the epileptic seizures stopped, but FN occurred, which indicated that the mental behavior abnormalities associated with FN have an anatomical basis[9]. On this basis, Wolf[18] proposed that the formation of FN may be the result of epileptic discharges that are not fully suppressed and spread along specific channels under the cortex after epileptic seizures are controlled, but the specific location is not clear.

Although the surgical methods and excision sites of patients undergoing epilepsy surgery are different, they can all develop FN, indicating that its anatomical basis is likely very extensive, and electrical ignition can activate these neuronal activities. The most obvious feature of FN is that when epileptic seizures are effectively controlled, abnormal mental behavior and emotional disorders appear. Electroshock can not only relieve the mental symptoms of patients with FN but also cause the occurrence of epilepsy, so it has effects on these mutually antagonistic outcomes, which indicates that it may participate in the formation of FN. After VNS, FN will occur with the reduction or cessation of seizures, which supports the hypothesis that electric ignition participates in the formation of FN and

plays an important role in FN[3,9,19].

FN caused by ASMs is related to "pharmacological kindling". It has long been known that certain drugs that selectively activate the limbic system can cause behavioral abnormalities, which are similar to the electrical activation of the limbic system; accordingly, this drug-induced activation is called pharmacological kindling. Many drugs can cause epilepsy, which supports the existence of pharmacological kindling. Existing studies have found that electrical kindling can effectively induce seizures, but pharmacological kindling can result in behavioral changes[9].

Pharmacological kindling is related to neurotransmitters. Brigo *et al*[20] reported on two patients with tuberous sclerosis with FN who had used VPA, LTG, rufinamide, carbamazepine (CBZ), topiramate (TPM), ZNS, and LEV. It has been found that all the drugs that can cause FN can affect the transmitter glutamate. Subsequent research found that drugs that can induce FN, such as TPM, ZNS, and LEV, can affect α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-mediated excitatory synaptic transmission, and drugs that enhance AMPA-mediated glutamatergic transmission can treat psychosis, which indicates that impaired glutamatergic neurotransmission may be related to FN. Additionally, researchers have found that repeated administration of small doses of dopamine agonists and stimulants will produce increased behavioral responses, while dopamine antagonists can cause seizures while producing antipsychotic effects. The mechanism of electroshock treatment of psychosis is also related to upregulating dopamine and its metabolites, which suggests that dopamine may play an important role in mediating FN, and the hypothesis of "dopamine igniting" has been proposed[9].

## CLINICAL FEATURES OF FN

The main clinical manifestations of FN are that patients with active epilepsy have abnormal mental behavior and mood disorders after the seizures are controlled, and most patients have improved or normal EEG synchronization[2-4]. Recently, Calle-López *et al*[5] analyzed 193 FN episodes reported in the literature and found that 69.4% of patients presented with mental disorders; 27.9%, mood disorders; and 10%, dissociation. The clinical features of FN are summarized in Table 1.

### *FN induced by different ASMs*

**LEV:** LEV is the ASM that most often causes FN, but whether FN occurs during LEV use is related to many factors.

Age of onset: FN induced by LEV, as currently reported in the literature, mostly occurred in patients between 9-56 years old. Kawakami *et al*[21] reported that a 9-year-old girl with idiopathic epilepsy had seizures and EEG results that gradually worsened after taking VPA and benzodiazepines and then was switched to LEV. The epileptic seizures stopped, and the epileptiform discharges on EEG disappeared, but the patient showed anger and violent behavior. The authors suggested that this was FN induced by LEV. Kikuchi *et al*[22] reported a 10-year-old girl with unclassified epileptic encephalopathy, and FN occurred after taking LEV. Topkan *et al*[11] reported that the age of the patient with FN after taking LEV was 56 years old.

Gender: FN often occurs in women. The Calle-López *et al*[5] review on FN found that 60% were women. Of the 10 patients reported by Carazo Barrios *et al*[3], 6 were women. At present, it has been reported in the literature that FN induced by LEV has occurred in females, with the exception of one male[3,11,19-22].

Time of onset: The onset time of FN is not certain. Topkan *et al*[11] reported that a 56-year-old woman was treated with LEV for epileptic seizures. Forty-five days after the seizures ceased, the patient had a personality change accompanied by visual hallucinations. The 24-h EEG examination was also normal. This author believes that this was FN induced by LEV. Kikuchi *et al*[22] reported a patient with epileptic encephalopathy. One day after taking LEV, his tonic and myoclonic seizures as well as the paroxysmal discharge on the EEG disappeared, but there was a slow response and dyskinesia. After the recurrence of myoclonic epilepsy, his psychiatric symptoms also disappeared. This author believes that this was FN caused by the administration of LEV. Green *et al*[19] reported a 14-year-old boy who had a history of mental illness. One month after treatment with olanzapine, he developed tonic-clonic epileptic seizures. LEV was used to prevent the seizures. After 6 mo, he developed FN manifesting as self-harming cutting behavior and auditory and visual hallucinations.

Main clinical manifestations: FN induced by LEV mainly manifests as abnormal mental behavior and dissociative personality. Topkan *et al*[11] reported that a 56-year-old patient had obvious personality changes after the seizures stopped that were accompanied by visual hallucinations and déjà vu, and the mental symptoms disappeared after treatment with quetiapine. Kawakami *et al*[21] reported that after the use of LEV in a patient with epilepsy, the epileptic seizures stopped, but FN occurred. The patient showed episodic anger and violent behavior. The simultaneous EEG examination revealed that the epileptiform discharge had disappeared. Green *et al*[19] reported a 27-year-old female patient with spastic cerebral palsy and febrile convulsions. At the age of 22, she was diagnosed with epilepsy, and treatment with LEV was initiated. Subsequently, FN occurred with many behavioral abnormalities, such as decreased alertness and concentration, confusion, delusions, and auditory and visual hallucinations.

**Table 1 Clinical features and treatment of forced normalization**

| Classification | | | Ref. |
|---|---|---|---|
| Clinical features | LEV | Abnormal mental behavior and dissociative personality | [11,19,21] |
| | ESM | Mania; visual and olfactory hallucinations; paranoid psychosis | [9,24,25] |
| | VPA | Paranoid thoughts, agitation, sleep disturbances, confusion | [26,27] |
| | LTG | Irritable, inattention, insomnia, paranoid thoughts, and hallucinations appearing | [3,10] |
| | LCM | Paranoid behavior and psychotic symptoms | [3,28,29] |
| | TPM | Abnormal mental behavior | [20] |
| | ZNS | Communication disorders, interpersonal tension and stereotyped behaviors | [20,30] |
| | VGB | Hallucinations and anxiety | [1,31] |
| | PHT | Paranoia, restlessness, aggressiveness, command hallucinations, and stereotyped, short-term psychomotor excitement and impulsive violent events, irritability | [3,12,32] |
| | ESL | Behavioral disturbances, psychosis | [3] |
| | BRV | Dysthymia, generalized anxiety disorder | [3] |
| Treatment | Dose reduction or drug withdrawal | | [3-5,10,11,15,21] |
| | Control of mental symptoms (haloperidol, risperidone) | | [2,3,5,25,26,33] |
| | Electroshock | | [19] |

LEV: Levetiracetam; ESM: Ethosuximide; VPA: Valproate; LTG: Lamotrigine; LCM: Lacosamide; TPM: Topiramate; ZNS: Zonisamide; VGB: Vigabatrin; PHT: Phenytoin; ESL: Eslicarbazepine; BRV: Brivaracetam.

The symptoms continued to worsen until the seizures reappeared; the psychiatric symptoms then began to improve, and the aggressive behavior decreased.

Possible mechanism of the FN induced by LEV: Helmstaedter *et al*[23] conducted genetic polymorphism analysis on 290 patients with mental symptoms taking LEV and found that patients who had dopaminergic genetic variants were prone to irritation and aggressive behavior after taking LEV, suggesting that it may be related to FN. This author believes that the use of pharmacogenomics methods to examine the side effects related to mental behavior may provide a useful tool for the prediction of poor mental outcomes related to ASMs.

**ESM:** ESM is the main ASM for the treatment of epileptic absence seizures and certain epileptic syndromes. It was also the first drug found to cause FN[9]. Recently, Yamamoto *et al*[24] reported an 11-year-old boy with intractable myoclonic epilepsy and severe psychomotor development delay treated with ESM. After his myoclonic seizures were fully controlled, he had episodic behavior changes (mainly mania), and the EEG examination at this time was almost completely normal. This author believes that this was FN caused by ESM. Apap Mangion *et al*[25] reported a man with drug-resistant epilepsy featuring both focal and generalized seizures. After ESM treatment was started, the seizures stopped, and the EEG was normal; however, 3 wk into the use of this medication, FN occurred and manifested as visual and olfactory hallucinations that rapidly deteriorated into paranoid psychosis. After ESM treatment was stopped and olanzapine was added for one month, his psychiatric symptoms disappeared; he then restarted taking a small dose of ESM without the recurrence of psychiatric symptoms.

**VPA:** VPA is another of the main drugs causing FN. Banwari *et al*[26] reported a case of an epilepsy patient who had a disease course of 13 years and had not been treated with ASMs. One week after the start of treatment with VPA, the patient's seizures stopped, but FN occurred. With low-dose risperidone treatment, the patient's mental symptoms disappeared. Turan *et al*[27] reported that a patient with epilepsy developed mental symptoms under combined treatment with VPA and LTG. This author believes that there are related underlying mechanisms among ASMs, seizure control and psychosis development.

**LTG:** Two of the 10 patients reported by Carazo Barrios *et al*[3] were patients with FN induced by LTG. Both of them were male; one of them was 41 years old at the time of FN, and another was 40 years old. The former had focal epilepsy, and the latter had generalized seizures. Clemens *et al*[10] also reported 2 patients with FN induced by LTG. One patient was a 10-year-old girl with normal development and no history of neuropsychiatric disease. At the age of 7 years, paroxysmal and transient clonic movements of

the right arm and hand occurred. She was diagnosed with epilepsy when she was 8 years old, and treatment with CBZ was ineffective. After switching to LTG, the epileptic seizures stopped, the epileptiform discharge of the interictal EEG disappeared, but mental and behavioral disorders appeared. After reducing the daily dose of LTG, the mental symptoms gradually disappeared. Another patient was a 43-year-old woman with temporal epilepsy, complicated partial seizures appeared from the age of 6 years, and treatment with CBZ was ineffective; CBZ was replaced with LTG, and the dose was gradually increased to 100 mg bid. After a few days, the seizures disappeared, but the patient became increasingly irritable with inattention and insomnia and finally paranoid thoughts and hallucinations appearing. At the same time, EEG showed that all paroxysmal activities had completely disappeared, and the diagnosis was FN. The dose of LTG was gradually reduced to 50 mg bid, and the mental symptoms disappeared after haloperidol treatment.

**Lacosamide:** Lacosamide (LCM) is a new ASM in clinical use in recent years. It is mainly used for the adjuvant treatment of partial seizures. It has a good safety profile with the most common side effects, including dizziness, headache, diplopia, nausea, nasopharyngitis and vomiting. In 2013, Chatzistefanidis *et al*[28] reported that young female patients with drug-resistant partial epilepsy developed FN after treatment with LCM. In 2015, Pinkhasov *et al*[29] reported that after using LCM, a young woman experienced psychiatric symptoms. This author believes that this is the first case report of FN induced by LCM in the United States. Carazo Barrios *et al*[3] reported three patients with FN related to LCM administration. Among them, one patient was a 44-year-old woman with focal seizures caused by cortical dysplasia, and FN occurred after taking LCM. Another patient was a 42-year-old woman with unknown disease etiology and developmental delay, presenting focal or focal secondary generalized seizures. The seizures disappeared after taking LCM, but behavioral abnormalities appeared. The other patient was a 66-year-old man with focal epilepsy caused by meningoencephalitis, and FN occurred after the use of LCM. This author believes that this was FN induced by LCM.

**TPM:** TPM is another ASM that can cause FN. Brigo *et al*[20] reported a 33-year-old female patient with tuberous sclerosis. The initial treatment with VPA, LTG, and rufinamide was ineffective. After switching to TPM, the patient's seizures stopped, and the epileptiform discharges on the 60-min EEG were reduced by more than 50%, but severe abnormal mental behavior appeared. These mental abnormalities disappeared after stopping the drug, and the patient developed mental abnormalities again after adding TPM. This author believes that this was FN caused by TPM.

**ZNS:** Hirose *et al*[30] reported a 5-year-old child with refractory epilepsy. After receiving ZNS treatment, the seizures stopped, but FN appeared, manifesting as communication disorders, interpersonal tension and stereotyped behaviors. This situation persisted after ZNS was stopped, and seizures then reappeared. This author believes that although most of the patients with FN are adults and adolescents, ZNS can induce mental disorders even in young children. Brigo *et al*[20] reported a 33-year-old female patient with vascular encephalopathy following cerebral bleeding due to moyamoya disease who had seizures, and VPA treatment was ineffective. After switching to ZNS, the epileptic seizures stopped, but the patient showed obvious mental and behavioral abnormalities. This author believes that this is consistent with a diagnosis of FN and that these contradictory outcomes with treatment are extremely challenging.

**Vigabatrin:** Vigabatrin (VGB) has also been reported to cause FN. Weber *et al*[31] reported that a young patient had symptomatic and refractory focal seizures due to middle cerebral artery obstruction. After five weeks of treatment with VGB, the seizures stopped, but obvious abnormal mental behavior appeared after two weeks. This author believes that this was FN caused by VGB. To date, there have been more than 13 patients with FN caused by VGB[1].

**PHT:** Hirashima *et al*[32] reported an 11-year-old girl with FN of occipital epilepsy. This patient had no family history of epilepsy or mental disorders and developed normally. At the age of 11, she developed a fever-free generalized tonic-clonic seizure and was diagnosed with epilepsy. After PHT (37.5 mg bid) was administered, the seizures were controlled. Three days later, she developed mental symptoms, paranoia, restlessness, aggressiveness, command hallucinations (command voices from strangers) and stereotyped, short-term psychomotor excitement and impulsive violent events; recurring, neurological examinations were normal, clinical chemistry and clinical hematology test values were within the normal range, and brain magnetic resonance imaging scanning and analysis also found no abnormalities. After stopping PHT, her mental condition did not improve. Based on the patient's clinical course, this author believes that she developed FN by taking PHT. Esang *et al*[12] reported a 26-year-old female patient with no history of mental illness. Her family members described that she had been diagnosed with epilepsy in 2016 and received LEV treatment, which was initially effective; however, she had frequent seizures 1 year later, and then PHT (0.1 g tid) was added. The epileptic seizures stopped, the EEG and the head CT scan were normal, but FN occurred. There were severe mental abnormalities, severe agitation, irritability, and "all day anger", and the patient was finally hospitalized for impulsive behavior. Carazo Barrios *et al*[3] also reported one patient with FN caused by PHT among 10 FN patients.

**Others:** Among the 10 patients reported by Carazo Barrios *et al*[3], FN was also caused by eslicarbazepine and brivaracetam.

## TREATMENT

De Toffol *et al*[4] advocated that the treatment of FN should be divided into two steps. First, it should be assessed whether the current ASM treatment is reasonable. Second, the appropriate antipsychotic should be selected. The reduction or withdrawal of suspicious ASMs and the addition of antipsychotic drugs are the main management methods of FN. The treatment of FN is summarized in Table 1.

### *Dose reduction or drug withdrawal*

In most cases, the reduction in the dose of the drug inducing FN or the withdrawal of the suspicious drug can effectively alleviate the clinical manifestations of FN. Among the 10 FN patients reported by Carazo Barrios *et al*[3], one patient stopped suspicious ASMs and started using antidepressants, and another patient reduced the dose of suspected ASMs, which relieved the symptoms. Topkan *et al*[11] reported that patients who took LEV had FN, and the symptoms disappeared after switching to PHT. Of the 193 FN episodes studied by Calle-López *et al*[5], 47% of the patients ceased using the suspected ASMs, 25% received a dose reduction, and 28% maintained use of the original drug. In 87% of patients who withdrew their medication, FN was completely in remission, compared with 75% of those who did not discontinue. However, the treatment recommendations across different drugs are not exactly the same. It is necessary for patients receiving LEV to stop the drug when FN occurs. The symptoms of FN caused by LTG will improve by dose reduction[3,10,15,21].

### *Control of mental symptoms*

The mental symptoms of patients with FN are often severe, which affects the quality of life of these patients. In severe cases, it may cause self-injury or other forms of injury, which requires antipsychotic treatment. Carazo Barrios *et al*[3] reported that 5 of 10 FN patients received antipsychotics or increased their antipsychotic doses, and 5 patients started taking antidepressants or increased their antidepressant drug doses. The symptoms of FN were subsequently relieved. In an analysis of 193 FN episodes, Calle-López *et al*[5] found that 73% of patients received antipsychotic treatment; haloperidol (35.4%) was used the most often, followed by risperidone (18.7%). These studies are supported by studies by Banwari *et al*[26] and Apap Mangion *et al*[25]. They also reported that the use of risperidone relieved the symptoms of FN patients. Domzał[33] suggested that haloperidol is a suitable treatment method. Agrawal *et al*[2] advocated a first choice of second-generation antipsychotic drugs, especially risperidone, because there is little interaction between this drug and other drugs, and the risk of side effects is also low.

However, whether antipsychotic treatment is provided does not affect the overall prognosis of patients. The complete remission rate of patients who received antipsychotic treatment was 56.2%, while the complete remission rate of those who did not receive antipsychotics was 92.8%. The reason is not clear[5].

### *Others*

Not all patients with FN can be treated by discontinuing or reducing the dose of suspicious drugs and adding antipsychotic drugs. For those who are unresponsive to drug treatment, Green *et al*[19] suggested that electroshock treatment can be considered; they reported that two patients with FN were treated with electroshock methods and achieved good results. Therefore, they suggested that this method may be a reasonable treatment for FN. Kikuchi *et al*[22] reported a patient with epileptic encephalopathy who developed FN after taking LEV. They did not change the original drug, and the patient subsequently experienced epilepsy; the original mental symptoms completely disappeared.

## PROGNOSIS

The overall prognosis for patients with FN induced by ASMs is good. Seven out of 10 patients reported by Carazo Barrios[3] had a good prognosis, with seizures not reappearing after the FN symptoms disappeared, and only 3 patients had a poor prognosis with recurrent attacks. Among the 193 episodes of FN studied by Calle-López *et al*[5], 65% of patients had complete control of their psychiatric symptoms, 27% had mild psychiatric symptoms, and 6% of patients had long-term symptoms. Among them, symptoms in women were more likely to be relieved than those in men, and children (< 14 years) were more likely to experience relief of their symptoms than adults. Seventy-five percent of patients with focal epilepsy experienced complete relief, and 61% of patients with generalized seizures experienced complete relief.

## CONCLUSION

In conclusion, FN is a unique and easily overlooked entity. When ASMs such as LEV, ESM, LTG, and VPA are used to control epileptic seizures, if abnormal mental behavior occurs despite successful seizure control and normal EEG results, the possibility of FN should be considered. FN often leads to failure of the treatment of epilepsy and affects the quality of life of the patient. However, if this phenomenon is detected in time and corresponding measures are taken, such as dose reduction or withdrawal of the causative drug and administration of antipsychotic drugs, the overall prognosis is good. Exploring the factors related to FN caused by different ASMs can further improve clinicians' understanding of FN. The specific pathogenesis of FN needs further research in the future.

## FOOTNOTES

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*MINIREVIEWS*

# Role of serendipity in the discovery of classical antidepressant drugs: Applying operational criteria and patterns of discovery

Francisco López-Muñoz, Pilar D'Ocón, Alejandro Romero, José A Guerra, Cecilio Álamo

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## Abstract

The role played by serendipity in the origin of modern psychopharmacology has proven to be controversial in scientific literature. In its original meaning (Walpole), serendipity refers to discoveries made through a combination of accidents and sagacity. We have implemented an operational definition of serendipity based on finding something unexpected or unintended, regardless of the systematic process that led to the accidental observation, and we have established four different patterns of serendipitous attributability. In this paper, we have analyzed the role of serendipity in the discovery and development of classical antidepressant drugs, tricyclic antidepressants and monoamine oxidase inhibitors as well as heterocyclic, "atypical" or "second generation" antidepressants. The discovery of the antidepressant properties of imipramine and iproniazid, the prototypes of tricyclic antidepressants and monoamine oxidase inhibitors, respectively, fits the mixed type II pattern; initial serendipitous discoveries (imipramine was an antipsychotic and iproniazid was an antituberculosis agent) led secondarily to non-serendipitous discoveries. But the other

components of these two families of drugs were developed specifically as antidepressants, modifying the chemical structure of the series leaders, thereby allowing all of them to be included in the type IV pattern, characterized by the complete absence of serendipity. Among the heterocyclic drugs, mianserin (originally developed as an antihistamine) also falls into the type II pattern.

**Key Words:** Serendipity; Antidepressants; Imipramine; Iproniazid; Psychopharmacology; History of neurosciences

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**Core Tip:** In this paper, we have analyzed, for the first time, the role of serendipity in the discovery and development of classical antidepressant drugs through our operational definition of serendipity. We have assigned each of the classic antidepressants its corresponding pattern of serendipitous attributability according to four different patterns.

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## INTRODUCTION

The era of modern psychopharmacology began in the late 1940s, with the publication of the antimanic effects of lithium by Australian psychiatrist Cade[1]. However, it was in the 1950s that what has come to be known as the "psychopharmacological revolution"[2] came into being, with the introduction of the large families of pharmacological agents that are still in use today: typical neuroleptics or antipsychotics, benzodiazepine anxiolytics and the two large groups of classic antidepressants, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)[3]. All of these psychotropic drugs drastically changed the state of psychiatric care, starting from a fundamentally empirical therapeutic approach, which nevertheless allowed for a gradual understanding of some of the neurobiological bases of mental illnesses and how to treat them.

The year 1957 should be regarded as a key date in modern psychiatry, as this was the year when the first two specific antidepressant drugs in history were introduced into clinical practice, belonging to two completely different pharmacological families and two completely different geographical areas of research. Iproniazid, an MAOI agent, was the result of a research process developed in the United States, and imipramine, the prototypical representative of the TCA family, was developed and studied in Europe[4]. Prior to the clinical introduction of these antidepressant agents, the therapeutic tools used to manage affective disorders were extremely limited[5]. At the beginning of the 20$^{th}$ century, chloral hydrate, barbiturates, amphetamines and opiate derivatives were used in agitated melancholic patients. During the first half of the century, excluding biological treatments (insulin comas, chemical, electrical shock therapies, and "sleep cures"), there were only a few nonspecific chemical preparations available to doctors, such as dinitrile succinate, malonic nitrite and lactic acid, all of which had rather unsatisfactory antidepressant results[6,7] confirmed in the few clinical studies carried out. However, this was also due in part to Freudian ideas prevalent until the 1950s that depressive syndromes had only psychodynamic, not biological, causes, meaning that these patients could not benefit from treatment with pharmacological agents[8,9].

In the specific field of antidepressant drugs, TCA agents that ushered in a new era in the treatment of depression are still the benchmarks today, especially in clinical research, and have the same efficacy rates as other antidepressants that have appeared since then. However, unlike TCAs, which continue to be used in clinical practice though not as a first-line treatment, the use of MAOIs has largely fallen off, due primarily to their adverse effects and problems of interactions with other psychostimulant drugs and tyramine-rich foods, which can lead to tragic hypertensive crises. However, atypical depressions are still candidates for treatment with these drugs. During the 1970s, new heterocyclic antidepressants appeared, known at the time as "atypical" or "second generation" antidepressants (maprotiline, mianserin, trazodone, viloxazine, nomifensine). The main characteristic of which was that they were more selective in their action on monoaminergic transmission systems. All of these drugs can be categorized as traditional antidepressants (Table 1).

**Table 1 Classification of classical monoaminergic antidepressants according to action mechanism and historical perspective on their clinical introduction**

| Family | Mechanisms of action | Acronym | Prototype substance | Period |
|---|---|---|---|---|
| Tricyclic antidepressants | 5-HT and NA reuptake inhibitors with blocking action of diverse receptors | TCA | Imipramine | 1957-1980 |
| Monoamine oxidase inhibitors | Irreversible MAO inhibitors | MAOI | Phenelzine | 1958-1965 |
| Heterocyclic or "second generation" antidepressants | NA reuptake inhibitors with blocking action of diverse receptors | | Maprotiline | 1967-1980 |
| | Antagonists of $\alpha_2$ auto-receptors | | Mianserin | 1970-1980 |
| | DA and NA reuptake inhibitors | | Nomifensine | 1970-1980 |
| | 5-HT reuptake inhibitor and antagonist of 5-$HT_2$ receptors | | Trazodone | 1970-1980 |

5-HT: Serotonin; NA: Norepinephrine; DA: Dopamine; TCAs: Tricyclic antidepressants; MAOIs: Monoamine oxidase inhibitors.

Finally, in the late 1980s, a new series of drug families were introduced into clinical practice, including selective serotonin reuptake inhibitors, which were widely used and accepted. These drugs offered considerable advantages over their predecessors, particularly in terms of safety and tolerability, and opened up the field of antidepressant therapy to non-psychiatrists. The first selective serotonin reuptake inhibitor was zimelidine, which was withdrawn from the market, but we can say that the period of "modern" antidepressants began with the successful clinical introduction of fluoxetine[10].

Serendipity may have played a crucial role in the process of discovering classic psychotropic drugs during the 1950s[11,12], although opinions in scientific literature in recent decades are rather contradictory possibly due to a lack of consensus on what is meant by serendipity. In the specific field of science, this concept has traditionally been associated with those discoveries or findings of a fortunate and unexpected nature, fortuitous events or accidental encounters ("happy accident," "pleasant surprise," *etc.*), although its meaning has also been linked to the very concept of chance, randomness or coincidence.

The differences in opinion about the role of serendipity or chance discoveries in science may lie in the semantic ambiguity of the term "serendipity." The origin of which can be traced to correspondence between the English writer, politician and historian Horace Walpole, 4$^{th}$ Earl of Oxford and the British diplomat Sir Horace Mann. One epistle in this fluid correspondence, which refers to the classic Persian tale *The Three Princes of Serendip*, contains the two components that should make up the concept of serendipity: accidents and sagacity[13]. Therefore, it is sagacity that marks the difference between serendipitous discovery and the absence of discovery in the presence of relevant accidental information. But is not sagacity a basic and indispensable component of the scientific mentality itself? If the answer is yes, this element must be present irrespective of whether the phenomena observed in the scientific discovery were foreseen or not. However, we have postulated that there is a structural difference in this approach. Sagacity always precedes and leads observation in non-serendipitous discoveries, but in serendipitous discoveries, sagacity manifests itself after the unexpected observation has been made. However, even this assessment leads to interpretative problems as once scientists have made their discovery, they tend to explain them as a consequence of perfectly planned working hypotheses even when they take place in a completely random way.

Thus, from a conceptual point of view, we can conclude that serendipitous discovery is the discovery of something unsought, regardless of the systematic process that led to the accidental observation. Viewed in this light, serendipity is undoubtedly a key factor in the creative process in the arts and humanities[14,15]. However, it can also be seen as an integral part of the development of social sciences and of course of biomedical sciences in general and psychopharmacology in particular.

Kubinyi[16] briefly analyzed the discoveries of different pharmacological agents in which serendipity was somehow involved, and Hargrave-Thomas *et al*[17] confirmed that 24% of all commercially available drugs were positively influenced by serendipity during their development, particularly psychopharmaceuticals. In this sense, the discovery of most of the psychopharmacological agents that revolutionized the care of mental illnesses during the 1950s has not escaped this conceptualization either[13]. However, although the researchers responsible for these discoveries have themselves reported that chance was a key factor in their findings, the role of serendipity in the early days of psychopharmacology is still far from being established.

To address this point further, we have established an operational definition of serendipity based on four different patterns of attributability[13,18], which allows us to reflect on the actual role that serendipity played in the findings that shaped the origins of modern psychopharmacology. In this paper following this approach, we will look at the role played by serendipity in the discovery of the classic antidepressant drugs.

## PATTERNS OF SERENDIPITOUS ATTRIBUTABILITY

In previous papers[13,18], we have proposed a standardized definition for the term serendipity in the field of science, given the semantic ambiguity of this concept. This "operational" definition would establish that serendipity is the discovery of something not sought. Moreover, we have proposed a working definition of serendipity[13,18] based on four different patterns of serendipitous imputation in the drug discovery process (Figure 1): (1) The first pattern, which would encompass pure serendipitous discoveries, was more frequent in the first half of the 20$^{th}$ century; (2) The second pattern, which is a variant of the previous one, would correspond to those initial serendipitous discoveries that secondarily lead to non-serendipitous discoveries; (3) The third pattern would include non-serendipitous discoveries that are secondarily partnered with serendipitous discoveries; and (4) The fourth pattern of non-serendipitous discoveries, in line with our operational definition of finding something unsought, has become more and more frequent since the second half of the last century. In the latter pattern, beyond serendipity, drugs evolved out of systematic research programs specifically designed to develop effective drugs for different pathological conditions.

Mixed discoveries (patterns 2 and 3) were very common towards the middle of the 20$^{th}$ century (coinciding with the so-called "golden decade" of psychopharmacology in the 1950s) and were characterized by initial serendipitous discoveries (in some cases in laboratory animals) leading secondarily to non-serendipitous discoveries and vice versa.

Prior to applying the attributability criteria, a detailed historical study of the development process of each of the antidepressant drugs analyzed was carried out, using the original articles in which the first pharmacological and clinical data on these drugs were published. This was done using most important databases in this field (Medline, Embase, Scopus), the documentation services of the pharmaceutical companies that have marketed these drugs and the documentation available in the Network for the History of Neuropsychopharmacology, coordinated by Thomas A. Ban (Vanderbilt University), the series of interviews entitled *The Psychopharmacologists*, by David Healy (Arnold-Oxford University Press), the *History of Psychopharmacology* collection of the Collegium Internationale Neuro-Psychopharmacologicum, coordinated by Thomas A. Ban, David Healy and Edward Shorter and edited by Animula and the documentary background on the history of psychopharmacology by Prof. López-Muñoz.

## SERENDIPITY IN THE PROCESS OF DISCOVERY OF CLASSICAL ANTIDEPRESSANT DRUGS

### *Discovery of the antidepressant properties of imipramine and TCAs*

The history of the clinical introduction of the first antidepressant drug (from the family of TCA), imipramine, was part of a search for antipsychotic drugs[19,20], following the therapeutic success reported with the clinical introduction of chlorpromazine[21] and reserpine, an alkaloid from *Rauwolfia serpentina*[22] in 1952 (Figure 2). See López-Muñoz *et al*[23-25] for details. These developments intensified the search for substances with similar properties by pharmaceutical companies. Accordingly, the pharmaceutical company J.R. Geigy (Basel) dusted off some phenothiazine substances that it had initially tried to develop unsuccessfully as dyes[8] and later on as antihistamines and hypnotics in the hope that they might have some other psychiatric benefit[8,9,26].

In this context, the Swiss psychiatrist Roland Kuhn, deputy medical director at the Cantonal Psychiatric Clinic in Münsterlingen (near Lake Constance), who had already studied the hypnotic and neuroleptic properties of certain Geigy phenothiazine agents[26,27], asked the Swiss company for new compounds from the phenothiazine family to test them in his psychotic patients. In early 1956, Kuhn received a preparation called G-22355, a substance with the same side chain as chlorpromazine, which had been synthesized by Franz Häfliger and Walter Schindler in 1948 from promethazine by replacing the sulfur bridge of phenothiazine with an ethylene bridge[28]. The substance had been registered in 1951 under United States license number 2554736[29].

Kuhn's extensive clinical research in 1956 soon showed that the agent G-22355 had no appreciable neuroleptic activity. Even patients who had previously been treated with chlorpromazine developed more severe psychotic symptoms not schizophrenic and became clinically disturbed and agitated[30]. However, Kuhn observed that 3 patients diagnosed with depressive psychosis showed a pronounced improvement in their general condition in just a few weeks. The antidepressant effect of this substance, later named imipramine, was therefore completely unexpected and its discovery entirely accidental. In

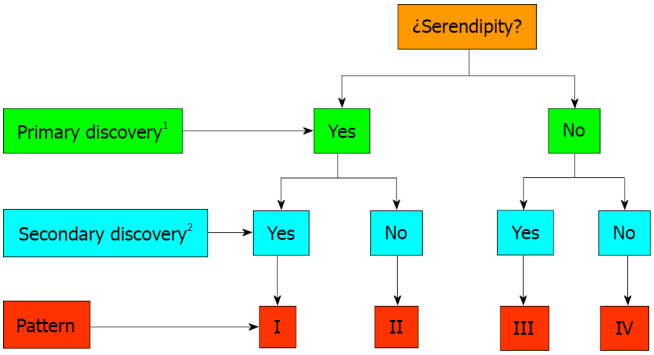


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**Figure 1 Diagram of the four patterns of serendipitous attribution in the discovery of pharmacological agents.** [1]They usually, but not always, relate to findings in laboratory animals; [2]Findings relating to clinical efficacy.

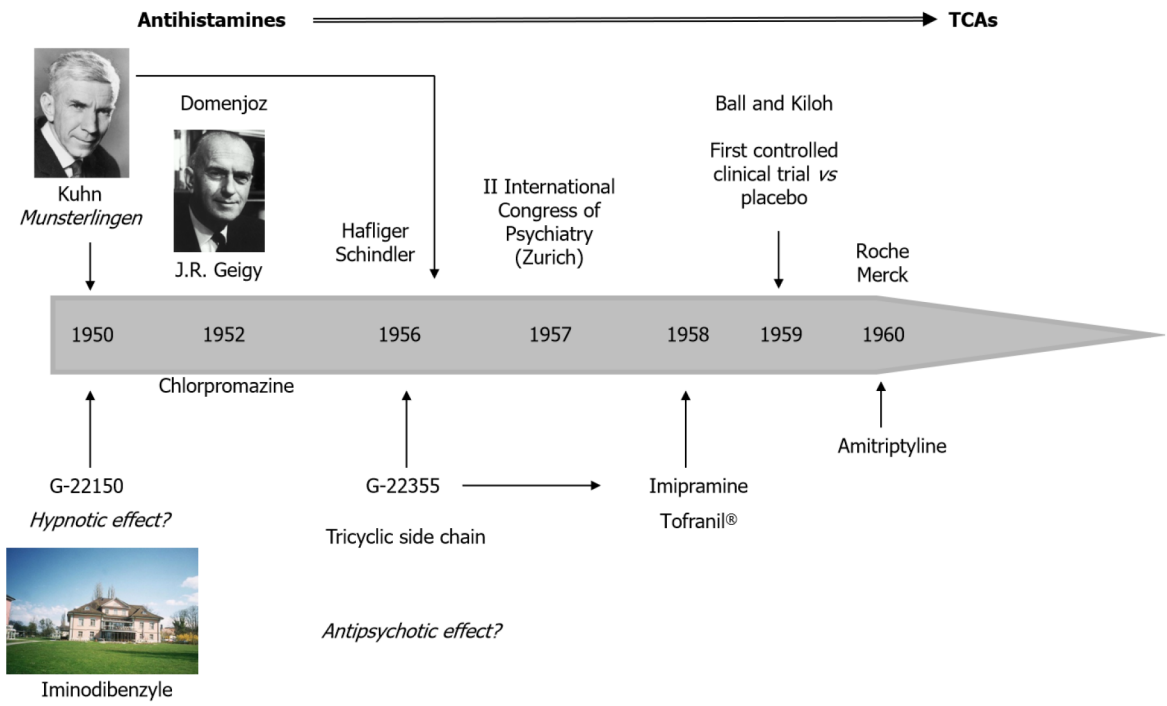


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**Figure 2 Historical process of the discovery of tricyclic antidepressants during the 1950s.** TCAs: Tricyclic antidepressants.

this regard, the possibility that this substance could have a therapeutic antidepressant effect was first raised by Kuhn in a written communication to Geigy dated February 4, 1956[31].

Subsequently, a further 37 patients with depressive disorders received this drug, demonstrating its particular efficacy in treating depressive disorders[26,32,33]: "The patients appear, in general, more animated, their voices, previously weak and depressed, now sound louder; they are more communicative, the lamentations and sobbing have disappeared. The depression, which had manifested itself through sadness, irritation and a sensation of disaffection, now gave way to friendly, joyous and accessible feelings"[32]. Kuhn presented his results at the 2nd International Congress of Psychiatry in Zurich in September 1957 to an audience of just 12 people, using the data obtained from the clinical follow-up of these 40 depressed patients. The proceedings of the conference were published in the August issue of the *Schwizerische Medizinische Wochenschrift*[32]. However, the following year, Kuhn republished his data (with a larger sample of patients) in the *American Journal of Psychiatry*[33], thereby making his discovery internationally known. In this paper, Kuhn extensively described the pharmacological effects, data on efficacy and the adverse effects of imipramine and provided recommendations for its clinical use, dosage and duration of treatment. In this work, Kuhn stated that "the patients got up in the morning voluntarily, they spoke in louder voices, with greater fluency and their facial expression became more lively. They began to do some individual activities, they once more sought to make contact with other people, they began to train on their own, to participate in games, to become happier,

and to recover their ability to laugh"[33].

Geigy introduced imipramine to the local Swiss market at the end of 1957 under the trade name of Tofranil®. It was subsequently introduced in the rest of the European market in the spring of 1958[8,29] and represented a giant step forward in the treatment of depression, being the first representative of a new family of drugs, known as imipraminic or TCAs.

Kuhn had the sagacity to recognize an antidepressant drug when looking for an antipsychotic drug. Kuhn himself commented: "Chance admittedly had something to do with the discovery of imipramine. Chance was not decisive, however, to this had to be added a measure of intellectual achievement that was able to "invent" something completely new, something hitherto unknown, namely a new disease. Göthe put the sense of the matter in a nutshell when he wrote: 'Discovery needs luck, invention, intellect–neither can do without the other'"[34]. Something similar pointed more than a century ago the great Louis Pasteur: "In the realm of scientific observation, luck is granted only to those who are prepared"[35].

The discovery of the antidepressant properties of imipramine is a representative example of how a serendipitous finding, the observation of schizophrenic patients treated with this drug looking for an antipsychotic effect, leads to a planned and non-serendipitous discovery, *i.e.* the antidepressant effect. Therefore, the antidepressant effect of imipramine would fit into the type II pattern of our serendipitous attributability criteria. This pattern of a mixture of serendipitous and non-serendipitous findings was possibly the most common during the early stages of modern psychopharmacology. But it is precisely this dual quality that has been a major source of controversy in attributing serendipity to psychopharmacological discoveries.

Despite the remarkable success of imipramine, the next TCA, amitriptyline, was not introduced to the market until 1961. This molecule was also investigated as an antipsychotic by the pharmaceutical company Merck and Co. For this, they made modifications in the central ring of the thioxanthene family, and in this way, they got the first compound of the dibenzocycloheptadiene group[36]. Merck commissioned Frank J. Ayd Jr., one of the American pioneers in the study of chlorpromazine, to conduct clinical research on this new compound. But Ayd tried it as an antidepressant, following in the wake of imipramine. Ayd treated 130 patients at Baltimore Square Hospital with amitriptyline and found that the antidepressant effect was similar to that of imipramine. The Food and Drug Administration approved amitriptyline for marketing as an antidepressant on April 7, 1961 and it received the trade name Elavil®. This molecule would retain some of the tranquillizing effects of thioxanthenes, thus displacing imipramine in the treatment of patients with agitated or anxious depression.

The introduction of amitriptyline, the second tricyclic agent, by Merck and Co. increased the confidence in these drugs of both general practitioners and specialists. Thanks to the commercial strength of these two pharmaceutical companies and a marketing agreement between them (the joint marketing of both products, Elavil Merck and Tryptizol Roche worldwide, except in the United States where it was only marketed by Merck), amitriptyline quickly became the most prescribed antidepressant at the time.

Simultaneously, Hoffmann-La Roche and H. Lundbeck and Co. had succeeded in synthesizing amitriptyline by modifying the chemical structure of imipramine accordingly. Although due to the priority of their application, Roche received the European marketing rights under the name Saroten® [37].

The discovery of the antidepressant properties of imipramine and its commercial success led to the development of a number of compounds with similar structures and activities (now called "me-too" compounds) in order to identify specific comparative advantages[38]. This subsequently became quite common practice in the field of pharmacological therapeutics. As a result, a number of TCAs were developed during the 1960s. In 1963, nortriptyline was approved in Britain under the name Allegron®, while in the United States it was approved by the Food and Drug Administration in November 1964, when desipramine (J.R. Geigy), the principal urinary metabolite of imipramine, was also approved; in 1966, trimipramine was introduced in Britain and other European countries under the name Surmontil®. These agents were followed by other TCAs: in 1966 by protriptyline (called Concordin® in Europe and Vivactil® in the United States); in 1967 by iprindole (Prondol®); in 1969 by dothiepin (Prothiaden®), an agent not approved in the United States; doxepin[39], introduced onto the European market by Galenus (Aponal®), a subsidiary of Boehringer, and in the United States by Pfizer (Sinequan®) [40]; and clomipramine (Anafranil®), introduced in Europe in 1970, which was not approved in the United States.

All components of the TCA series were developed specifically as antidepressant agents, following in the wake of imipramine and modifying its chemical structure, so they can all be included in the type IV pattern of our serendipitous attribution criteria, in which neither chance nor sagacity played a part (Table 2).

### *Discovery of the antidepressant properties of iproniazid and non-selective MAOIs*

The origin of the first specific antidepressant drugs, MAOIs, can be traced back to hydrazide antituberculosis agents, which had been used since the early 1950s[5,41] (Figure 3). In 1952, Selikoff *et al*[42] began to study the clinical effects of iproniazid at Sea View Hospital on Staten Island (New York). They observed that compared to isoniazid iproniazid had a greater stimulatory power on the central nervous

**Table 2 Attribution of serendipity in the discovery of classical antidepressant drugs**

| Group/Family | Drug | ATC code | Date of discovery (psychiatric introduction) | Effect/primary properties[1] | Effect/secondary properties[2] | Pattern of discovery |
|---|---|---|---|---|---|---|
| TCAs | Imipramine | N06AA02 | 1951 (1957) | S | NS | II |
| | Amitriptyline | N06AA09 | 1958 (1961) | NS | NS | IV |
| | Trimipramine | N06AA06 | 1964 (1966) | NS | NS | IV |
| | Butriptyline | N06AA15 | 1964 | NS | NS | IV |
| | Desipramine | N06AA01 | 1964 | NS | NS | IV |
| | Clomipramine | N06AA04 | 1963 (1970) | NS | NS | IV |
| | Nortriptyline | N06AA10 | 1963 (1967) | NS | NS | IV |
| | Protriptyline | N06AA11 | 1967 | NS | NS | IV |
| | Iprindole | N06AA13 | 1967 | NS | NS | IV |
| | Doxepin | N06AA12 | 1969 | NS | NS | IV |
| | Dibenzepin | N06AA08 | 1970 | NS | NS | IV |
| | Maprotiline[3] | N06AA21 | 1967 (1973) | NS | NS | IV |
| | Dosulepin | N06AA16 | 1977 | NS | NS | IV |
| | Amineptine | N06AA19 | 1978 | NS | NS | IV |
| | Amoxapine | N06AA17 | 1980 | NS | NS | IV |
| | Quinupramine | N06AA23 | 1983 | NS | NS | IV |
| | Lofepramine | N06AA07 | 1989 | NS | NS | IV |
| MAOI | Iproniazid | N06AF05 | 1952 (1957) | S | NS | II |
| | Isocarboxazid | N06AF01 | 1959 | NS | NS | IV |
| | Phenelzine | N06AF03 | 1960 | NS | NS | IV |
| | Tranylcypromine | N06AF04 | 1961 | NS | NS | IV |
| | Nialamide | N06AF02 | 1988 | NS | NS | IV |
| OCA | Trazodone | N06AX05 | 1966 (1973) | NS | NS | IV |
| | Nomifensine | N06AX04 | 1977 | NS | NS | IV |
| | Mianserin | N06AX03 | 1966 (1979) | S | NS | II |

[1]Usually, but not always, correspond to discoveries in laboratory animals.
[2]Discoveries related to clinical efficacy.
[3]Maprotiline is the first tetracyclic antidepressant and is included in the group of "second generation antidepressants." Antidepressant drugs were classified by the Anatomical Therapeutic Chemical classification system controlled by the World Health Organization Collaborating Centre for Drugs Statistics Methodology. This system classifies the active ingredient of a drug into groups according to the organ or system on which they have their effect. https://www.whocc.no/atc_ddd_index/?code=N06AX&showdescription=no.
NS: Non-serendipitous discovery; S: Serendipitous discovery; TCAs: Tricyclic antidepressants; MAOIs: Monoamine oxidase inhibitors; OCA: Other classical antidepressants; ATC: Anatomical Therapeutic Chemical.

system, an effect initially interpreted as a secondary effect of the preparation[42]. The psychological changes observed in tuberculosis patients treated with iproniazid were particularly striking[5,8,43]; these patients showed increased vitality, even a desire to leave the hospital and a gradual increase in social activity. In other types of patients treated with iproniazid, such as patients with rheumatoid arthritis or cancer, similar psychostimulant effects were also observed[44].

But the adverse effects of iproniazid, observed in the first clinical trials with tuberculosis patients, were more frequent than in the case of isoniazid. Therefore, it was abandoned, except for specific cases, such as that of David M. Bosworth, Director of the Department of Orthopedics at St. Luke's and Polyclinic Hospital (New York), who continued to defend the use of iproniazid in bone tuberculosis [45]. But a few astute clinicians saw a "primary effect" in the psycho-stimulant type of "secondary effect" discussed above, which could be useful in other types of patients, mainly of a psychiatric nature. This was the case of Jackson A. Smith (Baylor University, Waco, Texas), who, evaluating the "tranquil-

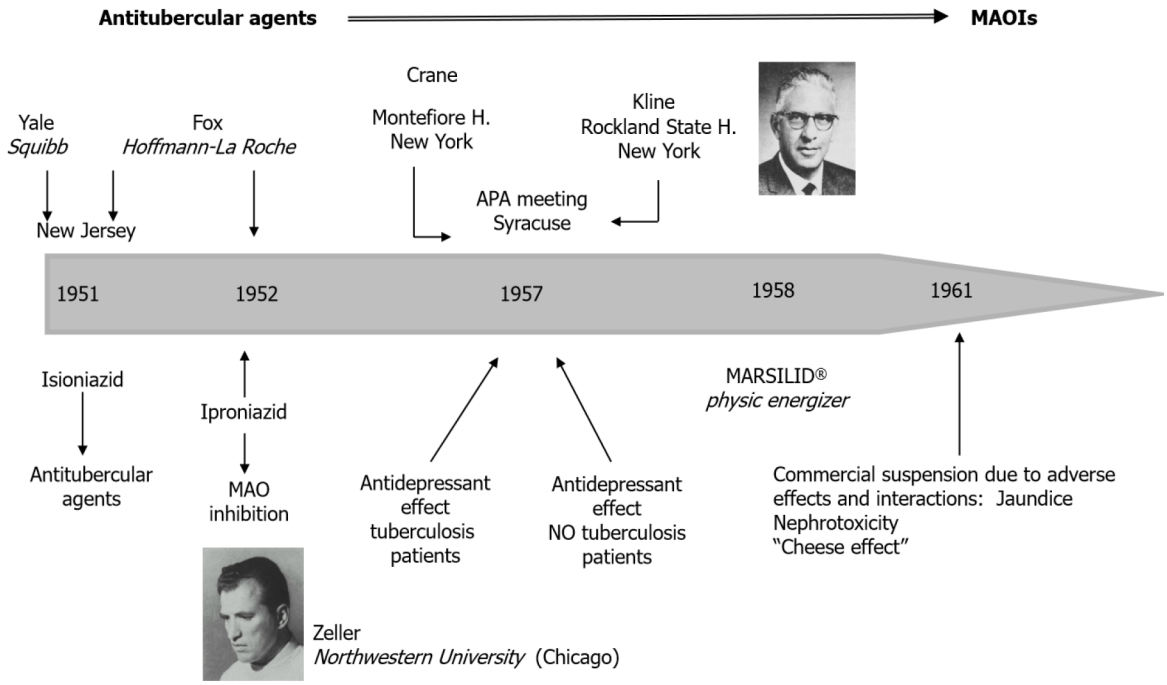


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**Figure 3 Historical process of the discovery of monoamine oxidase inhibitors during the 1950s.** APA: American Psychiatric Association; MAOI: Monoamine oxidase inhibitors.

lizing" effect of iproniazid observed that of a group of 11 patients treated for 2 wk with this drug, 2 of them experienced a certain improvement (increased appetite, weight gain, increased vitality and improved sleep)[46]. The same was true of Gordon R. Kamman, of the University of Minnesota (Twin Cities)[47] and Carlos Castilla del Pino of the University of Cordoba in Spain, who described the euphoriant and mood-elevating effects of hydrazide therapy in tuberculosis patients[48]. Some studies were even published assessing the mood elevating effect of isoniazid in psychiatric patients[49-51]. In fact, one of these researchers, Max Lurie (Cincinnati), may have coined the term "antidepressant" precisely to describe the effect that this drug had on depressed patients[52].

The year 1957 was fundamental in the history of hydrazide drugs as antidepressants, as the first data on the effects of iproniazid on depression were presented at a meeting of the American Psychiatric Association in Syracuse in April of that year. Although its use was much more limited than isoniazid, George Crane of Montefiore Hospital in New York reported improvement in the mood of 11 out of 20 tuberculosis patients with concomitant depression[53], as did Frank Ayd, an intern at Taylor Manor Hospital in Baltimore[54]. However, these researchers never mentioned iproniazid as an "antidepressant" agent.

Meanwhile, Nathan S. Kline and his colleagues (Harry P. Loomer and John C. Saunders) from Rockland State Hospital (Orangeburg, New York), who were aware of the work of Charles Scott's team at Warner-Lambert Research Laboratories (Morris Plains, New Jersey) particularly the ability of iproniazid to prevent reserpine-induced immobility in mice[55], were the first psychiatrists to assess the efficacy of iproniazid in non-tuberculous depressed patients (chronic psychotic depression). They performed the same procedures on humans as Scott had done on animals. For their study, they recruited 17 severely inhibited patients with schizophrenia and 7 patients with depression from Kline's private practice and gave them a dose of iproniazid 50 mg, 3 times a day. Their results revealed the stimulating effect of iproniazid on depressed patients; 70% of the patients treated with this drug experienced a great improvement, including increased mood, increased appetite and increased interpersonal skills, interest in the environment and in themselves. These same effects were already provided at the Syracuse Meeting, although they were not released until a few years later when they were published[56].

In 1957, Kline[57] published the first neuropsychiatric experiments with iproniazid (previously reported at the American Psychiatric Association Annual Meeting in Syracuse) during a meeting of the Committee on Appropriations of the United States Senate in May[57], proposing the term "physic energizer" to designate the activity of this drug[58]. Two years later, Werner Janzarik proposed at a symposium held in Montreal the use of the term "thymerethics," *i.e.* compounds that act by increasing the stimulatory effects, to refer to all those drugs with effects similar to the new MAOIs.

Although iproniazid was only authorized (with the trade name of Marsilid) for the treatment of tuberculosis patients, its use in depressive patients was massive. Only 1 year after the Syracuse Meeting,

it was estimated that more than 400000 patients with depression were treated with iproniazid[59]. This opened the door to a group of specifically antidepressant drugs, later known as MAOIs, due to the research of Ernst Albert Zeller's team at Northwestern University Medical School (Chicago, Illinois). It was known in 1952 that iproniazid was able to inhibit MAO[60]. Despite all this, iproniazid was withdrawn from the United States market in 1961 following allegations that it induced a number of cases of jaundice and nephrotoxicity.

Serendipity played an important role in the discovery of iproniazid[11]. Thanks to the sagacity of healthcare professionals dedicated to the care of tuberculosis patients, it was realized that certain "secondary effects" of anti-tuberculosis medication of a psychostimulant nature, which appeared by chance, could be useful in psychiatric patients diagnosed with depressive disorders. Therefore, this would fall under a type II pattern under our serendipitous attribution criteria.

Iproniazid soon gave way to other agents with much higher MAO inhibitory potency[61], such as Hoffman-LaRoche's isocarboxazid (Marplan®), marketed in 1959, phenelzine developed by Warner-Lambert (Nardil®)[62], which became available in 1960, and tranylcypromine (Smith, Kline & French) (Parnate®)[63,64], which entered the market in 1961, as well as other hydrazine derivatives (nialamide, mebanazine and pheniprazine) and indole derivatives (etryptamine)[65,66]. The origin of this agent, synthesized in 1948 by Alfred Burger and William L. Yost, is part of the search for new analogues of amphetamines (trans,dl-2 phenylcyclopropylamine sulfate)[67], although its MAOI activity was discovered much later in 1959 by Smith, Kline & French Laboratories[63,68]. Indeed, the fact that tranylcypromine was not a hydrazine derivative aroused some clinical interest, and it was speculated that it could have a better hepatic safety profile than that of other MAOIs known to date[69].

But tranylcypromine was also withdrawn from the United States market in 1964, albeit for other safety reasons, when an increase in the number of drug-related hypertensive crises, some of them linked to intracranial subarachnoid hemorrhages, was reported. It was reintroduced in the same year at the request of specialists and is still in use today. Thanks to the contributions of Barry Blackwell, then a resident consultant in psychiatry at the Maudsley Hospital in London, it was confirmed that these crises were triggered by the concomitant consumption of certain cheeses, given their high tyramine content, hence the term "cheese effect"[70]. The link between the hypertensive crises described by Blackwell and the consumption of tyramine-rich foods is also a clear example of the phenomenon of "serendipity" in psychiatry, according to Blackwell himself[71]. A hospital pharmacist in Nottingham, called G.E.F. Rowe, read an article published by Blackwell[70] in 1963 in *The Lancet* on tranylcypromine and its adverse effects[70] and noted that the symptomatology described was alarmingly similar to that experienced by his own wife when she consumed certain cheeses. These episodes were described in detail in a letter Rowe sent to Blackwell, who was alerted to this dangerous association. Many other foods (yeast products, chicken liver, snails, pickled herring, red wines, some varieties of beer, canned figs, beans, chocolate and cream products, *etc.*) were subsequently found to contain indirectly acting amines (mainly tyramine), which could also cause hypertensive episodes in patients treated with MAOIs.

After the use of iproniazid as an antidepressant, the other agents in this family were incorporated into the antidepressant therapeutic arsenal thanks to recognition of their MAO inhibitory effect, meaning that they would fall into the type IV pattern under our serendipitous attribution criteria, where chance no longer played a role (Table 2).

### *Heterocyclic or "second-generation" antidepressants*

During the 1960s, many changes were made to the dibenzazepine structure of imipramine in order to obtain new antidepressants with superior efficacy and/or an improved adverse effect profile. As a result, the tetracyclic, heterocyclic or "second generation antidepressants"[36], such as maprotiline (Ludiomil®), marketed by Ciba-Geigy in Europe and Japan in 1972[8], mianserin (Tolvon®), nomifensine (Merital®) and trazodone (Desyrel®), were developed. Compared to the classic TCAs, which had a very unspecific mechanism of action [serotonin (5-HT) and norepinephrine reuptake inhibition with blocking action of diverse receptors][72], these drugs had a slightly cleaner pharmacodynamic profile.

The first tetracyclic antidepressant was maprotiline, developed as an antidepressant by Max Wilhelm and Paul Schmidt in 1967 at Ciba. However, the four rings of its chemical structure are not fused together as is the case with other tetracyclic antidepressants. Clinical trials of this agent were also conducted by Kuhn[73]. By contrast, nomifensine is a tetrahydoisoquinoline antidepressant that is not chemically related to TCAs, MAOIs or heterocyclic antidepressants. It is a dopamine and norepinephrine reuptake inhibitor developed as an antidepressant in the 1960s. The pharmacological effects of nomifensine were similar to those of TCAs in animal models of depression but with a much lower rate of sedation[74]. However, it was withdrawn from the market in 1986 due to safety concerns (immune related hemolytic anemia), including some cases of dependence, given its similar mechanism of action to psychoactive drugs such as cocaine.

As far as trazodone is concerned, it is now known to have a dual mechanism of action whereby it inhibits the serotonin transporter and blocks the 5-$HT_2$ serotonin receptors (both the 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors). But, like TCAs, it also exerts an antagonistic effect on $\alpha_1$- and $\alpha_2$-adrenergic receptors and histamine $H_1$ receptors, with almost no anticholinergic effects[75]. It was discovered in Italy in 1966 at Angelini Research Laboratories by Gorecki and Verbeeck[76] and developed as a second generation

antidepressant following the then current "mental pain" hypothesis, which postulated that clinical depression was associated with a reduced pain threshold[77]. Trazodone was patented and marketed in many countries around the world from 1973 and approved by the Food and Drug Administration as the first non-TCA, non-MAOI antidepressant in 1981. These three compounds can be included in our type IV pattern of attributability as serendipity was not involved in their discovery and development.

However, the development of mianserin is another example of serendipitous influence. As part of a research program carried out by Organon International, B.V. in Oss (The Netherlands), mianserin (a tetracyclic piperazino-azepine) was synthesized in 1966 by van der Burg *et al*[78], with the aim of confirming whether the antihistamine properties of phenbenzamine and the anti-serotonergic activity of cyproheptadine could be combined in a chemical structure that could be potentially useful for treating asthma, migraine or allergic diseases such as hay fever.

Early pharmacological studies confirmed that mianserin was capable of antagonizing the effects of serotonin in different samples of various animal tissues[79], including human blood vessels, and exhibited antihistamine properties[80]. These findings led to the launch of a pilot study in 1969, which was not published, in which the tetracyclic compound was administered to 10 asthmatic patients compared to an untreated control group. Patients who received mianserin had significantly fewer night-time asthma attacks. However, this line of research was not continued as a number of central adverse effects, mainly sedation, were also described[81]. Nevertheless, another study in Ireland also in 1969, found that mianserin had a marked positive effect in improving mood in some subjects, and they began to call mianserin the "good mood pill." This observation about the hypothetical antidepressant properties of mianserin spurred on the clinical development of the molecule[81]. A number of experimental studies carried out using computer analyses of electroencephalogram recordings and comparative pilot trials with amitriptyline confirmed the antidepressant efficacy of this drug[82], which was presented as the first representative of a new generation of antidepressants (heterocyclic antidepressant compounds). Clinical trials over the next few years revealed antidepressant efficacy similar to that of classical TCAs, but superior to that of other "second generation" agents such as nomifensine or trazodone[81].

As in the case of the two group-leading agents of TCAs and MAOIs, mianserin falls within the type II pattern under our serendipitous attribution criteria, *i.e.* an initial serendipitous discovery when looking for an antihistamine drug leading secondarily to a non-serendipitous discovery of an antidepressant agent (Table 2).

## NOTES FOR DIALOGUE

Serendipity is a phenomenon that has been regularly and constantly referred to when analyzing the great discoveries that supported the birth of modern psychopharmacology. But, as previously mentioned, the real role of serendipity in these processes has not been sufficiently well defined, possibly due to differences in opinion among authors given the semantic ambiguity of the term "serendipity" [83], and the degree of importance attributed at any given time to the two elements that make up the concept of serendipity: sagacity and unforeseen accidents. For this reason, our group[13,18] advocates the original meaning of the term, as "the discovery of something unexpected or not intentionally sought, in line with favors only the prepared mind"[35].

In fact, in the field of psychopharmacology, contrary to what has been postulated, pure serendipitous discoveries are rather rare, and most of them are of a mixed nature. Some authors refer to these patterns as "pseudo-serendipity"[84] or discoveries that are "serendipity analogues"[85].

These mixed serendipitous discoveries usually consist of a pattern that starts from an initial serendipitous observation and culminates in an intentionally sought-after discovery. For this reason, some authors and scholars may fall into the interpretative error of ascribing merit to chance or luck alone, seeing the results of research processes as a mere continuation of the initial serendipitous findings rather than as two manifestly different events. The cases presented in this paper on the discovery of the two families of classical antidepressants are proof of this: TCAs and MAOIs. Many other discoveries during the 1950s are included within this type II serendipitous attribution pattern that we have defined (initial serendipitous discoveries, in some cases made in laboratory animals, leading secondarily to non-serendipitous discoveries), such as the discovery of the antipsychotic properties of chlorpromazine and clozapine and the experimental tranquillizing properties of meprobamate and its subsequent anxiolytic effect in clinical trials. However, the clearest example was the discovery of the lethargic effect of lithium salts in guinea pigs and their subsequent antimanic effect in humans. Most authors consider the discovery of the antimanic effects of lithium to be purely serendipitous. However, Cade himself pointed out that the link between his casual observation of the lethargic effect in guinea pigs and the subsequent confirmation of the antimanic efficacy of lithium salts was far from obvious[86]. For more information on the historical development of these drugs, see the work of our group[19,20,23,25,41,87-89].

There are also examples of mixed serendipitous discoveries in reverse, included in our type III pattern (non-serendipitous discoveries partnered secondarily with serendipitous discoveries). The most representative example of this group would have to be barbiturates and their intended hypnotic effects,

which made the later serendipitous discovery of their anticonvulsant and antiepileptic effects possible [90].

But although serendipity does not usually work alone, there are also cases of pure serendipitous discoveries (type I pattern of attributability), such as the discovery of the anticonvulsant and mood stabilizing effects of valproic acid and valproate, respectively, or the discovery of the psychotropic effects of lysergic acid diethylamide. Similarly, other discoveries in the field of psychopharmacology during the golden decade of the 1950s should be included under the type IV pattern, namely non-serendipitous discoveries, in line with our operational definition of an unintended finding. Notable here is the discovery of the anxiolytic effect of chlordiazepoxide, the first benzodiazepine agent[91], and the antipsychotic effect of haloperidol and reserpine[24,92,93].

The clinical introduction of psychotropic drugs during the 1950s can be considered one of the great advances in medicine of the 20$^{th}$ century, and a major part of this breakthrough can be attributed to the discovery of the antidepressant effects of iproniazid and imipramine[3], a process in which serendipity played an essential role. But it is worth highlighting another series of contributions to the progress of biological psychiatry in addition to this great clinical contribution[3]. First, from a strictly pharmacological point of view, the development of imipramine led to the introduction of new methods for assessing the antidepressant activity of different substances[94]. Second, the discovery and subsequent therapeutic use of TCAs and MAOIs played a major role in developing the first etiopathogenic theories on affective disorders[95]. During the 1960s, catecholaminergic theories of depression blossomed, postulating a functional impairment of brain noradrenergic neurotransmission as the primary cause of affective disorders based on observations made on the effects of newly discovered antidepressant drugs, such as the blocking of synaptic reuptake of norepinephrine by imipramine[96]. Later, in 1968, Carlsson *et al*[97] described for the first time how imipramine was able to block the reuptake of serotonin in brain pathways, thereby laying the groundwork for the "serotonergic hypothesis" of depression.

However, the story of these two families of antidepressants evolved in completely different ways. Consequently, while TCAs continue to be used in clinical practice in an important way and constitute first-line tools in clinical research, MAOIs have suffered a large reduction in their use, except in the specific case of atypical depressions, largely due to their problems of interactions with other psychostimulant drugs and with tyramine-rich foods, which can lead to tragic hypertensive crises. However, despite this divergence, the importance of imipramine and iproniazid in the history of psychopharmacology is paramount.

## CONCLUSION

It is clear that during the 1950s and 1960s serendipity played an important role in the process of building modern psychopharmacology in general and the first groups of families of antidepressant drugs in particular giving way in later decades to another way of understanding scientific research in this field, namely the systematic and rational planning of projects to be developed. In recent decades, psychopharmacology is moving away from the influence of serendipity towards new scientific approaches, although this is a gradual process[98] as can be seen with the serendipitous introduction of ketamine into the antidepressant arsenal. In any event, the results of this work confirm that serendipity should be understood as more of an eminently scientific construct than a literary curiosity.

In the words of the discoverer of vitamin C, Albert Szent-Györgyi, "discovery consists of seeing what everybody has seen and thinking what nobody has thought"[99].

## FOOTNOTES

**Author contributions:** All authors have contributed to this work; López-Muñoz F and Álamo C designed the study; López-Muñoz F and Guerra JA analyzed the data; López-Muñoz F, D'Ocón P and Romero A wrote the manuscript; López-Muñoz F approved the final manuscript; all authors reviewed and approved the final draft.

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ORIGINAL ARTICLE

Observational Study

# Dimensional (premenstrual symptoms screening tool) *vs* categorical (mini diagnostic interview, module U) for assessment of premenstrual disorders

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## Abstract

***BACKGROUND***

Premenstrual syndrome (PMS) is the constellation of physical and psychological symptoms before menstruation. Premenstrual dysphoric disorder (PMDD) is a severe form of PMS with more depressive and anxiety symptoms. The Mini international neuropsychiatric interview, module U (MINI-U), assesses the diagnostic criteria for probable PMDD. The Premenstrual Symptoms screening tool (PSST) measures the severity of these symptoms.

***AIM***

To compare the PSST ordinal scores with the corresponding dichotomous MINI-U answers.

***METHODS***

Arab women ($n$ = 194) residing in Doha, Qatar, received the MINI-U and PSST. Receiver Operating Characteristics (ROC) analyses provided the cut-off scores on the PSST using MINI-U as a gold standard.

***RESULTS***

All PSST ratings were higher in participants with positive responses on MINI-U. In addition, ROC analyses showed that all areas under the curves were significant

with the cutoff scores on PSST.

*CONCLUSION*
This study confirms that the severity measures from PSST can recognize patients with moderate/severe PMS and PMDD who would benefit from immediate treatment.

**Key Words:** Premenstrual symptoms screening tool; Premenstrual dysphoric disorder; Arabs; Categorical *vs* dimensional classification

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**Core Tip:** This manuscript assesses the relationship between responses on the dichotomous the Mini international neuropsychiatric interview, module U (MINI-U) answers and the scores on the Premenstrual Symptoms screening tool (PSST). Our findings give reassurance that the MINI-U provides an adequate assessment for the probable diagnosis of Premenstrual dysphoric disorder (PMDD) and that the severity measures of the PSST can recognize patients with moderate/severe premenstrual syndrome and PMDD who would benefit from immediate treatment.

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## INTRODUCTION

Premenstrual syndrome (PMS) is characterized by a collection of mild to severe physical, affective, and behavioral symptoms experienced by many reproductive age women. The symptoms occur cyclically before or during the luteal phase of the menstrual cycle. During this period, the symptoms might cause impairment to the daily lives of women, disrupting both work and personal activities[1]. Premenstrual dysphoric disorder (PMDD) is a more severe form of PMS with a greater emphasis on depressive and anxiety symptoms[2]. PMS and PMDD usually resolve within a few days of menstruation. The etiology of PMS and PMDD is not clearly understood, but the onset of symptoms is associated with hypersensitivity to changes in the ovarian hormonal level during the menstrual cycle, dysregulated immune function[2], neurotransmitter dysregulation, stress, diet and lifestyle[3-5]. Treatment intervention is mostly tailored to the patient's symptoms profile because the cause of PMS and PMDD is unknown. Conventional nonpharmacological treatments are lifestyle interventions such as improved diet, increased exercise, sleep hygiene, and Cognitive Behavioral Therapy (CBT) for stress management. Pharmacological interventions include analgesic treatment, combined oral contraceptives[6], and selective serotonin reuptake inhibitors[7].

Overall, 75%-85% of women have experienced PMS symptoms[1,8], whereas PMDD affects 5%-8% of reproductive age women worldwide[9]. According to the International Classification of Diseases (ICD-10)[10], only one distressing symptom at the time of menstruation is required for PMS diagnosis. It does not consider the severity of the symptoms, and no clear definition exists when PMS becomes clinically significant. Contrarily, diagnosis of PMDD mandates the impairment of functioning by the symptoms [11]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[12], the criteria for the diagnosis of PMDD are: (1) At least five symptoms must be present in the final week before the onset of menses and resolve within a few days of the onset of menses, and these symptoms must occur in the majority of the menstrual cycles; (2) At least one symptom must be marked affective lability, marked irritability or anger or marked depressed mood or anxiety; (3) One or more of the following symptoms must be present: decreased interest in usual activities, difficulty in concentration, increased fatigue, change in appetite, marked change in sleep, feeling overwhelmed or physical symptoms; and (4) These symptoms should affect productivity at work or school, relationships, responsibilities, or social activities. These symptoms should not be attributable/resultant to symptoms from: (1) Another psychiatric disorder; or (2) Physiological effects of a substance. Finally, these symptoms should be confirmed by prospective daily ratings for at least two symptomatic cycles.

The Mini International Neuropsychiatric Interview (MINI) is a structured interview consisting of several modules developed to establish a diagnostic instrument that is easy to administer, inexpensive, highly sensitive, and specific to diagnose DSM-IV-TR psychiatric disorders[13,14]. Module U (MINI-U) is the corresponding module that categorically measures the presence or absence of symptoms to fulfill

diagnostic criteria for PMDD[15]. Prospective daily ratings have to be completed for at least two symptomatic cycles to confirm the diagnosis. Thus, they are the only way to measure severity and monitor symptoms over time[16]. However, completing daily ratings proved to be difficult in practice [17,18].

The Premenstrual Symptoms screening tool (PSST) is an instrument that includes all premenstrual symptoms and a measure of impairment as per DSM-IV-TR criteria. It also translates categorical DSM-IV-TR criteria into a dimensional rating scale to assess severity[16]. Thus, it is a useful diagnostic tool to capture moderate/severe PMS and PMDD diagnoses in symptomatic women who would benefit from treatment[19]. The Arabic version of PSST was already validated, where it showed good consistency and reliability (Cronbach's alpha = 0.92). The discriminant validity showed adequate specificity (95.6%) but low sensitivity (26.7%), indicating that PSST is a good screening tool to confirm the cases with true PMDD where treatment is possibly indicated. The positive and negative values (PPV and NPV) for PMDD were 85.2% and 58.3%, respectively. The construct validity was assessed using exploratory factor analysis, and the results showed that the original 19 items (14 questions on the symptoms and five on the interference with daily activities) of the PSST were grouped into five factors accounting for 66.73 % of the variance[20].

The MINI-U for diagnosis of PMDD relies mainly on the presence or absence of symptoms, including the impact on functioning. At the same time, PSST uses a dimensional scale to measure the severity of symptoms which ultimately is very important to determine the effects of symptoms on daily activities. Unfortunately, no studies compared the diagnostic categorical scales with dimensional measures of severity of PMDD symptoms. Such comparisons would enhance the accuracy of the psychometric measures of the combined approaches when diagnosing and monitoring patients with moderate/severe PMS and PMDD. Furthermore, the availability of valid cut-off scores from PSST tested through answers from MINI-U (DSM criteria) would give more confidence to diagnose PMDD based on the severity measures of PSST. This reassurance would facilitate the initiation of treatment for this group of patients instead of waiting two months, especially that the daily recording of symptoms has proven to be very difficult in practice[17,18]. Thus, the aims of this study were: (1) To compare the responses between the dichotomous MINI-U answers and the scores on the PSST items; and (2) To establish the cut-off scores on the dimensional PSST items by using the categorical MINI-U as a gold standard.

## MATERIALS AND METHODS

This cross-sectional study is part of a project to validate the Arabic version of the PSST[20]. This article reports a secondary analysis of the relationship between answers on the Arabic MINI-U with the corresponding items in the Arabic PSST (see Table 1).

### *Study setting and subjects*

The study took place in Doha, Qatar, a country experiencing rapid development and economic growth. As a result, the Qatari population includes many expatriate residents from different nationalities and ethnicities. However, the most stable populations are the Qatari and Arabs, representing respectively 15% and 13% of the population[21]. Arab women were recruited at two Primary Healthcare Centers between October 2013 and March 2014.

Participants were eligible to join the study if they were Arab females between 18 and 45 years old and with a regular menstrual cycle of 24 to 32 d. The following exclusion criteria were adopted to control other confounding conditions: women taking oral contraceptive pills, hormonal therapy, psychotropic medication, and suspected of being pregnant or in menopause. In addition, women with endometriosis, acute thyroid or pituitary disorders, or any other acute medical problem were ineligible to participate. Lastly, women with a history of drug and alcohol abuse or an active psychiatric disorder (other than PMDD), diagnosed in the previous six months, were excluded.

During the recruitment period, a total of 430 women were approached in primary healthcare centers to join the study. After an initial screening, 280 women were eligible for the study and agreed to learn more about the research project. However, only 194 women agreed to participate and were consented to join the study. Following consent, a further 15 participants were excluded from the study: 4 participants were pregnant, 4 elected to withdraw from the study, 4 participants spoke Arabic but were not originally from an Arab country, and 3 participants were excluded due to another possible psychiatric diagnosis as per the MINI screen. Therefore, the sample consisted of 179 female participants who completed all study procedures. This sample size was sufficient to detect the projected sensitivity or specificity of 85 percent and an estimated prevalence of severe PMS/PMDD of 20 percent, within a margin of error of 10 percent and a 95 percent confidence interval. This sample size was sufficient to detect the projected sensitivity or specificity of 85 percent and an estimated prevalence of severe PMS/PMDD of 20 percent, within a margin of error of 10 percent and a 95 percent confidence interval.

### *Research design*

This study is cross-sectional with no interventions, and all participants provided written consent before

**Table 1 Corresponding items between premenstrual symptoms screening tool and the Mini-premenstrual dysphoric disorder**

| Symptom | PSST | MINI-U |
|---|---|---|
| Anger/irritability | 1 | U3 - D |
| Anxiety/tension | 2 | U3 - B |
| Tearful/sensitive to rejection | 3 | U3 - C |
| Depressed mood /hopelessness | 4 | U3 - A |
| Decreased interest in work activities | 5 | U3 - E |
| Decreased interest in home activities | 6 | U3 - E |
| Decreased interest in social activities | 7 | U3 - E |
| Difficulty concentrating | 8 | U3 - F |
| Fatigue/lack of energy | 9 | U3 - G |
| Overeating/food cravings | 10 | U3 - H |
| Insomnia | 11 | U3 - I |
| Hypersomnia | 12 | U3 - I |
| Feeling overwhelmed or out of control | 13 | U3 - J |
| Physical symptoms | 14 | U3 - K |
| Symptoms interfered with: | | |
| Work efficiency/productivity | A | U2 |
| Relationship with co-workers | B | U2 |
| Relationship with family | C | U2 |
| Your social life activities | D | U2 |
| Home responsibilities | E | U2 |
| Most menstrual periods of last year are preceded by significant mood changes for almost one week | - | U1 |

PSST: Premenstrual Symptoms screening tool; MINI-U: The Mini International Neuropsychiatric Interview, Module U.

enrollment. The Institutional Review Boards of Hamad Medical Corporation and Weill Cornell Medicine in Doha, Qatar, approved this study. A licensed physician or nurse interviewed participants to confirm their eligibility. The psychiatrists then administered the Arabic Mini International Neuropsychiatric Interview Plus version 6 (MINI-Plus 6) to screen for any psychiatric disorders, including PMDD (MINI-U) as per DSM-IV-TR criteria[15]. An independent second rater, blinded to the results of the MINI, collected sociodemographic information, past medical and psychiatric history, smoking and exercise patterns, and administered the PSST. The independent raters were medical students or nurses who were formally trained to administer and rate the PSST. A good inter-rater agreement was established before the collection of data. A pilot sample (20 women) was assessed independently by more than two raters, and the interclass coefficient was 0.89.

### *Procedures*

Recruitment for this study commenced shortly after the introduction of DSM-5. However, no diagnostic instruments were available at the time to diagnose PMDD according to DSM-5 criteria; hence we used the MINI-U that followed DSM-IV-TR criteria. DSM-5 adopted the same criteria for the diagnosis of PMDD as DSM-IV-TR except for minor modifications. The only major shift is the recognition of PMDD as a distinct diagnostic entity in DSM-5[12], whereas it was classified as a Mood Disorder Not Otherwise Specified in DSM-IV-TR[22].

Module U in the MINI is a screening and diagnostic tool for PMDD. It is composed of 13 dichotomous questions (U1, U2, and U3-A to U3-K) (Table 1) with the possibility of answering "yes" or "no." The first two questions respectively assess mood changes before menstruation and if the subject experienced any difficulty at work or in usual activities and relationships during these periods. The last set of questions determines the presence of affective, behavioral, and physical symptoms using lettered questions U3-A to U3-K, as indicated in Table 1. A diagnosis of probable PMDD is reached if the first two questions U1 and U2, are answered positively together with at least one affective symptom from U3-A to U3-D and also four of the questions U3-A to U3-K were answered[14,22].

**Table 2 Sociodemographic characteristics**

| Variables | |
|---|---|
| Mean age (SD), yr | 32.12 (8.26) |
| Country born, *n* (%) | |
| Qatar | 111 (62.0) |
| Other | 68 (38.0) |
| Marital status, *n* (%) | |
| Married | 112 (62.6) |
| Never married | 55 (30.7) |
| Divorced/widowed | 12 (6.7) |
| Education level, *n* (%) | |
| Elementary or intermediate school | 11 (6.2) |
| Secondary or high school | 53 (29.9) |
| Vocational/associate degree | 55 (31.1) |
| University degree or postgraduate degree | 58 (32.7) |
| Employment status, *n* (%) | |
| Employed | 118 (66.6) |
| Housewife | 25 (14.1) |
| Jobseeker | 11 (6.2) |
| Student | 15 (8.5) |
| Retired | 2 (1.1) |
| Other | 6 (3.4) |
| Lifestyle, *n* (%) | |
| Current cigarettes smoker | 5 (2.8) |
| Current shisha smoker | 9 (5.1) |
| Regular exercise | 55 (30.7) |

SD: Standard deviation.

**Table 3 Clinical features of subjects**

| Medical Characteristics, *n* (%) | |
|---|---|
| PMS, according to PSST | 63 (35.2) |
| PMDD according to PSST | 25 (13.9) |
| PMDD according to MINI | 84 (46.7) |
| Previous diagnoses | |
| Psychiatric diagnosis | 6 (3.3) |
| Depression | 9 (5.0) |
| Chronic lung disease | 25 (13.9) |
| Hypertension | 7 (3.9) |
| Cardiac disease | 5 (2.8) |
| Arthritis | 20 (11.1) |
| Osteoporosis | 9 (5.0) |

| | |
|---|---|
| Kidney disease | 4 (2.2) |
| Diabetes | 10 (5.6) |
| Hypercholesterolemia | 20 (11.1) |
| Cancer | 2 (1.1) |
| Allergies | 52 (28.9) |

PMS: Premenstrual syndrome; PSST: Premenstrual Symptoms screening tool; PMDD: Premenstrual dysphoric disorder.

The PSST is composed of two sections representing the two domains as per DSM-IV-TR criteria for PMDD. The first section includes a list of 14 questions related to premenstrual symptoms, followed by the second section of 5 questions that measure the severity of interference of the symptoms on a woman's ability to function (Table 1). Responses are reported on a severity scale of "not at all," "mild," "moderate," or "severe," corresponding to a score of 1 to 4 in our study. The following criteria must be present for the diagnosis of PMDD: (1) At least one of the responses to questions 1-4 is severe; (2) In addition at least four of 1-14 questions are moderate to severe; and (3) At least one of A, B, C, D, E is severe. Also, the following criteria must be present for a diagnosis of moderate to severe PMS: (1) At least one of the responses to questions 1-4 is moderate to severe; (2) In addition at least four of 1-14 questions are moderate to severe; and (3) At least one of A, B, C, D, E is moderate to severe[16]. The original author[16] and McMaster University approved the translation of the PSST. The PSST was translated to Arabic using the repeated forward-backward procedure. All concerns were resolved by modifying the Arabic version of PSST until the original author approved the English back-translated version. Please refer to the study by Mahfoud *et al* for further details on the translation and validation procedures for the Arabic versions[20].

### Statistical analysis

All analyses were performed using IBM Statistical Package for Social Sciences (SPSS) for Mac version 24 [23]. The level of significance was set at 5%. Sociodemographic characteristics and clinical features were reported as means and standard deviations (SD) for continuous measures such as age and as frequency and percentage for categorical measures such as education level. To compare the scores on the PSST items by MINI-U responses (Yes *vs* No), we reported the median and interquartile range (IQR), and we used the Wilcoxon-Mann-Whitney test to determine if the PSST severity measures are valid to differentiate between those who answered Yes *vs* No on MINI-U. Bonferroni correction (an option in SPSS) was used to correct for the multiple comparisons. The comparisons were followed by receiver operating characteristics (ROC) analyses using the MINI-U answers as the gold standard to determine the cut-off scores on the PSST, in addition to their sensitivity and specificity measures. Finally, we used the highest Youden indices (J) to determine the best cut-off scores on each item in PSST and the corresponding sensitivity and specificity[24].

## RESULTS

### Sociodemographic and clinical characteristics

A total of 179 female participants completed all study procedures. The study sample had a mean age of 32.12 years (SD = 8.26). The majority of participants were born in Qatar (62.0%), married (62.6%), and employed (66.6%). Approximately 33% of participants had a university degree, and 31% practiced regular exercise. According to the PSST, 14% of participants had a PMDD diagnosis, and 35% had PMS. However, according to MINI-U, 49% of participants had a diagnosis of probable PMDD. A minority of participants had been diagnosed in the past with depression (5%) or other psychiatric illness (3.3%) (Tables 2 and 3).

### Frequency of symptoms as per MINI-U and PSST

According to the symptoms assessed by the PSST, the most common severe symptoms were anger or irritability (31.3%), physical symptoms (23%), and being tearful or sensitive to rejection (20.8%). The most common moderate symptoms reported by our participants were physical symptoms (36.5%), anger or irritability (34.6%), and fatigue or lack of energy (27.4%). The severity of these symptoms mainly affected their relationships with their family (moderate, 20.2% and severe 9%) and their work efficiency or productivity (moderate, 19.7% and severe 7.3%). The symptoms that our participants least experienced were feeling overwhelmed or out of control (57.4%), insomnia (58.4%), and difficulty concentrating (53.6%). According to the MINI-U, the most common symptoms were physical symptoms (86.7%), fatigue or lack of energy (74.4%), and anger or irritability (73.3%). The least reported symptoms were difficulty concentrating (31.7%), and feeling overwhelmed or out of control (36.7%) (Table 4).

**Table 4 Frequency of symptoms as per the Mini international neuropsychiatric interview, module U and premenstrual symptoms screening tool**

| | MINI-U (Yes) | Not at all | Mild | Moderate | Severe |
|---|---|---|---|---|---|
| PSST symptoms | *n* (%) | *n* (%) | *n* (%) | *n* (%) | *n* (%) |
| Anger/irritability | 132 (73.3) | 23 (12.8) | 38 (21.2) | 62 (34.6) | 56 (31.3) |
| Anxiety/tension | 98 (54.4) | 57 (32.0) | 46 (25.8) | 46 (25.8) | 29 (16.3) |
| Tearful/sensitive to rejection | 97 (53.9) | 83 (46.6) | 26 (14.6) | 32 (18.0) | 37 (20.8) |
| Depressed mood/hopelessness | 104 (57.8) | 78 (43.8) | 40 (22.5) | 35 (19.7) | 25 (14.0) |
| Decreased interest in work activities | 83 (46.1)(All three) | 65 (36.3) | 52 (29.1) | 41 (22.9) | 21 (11.7) |
| Decreased interest in home activities | | 53 (29.8) | 55 (30.9) | 44 (24.7) | 26 (14.6) |
| Decreased interest in social activities | | 79 (44.1) | 49 (27.4) | 30 (16.7) | 21 (11.7) |
| Difficulty concentrating | 57 (31.7) | 96 (53.6) | 53 (29.6) | 21 (11.7) | 9 (5.0) |
| Fatigue/lack of energy | 134 (74.4) | 47 (26.9) | 56 (32.0) | 48 (27.4) | 24 (13.7) |
| Overeating/food cravings | 98 (54.4) | 92 (51.7) | 27 (15.2) | 25 (14.0) | 34 (19.1) |
| Insomnia | 95 (52.8)(Both) | 104 (58.4) | 36 (20.2) | 21 (11.8) | 17 (9.6) |
| Hypersomnia (needing more sleep) | | 76 (42.7) | 39 (21.9) | 33 (18.5) | 30 (16.9) |
| Feeling overwhelmed or out of control | 66 (36.7) | 101 (57.4) | 22 (12.5) | 37 (21.0) | 16 (9.1) |
| Physical symptoms | 156 (86.7) | 16 (9.0) | 56 (31.5) | 65 (36.5) | 41 (23.0) |
| Symptoms interfered with: | | | | | |
| A - Work efficiency/productivity | 94 (52.2)(Altogether) | 85 (47.8) | 45 (25.3) | 35 (19.7) | 13 (7.3) |
| B - Relationship with co-workers | | 108 (61.4) | 41 (23.3) | 19 (10.8) | 8 (4.5) |
| C - Relationship with family | | 69 (38.8) | 57 (32.0) | 36 (20.2) | 16 (9.0) |
| D - Your social life activities | | 89 (50.0) | 49 (27.5) | 29 (16.3) | 11 (6.2) |
| E - Home responsibilities | | 89 (50.0) | 55 (30.9) | 23 (12.9) | 11 (6.2) |

PSST: Premenstrual Symptoms screening tool; MINI-U: The Mini international neuropsychiatric interview, module U.

### *Scores on PSST items by MINI-U dichotomous responses*

We used the Wilcoxon-Mann-Whitney test to assess if the ordinal scores on the PSST items are different between those who answered Yes vs. No on the MINI-U. Among the MINI-U dichotomous answers, all PSST ratings were significantly higher among participants who answered Yes ($P < 0.01$). Participants who answered "No" on the MINI-U had a median score of 1 (Not at all) for all the symptoms except for: (1) Anger or irritability; (2) Anxiety or tension; (3) Decreased interest in home activities; and (4) Physical symptoms where the median rating was 2 (mild). Participants who answered "Yes" had a median score from 1.5 (not at all to mild) to 3 (moderate). Out of the 14 symptoms assessed, nine had a median score of 3 (moderate), four symptoms had a median rating of 2 (mild), and one symptom had a median rating of 1.5 (not at all to mild) (Table 5). The median rating of the interference of these symptoms on work or productivity, relationship with family, relationship with co-workers, relationship with family, on social life activities, and home responsibilities was 2 (mild) (Table 5).

### *Cut-off scores on PSST items by MINI-U dichotomous responses*

ROC analyses showed that all areas under the curves were significant with the cut-off scores (and the corresponding sensitivity and specificity values using the Youden index) on the corresponding PSST items using the MINI-U questions as the gold standard. The cut-off scores for the items on anger or irritability, anxiety or tension, decreased interest in work or home activities, overeating, hypersomnia, and physical symptoms were 2.5 on the corresponding PSST items. The remaining items had a corresponding cut-off score of 1.5. The balanced sensitivity and specificity values for all the corresponding cut-off scores were adequate, ranging from 0.50 to 0.83 (Table 6).

**Table 5 Scores on Premenstrual Symptoms screening tool items by the Mini international neuropsychiatric interview, module U dichotomous responses**

| | MINI-U | | | | |
|---|---|---|---|---|---|
| | No | | Yes | | |
| PSST | Median | IQR | Median | IQR | *P* value[1] |
| Anger/irritability | 2 | 2 | 3 | 1 | < 0.001 |
| Anxiety/tension | 2 | 1 | 3 | 2 | < 0.001 |
| Tearful/sensitive to rejection | 1 | 0 | 3 | 2 | < 0.001 |
| Depressed mood/hopelessness | 1 | 1 | 2 | 2 | < 0.001 |
| Decreased interest in work activities | 1 | 1 | 3 | 1 | < 0.001 |
| Decreased interest in home activities | 2 | 1 | 3 | 1 | < 0.001 |
| Decreased interest in social activities | 1 | 1 | 3 | 1 | < 0.001 |
| Difficulty concentrating | 1 | 1 | 2 | 1 | < 0.001 |
| Fatigue/lack of energy | 1 | 1 | 2 | 1 | < 0.001 |
| Overeating/food cravings | 1 | 1 | 2 | 2 | < 0.001 |
| Insomnia | 1 | 1 | 1.5 | 2 | 0.004 |
| Hypersomnia (needing more sleep) | 1 | 1 | 3 | 3 | < 0.001 |
| Feeling overwhelmed or out of control | 1 | 1 | 3 | 2 | < 0.001 |
| Physical symptoms | 2 | 2 | 3 | 2 | < 0.001 |
| **Symptoms interfered with:** | | | | | |
| Work efficiency/productivity | 1 | 1 | 2 | 2 | < 0.001 |
| Relationship with co-workers | 1 | 0 | 2 | 2 | < 0.001 |
| Relationship with family | 1 | 1 | 2 | 1 | < 0.001 |
| Your social life activities | 1 | 1 | 2 | 2 | < 0.001 |
| Home responsibilities | 1 | 1 | 2 | 2 | < 0.001 |

[1]Wilcoxon-Mann-Whitney test was used to compare the PSST severity scores.
PSST: Premenstrual Symptoms screening tool; MINI-U: The Mini international neuropsychiatric interview, module U.

## DISCUSSION

The first aim of this study was to compare the responses between the dichotomous MINI-U answers and the scores on the PSST items. Our study showed a discrepancy in the prevalence of PMDD diagnosis between the MINI criteria (46.7%) and PSST criteria (13.9%). The discrepancy between the two could be attributed to the dichotomous nature of MINI-U questions that assess only the presence or absence of symptoms. At the same time, those in PSST focus more on the severity of symptoms to establish PMDD diagnosis. The high prevalence of PMDD is also higher than that reported worldwide (5%-8%)[9]. Other countries such as Iran[25], Jordan[8], India[26], and Brazil[27] reported a similarly high prevalence of PMDD suggesting that there are ethnic variations in the prevalence of PMDD. It also highlights the need for an efficient and valid diagnosis of PMDD to recognize these patients and initiate treatment as early as needed. In comparing the participants who answered positively vs. negatively on the MINI questions, we found that all PSST symptom ratings were significantly higher among those who answered positively. Furthermore, most symptoms on PSST had a median rating of "moderate," indicating clinical significance (Table 5). The PSST severity measures might allow distinguishing which symptoms are clinically significant. Previous studies reported that 20% of women have subthreshold PMDD and can benefit from further monitoring and treatment[28]. The most commonly reported moderate/severe symptoms for our population were anger/irritability, anxiety, and physical symptoms (Table 4). These were also common complaints among Jordanian and Emirati women[29,30]. One of the major concerns with the MINI and PSST is the requirement to have daily ratings of symptoms for a minimum of two cycles per DSM criteria to confirm the cyclical presence of symptoms for moderate/severe PMS and PMDD. Keeping a daily diary before initiating treatment may cause resistance for women to seek treatment. In research settings, an epidemiological study found that 30% of

**Table 6 The cut-off scores of the Premenstrual Symptoms screening tool items with the corresponding the Mini international neuropsychiatric interview, module U items**

| Symptom | PSST | MINI-U | AUC | 95%CI | *J* | Cut-off | Sensitivity | Specificity |
|---|---|---|---|---|---|---|---|---|
| Anger/irritability | 1 | U3 - D | 0.804[a] | (0.73-0.88) | 0.48 | 2.5 | 0.780 | 0.696 |
| Anxiety/tension | 2 | U3 - B | 0.740[a] | (0.67-0.81) | 0.41 | 2.5 | 0.608 | 0.800 |
| Tearful/sensitive to rejection | 3 | U3 - C | 0.835[a] | (0.77-0.90) | 0.63 | 1.5 | 0.814 | 0.812 |
| Depressed mood/hopelessness | 4 | U3 - A | 0.735[a] | (0.66-0.81) | 0.38 | 1.5 | 0.718 | 0.658 |
| Decreased interest in work activities | 5 | U3 - E | 0.752[a] | (0.68-0.83) | 0.45 | 2.5 | 0.590 | 0.860 |
| Decreased interest in home activities | 6 | U3 - E | 0.743[a] | (0.67-0.82) | 0.39 | 2.5 | 0.602 | 0.783 |
| Decreased interest in social activities | 7 | U3 - E | 0.768[a] | (0.70-0.84) | 0.43 | 1.5 | 0.795 | 0.634 |
| Difficulty concentrating | 8 | U3 - F | 0.806[a] | (0.74-0.88) | 0.55 | 1.5 | 0.842 | 0.706 |
| Fatigue/lack of energy | 9 | U3 - G | 0.728[a] | (0.64-0.81) | 0.36 | 1.5 | 0.823 | 0.535 |
| Overeating/food cravings | 10 | U3 - H | 0.700[a] | (0.62-0.78) | 0.36 | 2.5 | 0.495 | 0.861 |
| Insomnia | 11 | U3 - I | 0.614[a] | (0.530.70) | 0.17 | 1.5 | 0.500 | 0.671 |
| Hypersomnia | 12 | U3 - I | 0.732[a] | (0.66 0.81) | 0.39 | 2.5 | 0.537 | 0.852 |
| Feeling overwhelmed or out of control | 13 | U3 - J | 0.714[a] | (0.63 0.80) | 0.39 | 1.5 | 0.667 | 0.722 |
| Physical symptoms | 14 | U3 - K | 0.723[a] | (0.60 0.85) | 0.33 | 2.5 | 0.643 | 0.682 |
| Symptoms interfered with: | | | | | | | | |
| Work efficiency/productivity | A | U2 | 0.696[a] | (0.62 0.77) | 0.32 | 1.5 | 0.677 | 0.639 |
| Relationship with co-workers | B | U2 | 0.674[a] | (0.60 0.75) | 0.30 | 1.5 | 0.527 | 0.771 |
| Relationship with family | C | U2 | 0.686[a] | (0.61 0.76) | 0.30 | 1.5 | 0.753 | 0.542 |
| Your social life activities | D | U2 | 0.729[a] | (0.65 0.80) | 0.38 | 1.5 | 0.677 | 0.699 |
| Home responsibilities | E | U2 | 0.724[a] | (0.65 0.80) | 0.40 | 1.5 | 0.688 | 0.711 |

[a]$P <$ 0.01. PSST: Premenstrual Symptoms screening tool; MINI-U: The mini international neuropsychiatric interview, module U; AUC: Area under the curve; CI: Confidence interval; *J*: Youden index.

women refused to participate in a study because they did not want to fill daily ratings, and the latter is usually associated with a high dropout rate[31]. Our results suggest that the severity measures of PSST can capture the PMDD cases with significantly severe symptoms who would benefit from treatment initiation.

The study's second aim was to establish the cut-off scores on the dimensional PSST items by using the categorical MINI-U as a gold standard. All the cut-off scores showed significant differentiation and ranged from 1.5 to 2.5 with adequate sensitivity and specificity (Table 6). The MINI-U is a diagnostic instrument, whereas the PSST is a diagnostic and dimensional instrument[16]. However, both scales are based on DSM-IV-TR criteria for diagnosing PMDD and thus are assessing the same symptoms (Table 1). The concordance between these instruments showed that most symptoms corresponding to a "Yes" in the MINI-U had a cut-off score of 1.5 or a rating of at least 'mild' on the corresponding PSST items. On the other hand, affirmative answers to anger/irritability, anxiety/tension, decreased interest in home activities, and physical symptoms in the MINI-U had a corresponding cut-off score of 2.5 or at least 'moderate' symptoms in the PSST, meaning that the latter captured mainly the moderate to severe cases. However, the challenge is distinguishing which women need treatment from those whose symptoms are not clinically relevant[31]. Moderate/severe PMS and PMDD are poorly diagnosed and mostly untreated conditions[32]. Furthermore, women with moderate/severe PMS symptoms have a higher rate of work absences and increased medical expenses[1]. Therefore, these women can benefit from a prompt referral and timely treatment[1].

### *Limitations*

This study has many strengths, like its design and applying the validated Arabic dimensional PSST with the Arabic equivalent categorical scale MINI. Still, a few limitations can affect the results of our study. The sample size is probably not large enough to cover the representation of the multiple Arabic countries and the potential variability in PMDD presentation in different countries. It is worth adding

that the cut-off scores on PSST are based on retrospective symptoms, and DSM requires daily records for two consecutive months to confirm the diagnosis. Thus, further validation of the significant and relevant cut-off scores on PSST against future prospective recordings is necessary to confirm the utility of using the dimensional PSST in the early treatment of PMDD as defined in the categorical DSM.

## CONCLUSION

In conclusion, our results showed a significant relationship between the Arabic MINI-U and PSST responses, providing evidence to support that the PSST is a practical measure for PMDD. Participants who answered positively on the MINI had significantly higher ratings and relevant cut-off scores on the corresponding PSST items. Thus, this study reassures that the MINI-U provides an adequate assessment for the probable diagnosis of PMDD. Furthermore, the severity measures of the PSST can recognize patients with moderate/severe PMS and PMDD who would benefit from immediate treatment. Thus, there is a clear advantage of using PSST to early identify these patients with moderate/severe symptoms who clinically cannot wait for the daily measures of MINI-U. In addition, these patients with significant mood symptoms can benefit from treatment with selective serotonin inhibitors[33]. However, prospective studies are still needed to confirm the validation scores and comply with the DSM criteria.

## ARTICLE HIGHLIGHTS

### *Research background*

Premenstrual symptoms (PMS) are very common in child-bearing women and include several physical and emotional symptoms lasting for one week before menstruation. The premenstrual dysphoric disorder consists of the symptoms of PMS and, more significant depressive symptoms that affect the functioning of women. Some instruments measure the severity of these symptoms (Premenstrual Symptoms screening tool, PSST). Others assess the presence or absence of these symptoms and are usually used to diagnose if the premenstrual symptoms recur over two consecutive cycles (Mini international neuropsychiatric interview, module U).

### *Research motivation*

As required by the Diagnostic and Statistical Manual of Mental Disorders, the daily recording of symptoms over two months is challenging to comply with regularly. Further, women might not receive the proper treatment if no adequate assessment or diagnosis is made. We believe that using appropriate scales like PSST that measures the severity of symptoms can be validated as tools for diagnosis.

### *Research objectives*

To compare the scores of both PSST and MINI module U. We also calculated the cut-off scores on the dimensional PSST items by using the categorical MINI-U as a gold standard.

### *Research methods*

We recruited eligible women from primary care centers. Two blinded raters independently administered the dichotomous Arabic MINI module U and the Arabic PSST to women. We compared the scores on the PSST items by MINI-U responses (Yes *vs* No) using the median and interquartile range. To determine the cut-off scores on the PSST (including sensitivity and specificity measures), we used the receiver operating characteristics analyses using the MINI-U answers as the gold standard.

### *Research results*

According to the MINI-U, the most common symptoms were physical symptoms (86.7%), fatigue or lack of energy (74.4%), and anger or irritability (73.3%). Out of the 14 symptoms assessed, nine had a median score of 3 (moderate), four symptoms had a median rating of 2 (mild), and one symptom had a median rating of 1.5 (not at all to mild). Among the MINI-U dichotomous answers, all PSST ratings were significantly higher among participants who answered Yes ($P < 0.01$). The cut-off scores for the items on anger or irritability, anxiety or tension, decreased interest in work or home activities, overeating, hypersomnia, and physical symptoms were 2.5 on the corresponding PSST items. The balanced sensitivity and specificity values for all the corresponding cut-off scores were adequate, ranging from 0.50 to 0.83.

### *Research conclusions*

Our results suggest that the severity measures of PSST can capture the PMDD cases with significantly severe symptoms who would benefit from treatment initiation. Furthermore, women with moderate/severe PMS symptoms have a higher rate of work absences and increased medical expenses.

These women can, therefore, benefit from a prompt referral and timely treatment.

### *Research perspectives*

Larger prospective studies are needed to further validate the utility of cut-off scores from PSST to confirm the diagnosis and justify the initiation of treatment.

## FOOTNOTES

**Author contributions:** Hassen A and Rana E designed the research; Rifka C performed the research; Ziyad M and Rifka C analyzed the data; all authors wrote the paper.

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SYSTEMATIC REVIEWS

# Lidocaine in fibromyalgia: A systematic review

Jozélio Freire de Carvalho, Thelma L Skare

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## Abstract

***BACKGROUND***

Fibromyalgia (FM) patients are treated with antidepressants, and in most cases, these drugs lose efficacy or present side effects. Intravenous lidocaine (IL) is an anesthetic drug used in some FM trials.

***AIM***

To systematically review the safety and efficacy of IL in FM patients.

***METHODS***

To systematically search PubMed for articles in English, Spanish, and Japanese with English Abstracts on FM and lidocaine between 1966 and February 2021. This study was registered at PROSPERO.

***RESULTS***

We found only ten articles published in this field, with a total of 461 patients. Females predominated varying from 95% to 100% in the studies. Age varied from 40.9 to 55 years old. Disease duration varied from 1 mo to 6.4 years. Lidocaine dose varied from 2 to 7.5 mg/kg *via* intravenous infusion. Follow-up period varied from 65.7 to 90 days. Regarding outcomes, most studies used the visual analogue scale (VAS) for pain; before short-term lidocaine administration, VAS was between 6.1 and 8.1 and after treatment was between 1.7 and 4.5 mm. Concerning long term lidocaine, VAS varied from 30% to 35.4% after lidocaine infusion. Side effects were observed in 0% to 39.6% of cases, they were usually mild or moderate.

***CONCLUSION***

This study demonstrates the short-term effectiveness and safety of intravenous lidocaine in FM patients. However, more studies, including long-term follow-up, are still needed.

**Key Words:** Lidocaine; Fibromyalgia; Pain; Intravenous infusions

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**Core Tip:** This is the first systematic review on lidocaine studies in fibromyalgia patients.

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## INTRODUCTION

Fibromyalgia is a painful chronic disease characterized by diffuse pain for over three months with associated co-morbidities including headaches, irritable bowel syndrome, anxiety, depression, and others[1]. FM is the third most common musculoskeletal condition and may affect 0.4% (in Greece) to 8.8% (in Turkey) of a population and has a global prevalence of 2.7%[1].

Standard treatments for FM include physical exercise, psychological intervention, and medication. Regarding pharmacological treatment, antidepressants are the leading choice for this condition. However, adverse effects can lead to dropouts, which range from 9% to 23% in short-term studies and from 11.4% to 27.2% in long-term studies[2]. Lack of efficacy is also observed during FM treatment, which can reach between 50 to 60% of cases[2]. Thus, different treatment modalities are desired for unresponsive patients or who present side effects with drugs.

Lidocaine is a topical anesthetic drug used worldwide to treat specific clinical situations such as systemic sclerosis. It is used intravenously in chronic pain and arrhythmia cases[3]. Intravenous lidocaine has been shown to control the symptoms of diabetic neuropathy[4]; there are some studies on intravenous lidocaine use in FM patients with controversial results[5-14].

In light of this, the objective of this article is to perform a systematic review of the safety and efficacy of lidocaine in FM patients.

## MATERIALS AND METHODS

### *Literature review*

We performed a systematic search of articles published in PubMed/MEDLINE, Web of Sciences, LILACS, and Scielo from 1966 to November 2020 using the following MeSH entry terms: "lidocaine" and "fibromyalgia." We used equivalent strategies in other databases. All related articles are based on "lidocaine" and "fibromyalgia" without language restriction. The reference lists in the selected articles were analyzed to identify other publications. Initially, two authors (JFC and TLS) performed the literature search and independently selected the study abstracts. In the second stage, the same reviewers independently read the full-text articles selected by abstracts. Disagreements arising in consensus meetings were resolved by a third reviewer. The authors followed PRISMA guidelines[15]. We designed a standardized form to extract the following information from relevant articles regarding authors, year of publication, number of patients studied, demographic data, disease duration, study follow-up, pre- and post-intervention VAS, lidocaine posology, and outcomes (Figure 1).

This study was registered at PROSPERO under number CRD42021227210.

## RESULTS

Demographic and clinical data and pre- and post-lidocaine treatment VAS scores for FM patients are shown in Table 1.

There were only ten articles published in this field, with a total of 461 patients. Females predominated varying from 95% to 100% in the studies. Age varied from 40.9 to 55 years old. Disease duration varied from 1 month to 6.4 years.

Lidocaine IV dosage varied from 2 to 7.5 mg/kg. Follow-up was from 65.7 to 90 d.

Regarding outcome, most studies evaluated VAS. Before lidocaine, VAS ranged from 6.1 to 8.1 and after treatment, from 1.7 to 4.5 mm in the short term. Concerning long term after lidocaine infusion,

**Table 1 Clinical and demographic characteristics of the xx studies on fibromyalgia and lidocaine treatment**

| Ref. | Study design | N, female sex | Age, yr | Disease duration | Follow-up | Lidocaine prescription | Concomitant treatment | Short-term VAS, | | Long-term VAS | | Other outcomes | Adverse effects |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Pre and post lidocaine | Pre and post, placebo | Pre and post lidocaine | Pre and post placebo | | |
| Verd *et al* [5] | Prospective | 48, 95.8% | Median age-55 | | 90 d | Escalating dose from 2 mg/kg to 5 mg/kg per day, IV during 10 d | - | Pain measured by BPI 29.5→26.5 | - | In 90 d BPI = 30.0 | - | Improved in MOS and EXPEC; Short-lived improvement in BPI, BFI and depression | Nausea ($n$ = 8); Worsening pain ($n$ = 1) |
| Wilderman *et al*[6] | Retrospective | 74, 9.7% | 51.3 | NA | 5 mg/kg→65.7 d; 7.5 mg/kg→86.3 d; 7.5 mg/kg→90.9 d | Escalating doses: 5 mg/kg, 7.5 mg/kg and 7.5 mg/kg + magnesium 2.5 g IV | None | Δ VAS in 5 mg/kg = 2.41; Δ VAS in 7.5 mg/kg = 3.15; Δ VAS in 7.5 mg/kg + Mg = 3.62 | NA | Pain relief:In 30.2% of 5 mg/kg-median time 62 d; In 39.1% in 7.5 mg/kg; median time 62.5 d; 40.6% in 7.5 mg/kg + Mg; Median time 64 d | NA | - | 24/222 infusions (10.8%)-dizziness, nausea, hyperglycemia, headache, lip numbness and mild dyspnea |
| Kim *et al*[7] | Retrospective | 55, 94.5% | NA | NA | After 1 infusion | 5 mg/kg (maximum of 500 mg), IV | | 7.6 ± 1.6→5.8 ± 2.2 | - | - | - | Caucasians and non-smokers had better results | NA |
| Albertoni Giraldes *et al*[8] | RCT | 42, 95% | 42.4 ± 9.4 | 6.0 ± 5.05 | 8 wk | 250 mg/wk – for 4 wk IV; *vs* saline | Amitriptyline 25 mg, paracetamol if needed. | 6 ± 1.3 3.9 ± 2.8 | 7.2 ± 1.3→2.7 ± 2.9 | - | - | IL-1, IL-6 and IL-8 values did not change | Placebo equal to lidocaine: nausea, vomiting, drowsiness, paresthesia, constipation and dry mouth |
| Staud *et al* [9] | Prospective | 62, 100% | 45.8 ± 14.8 | NA | Data collection just after injections | Group 1 ($n$ = 20)- 4 injections of 50 mg lidocaine, IM; Group 2 ($n$ = 21)- 2 injections 50 mg lidocaine + 2 saline, IM; Group 3 ($n$ = 21)- four | Muscle relaxing drugs and/or tricyclics were allowed | VAS declined 38% | - | - | - | Mechanical and heat hyperalgesia decreased significantly | NA |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | injections saline, IM | | | | | | | |
| Vlainich *et al*[10] | RCT, | 30, 100% | Group 1-40.9 ± 11.6; Group 2-44.7 ± 10.5 | NA | 4 wk | Group 1- (*n* = 15) lidocaine 240 mg/wk for 4 wk, IV; Group 2- (*n* = 15) Saline | Amitriptyline 25 mg | 7.6 ± 0.8→4.1 ± 2.3 | 7.0 ± 1.2→4.0 ± 2.1 | - | - | norepinephrine and serotonin levels unchanged dopamine levels ↑ week 4 in the placebo group. | No |
| Schafranski *et al*[11] | Prospective | 23, 95.6% | NA | NA | 4 wk | Sequential lidocaine infusions from 2-5 mg/kg for 5 d, IV | None | 8.1 ± 1.7→6.8 ± 2.4 | - | Mean VAS of pain = 7.1 ± 2.3 in 30 d | - | FIQ, HAQ improved significantly | No |
| Raphael *et al*[12] | Prospective and retrospective | 106, 92% prospective arm (to see side effects); 50, 82%retrospective arm (to see efficacy) | 51.4 prospective arm; 50.2 retrospective arm | Prospective arm- NA; 6.6 ± 4.5 yr in retrospective arm | N/A | Started at 5 mg/kg-100 mg and increased to 5 mg/kg+150 mg (maximum 550 mg) IV; For 6 consecutive days | None | Only in the retrospective arm 9→5; Mean duration pain relief 11.5 ± 6.5 wk | - | | - | No improvement in work status; improvement in several sociological and psychological dimensions | Only in the prospective arm; 2 major effects: (pulmonary edema and supra ventricular tachycardia); 42/106 minor effects: Hypotension (*n* = 17); Headache (*n* = 8), hypertension (*n* = 5), tachycardia (*n* = 1), arrhythmia (*n* = 1), pulmonary edema (*n* = 1) |
| Bennett *et al*[13] | Prospective | 10, 100% | 44.2 | 16 (1-192) mo | 4 wk | Started at 250 mg/d and increased by 50 mg/d to 500 mg/dfor 6 d, IV | Haloperidol 0.5 mg/d + clomipramine 10 mg/d or Amitriptyline 10 mg/d | 8 4.1 | - | Mean VAS of pain = 5.4 in 30 d | - | Stopped analgesics. Mood improved but not statistically significant | None |
| Sörensen *et al*[14] | Double blind, placebo-controlled | 11, 100% | 41, (range 21-59) | 5 yr (range 2-11) | 1 wk after 2nd injection | 2 injections, IV; 5 mg/kg *vs* saline | Paracetamol or dextropropoxyphene | (VAS from 0-100); 6.1→4.5 | (VAS from 0-100); 51→51 | - | - | Tender points, muscle endurance and muscle strength (except dorsiflexors of wrist) unchanged | NA |

VAS: Visual analogue scale from 0-10 except Sörensen *et al*[14], which was 0-100; Δ VAS: Difference in VAS pre and post infusions; IV: Intravenous; IM: Intra muscular; NA: Not available; RCT: Randomized controlled trial; IL: Interleukin, MOS: Medical outcome sleep scale; EXPEC: Patient'S expectations; BPI: Brief pain inventory; BFI: Big five inventory.

VAS varied 30% to 35.4%.

Side effects were observed in 0% to 39.6% of cases, usually with mild or moderate repercussions. These effects were dizziness, nausea, vomiting, hyperglycemia, headache, lip numbness, mild dyspnea, paresthesia, dry mouth, and increasing pain. The significant effects were pulmonary edema and supraventricular tachycardia.

## DISCUSSION

This is the first study to systematically review the therapeutic effects of intravenous lidocaine in FM patients.

The study strengths are: (1) The inclusion of studies with patients with international criteria for FM; and (2) The exclusion of case reports, case series, and observational studies. Prospective studies present a higher degree of evidence.

The analgesic properties of intravenous lidocaine were first observed in 1962 when used to treat postoperative pain[16]. Thirty-six years later, a study demonstrated that lidocaine might be used to treat postoperative pain, reducing hospital stay in patients who had undergone radical prostatectomy[17]. Lidocaine acts by blocking sodium channels on the neuronal membrane that may play a role in the pathogenesis of inflammatory and neuropathic pain[6].

Previous studies have demonstrated the efficacy of intravenous lidocaine in FM patients. Bennett and Tai[13] described improvement in pain scores were maintained even 30 d after lidocaine infusion. Furthermore, Sörensen *et al*[14] evaluating 12 fibromyalgia patients showed improvements in VAS pain scores during and 15 min after a 30 min infusion of lidocaine in a double-blind placebo-controlled crossover study. Three of the 12 patients who responded to lidocaine had their pain reduced. The authors reported no statistically significant differences between FM and placebo groups in tender points, muscle strength (hip flexors and handgrip), and muscle endurance. However, the lidocaine group exhibited a significant improvement in wrist dorsiflexion muscle strength[14].

Raphael *et al*[12] conducted a prospective study of the adverse effects of lidocaine in 106 patients with FM and a retrospective questionnaire study of the efficacy of this drug in 50 FM patients. Serial infusions of IV lidocaine were administered for six consecutive days at 5 mg/kg minus 100 mg and increased by 50 mg/d to 5 mg/kg plus 150 mg over 6 h, with the maximum allowable dose being 550 mg. Pain was measured using an 11-point VAS, in a 4-point verbal scale of pain severity (none, mild, moderate, severe), and according to the average number of hours per day in pain. Pain relief was also measured on the 11-point VAS along with pain relief duration. The psychological and social impact of the pain were evaluated by measuring depression, coping ability, dependency, and several other items using the 11-point scales. Pain score and relief interruption, pain mean duration, and verbal assessment were significantly reduced following lidocaine treatment. Mean pain relief duration was 11.5 ± 6.5 wk, ranging from 0 to 36 wk. Psychosocial measurements significantly improved after lidocaine treatment in all parameters except work status.

Schafranski *et al*[11], in an open trial, showed similar results after five sequential lidocaine infusions with rising dosages (2-5 mg/kg, days 1-5). The Fibromyalgia Impact Questionnaire (FIQ) and a VAS for pain were applied before lidocaine infusion and immediately, and 30 d after the 5th infusion. They observed significant reductions in FIQ and VAS after the fifth infusion which were maintained after 30 d [11].

Finally, some limitations were observed in our study. For instance, no comparison between lidocaine and classical antidepressants used in FM were available in literature. The number of participants was low and future studies should include large patient samples with more long-term follow-up; this would enable a better understanding of the course of this therapeutic modality in FM.

## CONCLUSION

The present study was a systematic review of all prospective studies that evaluated the role of lidocaine in FM patients and found excellent short-term efficacy. Future studies using larger FM patient samples and long-term follow-up which address the safety and efficacy of lidocaine are needed.

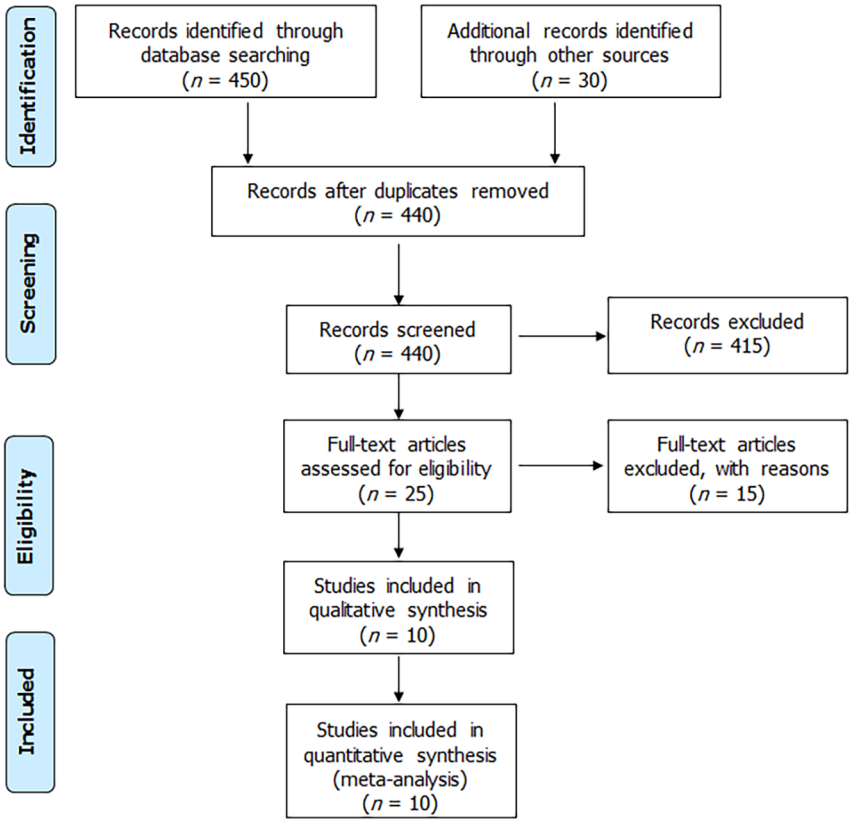


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**Figure 1 Flow chart of included articles, following PRISMA.**

## ARTICLE HIGHLIGHTS

### *Research background*

Lidocaine is used to treat fibromyalgia patients.

### *Research motivation*

As there are some articles that evaluated the role of lidocaine as therapy of fibromyalgia patients, the authors thought it is important to systematically review this literature.

### *Research objectives*

The authors had the objective to perform the first systematic review on lidocaine in the treatment of fibromyalgia.

### *Research methods*

Systematic review based on PRISMA guidelines and PROSPERO register.

### *Research results*

Most studies showed reduction of pains measured by visual analogic scale after lidocaine infusion.

### *Research conclusions*

This systematic review showed that lidocaine is effective and safe for fibromyalgia treatment, mainly in short-term.

### *Research perspectives*

Future studies with large number of participants to evaluate the safety and efficacy of lidocaine for fibromyalgia is needed, as short and long-term studies.

## FOOTNOTES

**Author contributions:** de Carvalho JF and Skare TL contributed equally to this work; de Carvalho JF and Skare TL designed the research study, performed the research, and analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

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SYSTEMATIC REVIEWS

# Psychiatric comorbidities in cancer survivors across tumor subtypes: A systematic review

Anne Bach, Klara Knauer, Johanna Graf, Norbert Schäffeler, Andreas Stengel

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**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**
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## Abstract

***BACKGROUND***

Psychiatric disorders are common but underdiagnosed in cancer survivors. Research suggests that tumor type has an effect on the prevalence of clinically relevant depression, anxiety, comorbid anxiety-depression and posttraumatic stress disorder (PTSD).

***AIM***

To identify studies that examined the prevalence of clinically relevant levels of depression, anxiety, comorbid anxiety-depression and PTSD for patients with one or more tumor sites and compare those prevalences between cancer subtypes.

***METHODS***

Four databases (PubMed, PsycInfo, PubPsych and the Cochrane Database) were searched and resulted in a total of 2387 articles to be screened. To be included, a study must have investigated cancer-free and posttreatment survivors using tools to assess clinically relevant levels of the listed psychiatric comorbidities. All articles were screened by two authors with a third author reviewing debated articles.

***RESULTS***

Twenty-six studies on ten different tumor types fulfilled all inclusion criteria and were included in the review. The studies showed heterogeneity regarding the study characteristics, number of participants, time since diagnosis, and assessment tools. Generally, all four comorbidities show higher prevalences in cancer survivors than the general population. Brain tumor survivors were reported to

have a relatively high prevalence of both depression and anxiety. Studies with melanoma survivors reported high prevalences of all four psychiatric comorbidities. Regarding comorbidities, a wide range in prevalence existed across the tumor types. Within one cancer site, the prevalence also varied considerably among the studies.

*CONCLUSION*

Psychiatric comorbidities are more frequent in cancer survivors than in the general population, as reflected by the prevalence of depression, anxiety, comorbid anxiety-depression and PTSD across all tumor subtypes. Developing generalized screening tools that examine psychological distress in cancer survivors up to at least ten years after diagnosis could help to understand and address the psychological burden of cancer survivors.

**Key Words:** Cancer survivor; Cancer type; Prevalence; Psychiatric disorder; Psychiatric comorbidity; Survivorship; Tumor site

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**Core Tip:** Psychiatric disorders are a common comorbidity in cancer survivors, even years after diagnosis. Studies have found that tumor type has an effect on the prevalence of clinically relevant depression, anxiety, comorbid anxiety-depression and posttraumatic stress disorder. This systematic review compared the prevalence of these four psychiatric disorders in cancer survivors among tumor types. The results suggest that there are variations in the prevalence of all comorbidities across and within cancer types. A future direction should be the development of a screening tool to regularly assess cancer survivors' psychological distress for at least 10 years after the initial disease.

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## INTRODUCTION

Before, during and after treatment, patients with cancer are exposed to a variety of factors (physical constraints, fatigue, financial problems, *etc*.) that may impact their psychological state. This is in addition to the possible trauma caused by a cancer diagnosis and treatment. With the number of cancer survivors growing due to longevity and medical progress, the evaluation of long-term psychological aftereffects and their predispositions becomes more relevant[1]. Over the last decades, the examination of psychiatric comorbidities in cancer survivors has become a growing research field. According to several studies, tumor type can have an impact on the risk of developing a psychiatric comorbidity[2-4]. This paper aimed to review the literature about psychiatric comorbidities in cancer survivors across cancer types to identify their commonalities and differences.

Cancer survivors experience several challenges even after finishing acute treatment. Chemotherapy, radiation and other kinds of treatment often bear the risk of long-term side effects. This can lead to clinically relevant levels of psychological distress, and survivors have an increased risk for mood alterations compared to the general population[5]. The simultaneous presence of two or more clinical conditions is referred to as comorbidity, which requires special attention when strategizing treatment [6]. Some of the most frequent psychiatric comorbidities in long-term cancer survivors are depression, generalized anxiety disorder and posttraumatic stress disorder (PTSD), all of which can depend on the type of cancer.

The response to each cancer type calls for unique treatment plans and exposes survivors to a particular risk of recurrence. Therefore, cancer survivors of different tumor types are exposed to several burdens, not only during the acute treatment phase but also after the treatment is finished. Studies have found that patients with specific tumor types may experience more psychological distress than others. Muzzatti *et al*[4] found that survivors with a history of breast cancer showed more anxiety and depression than those with a history of lymphoma or genitourinary tumors. Similarly, Götze *et al*[3] described that breast and skin cancer survivors showed the highest levels of anxiety and depression, whereas prostate cancer survivors showed the lowest levels. Another study showed significant variation in psychological distress across cancer types[7]. In contrast, there are studies that did not find a significant difference between cancer sites and clinical levels of depression, anxiety or PTSD[8-10]. In these studies, other patient characteristics, such as sex and age at the time of diagnosis, were proposed

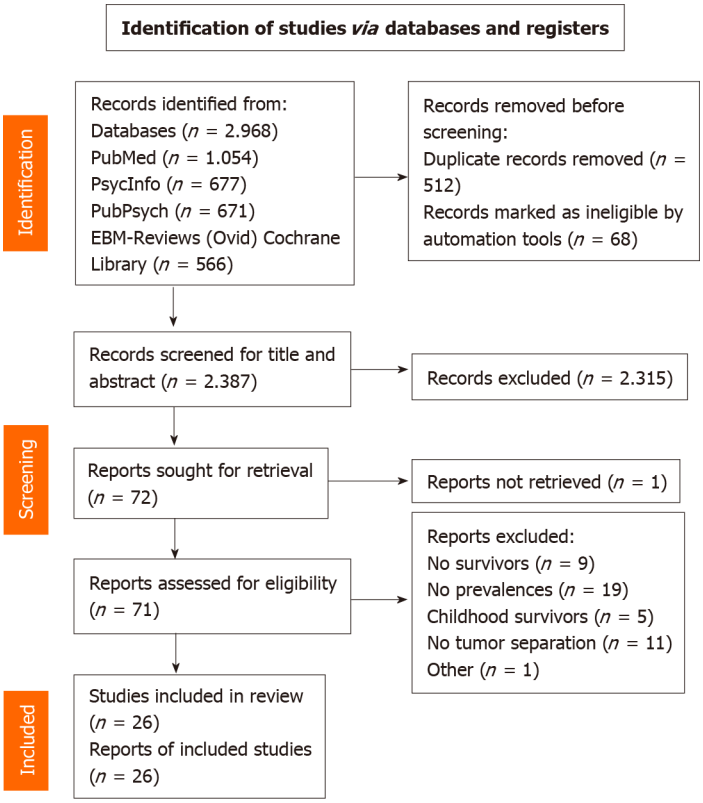


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**Figure 1 PRISMA flow diagram.**

to have an influence on the prevalence of psychiatric comorbidities. Another argument by Deimling *et al* [10] is that with increasing time since diagnosis, cancer type and treatment-specific stressors are removed, and psychological stressors become more homogeneous.

Identifying whether there are specific influences on distress depending on a survivor's cancer site could help to identify necessary adjustments to survivorship programs and medical follow-up treatments. To do so, it is important to know which patient characteristics and tumor entities have an effect on psychological distress and further effects on the development of psychiatric disorders due to disease-related burdens. Additionally, this could provide more insight into cancer site-specific psychological guidelines for the psychological care of cancer survivors after treatment.

Therefore, this systematic review aimed to identify studies that examined clinically relevant levels of depression, anxiety, comorbid anxiety-depression and PTSD across tumor types.

## MATERIALS AND METHODS

The systematic review was conducted according to the PRISMA statement criteria[11]. The review protocol is registered in PROSPERO, the International Prospective Register of Systematic Reviews (CRD42021253430).

### *Literature search*

We searched four databases between February 8th and 19th, 2021: PubMed, PsycInfo, PubPsyc and the Cochrane Database. Articles published in any year were included. Our search terms were as follows: [(Psychiatric OR psych*) AND (comorbidity OR disorder)] AND (cancer OR tumor OR neoplasm OR oncolog*) AND (survivor OR survivorship OR long-term).

### *Inclusion and exclusion criteria*

The eligibility criteria were based on the five PICOS dimensions. P: The participants were cancer survivors with the following characteristics: Adults at the time of cancer diagnosis and not in (primary) acute treatment. Survivors were defined according to the World Health Organization (WHO) as patients who have had cancer and are, following treatment, now cured of the disease[12]. This implies that all studies where all/a subpopulation(s) of survivors were still in active treatment were excluded. I: Studies with any kind of intervention were excluded. C: A control group was not necessary. O: The outcomes

**Table 1 Assessment tools**

| Assessment tool | | Used in study (No. of occurrences) |
|---|---|---|
| EDS | Edinburgh Depression Scale | 1 (1) |
| HADS | Hospital Anxiety and Depression Scale | 1, 3, 5, 6, 8, 9, 15, 19, 21, 22, 23 (11) |
| SCID | Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders | 1, 22, 23, 26 (4) |
| PTSD-(inventory) scale | Self-report scale based on DSM-III-R criteria with items corresponding to PTSD symptoms | 2, 16 (2) |
| SCL-90 | Symptom Checklist 90 | 2 (1) |
| PCL-C/PCL-S | Posttraumatic Stress Disorder Checklist-Civilian Version/Posttraumatic Stress Disorder Checklist-Specific | 3, 5, 13, 14 (4) |
| UW-QOL | The University of Washington Quality of Life instrument - brief, self-administered questionnaire to analyze rates of depression | 11 (1) |
| IES | Impact of Event Scale | 7, 20 (2) |
| BDI | Beck Depression Inventory | 4, 18, 20 (3) |
| PHQ-9 | Patient Health Questionaire-9 | 10, 17 (2) |
| GAD-7 | Generalized Anxiety Disorder 7 | 10, 17, 24 (3) |
| GDS-SF/GDS-15 | Geriatric Depression Scale-Short Form/Geriatric Depression Scale-15 | 12, 25 (2) |
| DASS | Depression-Anxiety-Stress-Scale | 24 (1) |
| MINI | Mini International Neuropsychiatric Interview | 4 (1) |
| SAI | Spielberger State Anxiety Inventory | 20 (1) |

EDS: Edinburgh Depression Scale; HADS: Hospital Anxiety and Depression Scale; SCID: Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders; PTSD: Posttraumatic stress disorder; SCL-90: Symptom Checklist 90; PCL-C: Posttraumatic Stress Disorder Checklist-Civilian Version; PCL-S: Posttraumatic Stress Disorder Checklist-Specific; UW-QOL: The University of Washington Quality of Life; IES: Impact of Event Scale; BDI: Beck Depression Inventory; PHQ-9: Patient Health Questionaire-9; GAD-7: Generalized Anxiety Disorder 7; GDS-SF: Geriatric Depression Scale-Short Form; GDS-15: Geriatric Depression Scale-15; DASS: Depression-Anxiety-Stress-Scale; MINI: Mini International Neuropsychiatric Interview; SAI: Spielberger State Anxiety Inventory.

were the prevalence of psychiatric comorbidities, more specifically, the clinically relevant levels of depression, anxiety, comorbid anxiety-depression and PTSD. S: The study designs included in the review were observational, cross-sectional and longitudinal designs.

The exclusion criteria were: (1) Studies with no cancer patients; (2) Studies with no survivors; (3) Studies with no psychiatric/psychological assessment; (4) Studies with a patient group < 18 years old at the time of cancer diagnosis; (5) Studies not in accordance with the predefined study designs; (6) Articles with missing information or not written in English; (7) Studies including an intervention; and (8) Studies that did not separate the different tumor types.

### Data extraction

After removing duplicates, the articles were screened for relevant titles by two authors. For papers where the first two authors did not agree, a third author decided. The remaining articles were screened for abstracts again by the two authors, with the third author reviewing debated articles. Then, all three authors came to a consensus. One author screened the remaining articles for the full texts. The studies that were considered eligible were included in the review, and the relevant data were extracted.

### Quality assessment

The quality of each study was assessed according to the study design, participant selection and method of patient evaluation[13].

### Statistical analyses

The included papers showed high heterogeneity in the number of participants, time since diagnosis and assessment tools used (Table 1). Furthermore, there were a limited number of articles per tumor site ( *e.g.*, 4 articles related to breast cancer *vs* 1 article related to brain tumors). Therefore, this review aimed to perform a descriptive data analysis rather than a meta-analysis. The descriptive analysis focused on the prevalence of the mentioned psychiatric comorbidities in cancer survivors with a focus on similarities and differences among the tumor types.

## RESULTS

The literature search of the four scientific databases provided 2968 results. After removing duplicates, 2387 articles were left for screening. Title screening reduced the number to 102 articles, which was further filtered to 72 for full text screening. Finally, 26 studies were considered relevant to the topic and were included in the review (Figure 1). Table 2 shows the extracted data (reference, tumor type, study population, time since diagnosis, screening tools to assess psychiatric comorbidity, prevalence of comorbidity and potential bias) of the included articles. Several studies had to be excluded after full text screening because of missing reports of the prevalence in percentages and instead reporting the mean results of the questionnaires.

### *Quality assessment*

The studies included in the review were assessed for possible risks of bias. The natures of the study designs analyzed here are known to favor certain biases[13]. Table 2 shows the reviewed studies with the study design (self-report questionnaire, personal interview, *etc.*) and possible type of bias. All studies used a cross-sectional design, with only some having a matched comparison group, and therefore bear the risk of selection bias. Two qualities of the reviewed studies presented a risk of response bias: Cancer survivors with specific (psychological or physical) symptoms may be more likely to respond to a study invitation, and most studies were self-report questionnaires. Performance bias may have occurred in the studies that used personal interviews. Exclusion bias may be present in the studies where a specific group of participants was not included in the results (Table 2).

### *Study characteristics*

There was a wide range of study characteristics within the included articles. We extracted data for ten different broad tumor sites. For each site, the number of articles included were as follows: Breast (5), gynecological/cervical (2), hematological (4), testicular (5), prostate (1), head and neck (3), stomach (1), melanoma (3), brain (1) and lung (1). The number of participants ranged between 17[13] and 1260[14]. The studies were published between 2002 and 2020. The age of the participants ranged between 18 and 93 years. Seven studies included only women, and six studies included only men because of the specificity of the cancer site. The remaining thirteen studies included both men and women.

### *Assessment tools*

In the studies, psychiatric comorbidities were evaluated with a variety of assessment tools, including questionnaires and personal interviews. Table 1 shows all the assessment tools and their abbreviations with regard to the study they were used in. The most common questionnaire was the Hospital Anxiety and Depression Scale (HADS), which was used in eleven of the 26 studies. The assessment tool used in each article is shown in the summary of the findings (Table 2). Most articles included the screening of more than one psychiatric comorbidity (*e.g.*, depression and anxiety), while others focused on only one.

### *Time since diagnosis*

The studies included in this review ranged from 144 d[16] to more than 11 years since diagnosis[17-19]. Some studies found an effect of time since cancer diagnosis and psychological distress. According to Mols *et al*[20], depressive symptoms declined over time, whereas anxiety scores stayed stable across a 4-year period.

### *Depression*

Twenty-one of the 26 articles assessed the prevalence of depression in cancer survivors, including all ten tumor sites. Table 3 shows the studies organized by tumor site and the extracted percentages for clinical levels of depression. Comparing the prevalences among tumor types, a high variability, between 7.9% and 48%, can be seen. Whereas most tumor sites showed a range between 8% and 22% for clinical levels of depression, four cancer subtypes showed a much higher prevalence (above 40%): Head and neck[21], stomach[22], melanoma[14] and brain[23] cancer.

Furthermore, within one cancer site, the prevalence varied. For testicular cancer survivors, the prevalence of depression was relatively stable across the four studies included in the review (between 7.9%[19] and 9.7%[15,24]). For patients with breast cancer, the prevalence varied between 8%[16] and 22%[25].

### *Anxiety*

Fifteen of the eligible studies assessed the prevalence of clinical levels of anxiety in cancer survivors. Among these, six different tumor types were assessed: Breast, testicular, hematological, cervical/gynecological, melanoma and brain tumors (Table 3). The percentage for anxiety ranged between 3.5% and 58.5%. A study on brain tumor survivors showed a high prevalence of clinical levels of anxiety of almost 60%[23], whereas across the other tumor sites, the prevalence ranged between 6.1%[19] and 20.2%[15].

**Table 2 Summary of findings for included articles, organized by tumor subtypes**

| No. | Ref./country | Tumor site | Number of participants/gender/age in years | Time since diagnosis | Parameters and tests (related to psychiatric disorders) | Key results: Prevalence of clinical levels of: Anxiety/depression/PTSD/comorbid anxiety-depression | Possible bias |
|---|---|---|---|---|---|---|---|
| 1 | Alexander *et al* [26], 2010; United Kingdom | Breast | *n* = 200; 100% female; mean: 58.1, range: 29-89 | Mean time since last treatment: 10.1 mo | EDS; HADS; SCID | Depression: 9%; anxiety: 3.5%; comorbid: 1.5 | Selection bias; response bias |
| 2 | Amir *et al*[28], 2002; Israel | Breast | *n* = 39; 100% female; range: 37-60 | ≥ 5 yr | PTSD-scale; SCL-90 | Full PTSD: 18%; partial PTSD: 56% (additional) | Selection bias; response bias |
| 3 | Mehnert *et al* [25], 2008; Germany | Breast | *n* = 1083; 100% female; mean: 61.8, range: 31-81 | Average: 47 mo | HADS; PCL-C | Moderate to high anxiety: 38% (high: 20.1%); moderate to high depression: 22% (high: 11.3%); PTSD: 12% | Selection bias; response bias |
| 4 | Qiu *et al*[42], 2012; China | Breast | *n* = 505; 100% female; mean: 52.02 | Mean time after surgery: 17.6 mo | BDI; MINI | Depression: 20.59% | Response bias; performance bias |
| 5 | Vazquez *et al* [16], 2020; United States | Breast | *n* = 700; 100% female; median: 37, range: 17-40 | 144 d: HADS; 30 mo (PCL-S) | PCL-S; HADS | PTSS: 6.3%; depression: 8%; anxiety: 23% | Selection bias; response bias |
| 6 | Dahl *et al*[24], 2005; Norway | Testicular | *n* = 1408; 100% male; mean: 44.6 | Mean: 11.3 yr | HADS | Anxiety: 19.2%; depression: 9.7%; comorbid: 6.8% | Selection bias; response bias |
| 7 | Dahl *et al*[17], 2016; Norway | Testicular | *n* = 1418; 100% male; mean: 44.6 | Mean: 11 yr | IES | Full PTSD: 4.5%; partial PTSD: 6.4%; probable PTSD (combination of the 2): 10.9% | Selection bias; response bias |
| 8 | Fosså *et al*[43], 2003; Norway | Testicular | *n* = 791; 100% male; median: 44, range: 23-75 | Median: 12 yr | HADS | Anxiety: 19%; depression: 9% | Selection bias; response bias |
| 9 | Thorsen *et al* [15], 2005; Norway | Testicular | *n* = 1260; 100% male; median: 42 | Mean: 11 years | HADS | Anxiety: 20.2%; depression 9.7% | Selection bias; response bias |
| 10 | Vehling *et al*[19], 2016; Germany | Testicular | *n* = 164; 100% male; mean: 44.4 | Mean: 11.6 yr | GAD-7; PHQ-9 | Anxiety: 6.1%; depression: 7.9% | Selection bias; response bias |
| 11 | Chen *et al*[33], 2013; United States | Head and neck | *n* = 211; 58% male; median: 57, range: 21-93 | Disease free at least 1 yr | UW-QOL | Depression: 17% | Response bias |
| 12 | Lambert *et al* [21], 2005; United States | Head and neck | *n* = 694; 84.6% male; mean: 61.8 | At least 6 mo | GDS-SF | Depression: 44.1% | Selection bias; response bias |
| 13 | Moschopoulou *et al*[44], 2018; United Kingdom | Head and neck | *n* = 93; 58.1% male; mean: 66 | Mean: 6 yr | PCL-C | PTSD: 11.8% | Selection bias; response bias |
| 14 | Black *et al*[45], 2005; United Kingdom | Hodgkin's lymphoma non-Hodgkin's lymphoma; acute leukemia | *n* = 36; 50% female; adults | ? - complete remission | PCL-C | PTSD: 17% | Selection bias; response bias |
| 15 | Daniëls *et al*[46], | Hodgkin's | *n* = 180; 55% male; | Mean: 4.6 | HADS | Anxiety: 23%; depression: 18% | Selection |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2014; The Netherlands | lymphoma | median: 46 | yr | | | bias; response bias |
| 16 | Geffen *et al*[35], 2003; Israel | Hodgkin's lymphoma; non-Hodgkin's lymphoma | HD: *n* = 8; nHL: *n* = 36; 46% male; median: 51; range: 27-80 | At least 2 yr after treatment completion | PTSD-inventory scale | Full or partial PTSD: 32%; full PTSD: 18%; partial PTSD: 13% (additional) | Selection bias; response bias |
| 17 | Kuba *et al*[47], 2019; Germany | Hematological | *n* = 922; 57% male; range: 18-85 | 3 yr | PHQ-9; GAD-7 | Anxiety: 9%; depression: 15% | Selection bias; response bias |
| 18 | Han *et al*[22], 2013; Korea | Stomach | *n* = 391; 72.9% male; mean: 54.5 | Mean (time since operation): 27.4 mo | BDI | Depression: 43.9% | Selection bias; response bias |
| 19 | Hanprasertpong *et al*[48], 2017; Thailand | Cervical | *n* = 700; 100% female; mean: 53 | Completion of treatment 3 mo - 10 yr before study | HADS | Anxiety: 20.46%; depression: 9.44% | Selection bias; response bias |
| 20 | Urbaniec *et al* [18], 2011; Australia | Gynecological | *n* = 45; 100% female; mean: 56.7, range: 23-83 | Mean: 4 yr; range: 0.9-11.6 yr | BDI-II; SAI; IES-Revised | Anxiety: 28.9%; depression: 20%; probable PTSD: 15.6 | Selection bias; response bias |
| 21 | Krajewski *et al* [49], 2018; Germany | Melanoma | *n* = 561; 51.2% male; mean: 62.1 | 4 yr | HADS | Anxiety: 10.2%; depression: 10.3% | Selection bias; response bias |
| 22 | Rogiers *et al*[27], 2020; Belgium | Melanoma | *n* =25; 28% male; median: 58, range: 28-86 | Median: 30 mo | SCID-IV-CV; HADS | HADS: Anxiety: 32%; depression: 20%; comorbid: 12%. SCID: PTSD: 48%; depression: 0% | Selection bias; response bias; performance bias |
| 23 | Rogiers *et al*[14], 2020; Belgium | Melanoma | *n* = 17; 29% male; median: 57, range: 33-86 | Median: 5.6 yr | SCID-IV-CV; HADS | HADS: Anxiety: 35%; depression: 41%; comorbid: 30%. Interview: PTSD: 35%; depression: 11.76% | Selection bias; response bias; performance bias |
| 24 | Nicol *et al*[23], 2019; Australia | Brain | *n* = 65; 35.4% male; mean: 49.97; range: 22-75 | Mean: 5.29 yr | DASS-Depression; GAD-7 | Anxiety: 58.5%; depression: 43.1% | Selection bias; response bias |
| 25 | Recklitis *et al* [50], 2014; United States | Prostate | *n* = 693; 100% male; mean: 67.1 | Range: 3-8 yr | GDS-15 | Depression: 15% | Selection bias; response bias |
| 26 | Uchitomi *et al* [51], 2003; Japan | Lung | *n* = 212; 60.4% male; mean: 62.1, range: 22-83 | 1 mo after surgery | SCID, Revised; POMS scale | Depression: 8% | Selection bias; performance bias |

EDS: Edinburgh Depression Scale; HADS: Hospital Anxiety and Depression Scale; SCID: Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders; POMS: Profiles of Mood States; GDS-15: Geriatric Depression Scale-15; GAD-7: Generalized Anxiety Disorder 7; SCID-IV-CV: Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Clinical Version; BDI: Beck Depression Inventory; SAI: Spielberger State Anxiety Inventory; IES: Impact of Event Scale; PHQ-9: Patient Health Questionaire-9; PTSD: Posttraumatic stress disorder; UW-QOL: The University of Washington Quality of Life; GDS-SF: Geriatric Depression Scale-Short Form; PCL-C: Posttraumatic Stress Disorder Checklist-Civilian Version; MINI: Mini International Neuropsychiatric Interview; PCL-S: Posttraumatic Stress Disorder Checklist-Specific.

### *Comorbid anxiety-depression*

Only four of the 26 articles assessed the prevalence of comorbid anxiety-depression in cancer survivors (Table 3). The included tumor types were breast, testicular and melanoma (2 studies). The two studies assessing the prevalence in melanoma patients showed a prevalence of comorbid anxiety-depression in up to 40%[14] of survivors. The smallest prevalence was found in breast cancer survivors, with a study indicating a prevalence of comorbid anxiety-depression of 1.5%[26].

**Table 3 Prevalence of psychiatric comorbidities in % sorted by tumor site**

| No | Tumor site | Key result in % | | | | Ref. |
|---|---|---|---|---|---|---|
| | | Depression | Anxiety | Comorbid anxiety-depression | PTSD | |
| 1 | Breast | 9 | 3.5 | 1.5 | - | Alexander *et al*[26], 2010 |
| 2 | | - | - | - | 18 | Amir *et al*[28], 2002 |
| 3 | | 22 | 38 | - | 12 | Mehnert *et al*[25], 2008 |
| 4 | | 20.6 | - | - | - | Qiu *et al*[42], 2012 |
| 5 | | 8 | 23 | - | 6.3 | Vazquez *et al*[16], 2020 |
| 6 | Testicular | 9.7 | 19.2 | 6.8 | - | Dahl *et al*[24], 2005 |
| 7 | | - | - | - | 4.5 | Dahl *et al*[17], 2016 |
| 8 | | 9 | 19 | - | - | Fosså *et al*[43], 2003 |
| 9 | | 9.7 | 20.2 | - | - | Thorsen *et al*[15], 2005 |
| 10 | | 7.9 | 6.2 | - | - | Vehling *et al*[19], 2016 |
| 11 | Head and neck | 17 | - | - | - | Chen *et al*[33], 2013 |
| 12 | | 44.1 | - | -- | - | Lambert *et al*[21], 2005 |
| 13 | | - | - | | 11.8 | Moschopoulou *et al*[44], 2018 |
| 14 | Hematological | - | - | - | 17 | Black *et al*[45], 2005 |
| 15 | | 18 | 23 | - | - | Daniels *et al*[21], 1976 |
| 16 | | - | - | - | 18 | Geffen *et al*[35], 2003 |
| 17 | | 15 | 9 | - | - | Kuba *et al*[47], 2019 |
| 18 | Stomach | 43.9 | - | - | - | Han *et al*[22], 2013 |
| 19 | Cervical, gynecological | 9.4 | 20.5 | - | - | Hanprasertpong *et al*[48], 2017 |
| 20 | | 20 | 28.9 | - | 15.6 | Urbaniec *et al*[18], 2011 |
| 21 | Melanoma | 10.3 | 10.2 | - | - | Krajewski *et al*[49], 2018 |
| 22 | | 20 | 32 | 12 | 48 | Rogiers *et al*[27], 2020 |
| 23 | | 41 | 35 | 30 | 35 | Rogiers *et al*[14], 2020 |
| 24 | Brain | 43.1 | 58.5 | - | - | Nicol *et al*[23], 2019 |
| 25 | Prostate | 15 | - | - | - | Recklitis *et al*[50], 2014 |
| 26 | Lung | 8 | - | - | - | Uchitomi *et al*[51], 2003 |

PTSD: Posttraumatic stress disorder.

### *PTSD*

Ten studies assessed PTSD in cancer survivors across 6 different tumor types. Whereas testicular cancer survivors showed a comparably low level of full PTSD with a prevalence of 4.5%[17], the two studies including melanoma patients showed numbers as high as 48%[14,27]. For breast cancer survivors, the prevalence ranged from 6.3%[16] to 18%[28].

## DISCUSSION

This systematic review aimed to describe differences and commonalities between psychiatric comorbidities in cancer survivors across ten tumor types. Twenty-six studies that matched all the inclusion criteria and provided the prevalence of at least one of the four psychiatric comorbidities as a percentage were included.

Studies on psychological distress in cancer survivors found that there are risk factors for developing clinical levels of mood disorders. A systematic review on the prevalence of depression in breast cancer survivors reported several factors associated with depression: Fatigue, low income or poor financial status, low education level and younger age[29]. A review with testicular cancer survivors found that

poorer psychological health was related to living alone, being unemployed or having a low socio-economic status and experiencing worse symptoms/side effects[30].

We observed differences across the studies in the prevalence of psychiatric comorbidities after a cancer diagnosis, even when patients were no longer in treatment and there was no sign of disease recurrence. It was not clear whether these differences were partly caused by the type of cancer. Other factors, such as the time since diagnosis, participant demographics, and the assessment tool, may have similarly influenced the prevalence of clinical levels of depression, anxiety, and PTSD. Andrykowski *et al*[31] found a wide range of reported anxiety and depression levels in cancer survivors, which was due to challenges in identifying the rate of psychological distress in cancer survivors. One of the difficulties is the variation in detecting a psychiatric disorder due to the range of screening tools and criteria. The studies in this review used a variety of assessment tools. Furthermore, the studies demonstrated a wide range of sample sizes and participant demographics, including the risk factors mentioned above. The country of origin has similarly been shown to have an effect on cancer survivors' psychological distress. For example, a comparison between Hong Kong Chinese and German Caucasian women with breast cancer showed that greater unmet psychological needs were detected in Germany[32].

### Depression

Our results show a higher prevalence of depression in cancer survivors than in the general population. Whereas some of the studies reported prevalences in the normal range, more than half of the prevalences were 15% or higher. Furthermore, one longitudinal study[33] found that the prevalence of depression did not differ significantly over the course of five years for head and neck cancer survivors. A comparison of cancer types regarding depression showed consistently lower levels of depression in testicular cancer survivors than in breast cancer survivors, where the prevalence varied from 8% to 22%. Patients with several tumor entities, namely, head and neck, stomach, melanoma and brain tumors, demonstrate higher levels of depression, between 41% and almost 50%, indicating the need for special support for these groups of cancer survivors.

### Anxiety

Anxiety scores were reported by 15 studies and showed a very wide range of prevalences from 3.5% to almost 60%. Moreover, our review showed that anxiety prevalence was higher than the prevalence of clinical levels of depression. Similarly, among United States adults, data on anxiety disorders shows a higher prevalence than the prevalence of depression[34]. The highest prevalences of anxiety were seen in breast, melanoma and brain tumor survivors, although one study on breast cancer survivors reported a prevalence as low as 3.5%. The study by Nicol *et al*[23] with brain tumor survivors reported an especially high number of survivors showing clinically relevant levels of anxiety, with a prevalence of 58.5%.

### Comorbid anxiety-depression

Comorbid anxiety-depression was assessed in only four of the 26 included studies. A useful comparison among cancer types is therefore difficult. In contrast to the two studies on breast and testicular cancer survivors that reported a prevalence of 1.5% and 6.8%, respectively, the prevalences in two studies with melanoma survivors were higher (up to 40%)[14,27]. For all three of the previously mentioned psychiatric comorbidities, melanoma survivors seemed to show relatively high prevalences, which might indicate a distinctive demand for psychological support for this survivor group.

### PTSD

Ten studies examined posttraumatic stress syndrome in cancer survivors. Geffen *et al*[35] compared survivors who either had Hodgkin's disease or non-Hodgkin's lymphoma with a matched control group that had experienced at least one traumatic life event. They did not find significant differences between the survivors and control group in the occurrence of posttraumatic stress symptoms, suggesting that a cancer diagnosis might have the same impact as experiencing a traumatic event. Again, studies on melanoma cancer survivors showed a particularly high prevalence of PTSD (35% and 48%), which was assessed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Clinical Version, at a median time of 30 mo and 5.6 years after the diagnosis, respectively[14,27]. Another study investigated the occurrence of PTSD in testicular cancer survivors 11 and 19 years after diagnosis and found that the prevalence of clinically relevant PTSD symptomatology was reduced by more than half at the latter time point[17].

### Limitations

This review contains some limitations, with the most obvious being the limited number of studies per cancer site. Since we employed stringent inclusion and exclusion criteria, many studies were not included in the review. It was important to include only cancer survivors based on the WHO definition, meaning that the survivors were not going through acute treatment. This exclusion criterion was chosen to ensure that the prognosis and side effects of the treatment were not likely to influence the results of a psychiatric assessment. Several studies included a noteworthy number of survivors who still received

some kind of treatment, from radiotherapy to immunotherapy[3,36]. This limitation is likely influenced by the lack of a unique definition of cancer survivorship[37], which may have complicated the literature search.

Some studies have already investigated psychiatric comorbidities across different cancer types[4,9]. These studies did not include the separate prevalences per tumor type in their papers and therefore could not be reported in this review. Several studies reported the mean results on the questionnaires; however, the prevalence of clinical levels of depression, anxiety or PTSD could not be extracted. This review focused on four types of psychiatric comorbidities in cancer survivors, which represent the most common mental health disorders. Less common psychiatric comorbidities, such as acute psychosis, are likely present in cancer survivors (although at very low prevalence) but were beyond the scope of this review. Future work should address these.

We explored the extracted data with a focus on differences among cancer types. The studies that were reviewed displayed a high heterogeneity in key study characteristics (*e.g.*, the number of participants, time since diagnosis, assessment tools), which may have had a significant influence on the results and was not considered in our review. The various screening tools possibly measure psychological distress and clinical relevance in a way that cannot be easily compared[31]. A systematic review on the HADS indicated that the assessment tool might underestimate true levels of anxiety and depressive symptoms because it does not include somatic symptoms[38]. This may have impacted the generalizability of the HADS-based results.

### Future directions

The increased prevalence of clinical levels of psychological distress for cancer survivors remains an issue to be adequately addressed. Whereas many survivorship programs are being developed, the specific needs of cancer survivors depending on their own personal experiences have not yet been widely explored. Beutel *et al*[39] suggest general screening even 10 years after diagnosis, which would show the objective and subjective needs of each cancer survivor. Götze *et al*[40] supported this recommendation following their examination of emotional distress in cancer survivors. They compared a group of survivors five years after diagnosis with a group 10 years post-diagnosis and found no significant difference in emotional distress between the groups. However, a significant difference between tumor entities was detected, with breast and skin cancer survivors showing the highest levels of anxiety and depression and prostate cancer survivors showing the lowest levels. Furthermore, Kypriotakis *et al*[41] compared long-term cancer survivors of different tumor sites at four different time points. They found that cancer stage at the time of diagnosis was a significant predictor of initial depressive symptoms. Therefore, a future direction could be the development of screening tools to repeatedly measure cancer survivors' psychological distress up to 10 years after the last acute treatment phase. According to Beutel *et al*[39], such screening would include survivors who are below the threshold of a mental disorder but still have difficulties adjusting to being a cancer survivor.

## CONCLUSION

The articles included in this review showed high heterogeneity in several study characteristics (the number of participants, time since diagnosis, assessment tools, *etc.*) and showed that psychological distress in survivors is dependent on multiple factors. We aimed to describe the differences among tumor types, which were limited by missing data and/or the lack of a clear definition for survivorship. More research is needed that evaluates the specific psychological needs of cancer survivors and how to address them in survivor programs. Future research should have a clear definition of cancer survivorship and take participant characteristics such as the tumor subtype, the time since diagnosis and demographics into account. Furthermore, our results strongly suggest future guidelines for psychiatric and distress screenings for at least ten years after a cancer diagnosis, even when there is no sign of recurrence.

## ARTICLE HIGHLIGHTS

### Research background

Psychiatric disorders are common but underdiagnosed in cancer survivors. Research suggests that tumor type has an effect on the prevalence of clinically relevant depression, anxiety, comorbid anxiety-depression and posttraumatic stress disorder (PTSD) symptoms.

### Research motivation

Detecting differences in the prevalence of four common mental disorders that can occur as a comorbidity in cancer survivors might lead to a better understanding of cancer survivors' psychological distress. This might help to address the psychological concerns of cancer survivors more effectively.

### *Research objectives*

The aim of this review was to identify studies in which clinically relevant levels of common mental disorders in cancer survivors were examined. The prevalence rates were compared among different cancer types.

### *Research methods*

Four databases were searched for studies that investigated cancer-free, posttreatment survivors with screening tools that assess clinically relevant levels of four common mental disorders. Two authors screened all articles, with a third author reviewing debated articles.

### *Research results*

Twenty-six studies were included in the article and indicated the prevalence of one or more of the four mental disorders. Ten different tumor types were examined in the included papers. Generally, all four comorbidities show higher prevalences in cancer survivors than in the general population. The studies showed heterogeneity regarding the study characteristics, number of participants, time since diagnosis, and assessment tools. Each comorbid disorder had a variable prevalence across tumor subtypes. Within one cancer site, the prevalence also varied considerably among the studies.

### *Research conclusions*

Psychiatric comorbidities are high in cancer survivors relative to the general population, as reflected by the prevalences of depression, anxiety, comorbid anxiety-depression and PTSD across all tumor types. This enhanced distress is clinically relevant even years after a cancer diagnosis. The lack of a concise definition of cancer survivorship likely contributes to the high heterogeneity among studies focusing on cancer survivors' psychological distress, which might hinder significant comparisons among studies.

### *Research perspectives*

Developing generalized screening tools that examine psychological distress in cancer survivors for at least ten years after diagnosis could help to understand and address the psychological burdens of the survivors.


## FOOTNOTES


**Author contributions:** Bach A wrote the paper; Bach A, Knauer K and Graf J screened the literature; Graf J and Stengel A planned and supervised the project and thoroughly revised the paper; Schäffeler N thoroughly revised the paper.

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META-ANALYSIS

# Effects of mindfulness-based intervention programs on sleep among people with common mental disorders: A systematic review and meta-analysis

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## Abstract

### *BACKGROUND*

Sleep problems are particularly prevalent in people with depression or anxiety disorder. Although mindfulness has been suggested as an important component in alleviating insomnia, no comprehensive review and meta-analysis has been conducted to evaluate the effects of different mindfulness-based intervention (MBI) programs on sleep among people with depression or anxiety disorder.

### *AIM*

To compare the effects of different MBI programs on sleep among people with depression or anxiety disorder.

### *METHODS*

Related publications in Embase, Medline, PubMed and PsycINFO databases were systematically searched from January 2010 to June 2020 for randomised controlled trials. Data were synthesized using a random-effects or a fixed-effects model to analyse the effects of various MBI programs on sleep problems among people with depression or anxiety disorder. The fixed-effects model was used when heterogeneity was negligible, and the random-effects model was used when heterogeneity was significant to calculate the standardised mean differences (SMDs) and 95% confidence intervals (CIs).

### *RESULTS*

We identified 397 articles, of which 10 randomised controlled trials, involving a total of 541 participants, were included in the meta-analysis. Studies of internet mindfulness meditation intervention (IMMI), mindfulness meditation (MM), mindfulness-based cognitive therapy (MBCT), mindfulness-based stress reduction

(MBSR) and mindfulness-based touch therapy (MBTT) met the inclusion criteria. The greatest effect sizes are reported in favour of MBTT, with SMDs of -1.138 (95%CI: -1.937 to -0.340; $P$ = 0.005), followed by -1.003 (95%CI: -1.645 to -0.360; $P$ = 0.002) for MBCT. SMDs of -0.618 (95%CI: -0.980 to -0.257; $P$ = 0.001) and -0.551 (95%CI: -0.842 to -0.260; $P$ < 0.0001) were reported for IMMI and MBSR in the pooling trials, respectively. Significant effects on sleep problem improvement are shown in all reviewed MBI programs, except MM, for which the effect size was shown to be non-significant.

***CONCLUSION***

All MBI programs (MBTT, MBCT, IMMI and MBSR), except MM, are effective options to improve sleep problems among people with depression or anxiety disorder.

**Key Words:** Mindfulness-based intervention programs; Common mental disorders; Sleep; Systematic review; Meta-analysis

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**Core Tip:** This meta-analysis provides evidence as to whether various kinds of mindfulness-based intervention programs can help improve sleep problems among people with common mental disorders. Our study indicated that integrative forms of mindfulness-based intervention programs (including mindfulness-based touch therapy, mindfulness-based cognitive therapy, internet mindfulness meditation intervention, and mindfulness-based stress reduction) have shown promising results. However, using mindfulness meditation solely should lead to insignificant effects.

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## INTRODUCTION

Depression and anxiety disorder, also known as common mental disorders, are conditions that critically affect people's emotions, energy and ability to function. Approximately 1 in 5 adults were identified as meeting criteria for a common mental disorder over the past 12 mo, with the lifetime prevalence reported as 20.8% and 28.8% for depression and anxiety disorder, respectively[1,2]. Both depression and anxiety disorder are among the top 10 causes of disease burden worldwide[3], prompting the necessity to find ways for better treatment and planning of care.

Insomnia frequently co-occurs with both depression[4] and anxiety disorder[5]. Sleep problems, which include difficulty in falling asleep, early awakening, poor sleep quality, daytime sleepiness and poor adherence to the sleep-wake cycle pattern, are particularly prevalent among people with depression and anxiety disorder[6]. The relationships between insomnia and common mental disorders appear to be bidirectional[7]. Symptoms of anxiety and depression, such as worry and rumination, can contribute to insomnia. Alternatively, insomnia can also increase the likelihood of developing depression or anxiety disorder, possibly due to the psychological distress as well as hormonal and neurochemical disturbances caused by poor sleep[8,9]. Thus, interventions aiming at reducing symptoms of insomnia should provide benefit for the disorder *per se*[10].

Individuals may consider psychotherapy instead of pharmaceutical treatment, due to possible side effects and potential dependence on medication[11-13]. Cognitive behavioural therapy (CBT) has been substantially confirmed to be an effective psychosocial treatment in managing depression and anxiety [14,15]. In a meta-analysis of 1205 CBT trials for anxiety disorders, results indicated that CBT for anxiety has a moderate effect on sleep[16]. In terms of the treatment of both depression and insomnia, another study found that the addition of CBT for insomnia (known as CBT-I) to antidepressant medication treatment can lead to better treatment outcomes[17]. However, some reviews showed that the effect sizes of CBT for depression have steadily decreased since its inception four decades ago[18,19]. Therefore, merely employing CBT might not be sufficient for managing mood disorders and their corresponding sleep problems.

Due to the limitations of traditional treatments, many people who experience insomnia are willing to consider using complementary and alternative medicine (CAM) as an alternative therapeutic option,

including natural herbal products, acupuncture, or mind-body interventions, for example. A national health survey revealed that approximately 1.6 million adults in the United States have used CAM therapies to treat sleep problems[20]. Among different CAM therapies, the mind-body domains are by far the most commonly used[20]. Mindfulness-based interventions (MBIs), as a kind of CAM mind-body treatment with a focus on cultivating a sense of awareness, was originally developed to help people dealing with stress, anxiety, depression, or pain[21]. Mindfulness (Pali: *sati*) originated from Buddhism. As such, mindfulness can be defined as deliberately cultivating non-judgmental moment-to-moment awareness and experiences, through observing one's own mind in a detached manner[22]. Various formal and informal mindfulness activities, such as body scan and sitting meditation, are included within the MBIs. Through these practices, the technique of 'focusing on present moment' can be acquired based on approach, compassion and decentring[23]. The inquiry process, which assists participants in identifying their thoughts, emotions and behaviours, is also included in these programs to help participants respond with more flexibility and awareness[24].

Conventional MBI has standardised protocols, and typically incorporates three formal mindfulness practices, namely body scan, mindful movement and sitting meditation[23]. A traditional program called mindfulness-based stress reduction (MBSR), kicking off the development of the mindfulness-based program in the health care domain, was first introduced by Kabat-Zinn[22]. It is an 8-wk program using mindfulness meditation (MM) and mindfulness practice in everyday life to relieve stress. Since then, another well-researched program — mindfulness-based cognitive therapy (MBCT) — was developed with comparable structures[25]. It is also an 8-wk program, which includes mindfulness practice and psychoeducation about depression, promoting awareness, acceptance and adaptive reaction towards negative automatic thoughts[25]. Apart from preventing relapse in depression, MBCT is also used to treat patients with psychiatric conditions, like anxiety disorders and post-traumatic stress disorder (PTSD)[26,27].

Since the commencement of MBSR, various forms of mindfulness programs have evolved with different adaptations or modifications, such as the Mindfulness-Based Therapy for Insomnia (MBTI)[28], internet mindfulness meditation intervention (IMMI)[29], Mindfulness Awareness Program (MAP)[30], or mindfulness-based touch therapy (MBTT)[31]. Specifically, MBTI was developed for patients with insomnia. It integrates mindful meditation and behavioural therapy. By promoting awareness and adaptive response towards sleep disturbances, MBTI helps people with chronic insomnia with sleep restrictions and stimulus control[28]. IMMI was developed to offer mindfulness training anytime and anywhere by use of an Internet mode of delivery. IMMI includes six 1-h weekly sessions with 20 min of home-practice meditation between sessions[29]. MAP aims to teach participants principles of mindfulness, develop meditation practice and apply them in daily lives. MAP is mainly conducted in community settings, with a combination of lecture, hands-on practice, group feedback and discussion[30]. MBTT is an 8-wk program that combines components of MBSR and touch therapy. It was inspired by Ogden *et al*[32]'s model of hierarchical information processing, in which touch stimulus triggers sensorimotor reaction, which is then experienced as emotions and interpreted cognitively. Touch is believed to have healing effects on both the mind and body[31].

At present, various studies have been published for the different MBIs. However, the review type studies usually focus on the conventional programs, like MBSR or MBCT[33,34]. While there are different forms of emerging MBIs in recent years, it is essential to have a comprehensive evaluation on their clinical effectiveness. Moreover, the traditional MBI programs have usually targeted general physical and psychiatric conditions; later on, they were used in the management of various kinds of physical or psychosomatic conditions, and even insomnia problems[35]. Recent meta-analyses indicated that MBIs show promising effects on the reduction of sleep problems[36-39]. However, these meta-analyses focused on the general population only or on people with physical comorbidities, such as cancer and fibromyalgia. Therefore, systematic review and meta-analysis on the effectiveness of the various MBI programs for sleep problems in individuals with depression or anxiety disorders is implied.

The objective of this meta-analysis was to determine and compare the clinical importance of different MBI programs on sleep problems among individuals with common mental disorders. Based on our research, this meta-analysis is uniquely able to fill a crucial gap in the field.

## MATERIALS AND METHODS

### *Literature search*

Literature searches were performed according to the 2009 PRISMA Statement for systematic reviews, by two independent researchers (Lui D and Chan H). The search keywords of "mindfulness" and "mood or anxiety or depress*" and "sleep or insomnia" were used to ensure comprehensive coverage. Keyword searches were conducted in Embase, Medline (accessed through EBSCOhost), PubMed and PsycINFO (accessed through ProQuest) databases. Papers published between January 2010 and June 2020 were included. Publications were only restricted to English language and peer-reviewed.

### Study eligibility

Titles and abstracts were screened, and full texts were selected for further review according to the following criteria. The inclusion criteria were as follows: (1) Experimental study with MBI; (2) Subjects selected for depression or anxiety disorder; (3) Sleep-related data taken at baseline and post-intervention; and (4) Randomised controlled trials (RCTs). The exclusion criteria were as follows: (1) Mixed intervention; or (2) Subjects with comorbidities other than depression or anxiety disorders. The selection criteria were confirmed according to the results of searching. The PRISMA flow diagram is shown in Figure 1.

### Data extraction

An extraction form was used for each article to collect the following data: year of publication; subject setting; inclusion and exclusion criteria for participants; sample size for the experimental and control groups; participants' age and sex; intervention given; and outcome measures related to sleep quality. Relevant statistics and effect sizes were also extracted, if available.

### Assessment on quality

Two reviewers (Lui D and Yip H), working independently, assessed the level of evidence (LoE) and appraisal stage for each of the articles using a standard quality assessment, namely the LoE[40] and revised cochrane risk-of-bias tool for randomised trials (RoB)[41] respectively. The LoE categorizes different experimental studies into different levels on a scale of I to V, with a smaller number indicating a higher LoE. The RoB was used to assess the risk of bias in the RCTs. A series of signalling questions were available in each of the five domains of assessment, and judgements were facilitated by an algorithm that maps responses to the signalling questions to a proposed judgement. Overall risk of bias of the individual study would be reported as "low risk of bias", "some concerns" or "high risk of bias". Disagreements between the two independent reviewers were resolved by a third reviewer through a consensus-based discussion.

### Statistical analysis

Statistical analysis of the pooled results was carried out using the Comprehensive Meta-Analysis software version 3.0 (https://www.meta-analysis.com). In nine of the ten studies, standardised mean differences (SMDs) and 95% confidence intervals (CIs) were calculated using post-intervention differences between the mean of mindfulness-based programs and the mean of controls, divided by the pooled standard deviation. No real differences in variability among studies were assumed according to the Cochrane Handbook for Systematic Reviews of Interventions[42]. A global estimation of $r = 0.6$ was, therefore, used as the correlation coefficient between post-treatment scores. In the remaining study, Cohen's $d$ was calculated using the two groups, *via* the one-way $F$-test using a practical meta-analysis effect size calculator[43]. When there was more than one group compared to the MBI group in the RCT, the non-intervention group was used as the control. The $Q$-statistic was used as the heterogeneity test, in which a statistically significant level of $P < 0.05$ indicated the variations in effect sizes were due to heterogeneity rather than sampling error. A random-effects model would be used when there was notable heterogeneity. Random-/fixed-effects models were used as the intervention effects are unlikely to be identical[44] given that there are significant variations in characteristics of each sample population. Publication bias was assessed by funnel plot, trim-and-fill and failsafe N. Unless otherwise specified, all statistical tests were two-sided with a significance level of 0.05.

## RESULTS

### Study selection

A total of 808 entries were identified through database searches, and 397 of them were screened after duplicates removed. After reading the abstract and title of the remaining 397, we removed 25 reviews, case reports, and protocols. Full versions were retrieved for 372 papers, after which they were reviewed by two independent researchers (Chan H and Sum K) and disagreements were resolved by a third reviewer (Lui D) on a consensus-based discussion. In total, 362 full articles were excluded for not meeting all the inclusion criteria. Finally, 10 eligible studies were selected for systematic review and meta-analysis (details shown in Figure 1).

### Study characteristics

Ten studies met the inclusion criteria, overall reporting five different kinds of mindfulness-based programs, including IMMI, MM, MBCT, MBSR and MBTT. Table 1 shows the study characteristics of the 10 trials. The studies were conducted in the United States, Germany, Norway, Australia and Austria, within years that fell between 2010 and 2019. A total of 541 participants were included in the intervention groups and comparison groups. When there were multiple intervention groups, we chose the mindfulness-based programs as the major intervention groups[45-47].

**Table 1 Characteristics of studies**

| Ref. | Country | Sample | Age range (mean) | Women, *n* (%) | Randomisation | Intervention group (comparison group) | Intervention duration | Group size for effect size calculation, *n* | Drop-out rate[1] (%) | Outcome measure for sleep |
|---|---|---|---|---|---|---|---|---|---|---|
| Wahbeh [29], 2018 | United States | Older adult with depression symptoms | 55-80 (64.8) | 21 (81) | R | IMMI (waitlist control) | 6 wk | I = 26 C = 24 | 20.00 | Sleep disturbance, ISI |
| Boettcher *et al*[50], 2014 | Germany | Community dwellers with anxiety disorders | 18+ (37) | 34 (75.6) | R | IMMI (discussion forum control group) | 8 wk | I = 45 C = 46 | 7.69 | ISI |
| Wahbeh *et al*[47], 2016 | United States | Combat veterans with post-traumatic stress disorder | 25-65 (I = 53.3; C = 53.0) | 2 (7) | R | MM (sitting quietly) | 6 wk | I = 27 C = 25 | 0 | PSQI |
| Britton *et al*[49], 2012 | United States | Antidepressant medication users with sleep complaints | 24-61 (47.0) | 21 (80.8) | R | MBCT (control) | 8 wk | I = 14 C = 10 | 7.69 | TIB, TST, SE, SOL, WASO, TWT, Stage 1, SWS, Quality |
| Vøllestad *et al*[51], 2011 | Norway | Community dwellers with anxiety disorders | 18-65 (42.5) | 26 (66.7) | R | MBSR (waitlist control) | 8 wk | I = 39 C = 37 | 14 | BIS |
| Britton *et al*[48], 2010 | United States | Community dwellers with partially remitted depression | 33-64 (45.4) | 9 (69.2) | R | MBCT (control) | 8 wk | I = 13 C = 8 | 19.23 | TIB, TST, SE, SOL, WASO, NWAK, Arousals, Stage 1, SWS, Quality |
| Hoge *et al* [52], 2013 | United States | Referral/community dwellers with generalized anxiety disorder | 18+ (I = 41; C = 37) | 23 (47.9) | R | MBSR (stress management education) | 8 wk | I = 48 C = 45 | 4.30 | Sleep quality, PSQI |
| Horenstein *et al*[45], 2019 | United States | Adults with social anxiety disorder | 18+ (32.7) | Not specified | R | MBSR (control) | 12 wk | I = 36 C = 36 | 15.28 | Sleep quality, PSQI |
| Pinniger *et al*[46], 2013 | Australia | Adults with self-reported feelings of stress, anxiety, and/or depression | 18-68 (39.5) | 10 (90.9) | R | MM (waitlist control) | 8 wk | I = 11 C = 23 | 30.60 | Sleeping difficulty/insomnia, ISI |
| Stötter *et al* [31], 2013 | Austria | Patients of the psychiatric hospital of Hall in Tirol | 18+ (I = 42.8; C = 41.4) | 11 (68.75) | R | MBTT (control) | 8 wk | I = 14 C = 14 | 0 | Sleep-onset disorder, Sleep maintenance disorders, Terminal sleep disorders, HDRS |

[1]When there are multiple intervention groups, the drop-out rate is based on the number of participants in Mindfulness-Based Program and comparison group only. BIS: Bergen insomnia scale; C: Comparison group; I: Intervention; HDRS: Hamilton's depression rating scale; IMMI: Internet mindfulness meditation intervention; MBCT: Mindfulness-based cognitive therapy; MBSR: Mindfulness-based stress reduction; MBTT: Mindfulness-based touch therapy; NWAK: Number of awakenings; ISI: Insomnia severity index therapy; MM: Mindfulness meditation; PSQI: Pittsburgh sleep quality index; R: Randomised; SE: Sleep efficiency; SOL: Sleep onset latency; Stage 1: Sleep onset was defined by the first epoch of any stage of sleep; SWS: Short-wave sleep; TIB: Time in bed; TST: Total sleep time; TWT: Total wake time; WASO: Wake after sleep onset.

Across studies, participants had a range of mean age between 32.7 and 64.8 years. Seven out of ten (70%) of the studies had a majority of female participants. Four out of ten studies (40%) focused on community dwellers with anxiety and/or major depressive disorder. One study included participants of veterans with PTSD. Six out of ten studies reported significant improvement in sleep quality as measured by insomnia severity index (ISI), Pittsburgh sleep quality index (PSQI), Bergen insomnia scale (referred to as BIS), Hamilton depression rating scale (HDRS) and sleep diaries, provided that the *P* value of the experiment was lower than 0.05. All of the studies were RCTs. The duration of the intervention ranged from 6 wk to 12 wk and delivered over 6 to 12 sessions. Details of intervention techniques and selected outcome measures of each study are provided in Table 2.

**Table 2 Interventions' technique, components and selected outcome measures for effect size calculation**

| Mindfulness-based program | Intervention components | | Selected outcome measures for effect size calculation | Ref. |
|---|---|---|---|---|
| | Intervention group | Comparison group | | |
| IMMI | DI + MM + MPS | WL | ISI | Wahbeh[29], 2018 |
| | ME + psychoeducation | DF | ISI | Boettcher *et al*[50], 2014 |
| MM | BS | SB | PSQI | Wahbeh *et al*[47], 2016 |
| | BS | BS + SB | PSQI | Wahbeh *et al*[47], 2016 |
| | BS | SQ | PSQI | Wahbeh *et al*[47], 2016 |
| | BS + MB + MW + music meditation | WL | ISI | Pinniger *et al*[46], 2013 |
| MBCT | MA + HW (Guided audio CD) | Control | Sleep diary | Britton *et al*[48], 2010 |
| | MA (MB + MS + MW + lying + other simple movement) + HW (MM using audio CD + worksheet) | Control | Sleep diary | Britton *et al*[49], 2012 |
| MBSR | BS + SM + MB + AR + DI + ME + MMV + HW | WL | Bergen insomnia scale | Vøllestad *et al*[51], 2011 |
| | BS+ BA+ gentle Hatha Yoga | SME | PSQI | Hoge *et al*[52], 2013 |
| | BS + SM + MS + MPS | WL | PSQI | Horenstein *et al*[45], 2019 |
| MBTT | BA + touch + HW + counselling | BMT | HDRS | Stötter *et al*[31], 2013 |

AR: Adaptive response; BA: Bodily awareness; BMT: Basic medicinal therapy; BS: Body scan; DF: Discussion forum; DI: Didactic instruction; HDRS: Hamilton depression rating scale; HW: Homework; IMMI: Internet mindfulness meditation intervention; ISI: Insomnia severity index; MA: Mindfulness awareness; MB: Mindful breathing; ME: Mindfulness exercise; MBCT: Mindfulness based cognitive therapy; MBSR: Mindfulness based stress reduction; MBTT: Mindfulness based touch therapy; MM: Mindfulness meditation; MMV: Mindful movement; MPS: Mindfulness problem-solving; MS: Mindful stretching; MW: Mindful walking; PSQI: Pittsburgh sleep quality index; SB: Slow breathing; SM: Sitting meditation; SME: Stress management education; SQ: Sitting quietly; WL: Waitlist control.

### *Assessment of quality*

Results from quality assessments are presented in Tables 3 and 4. All studies were RCTs. All trials had adequate sequence generation, among which five (50%) indicated a concealed allocation[49-51]. As for blinding, two trials adopted double-blind design[48,49], one trial used single-blind design[31] and two used blind evaluators[47,52]. The drop-out rates of the trials ranged from 0% to 30.6%, as shown in Table 1. Of the 10 trials, 3 had low drop-out rates (≤ 5%)[31,47,52] and two had high drop-out rates (≥ 20%)[29,46]. The overall LoE was level II ($n$ = 10), showing that the papers under current review were of high LoE. The overall RoBs were as follows: low ($n$ = 2); some concerns ($n$ = 6); and high ($n$ = 2). The majority of papers showed some concerns of risk of bias, mainly due to bias in the measurement of outcome.

### *Analysis of overall effect*

This meta-analysis focused on examining the effect at the end point of different mindfulness-based programs, including IMMI, MM, MBCT, MBSR and MBTT, due to variations in follow-up periods and absence of reported follow-up effects in several studies. The overall effect analysed was based on the comparison between different mindfulness-based programs and comparison groups, including discussion forum, waitlist control, slow breathing, stress management education, sitting quietly and basic medicinal therapy. Self-rated outcome measurements were reported in the 10 RCTs assessed, including PSQI, ISI, sleep quality of sleep diary, and sleep maintenance of HDRS. The overall scores of sleep quality were reported in PSQI, ISI, BIS and sleep diaries. On the other hand, there was no overall score on sleep quality presented in HDRS. The component of sleep maintenance in HDRS was, therefore, selected. Sleep maintenance was selected instead of sleep onset and sleep termination, as the level of sleep maintenance better predicts perceived sleep quality[53]. Other outcome measurements which are not self-rated, including sleep onset latency, total sleep time and wake after sleep onset, were not reported in this meta-analysis.

The mean effect sizes on sleep problem improvement of different mindfulness-based programs, as compared with control groups, are provided in Table 5. The forest plot in Figure 2 shows the effect sizes and 95%CIs of the 10 studies assessed. The meta-analysis reveals a moderate pooled effect size ($g$ = -0.527, 95%CI: -0.701 to -0.353) in favor of MBI program. Significant effects on sleep problem improvement were shown in four out of five of the different mindfulness-based programs under

**Table 3 Research design and level of evidence**

| Ref. | Research design | Level of evidence |
|---|---|---|
| Wahbeh[29], 2018 | RCT, crossover design | II |
| Boettcher *et al*[50], 2014 | RCT, crossover design | II |
| Wahbeh *et al*[47], 2016 | RCT, multi-group pre-/post-test design | II |
| Britton *et al*[49], 2012 | RCT, pre-/post-test control group design | II |
| Vøllestad *et al*[51], 2011 | RCT, crossover design | II |
| Britton *et al*[48], 2010 | RCT, pre-/post-test control group design | II |
| Hoge *et al*[52], 2013 | RCT, two group pre-/post-test design | II |
| Horenstein *et al*[45], 2019 | RCT, multi-group pre-/post-test design | II |
| Pinniger *et al*[46], 2013 | RCT, multi-group pre-/post-test design | II |
| Stötter *et al*[31], 2013 | RCT, pre-/post-test control group design | II |

RCT: Randomised controlled trial.

**Table 4 Risk of bias in the studies**

| Ref. | Randomisation process | Deviation from intended intervention | Missing outcome data | Measurement of outcome | Selection of the reported results | Overall |
|---|---|---|---|---|---|---|
| Wahbeh[29], 2018 | Low risk | Low risk | Some concerns | Some concerns | Low risk | High |
| Boettcher *et al*[50], 2014 | Low risk | Low risk | Low risk | Some concerns | Low risk | Some concerns |
| Wahbeh *et al*[47], 2016 | Low risk | Low risk | Low risk | Some concerns | Low risk | Some concerns |
| Britton *et al*[49], 2012 | Low risk | Low risk | Low risk | Some concerns | Low risk | Some concerns |
| Vøllestad *et al*[51], 2011 | Low risk | Low risk | Low risk | Some concerns | Low risk | Some concerns |
| Britton *et al*[48], 2010 | Low risk | Some concerns | Low risk | Low risk | Low risk | Some concerns |
| Hoge *et al*[52], 2013 | Low risk | Low risk | Low risk | Low risk | Low risk | Low |
| Horenstein *et al*[45], 2019 | Low risk | Low risk | Low risk | Some concerns | Low risk | Some concerns |
| Pinniger *et al*[46], 2013 | Low risk | High risk | Some concerns | Low risk | Low risk | High |
| Stötter *et al*[31], 2013 | Low risk | Low risk | Low risk | Low risk | Low risk | Low |

review, namely MBTT, MBCT, IMMI and MBSR (reflecting descending order of effect sizes). The greatest effect sizes were reported in favour of MBTT, with SMDs of -1.138 (95%CI: -1.937 to -0.340; $P$ = 0.005), followed by -1.003 (95%CI: -1.645 to -0.360; $P$ = 0.002) for MBCT. SMDs of -0.618 (95%CI: -0.980 to -0.257; $P$ = 0.001) and -0.551 (95%CI: -0.842 to -0.260; $P$ < 0.0001) were reported for IMMI and MBSR in the pooling trials, respectively. However, among the five kinds of mindfulness-based programs under review, the mean effect size for MM on sleep was non-significant, with SMD of -0.264 (95%CI: -0.699 to 0.172; $P$ = 0.236).

### *Heterogeneity test and publication bias*

Table 5 shows that all the heterogeneities ($Q$) were non-significant across the different MBI programs. The non-significant $Q$-statistics might suggest that the variation in the effect sizes across the studies was simply due to low power but not the study characteristics. Three sets of asymmetry tests — namely, funnel plots of precision, trim-and-fill and failsafe N — were used to estimate the publication bias in each study. Symmetrical distribution of the combined effect size revealed the absence of publication bias

**Table 5 Overall effects of different interventions**

| Ref. | Mindfulness-based program | *k* | Subjects, *n* | SMD (95%CI) | *P* value | Overall SMD (95%CI) | Overall *P* value | *Q* |
|---|---|---|---|---|---|---|---|---|
| Wahbeh[29], 2018 | IMMI | 2 | 124 | -0.881 (-1.531 to -0.231) | 0.008 | -0.618 (-0.980 to -0.257) | 0.001 | 0.912 (*P* = 0.34) |
| Boettcher *et al*[50], 2014 | | | | -0.500 (-0.935 to -0.066) | 0.024 | | | |
| Wahbeh *et al*[47], 2016 | MM | 2 | 86 | -0.267 (-0.814 to 0.279) | 0.337 | -0.264 (-0.699 to 0.172) | 0.236 | 0.001 (*P* = 0.981) |
| Pinniger *et al*[46], 2013 | | | | -0.257 (-0.978 to 0.464) | 0.485 | | | |
| Britton *et al*[48], 2010 | MBCT | 2 | 43 | -1.073 (-1.953 to -0.192) | 0.017 | -1.003 (-1.645 to -0.360) | 0.002 | 0.052 (*P* = 0.82) |
| Britton *et al*[49], 2012 | | | | -0.923 (-1.862 to 0.016) | 0.054 | | | |
| Hoge *et al*[52], 2013 | MBSR | 3 | 187 | -0.449 (-0.942 to 0.043) | 0.074 | -0.551 (-0.842 to -0.260) | < 0.0001 | 0.332 (*P* = 0.847) |
| Horenstein *et al*[45], 2019 | | | | -0.555 (-1.056 to -0.053) | 0.03 | | | |
| Vøllestad *et al*[51], 2011 | | | | -0.660 (-1.178 to -0.141) | 0.013 | | | |
| Stötter *et al*[31], 2013 | MBTT | 1 | 28 | -1.138 (-1.937 to -0.340) | 0.005 | -1.138 (-1.937 to -0.340) | 0.005 | 0 (*P* = 1) |

CI: Confidence interval; IMMI: Internet mindfulness meditation intervention; MBCT: Mindfulness-based cognitive therapy; MBSR: Mindfulness-based stress reduction; MBTT: Mindfulness-based touch therapy; MM: Mindfulness meditation; SMD: Standardised mean difference.

upon visual inspection of the funnel plots (Figure 3). To further examine the funnel plot symmetry, Duval and Tweedie's trim-and-fill procedure was used. No significant adjustment was needed and no study was trimmed due to the absence of unmatched observations from the funnel plots. Failsafe N analyses demonstrated that 96 missing studies with a zero effect size have to be added to reduce the significant overall effect size to statistically non-significant levels.

## DISCUSSION

This meta-analysis showed that MBTT imparts the largest effect on sleep problems among the five different kinds of mindfulness-based programs under review, followed by MBCT, IMMI and MBSR. According to Cohen[54]'s thresholds for interpreting effect size, SMDs smaller than 0.20 would be regarded as small effect size, 0.50 as medium, 0.80 as large and 1.30 as very large. However, it is important to point out that Cohen defined the medium effect size based on his literature review using the *Journal of Abnormal and Social Psychology* during the 1960s. These small, medium, and large effect sizes are, thus, specific to a particular domain (abnormal and social psychology) and as such these cut-off points should not be treated as absolute or universal. By Cohen's convention, MBTT and MBCT have large effect sizes. IMMI and MBSR have medium effect sizes, and MM has a small effect size. It should be noted that, despite the large effect size of MBTT on sleep, only one study contributed to this result, while the results of the remaining four different kinds of mindfulness-based programs were supported by at least two or more studies. In addition, the effect of MM on sleep did not reach a significant level, despite having a small effect size. This may be explained by the unexplored improvements in sleep problems in the comparison group, leading to the comparatively non-significant effect of MM. Although previous findings suggested that MM is an effective treatment for insomnia[37], its effect on sleep for people with depression and anxiety disorder remains questionable, as shown in this meta-analysis.

As such, MBTI has been commonly used to treat patients with chronic insomnia or sleep problems [35]. However, many studies involving MBTI[28,55] did not target people with depression or anxiety disorder, so MBTI was not selected in the current meta-analysis (according to the inclusion criteria). When further scrutinized, the goals of MBTI usually aim at promoting the adaptive response towards the emotional distress caused by sleep disturbances and daytime fatigue among people with chronic insomnia. However, the present review study revealed that those MBI programs which can improve sleep problems among people with depression or anxiety disorder may have additional characteristics. More specifically, those MBI programs under review were found to ameliorate both the mood and sleep

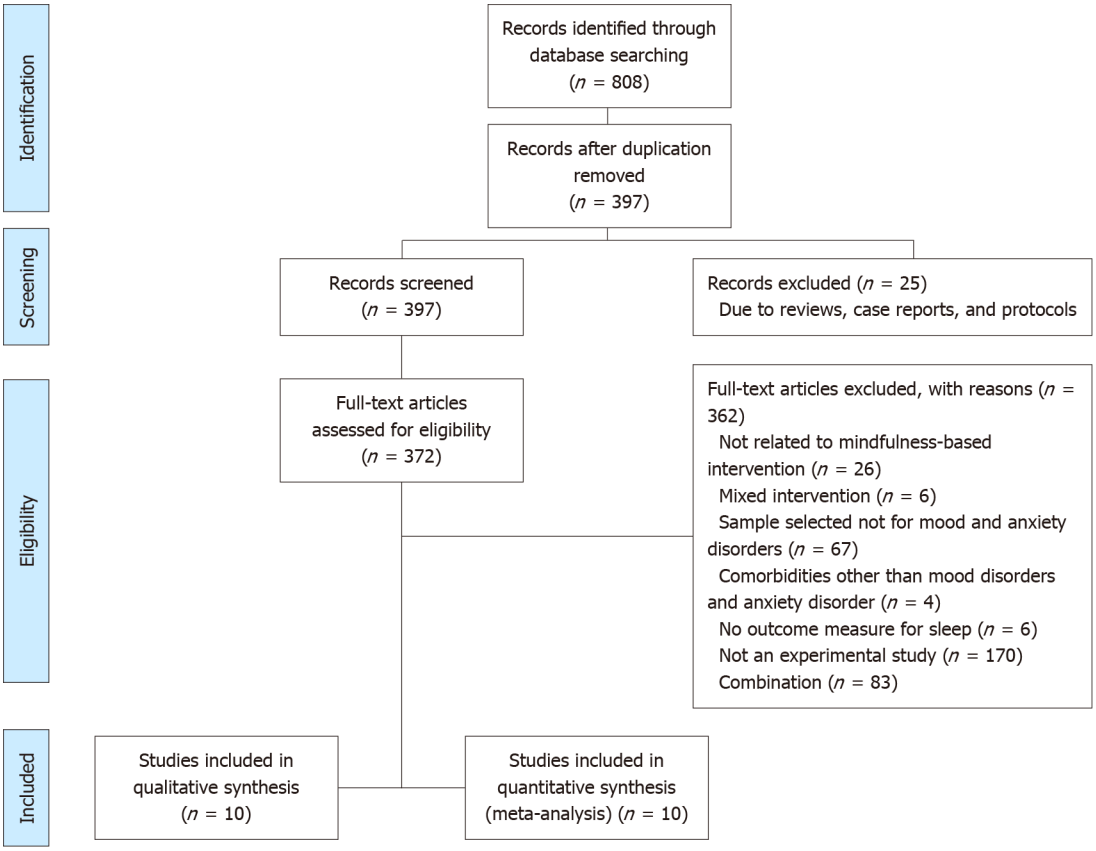


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**Figure 1 PRISMA flow diagram of the study.**

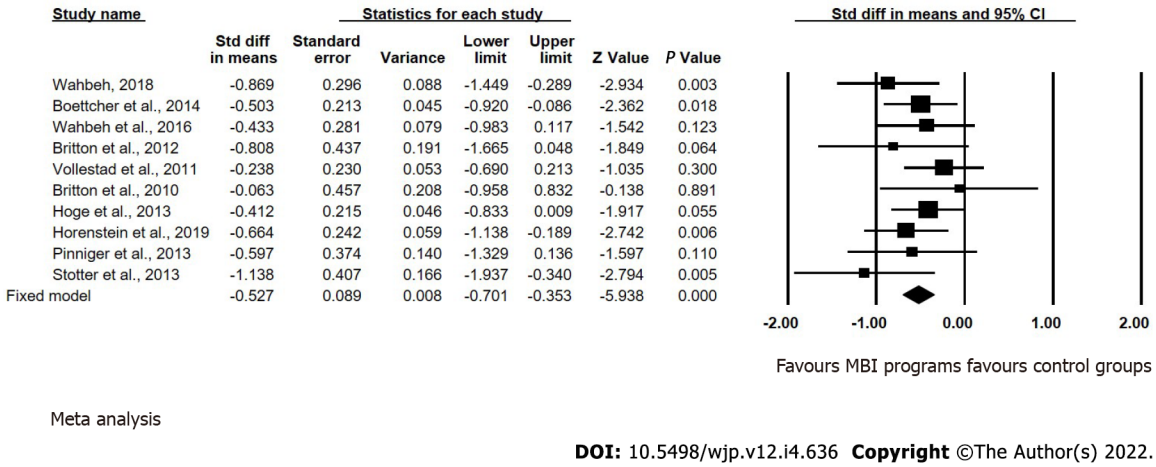


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**Figure 2 Forest plot of effect sizes.** MBI: Mindfulness-based intervention; CI: Confidence interval.

problems concurrently. In other words, these MBI programs could target both the antecedents and consequences of sleep problems for people with common mental disorders.

MBTT[31] was found to have the largest effect on sleep problems, according to the meta-analysis. MBTT, which is based on mindfulness practice and various forms of massage and bodywork, could improve sleep by restoring interception and sensorimotor processing of individuals with depression and anxiety disorder. Regarding the effect of touch *per se*, the rhythmic and gentle massage produced a direct bodily and sensory experience[31]. This resulted in an antidepressant effect mediated by restoration of the impaired interoceptive functioning, which is associated with depression and anxiety [56,57], through stimulation of specific mechanoreceptors[58]. Adding to the independent effect of touch, a possible explanation for the synergistic effects of combining mindfulness practice and therapeutic touch is the model of hierarchical information processing, which suggested that mindfulness-based touch intervention gave rise to the integration of sensorimotor bodily experience

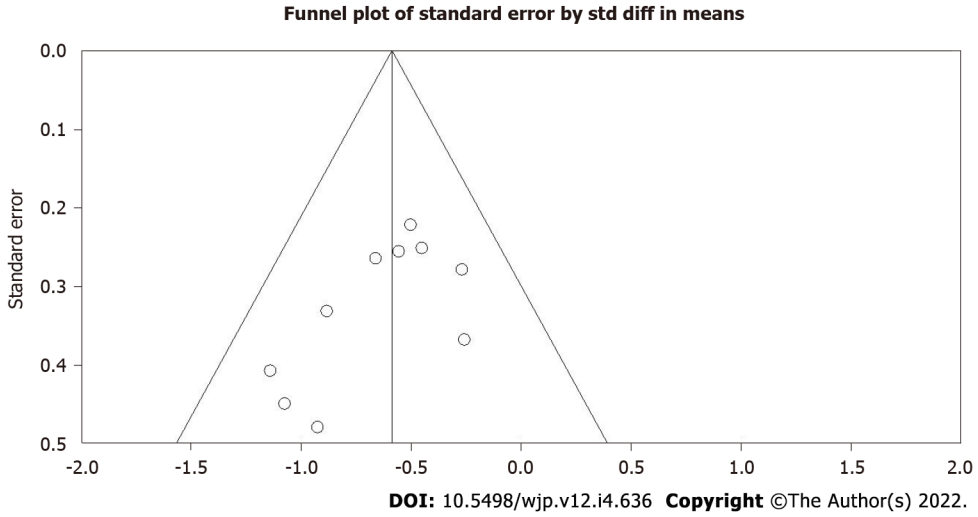


**Figure 3 Funnel plot of standard error by standard difference in means.**

with mindful cognitive self-awareness[32]. In line with this explanation, a cortical plasticity model suggested that the sensory reorganization sprung from touch therapy was a mechanism for pain remediation[59]. Similarly, considering a previous study documenting the relationship between sensory processing and sleep quality[60], it is plausible that improving sensory processing through a mindfulness-orientated touch approach could, in turn, ameliorate sleep disturbance in people with depression or anxiety disorder.

Besides, we also found that MBCT[48,49] can help improve sleep problems among people with depression or anxiety disorder, with large effect sizes. In addition to traditional mindfulness skills, MBCT incorporates cognitive behavioural skills which can enhance the effectiveness in coping with depressive mood and sleep problems. Despite the interrelated nature of depression and insomnia, it is theoretically debatable whether insomnia should be treated as a distinct diagnosis or a symptom of mood disorders[61]. Considering the complexity of insomnia, Shallcross *et al*[62] proposed a theoretical model to summarize the utility of MBCT in treating insomnia, suggesting that there are three treatment components (*i.e.*, acceptance, attention control and experiential awareness) with different therapeutic functions across the integrated process model of insomnia. It is worth noting that the model of insomnia is in line with symptoms of people with depression. For example, rumination is associated with both depressive mood and sleep quality[63] and upregulated arousal is linked to sleep problems (*e.g.*, longer sleep latency) in people with depressive syndromes[64,65]. The review studies suggested that MBCT can ameliorate the sleep disturbance of people who have achieved partial remission of depression (both with and without taking an anti-depressant) as well as significant mood improvement. It is possible that MBCT is not only a promising program for depression or insomnia alone, but also for improving sleep problems in people with depression. In addition, recent research has indicated that acceptance lessened the positive relation between awareness and sleep disturbance, with reduced stress level identified as a mediator[66]. This mechanism is consistent with the Monitor and Acceptance Theory[67], which proposes that awareness and acceptance may jointly improve emotional regulation, including that of stress. In this sense, the effectiveness of MBCT to reduce stress[68,69] can partially explain the potential utility of MBCT in improving sleep outcomes.

Therefore, solely utilizing MM[46,47] may not be robust enough to improve sleep problems among people with depression or anxiety disorder, as indicated by the insignificant effect size shown in this study. No wonder recent meta-analyses[70,71] supported that MM is effective in reducing symptoms such as rumination among people with depression or anxiety disorder, but the sleeping problem might be improved in the short-term only. As a bidirectional relationship has been revealed between sleep disturbance and common mental disorders[7], it seems that a more integrated approach should be considered in order to enhance robustness of the intervention effects. For instance, the addition of a touch approach[31], cognitive component[50] or health qigong[72] should help in promoting the effectiveness of mindfulness practice, as applied in different clinical populations. Thus, the evolution of various kinds of integrated MBI programs should mark the necessity for meeting the increasing demand of various physical and mental health problems.

Our analysis showed that the majority of studies were coded as having some concerns by RoB. Most concerns arise from measurement of outcome, as most sleep measurements, such as PSQI, ISI and sleep diary, rely on self-report by the patients. With the awareness of the treatment received, the non-blind allocation should lead to increased risk of bias. In addition, improvements in sleep cannot be merely assessed by objective tools like polysomnography but will also still rely on self-rated assessment tools. Thus, there is a possibility that some studies of good quality are not coded as low RoB due to the strict

restrictions in outcome measurement tools, as stated in the RoB tool used in the current study. The studies included in this meta-analysis involved diverse sample populations in various age groups and with different emotional disorders, including mood disorders, anxiety disorders and PTSD. However, the heterogeneities were not significant, despite the variations in study characteristics. This may be explained by the high similarity in outcome measurement tools, among which PSQI, ISI and sleep diary were widely used to assess sleep outcome in the studies. Moreover, many of the studies under review had similar study protocols, and some were even conducted by the same group of researchers. The non-significance in heterogeneity may also be attributed to the low power of the studies. Nevertheless, moderator analysis can be considered in the future for possible effects of the potential moderators.

Although the present meta-analysis suggests considerable clinical benefits of MBTT, MBCT, IMMI and MBSR on sleep among people with depression or anxiety disorder, the findings should be interpreted with caution. It should be noted that this meta-analysis has been primarily concerned with its limited power. A limited number of clinical trials on MBI programs are available in the literature databases, and many of the studies targeted populations with physical complications or other comorbidities. The result was that a relatively small number of trials met inclusion criteria. For example, there was only one study regarding MBTT that could be included. Thus, the effect of MBTT in our meta-analysis was solely determined by one study. The ability of funnel plot to detect publication bias was also restrained by the few number of trials included in our meta-analysis. Thus, there is a need to include larger clinical trials in the future to increase the study power. This analysis has concentrated on studying different kinds of MBI programs but not the specific components in the programs. It caused our study to have low generalizability compared to all the other protocols of the studied programs, because variations exist under the same program between different studies. For instance, gentle Hatha Yoga was included in one study of MBSR[52] but not in other trials[45,51]. Therefore, the effects of the MBI programs in this study are composed of various but nonspecific components. Further studies on specific intervention components, such as body scan, mindful walking, bodily awareness and mindful breathing are required. A further potential limitation of this review stems from the fact that the outcome measures of sleep focus on the subjective measurements only. The discrepancies in sleep measurement may have complicated the comparison. It is suggested that more objective and uniform measurement tools for sleep should be used in future studies in this field to facilitate a larger sample size and power in prospective systematic reviews and meta-analyses. For instance, polysomnography and electrocardiogram use scientific technology to investigate some objective components of sleep and can be considered[49,73]. These could provide more objective evidence than self-rated scales. Lastly, the lack of Asian studies means that we cannot be certain that the findings can be generalized to an Asian population. Studies included in the current review were carried out only in the United States, Germany, Norway, Australia and Austria. More clinical trials in Asian countries are encouraged to increase generalizability of findings from future studies. It is also suggested that a more specific age group could be targeted to study the effect of MBIs on different age groups, like elderly and adolescent.

Despite these limitations, this review study adds to the literature by investigating different kinds of MBI programs on sleep problem among people with common mental disorders. The comprehensive inclusion and exclusion criteria contribute to the uniqueness of this meta-analysis. Studies that included subjects with comorbidities and with mixed intervention were excluded and, at the same time, a wide variety of MBI programs were included. The criteria allowed this meta-analysis to focus more on the effect of different MBI programs in order to fill in a lacuna in the research. Additionally, this meta-analysis has the following strengths. First, it followed the guidelines of the Cochrane Collaboration, which provided a standard process of analysis. The PRISMA Statement was also adopted to support the integrity of its systematic review process. Second, only RCTs were included in this analysis. All the studies analysed had high LoEs and most of them had low to moderate risk of bias. Bias is reduced by study design of adequate concealed allocation and blinding. The high quality of study design of the 10 included studies assured the reliability and validity of their results. Thus, this meta-analysis truly reflects the effect of different MBI programs. Third, all the studies analysed were conducted in the last decade. Since the first introduction of MBCT and MBSR by Kabat-Zinn[22], many innovative forms of MBI have been developed, as mentioned in the introduction. The clinical interest towards MBI has continued throughout the years. The meta-analysis in this paper included studies conducted in 2011-2019, providing up-to-date information about the effect of different MBI programs on sleep among people with depression or anxiety disorders. The meta-analysis in this paper also focused on a specific client group and, as such, was able to provide an updated overview of comparison with traditional MBI and the newly developed programs.

## CONCLUSION

The findings of our comprehensive systematic review and meta-analysis provide preliminary evidence that MBTT, MBCT, IMMI and MBSR are effective options to improve sleep among people with depression and anxiety disorder. MM, which has confirmed to be effective in improving sleep in people with chronic insomnia, may not be effective in our targeted population. Taken together, these results

might provide a first step toward designing more integrated effective interventions for this specified clinical population who are suffering from sleep problems. We are hopeful that the findings of our research will inform health practitioners and other researchers on the extent of effectiveness of the different, latest and integrated MBI programs.

## ARTICLE HIGHLIGHTS

### *Research background*

Sleep problems are particularly prevalent in people with depression or anxiety disorder. Although mindfulness has been suggested as an important component in alleviating insomnia, no comprehensive review and meta-analysis has been conducted to evaluate the effects of different kinds of mindfulness-based intervention (MBI) programs on sleep among people with depression or anxiety disorder.

### *Research motivation*

The present study aimed to assess randomised controlled trials of various types of MBI programs for improving sleep problems in people with common mental disorders.

### *Research objectives*

The main objective was to evaluate and update evidence of effectiveness of the different, latest and integrated MBI programs.

### *Research methods*

We performed a systematic literature search on Embase, Medline, PubMed and PsycINFO databases from January 2010 to June 2020 for randomised controlled trials. Data were synthesized using a random-effects or a fixed-effects model to analyse the effects of various MBI programs on sleep problems among people with depression or anxiety disorder. The fixed-effects model was used when heterogeneity was negligible, and the random-effects model was used when heterogeneity was significant to calculate the standardised mean differences (SMDs) and 95% confidence intervals (CIs).

### *Research results*

We identified 397 articles, of which 10 randomised controlled trials, involving a total of 541 participants, were included in the meta-analysis. Studies of internet mindfulness meditation intervention (IMMI), mindfulness meditation (MM), mindfulness-based cognitive therapy (MBCT), mindfulness-based stress reduction (MBSR) and mindfulness-based touch therapy (MBTT) met the inclusion criteria. The greatest effect sizes are reported in favour of MBTT, with SMDs of -1.138 (95%CI: -1.937 to -0.340; $P$ = 0.005), followed by -1.003 (95%CI: -1.645 to -0.360; $P$ = 0.002) for MBCT. SMDs of -0.618 (95%CI: -0.980 to -0.257; $P$ = 0.001) and -0.551 (95%CI: -0.842 to -0.260; $P$ = 0.000) were reported for IMMI and MBSR in the pooling trials, respectively. Significant effects on sleep problem improvement are shown in all reviewed MBI programs, except MM, in which its effect size was shown to be non-significant.

### *Research conclusions*

This review presents a comprehensive meta-analysis of various forms of MBI programs on helping sleep problems among people with common mental disorders. We found that all MBI programs (in terms of MBTT, MBCT, IMMI and MBSR), except MM, are effective options to improve sleep problems among people with depression or anxiety disorder.

### *Research perspectives*

The current meta-analysis suggests that solely utilizing MM may not be robust enough to improve sleep problems among people with depression or anxiety disorder. As a bidirectional relationship was revealed between sleep disturbance and common mental disorders, it seems that a more integrated approach should be considered in order to enhance robustness of the intervention effects.

## FOOTNOTES

**Author contributions:** Chan SHW conceived and guided the study; Lui D and Chan H carried out the literature searches; Chan H and Sum K extracted the data; Lui D and Yip H assessed the study quality; Yu CH, Lui D and Sum K performed the statistical analyses; Chan SHW, Lui D, Cheung A and Yip H wrote and revised the paper.

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OPINION REVIEW

# False dogmas in mood disorders research: Towards a nomothetic network approach

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## Abstract

The current understanding of major depressive disorder (MDD) and bipolar disorder (BD) is plagued by a cacophony of controversies as evidenced by competing schools to understand MDD/BD. The DSM/ICD taxonomies have cemented their status as the gold standard for diagnosing MDD/BD. The aim of this review is to discuss the false dogmas that reign in current MDD/BD research with respect to the new, data-driven, machine learning method to model psychiatric illness, namely nomothetic network psychiatry (NNP). This review discusses many false dogmas including: MDD/BD are mind-brain disorders that are best conceptualized using a bio-psycho-social model or mind-brain interactions; mood disorders due to medical disease are attributable to psychosocial stress or chemical imbalances; DSM/ICD are the gold standards to make the MDD/BD diagnosis; severity of illness should be measured using rating scales; clinical remission should be defined using threshold values on rating scale scores; existing diagnostic BD boundaries are too restrictive; and mood disorder spectra are the rule. In contrast, our NNP models show that MDD/BD are not mind-brain or psycho-social but systemic medical disorders; the DSM/ICD taxonomies are counterproductive; a shared core, namely the reoccurrence of illness (ROI), underpins the intertwined recurrence of depressive and manic episodes and suicidal behaviors; mood disorders should be ROI-defined; ROI mediates the effects of nitro-oxidative stress pathways and early lifetime trauma on the phenome of mood disorders; severity of illness and treatment response should be delineated using the NNP-derived causome, pathway, ROI and integrated phenome scores; and MDD and BD are the same illness.

**Key Words:** Nomothetic network psychiatry; Depression; Mood disorders; Affective disorders; Inflammation; Oxidative and nitrosative stress; Neuro-immune

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**Core Tip:** We review the merits of machine learning-derived nomothetic network psychiatry (NNP) models of mood disorders. The NNP models of mood disorders show that major depressive disorder/bipolar disorder are not mind-brain or psycho-social but systemic medical disorders. The DSM/ICD taxonomies are counterproductive. A shared core, namely the reoccurrence of illness (ROI), underpins the intertwined recurrence of depressive and manic episodes and suicidal behaviors. Mood disorders should be ROI-defined. ROI mediates the effects of nitro-oxidative stress pathways and early lifetime trauma on the phenome of mood disorders. Severity of illness and treatment response should be delineated using NNP-derived causome, adverse outcome pathways, ROI and phenome scores.

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## INTRODUCTION

The current status-quo view is that mood disorders are disorders of the brain associated with chemical imbalances and should be regarded as mental disorders with a multi-factorial etiology. The status-quo is that mood disorders should be diagnosed using DSM criteria[1] or ICD[2] criteria and that different subtypes of mood disorders exist including unipolar [major depressive disorder (MDD)] and bipolar disorder (BD), either manic or a major depressive episode (MDE). It is thought that MDD and BD-type 1 (BP1) are qualitatively distinct categories, although MDD and BD-type 2 (BP2) show quantitative differences. Furthermore, both MDD and BD show many comorbidities with neurological and medical disease and depression due to these conditions may be explained by psychosocial factors including loss of health or independence. Moreover, the status-quo dictates that severity of illness should be measured using the summed score of items of rating scale scores that assess depressive symptoms.

The conceptual MDD/BD frameworks are plagued with a cacophony of controversies, as evidenced by competing and even mutually antagonistic approaches to understanding these disorders including psychoanalysis (depression is a defense against loss and mourning), psychodynamic psychiatry (depression is the consequence of a pathological object relationship between parts of the self), commonsense or folk psychology (depression is a response to a psychological problem), self-system therapy (the primary factor in depression is problematic self-regulation), systemic therapy (systems *e.g.*, the family create depression), biological psychiatry (depression is the consequence of chemical aberrations in the brain, *e.g.*, a deficiency in serotonin), animal experiments (depression is sickness behavior or is the consequence of learned helplessness), the biopsychosocial model (biological as well as psychosocial factors are involved), cognitive-behavioral therapy (depression is the consequence of negative cognitions), cognitive neuropsychiatry (cognitive impairments in memory or attention are involved), the mind-brain dualism (mental and neural processes interact to cause depression), postpsychiatry (community development and engagements with communities are central and boredom and depression are the characteristic moods of our epoch), molecular psychiatry (genes and intracellular networks explain depression) and pan-omics and precision psychiatry (pan-omics data will reveal the true nature of depression phenotypes or transdiagnostic pathway-phenotypes). A latest new development, which indicates that contemporary psychiatry faces a profound crisis, is critical psychiatry with psychiatric survivor networks which question psychiatric practice, treatment, scientific methods, knowledge base, and the decontextualization of experience, and accuse status quo psychiatrists of harmful and unethical principles[3-5].

Another new direction in psychiatry is the research domain criteria (RDoC) developed by the National Institute of Mental Health (NIMH)[6]. Apart from criticizing and further undermining the credibility of the DSM categorizations, RDoC relies on dimensions as critical measures of psychopathology, which arises from aberrations in neural circuits in the brain, and should be examined by a matrix with 8 columns (genes, molecules, cells, circuits physiology, behavior, self-reports and paradigms) and a number of rows including memory, rewards, threat and perception. Nevertheless, there is no evidence base for the RDoC matrix approach which is developed in a top-down manner.

All medical disciplines, except psychiatry, are exclusively based on nomothetic network definitions of disease, as a default mode of clinical and research operations. The term "nomothetic" means the tendency to derive laws from indicator (independent) variables, which explains the variability in phenomena and allows us to generalize the model[7-9]. Nomothetic definitions include a variety of biological signatures which correspond to clinical measures and constitute drug targets for

implementation of treatment. For example, the diagnosis of atherosclerosis, implies that the patient suffers from atherosclerotic plaques caused by a defined process which progressively worsen. In contrast, the diagnosis of MDD and BD according to DSM/ICD criteria are mere de-contextualized narratives devoid of any explanatory mechanisms.

The aim of this paper is to review the many false dogmas which determine current research in mood disorders; and to discuss these flaws with respect to the new, data-driven, machine learning method to model psychiatric illness, namely nomothetic network psychiatry (NNP)[10-13]. In line with a dichotomy[14], it could be considered that there is a co-existing of two major types of scientific psychiatric knowledge. The first is idiographic and is driven by "understanding" of subjective experiences and inter-subjective narratives, and the second is nomothetic and is governed by laws of natural and mathematical sciences representing explanatory models of disease[15,16]. With every respect and awareness of the values represented in subjective narrative and relevant cultural contexts [17], in this review we focus on the many caveats in scientific psychiatry which undermine the nomothetic approach. Moreover, we show that our novel nomothetic models also contain subjective experiences of the patient and that these idiographic experiences increase the richness and complexity of the nomothetic models. Finally, we will introduce a new mathematical index reflecting the reoccurrence of illness (ROI), which is a key factor in our nomothetic models[18,19].

## NNP

### *NNP models*

None of the previous psychiatric models tried to reunite the different buildings blocks of an illness into a data-driven model which includes causome and protectome features (or a deduced risk/resilience ratio), adverse-outcome pathways (AOPs), brainome features (the aggregate of aberration in brain regions), cognitome features (the aggregate of cognitive impairments), and ROI, symptomatome (the aggregate of different symptom domains or clinical phenotypes), and phenomenome (the self-description of the self-experience of the illness) features[10-13].

Figure 1 displays a theoretical framework of MDD/BD which is based on current state-of-the-art knowledge and causal reasoning and reunites the different building blocks into a causal model. It should be noted that this framework allows for the entry and analysis of a wide range of data into the model, including genome (genomics) and environmentome (psychosocial aspects, context-centered hermeneutic data), pan-omics data, functional brain imaging including connectome data, neurocognitive test results, descriptive psychopathological assessments including symptoms rated *via* interviews, and idiographic or phenomenological features as assessed with self-rating scales, including health-related quality of life (HR-QoL) data.

This theoretical causal framework can be tested and validated using partial least squares (PLS) pathway analysis[10-13]. Figure 2 shows the outcome of such a PLS model (NNP1) comprising causal links between three risk/resilience ratios, namely early lifetime trauma (ELT) indicators and paraoxonase (PON)1 genotype combined with PON1 enzymatic activity, two AOPs, namely an antioxidant and a neuro-oxidative toxicity indicator, one ROI-index, and the phenome of mood disorders[10]. In NNP1, the severity of ROI is represented as a reflective latent vector extracted from the number of lifetime depressive episodes in MDD, (hypo)manic and depressive episodes in BD and number of lifetime suicidal attempts in either MDD or BD[10]. The phenome of mood disorders is conceptualized as a factor (latent vector) extracted from symptomatome features (severity of depression, anxiety and global clinical impression and current suicidal ideation) and phenomenome features, including self-rated disabilities (scoring three subdomains, namely work/school, social and family) and self-rated HR-QoL (four subdomains, namely physical and psychological health, and social relationships and environment)[10].

Simeonova *et al*[12] constructed another NNP model (NNP2) whereby indicants of increased bacterial translocation [increased immunoglobulin (Ig)A and IgM responses to lipopolysaccharides (LPS) of specific Gram-negative bacteria] were entered as causome factors leading to three AOPs, namely increased autoimmune responses to oxidized low-density lipoprotein, peroxide levels and IgM responses to a multitude of oxidative specific epitopes. These three AOPs and an ROI index significantly predict the phenome which was conceptualized as a factor extracted from the severity of illness score, the presence of mood disorders, MDD and BP1, treatment resistance and melancholia.

Figure 3 shows how PLS analysis was employed to construct and validate novel NNP models. As explained previously, different statistical tests should be used to validate the outer and inner models and the PLS models[11]. Goodness of fit should be checked with standardized root mean square residuals to avoid model misspecifications. The validity reliability of the latent factors should be checked using composite reliability, rho A, or Cronbach's alpha and the average variance extracted. All indicators of the latent vectors should display loadings > 0.5 or by preference > 0.66[10-12] and Confirmatory Tetrad Analysis should be employed to check whether the latent factors are not mis-specified as reflective models. Other tests including blindfolding and PLS predict with 10-fold cross-validation and may be used to assess the predictive value of the model[10-13]. There are different

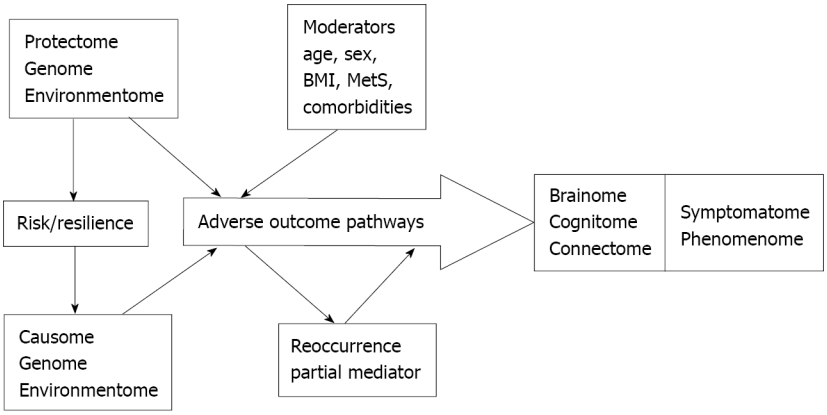


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**Figure 1 Theoretical framework of mood disorders.** Adapted from Maes *et al*[10]. BMI: Body mass index; Mets: Metabolic syndrome.

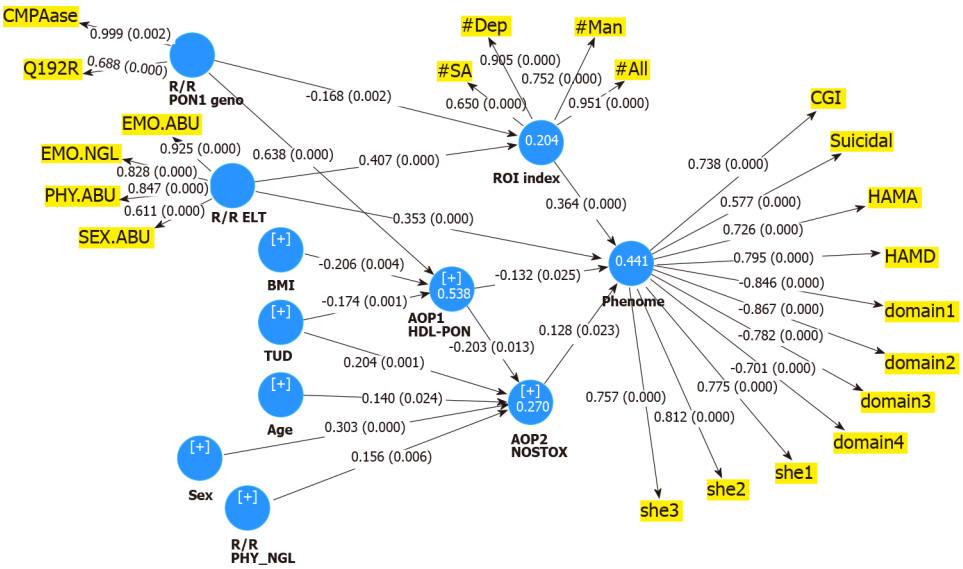


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**Figure 2 Results of partial least squares analysis.** R/R: Risk/resilience; AOP: Adverse outcome pathways; PON1: Paraoxonase; ELT: Early lifetime trauma; EMO.ABU: Emotional abuse; EMO.NEGLECT: Emotional neglect; PHY.ABU: Physical abuse; PHY.NGL: Physical neglect; SEX.ABU: Sexual abuse; BMI: Body mass index; HDL: High density lipoprotein cholesterol; NOSTOX: Nitro-oxidative stress toxicity; ROI: Reoccurrence of illness; Dep: Depressive; Man: (Hypo)mania; SA: Suicide attempts; CGI: Clinical global impression; HAMD/HAMA: Hamilton Depression and Anxiety Rating Scale; Domains (1-4): Domains of the WHO-Quality of Life questionnaire; She (1-3): Sheehan Disability Scale (domains 1-3).

methods to determine, a priori, the estimated number of cases including methods based on the psychometric properties and the strength of the intercorrelations among the factors and the factor loadings, the number of arrows pointing to a latent factor and its explained variance, and power analysis specific to multiple regression analysis[11]. An advantage is that these methods show that relatively small sample sizes of 70-127 cases may be sufficient to achieve a power of 0.8[11]. Most importantly, complete PLS analysis conducted on bootstrapped samples (*e.g.*, 5.000) allows to compute the path coefficients with *P* values as well as the specific indirect, total indirect and total effects. This method allows to examine multi-step and multiple mediation paths as for example the links from PON1 genotype to ROI to phenome, and PON1 genotype to AOP1 and to AOP2 to phenome.

As such we were able to build reliable and replicable, bottom-up, data-driven nomothetic models of BD/MDD, which comprise key features of mood disorders assembled in a knowledge-based causal framework as indicated in Figures 1 and 2[10-13]. These NNP models integrate phenome with functional and molecular pathways and, therefore, "translate" those pathways into phenome features thereby objectivating the clinical phenome, a method named "reification of the clinical diagnosis"[10-13]. The NNP method also allows to construct pathway-phenotypes (biosignatures), for example, by constructing latent vectors which comprise pathway and phenome features[20] and pathway classes, as described in the next section.

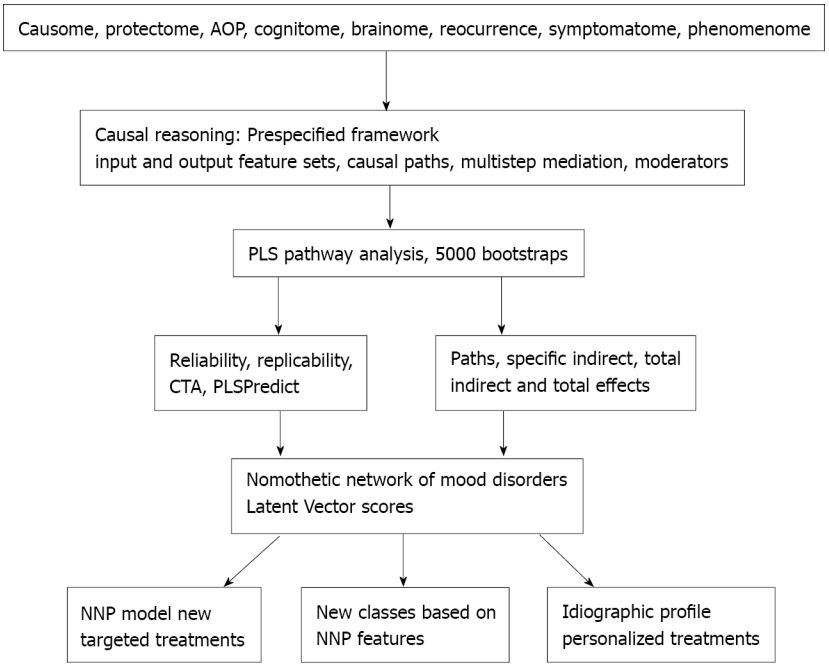


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**Figure 3 How to construct nomothetic network psychiatry models and disclose new patient clusters.** AOP: Adverse outcome pathways; PLS: Partial least squares; CTA: Confirmatory Tetrad Analysis; NNP: Nomothetic network psychiatry.

Importantly, our NNP models may pass critical rationalism tests as proposed by Popper[21]. First of all, our NNP models can be refuted or corroborated and, thus, are falsifiable. Second, our NNP frameworks are based on state-of-the-art knowledge including on causome, protectome, AOP, and phenome data and, thus, are progressive. Third, new research should elaborate on our NNP models and enrich the indicators or feature sets with pan-omics and brainome data, delete less robust features and therefore, our models are changeable and provisional. Finally, through feature selection (only significant indicators are included in the model) and feature reduction (latent vectors are constructed based on strongly related indicators), our NNP models are parsimonious representations of the building blocks of the illness.

### *NNP networks reveal drug targets at the model and idiographic level*

Once the nomothetic network is constructed, latent variable scores may be calculated which reflect the severity of causome factors, interactions between causome and protectome factors (for example, integrated in a risk/resilience ratio), different AOPs, the ROI-index and the phenome. These latent variable scores, therefore, reflect severity of the different building blocks of the illness. Our NNP models also contain idiographic features as for example self-rated severity of depression and anxiety, and self-rated HR-QoL and disabilities[10]. As a consequence, those latent variable scores not only define the nomothetic network model, but also an idiographic image or feature profile which is unique for every individual.

Consequently, our NNPs disclose new drug targets: (1) At the model level, namely causome factors such as PON1 activity, ELT, bacterial translocation; AOPs, including damage due to oxidative and nitrosative stress (O&NS) and lowered antioxidant defenses, and ROI, which is in part determined by causome features; and (2) In each individual because the idiomatic profile discloses specific aberrations.

### *New classifications based on NNP features*

The NNP factor scores may be employed in consequent unsupervised machine learning techniques including clustering analysis methods to expose novel natural clusters of patients. Previously[10-12], we used K-median, Two-step, K-mean, Ward and Forgy's clustering analysis to discover new categories based on the causome, AOPs, ROI and phenome latent vectors. Cluster analysis conducted on NNP1 models disclosed that 69.5% of mood disorder patients were allocated to a cluster with increased causome factors (interaction PON1 genotypes and PON1 enzymatic activity and ELT), O&NS-associated AOPs and increased ROI and phenome scores. Cluster analysis conducted on the NNP2 model showed that around 70% of the patients were allocated to a cluster with increased bacterial translocation, O&NS-associated AOPs and phenome severity[12]. Consequently, we have proposed to name the clusters with high causome, AOP, and ROI scores "Major DysMood Disorder due to neuro-affective toxicity" and the cluster with normal causome and AOP scores "DysMood Disorder"[10,12].

### *NNP-associated pathways*

Nevertheless, both NNP1 and NNP2 are limited in that they focus on O&NS-related and bacterial-derived features and do not comprise other well-known causome/AOP factors of mood disorders, such as indicants of activated immune-inflammatory pathways[22]. The latter will be addressed in other NNP models as reviewed in false dogmas in mood disorders. Using (un)supervised learning techniques, we repeatedly showed that large subgroups of patients with mood disorders (MDD or MDE) show signs of immune activation including increased expression of T cell activation markers such as CD7+, CD25+ and CD2+, human leukocyte antigen (HLA)DR+ and cell surface antigens such as CD25+ [interleukin (IL)-2 receptor], class II Major Histocompatibility Complex HLA-DR, CD4+CD45RA, CD4+CD45RA+ and surface Ig[23,24]. These findings were further corroborated by data that mood disorders are accompanied by: (1) Increased levels of pro-inflammatory cytokines including IL-2, IL-1β, interferon (IFN)-γ and tumor necrosis factor (TNF)-α; (2) Increased expression of positive acute phase proteins such as haptoglobin and C-reactive protein (CRP); and (3) Lowered levels of negative acute phase proteins including albumin[22,25]. Based on these findings, there is now evidence that MDD/BD are immune-inflammatory and O&NS (IO&NS) disorders[22,25].

Enrichment and annotation analysis using the Gene Ontology knowledgebase pathways (Gene Ontology Resource) indicates that the protein-protein interactions in mood disorders are associated with peripheral IO&NS pathways which are highly significantly associated with a response to a bacterium, a response to LPS, or a cellular response to LPS, indicating that the increased bacterial translocation established in NNP2 is causally associated with IO&NS pathway activation (Maes *et al*, personal data). Moreover, the GO computational model of biological systems (Gene Ontology Resource) also shows that the IO&NS profile established in mood disorders is accompanied by different impairments in neuronal functions including microglial cell activation and neuroinflammation, positive regulation of gliogenesis, modulation of chemical synaptic transmission, synapse assembly, neurogenesis and neuroblast proliferation, axonogenesis, regulation of axon extension, retrograde axonal transport, synaptic pruning and more functional and molecular pathways (Maes *et al*, personal data). As explained previously, the pathway findings in mood disorders may be summarized as indicating increased neurotoxicity and reduced neuroprotection leading to IO&NS-induced neuro-affective toxicity[22,25].

Recently, dysfunctional and degenerative processes were established in the brain of mood disorder patients. For example, altered expressions of connectome circuits in the brain were established including downregulated anterior insula connectivity, and upregulated circuits from middle frontal gyrus and hippocampus to the frontal eye fields, the anterior insula to the amygdala and middle frontal gyrus to the amygdala (Kandilarova *et al*[26], to be submitted). Moreover, using a voxel-based morphometry method using a 3T magnetic resonance imaging (MRI) system, Kandilarova *et al*[26] reported that MDD is characterized by significant reductions in grey matter volume in anterior cingulate cortex and medial frontal and regions on the left side, and inferior frontal gyrus, middle frontal gyrus, medial orbital gyrus and middle temporal gyrus on the right side. Such gray matter degeneration and dysfunctional brain connectome circuits may be predicted by increased neurotoxicity affecting brain functions and neuronal circuits[22,25]. It follows that our NNP1 and NNP2 models should be enriched with connectome (fMRI measurements) and brainome (*e.g.*, MRI measurements) features, yielding causal pathways from peripheral or gene X environmental interactions to peripheral AOPs to central AOPs to connectome and brainome to ROI to phenome. We will now discuss false dogmas in mood disorders research with respect to the new knowledge obtained in our NNP models.

## FALSE DOGMAS IN MOOD DISORDERS

### *False dogma 1: Mood disorders are mind-brain disorders that are best conceptualized using a bio-psycho-social model or mind-brain interactions*

MDD/BD is most often conceptualized as a brain - mind illness as it is thought that the brain mediates the mind and that psychosocial factors may alter the brain - mind axis to cause mood disorders[27]. Another predominant view is that MDD/MDE are brain disorders which are caused by a faulty mood regulation as a consequence of interactions between a number of factors including biological features, genetic vulnerability, psychosocial stressors including losses and ELT, temperament and comorbidities [28]. Other theories posit that psychosocial stressors cause changes in chemicals (*e.g.*, serotonin) especially in the brain regions which mediate mood, affection and reward including the thalamus, amygdala and hippocampus[28]. According to Kendler[29], the goal should be to understand how the psychosocial environment interacts with the networks within the mind-brain system that cause psychiatric illnesses. Accordingly, Kendler[29] proposed a philosophical structure for psychiatry with the acceptance of a bidirectional brain to mind and mind to brain causality. Nevertheless, the discussions as exemplified in Kendler[29]'s paper are reductionist. Why would psychosocial stressors be the sole stressors that induce MDD/MDE, while other environmentome variables such as viral and bacterial infections, environmental toxins and dietary factors are not taken into account?

Nevertheless, as described in NNP-associated pathways, we have shown that MDD/BD may have a peripheral origin and as a consequence should be regarded as a systemic disease. There is a growing realization that the AOPs of mood disorders are 'holistic' in nature comprising not only central but also peripheral processes. Thus, NNP2 showed that increased gut permeability and increased peripheral levels of neurotoxic substances (including LPS) are major causome factors in mood disorders which, in turn, may cause activated peripheral IO&NS pathways and neuroinflammation[22,25,30]. Our NNP models showed causal links from strictly peripheral factors (bacterial translocation) or gene X environmental interactions (PON1 gene x ELT) to AOPs (IO&NS pathways) and ROI to phenome. Enrichment and annotation analysis show how these peripheral pathways may cause neuro-affective toxicity which may explain fMRI and 3T MRI findings and the phenome of mood disorders (see NNP-associated pathways). Moreover, it should be added that a larger part of the variance in the severity of the phenome is explained by direct and indirect effects of causome, AOP and ROI features, namely around 57.7% and 44.2% in NNP2 and NNP1, respectively[10,12]. This evidence contrasts the view that mood disorders should be regarded as pure brain disorders or mind-brain disorders and that mind to brain causality and or psychosocial stress to brain dysfunctions are the main drivers of the illness.

### *False dogma 2: Mood disorders due to brain disease are attributable to psychosocial stress or chemical imbalances*

A number on neurological brain disorders are associated with MDD/MDE (symptoms) including Parkinson's and Alzheimer's disease, multiple sclerosis, stroke and Huntington's disease[31]. The widely held belief is that comorbid depression is caused by chemical imbalances in the brain (*e.g.*, dopamine and serotonin), or that it is the result of negative thoughts following a diagnosis, helplessness, severe stress from living with a medical disorder, loss of independence or as a side effect of medication used to treat brain disorders[28]. Nonetheless, comorbid depression may worsen the morbidity and cause increased mortality of some brain disorders and the existence of depression may precede some neurological disorders, such as Alzheimer's and Parkinson's disease, implying that depression is a key component of these conditions[31].

In addition, in these neuro-immune and neurodegenerative brain disorders, depressive symptoms are associated with increased IO&NS pathways. For example, depression due to multiple sclerosis is associated with increased IL-6 and lowered albumin[32]. Depression due to stroke is largely predicted by hypertension and atherosclerosis as indicated by white matter hyperintensities (assessed with T2-weighted and fluid-attenuated inversion recovery MRI) and the volume of the acute stroke lesions (measured with diffusion-weighted MRI)[33]. White matter hyperintensities are a consequence of a chronic mild inflammatory process while the acute stroke lesions are accompanied by peripheral and central IO&NS responses[34-36]. The severity of the disabilities induced by stroke was not associated with the onset of depressive symptoms, indicating that the latter are a consequence of IO&NS pathways associated with the cause of stroke (atherosclerosis) as well as the systemic inflammation and neurodegeneration due to stroke[33]. In schizophrenia, another systemic neuro-immune disease[20], the severity of depression and manic symptoms is significantly associated with IO&NS indicants including increased levels of IL-6, high mobility group box1 and cytokine-induced activation of the tryptophan catabolite pathway[37,38]. In temporal lobe epilepsy (TLE), depression, anxiety and excitation aggregate with the clinical hallmarks of the illness (including seizure frequency, controlled *vs* uncontrolled TLE, presence of post-ictal confusion and aura) and a latent vector extracted from these clinical features is associated with PON-1 genotype-associated reductions in enzyme activity[39,40]. Furthermore, affective symptoms in TLE are strongly associated with protein oxidation and aldehyde formation and lowered-thiol groups indicating that damage to oxidative stress plays a key role in affective symptoms due to TLE[39,40]. In Parkinson's disease, increased CRP, and chemokine (C-C motif) ligand 2 (a pro-inflammatory chemokine) are associated with the severity of depressive symptoms[41].

To sum it up, the current theory that depression in neuroinflammatory and neurodegenerative brain disorders is caused by psychological stress or chemical imbalances in neurotransmission is at best skewed toward reductionism and should be abandoned in favor of the novel findings that (neuro)inflammatory processes are to blame for these disorders' associated mood symptoms.

### *False dogma 3: Mood disorders due to comorbid systemic illness are attributable to psychosocial stress*

According to the ABC of psychiatric medicine, depression caused by medical diseases is explained by a variety of stressors linked to the illness, such as functional losses, the personal meaning ascribed to these stressors and attitudes about the illness itself[42]. Furthermore, personality traits, social support and stage of life, as well as earlier experiences, modify those personal meaning and beliefs[42]. Once sadness, anxiety and somatic distress appear, the risk to develop depressive disorders and persistent subthreshold symptoms is increased and modified by social support, medical complications, genetic loading and coping strategies.

It appears that these authors and the psycho-social school in general take for granted that a load on the mind-brain pathway causes depression, a folk psychology explanation. Folk or commonsense psychology explains the "mental state" of behaviors as the outcome of daily life experiences, as for

example, "depression" is a response to a perception, pain, a belief, *etc*[11]. Based on these folk-like theories, treatment plans are then worked out to treat depression due to medical disease and these comprise advice, education and reassurance, specialized cognitive or dynamic behavioral psychotherapies, interpersonal therapy, problem solving and of course antidepressant treatment[41]. Some of these treatments may even be performed by non-specialists in primary and secondary care, including cognitive therapy to correct distorted thinking, encourage a sense of mastery and promote more accurate coping strategies.

Nevertheless, this psycho-social dogma fails to explain how or why the mind or mental pathways could lead to the behavioral and cognitive changes associated with MDD/MDE. In fact, depression due to a variety of medical illnesses may be attributed to the activated IO&NS pathways which characterize these disorders[31]. Thus, diabetes mellitus type 1 and 2, rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, lupus erythematosus, chronic obstructive pulmonary disease, chronic kidney disease and psoriasis are all IO&NS disorders accompanied by a significantly higher prevalence of mood disorders[31]. The post-partum period, blood dialysis and IFN-α treatment are frequently accompanied by depression and also these conditions are characterized by activated IO&NS pathways [31].

New evidence shows that activated peripheral IO&NS pathways are directly associated with depressive symptoms in medical disorders. For example, depression is strongly comorbid with chronic apical periodontitis (CAP)[43]. Root canal LPS levels are increased in patients with CAP and are significantly associated with clinical depression due to CAP, as well as with severity of depression and HR-QoL[43]. Moreover, MDD due to CAP is characterized by increased indicants of O&NS including increased nitric oxide metabolites, lipid hydroperoxides and advanced oxidation protein products[43].

Moreover, previous NNP research examining depression associated with medical disease demonstrated that depressive and anxious symptoms are part of the same clinical core that encompasses the characteristics of those medical disorders. For example, in atherosclerosis and unstable angina, depression severity is substantially associated with the same core (latent vector), which also includes clinical characteristics such as atherosclerosis, unstable angina, class III/IV unstable angina and enhanced atherogenicity and insulin resistance[43]. The latter features are reflective manifestations of a common core, namely severe heart disease, which, therefore, is the cause of its manifestations. Moreover, a larger part of the variance (66.6%) in this common core was explained by peripheral IO&NS pathways[44].

A recent NNP constructed in children with depression due to transfusion-dependent thalassemia showed that depressive symptoms are strongly associated with indicants of peripheral iron-overload and immune-inflammatory responses caused by thalassemia and the repeated transfusions[45]. Moreover, the constructed NNP model showed that iron-overload indices (increased iron and ferritin) and immune-inflammatory biomarkers (increased IL-1β, TNF-α and IL-10) and key depressive subdomains such as sadness, physio-somatic symptoms (fatigue and pain), social isolation and irritability symptoms and lowered self-esteem belong to the same core. Furthermore, 73.0% of the variance in this common core was explained by number of transfusions and hospital admissions and use of Desferal[45].

We constructed another NNP in depression due to type 2 diabetes mellitus and established that 61.7% of the variance in depressive and anxiety symptoms could be explained by indicants of immune activation and the combined effects of insulin resistance and atherogenicity, which partially mediated the effects of immune activation on depressive symptoms[46]. In patients with depression and anxiety due to established coronavirus disease 2019 infection, we found that 70.0% of the variance in the severity of affective symptoms was explained by the combined effects of lung inflammation (as assessed with lung computed tomography scan) and reduced oxygen saturation and that these effects were partially mediated by IL-6, IL-10, CRP, soluble advanced glycation products and lowered albumin[47]. Overall, the current view that depression caused by medical disorders should be explained by losses or beliefs about the illness is at best reductionist and should be replaced by NNP models indicating that activated IO&NS pathways in medical disease are responsible for comorbid depression.

### *False dogma 4: DSM/ICD are the gold standards to make the MDD/BD diagnosis*

MDD/MDE are commonly defined as a cluster of symptoms which are more severe than sadness and may be discriminated from the latter by the duration of symptoms (more than two weeks according to DSM) and the number of symptoms (more than 5 in DSM). However, the decision whether a patient suffers from MDD/MDE rather that a sadness reaction is made by the clinician (either psychiatrist or general practitioner) who will treat the patient with antidepressants depending on whether MDD is present or not. BD formerly known as manic-depressive psychosis is characterized by recurrent episodes of MDE and mania (BP type 1) or hypomania (BP type 2). ICD classifies "mood disorders" which is further subdivided into MDD and BD, whereas the DSM-5 classifies two separate categories, namely MDD and BD[1,2].

Nevertheless, there are several serious problems with the DSM/ICD case definitions of MDD, MDE and BD, BP1 and BP2. First, the case definitions are often unreliable with an intraclass kappa reliability of 0.28 indicating minimal agreement among psychiatrists[48,49]. Furthermore, the DSM case definitions of affective disorders are unreliable and invalid[49,50]. BD is often over diagnosed with

studies showing that only 42.9% of patients diagnosed with the DSM criteria of BD meet the diagnostic criteria[50]. The misdiagnosis rate is associated with the low demarcation of BD from personality disorders including borderline personality disorder, polysubstance abuse and attention deficit disorder [50]. BD patients are often misclassified as suffering from MDD or other conditions with a rate as high as 60%[51]. Another major problem is that the diagnosis of BD is often underrated when the patient presents with a depressive index episode and an atypical course of manic or hypomanic symptoms[50].

A more fundamental flaw of the DSM/ICD case definitions of mood disorders is their top-down manner of generation[11]. Both taxonomies diagnose mood disorders prior to biomarker and neurocognitive investigation, treating these features as ancillary data that may or may not support the diagnosis [10-13]. Most current biological, neurocognitive and molecular research employs these top-down case definitions as independent variables, while the key features and even causome, protectome and cognitome features are employed as dependent variables in statistical analyses. Nevertheless, causal reasoning indicates that those features should be the explanatory variables, while the diagnosis of mood disorders is a higher-order concept constructed using these features[10-12]. Based on these inadequate model assumptions, researchers then use unreliable diagnostic classes, based on value laden and controversial criteria, as explanatory variables in analysis of variance to analyze biomarker levels, brainome data, and neurocognitive test scores and sometimes even causome/protectome data. As such, current biomarker research continues to employ unreliable diagnostic classes applied in inadequate model assumptions further confounded by the use of inappropriate statistical analysis[10,11]. Overall, no falsification of the dogma-like, top-down DSM/ICD classes or criteria is possible using data from sources other than the DSM/ICD, precluding a deductive approach[11].

### *False dogma 5: Severity of illness should be measured using rating scales*

Another gold-standard dogma is that the severity of mood disorders should be assessed using rating scales such as the Hamilton Depression Rating Scale (HDRS)[52]. Instruments which aim to assess severity of depression encompass a number of observable or self-rated symptoms including loss of interest, sadness, fatigue, concentration problems, insomnia, lowered self-esteem, feelings of worthlessness or suicidal ideation. Because psychiatrists consider such symptoms to be reflective measurements of an underlying phenomenon, they typically add the scores on the separate items and construct an unweighted sum-score, which is thought to reflect severity of illness. However, to compute such sum scores, rating scales should be unidimensional, *i.e.*, all items should load heavily on one primary factor that has additional adequate psychometric properties[53,54]. We discussed before[54] that the indicators of latent vectors should have loadings > 0.5 with Cronbach alpha > 0.7, composite reliability > 0.8, and average explained variance > 0.5 while Confirmatory Tetrad Analysis should show that the model is not mis-specified as a reflective model. Our analyses showed that the HDRS (and other scales as well) do not comply with these criteria and that the total unweighted sum of the items may not be used as a severity index. Fried *et al*[53] reported that the HDRS and other commonly used rating scales of depression do not comply with the unidimensionality criterion. Moreover, these rating scales cannot be used as outcome variables in randomized controlled studies because in order to interpret repeated measurements, rating scales must be unidimensional and show measurement invariance[53].

There are more serious issues with the rating scales currently in use. Numerous items on these rating scales are based on descriptions from folk psychology, such as “I feel down”, “I feel depressed”, “I cry easily”, “I feel sad” and “I feel disappointed”. To obtain meaningful data for psychiatric inventories, folk psychology-like terminology is translated into Likert scale items and useful statistical entities are created after some window dressing[11]. As such, commonsense psychology terms are used as proxies for severe symptoms such as anhedonia and feelings of guilt and incorporated as criteria to make the diagnosis of mood disorders without reference to any independent validator, including causome, AOP or brainome markers.

Of course, psychological concepts such as mood cannot be directly assessed, but the best approach is to assess multiple observable manifestations of the underlying construct, which is the cause of the covariation among its indicators. In fact, our NNP models consist of unidimensional, reliable, validated and replicable latent vectors, including a phenome latent vector[10]. In fact, the severity of illness should not be assessed using one folk-psychology-derived rating scale, but by the causome, AOP, ROI and phenome latent vector scores. The latter should be based on various assessments including interview-based measurements of illness severity and suicidal ideation, and self-rated scores, including HR-QoL and disabilities[10]. We are aware that the final reflective latent vector (based on feature selection and reduction), will almost certainly contain folk psychology-like expressions, but this is less significant in the context of a NNP model, as the clinical phenome latent vector is reified as a concrete construct.

### *False dogma 6: Clinical remission should be defined using threshold values on rating scale scores*

It is common practice to employ rating scale scores to define remission and partial remission. For example, influential psychiatrists, including Eugene Paykel, David Kupfer, Michael Thase and Roger McIntyre developed criteria to delineate remission and partial remission based on a single depression rating scale score, often the HDRS. However, such methods are not accurate. Firstly, as described above, the HDRS cannot be employed as a measure of change during treatment[54]. Secondly, and more importantly, remission, partial remission and relapse should be defined using the modifiable building

blocks of the illness (thus excluding genotypes and the ROI-index), namely causome, AOP, cognitome, brainome and phenome features as computed in our NNPs.

Furthermore, remission of a psychiatric disorder should be delineated using Soft Independent Modelling of Class Analogy (SIMCA) and not by a threshold value applied to an unreliable scale[20]. Thus, a principal component model should be built around the healthy control class using causome, AOP and phenome features (excluding the unmodifiable features) and the apparent remitters should be projected into this SIMCA model and be authenticated as controls (that is, being allocated to the healthy class) or rejected as belonging to the control class[55]. Cases that cannot be authenticated as normal controls are non-remitters and, in the latter, the "relative improvement" should be assessed as an improvement in the modifiable AOPs, brainome, cognitome and phenome latent vector scores.

### *False dogmas 7: Existing diagnostic boundaries are too restrictive and spectra are the rule*

**The diagnosis of BD should be inclusive:** Another problem is that the diagnosis of BD became more and more inclusive and that the diagnosis of MDD became more restricted[50]. As such, the classical prevalence rate of BD, which is around 0.5% to 1.5%, has increased and may even reach a rate as high as 10%[56]. It is debated whether a lack of well-defined MDD and BD case definitions leads to an overdiagnosis of MDD or BD to the detriment of BD or MDD[50]. The downside of over diagnosing BD is that patients with other conditions will be treated with mood stabilizers some of which have detrimental side effects on HR-QoL[57]. The downside of over diagnosing MDD to the detriment of BD is that those patients will be devoid of more targeted treatments with mood stabilizers. In fact, another pointless debate is that BD is frequently undiagnosed[57] or over diagnosed[59].

An even greater problem is the status of BP2. Some studies suggest that BP2 is a distinct category which should be separated from recurrent MDD and BP1 and this is based on proband studies[60]. Nevertheless, some studies suggest that the reliability coefficient of BP2 is not greater than that of chance, whereas other authors claim that a good interrater reliability may be obtained when BP2 is diagnosed by experienced psychiatrists[60]. Consequently, some authors have relaxed the case definitions of BP2 for example using new hypomania checklists which include subsyndromal hypomania or subthreshold bipolarity, which is considered to belong to the soft BP spectrum[61,62]. Consequently, these authors use this checklist, which shows a sensitivity of 80% to detect true bipolar patients and a specificity of 51% (computed *vs* MDD) to diagnose BD. Consequently, up to 79% of fibromyalgia patients suddenly belong to the bipolar spectrum using a diagnostic algorithm which is grossly inadequate[63].

**BD subtypes shape a continuum:** Some authors proposed the "bipolar spectrum" concept which considers that bipolarity occurs along a continuum from soft to clear forms of BD, thus contrasting the categorical view of the DSM[64]. As a result, the increased prevalence of BD may be explained by the detection of softer BD phenotypes such as BP-2, BP-3, rapid cyclers and cyclothymia[56]. The BP spectrum may also comprise MDD with hyperthymic traits, depressive mixed states with hypomanic symptoms including sexual arousal, ultrarapid-cycling forms, patients with lifelong temperamental dysregulation, and cyclic irritable-dysphoric, intermittently explosive or impulse-ridden clinical expression[56]. Even the status of agitated depression appears to have remained elusive, with some suggesting that this type of depression is a mixed state or, more accurately, "pseudo-unipolar", and should be renamed "excited mixed depression"[65]. One can only speculate on the number of additional surreal labels that will be coined in the near future.

**Mood disorders subtypes are part of a continuum:** Another heavily debated issue is whether MDD and BP belong to a continuum (continuous theory) or whether they constitute distinct categories (discontinuous theory)[66,67]. Some authors claim that research consolidated the existence of a broad bipolar spectrum between the extremes of unipolar MDD and psychotic manic-depressive illness[68]. It is thought that the continuity spectrum between MDD and BD is supported by a number of findings including the presence of mixed states (both mania and depressive symptoms co-occur), no real separation between MDD and MDE in BD, and that many MDD patients may shift into BD. On the other hand, some findings would support the discontinuous theory, namely BP occurs more frequently in BP probands' relatives and BD shows an equal sex distribution whereas MDD shows a higher frequency in females; and BP shows a more recurrent course than MDD[66,67]. Nevertheless, some results support the dimensional and categorical approach with the mood disorders extremes (severe MDD and BP1) showing a categorical distinction, and the moderate mood disorders (BP2 and MDD) showing continuous differences[67]. Nevertheless, these studies have no merit because the accurate machine learning tests were not used to examine the continuum *vs* discontinuum theories.

**There are different depressive subtypes:** Modern psychiatry generally considers that there are different MDD/MDE subtypes including atypical depression, melancholia, recurrent depressive disorder, dysthymia, bipolar depression, double depression, psychotic depression, seasonal affective disorder, depression with postpartum onset, perinatal depression, postpartum depression, prenatal depression, depression with catatonic features, chronic depression, persistent depressive disorder, geriatric depression, premenstrual dysphoric disorder and treatment resistant depression[1,69]. Some of these subtypes came and went including reactive depression, situational depression, vital depression,

endogenous depression, endogenomorph depression, hidden depression, concealed depression, anxious depression and a mixed episode in BDs.

Nevertheless, because the reliability of their parent classes (MDD and MDE) is very low, we may speculate that those different classes have zero reliability. In addition, virtually none of these classes, except melancholia, has been validated using unsupervised and supervised machine learning techniques[70]. Using both supervised (SIMCA) and unsupervised (clustering and factor analysis) methods we were able to show that melancholia is at the same time a continuous and a discrete class [70]. Thus, along the continuum of severity of illness, some symptoms (namely the melancholic symptoms) become more severe and more prevalent and as, a consequence, may shape a distinct symptom profile, *i.e.*, major depression with melancholic features. As such, qualitative distinctions may be the result of quantitative distinctions, implying that all debates over continuum or discontinuum theories are pointless.

**There are differences between unipolar MDD *vs* bipolar MDE:** Another pointless discussion is whether there are differences between unipolar MDD and bipolar MDE, and whether they are the same or different diseases[71]. As a result, "depression with and without mania might be understood as the same condition", while "BD disorder" could be thought of as mania, with or without depression. Another point of view is that unipolar MDD and BD depression are separate illnesses that can coexist [71]. Biological dysregulation is a risk factor for both MDD and BD, although it appears to be more strongly linked to BD than unipolar MDD, implying that BD is linked to more excessive responses to psychosocial stresses than MDD[71]. From a biological standpoint, the IO&NS pathways in MDD, BP1 and BP2 differ significantly, with those pathways being more expressed in MDD and BP1 than in BP2 and more in MDD than in BP1[72]. In depression, cell-mediated immunity is activated as well, but not in mania or hypomania[73]. All the changes, however, are quantitative rather than qualitative and some studies found immune-inflammatory pathway differences between unipolar and bipolar depression [74], while others found no IO&NS differences between MDE in MDD and BD[75].

**It is better to abolish all psychiatric diagnostic systems:** Overall, the dimensional approach to the mood disorders spectrum idea, as well as the over diagnosing of BD with more inclusive diagnostic criteria, have blurred the lines between distinct diagnostic categories, lowering the diagnostic reliability of these mood disorders[75]. Given the above it is not surprising that the DSM and ICD taxonomies lack reliability, validity and therefore, are counterproductive for research purposes[6,77-79]. As a result, it is not unexpected that some authors came to the conclusion that all psychiatric diagnostic systems should be abolished[80].

Based on the NNP models we developed in our research, we believe it is best to eliminate all the above-mentioned mood disorders diagnostic classes and labels. To begin with, none of these classes has been designated as a separate category. Second, our NNP models show that none of the major classes MDD, BD, BP1, or BP2 are significant. For example, supervised methods like SIMCA were unable to validate these classes as distinct entities when applied to clinical and biomarker data in our data set (personal data). More importantly, two-step cluster analyses using all features of NNP1 and NNP2 as categorical variables revealed new trans-diagnostic clusters (see new classifications based on NNP features), which are more influential than the classification into MDD, BD, BP1 and BP2[10,12]. These negative findings on the MDD and BD classifications may be explained by the fact that: (1) They are binary concepts (present or not present); (2) They are top-down taxonomies based on unreliable clinical criteria and without external validation; and (3) The latent vector scores of causome, AOP, cognitome, ROI and phenome contain more accurate information on mood disorders than the binary diagnosis into MDD and BD.

**Dogma 8: No need to ROI-define mood disorders:** The DSM and ICD categorization systems have never placed a high value on course trajectory specifiers. Symptoms, symptom clusters and BD polarity, as well as a few course specifiers like rapid cycling, chronic depression and seasonal patterns, are used to classify DSM/ICD disorders. Interestingly, a recent project proposed to make a clinical course-graphing scale for DSM-5 disorders, namely the Timeline Course Graphing Scale for the DSM-5 Mood Disorders (TCGS)[81]. This new method takes a more systematic approach to graphing the course of mood disorders, allowing researchers to estimate the onset of mood disorders (early *vs* late onset) as well as the severity of the illness (chronicity, subthreshold syndrome, and so on). The TCGS' major goal is to distinguish MDD from the new DSM-5 class Persistent Depression, because it was anticipated that failing to distinguish the two diseases could cause treatment efforts to fail[81]. Another way to prospectively study the alternating symptoms in BD is the NIMH Life Chart Method[82].

Nevertheless, the DSM/ICD categorization systems and the TCGS/NIMH proposals do not take into account the disease's recurrence pattern, severity of recurrence, recurrence of suicidal behaviors, and recurrence-related worsening in cognitive functioning, HR-QoL life, and increased impairments[18]. Previously, some authors proposed staging models which included criteria considering functional and cognitive impairments[83-86]. However, these were theoretical models, whereas the ROI-index produced from the NNP model is calculated using predictive mathematical algorithms and real patient data. Furthermore, earlier theoretical models provided phase-related classifications of unipolar and

**Table 1 Characteristics of the three stages of affective disorders[18]**

| Stages | Phase 1: Early phase | Phase 2: Relapse-regression | Phase 3: Suicidal regression |
|---|---|---|---|
| Early lifetime trauma | - | + | ++ |
| Number of depressive episodes | + | ++ | +++ |
| Number of (hypo)manic episodes | + | ++ | ++ |
| Number of suicidal attempts | + | + | +++ |
| A lifetime history suicidal ideation | + | + | ++ |
| Current suicidal ideation | + | + | +++ |
| Lower income | + | ++ | +++ |
| Disabilities | + | ++ | ++ |
| Reduced health-related quality of life | + | ++ | ++ |
| Reduced cognitive processing speed | + | ++ | ++ |
| Deficits in executive functioning | - | - | + |

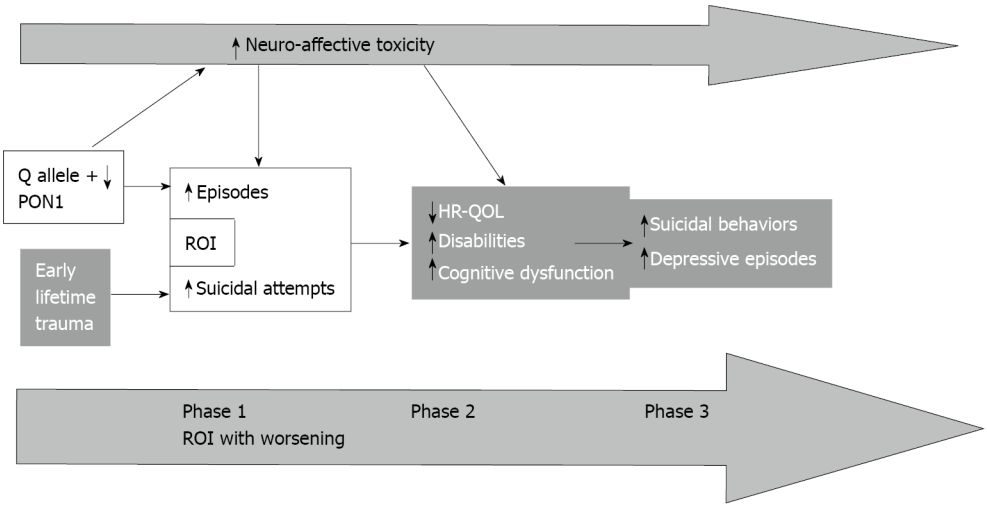


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**Figure 4 Causal links from early lifetime trauma and paraoxonase 1 genotype and enzymatic activity to reoccurrence of illness to phenome including health-related quality of life.** ROI: Reoccurrence of illness; HR-QOL: Health-related quality of life; PON1: Paraoxonase 1.

bipolar patients, but we computed continuous ROI scores in the combined MDD and BD group and derived externally validated ROI phases by binning the ROI into three ROI groups[18]. This ROI, as discussed in NNP models, includes information on episode and suicide recurrence, as well as the binary classification of BD and MDD/MDE.

The ROI is a crucial component of the NNP models because it predicts the phenome of mood disorders and mediates the effects of the causome (interactions between the PON1 gene and ELT) on the phenome, as detailed in NNP models. Furthermore, ROI was found to be associated with not only the phenome[10], but also the severity of depressive and manic symptoms, current suicidal ideation, and cognitive impairments in semantic memory and executive functions, as well as socioeconomic status, treatment, and biomarkers such as lowered antioxidant defenses, increased nitro-oxidative stressors, insulin resistance, CRP and a variety of other biomarkers[19]. More crucially, the ROI index is influenced by the interactions between ELTs and PON1 enzymatic activity[10].

Most importantly, our ROI latent vector is unidimensional and fits a reflective model with adequate reliability validity and replicability and, therefore, the ROI (*i.e.*, its organic substrate) is the cause of the reoccurrence of depressive episodes in MDD and depressive and manic episodes in BD and suicidal attempts in both MDD/BD as well. By inference, the reoccurrence of these phenomena is determined by a same underlying phenomenon which is partly determined by PON1 genotype and ELT interactions, and IO&NS pathways[10]. The ROI-index is not only strongly associated with PON1 gene x ELT interactions, but also with O&NS pathways indicating lipid and protein oxidation[18]. Moreover, a recent meta-analysis showed that there are strong associations between suicide attempts and ideation

and IO&NS pathways with a high effect size[87]. There is also some evidence that sensitization of IO&NS pathways may underpin this reoccurrence[73].

Through binning, we constructed three patient groups that reflect relevant phases of mood disorders, namely: "(1) An early phase; (2) A relapse-retrogression phase; and (3) A suicidal-retrogression phase" [18]. Table 1 shows that these phases are externally validated by clinical features. Figure 4 shows that the causal links from ELTs and PON1 genotype to ROI to phenome capture the lifetime trajectory of MDD/BD patients from childhood to an increasing number of episodes and suicidal behaviors to the progressive worsening of disease in terms of cognitive deficits, HR-QoL, and disabilities[18].

Such findings indicate that MDD, BD, and recurrent episodes and suicidal attempts share a common substrate and that MDD and BD should be regarded as the same disorder, namely "DysMood disorder" whereby the causome, AOPs, and ROI shape a distinct class namely "Major DysMood Disorder due to neuro-affective toxicity".

## CONCLUSION

Psychosocial or mind-brain models have traditionally been used to explain mood disorders, but these models are inadequate because such models are not even falsifiable. The DSM/ICD criteria for mood disorders are narratives that have been stripped of their context and are therefore without any mechanistic explanation. The DSM/ICD classifications of mood disorders are not only unreliable but their dogma-like nature prevents inductive (as top-down) and deductive (as incontrovertible) remodeling of the case-definitions.

We built new bottom-up, data-driven, machine learning NNP models of mood disorders that reify all the components of mood disorders, as is the case in all medical disciplines where diagnosis offers a pathophysiological explanation. Neuro-affective toxicity causes functional and structural impairments in the brain, as shown by these NNP models and enrichment/annotation analysis. In mood disorders, the ROI index plays a critical role in mediating the effects of causome pathways on the phenome. The ROI index is also significantly linked to a progressive worsening of cognitive impairments, phenome severity, disabilities and HR-QoL. As a result, MDD and BD should be treated as if they were one and the same illness.

Our findings show that the causome, AOP and ROI features identified in our NNPs should be new drug targets for treating "Major DysMood Disorder", rather than the binary diagnosis of BD or MDD. The new drug targets include: Reduced PON1 enzyme activity and its consequences, increased Gram-negative bacteria or LPS translocation, increased ELTs and their consequences, lowered levels of antioxidants and elevated reactive oxygen and nitrogen species, lipid peroxidation with higher levels of aldehydes, protein oxidation and formation of oxidative-specific epitopes, nitrosative stress and increased autoimmune responses to oxidative-specific epitopes. As discussed in NNP-associated pathways, these O&NS disorders are strongly linked to activated immune-inflammatory pathways and together they may cause functional and structural changes in the brain indicative of neuro-affective toxicity. It is important to note, as well, that PON1 activity and ELT-associated sensitization of IO&NS pathways are new drug targets, and that targeted treatments may help prevent further episodes and worsening of the disease, including progression into later phases with increased cognitive and functional deterioration, as well as suicide risk.

## FOOTNOTES

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OPINION REVIEW

# Eco-crisis and mental health of children and young people: Do child mental health professionals have a role?

Sundar Gnanavel

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## Abstract

Child mental health professionals have an extremely important role to play in their distinct roles as clinicians, therapists, researchers, policy makers, advocates, preventative public health professionals and service developers pertaining to eco-crisis in the child and adolescent populations. This article provides examples of how this can be done.

**Key Words:** Eco-crisis; Children; Mental; Mental health

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**Core Tip:** Child mental health professionals can perform different and effective roles pertaining to eco-crisis and mental health of children and young people. They can be clinicians, researchers, preventative professionals, service builders and policy makers in this regard. I believe this would be a moral obligation and a professional duty to the population that we are privileged to serve.

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## INTRODUCTION

International experts widely accept that climate change is under way and it poses a critical threat to the future of mankind. The 2015 Paris Agreement acknowledges that climate change is an urgent and potentially irreversible threat to the planet (Interna-

tional Panel on Climate Change, 2018)[1]. These changes can potentially affect food and water availability, agricultural productivity, natural ecosystems and result in a variety of health disorders (Intergovernmental Panel on Climate Change, 2014)[2].

There are emerging studies that demonstrate the physical health effects of climate change, but research is relatively scarce on the psychological effects. In particular, there is a lacuna in our understanding of psychological effects in children and adolescents who in fact might be disproportionately affected[3]. Climate change could induce or precipitate psychiatric disorders and might worsen existing mental illnesses among children and adolescents experiencing climate anxiety.

Mental health professionals, policy makers and advocates need robust evidence to mitigate the effects of climate anxiety on the short-term and long-term mental health of young people. The role of child mental health professionals as an advocate, researcher, or policy maker is crucial. This review aims to demonstrate the multiple effective roles that they can play in this regard with examples to demonstrate in each of these roles (Figure 1).

## AS A CLINICIAN AND A THERAPIST

Empirical evidence demonstrates that both the acute and chronic mental health effects of climate change has risen sharply in the past decade. Several recent studies have explored the mental health effects of climate-related psychological disorders, including depression, anxiety, post-traumatic stress disorder, the exacerbation of psychotic symptoms, suicidal ideation and completed suicides, including in the child and adolescent population[4]. Child mental health clinicians are appropriate professionals for conducting a detailed assessment in addition to developing and implementing appropriate assessment strategies.

In addition to diagnosable mental health disorders, experiences of ecological anxiety (*i.e.* apprehension about anticipated threats to salient ecosystems) and ecological grief (*i.e.* grief in relation to ecological loss) are commonly noted as psychological phenomena (though poorly understood) causing distress in children and adolescents. The grief phenomena associated with loss of the ecosystem is commonly categorised into: grief associated with physical ecological losses, grief associated with the loss of environmental knowledge and grief associated with anticipated future losses[5]. It is to be noted that these phenomena which can be debilitating are not diagnosable as a psychiatric disorder in the current diagnostic & classificatory systems.

Enhanced and detailed clinical assessments are needed for this population. For some people suffering from ecological grief and anxiety, clinical support might be required, particularly if their personal safety or daily functioning are affected. It is important to discern this from reactive emotions which can be unpleasant and at times painful but do not impair daily functioning and rather may assist in making productive and positive changes, including in the implementation of climate change related solutions. Screening for psychiatric comorbidity including mood and anxiety disorders with subsequent management is also crucial for a holistic plan.

Existing individual and group therapy strategies could be adapted and improvised for children and adolescents experiencing co-anxiety. The role of child psychiatrists and psychologists would be crucial in this regard. For example, interpersonal group therapy would be one option to consider[6]. There are some examples of networks that have been created to support climate-related mental wellbeing like the Good Grief Network.

Social prescribing and facilitating social connectedness would be an important part of the management plan. This would help in managing some of these psychological phenomena causing distress but with no diagnosable psychiatric disorder. The benefits would include avoiding over-pathologising and inappropriate management of these issues within a medical model[7]. For example, prescribing spending time in nature, engaging in community-based work for increasing the number of trees in urban spaces, improving the infrastructure for active commuting and reducing air pollution through a shift to clean energy might be beneficial.

Child mental health professionals are well regarded for their systemic approach to managing mental health. In this case, helping the parents/family members acknowledge the challenge, encourage parental insight into children's responses, encouraging empathetic communication with children and adolescents, validating their feelings of fear and disillusionment and mobilising hope through meaningful goal-directed activities would be appropriate measures[7].

## AS A RESEARCHER

As mentioned earlier, there is scarce research into the psychological effects of climate change in children and adolescents. The primary focus of the existing studies is assessing participants' knowledge, perceptions and attitudes about climate change. For example, a recent survey-based study of 10000 young people demonstrated significant respondents were worried about climate change (59% very or extremely worried, 84% at least moderately worried)[8]. Existing literature suffers from several method-

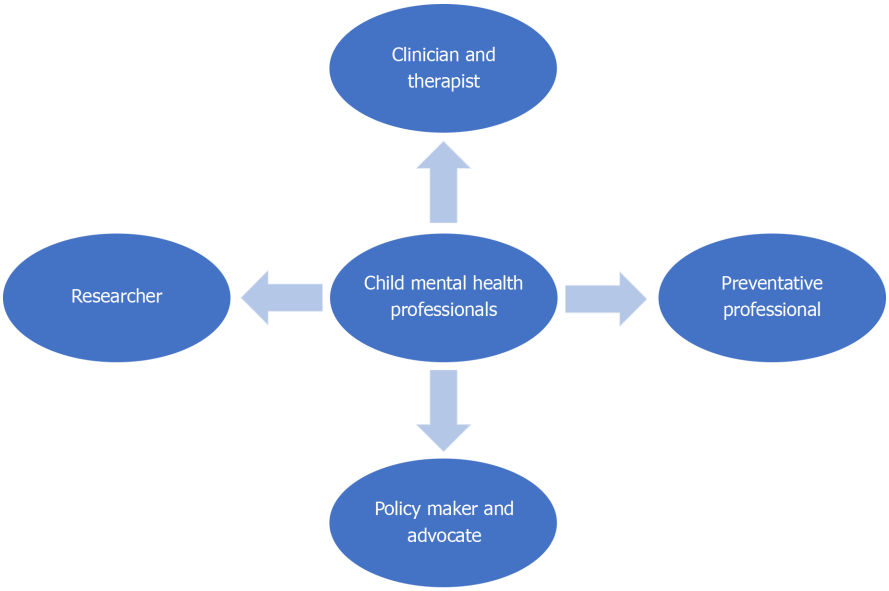


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**Figure 1 Roles of child mental health professionals in ecological crisis.**

ological challenges that limits the interpretation of study results. This includes the use of self-report instruments exclusively, extrapolating adult surveys to children, limited sample frame (lack of representativeness), use of closed form surveys, common methodological biases, such as social desirability, item ambiguity or demand characteristics that may result in measurement error and not taking developmental perspective (*e.g.*, children *vs* adolescents) into consideration[9].

The need of the hour is to develop psychometric instruments that can accurately screen for and measure the severity of eco-anxiety in children and adolescents. This is important to quantify differences between subjects and across time-points. This is also important for accurately assessing the relationships between climate change distress/anxiety and other known constructs, such as environmental concern and general anxiety. Of course, this is also vital for measuring response to treatment that we provide as child mental health professionals[10]. Prior to developing psychometric instruments, a clear conceptualization of the construct of eco-anxiety is imperative and a consensus needs to be reached on this. This is also important from the perspective of diagnostic and classificatory systems to explore if this could merit a primary psychiatric diagnosis on its own.

In addition to developing valid psychometric instruments, child mental health professionals are well positioned to explore a number of other poorly understood aspects including differences in perception of climate change according to age, differences in perception based on location (*e.g.*, developing *vs* developed countries; rural *vs* urban population; low *vs* higher socio-economic group), prevalence of comorbid psychiatric disorders with eco-anxiety and effectiveness of different therapeutic interventions for the same.

Future high-quality research on this subject should employ a variety of methods both quantitative and qualitative, to elicit a broad understanding of factors in addition to knowledge. Different methodological biases should be carefully considered to devise the study as well as to interpret the study findings. This could be at the individual, collective, and situational levels as all these impact adolescents' climate-related concepts[11]. The use of open-ended questions would be invaluable in exploring the views of this group without limiting their responses. Also, using reverse coding rather than questions with negations would be a useful strategy to circumvent the cognitive limitations particularly in younger children.

## AS A PREVENTATIVE PROFESSIONAL (PUBLIC HEALTH)

Research on resilience and positive development identifies the characteristics that will be most valuable for the next generation to adapt successfully to climate change related difficulties. These can be grouped into individual skills and capacities, interpersonal skills and relationships and social/civic engagement [12].

Individual characteristics include emotional self-regulation (*e.g.*, meaning-focused coping strategies), behavioural and attentional self-regulation, empathy and beliefs in social justice, adaptability and creativity. Interpersonal skills include negotiation, conflict-resolution skills and the capacity to work cooperatively. Social and civic engagement includes volunteering and joining community groups, and

engaging in active citizenship (*e.g.*, speaking out on issues of concern, communicating with policy makers)[13]. Models of positive development indicate that these are desirable developmental outcomes.

Child mental health professionals play a valuable role in both researching on as well as implementing these resilience-based preventative public health strategies in both school and other community-based settings. They are obvious stakeholders who should be involved in developing, trialling and implementing the educational/curricular changes in this regard, possibly in conjunction with educational psychologists. Also, developing nature friendly schools projected along with educational professionals is likely to be helpful. Also, this approach is likely to be helpful in developing nature based positive behavioural support strategies for children and adolescents with intellectual disabilities.

## AS A POLICY MAKER AND ADVOCATE

Child mental health professionals are extremely well placed to actively advocate for climate change mitigation and adaption. Through their membership in different professional and government committees, they could influence policy making as relevant to children and adolescents. For example, The Royal College of Psychiatry, United Kingdom is a member of the United Kingdom health alliance on climate change bringing together the voices of a multitude of health care professionals to advocate for action on climate change and study its psychological impact. The college also published a position paper on sustainability which highlights the need to develop carbon efficient mental health services as part of sustainable mental health[14].

There are several recently implemented programs at local, national and international levels that support actively engaging children and adolescents in increasing awareness of climate change, promoting renewable energy, developing environmentally sustainable practices and advocating for urgent action on the climate crisis[13]. Child psychiatrists and other child mental health professionals have a lot to contribute to these crucial efforts. They can help in identifying the subset of children and adolescents most likely to benefit from these efforts and help in developing the program and in evaluating its effectiveness.

## AS A PROMOTER OF HEALTH EQUITY (PUBLIC HEALTH PERSPECTIVE) AND AS A SERVICE DEVELOPER

Access to mental health care in relation to eco-crisis can be impeded by inadequate mental health-care infrastructure in certain areas, cultural practices and practitioner's familiarity with climate-related anxiety and grief, existing burden on mental health care services and disparities in underlying determinants of health (*e.g.*, socio-economic factors)[14,15]. There is some evidence that those who experience the most acute forms of ecological anxiety are also those with relatively less access to mental health resources[5]. Hence, the role of these professionals is crucial for ensuring fair access for all to the services and building a resilient service in this regard.

Also, looking at a global level, most of the world's children (about 85%) live in low- and middle-income countries, which tend to be in geographic locations more vulnerable to the impacts of climate change. These developing nations also tend to have weaker mental health care infrastructure and fewer support services with which to prepare for and adapt to the impact of climate change[3]. Hence, the role of clinicians serving children and adolescents in the developing world and those working with global agencies [*e.g.*, the World Health Organization (WHO)] are even more crucial for ensuring health equity for children and adolescents globally, pertaining to eco-anxiety. Influencing decision-makers who are crucial for ensuring health equity for children and adolescents globally and pertaining to eco-anxiety is an important role that we could play. This would include local, regional or national leaders; WHO and charitable organizations.

## CONCLUSION

As highlighted through numerous examples above, child mental health professionals have an extremely important role to play in their distinct roles as clinicians, therapists, researchers, policy makers, advocates, preventative public health professionals and service developers pertaining to eco-crisis in both the children and adolescent populations. This would be even more important in developing countries where the majority of the children live. These countries typically have weaker pre-existing mental health services which need to be strengthened. I believe this would be a moral obligation and a professional duty to the population we are privileged to serve.

## FOOTNOTES

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*MINIREVIEWS*

# Dysregulated cortical synaptic plasticity under methyl-CpG binding protein 2 deficiency and its implication in motor impairments

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## Abstract

Caused by the mutation of methyl-CpG binding protein 2 (MeCP2), Rett syndrome leads to a battery of severe neural dysfunctions including the regression of motor coordination and motor learning. Current understanding has revealed the motor cortex as the critical region mediating voluntary movement. In this review article, we will summarize major findings from human patients and animal models regarding the cortical synaptic plasticity under the regulation of MeCP2. We will also discuss how mutation of MeCP2 leads to the disruption of cortical circuitry homeostasis to cause motor deficits. Lastly, potential values of physical exercise and neuromodulation approaches to recover neural plasticity and motor function will be evaluated. All of this evidence may help to accelerate timely diagnosis and effective interventions for Rett syndrome patients.

**Key Words:** Rett syndrome; Motor function; Motor cortex; Synaptic plasticity; Physical exercise; Methyl-CpG binding protein 2

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**Core Tip:** In this mini-review, Zhang WJ summarized current findings for the synaptic plasticity in the cortex and related motor learning functions under the scenario of Rett syndrome. The discussion of neuropathological mechanisms can help us to better understand the disease progression and more importantly to develop more effective measures to counteract motor deficits.

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## INTRODUCTION

Rett syndrome is one neurodevelopmental disorder that is caused by the genetic mutation of methyl-CpG binding protein 2 (MeCP2)[1]. Predominantly found in females with about a 0.01% incidence[2], Rett syndrome has been recognized as one of the major genetic conditions that affects neurodevelopment. As clinical features, about 61% of Rett syndrome patients developed autism spectrum disorder (ASD)-like symptoms[3], making it one major genetic contribution to autistic syndromes. Other behavioral features of Rett syndrome include cognitive and verbal disabilities[4] as well as the retardation of general development[5]. Among various clinical manifestations, deficits of motor function can be found in early stages of disease progression (around 12-18 mo in patients), as displayed by the gradual deterioration of normal motor functions and the occurrence of repetitive movements[6]. As a result, the gradual loss of acquired motor skill has been recognized as one prominent feature of Rett syndrome[7], further highlighting the relationship between motor functions and MeCP2. In this mini-review, we will summarize current major findings regarding motor dysfunctions in Rett syndrome and discuss their correlation with MeCP2-mediated synaptic plasticity of motor circuits, especially those in the motor cortex. In addition, we will also explore the possibility of non-drug intervention strategies including noninvasive neuromodulation and physical exercise in relieving these motor syndromes.

## DYSREGULATED CORTICAL SYNAPTIC PLASTICITY IN RETT SYNDROME

Recent studies have demonstrated the pleiotropic functions of MeCP2 in mediating early events of neurodevelopment including neurogenesis, migration and patterning[8-10]. Deficits of neural network formation frequently lead to abnormal functions. In the cortical region, MeCP2 mutation disrupts the normal excitatory-inhibitory (E/I) balance, resulting in altered synaptic computation[4,7,11-13]. In specific studies, MeCP2-null knockout mice presented elevated GABAA and N-methyl-D-aspartic acid (NMDA) receptors in the barrel cortex[13]. However, using MeCP2-mutant mice, both excitatory and inhibitory conductance were reduced *in vivo* while the E/I ratio was increased[11]. In another study using MeCP2-mutant mice, cortical pyramidal neurons (PNs) displayed decreased spontaneous activity probably due to the reduced miniature excitatory postsynaptic currents (mEPSCs) amplitude while the inhibitory input did not change[12]. Those seemingly contradictory results further suggested the complicated mechanism of MeCP2 in mediating cortical network. A possible approach for further investigation can be achieved *via* cell type-specific study of MeCP2 function. For example, parvalbumin (PV)-specific MeCP2 deletion recapitulated reduced cortical excitability by global MeCP2 deletion[11]. Multiple mechanisms including ion permeability, neurotransmitter receptor or synaptic structural proteins can be further interrogated, as MeCP2 works as a transcriptional regulatory factor to potentially affect their gene expression. Since the neural plasticity of the cortical network is closely correlated with motor learning[14,15], the dysregulated function of MeCP2 may confer motor deficits. Further interrogation of MeCP2-dependent synaptic regulation can help to reveal the pathological process of related motor impairments in order to provide diagnostic and treatment targets.

When examining the neural mechanism of Rett syndrome-associated behavioral symptoms, it is suggested that MeCP2 works as one methyl-DNA binding protein[16]. The loss-of-function mutation of MeCP2 in Rett syndrome thus can be generalized as the deprivation of transcription repression, although recent studies are suggesting its multifaceted roles including activation or suppression of specific genes[17]. Across different brain regions, MeCP2 mediates the gene expressional network in a similar pattern[18], suggesting the brain-wide effect. When examining the transcriptional regulatory mechanism, a recent study identified the prominent role of MeCP2 in suppressing the initiation of gene regions with high CG-methylation levels[19]. For those non-CG methylated gene regions, MeCP2 also exerts a suppressor role *via* repressing enhancer activity[20]. In the exploration of MeCP2-targeted molecules, key modulators of neural plasticity have been recovered. For example, MeCP2 affects the transcription of BDNF to affect myelination and remyelination[21]. An early study further showed that MeCP2 associated with the transcriptional activator CREB1 to mediate a wide range of brain genes[17]. Moreover, MeCP2 interacts with a lot of neuronal genes in positive or negative manners. The transcriptional factor forkhead box protein O3 (FOXO3) has been found to be positively regulated by MeCP2 *via* deacetylation[22]. Those effects on transcriptional factors highlight the role of MeCP in the top layer of the gene regulatory network. Besides those transcriptional factors and neurotrophic molecules, MeCP2 also affects the post-translational modification of neuronal genes. For example, the histone modification

has been shown to be mediated by MeCP2 *via* recognizing H3K27me3[23]. Furthermore, the phosphorylation of MeCP2 itself adds further layers onto its regulatory network. The brain-specific phosphorylation of MeCP2 is known to regulate BDNF expression, contributing to neuronal growth and maturation[24]. In a broad sense, activity-dependent MeCP2 phosphorylation affects its interaction with transcriptional repressors[25], providing an epigenetic mechanism. During neurodevelopment, cell cycle-associated MeCP2 phosphorylation modulates adult neurogenesis[26] and nervous system functions[27]. Combining all these results, MeCP2 regulates the expression of neuronal genes *via* different pathways at transcriptional and post-transcriptional levels (Figure 1).

In neural tissues, gene transcription plays a critical role in various forms of synaptic plasticity such as the long-term potentiation (LTP) and long-term depression (LTD)[28]. People are thus beginning to dissect the neuropathological mechanism of Rett syndrome from the synaptic perspective[29]. Current knowledge has observed the disruption of normal synaptic plasticity under MeCP2 loss-of-function mutation across different brain regions including the hippocampus[30], the cerebellum[31], the visual pathway[32] and the amygdala nuclei[33]. As the critical region for high-order cognitive and mental regulation, the cortical region is also affected by MeCP2 mutations. For example, MeCP2 insufficiency in mouse auditory cortex affected the local network and disrupted maternal pup-retrieval behaviors[34]. In mouse primary visual cortex (V1), MeCP2 deficiency remarkably disrupted the early-stage development of neural plasticity during the so-called "critical period"[35,36]. The abnormal synaptic development resulted in the morphological deficits of synapse, including decreased spine density[37], altered spine morphology or dendritic complexity[38], shorter dendritic lengths[39] and alternation of synaptic protein expression in primary motor cortex (M1)[40,41]. Furthermore, the reduced neuronal size can be observed in layer V PNs of M1 in Rett syndrome model mice[42]. These findings provide the first-hand evidence for the disruption of structural and functional plasticity in the cortical region upon MeCP2 deprivation, highlighting the necessity and importance to elaborate the cortical neuropathology of Rett syndrome.

It is important to notice that both cell autonomous and non-autonomous mechanisms reside in MeCP2-mediated cell plasticity. For example, the loss of MeCP2 affects the autocrine brain derived neurotrophic factor (BDNF) signaling in excitatory neurons to affect neural plasticity, as wildtype neurons cannot rescue mutant cells in the area[43]. Such results provide further clues for clinical manifestations as mosaic patterns of mutations frequently occurs in Rett syndrome patients[44]. Although the primary cause of Rett syndrome is believed to be cell autonomous, non-autonomous mechanism has been revealed as the culture medium from MeCP2-mutated astrocytes disrupted dendritic morphology of wildtype hippocampal neurons[45]. Therefore, MeCP2 affects neural function *via* a complex network and further elaborations are required to study the cell-specific effect.

To attribute the factors for disrupted cortical synaptic plasticity under MeCP2 mutation, recent advances are highlighting the role of local inhibitory transmissions. In the mouse auditory cortex, independent lines of evidence are suggesting that the abolishment or insufficiency of MeCP2 suppresses normal activity of PV-interneurons, resulting in failures of maternal caring behaviors[34,46]. In primary somatosensory cortex (S1) and M1, the learning-associated modulation of plasticity of PV-interneurons was impaired in MeCP2 knockout mice as well as under heterogenous mutation of MeCP2[47]. In the barrel region, the loss of MeCP2 also enhanced glutamatergic transmission[13]. Such interruption of normal cortical network homeostasis might be explained by MeCP2 influence on synaptic plasticity during the critical period in early-stage development[36]. Such opinions were further supported by the conditional knockout of MeCP2 in PV-interneurons resulting in the absence of neural plasticity of V1 during the critical time[35]. To figure out the molecular mechanism, current studies are suggesting the role of neurotrophic factors. For example, BDNF was downregulated under MeCP2 deficiency[48]. As an intervention trial, insulin-like growth factor-1 (IGF-1) partially relieved such neurodevelopmental deficits under MeCP2 deficiency[49] and recovered cortical plasticity[50]. An alternative explanation exists in the cortical perineuronal nets (PNNs) whose formation is dependent on MeCP2[51]. Since PNNs are known to mainly surround PV-interneurons[52], the extracellular modulation may provide a model to explain how pan-neuronal mutation of MeCP2 leads to PV-interneuron specific defects.

The converging evidence of deficient GABAergic transmission upon MeCP2 mutation implies the hyper-excitation of the cortical network. In Rett syndrome patients, clinical recording supported such hypothesis by displaying significant increases of the excitation index of M1 in association with reduced short-interval inhibition[53] plus decreased inhibitory motor control[54]. Mouse model studies also suggested aberrantly high cortical excitability upon MeCP2 deficiency[49], probably due to diminished extracellular GABA transporter activity[55] or under-development of dendritic spines[40]. However, other studies supported the enhanced GABA transmission under MeCP2 knockout[13]. In a short summary, both presynaptic function such as GABA transporter and postsynaptic mechanism including spine formation and synaptic transmission are involved in MeCP2-mediated cortical plasticity. To better dissect the molecular pathway, cell-specific genetic manipulation and functional studies can be performed. For example, PV-specific MeCP2 deletion mimics the effect of global gene knockout[11]. In the future, MeCP2 can be studied in other neuronal and glial cell subpopulations in the cortex.

Based on these facts of disrupted cortical E/I balance, the application of neuromodulator drugs or neuromodulation stimulus may provide a promising future for region-specific intervention of motor symptoms under MeCP2 deficiency. In the last part of this article, we will summarize major findings

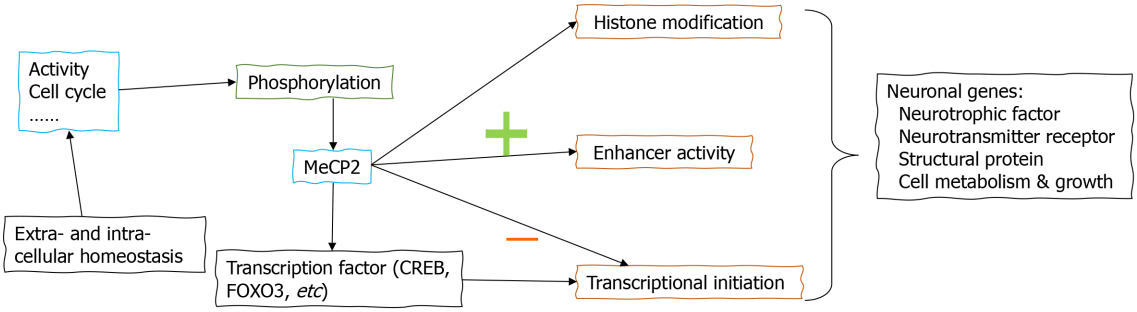


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**Figure 1 Graphic illustration for methyl-CpG binding protein 2-mediated pathway of neuronal gene transcription.** The activity of methyl-CpG binding protein 2 (MeCP2) is mediated by phosphorylation, which can response to cell cycle or cellular activity. MeCP2 exerts pluripotent functions at genetic and epigenetic layers, including directly or indirectly affecting gene transcription, or modifying chromatin structures. Such modulatory network eventually affects both structure and function of neurons[17-20,23,26].

and prospective regarding the neuromodulation approaches for alleviating motor symptoms of Rett syndrome.

## SYNAPTIC DYSFUNCTION IN MOTOR CORTEX IN RETT SYNDROME AND RELATED MOTOR DYSFUNCTIONS

Among the major clinical features of Rett syndrome, motor deficits occur early during the disease development and persist across the whole disease process: The motor delay becomes apparent among 1.5-years-old and 3-years-old, after a seemingly normal early postnatal period[4]. During the adolescent and adulthood period, the progressively declined motor function can be presented as Parkinsonism-like features[56]. Such progression of motor symptoms usually develops into severe ataxia and deprives the patients of the ability to walk or stand during the teenage period[7]. These clinical manifestations can be replicated in mouse models: In MeCP2-null knockout mice, early-onset motor abnormalities were found to induce higher lethal rates[57]. In addition, these model animals presented regression of acquired psychomotor skills under a social interaction scenario[58]. These behavioral deficits clearly suggested the involvement of the motor system in Rett syndrome pathology.

Distinct brain regions and neural ensembles regulate voluntary movement, including the forebrain sensorimotor region, the midbrain nuclei such as the thalamus and basal ganglia, as well as the hindbrain regions plus the cerebellum. The motor cortex is innervated by distinct neuromodulator systems including dopamine, noradrenaline and serotonin. The brain-wide deficiency of MeCP2 thus may affect motor cortical plasticity *via* disruption of subcortical inputs. For example, the ablation of MeCP2 in aminergic neurons produced cell autonomous effects resulting in behavioral abnormalities [59]. The pharmaceutical potentiation of the serotonergic pathway improved cortical microcircuits and recovered motor learning behaviors[60]. Another study further revealed that striatal MeCP2 was critical for maintaining dopaminergic transmission of psychomotor regulation[61]. These findings supported the indispensable role of MeCP2 in the neural network related with cortical activity.

Although the site-specific gene knockout study has suggested the role of MeCP2 in mediating motor behaviors across different neural networks such as the noradrenergic transmission, the motor cortex remains as the prominent brain region in which fine motor control is regulated. Within the motor cortex, both excitatory PNs and GABAergic interneurons form the local network to drive the voluntary movement. PNs were once believed to be the principal projecting neurons in the cortical region and their structural and functional plasticity largely affects motor functions[62,63]. MeCP2 was known to mediate synaptic structures in the motor cortex as it can regulate the dosage of gene expression *via* homeostatic control of DNA methylation. The over-expression of MeCP2, for instance, resulted in altered structural plasticity of cortical dendritic spines[64]. On the other hand, the deficiency of MeCP2 led to remarkably shorter dendrites of PNs in the motor cortex in human patients across different age groups[38]. Similar phenotypes were observed in mouse models, which presented reduced spine density, shorter dendrite lengths[37], irregular spine clustering or shapes[65] and reduced dendritic complexity[39]. Such evidence clearly demonstrates the relationship between MeCP2 and synaptic plasticity and implies the participation of MeCP2-mediated synaptic defects in Rett syndrome.

Besides the excitatory neurons, GABAergic inhibitory neurons in the motor cortex also tightly regulates motor coordination and motor learning functions, as they can provide both inhibitory synaptic inputs and subthreshold oscillation wave onto excitatory neurons. For example, the somatostatin (SST)-interneuron is found to actively participate in the acquisition and retrieval of complex motor skills as suggested by an *in vivo* recording study[66], and our recent work has revealed the abnormally

suppressed activity of those SST-interneurons under a Parkinson's disease (PD) mouse model, leading to pathologically over-excitation of pyramidal cells[67]. Such phenomena revealed cortical dysfunctions due to the loss of normal inhibitory inputs onto the pyramidal projecting neurons, leading to their hyperactivation and related neural symptoms. Besides the local regulation of cortical inhibition, GABAergic neurons received inputs from subcortical nuclei which consisted of multiple monoaminergic systems. For instance, the α2A -adrenoceptor was found to suppress the activity of cortical inhibitory neurons[68]. The dopamine receptor D1 and D2 have been known to affect the density of cortical inhibitory neurons, including PV- and SST-interneurons[69]. In the human motor cortex, serotonin was also reported to enhance GABAergic transmission[70]. No direct study, however, has investigated the modulation of cortical inhibitory neurons by the monoaminergic system under MeCP2 deficiency. Further work thus can be performed to dissect the circuitry pathway of MeCP2 in affecting motor learning functions.

When one broadens their scope of neurological diseases, it is interesting to find that the "cortical disinhibition" model can be found across different neurological disease models such as Alzheimer's disease (AD)[71], amyotrophic lateral sclerosis (ALS)[72] and Huntington's disease (HD)[73]. In a primate model of Rett syndrome, MeCP2 is expressed in both excitatory and inhibitory neurons in cortical regions[74], implying the possible role for mediating glutamatergic and GABAergic transmission. In specific, the conditional knockout of MeCP2 in cortical vasoactive intestinal peptide (VIP)-interneurons resulted in the deficits of social and mental functions[75]. It thus seems that the abovementioned correlation between MeCP2 and motor function may reside in the inhibitory neurons of the motor cortex. In fact, the cellular pathological studies have also attributed motor dysfunction to MeCP2 deficiency in PV-interneurons in the motor cortex as suggested by a conditional gene knockout model[76]. In a similar manner, the deletion of MeCP2 in SST-interneurons resulted in stereotypic and repetitive behaviors, highlighting the distinct functions of interneuron subtypes in fine motor control [76]. On the other hand, PNs may also be affected under MeCP2 deficits which can impair the structural or functional integrity of the excitatory synapse[11,38,42]. For example, MeCP2 deletion in glutamatergic neurons resulted in much more severe symptoms than those from inhibitory neuron-specific deletion[77]. As the restoration of MeCP2 in GABAergic neurons only partially rescued symptoms in null knockout mice[78], the integrity of local E/I homeostasis is of critical importance for relieving cortical neuropathology in Rett syndrome. Combining all data, it is promising that targeting the E/I balance in the motor cortex, especially by potentiating the inhibitory transmission, may aid in retarding or alleviating the motor syndrome in patients.

## THE POTENCY OF EXERCISE TRAINING AND NEUROMODULATION IN FUNCTIONAL REHABILITATION

Based on motor deficits and dysregulated neural plasticity of motor circuits upon MeCP2 dysfunction as aforementioned, it is possible that certain neuromodulation approaches targeting circuitry function might help to ameliorate those motor symptoms. As supporting evidence, environmental enrichment helped to relieve the behavioral deficits including motor learning functions in MeCP2 null knockout mice, in addition to the rescue of cortical LTP function[31]. In a clinical trial of Rett syndrome patients under the age of 6 years, the 6-mo environmental enrichment training paradigm improved motor functions[79]. These examples clearly suggested the possibility of environmental intervention in relieving Rett syndrome symptoms.

Physical training, as one widely accepted life-style intervention to facilitate neurogenesis and cognitive functions[80], has been recently demonstrated by our group to improve motor learning abilities *via* stimulating structural and functional plasticity of synapses in mouse motor cortex[81]. Therefore, exercise training may work as one promising approach to relieve motor deficits of Rett syndrome patients. Such a proposal was supported by several clinical reports in which daily activities and rehabilitation helped to maintain motor abilities[82,83] or to prevent functional deterioration[84]. Specifically, a recently published case report found that periodic exercise rehabilitation at 2 years of age helped to maintain normal motor function[82]. Another study recruited 4 girls under the age of 11 years and found that 2-mo treadmill training helped to improve the general body fitness and behavioral scores[84]. Although these preliminary studies only included a small cohort of patients, the potency of physical exercise in early intervention of Rett syndrome-related motor dysfunction can be tested by large-scale clinical trials in the future.

To provide neurobiological evidence for physical exercise, Zoghbi *et al*[85] recently reported the effectiveness of pre-symptomatic training in the mitigation of specific motor impairments using a mouse Rett syndrome model. In particular, exercise training repeatedly activated a specific population of neurons that developed more dendritic arbors and higher excitability to enhance motor function[85]. These data suggested a possibly new intervention strategy by which endurance exercise works to retard the deterioration of motor dysfunctions. When examining the molecular mechanism underlying exercise intervention on Rett syndrome, BDNF upregulation has been reported upon exercise paradigm in both rodent models[86] and human cohorts[87]. At the downstream of BDNF activation, it is worth noting

that physical training boosted the activity of the mechanistic target of rapamycin (mTOR) pathway for improving structural and functional plasticity of dendritic spines in the motor cortex[81]. Since previous knowledge has established the role of mTOR down-regulation upon Mecp2 mutation[88,89] to generate the phenotypes of Rett syndrome[90], it is highly likely that exercise may help to relieve neural dysfunctions *via* moderately stimulating mTOR pathways. As functional evidence, both *in vitro* and *in vivo* data have proved the down-sized neurons across multiple brain regions in mice carrying the A140V mutation of Mecp2, in association with mTOR activity inhibition[88]. On the other hand, human brain samples presented abnormally upregulated mTOR activity under Rett syndrome[91]. Such discrepancy between human patients and animal models may arise from the different mutational sites or distinct disease stages. Nevertheless, the critical role of the mTOR pathway in MeCP2-related dysfunction and the modulatory role of mTOR by exercise training cannot be neglected. This further highlights the promising future of using endurance training for alleviating cellular and behavioral deficits of Rett syndrome.

Currently, few available intervention strategies have been adopted to benefit Rett syndrome patients. Besides the potential usage of exercise training at early stages as aforementioned, non-invasive neuromodulation approaches provide alternative choices for alleviating behavioral deficits. Various methods including electric, magnetic and ultrasound stimulations have been approved as safe means to modulate neural functions, mainly focusing on the cortical region. The application of transcranial magnetic stimulation (TMS) has been accepted to evaluate the excitability and E/I balance of the M1 neural network[53,54], despite relatively small sample sizes. As an alternative neuromodulation approach, transcranial direct current stimulation (tDCS) has recently been tested on Rett syndrome patients. In one study recruiting 31 patients, tDCS effectively improved attention and verbal functions [92]. A second study also reported enhancement of language skills by tDCS[93]. These neuromodulation approaches thus may have potential values in improving neural functions. Due to the early-onset and persistency of motor deficits, the targeted intervention on the motor cortex may be worth further testing by employing large-scale and multi-centered clinical trials. When considering neuromodulation in large cohorts of patients, however, some concerns may arise as it may result in episodes of epilepsy[94], whose susceptibility rises in Rett syndrome patients[95]. These safety issues also remind that environmental intervention such as exercise training might be a more preferrable and safer way in treating Rett syndrome.

## CONCLUSION

In summary, MeCP2 mediates the synaptic plasticity and neural circuitry in the motor cortex and its genetic mutation leads to the disruption of neural transmission, thereby causing the dysfunction of fine motor coordination and motor learning abilities in Rett syndrome. Targeting the motor cortex by either physical training or neuromodulation approaches thus have become accessible and promising strategies for alleviating motor symptoms in Rett syndrome and is worth of more investigations from both basic science and the clinical fields.

## FOOTNOTES

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*MINIREVIEWS*

# Differences between delusional disorder and schizophrenia: A mini narrative review

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## Abstract

Psychotic syndromes are divided into affective and non-affective forms. Even among the non-affective forms, substantial differences exist. The aim of this relatively brief review is to synthesize what is known about the differences between two non-affective psychoses, schizophrenia and delusional disorder (DD), with respect to clinical, epidemiological, sociodemographic, and treatment response characteristics. A PubMed literature search revealed the following: in schizophrenia, hallucinations, negative symptoms and cognitive symptoms are prominent. They are rare in DD. Compared to schizophrenia patients, individuals with DD maintain relatively good function, and their delusions are believable; many are beliefs that are widely held in the general population. Treatments are generally similar in these two forms of psychosis, with the exception that antidepressants are used more frequently in DD and, for acute treatment, effective antipsychotic doses are lower in DD than in schizophrenia. It is with the hope that the contrasts between these two conditions will aid in the provision of safe and effective treatment for both that this review has been conducted.

**Key Words:** Non-affective psychosis; Delusional disorder; Schizophrenia; Epidemiology; Symptoms; Treatment response

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**Core Tip:** Although patients with delusional disorder and schizophrenia share clinical similarities, epidemiological and treatment outcomes suggest that these two conditions belong to different diagnostic categories. The onset of delusional disorder (DD) occurs at a relatively late age and, in contrast to schizophrenia, everyday functioning is preserved. Treatment is similar, with more frequent use of antidepressants in DD. Effective targeting of symptomatic domains is important in both these forms of psychosis.

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## INTRODUCTION

Schizophrenia and delusional disorder (DD) are both non-affective psychoses and symptoms overlap in many ways. Both conditions are characterized by the presence of delusions although, in schizophrenia, hallucinations, cognitive deficits, and features such as thought disorder, apathy, and social isolation are as much in evidence as are delusions. In both disorders, delusions are usually centered around themes of persecution, but grandiosity, morbid jealousy, erotomania, and delusionally interpreted somatic sensations are also very common[1] (Table 1). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), delusions, in whatever psychotic illness they are found, are defined as fixed beliefs that are not easily amenable to correction, despite proof to the contrary.

Although Table 1 represents the current sub-classification of DD, several investigators have attempted to introduce different groupings within this diagnostic category. Wustmann and collaborators[2] classified DD patients into three groups: erotocentric (erotomanic delusions and delusions of jealousy), somatocentric (delusions of health threat and somatic delusions) and securocentric (persecutory, querulous, litigious delusions, and delusions of reference). Some patients present with two or more different types of delusion over time. In the schizophrenia literature, although some contemporary writers still refer to paranoid schizophrenia as a subtype, sub-grouping according to delusional content is largely obsolete.

The aim of this brief narrative review is to search the existing psychiatric literature in order to address the following questions: (1) Do epidemiological data differentiate DD from schizophrenia? (2) Do clinical features or psychiatric comorbidities differ in DD and schizophrenia? And (3) Are there data that show differences between DD and schizophrenia with respect to response to treatment, both pharmacological and psychosocial?

## THEORETICAL SPECULATIONS ON THE ORIGIN OF DELUSIONS

How delusions take root and grow in a human mind is a much-debated topic, which, it is agreed, results from the interaction of biological, psychological and environmental factors.

Theorists believe that delusions arise from chance exposure to an event that feels special, out of the ordinary[3]. A preoccupation with "how could this possibly have happened to me?" begins to torment the individual until a 'eureka' moment is reached when everything falls into place[4]. This has been called the "aha" experience[5] when an explanation, sometimes seemingly outlandish, has at last been found.

Despite the fact that the eureka explanation sounds, when shared, implausible to others, it can germinate and plant itself firmly in the mind of a biologically vulnerable individual and become a quasi-permanent, salient feature in that person's life[6]. Family members and friends question the explanation, argue against it, which frequently leads to conflicts that culminate in the social isolation of the deluded person[7]. To account for this process in the context of schizophrenia, most of the literature assumes a genetic predisposition inherent in the deluded person; in DD, on the other hand, because delusions emerge later in life, they are often attributed to acquired brain pathology[7]. In both conditions, biological underpinnings that make the ground fertile to delusions are assumed, but clear evidence of brain structure/function impairment is usually lacking[8].

Psychological origin theories are not excluded[9,10], especially not in DD. Formative traumatic experiences are thought to lead to negative emotions such as shame, guilt, or fear, resulting in a "be on your guard" attitude that transforms ordinary events into threats that grow to become convictions of deliberate persecution[11]. Some have argued that emotionally aroused states facilitate hypervigilance to threat, and that such states of mind lead to both misinterpretations and, especially in schizophrenia, misperceptions[12].

**Table 1 Subtypes of delusional disorder in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[1]**

| Subtypes of delusional content | |
|---|---|
| Persecutory type | A preoccupation with the belief that one is being persecuted or conspired against |
| Somatic type | A conviction that one's body is defective or infested or malformed |
| Jealous type | A conviction that one's lover is unfaithful |
| Grandiose type | A belief that one is somehow superior to others |
| Erotomanic type | A false belief that one has aroused the passionate love of someone important |
| Mixed type | False beliefs that combine the above themes |
| Unspecified type | A vagueness in the expression of one's beliefs that does not permit sub-classification |

It is possible that phenomena such as these arise frequently in many people but are then aborted by feedback from trusted others. Individuals who are socially isolated may not have access to such feedback. It is also possible that, occasionally, delusional explanations for extraordinary events persist because they are reinforced by external affirmation[13].

There is a school of thought that attributes the persistence of a delusion not only to outside reinforcement but also to the susceptible person's habitual form of reasoning, or cognitive biases. Such biases have biological underpinnings but may also represent learned phenomena. One example of a cognitive bias is the tendency to jump too quickly to unwarranted conclusions[14]. As described by Laukkonen *et al*[4], the more that a person comes to faulty conclusions about everyday events, the more 'proofs of concept' are incorporated into an ever-expanding delusional system. It is psychologically easy to attribute mistakes and disappointments to perceived foes and conspirators[15]. Gunn and Bortolotti [16] note that paranoid delusions, by placing blame for missteps on outside persecutors, serve as 'secondary gain,' allaying the guilt and shame of personal failings. In cultural anthropology, an important distinction has been made between guilt cultures, shame cultures, and cultures of fear[17], classified on the basis of traditionally preferred ways by which parents socialize their children. In this context, Matos *et al*[18] speak of shame memories as central to the development of paranoia. Carvalho *et al*[19] emphasize instead the influence of family narratives and childhood memories on the emergence of paranoid ideation. In a much-cited paper, Kirmayer and Ryder[20] conclude that cultural habits are embedded in the brain as neural correlates of emotion[21], and can thus predispose to different forms of mental symptoms in different cultures.

The literature continues to leave the issue of the origin of delusions open. It is possible, however, to arrive at a conclusion that delusional thinking in psychoses that begin at older ages (such as DD) is likely to originate mainly in life experiences whereas delusions that begin in youth (as in schizophrenia) are rooted in neurodevelopment, with most current research centered on aberrations of neurotransmission, especially dopamine transmission[22-24]. A recent positron emission tomography study found dopamine dysregulation in both schizophrenia and DD[25]. This suggests a neurocognitive model for delusion formation that links aberrant salience of a chance stimulus, often threat-related, with mesostriatal dopamine signaling. Secondary cognitive processes are recruited to try to make sense of what is perceived as a highly unusual, highly significant experience. These processes, namely jumping to conclusions, unswerving attachment to one's original conclusions, and inattention to counterarguments, for which dopamine dysregulation may also be responsible, maintain and sustain the delusion [26]. This is a model of delusion formation that also leaves room for a major contributory role for prior experience of trauma and sociocultural input[27].

## EPIDEMIOLOGY

The lifetime prevalence of schizophrenia, despite variations in study design, geographic source, and study quality, is estimated at 0.48%-1%[28]. This is in contrast to the lifetime prevalence of DD, rated as 0.2%[1], but reported by some researchers to be a decimal place rarer - 24 to 30 per 100000[29]. Prevalence varies with the characteristics of the study sample and the setting of the investigation[30].

A major difference between schizophrenia and DD is the age of onset, late teens and early adulthood in schizophrenia, middle age and above in DD[30]. Onset age is critical in many ways. For example, the fact that DD first occurs, for the large part, in postmenopausal women may explain why gender differences during the reproductive years are not as marked in this disorder as they are in schizophrenia, where circulating estrogen levels protect the brains of reproductive age women[30,31]. Onset age may also affect the thematic content of delusions. In DD, erotomania, for instance, has been found to be more frequent in women with premenopausal onset while somatic and jealous delusions are more common in women whose onset is postmenopausal[32].

Epidemiological differences between DD and schizophrenia depend to a significant degree on the diagnostic instrument and the diagnostic criteria and the specific syndromes that are included under the two categories. Some syndromes within the schizophrenia spectrum, such as paranoia querulans (incessant legal actions to obtain compensation for perceived wrongs) and paraphrenia (psychotic symptoms first diagnosed in the elderly) have been removed from current classification systems and are now subsumed under either DD or schizophrenia. This is notably the case for paraphrenia, which is now variably categorized as late onset schizophrenia, atypical psychosis, schizoaffective disorder or DD [33]. Shifts such as these in diagnostic labeling contribute to changes in reported prevalence of the two disorders.

With respect to the prevalence of subtypes, most investigations agree that persecutory delusions are the most common in both conditions[34], followed, in DD, by jealous, somatic and erotomanic delusions [32,35].

In contrast to schizophrenia which, in addition to delusions, comes with prominent hallucinations, negative, and cognitive symptoms, DD is usually considered a disorder of delusions only. Phenotypic factorial analyses of DD, however, have identified 4 independent symptom areas: delusions, hallucinations, depression, and irritability[36]. This suggests that DD, as diagnosed today, is symptomatically heterogeneous, with symptoms that overlap to a considerable degree with those of schizophrenia. de Portugal and co-workers[37], who also investigated this question, found 4 symptom categories in DD, paranoid, cognitive, schizoid and affective, which, together, explained 59% of the variance in symptomatology.

In clinical practice, both schizophrenia and DD patients frequently present with psychiatric comorbidities, mainly affective disorders. In DD, depressive disorders have been found in 21%-55.8% of patients[38]. Women may present with more mood symptoms than men, but findings in this area are controversial[2,35]. In schizophrenia, it has been noted that delusional themes can change over time in approximately one-third of cases[39]. In terms of functional ability, patients with DD show a significantly superior global functioning than patients with schizophrenia, suggesting that DD is distinct from schizophrenia, and, on the whole, less severe[40].

## CLINICAL APPROACH TO PATIENTS WITH DELUSIONS

The literature strongly suggests that, when beginning treatment with a person who is delusional, whatever the specific diagnosis, the first concern must be safety - safety for the patient, for persons who the patient believes are enemies and for family members and treating personnel who may become incorporated into the patient's delusional system. Suicide is a risk because low self-esteem often lies at the core of delusions. Adding to the concern for safety is the fact that, depending on a jurisdiction's mental health legislation, involuntary treatment can be difficult for the family to arrange, even in situations of imminent danger[41].

Once safety concerns have been allayed, the next challenge is to build a therapeutic alliance by patient and clinician working together toward common goals[42]. Clinical practice suggests that initial goals need not be ambitious but must have patient buy-in. For instance, because delusions take their toll on sleep quality, working together to improve sleep by using sleep hygiene techniques and sedatives is likely to engage initially treatment-resistant patients[43].

Succeeding at something together builds trust and paves the way to information-sharing and, ultimately, to discussion of sensitive topics such as the objective veracity of a delusional belief. But this can wait[44]. Experienced clinicians always acknowledge the subjective veracity of the belief.

When engaging patients who have difficulty with trust, many therapists recommend starting by discussing early childhood because patients are less likely to perceive past issues as threatening compared to the potential threat of the therapist dismissing their accounts of current history[45]. Whereas experience and skill are always clinically useful, there is a consensus that a therapist's genuineness is the most important ingredient in forging a trusting therapeutic bond[46].

Ongoing therapy largely consists of enhancing the patient's self-esteem, bolstering resilience and improving metacognitive skills[47]. Judiciously planting seeds of doubt about the reality of a delusion by exploring alternate explanations is a key metacognitive technique[48]. Cognitive-behavioral techniques have successfully eliminated delusional ruminations, negative beliefs about the self, interpersonal oversensitivity, as well as sleep disturbance, each of which has been shown capable of reinforcing delusions[49].

Techniques recommended for delusional jealousy consist of targeting common tendencies found in such patients, *e.g.*, inferring the emotions and intentions of others, personalizing chance occurrences, overgeneralizing from one or two experiences, and persistently anticipating catastrophe[50]. Other therapeutic targets are hypervigilance, negative self-esteem, and the inclination to mistrust others. Reframing a patient's view of a situation is an important therapeutic technique[51] *e.g.*, "He does go out a lot, but it might be because you give him a hard time at home rather than because he's seeing another woman." Experienced clinicians believe that therapists do well to embrace the role of educator, teaching patients about emotions and the many ways in which strong feelings can drive behavior[52]. Practice

sessions and homework assignments relevant to the expression of emotions are cited as a vital part of cognitive therapy and rehabilitation protocols for all forms of delusions[53].

These recommendations apply to the initial approach to patients with both DD and schizophrenia, but are less effective when the patient's cognition is impaired. Table 2 summarizes the main recommendations for an initial approach to DD.

## PHARMACOLOGICAL TREATMENT

Definitions of response to antipsychotic or other pharmacological treatment vary. Response criteria based on reduction in standard rating scale scores, as is done in schizophrenia[54], have been recommended in DD[55] where, thus far, response has been defined on the basis of clinical opinion.

The most recent study in this area was an observational registry- based cohort study in a Swedish population diagnosed with DD[56]. Hospitalization and work disability were found to be less likely occurrences when antipsychotic were prescribed, compared to when they were not. Protection was best conferred by clozapine, olanzapine and all long-acting injectable antipsychotics. When comparisons were made between DD and schizophrenia, a relatively smaller dose of haloperidol (4.7 mg/d) was effective in suppressing delusional symptoms in DD than in schizophrenia (12.7 mg/d)[57]. Treatment was shorter (65 d) in DD compared to 104 d in schizophrenia. At hospital discharge, the global assessment of functioning score was also significantly higher in DD[57]. Although more studies are needed, this suggests that an acute episode of DD may respond to treatment at lower doses and within a shorter time period than an acute episode of schizophrenia. Studies on comparative longer-term response to antipsychotics are, however, lacking.

### *Factors influencing drug response*

Adherence to prescribed drug regimens is generally acknowledged as a critical factor influencing therapeutic response. In turn, adherence is influenced by the patient's gender, age, duration of illness, comorbidities, number of concomitantly prescribed drugs, simplicity of the drug regimen, and quality of the therapeutic relationship[2,58]. Thomas and colleagues[59] have studied these factors as they pertain to schizophrenia, but this has not yet been done in DD.

Specific host genes may enhance or diminish drug response. Morimoto *et al*[57] investigated the relationship between variants of dopamine receptor genes and the tyrosine hydroxylase gene in DD patients, schizophrenia patients, and healthy controls. They found an association between genetic variability in DRD3 and plasma homovannilic acid (pHVA). Specifically, patients with DD homozygous for the DRD3 gene Ser9Ser showed higher pretreatment levels of pHVA than others, an effect especially marked, in this sample, among patients with the persecutory subtype of DD. Aided by structural and functional neuroimaging, work on the genetics of drug response in DD and schizophrenia is underway.

A multicenter positron emission tomography and magnetic resonance spectroscopy study (STRATA) tested whether striatal dopamine synthesis capacity and/or elevated anterior cingulate cortex glutamate levels can differentiate between patients with psychosis who do and do not respond to antipsychotic medications[60]. The findings revealed a potential role of glutamate levels (but not striatal dopamine synthesis) in the prediction of response.

Very few studies have investigated the biological basis of treatment response in DD. In the case of the delusional infestation subtype of DD, one study, however, identified distinct patterns of prefrontal, temporal, parietal, insular, thalamic and striatal dysfunction implicated in response[61].

Therapeutic drug monitoring is currently a promising technique that can evaluate treatment efficacy, correlate adverse events to prescribed doses and assess adherence. While it is often used in the treatment of schizophrenia, it is still rarely done when treating DD patients.

### *Use of antidepressants*

Antidepressants have been used as monotherapy in DD when clinicians believe that the delusion is caused by depression. Paroxetine and clomipramine are examples of antidepressants commonly used [62]. Antidepressants used as an adjunct to antipsychotics is a frequent treatment strategy in both DD and schizophrenia.

## NON-PHARMACOLOGICAL TREATMENTS

Cognitive therapy has been shown to be helpful in DD[63], as it is in schizophrenia[64,65]. Patients receiving CBT show a significant reduction in the strength of their delusional conviction, in the intensity of the affect associated with their delusion, and in the frequency of behaviors resulting from their delusion.

Table 3 presents the main pharmacological and psychosocial interventions used in the management of patients with DD and schizophrenia.

**Table 2 Initial approach to patients with delusional disorder**

| Issue | Target | Recommendation |
|---|---|---|
| Safety | For patient, imagined persecutor, and personnel | Safety is the first step |
| Therapeutic alliance | Patient-clinician relationship is crucial (determines adherence to follow-up) | Building trust for working together on common goals |
| Enhancing self-esteem and improving skills | Supporting self-esteem and modeling cognitive and social skills | Improving metacognitive and social skills |
| Targeting emotions and behaviors | Helping patients to identify emotions and prevent acting on delusions | Cognitive-behavioral therapies identify stressors and risk behaviors |

**Table 3 Main interventions for the treatment of delusional disorder and schizophrenia**

| Interventions | Explanation | Remarks |
|---|---|---|
| Antipsychotics[57-60] | Antidopaminergic action of these drugs dominates the literature | Genetic studies are inconclusive about the role of dopamine |
| Antidepressants[62] | Antidepressants treat comorbid depression | Reversing depression can sometimes eliminate delusions |
| Cognitive behavioral therapy[63-65] | Addresses cognitive biases and unwanted behavior | Stops adverse behaviors and improves adherence to treatment |

## RISK OF SUICIDE

Neither suicide antecedents nor suicide rates have, to date, been compared in DD and schizophrenia. Existing studies have established the percentage of suicidal behavior in patients with DD to be between 8% and 21%[66]. In schizophrenia, it hovers around 10%[67]. In both disorders, men are more at risk for completing suicide than women[38]. The somatic subtype and the persecutory subtype of DD are most associated with suicide[30] whereas, in schizophrenia, suicide appears to depend not on delusional theme but on the presence of command hallucinations[68].

## DISCUSSION

When we began our review, we wanted to address 3 questions: (1) Do epidemiological data differentiate DD from schizophrenia? (2) Do clinical features or psychiatric comorbidities differ in DD and schizophrenia? And (3) Are there data that show differences between DD and schizophrenia with respect to treatment response to either pharmacological or non-pharmacological treatment?

We found an overlap between the diagnosis of DD and schizophrenia, with boundaries often very blurred. As characterized in DSM-5, the middle age onset of DD distinguishes it from the earlier onset in schizophrenia. The literature gives a prototypical picture of schizophrenia as one of hallucinations, cognitive, and negative symptoms in addition to delusions, with function deteriorating over time. Relatively good function is maintained in DD. While this disorder is also characterized by symptoms other than delusions (mainly affective symptoms), delusions predominate. Treatment response to antipsychotic medication appears to be similar in the two conditions, although DD patients, as a group, are older, and would be expected, as one study has shown, to require comparatively lower doses to achieve symptom reduction. When compared to younger age, older age, however, can limit the benefits of pharmacotherapy because of an increased frequency of potential drug interactions and adverse events. An adequate long term comparison of drug response in the two conditions is lacking. Clinical reports recommend the addition of antidepressants to the medication regimen of patients with DD, but large-scale trials to prove the usefulness of this strategy have not yet been conducted. Specific symptoms, when targeted by cognitive behavioral therapies, respond in both DD and schizophrenia, although efficacy trials in DD are, to date, limited.

The content of delusions seems more understandable in DD than it often is in schizophrenia but the major theme is one of persecution in both conditions. In general, the prevalence rate for delusional disorder is significantly lower than that for schizophrenia.

Importantly, a persecutory delusion is such a firmly held belief that it can often lead to behavior which endangers the believer and the persons implicated in the delusion. Safety is a paramount concern; suicide is an important risk. Evidence for the success of current interventions into prevention of suicide and aggression remains relatively weak.

There are many limitations to this narrative review. There is an extremely large literature on schizophrenia, with well-controlled randomized trials of treatment options. This does not yet exist for delusional disorders. Because of the symptom overlap and the prevalence disparity as well as the age discrepancy, well-defined comparative groups are difficult to recruit. Much of the literature on delusional disorders consists of small case series or reports of individual cases. To accurately answer the questions posed in this review, methodologically well-conducted, multicenter trials are required. The review should nonetheless be helpful for clinicians, especially with respect to initial approaches to patients with delusions, and the cautions about safety.

## CONCLUSION

This brief review covers the recent literature on difference between two non-affective psychoses, DD and schizophrenia. The former is much rarer and presents at older ages. More often than schizophrenia, DD is accompanied by depression, which increases the risk for suicide. Acting out against imagined persecutors is a potential danger in both disorders. While delusions are prominent in both schizophrenia and DD, other psychiatric symptoms may also be present and may require targeted treatment. In contrast to schizophrenia, outside the sphere of the delusion, cognitive functions are usually not impaired in DD, so that a therapeutic alliance is possible and is essential for treatment to succeed. Research into the efficacy of specific treatments is, however, sparse in DD.

This review covers what is known and not known about similarities and differences between schizophrenia and DD, with the hope that highlighting contrasts between these two overlapping conditions will ultimately improve the treatment of both. Future research must address the difficult task of designing rigorous clinical trials that compare response to therapeutic interventions for delusions in individuals whose primary diagnoses may vary.

## FOOTNOTES

**Author contributions:** Gonzàlez-Rodriguez A conceived the idea of writing this review, based on our joint clinical experience treating patients with delusional disorder and schizophrenia; both authors contributed equally to decisions about the method and the content; both authors contributed equally to the literature search, and to decisions about what studies to include; both authors shared in the clinical contributions; there were several drafts; Seeman MV perfected the final version.

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ORIGINAL ARTICLE

Case Control Study

# Altered thalamic subregion functional networks in patients with treatment-resistant schizophrenia

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## Abstract

### *BACKGROUND*

The thalamus plays a key role in filtering information and has extensive interconnectivity with other brain regions. A large body of evidence points to impaired functional connectivity (FC) of the thalamocortical pathway in schizophrenia. However, the functional network of the thalamic subregions has not been investigated in patients with treatment-resistant schizophrenia (TRS).

### *AIM*

To identify the neural mechanisms underlying TRS, we investigated FC of thalamic sub-regions with cortical networks and voxels, and the associations of this FC with clinical symptoms. We hypothesized that the FC of thalamic sub-regions with cortical networks and voxels would differ between TRS patients and HCs.

### *METHODS*

In total, 50 patients with TRS and 61 healthy controls (HCs) matched for age, sex, and education underwent resting-state functional magnetic resonance imaging (rs-fMRI) and clinical evaluation. Based on the rs-fMRI data, we conducted a FC analysis between thalamic subregions and cortical functional networks and voxels, and within thalamic subregions and cortical functional networks, in the patients with TRS. A functional parcellation atlas was used to segment the thalamus into nine subregions. Correlations between altered FC and TRS symptoms were explored.

### *RESULTS*

We found differences in FC within thalamic subregions and cortical functional networks between patients with TRS and HCs. In addition, increased FC was observed between thalamic subregions and the sensorimotor cortex, frontal medial cortex, and lingual gyrus. These abnormalities were associated with the pathophysiology of TRS.

*CONCLUSION*
Our findings suggest that disrupted FC within thalamic subregions and cortical functional networks, and within the thalamocortical pathway, has potential as a marker for TRS. Our findings also improve our understanding of the relationship between the thalamocortical pathway and TRS symptoms.

**Key Words:** Treatment-resistant schizophrenia; Thalamus; Rs-fMRI; Functional connectivity; Thalamocortical pathway

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**Core Tip:** The thalamus represents the interface between the sensory and motor systems, and is a major hub for cognitive processes. A large body of evidence has demonstrated involvement of the thalamus in the pathophysiology of schizophrenia. Most previous studies employing resting state functional magnetic resonance imaging used the whole thalamus as a seed region to identify abnormalities in thalamic connectivity. To identify more specific disturbances, we conducted functional connectivity analysis of thalamic subregions with cortical networks and voxels in patients with treatment resistant schizophrenia. Important novel findings regarding the pathophysiology of treatment resistant schizophrenia were obtained.

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## INTRODUCTION

The thalamus is an important deep gray matter structure that transmits sensory information from the peripheral sensory nervous system to the cortex, and serves as a major hub for cognitive processes[1]. Given its 'central roles' in perception and cognition, disturbances of which are major symptoms of schizophrenia (SZ), the thalamus has been focused on in brain imaging studies of SZ. Structural magnetic resonance imaging (sMRI) studies revealed thalamic surface deformation in patients with first-episode and chronic SZ, as well as reduced thalamus volume in a cohort of early onset psychosis patients[2-5]. Moreover, resting state functional magnetic resonance imaging (rs-fMRI) studies have consistently revealed decreased thalamic connectivity with the prefrontal cortex (PFC) in SZ, as well as increased connectivity with motor and somatosensory cortical areas[6]. Furthermore, these aberrant connectivities were also observed in clinical high-risk (CHR) individuals, suggesting that thalamic dysconnectivity onsets prior to the disease itself[7,8].

Previous studies treated the thalamus as a homogeneous structure, averaging blood oxygen level-dependent (BOLD) signals across the entire thalamus. However, this approach may fail to capture disturbances in specific networks, so it is necessary to investigate functional connectivity (FC) between sub-regions of the thalamus and cortex to better understand altered neural circuits in SZ. Several atlases segment the thalamus, including histological-[9,10], structural-[11,12] and functional-based atlases[13]. In this study, we used a functional parcellation atlas to identify nine thalamic sub-regions having strong FC with various cortical functional networks[13]. The atlas allows the topological roles of thalamic nuclei in functional brain networks to be elucidated through graph-theoretic network analysis of rs-fMRI data. Few studies have examined altered FC in thalamic sub-regions in SZ. Three studies reported findings similar to those of investigations using average BOLD signals for the thalamus, *i.e.*, weaker PFC-thalamic network connectivity and stronger motor-thalamic and somatosensory-thalamic network connectivity compared to healthy controls (HCs)[14,15,16]. On the other hand, Gong *et al*[17] observed loss of connectivity between several thalamic sub-regions and the sensorimotor system, anterior cingulate cortex, and cerebellum in patients with SZ. To the best of our knowledge, no study has examined the FC of thalamic sub-regions in patients with treatment-resistant schizophrenia (TRS).

We hypothesized that the FC of thalamic sub-regions with cortical networks and voxels would differ between TRS patients and HCs. To identify the neural mechanisms underlying TRS, we investigated FC of thalamic sub-regions with cortical networks and voxels, and the associations of this FC with clinical symptoms.

## MATERIALS AND METHODS

### Participants

This study included 111 subjects (50 patients with TRS and 61 HCs). SZ was diagnosed based on the DSM-IV[18] criteria by a board-certified psychiatrist and psychiatric residents. The exclusion criteria were as follows: alcohol or substance use disorder; intellectual disability (IQ ≤ 70); current or past neurological disease, serious medical illness, or pregnancy; and claustrophobia. Treatment resistance was defined as follows: failure to respond to at least two different antipsychotic medications administered in adequate doses (equivalent to ≥ 600 mg/day of chlorpromazine [CPZ]) for at least 6 wk; and persistence of clinically relevant positive or negative symptoms (at least one positive or negative symptom and a Positive and Negative Syndrome Scale (PANSS) score of ≥ 4)[19]. The second criterion was not applied to patients on clozapine. The severity of symptoms was evaluated within a week of fMRI using the PANSS[20,21]. HCs were recruited *via* advertisements and interviewed using the Structured Clinical Interview for DSM, Non-Patient Edition (SCID-NP)[22]. A requirement for study inclusion was no previous or current psychiatric disorders, neurological disorders, or significant medical conditions. Controls having a first-degree relative with a psychiatric disorder were also excluded. All participants were aged between 19 and 60 years, and all were confirmed as right-handed by the Edinburgh Handedness Inventory[23]. They all participated voluntarily and provided written informed consent. The study was approved by the Ethics Committee of Jeonbuk National University Hospital (approval number: CUH 2012-08-001).

### Image acquisition and preprocessing

The rs-fMRI and sMRI data were obtained at the Jeonbuk National University Hospital using a 3T Verio scanner (Magnetom Verio; Siemens, Erlangen, Germany) with a 12-channel standard quadrature head coil. Three-dimensional T1-weighted images were acquired using a magnetization-prepared rapid gradient echo sequence (repetition time [TR]: 1,900 ms; echo time [TE]: 2.5 ms; flip angle: 9°; field of view [FOV]: 250 mm; image matrix: 256 × 246 mm; voxel size: 1.0 × 1.0 × 1.0 $mm^3$; 176 slices). A 5-minute resting-state scan consisting of 150 contiguous echo-planar imaging functional images (TR: 2,000 ms; TE: 30 ms; flip angle: 90°; FOV: 220 mm; image matrix: 64 × 64 mm; voxel size: 3.4 × 3.4 × 5.0 $mm^3$; 26 slices) was also obtained. During resting-state image acquisition, participants were asked to relax with their eyes closed, but not to sleep. MRI data processing was conducted using the Statistical Parametric Mapping software package, version 12 (SPM12; Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (MathWorks, Natick, MA, United States). The first three volumes were discarded to adjust for magnetization equilibrium. Functional images were slice-time corrected, realigned to the first image of each series, and co-registered with each participant's structural image. Then, the co-registered functional data were transformed into standard anatomical space through spatial normalization of each T1 image to the Montreal Neurological Institute (MNI) template. Normalized images were smoothed using an 8 mm full-width at half-maximum isotropic Gaussian kernel. The voxels were resampled (2.0 mm × 2.0 mm × 2.0 mm). Head motion was considered excessive when framewise displacement (FD) was > 0.5 mm. FD values were computed using the CONN toolbox (version 14f; http://www.nitrc.org/projects/conn). Participants for whom more than 10% of the volumes showed excessive head motion were excluded from the analysis[24]. The component correction (CompCor)[25] function of the CONN toolbox was used to increase the accuracy of grey matter (GM) signals by removing physiological noise, such as heart rate and breathing signals, followed by removal of the components of interest from the global, white matter (WM), and cerebrospinal fluid (CSF) signals. The linear trend was then removed and a band-pass filter (0.008 < f < 0.09 Hz) was applied.

### Functional connectivity analysis

The functional parcellation atlas[13] was used to segment the thalamus into nine subregions (Supplementary Figure 1). Nine thalamic subregions showing strong FC with nine cortical functional networks were identified, *i.e.,* the default mode (DM), cingulo-opercular occipital (CO), somatomotor (SM), frontal parietal (FP), lateral occipital (LO), medial occipital (MO), medial temporal (MT), temporal, and superior FP networks. The components of each cortical functional network are described in Supplementary Table 1. For each region of interest (ROI) of the thalamus and cortical functional networks, the BOLD signal was averaged to generate the BOLD time series. FC analysis was performed between thalamic ROIs and cortical functional network ROIs, within the nine thalamic and nine cortical functional network ROIs, and between the thalamic ROIs and all cortical voxels (using the CONN toolbox). The patient and HC groups were compared using one-way analysis of variance (ANOVA). We used a voxel-level height threshold of $P < 0.01$ (uncorrected) and a cluster-level extent threshold of $P < 0.05$, corrected for multiple comparisons using the family wise error (FWE). We performed 10,000 permutation tests using the CONN toolbox (www.nitrc.org/projects/conn, RRID:SCR_009550).

### Statistical analysis

Demographic and clinical data were compared between the two groups using a two-sample *t*-test or

Chi-square test. For partial correlation analysis, a ROI extraction tool (http://software.incf.org/software/rex)in the CONN toolbox was used to extract Fisher's Z-transformed signal intensity values for brain regions with significant group differences at an uncorrected p-value of < 0.01. Relationships between the extracted Z-scores and PANSS scores were analyzed using age, sex, and FD as covariates. The analyses were performed using SPSS software (ver. 20.0; SPSS Inc., Chicago, IL, United States).

## RESULTS

### *Functional connectivity between and within thalamic subregions and cortical functional networks in TRS*

There were no significant differences in age, sex, or education level between the two groups (Table 1). The TRS group showed significantly increased FC between thalamic subregion 2 and the MO network ($t$ = 2.78, $P$ < 0.05) compared to the HC group. The TRS group also exhibited significantly increased FC of the CO network with the MO ($t$ = 3.29, $P$ < 0.05) and superior MT networks, and between the MT network and superior FP network ($t$ = 2.63, $P$ < 0.05) ($t$ = 4.31, $P$ < 0.05) compared to the HC group. On the other hand, the TRS group exhibited decreased FC of thalamic subregion 1 with thalamic subregions 2 and 9 ($t$ = -2.95, $P$ < 0.05) and of thalamic subregion 2 with thalamic subregions 3 and 4 ($t$ = -4.58, $P$ < 0.05), compared to the HC group. Also, in the TRS group, decreased FC of the FP network was observed with the MT ($t$ = -2.69, $P$ < 0.05) and superior FP networks ($t$ = -2.73, $P$ < 0.05), between the DM and CO networks ($t$ = -2.90, $P$ < 0.05), and between the MO and MT networks ($t$ = -2.90, $P$ < 0.05), compared to the HC group (Table 2, Figure 1).

### *Functional connectivity between thalamic subregions and cortical voxels in TRS*

Compared to the HC group, the TRS group exhibited significantly increased FC between thalamic subregion 1 and the left lingual gyrus ($t$ = 5.22, $P$ < 0.05), thalamic subregion 2 and the left precentral gyrus ($t$ = 5.22, $P$ < 0.05), thalamic subregion 3 and the right supplementary motor cortex ($t$ = 5.26, $P$ < 0.05), thalamic subregion 6 and the frontal medial cortex ($t$ = 7.05, $P$ < 0.05), the left postcentral gyrus ($t$ = 5.26, $P$ < 0.05) and right precentral gyrus ($t$ = 4.79, $P$ < 0.05), and thalamic subregion 9 and the left precentral gyrus ($t$ = 5.26, $P$ < 0.05). On the other hand, the TRS group exhibited significantly decreased FC between thalamic subregion 3 and the left intracalcarine cortex ($t$ = -4.18, $P$ < 0.05) compared to the HC group (Table 3, Figure 2).

### *Correlations between altered ROI-to-ROI functional connectivity and PANSS scores*

The Z-values of FP and MT network connectivity were negatively correlated with positive symptoms, negative symptoms, general pathophysiology, and PANSS total scores ($r$ = -0.411, $P$ = 0.005; $r$ = -0.414, $P$ = 0.004; $r$ = -0.427, $P$ = 0.003; and $r$ = -0.472, $P$ = 0.001, respectively) in the TRS group. Also, negative correlations were observed between the Z-value of the DM and MT networks and negative symptoms, general pathophysiology, and the PANSS total score ($r$ = -0.316, $P$ = 0.032; $r$ = -0.322, $P$ = 0.029; and $r$ = -0.298, $P$ = 0.044, respectively) (Table 4, Figure 3).

### *Correlations between altered seed-to-voxel functional connectivity and PANSS scores*

No significant relationship was found between altered FC and PANSS scores at an uncorrected p-value of < 0.01 (Supplementary Table 2). Therefore, the analysis was performed against an uncorrected p-value of < 0.05 (Supplementary Table 3). In the TRS group, the Z-value of thalamic subregion 3 and the right lingual gyrus FC was negatively correlated with positive symptoms, negative symptoms, general pathophysiology, and the PANSS total score ($r$ = -0.342, $P$ = 0.020; $r$ = -0.355, $P$ = 0.015; $r$ = -0.350, $P$ = 0.017; and $r$ = -0.396, $P$ = 0.007, respectively). However, there was a positive correlation between the Z-value of thalamic subregion 2 and the left precentral gyrus and the score for general pathophysiology ($r$ = 0.292, $P$ = 0.049) (Table 5, Figure 4).

## DISCUSSION

The thalamus represents the interface between the sensory and motor systems, and is a major hub for cognitive processes. A large body of evidence has demonstrated involvement of the thalamus in the pathophysiology of SZ. Most previous studies employing rs-fMRI used the whole thalamus as a seed region to identify abnormalities in thalamic connectivity. To identify more specific disturbances, we conducted FC analysis of thalamic subregions with cortical networks and voxels in patients with TRS. Important novel findings regarding the pathophysiology of TRS were obtained, and are discussed below.

**Table 1 Demographic and clinical characteristics of patients with treatment-resistant schizophrenia and healthy controls**

| Characteristics | TRS (*n* = 50) | HCs (*n* = 61) | *P* value |
|---|---|---|---|
| Age (yr) | 42.64 (9.79) | 39.89 (9.52) | 0.137 |
| Sex | | | |
| Male (%) | 32 (64%) | 29 (48%) | 0.083 |
| Female (%) | 18 (36%) | 32 (52%) | |
| Education (years) | 13.53 (2.27) | 13.33 (1.92) | 0.613 |
| Duration of illness (mo) | 215.22 (110.09) | - | - |
| PANSS | | | |
| Positive symptoms | 15.96 (4.99) | - | - |
| Negative symptoms | 16.00 (7.30) | - | - |
| General psychopathology | 28.40 (7.74) | - | - |
| Total | 60.36 (17.52) | - | - |
| SOFAS | 49.00 (8.81) | - | - |
| Medication | | | |
| Chlorpromazine equivalent (mg/d) | 915.33 (411.41) | - | - |

Data given as mean (SD). HCs: Healthy controls; PANSS: Positive and Negative Syndrome Scale; SOFAS: Social and Occupational Functioning Assessment Scale; TRS: Treatment Resistant Schizophrenia.

**Table 2 Comparison of between- and within-functional connectivity of thalamic subregions and cortical functional networks between patients with treatment-resistant schizophrenia (*n* = 50) and HCs (*n* = 61)**

| Seed region | *t* value | *P* FWE | *P*-unc | Brain region |
|---|---|---|---|---|
| TRS > HCs | | | | |
| Thalamic subregion 2 | 2.78 | < 0.001 | 0.006 | Medial occipital network |
| Cingulo-opercular network | 3.29 | 0.008 | 0.001 | Medial occipital network |
| | 2.63 | 0.008 | 0.010 | Superior fronto-parietal network |
| Medial temporal network | 4.31 | < 0.001 | < 0.001 | Superior fronto-parietal network |
| TRS < HCs | | | | |
| Thalamic subregion 1 | -4.58 | < 0.001 | < 0.001 | Thalamic subregion 2 |
| | -2.95 | 0.019 | 0.004 | Thalamic subregion 9 |
| Thalamic subregion 2 | -3.16 | < 0.001 | 0.002 | Thalamic subregion 3 |
| | -3.38 | < 0.001 | 0.001 | Thalamic subregion 4 |
| Fronto-parietal network | -2.69 | < 0.001 | 0.008 | Medial temporal network |
| | -2.73 | 0.008 | 0.007 | Superior fronto-parietal network |
| Default mode network | -2.90 | < 0.001 | 0.004 | Cingulo-opercular network |
| | -3.37 | < 0.001 | 0.001 | Medial occipital network |
| | -5.40 | < 0.001 | < 0.001 | Medial temporal network |

Thresholded at $P < 0.01$, uncorrected; $P < 0.05$, Family Wise Error rate corrected. TRS: Treatment-resistant schizophrenia; HCs: Healthy controls.

The network analysis revealed significant FC only between thalamic subregion 2 and the MO network. By mapping the coordinates of 333 cortical ROIs, identified using the Gordon atlas[26], to the masks of cortical functional networks[13], we were able to identify subcomponents of the MO network, including the superior frontal gyrus, superior parietal gyrus, inferior parietal gyrus, precentral gyrus, postcentral gyrus, supplementary motor area, insula, precuneus, Rolandic operculum, and paracentral

**Table 3 Comparison of functional connectivity of thalamic subregions with cortical voxels between patients with treatment-resistant schizophrenia (*n* = 50) and healthy controls (*n* = 61)**

| Seed Region | MNIcoordinate | Cluster Size | *t* value | *P* FWE | *P*-unc | Name (voxel size - region) |
|---|---|---|---|---|---|---|
| TRS > HCs | | | | | | |
| Thalamic subregion 1 | -14 -44 -12 | 612 | 5.22 | 0.009 | < 0.001 | 339 - Left lingual gyrus142 - Left cerebellum 4_5 |
| Thalamic subregion 2 | -28 -10 66 | 1309 | 5.30 | < 0.001 | < 0.001 | 604 - Left precentral gyrus483 - Left postcentral gyrus |
| Thalamic subregion 3 | 10 6 54 | 523 | 5.26 | 0.003 | < 0.001 | 173 - Right supplementary motor cortex |
| Thalamic subregion 6 | -8 38 -22 | 1229 | 7.05 | < 0.001 | < 0.001 | 186 - Frontal medial cortex |
| | -36 -34 62 | 358 | 5.26 | 0.030 | < 0.001 | 342 - Left postcentral gyrus |
| | 26 -28 60 | 467 | 4.79 | 0.006 | < 0.001 | 305 - Right precentral gyrus132 - Right postcentral gyrus |
| Thalamic subregion 9 | -44 -14 42 | 380 | 5.26 | 0.020 | < 0.001 | 281 - Left precentral gyrus |
| TRS < HCs | | | | | | |
| Thalamic subregion 3 | 6 -90 -2 | 458 | -4.18 | 0.008 | < 0.001 | 163 - Left intracalcarine cortex |

Thresholded at $P < 0.01$, uncorrected; $P < 0.05$, Family Wise Error rate corrected. TRS: Treatment-resistant schizophrenia; HCs: Healthy controls.

**Table 4 Correlation between Z score of significantly altered between-and within-connectivity of thalamic subregions and cortical functional networks between groups and Positive and Negative Syndrome Scale[1]**

| Connectivity | *r* value | *P* value |
|---|---|---|
| Positive symptoms | | |
| Thalamic subregion 1 - Thalamic subregion 9 | -0.267 | 0.073 |
| Fronto-parietal network - Medial temporal network | -0.411 | 0.005 |
| Negative symptoms | | |
| Default mode network - Medial temporal network | -0.316 | 0.032 |
| Fronto-parietal network - Medial temporal network | -0.414 | 0.004 |
| General psychopathology | | |
| Default mode network - Medial occipital network | -0.257 | 0.085 |
| Default mode network - Medial temporal network | -0.322 | 0.029 |
| Fronto-parietal network - Medial temporal network | -0.427 | 0.003 |
| Total | | |
| Default mode network - Medial temporal network | -0.298 | 0.044 |
| Fronto-parietal network - Medial temporal network | -0.472 | 0.001 |

[1]Partial correlation analysis with age, sex, and head motion (framewise displacement) as covariates; $P < 0.01$, uncorrected; $P < 0.05$, Family Wise Error rate corrected.

lobule. As the MO network consists of many different regions, it is difficult to determine which of them have the most clinical importance. However, thalamic subregion 2 has a high participation coefficient (PC), indicating that it serves as a connector hub[13]; as such, altered functioning of thalamic subregion 2 may mediate cortical-to-cortical communication in patients with TRS. The other significant FC results were related to connectivity between thalamic subregions and cortical functional networks. Among these, decreased FC between several thalamic subregions in TRS patients was of particular interest, because previous studies mainly focused on the thalamocortical or corticothalamic pathway. In line with our results, Gong *et al* (2019)[17] reported deceased within-thalamic FC in an SZ group compared to controls. Furthermore, a decreased thalamic volume in chronic SZ patients was seen[27,28,29] as well as reduced regional glucose metabolism in the medial dorsal nucleus and posterior thalamus of

**Table 5 Correlation between Z score of significantly altered connectivity between thalamic subregions and cortical voxels between groups and Positive and Negative Syndrome Scale[1]**

| Connectivity | *r* value | *P* value |
|---|---|---|
| Positive symptoms | | |
| Thalamic subregion 3 - Right lingual gyrus | -0.342 | 0.020 |
| Thalamic subregion 2 - Right precentral gyrus | 0.270 | 0.069 |
| Thalamic subregion 7 - Precuneus cortex | -0.285 | 0.055 |
| Negative symptoms | | |
| Thalamic subregion 3 - Right lingual gyrus | -0.355 | 0.015 |
| Thalamic subregion 6 - Right precentral gyrus | -0.247 | 0.098 |
| General psychopathology | | |
| Thalamic subregion 2 - Left precentral gyrus | 0.292 | 0.049 |
| Thalamic subregion 3 - Right lingual gyrus | -0.350 | 0.017 |
| Thalamic subregion 9 - Left precentral gyrus | 0.262 | 0.079 |
| Total | | |
| Thalamic subregion 3 - Right lingual gyrus | -0.396 | 0.007 |

[1]Partial correlation analysis with age, sex, and head motion (framewise displacement) as covariates; $P < 0.05$, uncorrected; $P < 0.05$, Family Wise Error rate corrected.

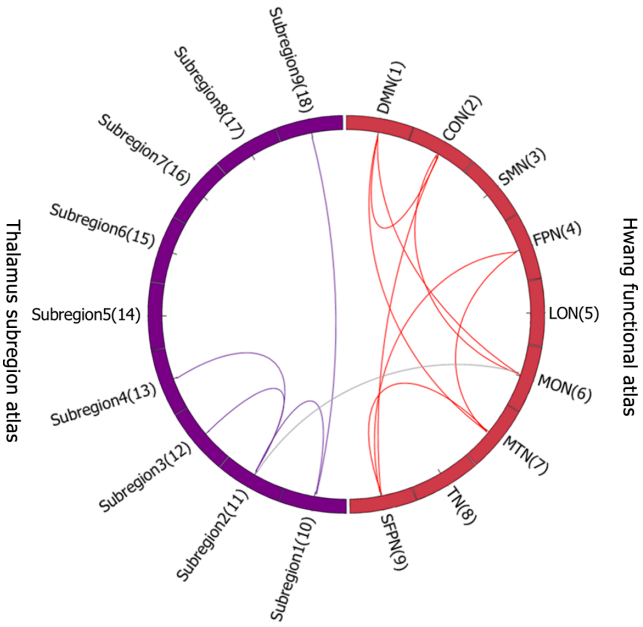


**Figure 1 Altered functional connectivity of thalamus subregions and cortical functional networks between treatment resistant schizophrenia and healthy control groups.** Between- and within-connectivity were presented in grey color and in each network's color respectively. CON: Cingulo-Opercular Network; DMN: Default Mode Network; FPN: Fronto-Parietal Network; LON: Lateral Occipital Network; MON: Medial Occipital Network; MTN: Medial Temporal Network; SFPN: Superior Fronto-Parietal Network; SMN: Somato-Motor Network; TN: Temporal Network.

antipsychotic-naïve patients with SZ[30]. It may be that reduced intrathalamic connectivity mediates the key role of the thalamus in perception, motor function, and cognitive integration[1], in turn contributing to the development of pathophysiology in TRS. More commonly described abnormalities in TRS include hyperconnectivity and hypoconnectivity between cortical functional networks. In this study, each cortical functional network consisted of many heterogeneous areas, and the results were significant even when using the BOLD time series for large cortical areas. Therefore, these findings may be considered as functional biomarkers for TRS. However, our expectation that the role of the thalamus as a connector hub would be disrupted in TRS was not confirmed.

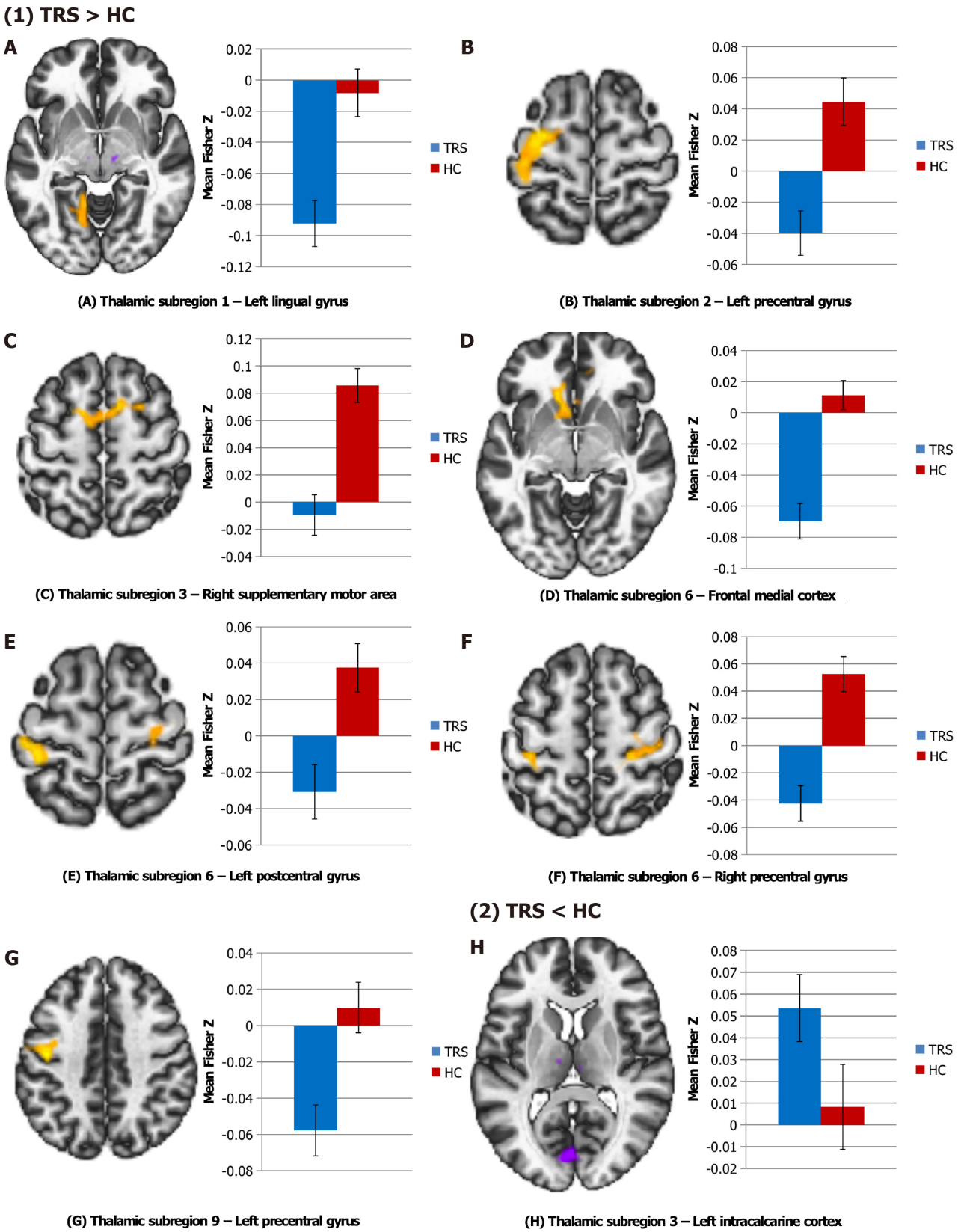


**Figure 2 Altered thalamus subregion-based functional connectivity between treatment resistant schizophrenia and healthy control groups.** Significant differences were revealed between the (A) Thalamic subregion 1 and Left lingual gyrus; (B) Thalamic subregion 2 and Left precentral gyrus; (C) Thalamic subregion 3 and right supplementary motor area; (D) Thalamic subregion 6 and Frontal medial cortex; (E) Thalamic subregion 6 and Left postcentral gyrus; (F) Thalamic subregion 6 and Right precentral gyrus; (G) Thalamic subregion 9 and Left precentral gyrus; and (H) Thalamic subregion 3 and Left intracalcarine cortex. The functional connectivity Z values of regions showing significant differences are presented in bar graph.

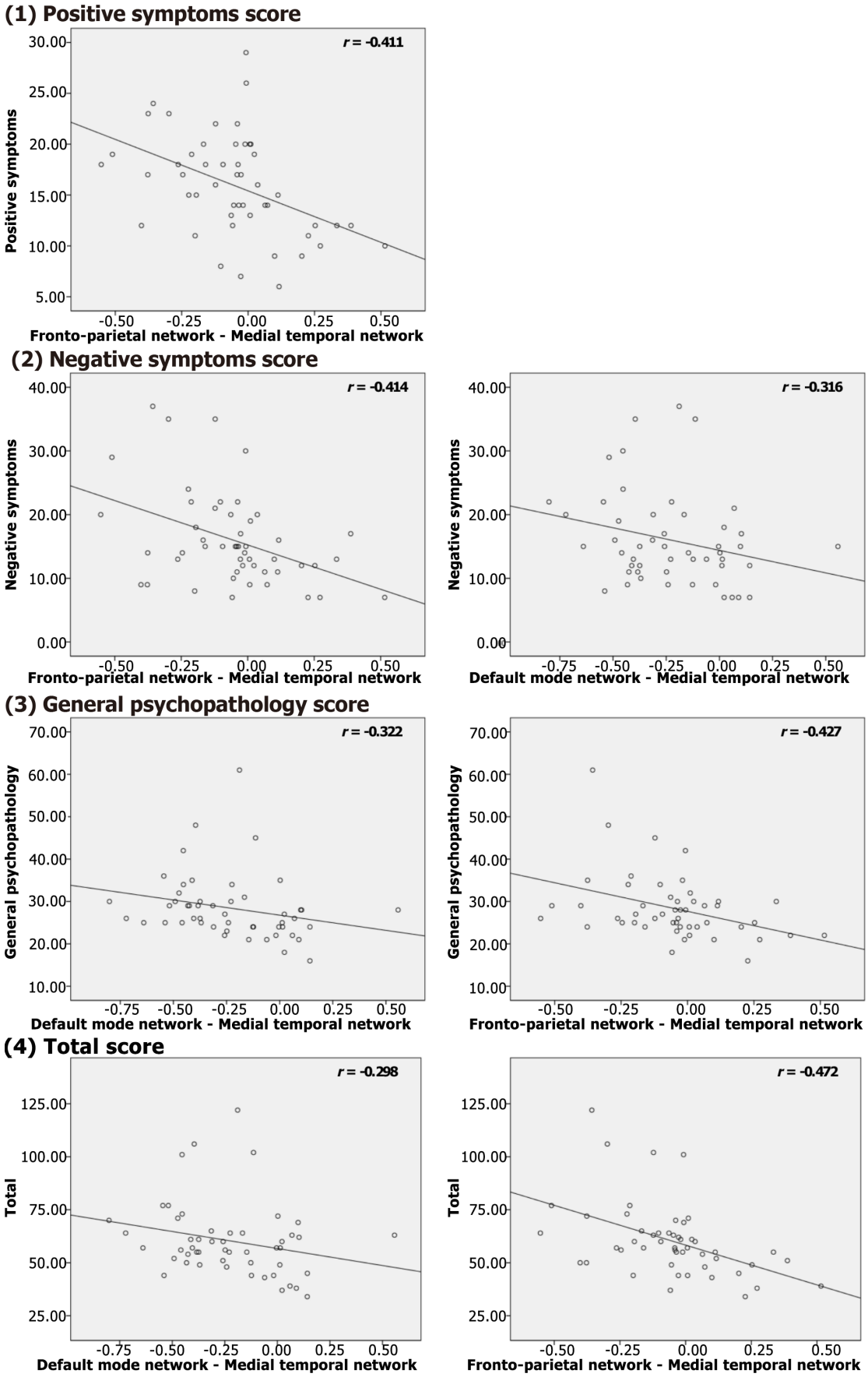


**Figure 3 Associations between the significantly altered region of interest to region of interest functional connectivity and Positive and Negative Syndrome Scale scores in the treatment resistant schizophrenia group.**

With respect to thalamic connectivity with cortical voxels, we identified significant hyperconnectivity of five thalamic subregions with various cortical regions in patients with TRS compared to HCs. Interestingly, most of these involved increased connectivity to the precentral and postcentral gyri and supplementary motor cortex. Considering the role of these areas in integrating sensorimotor information and coordinating physical movements[31,32], these findings may be relevant to the sensory and motor abnormalities found in TRS, such as hallucinations and neurological soft signs. Many studies have reported increased functional coupling between the thalamus and sensorimotor cortices in SZ[33,34,35,36,37]. However, this is the first study to report hyperconnectivity between thalamic subregions and the sensorimotor cortex in TRS. We also found increased connectivity to the frontal medial cortex and lingual gyrus. This is in contrast to previous research showing a reduction in FC of the thalamus with the prefrontal and cingulate cortices in SZ, based on signals averaged across the entire thalamus [33,34,36,38,39,40,41] as well as separate signals for individual thalamic subregions[15,16,17]. However, the subjects in previous studies were not patients with TRS. The medial PFC has been shown to play a fundamental role in a wide range of social cognitive abilities, such as self-reflection, person perception, and theory of mind/mentalizing[42]. Also, the lingual gyrus has been implicated in visual memory[43] and divergent thinking[44]. Therefore, increased thalamo-frontal or thalamo-lingual connectivity might serve as a marker for TRS. The potential associations of FC with social cognition and divergent thinking warrant further investigation. Finally, decreased connectivity of thalamic subregion 3 with the intracalcarine cortex was observed in our TRS patients. A similar result was reported in chronic SZ[17]. Given that the calcarine cortex is known to be involved in the processing of visual mental imagery[45], an fMRI study using a visual mental imagery task could be useful for exploring the pathophysiological mechanisms of TRS.

With regard to our analyses of altered ROI-to-ROI FCs, FC between the FP and MT networks, and between the DM and MT networks, showed negative relationships with positive symptoms, negative symptoms, general pathophysiology, and PANSS total scores. These findings suggest that altered connectivity between intracortical functional networks is associated with overall pathophysiology rather than specific symptom domains. This is intuitive considering that each cortical functional network consists of many heterogenous cortical regions. Regarding our analyses of cortical voxels, FC between thalamic subregion 3 and the right lingual gyrus showed negative relationships with positive symptoms, negative symptoms, general pathophysiology, and PANSS total scores. Even after considering the role of the lingual gyrus in visual memory and divergent thinking, it is difficult to determine how this altered FC is associated with overall pathophysiology. However, it may be that impairment of thalamic subregion 3, in terms of its role as a connector hub, has significant effects on the integration of cortical information. Finally, the positive association of FC between thalamic subregion 2 and the precentral gyrus with general pathophysiology accords with the findings of prior studies[17,33]. Even though patients with SZ often show abnormal involuntary movements or neurological soft signs related to the function of the precentral gyrus, it is difficult to identify relationships between motor functions and general pathophysiology[46].

## CONCLUSION

Several limitations of this study need to be considered. First, although the use of a functional parcellation atlas to segment the thalamus into subregions was a strength of this study, the roles and precise locations of thalamic subregions are still largely unknown, making it difficult to determine which specific regions had the largest effect on the results. Second, we did not recruit all subtypes of TRS patients, as recommended by the Treatment Response and Resistance in Psychosis Working Group[19]. The proportions of positive, negative, and positive and negative subtypes were 22%, 14%, and 32%, respectively. The remaining 32% of patients did not meet the criteria for the positive or negative subtype, because we applied a rating of moderate severity to just one symptom item. This should be addressed in future studies. Third, the TRS patients were all heavily medicated, so it is unclear whether the significant changes in FC reported above were a consequence of the disease process or medication. In this context, it will be important to determine the relative importance of illness duration, the number of psychotic episodes, and medication. Despite these weaknesses, this is the first report on altered FC of the thalamocortical pathway in TRS using thalamic subregions as seeds. In summary, in our TRS patients, we found altered FC between various thalamic subregions, between various cortical functional networks, and between thalamic subregions and various cortical regions. These abnormalities were associated with overall pathophysiology. Collectively, these results suggest that disrupted FC within thalamic and cortical functional networks, and within the thalamocortical pathway, could serve as markers for TRS. This study improves our understanding of the relationships between the thalamocortical pathway and symptoms of TRS.

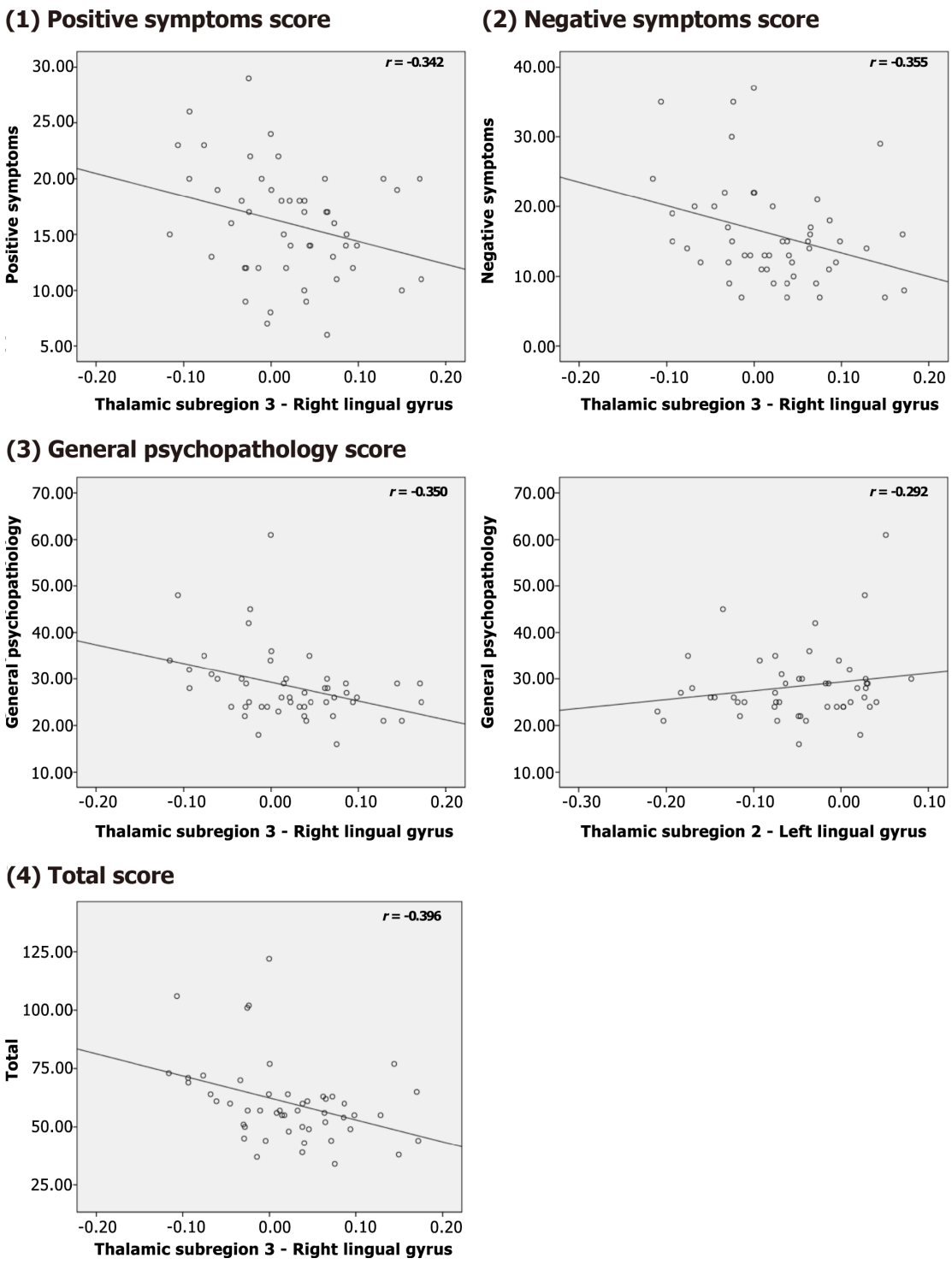


**Figure 4 Associations between the significantly altered seed to voxel functional connectivity and Positive and Negative Syndrome Scale scores in the treatment resistant schizophrenia group.**

## ARTICLE HIGHLIGHTS

### *Research background*

The thalamus is an important deep gray matter structure that transmits sensory information from the peripheral sensory nervous system to the cortex, and serves as a major hub for cognitive processes. Previous studies treated the thalamus as a homogeneous structure, averaging blood oxygen level-dependent signals across the entire thalamus. However, this approach may fail to capture disturbances in specific networks, so it is necessary to investigate functional connectivity (FC) between sub-regions of the thalamus and cortex to better understand altered neural circuits in Schizophrenia (SZ).

### Research motivation
To the best of our knowledge, no study has examined the FC of thalamic sub-regions in patients with treatment-resistant schizophrenia (TRS).

### Research objectives
To identify the neural mechanisms underlying TRS. We hypothesized that the FC of thalamic sub-regions with cortical networks and voxels would differ between TRS patients and HCs (Healthy Controls).

### Research methods
This study included 111 subjects (50 patients with TRS and 61 HCs). The rs-fMRI and sMRI data were obtained at the Jeonbuk National University Hospital using a 3T Verio scanner (Magnetom Verio; Siemens, Erlangen, Germany) with a 12-channel standard quadrature head coil. The functional parcellation atlas was used to segment the thalamus into nine subregions. FC analysis was performed between thalamic ROIs and cortical functional network ROIs, within the nine thalamic and nine cortical functional network ROIs, and between the thalamic ROIs and all cortical voxels. Demographic and clinical data were compared between the two groups using a two-sample *t*-test or Chi-square test. For partial correlation analysis. Relationships between the extracted Z-scores and PANSS scores were analyzed using age, sex, and FD as covariates.

### Research results
There were no significant differences in age, sex, or education level between the two groups. We found differences in FC within thalamic subregions and cortical functional networks between patients with TRS and HCs. In addition, increased FC was observed between thalamic subregions and the sensorimotor cortex, frontal medial cortex, and lingual gyrus. These abnormalities were associated with the pathophysiology of TRS.

### Research conclusions
The thalamus represents the interface between the sensory and motor systems, and is a major hub for cognitive processes. A large body of evidence has demonstrated the involvement of the thalamus in the pathophysiology of SZ. we found altered FC between various thalamic subregions, between various cortical functional networks, and between thalamic subregions and various cortical regions. These abnormalities were associated with overall pathophysiology. Collectively, these results suggest that disrupted FC within thalamic and cortical functional networks, and within the thalamocortical pathway, could serve as markers for TRS.

### Research perspectives
This study improves our understanding of the relationships between the thalamocortical pathway and symptoms of TRS.

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## FOOTNOTES
**Author contributions:** Chung YC conceptualized the study; Tsogt U, Shen J, Kim WS, Odkhuu S, and Chung YC performed the study and acquired data; Kim WS conducted experiment and statistical analysis; Kim WS drafted the manuscript; Tsogt U, Shen J, Kim WS, and Odkhuu critically reviewed the manuscript; Chung YC finalized the manuscript; all authors approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

# Changes in the amplitude of low-frequency fluctuations in specific frequency bands in major depressive disorder after electroconvulsive therapy

Xin-Ke Li, Hai-Tang Qiu, Jia Hu, Qing-Hua Luo

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## Abstract

### *BACKGROUND*

Major depressive disorder (MDD) tends to have a high incidence and high suicide risk. Electroconvulsive therapy (ECT) is currently a relatively effective treatment for MDD. However, the mechanism of efficacy of ECT is still unclear.

### *AIM*

To investigate the changes in the amplitude of low-frequency fluctuations in specific frequency bands in patients with MDD after ECT.

### *METHODS*

Twenty-two MDD patients and fifteen healthy controls (HCs) were recruited to this study. MDD patients received 8 ECT sessions with bitemporal placement. Resting-state functional magnetic resonance imaging was adopted to examine regional cerebellar blood flow in both the MDD patients and HCs. The MDD patients were scanned twice (before the first ECT session and after the eighth ECT session) to acquire data. Then, the amplitude of low-frequency fluctuations (ALFF) was computed to characterize the intrinsic neural oscillations in different bands (typical frequency, slow-5, and slow-4 bands).

### *RESULTS*

Compared to before ECT (pre-ECT), we found that MDD patients after the eighth ECT (post-ECT) session had a higher ALFF in the typical band in the right middle

frontal gyrus, posterior cingulate, right supramarginal gyrus, left superior frontal gyrus, and left angular gyrus. There was a lower ALFF in the right superior temporal gyrus. Compared to pre-ECT values, the ALFF in the slow-5 band was significantly increased in the right limbic lobe, cerebellum posterior lobe, right middle orbitofrontal gyrus, and frontal lobe in post-ECT patients, whereas the ALFF in the slow-5 band in the left sublobar region, right angular gyrus, and right frontal lobe was lower. In contrast, significantly higher ALFF in the slow-4 band was observed in the frontal lobe, superior frontal gyrus, parietal lobe, right inferior parietal lobule, and left angular gyrus.

*CONCLUSION*
Our results suggest that the abnormal ALFF in pre- and post-ECT MDD patients may be associated with specific frequency bands.

**Key Words:** Electroconvulsive therapy; Resting-state functional magnetic resonance imaging; Major depressive disorder; Amplitude of low-frequency fluctuations; Specific frequency bands

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**Core Tip:** In this study, we explored changes in the intrinsic neural activity in major depressive disorder (MDD) patients who underwent electroconvulsive therapy (ECT) procedures by calculating amplitude of low-frequency fluctuations (ALFF) values for different bands. Compared to pre-ECT values, the ALFF in the slow-5 band was significantly increased in the right limbic lobe, cerebellum posterior lobe, right middle orbitofrontal gyrus, and frontal lobe in post-ECT patients, whereas the ALFF in the slow-5 band in the left sublobar region, right angular gyrus, and right frontal lobe was lower. In contrast, significantly higher ALFF in the slow-4 band was observed in the frontal lobe, superior frontal gyrus, parietal lobe, right inferior parietal lobule, and left angular gyrus. Our findings demonstrated that the ALFF alterations in post-ECT patients are dependent on specific frequency bands. These results may help us to understand more fully the potential therapeutic mechanisms of ECT for MDD patients.

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## INTRODUCTION

Depression is a common mental illness with a high recurrence rate and risk of suicide. The main clinical manifestations are persistent depression, lack of interest in and pleasure from normal activities, severe grief, and even stupor[1-3]. According to the latest report released by the World Health Organization in 2017[4], approximately 322 million people suffer from depression worldwide. The prevalence rate is 4.4%, and more than 1 million people commit suicide every year due to depression. The lifetime prevalence of major depression is 16.2%. Antidepressants and behavioral therapies are the most commonly used treatments, but as many as one in three patients remain unresponsive to initial treatment[5,6]. With rapid and high response rates, electroconvulsive therapy (ECT) is usually used when other treatments fail. It is particularly important in suicidal, psychotic, or catatonic depression[7]. Although clinical efficacy has suggested that ECT is the most effective treatment for major depressive disorder (MDD), the mechanism of action of ECT is unclear[8], and little is known about the relationship between symptom improvement and the neurobiological effects associated with ECT. Some neurobiological effects are not necessary for therapeutic effects during ECT[9], and the potential adverse reactions require its clinical application to be very cautious and limited.

Antidepressant treatment response studies have reported changes in gray matter volumes and cortical thickness associated with improvement in MDD patients[10-12]. For ECT treatment, some changes have been reported in the structure of the gray matter in MDD patients. Yrondi *et al*[13] reported that gray matter changes occurred after several ECT sessions. Some studies have confirmed that ECT can also induce changes in the hippocampal formation and other brain regions[14-18]. Abbott *et al*[14] found a significant increase in the volume of the right hippocampus. Bouckaert *et al*[15] found that the caudate nucleus increased in volume. ECT also had vital effects on the dentate gyrus[19].

In addition to measuring alterations in brain structure in patients with MDD after ECT treatment, functional magnetic resonance imaging (fMRI) also has been used to detect changes in brain activity. Beall *et al*[20] adopted task fMRI to find that remission after ECT for MDD is connected to decreased activation in emotional regulation but increased resting connectivity. Abbott *et al*[21] used resting-state fMRI to measure the variations in MDD patients after multiple ECT sessions. This research reported that functional connectivity increased in two networks: (1) Posterior default mode (p_DM) and the dorsomedial prefrontal cortex (DMPFC); and (2) The left dorsal lateral prefrontal cortex (l_DLPFC) and p_DM. The fronto-temporal connectivity and the functional connectivity strength of the left angular gyrus in MDD were also found to be responses to ECT[7,22]. Redlich *et al*[9] used fMRI to find an increase in amygdala activity in patients with ECT, whereas activity after ECT was significantly reduced. Sinha *et al*[23] applied graph theory to fMRI data and revealed significant differences in the brain regions of patients with depression before and after ECT. To assess the alterations in depressive patients with ECT, data-driven methods also have been adopted[24,25]. However, there were still no consistent antidepressant responses observed in previous studies[26].

Many studies have revealed different functional activities of the brain since rs-fMRI was adopted by Biswal *et al*[27] to study spontaneous brain activity. To date, most studies have examined spontaneous low-frequency oscillation (LFO) activities at the frequency band of 0.01-0.1 Hz. However, some studies observed that neuronal oscillations are distributed linearly on the natural logarithmic scale and that independent frequency bands are generated by distinct oscillators with specific properties and physiological functions[28-30]. Moreover, neighboring frequency bands within the same neuronal network may compete or interact with each other[31]. The rs-fMRI LFO can be decomposed into the following frequency bands: slow-6 (0-0.01 Hz), slow-5 (0.01-0.027 Hz), slow-4 (0.027-0.073 Hz), slow-3 (0.073-0.198 Hz), and slow-2 (0.198-0.25 Hz). Zuo *et al*[32] found that the low-frequency amplitudes in the slow-5 band are smaller than those in the slow-4 band in the basal ganglia, thalamus, precuneus, and so on. Meanwhile, many studies have presented different measures of the nature of rs-fMRI. Among them, the amplitude of low-frequency fluctuations (ALFF) is a reliable representation of whole-brain rs-fMRI signals[33-35]. ALFF has been widely adopted because it directly correlates with the intensity of spontaneous neural activity in the resting state with regard to energy metabolism[36,37]. Frequency-dependent changes in ALFF have already been used to investigate some brain network mechanisms and disease phenotypes, such as chronic schizophrenia, late-onset depression, chronic tinnitus, and social anxiety disorder[28,30-40]. These studies showed that intrinsic functional activities of brain networks are correlated with different frequency bands.

In the current study, we investigated the alterations of the ALFF at different frequency bands (slow-5 (0.01-0.027 Hz), slow-4 (0.027-0.08 Hz)) in MDD patients before and after ECT. Then, the differences before and after ECT were explored.

## MATERIALS AND METHODS

### Subjects

Twenty-two inpatients (14 females and 8 males, aged 34.4 ± 10.1, range 21-55 years old) who had been diagnosed with major depression at the Mental Health Center, the First Affiliated Hospital of Chongqing Medical University were recruited. Fifteen gender- and age-matched healthy controls (HCs) (10 females and 5 males, aged 36.1 ± 9.4, range 21-55 years old) were recruited to participate in the investigation. All patients underwent blood tests, electrocardiogram, electroencephalogram, X-ray, and physical examination before ECT[41]. The study was approved by the local ethics committee of Chongqing Medical University accordance with the ethical standards laid down in the Declaration of Helsinki. Each patient gave written informed consent.

The inclusion criteria for the MDD patients included the following: (1) Agreeing to receive ECT; (2) meeting the unipolar major depressive diagnostic criteria according to the Diagnostic Statistical Manual-IV[42] (two trained senior psychiatrists carried out the structured clinical interviews and made the diagnoses); (3) no contraindications to MRI scanning; (4) Hamilton Depression Scale (HAMD)[43] score greater than 21; and (5) age between sixteen and sixty years. The exclusion criteria for the patients were as follows: (1) Severe somatic disease; (2) substance abuse; (3) pregnancy or lactation; (4) depression with other mental illnesses[44]; and (5) exposure to ECT or mood stabilizers in the preceding one month. HCs had no history of their own or family mental illness.

### ECT procedures

The Thymatron DGx (Somatics LLC, Lake Bluff, IL, United States) was used to perform the ECT for all 22 MDD patients at the Mental Health Center of the First Affiliated Hospital of Chongqing Medical University. Each patient received eight ECT treatments within three weeks. Specifically, the procedures were administered 3 times per week (Monday, Wednesday, and Friday mornings) for the first two weeks and 2 times per week (Monday and Friday mornings) for the 3rd week. The time and frequency of ECT treatment were the same for all patients. Before ECT, water and food intake were restricted for the patients beginning at midnight. Before receiving the first ECT and after the eighth ECT, all patients were

administered MRI scans, fMRI scans, and HAMD scores. Antidepressants and antipsychotics were not used during the ECT treatment period.

In every ECT process, the patients received anesthesia with sodium thiopental (3.0-5.0 mg/kg) and succinylcholine (0.5-1.0 mg/kg). In this study, the ECT electrodes were placed in the bitemporal position. According to the seizure response and adverse reactions (if any) during ECT, the electrical stimulation intensity was individually accommodated. In the first ECT, the seizure threshold was measured by the minimum electrical dose that elicited a seizure for at least 25 s[45]. Each time the initial dose failed to cause seizures, the output charge of the 5% ECT device was increased, and the patient was re-stimulated after 30 s. The patient underwent up to three electrical stimulations at one ECT. If the seizure threshold measurements failed in the first session, stimulation with 2 times the last dose was performed in the next session. To achieve a therapeutic effect and reduce side effects, the electrical dosage was set at 1.5-2 times the seizure threshold in subsequent ECT treatment sessions according to the extent of seizure. If the clinician determined that the clinical symptoms of depression had not been adequately improved after eight sessions, we continued the ECT course for the patients to up to 12 ECT sessions. For the sake of the comparison, each patient underwent MRI scanning after the eighth ECT treatment.

### Mood ratings

Depression symptoms of the patients were measured by the 24-item HAMD Rating Scale on the same day as brain scanning. The psychiatrists performed the clinical assessments of depression for all patients twice. The first time was within 24 h before the 1$^{st}$ ECT treatment (pre-ECT). The second time was within 24 h after the 8$^{th}$ ECT treatment (post-ECT).

### Data acquisition

Image data were collected with the MRI scanner system (3.0-T, GE Signa) at the Mental Health Center of Chongqing Medical University. Both the HCs and the MDD patients were instructed to relax, stay awake, keep their eyes closed, and avoid thinking during the scanning process. The resting-state functional images were collected with an echo planar imaging sequence. The image parameters were recorded as follows: repetition time/echo time, 2 s/30 milliseconds; field of view, 240 mm × 240 mm; data matrix, 64 × 64; flip angle, 90°; slices, 30; slice thickness, 5 mm; volumes, 200. The scan lasted 6 min and 50 s per scan.

### Functional image data preprocessing

Using the statistical parametric mapping software platform, functional image data preprocessing was carried out by DPABI (Data Processing Assistant for rs-fMRI, http://www.restfmri.net, by YAN Chao-Gan *et al*[46]). The preprocessing procedure on the rs-fMRI data included the following: (1) We abandoned the first 10 volumes because the signals of the participants' adaptation to the scanning environment were unstable. Then, the remaining 190 volumes were retained; (2) Head motion correction was performed. Subjects with a head motion of more than 1.5 mm in any direction of the 3 coordinate axes ($x$, $y$, and $z$) or angular motion of more than 1.5° were excluded from this study; (3) Considering the delay of the acquisition, slice timing was conducted. There were 30 Layers in a scan. The odd-numbered layers started and were followed by the even-numbered layers; (4) Spatial normalization was carried out. The fMRI images were registered to the standard Montreal Neurological Institute space and were resampled to 3 mm × 3 mm; (5) We adopted the Gaussian kernel with full-width at half-maximum of eight mm to fulfill the spatial smoothing; and (6) The linear trend of the functional image data was removed. Finally, the normalized image data were subjected to bandpass filtering with frequency ranges of 0.01-0.08 Hz.

### ALFF analyses

A fast Fourier transform can be used to obtain the frequency domain for the time series signal. Moreover, we adopted the average square root of the power spectrum to denote the ALFF value of a given voxel. Then, the intensity of spontaneous LFO can be measured by the ALFF. In the present study, the ALFF was performed by the REST software toolkit (Resting-State fMRI Data Analysis)[47] in two different frequency ranges (slow-5: 0.01-0.027 Hz, slow-4: 0.027-0.073 Hz) separately. The ALFF of the typical band (0.01-0.08 Hz) was also computed for comparative purposes.

### Statistical analyses

To explore the changes in ALFF at different frequency bands before and after ECT, the effects of ECT treatment on MDD and frequency alterations were examined by REST[47]. Two-sample two-sided $t$-tests were adopted to assess the differences between the MDD group and the HC group. We applied paired $t$-tests to measure the ALFF alterations before and after ECT. The statistical maps were corrected by multiple comparisons with a significance level of $P < 0.05$ (bilateral) using AlphaSim as well as a height threshold of $P < 0.01$ and a minimum cluster size = 85. To find the difference between pre-ECT and post-ECT with the clinical measure, the significant alterations of ALFF values in the regions of interest (ROIs) in the brain were calculated. Moreover, the coordinates ($x$, $y$, and $z$) of the peak density of

**Table 1 Demographic data of the major depressive disorder patients and healthy controls**

| Characteristic | MDDs (*n* = 22) | | HCs (*n* = 15) | *P* value |
|---|---|---|---|---|
| Sex (male/female) | 8/14 | | 5/10 | |
| Age (mean ± SD) | 34.4 ± 10.1 | | 36.1 ± 9.4 | 0.495[1] |
| Education years (mean ± SD) | 11.61 ± 3.28 | | 14.93 ± 3.64 | 0.091[1] |
| HAMD | Pre-ECT | 30.59 ± 4.35 | 2.18 ± 1.32 | < 0.001[2] |
| | Post-ECT | 8.76 ± 5.58 | | |

[1]Mann-whitney *U* nonparametric tests (criteria alpha = 0.05).
[2]Paired *t* tests between pre- and post-electroconvulsive therapy major depressive disorder patients. MDDs: Major depressive disorder patients; HCs: Healthy controls; HAMD: Hamilton Rating Scale for Depressive; ECT: Electroconvulsive therapy.

the ROIs were described in the ALFF map.

## RESULTS

### Clinical results

In the present study, twenty-two MDD patients (14 women, 8 men, right-handed, 34.4 ± 10.1 years old) were recruited from the Inpatient Department of Psychiatry at the First Affiliated Hospital of Chongqing Medical University. Among them, 21 patients took at least one antidepressant, and the remaining patients were receiving no medication. We adopted the 24-item HAMD to examine all MDD patients. The average score for the patients pre-ECT was 30.59 ± 4.35 (as seen in Table 1).

After 8 ECT sessions, the depression symptoms improved greatly for all patients ($t_{21}$ = 12.61, $P$ < 0.0001; paired $t$ test). According to the clinical results, the HAMD scores of all 22 patients before and after ECT decreased by more than 50%. The HAMD scores of 10 patients were lower than 7. Therefore, they were considered to be remitted.

### ALFF results at the typical frequency band

Compared with HCs, pre-ECT MDD patients had significant alterations in ALFF values in some brain regions (as shown in Figure 1). The typical frequency band (0.01-0.08 Hz) is reported as follows. The ALFF values in the brain areas in pre-ECT patients were lower than those in HCs, which included the posterior lobe of the cerebellum, the cerebellar tonsil, inferior semilunar lobule, temporal lobe, inferior temporal gyrus, frontal lobe, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, limbic lobe, parietal lobe, occipital lobe, and inferior parietal lobule.

We used paired *t*-tests to identify differences, which are shown in Figure 2. Moreover, Table 2 shows the group differences in ALFF in the typical frequency band between before ECT and after ECT in patients with MDD. We found that the ALFF of the right middle frontal gyrus, posterior cingulate, right supramarginal gyrus, left superior frontal gyrus, and left angular gyrus increased significantly in MDD patients after ECT. However, that of the right superior temporal gyrus decreased significantly. In our study, Monte Carlo simulations were used to conduct the multiple comparison correction for all the statistical maps with a significance level of $P$ < 0.05. The individual voxel $P$ is lower than 0.05, and the cluster size is larger than 2079 $mm^3$[48].

### Differential ALFF values at the slow-5 frequency band between pre-ECT and post-ECT

The post-ECT MDD patients, relative to the pre-ECT MDD patients, demonstrated significantly higher ALFF in the slow-5 band in the right limbic lobe, bilateral cerebellum posterior lobe, right middle orbitofrontal gyrus, and frontal lobe, whereas they had lower ALFF in the slow-5 band in the left sublobar region, right frontal lobe, and right angular gyrus, as shown in Figure 3 and Table 3.

We measured the ALFF of two frequency bands (slow-4 and slow-5) in the groups after and before ECT. Significant difference maps using paired *t*-tests are shown in Figures 3 and 4.

### Differential ALFF values at the slow-4 frequency band between pre-ECT and post-ECT

Compared with the pre-ECT patients, the post-ECT patients showed significantly higher ALFF in the slow-4 band in the frontal lobe, superior frontal gyrus, bilateral parietal lobe, right inferior parietal lobule, and left angular gyrus (as shown in Figure 4 and Table 4).

**Table 2 Differences in amplitude of low-frequency fluctuations (0.01-0.08 Hz) between groups before and after electroconvulsive therapy**

| Brain region | Side | BA | MNI coordinates | | | Voxels | *t* values |
|---|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | | |
| Before ECT < after ECT | | | | | | | |
| Middle frontal gyrus | R | 10, 11 | 30 | 54 | 3 | 262 | 3.5547 |
| Posterior cingulate | R and L | 29, 30 | -3 | -45 | 9 | 92 | 4.0993 |
| Supramarginal gyrus | R | 7, 39, 40 | 51 | -48 | 30 | 187 | 3.7424 |
| Superior frontal gyrus | L | 9, 10 | -12 | 63 | 24 | 96 | 3.4006 |
| Angular gyrus | L | 39, 40 | -42 | -72 | 42 | 193 | 4.0957 |
| Before ECT > after ECT | | | | | | | |
| Superior temporal gyrus | R | 13, 22, 47 | 54 | -3 | 0 | 114 | -3.1055 |

MNI: Montreal Neurological Institute; ECT: Electroconvulsive therapy.

**Table 3 Brain regions showing significant differences in amplitude of low-frequency fluctuations at slow-5 (0.01-0.027 Hz) between groups before and after electroconvulsive therapy**

| Brain region | Side | BA | MNI coordinates | | | Voxels | *t* values |
|---|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | | |
| Before ECT < after ECT | | | | | | | |
| Limbic lobe | R | 36 | 33 | -21 | -30 | 105 | 3.0807 |
| Cerebellum posterior lobe | R and L | 18 | -12 | -82 | -27 | 116 | 3.4515 |
| Frontal_Mid_Orb_R | R | 11 | 45 | 48 | -15 | 187 | 3.7424 |
| Frontal lobe | R | 22 | 48 | 18 | 36 | 147 | 3.3909 |
| Frontal lobe | R and L | 6, 8, 9, 10 | -6 | 48 | 54 | 233 | 4.2748 |
| Before ECT > after ECT | | | | | | | |
| Sublobar | L | 22 | -42 | 3 | 3 | 111 | -4.015 |
| Angular gyrus | R | 13 | 39 | 12 | -3 | 124 | -3.1741 |
| Frontal lobe | R | 24 | 12 | -36 | 48 | 228 | -3.7067 |

MNI: Montreal Neurological Institute; ECT: Electroconvulsive therapy.

## DISCUSSION

To improve MDD patients' depressive symptoms, several treatments, including ECT and transcranial magnetic stimulation, can be applied[49]. There have also been some studies using resting-state fMRI to assess antidepressant treatment response[49]. Among these methods, ECT is an effective therapy for MDD patients. Abbott *et al*[21] investigated the differences between ECT remitters and nonremitters and suggested that thane increase in functional connectivity between p_DM network areas and the l_DLPFC is a potential biomarker of recovery from depressive disorder patients. Kong *et al*[34] used regional homogeneity and ALFF to measure changes in regional resting state function after ECT in elderly MDD patients. Their results demonstrated that ECT affected regional resting-state brain function in these patients. In this study, we investigated spontaneous neural activity changes in ALFF at different frequency bands (typical frequency, slow-5, and slow-4 bands) in patients with MDD before and after ECT. We found that post-ECT, compared to pre-ECT, patients showed significant alterations in ALFF within the frequency bands in some brain areas. Our findings further showed that the ALFF alterations in post-ECT patients were dependent on specific frequency bands.

Compared with HCs, MDD patients showed significant differences in ALFF with a frequency band of 0.01-0.08 Hz in numerous brain regions[50-53]. The present study also found that pre-ECT patients had lower ALFF values than HCs in widely distributed brain areas, including the cerebellum posterior lobe,

**Table 4 Brain regions showing significant differences in amplitude of low-frequency fluctuations at slow-4 (0.027-0.08 Hz) between groups before and after electroconvulsive therapy**

| Brain region | Side | BA | MNI coordinates | | | Voxels | *t* values |
|---|---|---|---|---|---|---|---|
| | | | *x* | *y* | *z* | | |
| Before ECT < after ECT | | | | | | | |
| Frontal lobe, superior frontal gyrus | R and L | 9, 10, 11, 47 | 51 | 45 | -15 | 243 | 3.3179 |
| Parietal lobe, inferior parietal lobule | R | 39, 40 | 57 | -60 | 21 | 131 | 2.8756 |
| Parietal lobe, angular gyrus | L | 39, 40, 19, 7 | -45 | -63 | 36 | 256 | 4.1322 |
| Parietal lobe | R | 7 | 15 | -69 | 63 | 129 | 3.9572 |

MNI: Montreal Neurological Institute; ECT: Electroconvulsive therapy.

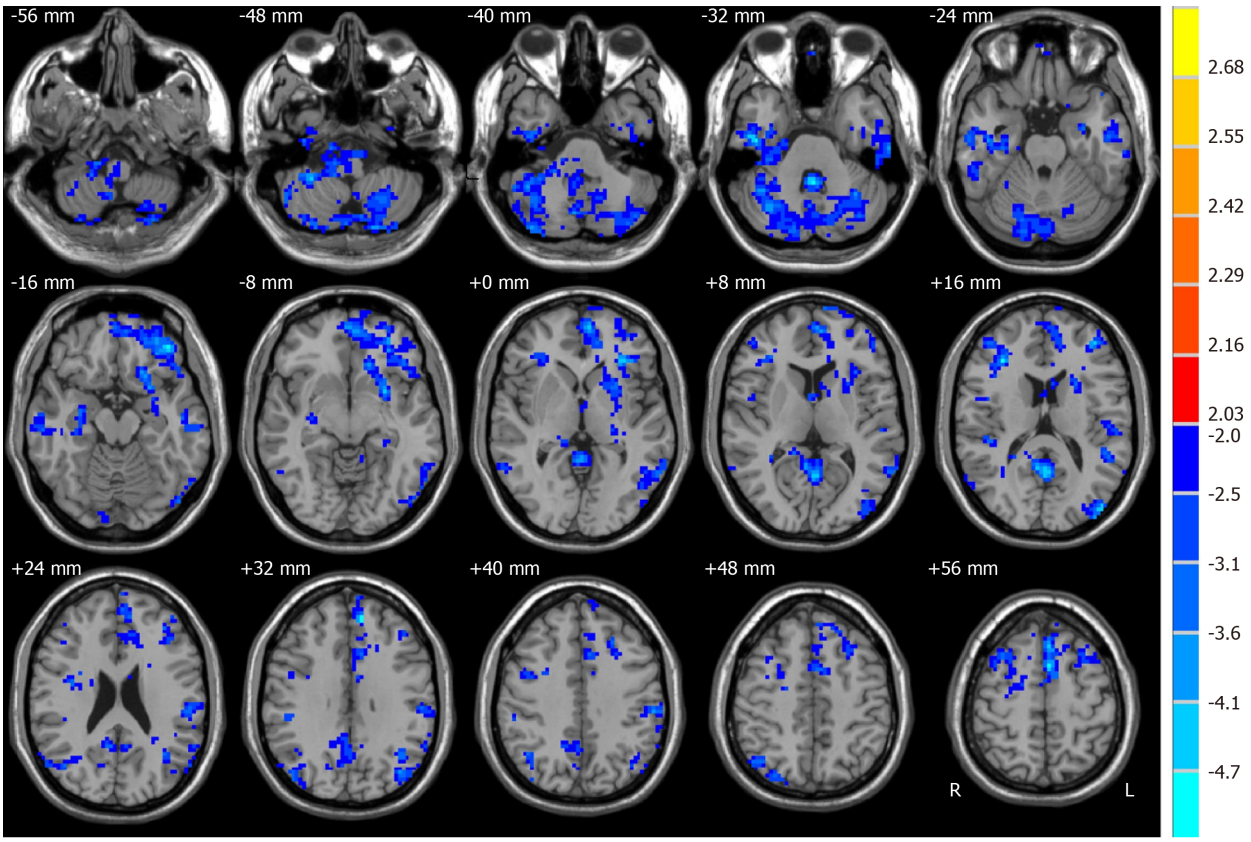


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**Figure 1 Brain regions with significant alterations in amplitude of low-frequency fluctuations in the typical band (0.01-0.08 Hz) between healthy controls and pre-electroconvulsive therapy patients.** The red region indicates that the amplitude of low-frequency fluctuations in pre-electroconvulsive therapy (ECT) patients was larger than that in healthy controls (HCs). In contrast, the blue region represents HCs that were larger than pre-ECT patients.

cerebellar tonsil, inferior semilunar lobule, temporal lobe, inferior temporal gyrus, frontal lobe, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, limbic lobe, parietal lobe, occipital lobe, and inferior parietal lobule. In the comparison of ALFF in the typical frequency band in MDD patients before and after ECT, we found that the right middle frontal gyrus, posterior cingulate, right supramarginal gyrus, left superior frontal gyrus, and left angular gyrus increased significantly after ECT. However, the right superior temporal gyrus decreased significantly. The results were similar to those of previous studies[34,41].

Baria *et al*[54] found that the lower frequency bands had higher power. Thus, subcortical structures with higher frequency bands usually have less power. In contrast, the brain cortexes, including the prefrontal and parietal cortexes, exhibit higher power[55]. In addition, Zuo *et al*[32] and Han *et al*[56] demonstrated that the regions of the default mode network are more active in the slow-5 band, whereas

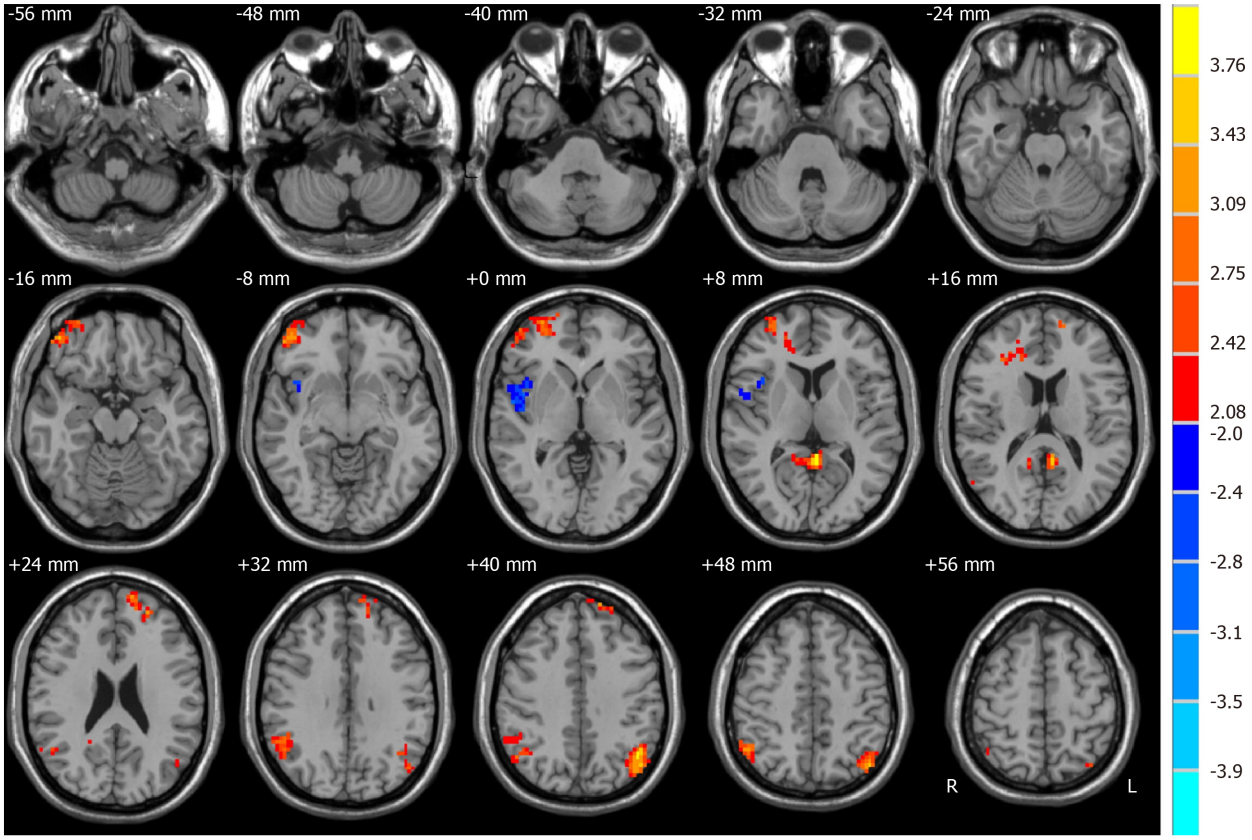


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**Figure 2 Brain regions with significant alterations in amplitude of low-frequency fluctuations in the typical band (0.01-0.08 Hz) for pre- and post-electroconvulsive therapy.** The red region indicates that the amplitude of low-frequency fluctuations (ALFF) in post-electroconvulsive therapy (ECT) patients was larger than that in pre-ECT patients. In contrast, the blue region represents areas for which the ALFF in pre-ECT patients was larger than that in post-ECT patients.

the basal ganglia are dominant in the slow-4 band. In this study, compared to pre-ECT patients, significantly higher ALFF was found in the slow-5 band in post-ECT patients in the right limbic lobe, cerebellum posterior lobe, right middle orbitofrontal gyrus, and frontal lobe. The sublobar region, angular gyrus, and frontal lobe were lower. Significantly higher ALFF in the slow-4 band was also observed in the frontal lobe, superior frontal gyrus, parietal lobe, right inferior parietal lobule, and left angular gyrus.

Many abnormal regions associated with the frontal lobe in MDD have been observed in previous studies[57,58]. Recently, a multisite rs-fMRI study reported MDD patients with hypoactivity in the medial orbitofrontal region[59]. We found a significantly higher ALFF both at the slow-5 band and slow-4 band in the frontal lobe post-ECT. As a result, abnormal activities in these brain areas might be normalized after ECT treatment[60], which might have improved the symptoms of depression. This may be considered evidence of the effectiveness of ECT for MDD.

Alterations of the limbic lobe have important effects in MDD patients[12,61]. For example, the amygdala and hippocampus are usually thought of as potential biomarkers for major depression. Compared to HCs, MDD patients illustrated decreased ALFF values in the limbic regions[50,51]. Jiao *et al*[62] and Liu *et al*[63] also demonstrated that MDD patients had abnormalities in prefrontal-limbic emotional processing. The results of the present study were consistent with these conclusions. Moreover, post-ECT patients, relative to pre-ECT patients, showed increased ALFF in the slow-5 band in the limbic lobe. This feature may also indicate an effective response to ECT treatment.

Recently, more interest has been drawn to the pathophysiology of the cerebellum in MDD[62,64,65]. Previous studies reported decreased ALFF values in the cerebellum in MDD patients[66,67]. Moreover, Zhou *et al*[66] concluded that reduced activity in the cerebellum in MDD might be a biomarker for patients. In the current study, compared with pre-ECT patients, post-ECT patients exhibited a significant increase in ALFF in the slow-5 band in the cerebellum posterior lobe. Thus, the hypothesis of Zhou *et al*[66] was supported by our results.

Post-ECT patients had lower ALFF values than pre-ECT patients for the angular gyrus in the slow-5 band. In contrast, the ALFF value was significantly increased in the slow-4 band. This was an interesting finding in the current study. The angular gyrus might play an important role in many functions, such as memory retrieval, spatial cognition, and semantic processing[68]. Previous studies reported

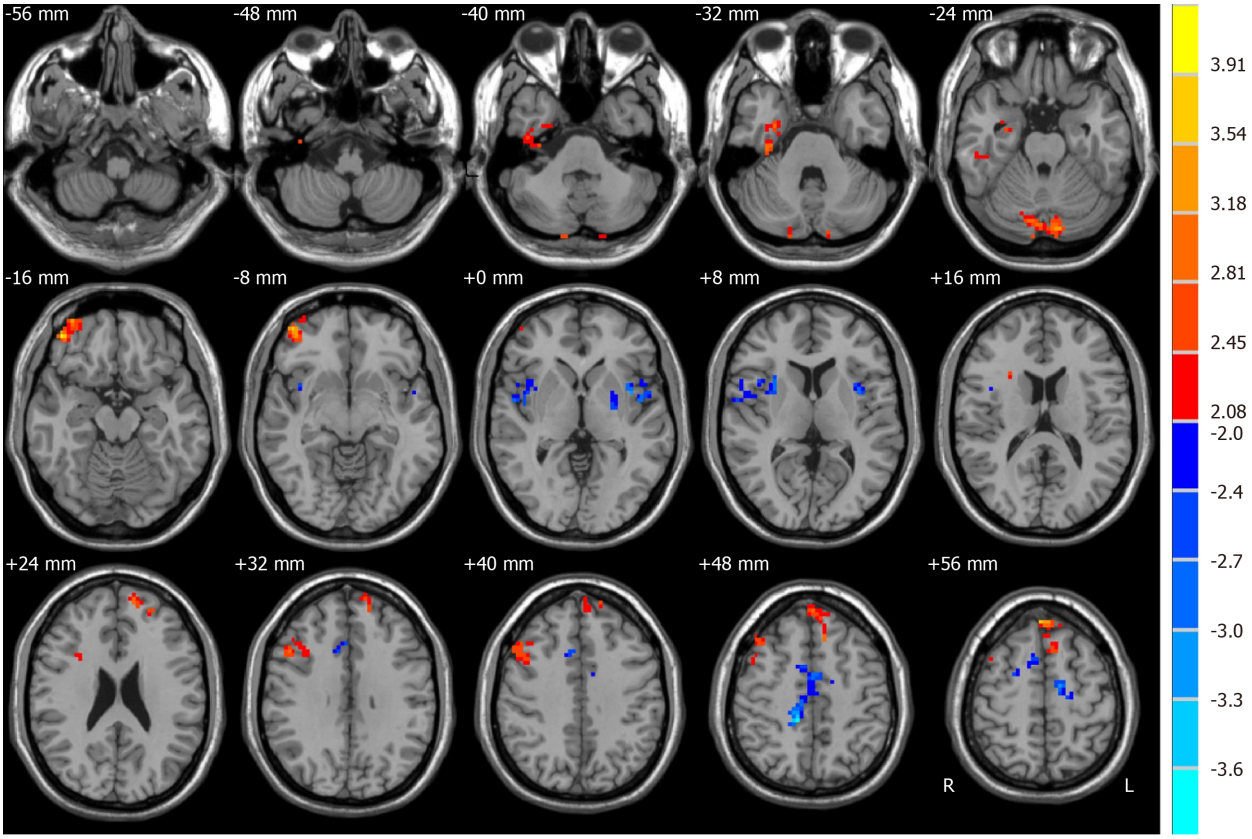


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**Figure 3 Brain regions with significant alterations in amplitude of low-frequency fluctuations at slow-5 (0.01–0.027 Hz) for pre- and post-electroconvulsive therapy.** The red region indicates that the amplitude of low-frequency fluctuations in post-electroconvulsive therapy (ECT) patients was larger than that in pre-ECT patients. In contrast, the blue region represents pre-ECT patients that were larger than that in post-ECT patients.

significantly increased spontaneous brain activity in the angular gyrus in MDD patients[69,70]. The alterations of ALFF in the angular gyrus at the slow-5 band in our findings can be viewed as consistent with these studies. Our study also demonstrated that the effectiveness of ECT treatment for MDD may be partly proven by significantly decreased ALFF in the slow-5 band.

Compared with HCs, decreased ALFF was exhibited in the parietal lobe in MDD patients[50,71]. In this study, the results of the comparison between HCs and pre-ECT patients were similar to this point. In addition, we found that ALFF increased significantly in the parietal lobe at the slow-4 band in post-ECT patients compared to pre-ECT patients. However, there was no difference in the slow-5 band.

There are some limitations of our study. First, the MDD patients were scanned only twice (before the first ECT session and after the eighth ECT session). To observe more alterations in spontaneous neural activity, more scans should be carried out during ECT treatment. Second, different MDD patients had divergent responses in speed and effectiveness in the practical clinic. Some unresponsive patients may receive more than eight ECT sessions[16]. For comparison, all patients were scanned after the eighth ECT session in this study. To find a more reliable relationship between ALFF and clinical symptoms, a more detailed longitudinal study should be performed pre- and post-ECT. Finally, the number of MDD patients and control subjects in the present study was relatively small. The multiple comparison tests failed due to the insufficient number of subjects. A larger sample would help us to achieve more robust results.

## CONCLUSION

In this study, we explored changes in the intrinsic neural activity in MDD patients who underwent ECT procedures by calculating ALFF values for different bands (typical frequency, slow-5, and slow-4 bands). For post-ECT patients, relative to pre-ECT patients, significantly higher ALFF in the slow-5 band was observed in the right limbic lobe, cerebellum posterior lobe, right middle orbitofrontal gyrus, and frontal lobe. The ALFF of the left sublobar region, right angular gyrus, and right frontal lobe were lower. Significantly higher ALFF in the slow-4 band was also observed in the frontal lobe, superior frontal gyrus, parietal lobe, right inferior parietal lobule, and left angular gyrus. Our findings demonstrated that the ALFF alterations in post-ECT patients are dependent on specific frequency bands.

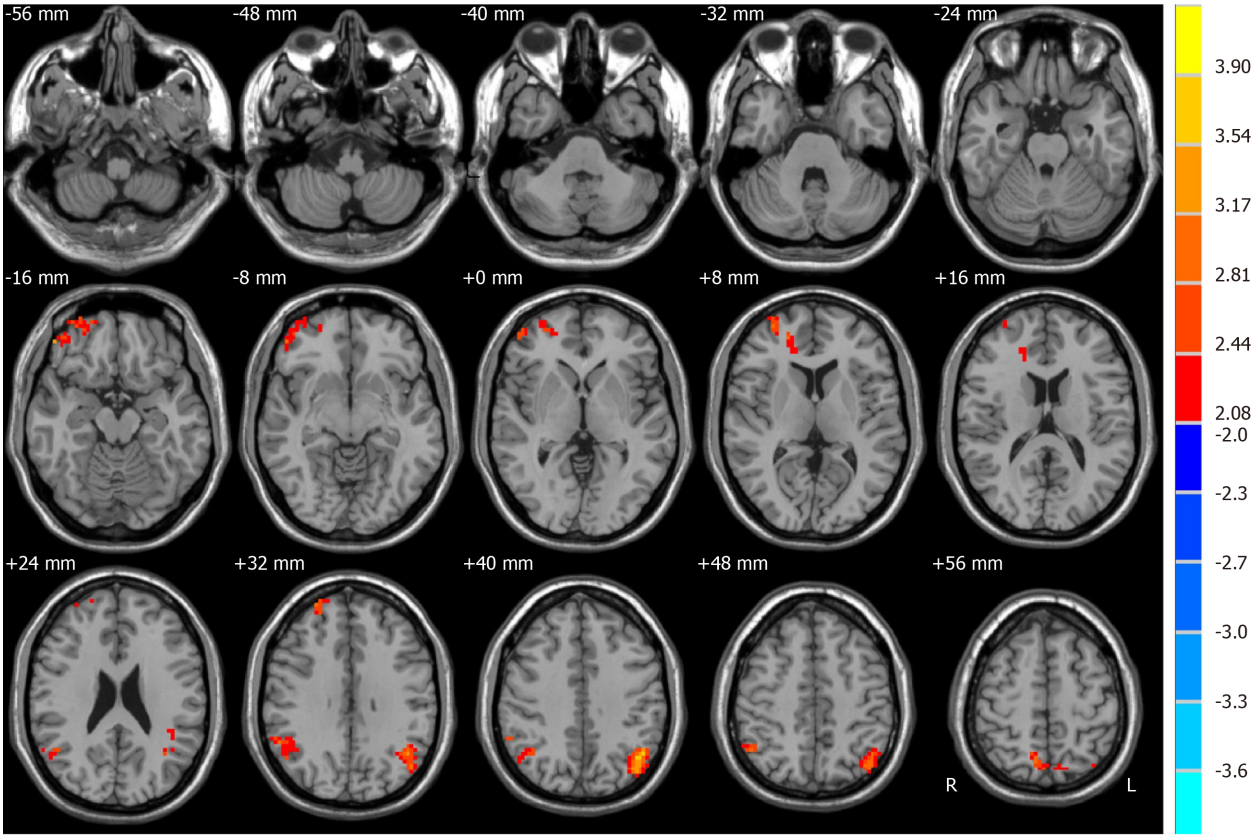


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**Figure 4 Brain regions with significant alterations in amplitude of low-frequency fluctuations at slow-4 (0.027-0.08 Hz) for pre- and post-electroconvulsive therapy.** The red region indicates that the amplitude of low-frequency fluctuations in post-electroconvulsive therapy (ECT) patients was larger than that in pre-ECT patients. In contrast, the blue region represents pre-ECT patients that were larger than that in post-ECT patients.

These results may help us to understand more fully the potential therapeutic mechanisms of ECT for MDD patients. In future work, we will recruit more patients and health controls to participate this investigation. More scans will be carried out for participants to obtain more robust results. The changes in cognitive function will also be monitored.

## ARTICLE HIGHLIGHTS

### *Research background*

The mechanism of efficacy of electroconvulsive therapy (ECT) for major depressive disorder (MDD) is still unclear. Intrinsic functional activities of brain networks are correlated with different frequency bands.

### *Research motivation*

The amplitude of low-frequency fluctuations (ALFF) at different frequency bands (slow-5 (0.01-0.027 Hz), slow-4 (0.027-0.08 Hz)) in MDD patients may be changed regularly before and after ECT.

### *Research objectives*

To investigate the alterations of the amplitude of low-frequency fluctuations in slow-5 (0.01-0.027 Hz) and slow-4 (0.027-0.08 Hz) in patients with MDD after ECT.

### *Research methods*

Resting-state functional magnetic resonance imaging and the intrinsic neural oscillations in different bands were adopted to analyze the changes in MDD patients before and after ECT.

### *Research results*

Compared to before ECT, we found that MDD patients after ECT had a higher ALFF in the typical band in some regions such as the right middle frontal gyrus and posterior cingulate. Moreover, there were

other changes in slow-5 band and slow-4 band.

### *Research conclusions*

Our findings showed that the ALFF alterations in post-ECT patients were dependent on specific frequency bands.

### *Research perspectives*

These changes may reveal some mechanism of efficacy of electroconvulsive therapy for major depressive disorder.

## FOOTNOTES

**Author contributions:** Li XK conducted the statistical analysis and wrote the manuscript; Qiu HT performed the study design and interpretation of findings; Luo QH recruited the patients, collected the data; Hu J revised the manuscript.

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**Institutional review board statement:** The study was reviewed and approved by the (the local ethics committee of Chongqing Medical University) Institutional Review Board (Approval No. 2020-97-2).

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** The authors have no conflict interest.

**Data sharing statement:** No additional data are available.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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ORIGINAL ARTICLE

Observational Study

# Relationship of depression and sleep quality, diseases and general characteristics

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## Abstract

***BACKGROUND***

Depression is the most common type of depressive disorder. The most common sleep disorder associated with depression is insomnia. Insomnia and depression are closely related.

***AIM***

To investigate the relationship of designed questionnaire items and depression, and analyze the related factors with depression.

***METHODS***

Questionnaire included Patient Health Questionnaire-9 (PHQ-9) and Pittsburgh sleep quality index (PSQI), 12 kinds of diseases, 8 general characteristics, and 20 insomnia characteristics, totally 56 items were filled out by 411 patients enrolled.

***RESULTS***

All the 9 items of PHQ-9, 6 components of PSQI (except sleep duration), education, living situation, exercise, years of insomnia, western medicine treatment, Chinese medicine treatment, psychotherapy, kinds of insomnia, treatment expected to treat insomnia, psychological counseling, habit of 1 h before bed, habit of lunch break, diagnosed depression, coronary heart disease, mental illness showed significant difference between without and with depression group. By univariate analysis and multivariate analysis. The odds ratio of education, exercise, kinds of insomnia, habit of 1 h before bed, diagnosed depression, coronary heart disease ($P$ = 0.01) showed significant difference. Their odds ratios were 0.71 (0.55, 0.93), 2.09 (1.32, 3.31), 0.76 (0.63, 0.91), 0.89 (0.81, 0.98), 0.32 (0.17, 0.60), 0.43 (0.23, 0.79).

*CONCLUSION*
We demonstrated that education, exercise, kinds of insomnia, habit of 1 h before bed, diagnosed depression and coronary heart disease affect the depression.

**Key Words:** Depression; Patient Health Questionnaire-9; Pittsburgh sleep quality index; Sleep; Insomnia

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**Core Tip:** Depression is the most common type of depressive disorder, manifesting as single or repeated episodes, with a high risk of recurrence. Depression affects the functions of the energy and digestive system and can also lead to varying degrees of sleep difficulties, insomnia, sleep arousal and other sleep disorders. In this study, we aimed to evaluate the related factor with depression, to provide theoretical support for detection and depression therapy.

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## INTRODUCTION

Depression is the most common type of depressive disorder, manifesting as single or repeated episodes, with a high risk of recurrence. There can be significant emotional, cognitive, and physical symptoms during episodes, and symptoms can resolve between episodes[1]. The main clinical manifestation is depression, which is not commensurate with the situation. It can range from sullenness to grief and even stupor. Some patients will have obvious anxiety and motor agitation. In severe cases, psychotic symptoms such as hallucinations and delusions may occur. Some patients suffer from self-injury, suicidal behavior, and even death[2]. With the accelerating pace of society, study pressure, work pressure, and life pressure increase, and the incidence of depression shows a significant upward trend. Depression has become the most important cause of the ten causes of disability-adjusted life years in every country in the world. The lifetime prevalence of depression is estimated to be 5% among adults[3, 4]. Depressive disorders have a high prevalence and high disease burden, but the treatment rates are low, with less than 10% of these patients receiving effective treatment in many countries; however, the medical prevention and treatment of depression in China still has a low recognition rate[5]. Hospitals above the prefecture-level city have a recognition rate of less than 20%, and less than 10% of patients receive relevant drug treatment. At the same time, the incidence of depression has begun to show a trend of younger age (college and even primary and secondary school students). The popularization, prevention and treatment of depression need urgent attention[6].

Depression affects the functions of the energy and digestive system and can also lead to varying degrees of sleep difficulties, insomnia, sleep arousal and other sleep disorders. Changes in sleep are one of the diagnostic criteria for depression. The probability of sleep disturbance in patients with depression is as high as 70%, which manifests as insomnia, lethargy, nightmares and disturbance of the sleep-wake cycle[7]. The most common sleep disorder associated with depression is insomnia. Insomnia and depression are closely related and share a bidirectional relationship with each other[8]. Insomnia is a demonstrated and a relative risk factor for depression. Treatment can improve or prevent major depressive episodes. The early identification of insomnia may also improve the outcomes of depression [9]. Insomnia and depression are heterogeneous processes, and the diagnostic components of insomnia and depression are likely to lead to translational progress at their nexus[10,11]. Studies have shown that poor sleep quality can lead to a decline in executive function, making it difficult to avoid negative thoughts, increasing nighttime unpleasantness, and triggering rumination, and repeated negative thoughts lead to increased suicide risk. In addition to insomnia, depressive patients may also experience somnolence during the course of the disease. Approximately 7%-8% of patients with major depressive disorder have somnolence and excessive sleep time, and approximately 25% of patients have both insomnia and somnolence[12]. More severe depression has now been shown to be associated with higher rates of substance use disorder and suicide attempts[13]. In addition, general characteristics, such as marital status and smoking, can affect subjective sleep quality. The relationship between marital status and sleep in women with depression showed that marital status was related to sleep efficiency. Married women had better sleep quality and significantly lower sleep delay than unmarried women. Compared with divorced or widowed patients, married depressed patients had better sleep quality; the stress of marriage breakdown and the loss of a partner had an important impact on sleep, and the

occurrence of an unhappy marriage and depressive symptoms caused changes in physical function, causing alcoholism and lack of sleep[14]. Smokers were reported to have more severe sleep problems than nonsmokers. Nicotine patches led to abnormal sleep, a lack of sleep, shortened sleep latency, and reduced nighttime sleep[15].

In our study, by the questionnaire designed by our team, which included a total of 56 items, we aimed to investigate the relationship between the designed questionnaire items and depression and analyze the factors related to depression.

## MATERIALS AND METHODS

### *Study subjects*

With written informed consent, this study was approved by the Fuxing Hospital affiliated with the Capital Medical University Institution Review Board. A total of 424 patients with insomnia in Yuetan Community Health Service Center and its subordinate community health service stations were enrolled as the research subjects in our study. Thirteen patients were excluded because they did not have a qualified questionnaire. Finally, 411 patients were included for further analysis. The inclusion criteria included the following items: (1) Patients who met the diagnostic points of nonorganic insomnia: their main complaints were difficulty falling asleep, difficulty maintaining sleep, or poor sleep quality; this sleep disorder occurred at least three times a week and lasted for one month or more. Focusing on sleep day and night, worrying too much about the consequences of insomnia, and dissatisfaction with sleep quantity and/or quality causes obvious distress or affects social and occupational functions. This criterion was met as long as dissatisfaction with the quantity and/or quality of sleep was the patient's only complaint; (2) Patients who had contacted their family doctor; and (3) Patients aged between 40 and 70 years old. The exclusion criteria included the following items: (1) Patients with insomnia as only one of multiple symptoms of a mental disorder or physical condition were excluded; insomnia was limited to the main mental or physical disorder; and (2) Patients with severe mental disorder were excluded.

The Patient Health Questionnaire-9 (PHQ-9) and the Pittsburgh Sleep Quality Index (PSQI) were included in our questionnaires. In addition, the questionnaires also included 12 kinds of diseases, including diagnosed depression, chronic diseases, high blood pressure, diabetes, coronary heart disease, cerebrovascular disease, enlarged prostate, cancer, mental illness, tuberculosis, chronic hepatitis, and cirrhosis. Eight general characteristics, including sex, age, education level, marital status, living situation, occupational status, income (yuan) per month and exercise, were analyzed. The percentage of sex, education level, marital status, living situation, occupational status, income (yuan) per month and exercise. The 20 insomnia characteristics included the following: years of insomnia; Western medicine treatmen; Chinese medicine treatment; psychotherapy; kind of insomnia; events related to insomnia; treatment expected to treat insomnia; traditional Chinese medicine foot baths; acupressure; psychological counseling; medicated diet; Tai Chi; traditional Chinese medicine; other traditional Chinese medicines; habit of 1 h before bed; habit of drinking tea; habit of drinking coffee; habit of drinking spirits; habit of smoking; and habit of taking a lunch break.

### *Survey method and quality control*

Questionnaires designed by our study team were distributed to respondents by uniformly trained investigators, and the relevant contents of the questionnaires were explained to the respondents face-to-face. Then, the questionnaires were investigated and completed. After taking back the questionnaires, unqualified questionnaires with missing items were eliminated, and valid questionnaires were sorted and numbered. Quality control was carried out at the stages of data collection, data collation and result analysis. The questionnaires were completed by trained investigators instructing the subjects one-on-one. Data were entered and reviewed by trained personnel to ensure the accuracy of data entry.

### *Depression severity degree assessed by the PHQ-9*

The PHQ-9 consists of 9 items as follows: "little interest or pleasure in doing things"; "feeling down, depressed, or hopeless"; "trouble falling or staying asleep, or sleeping too much"; "feeling tired or having little energy"; "poor appetite or overeating"; "feeling bad about yourself or that you are a failure or have let yourself or your family down"; "trouble concentrating on things, such as reading the newspaper or watching television"; "moving or speaking so slowly that other people could have noticed or being so fidgety or restless that you have been moving a lot more than usual"; and "thoughts that you would be better off dead, or thoughts of hurting yourself in some way". This questionnaire was used to evaluate depression and grade the severity of symptoms[16]. Higher PHQ-9 scores are related to decreased functional status and increased symptom-related difficulties. A PHQ-9 score of 0–4 represents no depression. Scores of 5–9 represent mild depression, 10–14 represent moderate depression, and 15–19 represent moderately severe depression. Scores of 20–27 represent severe depression.

### Sleep quality assessed by the PSQI

The PSQI was used to assess the sleep quality of the subjects in the last month. It consists of 19 self-assessment items and 5 other assessment items, of which the 19th self-assessment item and the 5 other assessment items are not included in the scoring. Only the remaining 18 self-assessment items are included in the scoring. The 18 items consist of the following 7 components: subjective sleep, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction; each component is scored on a scale of 0 to 3. The cumulative score of each component is the total PSQI score, and the total score ranges from 0 to 21. The higher the score, the worse the sleep quality. It took the subjects 5 to 10 minutes to complete the questionnaire. Scores of 0–5 represent that sleep quality is very good; scores of 6–10 represents that sleep quality is okay; scores of 11–15 represent that sleep quality is average; and scores of 16–21 represent that sleep quality is poor[17].

### Statistical analysis

SPSS 22.0 was used for data analysis. Excel and GraphPad Prism were used to draw the figures. Measurement data are expressed as the mean ± SD. Count data are expressed as $n$ (%). The measurement data that conformed to a normal distribution were compared by two independent sample $t$ tests or analysis of variance; the measurement data that did not conform to a normal distribution were compared by the rank sum test. Count data were compared by the $\chi^2$ test. Principal component analysis (PCA) was used to analyze the contributing rate to depression. The correlation between the 9 PHQ-9 items was analyzed by Pearson correlation regression. Univariate and multivariate logistic regression was used to analyze the factors significantly associated with depression. A $P < 0.05$ was considered a statistically significant difference.

## RESULTS

### Relationship of the PHQ-9 items and depression

According to their PHQ-9 scores, the individuals enrolled in our study were divided into a without depression group ($n$ = 190) and a depression group ($n$ = 221), which included mild ($n$ = 139), moderate ($n$ = 49), moderately severe ($n$ = 22), and severe depression ($n$ = 11). First, the 9 items, including "little interest or pleasure in doing things" (Item 1), "feeling down, depressed, or hopeless" (Item 2), "trouble falling or staying asleep, or sleeping too much" (Item 3), "feeling tired or having little energy" (Item 4), "poor appetite or overeating" (Item 5), "feeling bad about yourself or that you are a failure or have let yourself or your family down" (Item 6), "trouble concentrating on things, such as reading the newspaper or watching television" (Item 7), "moving or speaking so slowly that other people could have noticed, or so fidgety or restless that you have been moving a lot more than usual" (Item 8), and "thoughts that you would be better off dead, or thoughts of hurting yourself in some way" (Item 9), were compared between the without depression group and with depression group. As shown in Figure 1, the 9 items in the without depression group and with depression group were compared, and all 9 items showed significant differences ($P < 0.001$). Then, the 9 items were compared for the mild depression, moderate depression, moderately severe depression, and severe depression groups, as shown in Table 1. All 9 items also showed significant differences ($P < 0.001$). PCA was used to analyze the 9 items contributing to depression. As shown in Figure 2, the contributing rates of Items 1-9 were 36.00%, 15.59%, 9.96%, 9.09%, 7.32%, 6.18%, 5.94%, 5.40% and 4.53%, respectively. This item contributed the most to the depression analysis. In addition, the correlation coefficients of the 9 items were also analyzed. As shown in Figure 3, Item 7 and Item 8 showed the highest positive correlation coefficient, which was 0.585, but Item 7 and Item 3 showed the highest negative correlation coefficient, which was -0.033.

### Relationship of the PSQI components and depression

As shown in Table 2, the 7 PSQI components, which were subjective sleep, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction, were compared for the without depression group ($n$ = 190) and the with depression group ($n$ = 221), which included mild ($n$ = 139), moderate ($n$ = 49), moderately severe ($n$ = 22), and severe depression ($n$ = 11). After comparison, subjective sleep ($P < 0.001$), sleep latency ($P < 0.001$), habitual sleep efficiency ($P = 0.001$), sleep disturbances ($P < 0.001$), use of sleep medications ($P = 0.001$), and daytime dysfunction ($P < 0.001$) showed significant differences between the depression groups; however, sleep duration showed no significant difference ($P = 0.054$). As shown in Figure 4, the mean PSQI scores in the without depression group ($n$ = 190), mild depression group ($n$ = 139), moderate depression group ($n$ = 49), moderately severe depression group ($n$ = 22), and severe depression group ($n$ = 11) were 8.58, 10.63, 11.61, 13.41 and 15.00, respectively. With the progression of depression severity, the PSQI score also showed a significant increase ($P < 0.001$). In addition, the degrees of depression for the very good sleep quality (0-5), okay sleep quality (6-10), average sleep quality (11-15), and poor sleep quality (16-21) groups were also analyzed. As shown in Figure 5, for the 0–5 and 6–10 sleep quality groups, the

**Table 1 Relationship of Patient Health Questionnaire-9 items and depression**

| PHQ-9 item | Score | Mild (*n* = 139) | | Moderate (*n* = 49) | | Moderately severe (*n* = 22) | | Severe (*n* = 11) | |
|---|---|---|---|---|---|---|---|---|---|
| | | *n* | Percent | *n* | Percent | *n* | Percent | *n* | Percent |
| Item 1 | 0 | 32 | 23.02 | 2 | 4.08 | 0 | 0.00 | 0 | 0.00 |
| | 1 | 67 | 48.20 | 11 | 22.45 | 5 | 22.73 | 1 | 9.09 |
| | 2 | 36 | 25.90 | 27 | 55.10 | 10 | 45.45 | 2 | 18.18 |
| | 3 | 4 | 2.88 | 9 | 18.37 | 7 | 31.82 | 8 | 72.73 |
| Item 2 | 0 | 62 | 44.60 | 8 | 16.33 | 1 | 4.55 | 0 | 0.00 |
| | 1 | 62 | 44.60 | 14 | 28.57 | 4 | 18.18 | 0 | 0.00 |
| | 2 | 15 | 10.79 | 24 | 48.98 | 14 | 63.64 | 3 | 27.27 |
| | 3 | 0 | 0.00 | 3 | 6.12 | 3 | 13.64 | 8 | 72.73 |
| Item 3 | 0 | 10 | 7.19 | 0 | 0.00 | 0 | 0.00 | 1 | 9.09 |
| | 1 | 41 | 29.50 | 12 | 24.49 | 2 | 9.09 | 0 | 0.00 |
| | 2 | 52 | 37.41 | 19 | 38.78 | 9 | 40.91 | 1 | 9.09 |
| | 3 | 36 | 25.90 | 18 | 36.73 | 11 | 50.00 | 9 | 81.82 |
| Item 4 | 0 | 17 | 12.23 | 3 | 6.12 | 0 | 0.00 | 0 | 0.00 |
| | 1 | 66 | 47.48 | 9 | 18.37 | 1 | 4.55 | 0 | 0.00 |
| | 2 | 48 | 34.53 | 28 | 57.14 | 10 | 45.45 | 1 | 9.09 |
| | 3 | 8 | 5.76 | 9 | 18.37 | 11 | 50.00 | 11 | 100.00 |
| Item 5 | 0 | 69 | 49.64 | 10 | 20.41 | 3 | 13.64 | 0 | 0.00 |
| | 1 | 49 | 35.25 | 20 | 40.82 | 5 | 22.73 | 3 | 27.27 |
| | 2 | 19 | 13.67 | 17 | 34.69 | 7 | 31.82 | 1 | 9.09 |
| | 3 | 2 | 1.44 | 2 | 4.08 | 7 | 31.82 | 7 | 63.64 |
| Item 6 | 0 | 102 | 73.38 | 16 | 32.65 | 2 | 9.09 | 2 | 18.18 |
| | 1 | 32 | 23.02 | 24 | 48.98 | 5 | 22.73 | 0 | 0.00 |
| | 2 | 4 | 2.88 | 9 | 18.37 | 10 | 45.45 | 1 | 9.09 |
| | 3 | 1 | 0.72 | 0 | 0.00 | 5 | 22.73 | 8 | 72.73 |
| Item 7 | 0 | 85 | 61.15 | 15 | 30.61 | 1 | 4.55 | 0 | 0.00 |
| | 1 | 44 | 31.65 | 17 | 34.69 | 2 | 9.09 | 1 | 9.09 |
| | 2 | 9 | 6.47 | 14 | 28.57 | 12 | 54.55 | 2 | 18.18 |
| | 3 | 1 | 0.72 | 3 | 6.12 | 7 | 31.82 | 8 | 72.73 |
| Item 8 | 0 | 105 | 75.54 | 17 | 34.69 | 6 | 27.27 | 0 | 0.00 |
| | 1 | 28 | 20.14 | 25 | 51.02 | 5 | 22.73 | 0 | 0.00 |
| | 2 | 5 | 3.60 | 6 | 12.24 | 9 | 40.91 | 3 | 27.27 |
| | 3 | 1 | 0.72 | 1 | 2.04 | 2 | 9.09 | 8 | 72.73 |
| Item 9 | 0 | 134 | 96.40 | 40 | 81.63 | 13 | 59.09 | 3 | 27.27 |
| | 1 | 5 | 3.60 | 7 | 14.29 | 5 | 22.73 | 5 | 45.45 |
| | 2 | 0 | 0.00 | 2 | 4.08 | 2 | 9.09 | 1 | 9.09 |
| | 3 | 0 | 0.00 | 0 | 0.00 | 2 | 9.09 | 2 | 18.18 |

PHQ-9: Patient Health Questionnaire-9.

percentages of the without depression group (*n* = 190), mild depression group (*n* = 139), moderate depression group (*n* = 49), moderately severe depression group (*n* = 22), and severe depression group (*n* = 11) were 16.84%, 8.63%, 0%, 0%, 0% and 58.95%, 40.29%, 38.78%, 13.64%, 0%, respectively. The

**Table 2 Relationship of Pittsburgh sleep quality index components and depression**

| PSQI index | Score | Without (*n* = 190) | | With (*n* = 221) | | Mild (*n* = 139) | | Moderate (*n* = 49) | | Moderately severe (*n* = 22) | | Severe (*n* = 11) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *n* | Percent | *n* | Percent | *n* | Percent | *n* | Percent | *n* | Percent | *n* | Percent |
| Subjective sleep quality | 0 | 0 | 0.00 | 3 | 1.36 | 2 | 1.44 | 1 | 2.04 | 0 | 0.00 | 0 | 0.00 |
| | 1 | 87 | 45.79 | 27 | 12.22 | 22 | 15.83 | 4 | 8.16 | 1 | 4.55 | 0 | 0.00 |
| | 2 | 94 | 49.47 | 146 | 66.06 | 94 | 67.63 | 33 | 67.35 | 11 | 50.00 | 8 | 72.73 |
| | 3 | 9 | 4.74 | 45 | 20.36 | 21 | 15.11 | 11 | 22.45 | 10 | 45.45 | 3 | 27.27 |
| Sleep latency | 0 | 9 | 4.74 | 8 | 3.62 | 3 | 2.16 | 4 | 8.16 | 1 | 4.55 | 0 | 0.00 |
| | 1 | 52 | 27.37 | 31 | 14.03 | 23 | 16.55 | 5 | 10.20 | 3 | 13.64 | 0 | 0.00 |
| | 2 | 77 | 40.53 | 69 | 31.22 | 45 | 32.37 | 13 | 26.53 | 8 | 36.36 | 3 | 27.27 |
| | 3 | 52 | 27.37 | 113 | 51.13 | 68 | 48.92 | 27 | 55.10 | 10 | 45.45 | 8 | 72.73 |
| Sleep duration | 0 | 46 | 24.21 | 39 | 17.65 | 27 | 19.42 | 6 | 12.24 | 4 | 18.18 | 2 | 18.18 |
| | 1 | 62 | 32.63 | 68 | 30.77 | 42 | 30.22 | 19 | 38.78 | 4 | 18.18 | 3 | 27.27 |
| | 2 | 59 | 31.05 | 60 | 27.15 | 39 | 28.06 | 13 | 26.53 | 8 | 36.36 | 0 | 0.00 |
| | 3 | 23 | 12.11 | 54 | 24.43 | 31 | 22.30 | 11 | 22.45 | 6 | 27.27 | 6 | 54.55 |
| Habitual sleep efficiency | 0 | 64 | 33.68 | 48 | 21.72 | 34 | 24.46 | 10 | 20.41 | 3 | 13.64 | 1 | 9.09 |
| | 1 | 44 | 23.16 | 42 | 19.00 | 27 | 19.42 | 10 | 20.41 | 4 | 18.18 | 1 | 9.09 |
| | 2 | 41 | 21.58 | 48 | 21.72 | 28 | 20.14 | 12 | 24.49 | 4 | 18.18 | 4 | 36.36 |
| | 3 | 41 | 21.58 | 83 | 37.56 | 50 | 35.97 | 17 | 34.69 | 11 | 50.00 | 5 | 45.45 |
| Sleep disturbances | 0 | 3 | 1.58 | 2 | 0.90 | 1 | 0.72 | 1 | 2.04 | 0 | 0.00 | 0 | 0.00 |
| | 1 | 154 | 81.05 | 135 | 61.09 | 99 | 71.22 | 25 | 51.02 | 8 | 36.36 | 3 | 27.27 |
| | 2 | 32 | 16.84 | 79 | 35.75 | 37 | 26.62 | 22 | 44.90 | 13 | 59.09 | 7 | 63.64 |
| | 3 | 1 | 0.53 | 5 | 2.26 | 2 | 1.44 | 1 | 2.04 | 1 | 4.55 | 1 | 9.09 |
| Use of sleeping medications | 0 | 85 | 44.74 | 90 | 40.72 | 63 | 45.32 | 19 | 38.78 | 6 | 27.27 | 2 | 18.18 |
| | 1 | 28 | 14.74 | 15 | 6.79 | 9 | 6.47 | 4 | 8.16 | 1 | 4.55 | 1 | 9.09 |
| | 2 | 43 | 22.63 | 40 | 18.10 | 32 | 23.02 | 8 | 16.33 | 0 | 0.00 | 0 | 0.00 |
| | 3 | 34 | 17.89 | 76 | 34.39 | 35 | 25.18 | 18 | 36.73 | 15 | 68.18 | 8 | 72.73 |
| Daytime dysfunction | 0 | 161 | 84.74 | 94 | 42.53 | 71 | 51.08 | 18 | 36.73 | 5 | 22.73 | 0 | 0.00 |
| | 1 | 27 | 14.21 | 84 | 38.01 | 53 | 38.13 | 18 | 36.73 | 9 | 40.91 | 4 | 36.36 |
| | 2 | 2 | 1.05 | 37 | 16.74 | 14 | 10.07 | 12 | 24.49 | 6 | 27.27 | 5 | 45.45 |
| | 3 | 0 | 0.00 | 6 | 2.71 | 1 | 0.72 | 1 | 2.04 | 2 | 9.09 | 2 | 18.18 |

PSQI: Pittsburgh sleep quality index.

percentage of depression degree de-escalated. In the 11–15 and 16–20 sleep quality groups, the percentages of the without depression group ($n$ = 190), mild depression group ($n$ = 139), moderate depression group ($n$ = 49), moderately severe depression group ($n$ = 22), and severe depression group ($n$ = 11) were 1.58%, 5.04%, 16.33%, 18.18%, 27.27% and 22.63%, 46.04%, 44.90%, 68.18%, 72.73%, respectively. The percentage of depression degree escalated.

### *Comparison of disease status between the without depression and with depression groups*

As shown in Table 3, the disease status of the without depression and with depression groups was analyzed. Twelve kinds of diseases, including diagnosed depression, chronic diseases, high blood pressure, diabetes, coronary heart disease, cerebrovascular disease, enlarged prostate, cancer, mental illness, tuberculosis, chronic hepatitis, and cirrhosis, were compared between the without depression and with depression groups. Diagnosed depression ($P$ < 0.001), coronary heart disease ($P$ = 0.03), and mental illness ($P$ = 0.01) showed significant differences between the two groups. The percentages of

**Table 3 Comparison of diseases status between without depression and with depression groups, *n* (%)**

| Diseases | Status | Without depression | With depression | *P* value |
|---|---|---|---|---|
| Diagnosed depression | Yes | 17 (8.95) | 52 (23.53) | < 0.001 |
| | No | 173 (91.05) | 169 (76.47) | |
| Chronic diseases | Yes | 60 (31.58) | 68 (30.77) | 0.86 |
| | No | 130 (68.42) | 153 (69.23) | |
| High blood pressure | Yes | 100 (52.63) | 114 (51.58) | 0.83 |
| | No | 90 (47.37) | 107 (48.42) | |
| Diabetes | Yes | 49 (25.79) | 58 (26.24) | 0.92 |
| | No | 141 (74.21) | 163 (73.76) | |
| Coronary heart disease | Yes | 21 (11.05) | 42 (19) | 0.03 |
| | No | 169 (88.95) | 179 (81) | |
| Cerebrovascular disease | Yes | 14 (7.37) | 25 (11.31) | 0.17 |
| | No | 176 (92.63) | 196 (88.69) | |
| Enlarged prostate | Yes | 9 (4.74) | 14 (6.33) | 0.48 |
| | No | 181 (95.26) | 207 (93.67) | |
| Cancer | Yes | 6 (3.16) | 8 (3.62) | 0.80 |
| | No | 184 (96.84) | 213 (96.38) | |
| Mental illness | Yes | 1 (0.53) | 12 (5.43) | 0.01 |
| | No | 189 (99.47) | 209 (94.57) | |
| Tuberculosis | Yes | 0 (0) | 1 (0.45) | 0.35 |
| | No | 190 (100) | 220 (99.55) | |
| Chronic hepatitis | Yes | 1 (0.53) | 3 (1.36) | 0.39 |
| | No | 189 (99.47) | 218 (98.64) | |
| Cirrhosis | Yes | 3 (1.58) | 2 (0.9) | 0.53 |
| | No | 187 (98.42) | 219 (99.1) | |

diagnosed depression in the without depression and with depression groups were 8.95% and 23.53%, respectively. The percentages of coronary heart disease and mental illness in the two groups were 11.05% and 19.00%, and 0.53% and 5.43%, respectively. The other 9 kinds of diseases, including chronic diseases, high blood pressure, diabetes, cerebrovascular disease, enlarged prostate, cancer, tuberculosis, chronic hepatitis, and cirrhosis, showed no significant differences ($P > 0.05$).

### *Comparison of general characteristics between the without depression and with depression groups*

Eight general characteristics, including sex, age, education, marital status, living situation, occupational status, income (yuan) per month and exercise, were analyzed. The percentages of sex, education level, marital status, living situation, occupational status, income (yuan) per month and exercise in the without depression and with depression groups were compared by the chi-square test. As shown in Table 4, age was compared by the independent t test. Education level ($P = 0.04$), living situation ($P = 0.002$), and exercise ($P < 0.001$) showed significant differences between the two groups. The other 5 general characteristics showed no significant differences ($P > 0.05$). The most significant general characteristic was exercise; the percentages in the without depression and with depression groups were 78.95% and 62.44%, respectively. The percentages of elementary school education and below, junior high school education, secondary school or high school education, university education and above in the two groups were 1.05%, 13.16%, 38.42%, 47.37% and 1.81%, 23.53%, 29.86%, 44.80%, respectively. The percentages of living alone, living with a husband or wife, living with children, and others in the two groups were 5.79%, 59.47%, 32.11%, and 2.63% and 16.29%, 50.68%, 27.15%, and 5.88%, respectively.

### *Comparison of insomnia-related characteristics between the without depression and with depression groups*

Years of insomnia, Western medicine treatment, Chinese medicine treatment, psychotherapy, kind of

**Table 4 Comparison of general characteristics between without depression and with depression groups, *n* (%)**

| Characteristics | Status | Without depression | With depression | *P* value |
|---|---|---|---|---|
| Gender | Male | 51 (26.84) | 55 (24.89) | 0.65 |
| | Female | 139 (73.16) | 166 (75.11) | |
| Age (yr) | | 59.36 ± 7.46 | 59.66 ± 8.36 | 0.71 |
| Education | Elementary school and below | 2 (1.05) | 4 (1.81) | 0.04 |
| | Junior high school | 25 (13.16) | 52 (23.53) | |
| | Secondary school or high school | 73 (38.42) | 66 (29.86) | |
| | University and above | 90 (47.37) | 99 (44.8) | |
| Marital status | Unmarried | 6 (3.16) | 10 (4.52) | 0.05 |
| | Married | 170 (89.47) | 178 (80.54) | |
| | Divorced | 5 (2.63) | 18 (8.14) | |
| | Widowed | 9 (4.74) | 15 (6.79) | |
| Living situation | Living alone | 11 (5.79) | 36 (16.29) | 0.002 |
| | Live with husband or wife | 113 (59.47) | 112 (50.68) | |
| | Live with children | 61 (32.11) | 60 (27.15) | |
| | Other | 5 (2.63) | 13 (5.88) | |
| Occupational | On-the-job | 55 (28.95) | 49 (22.17) | 0.29 |
| | Retire | 130 (68.42) | 166 (75.11) | |
| | Unemployed | 5 (2.63) | 6 (2.71) | |
| Income (yuan) | 0-2000 | 4 (2.11) | 9 (4.07) | 0.09 |
| | 2000-4000 | 53 (27.89) | 81 (36.65) | |
| | 4000-6000 | 71 (37.37) | 78 (35.29) | |
| | ≥ 6000 | 62 (32.63) | 53 (23.98) | |
| Exercise | Yes | 150 (78.95) | 138 (62.44) | < 0.001 |
| | No | 40 (21.05) | 83 (37.56) | |

insomnia, events related to insomnia, treatment expected to treat insomnia, traditional Chinese medicine foot baths, acupressure, psychological counseling, medicated diet, Tai Chi, traditional Chinese medicine, other traditional Chinese medicines, habit of 1 h before bed, habit of drinking tea, habit of drinking coffee, habit of drinking spirits, habit of smoking, and habit of taking a lunch break were analyzed. As shown in Table 5, among the 20 insomnia-related characteristics, years of insomnia ($P < 0.001$), Western medicine treatment ($P = 0.02$), Chinese medicine treatment ($P < 0.001$), psychotherapy ($P = 0.002$), kind of insomnia ($P < 0.001$), treatment expected to treat insomnia ($P < 0.001$), psychological counseling ($P < 0.001$), habit of 1 h before bed ($P < 0.001$), and habit of taking a lunch break ($P < 0.001$) showed significant differences between the two groups. The other 11 characteristics showed no significant differences ($P > 0.05$). The years of insomnia in the without depression and with depression groups were 5.21 ± 6.06 years and 7.35 ± 7.48 years, respectively.

### *Logistic analysis of depression and the significant characteristics*

After comparing the disease status, general characteristics, and insomnia-related characteristics between the without depression and with depression groups, education level, living situation, exercise, years of insomnia, Western medicine treatment, Chinese medicine treatment, psychotherapy, kind of insomnia, treatment expected to treat insomnia, psychological counseling, habit of 1 h before bed, habit of taking a lunch break, diagnosed depression, coronary heart disease, and mental illness, which showed significant differences between the two groups, were further analyzed by logistic regression. As shown in Table 6, by univariate analysis, the ORs of education level ($P = 0.02$), exercise ($P = 0.02$), kind of insomnia ($P = 0.01$), habit of 1 h before bed ($P = 0.04$), diagnosed depression ($P = 0.03$), and coronary heart disease ($P = 0.02$) showed significant differences. Their odds ratios (ORs) were 0.71 (0.54, 0.94), 1.81 (1.11, 2.95), 0.79 (0.65, 0.95), 0.90 (0.81, 1.00), 0.48 (0.24, 0.94), and 0.46 (0.25, 0.86), respectively. Then, the characteristics that showed significant differences in the univariate analysis were further analyzed

**Table 5 Comparison of insomnia related characteristics between without depression and with depression groups, *n* (%)**

| Indicator | Status | Without depression | With depression | *P* value |
|---|---|---|---|---|
| Years of insomnia | | 5.21 ± 6.06 | 7.35 ± 7.48 | < 0.001 |
| Western medicine treatment | Yes | 102 (53.68) | 143 (64.71) | 0.02 |
| | No | 88 (46.32) | 78 (35.29) | |
| Chinese medicine treatment | Yes | 82 (43.16) | 143 (64.71) | < 0.001 |
| | No | 108 (56.84) | 78 (35.29) | |
| Psychotherapy | Yes | 6 (3.16) | 25 (11.31) | 0.002 |
| | No | 184 (96.84) | 196 (88.69) | |
| Kinds of insomnia | Difficult to fall asleep | 89 (46.84) | 140 (63.35) | < 0.001 |
| | Difficult to deep sleep | 20 (10.53) | 16 (7.24) | |
| | Easy to wake up | 53 (27.89) | 36 (16.29) | |
| | Wake up early | 28 (14.74) | 29 (13.12) | |
| Events related to insomnia | Work pressure | 42 (22.11) | 40 (18.1) | 0.10 |
| | Family life | 58 (30.53) | 66 (29.86) | |
| | Disease related | 49 (25.79) | 82 (37.1) | |
| | Sleep environment | 37 (19.47) | 31 (14.03) | |
| | Interpersonal communication | 4 (2.11) | 2 (0.9) | |
| Treatment expected to treat insomnia | Western medicine | 53 (27.89) | 36 (16.29) | < 0.001 |
| | Traditional Chinese Medicine | 97 (51.05) | 133 (60.18) | |
| | Psychotherapy | 14 (7.37) | 36 (16.29) | |
| | Other | 26 (13.68) | 16 (7.24) | |
| Traditional Chinese medicine foot bath | Yes | 50 (26.32) | 49 (22.17) | 0.33 |
| | No | 140 (73.68) | 172 (77.83) | |
| Acupressure | Yes | 51 (26.84) | 50 (22.62) | 0.32 |
| | No | 139 (73.16) | 171 (77.38) | |
| Psychological counseling | Yes | 1 (0.53) | 19 (8.6) | < 0.001 |
| | No | 189 (99.47) | 202 (91.4) | |
| Medicated diet | Yes | 16 (8.42) | 28 (12.67) | 0.17 |
| | No | 174 (91.58) | 193 (87.33) | |
| Tai Chi | Yes | 11 (5.79) | 5 (2.26) | 0.07 |
| | No | 179 (94.21) | 216 (97.74) | |
| Traditional Chinese medicine | Yes | 93 (48.95) | 120 (54.3) | 0.28 |
| | No | 97 (51.05) | 101 (45.7) | |
| Other traditional Chinese medicine | Yes | 17 (8.95) | 16 (7.24) | 0.53 |
| | No | 173 (91.05) | 205 (92.76) | |
| Habit of 1 hour before bed | Electronic products | 79 (41.58) | 125 (56.56) | < 0.001 |
| | Reading news or papers | 31 (16.32) | 22 (9.95) | |
| | Chat | 7 (3.68) | 10 (4.52) | |
| | Fitness | 0 (0) | 1 (0.45) | |
| | None | 12 (6.32) | 26 (11.76) | |
| | Watch TV | 61 (32.11) | 37 (16.74) | |
| Habit of drinking tea | Yes | 57 (30) | 81 (36.65) | 0.16 |

| | | | | |
|---|---|---|---|---|
| | No | 133 (70) | 140 (63.35) | |
| Habit of drinking coffee | Yes | 38 (20) | 35 (15.84) | 0.27 |
| | No | 152 (80) | 186 (84.16) | |
| Habit of drinking spirits | Yes | 3 (1.58) | 10 (4.52) | 0.09 |
| | No | 187 (98.42) | 211 (95.48) | |
| Habit of smoking | Yes | 24 (12.63) | 19 (8.6) | 0.18 |
| | No | 166 (87.37) | 202 (91.4) | |
| Habit of lunch break | Yes | 52 (27.37) | 82 (37.1) | < 0.001 |
| | No | 138 (72.63) | 139 (62.9) | |

**Table 6 Logistic analysis of depression and the significant characteristics**

| Characteristics | Univariate analysis | | | | | Multivariate analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Wals | *P* value | OR | 95% CI of OR | | Wals | *P* value | OR | 95% CI of OR | |
| | | | | Lower | Upper | | | | Lower | Upper |
| Education | 5.58 | 0.02 | 0.71 | 0.54 | 0.94 | 6.08 | 0.01 | 0.71 | 0.55 | 0.93 |
| Living situation | 0.38 | 0.54 | 0.91 | 0.67 | 1.23 | | | | | |
| Exercise | 5.63 | 0.02 | 1.81 | 1.11 | 2.95 | 9.89 | < 0.001 | 2.09 | 1.32 | 3.31 |
| Years of insomnia | 3.40 | 0.07 | 1.03 | 1.00 | 1.07 | | | | | |
| Western medicine treatment | 1.05 | 0.31 | 0.79 | 0.50 | 1.24 | | | | | |
| Chinese medicine treatment | 0.70 | 0.40 | 1.20 | 0.78 | 1.82 | | | | | |
| Psychotherapy | 1.30 | 0.25 | 0.53 | 0.18 | 1.57 | | | | | |
| Kinds of insomnia | 5.95 | 0.01 | 0.79 | 0.65 | 0.95 | 8.79 | < 0.001 | 0.76 | 0.63 | 0.91 |
| Treatment expected to treat insomnia | 0.74 | 0.39 | 1.12 | 0.87 | 1.44 | | | | | |
| Psychological counseling | 2.96 | 0.09 | 0.15 | 0.02 | 1.30 | | | | | |
| Habit of 1 hour before bed | 3.97 | 0.04 | 0.90 | 0.81 | 1.00 | 5.48 | 0.02 | 0.89 | 0.81 | 0.98 |
| Habit of lunch break | 0.12 | 0.73 | 1.08 | 0.68 | 1.71 | | | | | |
| Diagnosed depression | 4.64 | 0.03 | 0.48 | 0.24 | 0.94 | 12.94 | < 0.001 | 0.32 | 0.17 | 0.60 |
| Coronary heart disease | 5.91 | 0.02 | 0.46 | 0.25 | 0.86 | 7.43 | 0.01 | 0.43 | 0.23 | 0.79 |
| Mental illness | 2.87 | 0.09 | 0.16 | 0.02 | 1.34 | | | | | |

OR: Odds ratio.

by multivariate analysis. The ORs of education level ($P$ = 0.01), exercise ($P$ < 0.001), kind of insomnia ($P$ < 0.001), habit of 1 h before bed ($P$ = 0.02), diagnosed depression ($P$ < 0.001), and coronary heart disease ($P$ = 0.01) were significantly different. Their ORs were 0.71 (0.55, 0.93), 2.09 (1.32, 3.31), 0.76 (0.63, 0.91), 0.89 (0.81, 0.98), 0.32 (0.17, 0.60), and 0.43 (0.23, 0.79), respectively.

## DISCUSSION

Education level was a protective factor against depression and the OR was 0.71 (0.55, 0.93). Studies have found that academic achievement can influence employment, health care, and social communication[18-20]. The relationship between depression and academic achievement has drawn increasing attention. An overall negative association between depression and academic achievement for both sexes was demonstrated. Several studies have examined the associations between depression and academic achievement[21,22]. Our study results were consistent with these studies. People with higher education levels have good learning abilities, receive health-related knowledge, and have stronger abilities to cope with and solve problems, which may have a positive effect on obtaining better sleep quality. Some

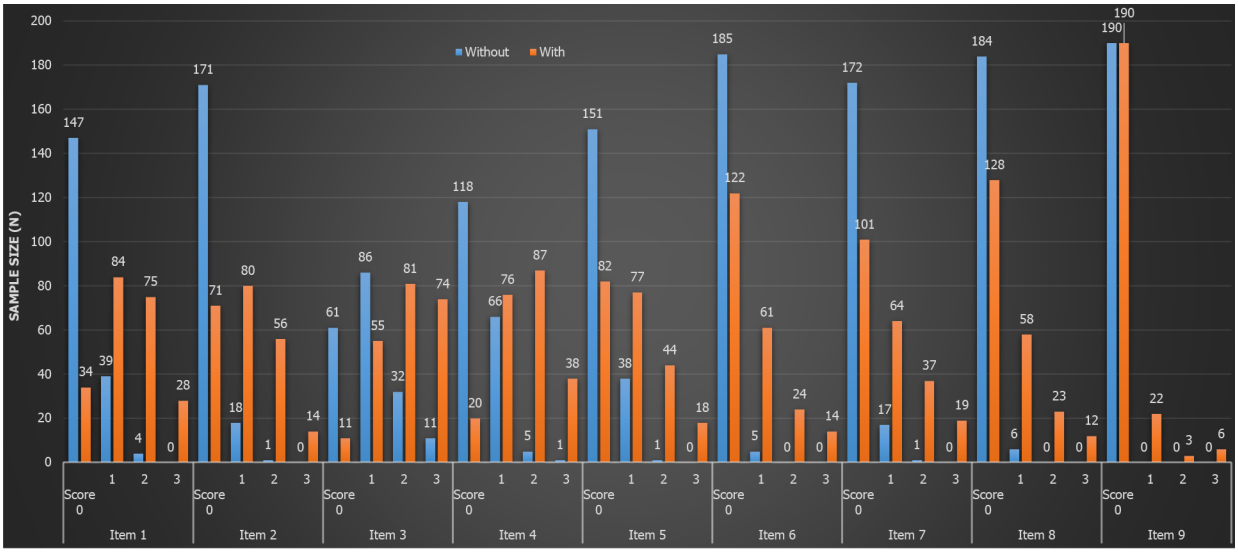


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**Figure 1 Comparison of the 9 items of Patient Health Questionnaire-9 in the without depression group and with depression group.**

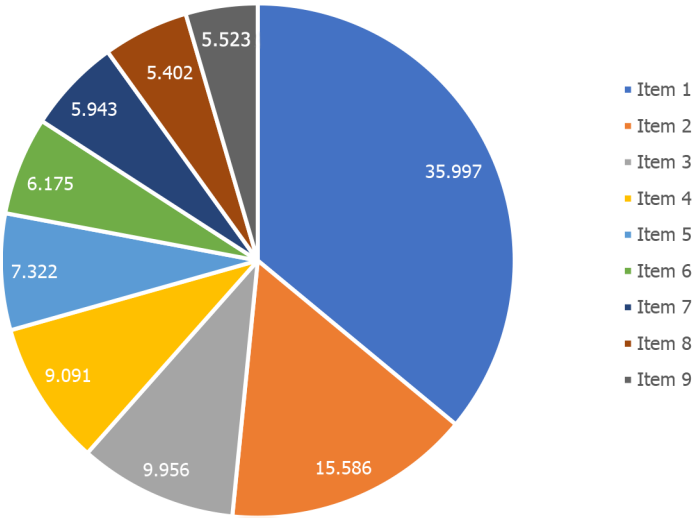


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**Figure 2 The contributing rate of 9 items of Patient Health Questionnaire-9 to depression (%).**

studies have shown that the number of years of education were associated with the recurrence of depression, and the shorter the years of education, the greater the possibility of depression recurrence [23,24]. Considering that years of education indirectly affect the sleep quality of patients through depressive symptoms, the relationship among the three factors needs to be further explored. There are some opposite results between depression and education level. On the one hand, educational attainment protects individuals from depression and improves their symptoms; however, individuals with higher education levels are more likely to suffer severe and recurrent episodes of major depression than individuals with low levels of education[25,26].

In our study, patients who did not exercise had an OR of 2.09 (1.32, 3.31) compared with the patients who did exercise. We demonstrated that exercise was a protective factor against depression. The protective effects of exercise and its mechanism on depression have been demonstrated in many studies [27] and support that physical exercise can reduce depression symptoms in patients[28,29]. In patients with depression (aged 18–60 years) who performed aerobic exercise or stretching exercises, there were significant short-term time effects for improving depression severity[30]. A meta-analysis study including 1452 depression patients found a protective effect on depression, regardless of the mode of exercise[31]. However, there are still some studies that found that there is no protective effect of exercise on treating depression. The provision of advice and encouragement for exercise did not improve the depression therapeutic effect when compared to regular care[32]. In another study, 1-week high cadence cycling did not improve depression symptoms[33]. Recently, exercise was not only used as a single

| | Item 1 | Item 2 | Item 3 | Item 4 | Item 5 | Item 6 | Item 7 | Item 8 | Item 9 |
|---|---|---|---|---|---|---|---|---|---|
| Item 1 | 1.000 | 0.395 | 0.138 | 0.390 | 0.154 | 0.227 | 0.213 | 0.182 | 0.142 |
| Item 2 | 0.395 | 1.000 | 0.035 | 0.319 | 0.195 | 0.393 | 0.401 | 0.369 | 0.304 |
| Item 3 | 0.138 | 0.035 | 1.000 | 0.306 | 0.011 | 0.023 | -0.033 | -0.012 | 0.014 |
| Item 4 | 0.390 | 0.319 | 0.306 | 1.000 | 0.227 | 0.204 | 0.229 | 0.175 | 0.133 |
| Item 5 | 0.154 | 0.195 | 0.011 | 0.227 | 1.000 | 0.315 | 0.312 | 0.307 | 0.236 |
| Item 6 | 0.227 | 0.393 | 0.023 | 0.204 | 0.315 | 1.000 | 0.507 | 0.512 | 0.443 |
| Item 7 | 0.213 | 0.401 | -0.033 | 0.229 | 0.312 | 0.507 | 1.000 | 0.585 | 0.400 |
| Item 8 | 0.182 | 0.369 | -0.012 | 0.175 | 0.307 | 0.512 | 0.585 | 1.000 | 0.381 |
| Item 9 | 0.142 | 0.304 | 0.014 | 0.133 | 0.236 | 0.443 | 0.400 | 0.381 | 1.000 |

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**Figure 3 The correlation coefficient of the 9 items of Patient Health Questionnaire-9.**

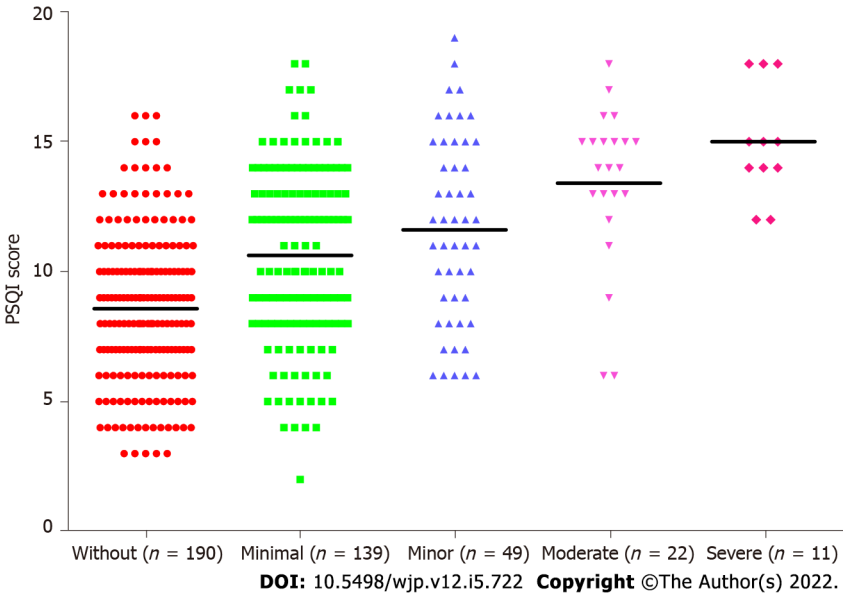


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**Figure 4 The mean Pittsburgh sleep quality index score.** The mean Pittsburgh sleep quality index score in the without depression group ($n$ = 190), mild ($n$ = 139), moderate ($n$ = 49), moderately severe depression ($n$ = 22), and severe depression ($n$ = 11) was 8.58, 10.63, 11.61, 13.41 and 15.00. PSQI: Pittsburgh sleep quality index.

treatment for depression but also an adjunct intervention therapeutic method for depression[34]. When exercise was used as a single therapy method, depression-related symptoms were significantly decreased after moderate aerobic exercise for 8 wk[35]. In addition, exercise was also recognized as an intervention with significant effects that can be used as an adjuvant therapy for depression[36]. The mechanisms underlying the antidepressant effects of exercise are closely related to psychological and physiological factors. Psychosocial and cognitive factors after exercise may include self-worth, self-esteem, self-efficacy, self-confidence, sleep quality, and life satisfaction[37-39]. Anti-inflammatory and

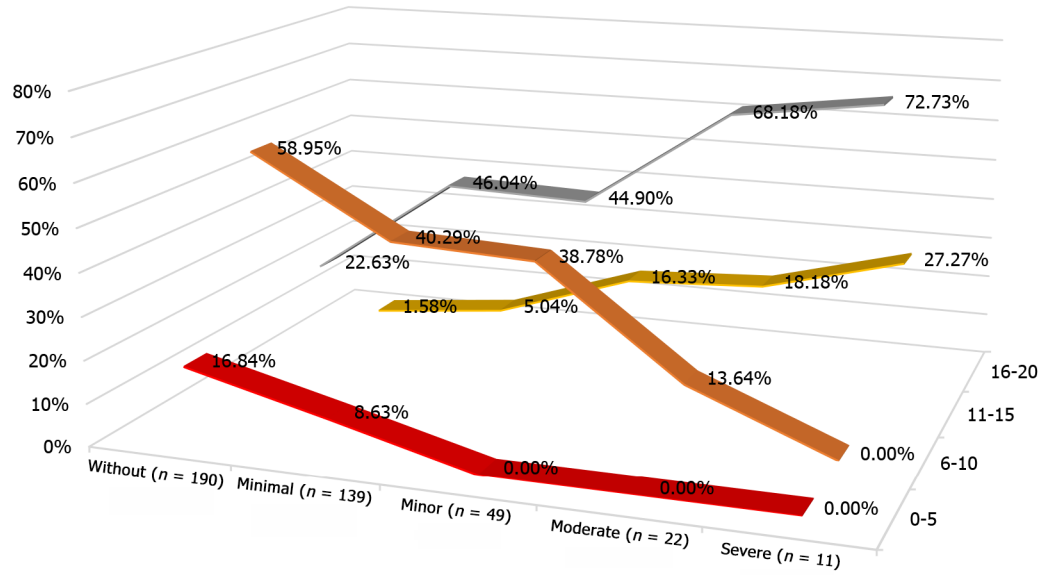


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**Figure 5 The percentage of Pittsburgh sleep quality index group.** The percentage of Pittsburgh sleep quality index group in without depression group (*n* = 190), mild (*n* = 139), moderate (*n* = 49), moderately severe depression (*n* = 22), and severe depression (*n* = 11).

antioxidant factors (interleukin-18, interleukin-1β, interleukin-6, tumor necrosis factor-α, caspase-1) were also demonstrated to be closely related to depression and anxiety[40-42]. The antidepressant effects of exercise are also related to elevated neurogenesis because of brain-derived neurotrophic factors[43-45].

This study found that the kind of insomnia was related to depression. Patients with major depressive disorder in the community had poor subjective sleep quality, prolonged sleep latency, short sleep duration, low sleep efficiency, sleep disturbances, and impaired daytime functioning[46]. These subjective sleep quality abnormalities were consistent with the objective measurements of sleep[47,48]. Some studies have shown that the polysomnography of patients with major depressive disorder shows that the rapid eye movement latency period is shortened, and the time of the first rapid eye movement period after falling asleep moves forward, which increases the proportion of rapid eye movement sleep and reduces the time of slow wave sleep[49-51]. Possible mechanisms include hyperexcitability of the hypothalamic–pituitary–adrenal axis; a glutamate deficiency, which plays an important role in both depression and sleep regulation; a marked reduction in plasma melatonin levels; alterations in the serotonergic system; and some increases in systemic markers of inflammation. The sleep quality of people with depression disorder in the past is different from that of the normal population[51,52]. The depressive symptoms disappear, but their sleep problems still persist. Some people think that persistent sleep disorder is a manifestation of the residual period of major depressive disorder. Depressive symptoms in patients with previous depressive disorder were not related to current sleep quality, while residence, years of education, work status and mental health were significantly correlated with sleep quality in patients with a previous depressive disorder[53,54]. Depressed patients living in rural areas were twice as likely to have good sleep quality compared with patients with previous depressive disorders living in urban areas. In our study, the absence of coronary heart disease was also demonstrated to be a protective factor against depression. Recently, the relationship between coronary heart disease and depression has received increased attention[55]. Patients with coronary heart disease are more likely to suffer from depression because they often endure unpleasant symptoms without warning and are required to take many medications for their lifestyle[55], leading to negative emotions such as anxiety or depression[56]. Approximately 20%–30% of patients with heart diseases are diagnosed with anxiety or depression. However, the percentage of patients affected with anxiety and depression was reported to be elevated to 15%–43% during the first 12 mo after an acute cardiac event [55]. Compared to depression, self-reported depression is more strongly related to cardiac morbidity and mortality[57].

Although we systematically analyzed the factors related to depression, including a depression evaluation, a sleep quality evaluation, general characteristics, and diagnosed disease status, there are still some limitations in this study. First, the sample size was relatively small. Some group sample sizes may affect the statistical results and lead to bias in the results. Second, although patients with depression in the past and patients who had been recently diagnosed with depression were enrolled in our study, the sample sizes of the two groups were small, and we did not compare their relative factors. Third, different therapeutic methods for depression were not performed. In our future study, we will perform a study that compares the therapeutic effects of different methods for treating depression.

## CONCLUSION

In conclusion, we demonstrated that education level, exercise, kind of insomnia, habit of 1 h before bed, diagnosed depression and coronary heart disease were the factors related to depression, which may provide some implications for the clinical practice of depression.

## ARTICLE HIGHLIGHTS

### *Research background*

Depression and sleep quality were demonstrated to be affected each other. In addition, the other factor, including diseases, general and insomnia characteristics also affect depression.

### *Research motivation*

The relationship of depression and sleep quality, diseases and general characteristics and depression should be systemically investigated.

### *Research objectives*

In this study, we aimed to investigate the relationship of depression and sleep quality, diseases and general characteristics.

### *Research methods*

Questionnaire included Patient Health Questionnaire-9 (PHQ-9) and Pittsburgh sleep quality index (PSQI), 12 kinds of diseases, 8 general characteristics, and 20 insomnia characteristics, totally 56 items were filled out by 411 patients enrolled.

### *Research results*

All the 9 items of PHQ-9, 6 components of PSQI (except sleep duration), 12 kinds of diseases, 3 general characteristics, and 9 insomnia characteristics showed significant difference between without and with depression group. By univariate analysis and multivariate analysis. The odds ratio of education, exercise, kinds of insomnia, habit of 1 h before bed, diagnosed depression, coronary heart disease showed significant difference.

### *Research conclusions*

Education, exercise, kinds of insomnia, habit of 1 h before bed, diagnosed depression and coronary heart disease are the related factor with depression.

### *Research perspectives*

Larger sample size and long-time span study should be designed and performed in the future study. Different therapeutic methods for depression should also be performed.

## FOOTNOTES

**Author contributions:** Jiang Y and Ding L designed the study; Jiang Y and Jiang T performed the research; Jiang Y, Jiang T and Xu LT analyzed the date; Jiang Y wrote the paper; Ding L revised the manuscript for final submission; Jiang Y and Jiang T contributed equally to this study; Ding L the co-corresponding author; and all authors approved the final version of the article.

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**Informed consent statement:** All study participants or their legal guardian provided written informed consent prior to study enrollment.

**Conflict-of-interest statement:** We declare that we have no financial or personal relationships with other individuals or organizations that can inappropriately influence our work and that there is no professional or other personal interest of any nature in any product, service and/or company that could be construed as influencing the position presented in or the review of the manuscript.

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**STROBE statement:** The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

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META-ANALYSIS

# Mental health impact of the Middle East respiratory syndrome, SARS, and COVID-19: A comparative systematic review and meta-analysis

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## Abstract

***BACKGROUND***

Over the last few decades, 3 pathogenic pandemics have impacted the global

population; severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2. The global disease burden has attributed to millions of deaths and morbidities, with the majority being attributed to SARS-CoV-2. As such, the evaluation of the mental health (MH) impact across healthcare professionals (HCPs), patients and the general public would be an important facet to evaluate to better understand short, medium and long-term exposures.

***AIM***

To identify and report: (1) MH conditions commonly observed across all 3 pandemics; (2) Impact of MH outcomes across HCPs, patients and the general public associated with all 3 pandemics; and (3) The prevalence of the MH impact and clinical epidemiological significance.

***METHODS***

A systematic methodology was developed and published on PROSPERO (CRD42021228697). The databases PubMed, EMBASE, ScienceDirect and the Cochrane Central Register of Controlled Trials were used as part of the data extraction process, and publications from January 1, 1990 to August 1, 2021 were searched. MeSH terms and keywords used included *Mood disorders, PTSD, Anxiety, Depression, Psychological stress, Psychosis, Bipolar, Mental Health, Unipolar, Self-harm, BAME, Psychiatry disorders and Psychological distress*. The terms were expanded with a 'snowballing' method. Cox-regression and the Monte-Carlo simulation method was used in addition to $I^2$ and Egger's tests to determine heterogeneity and publication bias.

***RESULTS***

In comparison to MERS and SARS-CoV, it is evident SAR-CoV-2 has an ongoing MH impact, with emphasis on depression, anxiety and post-traumatic stress disorder.

***CONCLUSION***

It was evident MH studies during MERS and SARS-CoV was limited in comparison to SARS-CoV-2, with much emphasis on reporting symptoms of depression, anxiety, stress and sleep disturbances. The lack of comprehensive studies conducted during previous pandemics have introduced limitations to the "know-how" for clinicians and researchers to better support patients and deliver care with limited healthcare resources.

**Key Words:** COVID-19; Middle East respiratory syndrome; SARS-CoV; SARS-CoV-2; Mental health; Wellbeing; Psychiatry; Healthcare professionals; Patients; Physical health; Public health; Outbreaks and pandemics

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**Core Tip:** Global research into exploring pandemics have been conducted for several decades. However, clinical research associated with mental health (MH) impact of Middle East respiratory syndrome, severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 was limited. This systematic review and meta-analysis is a comparison of the MH impact across, healthcare professionals, patients and the general public using the Monte-Carlo simulation method. Evaluated prevalence of multiple MH variables have been conducted using randomised controlled trials and cross-sectional studies. The study demonstrates the need to conduct comprehensive and longitudinal multi-morbid research to evaluate the true MH impact to aid better future pandemic preparedness. This systematic review and meta-analysis indicate a complex MH impact across all cohorts with the requirement for mechanistic relationships between physical and MH to be explored further.

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## INTRODUCTION

Human civilisations have endeavoured various infectious diseases over centuries with multiple causatives, increases in population density, and increases in migration could attribute to increase in risk of emerging infectious diseases leading to global endemics and pandemics. Medicine in the modern era provide solutions to manage and mitigate infectious threats although there are many challenges associated with communicable and non-communicable diseases.

Fast forward to the 21st century, there have been three prominent outbreaks caused by novel coronaviruses[1]. The World Health Organisation (WHO) have classified two of these outbreaks as pandemics. Understanding the coronavirus family to prevent future pandemics would be useful.

The 2003 severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) comprised of the Middle East respiratory syndrome coronavirus (MERS-CoV) which includes a family of enveloped, single-stranded and diverse RNA viruses consisting of four genera: alpha, beta, gamma and delta (*α*-, *β*-, *γ*- and *δ*-*CoV*). Of these, alpha and beta-coronaviruses appear to be more deadly due to its ability to transmit across animals and humans, leading to stronger pathogens. Coronaviruses were first identified in 1965[2]. The SARS-CoV was the first outbreak in 2012. Neither of the outbreaks reached a pandemic status. Genetically similar to SARS-CoV, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), officially declared as a pandemic on March 11, 2020, continues to engulf global populations.

In comparison to the current SARS-CoV-2 pandemic, the SARS-CoV outbreak was effectively managed with aggressive public health measures amongst the countries affected[3]. Although, there are multi-factorial composites to consider to assess physical and mental health impact on the previous and current populations. For example, SARS-CoV reported an incidence and mortality of 8096 and 774 respectively across 29 countries[4].

In contrast, MERS-CoV outbreaks were reported across 27 countries between 2012-2019, mainly within the Middle East, with Saudi Arabia reporting majority of the cases based on WHO data[5]. However, incidence reporting of MERS-CoV over the last 7 years have been sporadic, indicating it is less contagious compared to the current SARS-CoV-2 infection. To date, there have been 2578 reported cases and 888 deaths due to MERS-CoV, with a crude mortality rate of around 34.4%[5]. Management of these infections primarily consist of public health measures to identify and isolate patients and effective infection control measures to reduce transmission rates[6]. Failures in effectively managing these outbreaks have primarily been attributed to the late identification of the disease. Secondary measures include quarantine failures due to non-disclosures by patients and poor communication between officials and the public[7,8].

Most patients with SARS-COV-2 are asymptomatic or develop mild symptoms[9]. However, for a small minority, they are likely to require admission to hospital with severe respiratory compromise which can lead to critical illness with respiratory failure and multiple organ failure[9]. These cases require high-level medical care within an intensive care unit (ICU) setting, including ventilatory support. Dexamethasone and Remdesivir are used alongside supportive measures and have proved effective in reducing mortality and hospital length of stay[10,11]. Interventions such as pruning, which has been recommended in the treatment of severe COVID-19 disease[12], have become common place in ICU settings, but is a labour-intensive procedure, putting further pressure on staff.

### *The global response to SARS-COV-2*

The high degree of viral homology between SARS-COV-2 and previous coronavirus outbreaks directed the initial global response to the coronavirus disease 2019 (COVID-19) pandemic[13]. Given the relatively small population sizes involved in the first two novel coronavirus outbreaks, in addition to the geographical areas affected, the global understanding that shaped our response was probably limited in its scope. We recognise now it is in fact the differences, not the similarities, that have driven the rapid spread of the virus, including more prominent community spread and higher transmissibility of SARS-CoV-2, which includes asymptomatic and mildly symptomatic patients not seen in SARS-CoV [14].

### *The spread comparison between SARS-CoV, MERS-CoV and SARS-CoV-2*

The characteristics of the emerging SARS-CoV-2 appears to be changing with the appearance of new variants, which is different to its predecessors, SARS-CoV and MERS-CoV. At the height of the SARS-CoV era, 140 new infections were reported *per* week, whilst current data suggest SARS-CoV-2 transmits approximately 100000 new infections *per* week during its peak period between February and May 2020 [15,16]. In addition to the common transmission network, viral shedding for SARS-CoV-2 in particular starts prior to symptom onset, which was the opposite with SARS-CoV. Therefore, quarantine measures would have been more effective during SARS-CoV in comparison to SARS-CoV-2.

### *The mental health impact of SARS-CoV-2*

One of the long-term unknowns about the current pandemic is the physical manifestations and its impact on the mental health as well as the well-being of the public, patients and front-line healthcare professionals (HCPs). Experience from the previous novel coronavirus outbreaks suggests that the

psychological impacts will be widespread and long-lasting. Significant psychological symptomatology has been reported in the acute and early recovery phases associated with SARS-CoV[17-22] and MERS-CoV[17,23] in all three groups considered in this review. Importantly, when considering the long-term effects of this pandemic, the impact of the SARS-CoV pandemic was still recorded amongst infected individuals over four years after the reported outbreak, and in some cases with deteriorating symptoms [13].

The morphological and demographic features of the 3 viruses are vital to understand the mental health impact. Physical manifestations drive the mental health impact, often interacting as a planarian.

## MATERIALS AND METHODS

A systematic review protocol was designed, internally peer-reviewed and published on PROSPERO (CRD42021228697) with a comprehensive search strategy and data extraction method.

### *Research question/aims*

This study has 3 primary aims of identifying and reporting: (1) Mental health (MH) conditions commonly observed across all 3 pandemics; (2) Impact of MH outcomes across HCPs, patients and the general public associated with all 3 pandemics; and (3) The prevalence of the MH impact and clinical epidemiological significance.

### *Data searches*

Multiple databases of PubMed, EMBASE, ScienceDirect and the Cochrane Central Register of Controlled Trials were used to extract relevant data. MeSH terms and keywords used included *Mood disorders, PTSD, Anxiety, Depression, Psychological stress, Psychosis, Bipolar, Mental Health, Unipolar, Self-harm, BAME* (*Black, Asian and Minority Ethnic*), *Psychiatry disorders* and *Psychological distress*. The terms were expanded with a 'snowball' method that has been demonstrated with a PRISMA diagram. All publications that were peer-reviewed in English were included. The final dataset was reviewed independently before the analysis was conducted.

### *Data synthesis*

The data synthesis is based on the statistical data extracted from the studies included based on the eligibility criteria developed. This includes data associated with the mean ± SD and median along with $q_1$ (25% quantile) and $q_3$ (75% quantile). Q1 and $q_3$ are novel estimation methods used to improve existing meta-analysis as demonstrated by Wan and colleagues[24]. Most of the studies identified reported multiple MH outcomes such as depression, anxiety and psychological distress among people who experienced MERS, SARS-CoV and SARS-CoV-2. For studies that reported the median along with $q_1$ and $q_3$, the mean ± SD of the studies were estimated from the median, $q_1$ and $q_3$. Therefore, the following equation was used to analyse the data, where the $\Phi^{-1}$ represented the inverse of the standard normal distribution, as described below.

Most MERS-CoV studies only reported SD. Some studies included the median only, and these were transformed to $q_1$ and $q_3$, where the mean ± SD were estimated using the Monte-Carlo simulation method, with the cut off scores of the MH assessments used within the studies. This data was assumed to be normally distributed. Random effects models were used to conduct the meta-analysis to estimate the pooled prevalence. MH assessments reported within the studies included the Impact of Event Scale-Revised (IES-R), Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire (PHQ-9), Short Form 36 Health Survey (SF-36), General Anxiety Disorder (GAD-7) and State-Trait Anger Expression Inventory (STAXI). For this we assumed normal distribution of the data. A subgroup analysis was conducted to evaluate any identified heterogeneity. Funnel plots and Egger's tests were performed to demonstrate publication bias and a sensitivity analysis. A comparative analysis was conducted using the SAR-CoV and SARS-CoV-2 data published by Chau *et al*[25].

The full data analysis was conducted using the STATA 16.1 software application.

### *Risk of bias quality assessment*

A quality assessment was performed using the Newcastle-Ottawa-Scale (NOS) for studies included systematically (Supplementary Table 1). The NOS is an eight-item scale with three quality parameters: (1) Selection; (2) Comparability; and (3) Outcome. We rated the quality of the studies (good, fair and poor) by allocating each domain with stars in this manner: (1) A Good quality score was awarded 3 or 4 stars in selection, 1 or 2 in comparability, and 2 or 3 stars in outcomes; (2) A Fair quality score was awarded 2 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes; and (3) A Poor quality score was allocated 0 or 1 star(s) in selection, 0 stars in comparability, and 0 or 1 star(s) in outcomes domain.

## RESULTS

The comprehensive multiple database literature search included publications from January 1, 1990 to August 1, 2021. The PRISMA diagram reflects the total yielded studies and systematic inclusions prior to the completion of the meta-analysis as shown in Figure 1.

### *MERS-CoV*

A total of 58 studies were included in the systematic review for MERS as shown in Supplementary Table 2. The search for MERS-CoV yielded 14, 144 of which 152 articles met the inclusion criteria to be reviewed by title and abstract. Eleven duplicates were removed. A further 29 studies were excluded as these were not pertinent to the MERS-CoV demonstrating MH outcomes, and 38 studies were excluded due to the lack of statistical data. Fifteen articles that were not published in English was also excluded. Therefore, the meta-analysis was conducted on 21 studies as demonstrated in Table 1.

### *SARS-CoV*

In relation to the SARS-CoV, the systematic review was conducted on 80 studies, as detailed in Supplementary Table 3, and the meta-analysis included 39 studies, as shown in Table 2.

### *SARS-CoV-2*

A total of 513 studies were included in the systematic review for SARS-CoV-2, as shown in Supplementary Table 4. 287 of these studies are from the meta-analysis conducted by Phiri *et al*[26]. The meta-analysis was conducted on 188 studies, as demonstrated in Supplementary Table 5.

### *Meta-analysis*

**Anxiety:** Eight studies reported the prevalence of anxiety during the MERS-CoV outbreak. As demonstrated by Figure 2, the pooled prevalence of anxiety was 17.35% with a 95% confidence interval (CI): 8.36-36.02. A heterogeneity of $I^2$ = 95.62% was identified.

The systematic review indicates 14 studies report the prevalence of anxiety during SARS-CoV, although only 9 report the mean ± SD. Twenty-three studies were included into the meta-analysis. Figure 3 indicates the prevalence of anxiety during SARS-CoV where the pooled prevalence was 25.2%, with a 95%CI of 18.41-34.5. A high heterogeneity of $I^2$ = 93.47% was identified.

The systematic review identified 175 studies that reported anxiety as an outcome due to SARS-CoV-2 where 40 studies provided mean and SD. By utilizing the Monte-Carlo simulation on the studies that only provide mean and SD, we obtained twenty-five studies that reported the prevalence of anxiety. As for the anxiety resulting from SARS-CoV-2, Figure 4 shows a pooled prevalence of 21.44% with a 95%CI of 18.69-24.61. However, a high heterogeneity of 99.77% was identified.

Based on these results, the prevalence of anxiety during SARS-CoV is more significant in comparison to MERS-CoV and SARS-CoV-2.

### *Depression*

The systematic search for MERS-CoV yielded seven studies reporting depression. The meta-analysis is demonstrated in Figure 5 and shows a pooled prevalence of 33.65%. The 95%CI ranged between 22.02-51.42. A moderate heterogeneity of at $I^2$ = 69.86% was identified.

Thirty-eight studies reported the prevalence of depression during the SARS-CoV outbreak. Of these, 23 reported prevalence directly and 15 demonstrated the mean score and SD instead. By using the Monte-Carlo simulation method, thirty-eight results were meta-analysed as demonstrated in Figure 6. The pooled prevalence of depression during the pandemic of SARS-CoV was 23.1%, while the 95%CI was between 18.14-29.4. A high heterogeneity was calculated at $I^2$ = 95.03%.

One hundred and twenty-three studies reported on depression during SARS-CoV-2. Of these, 102 reported the prevalence of depression directly and 21 demonstrated mean and SD values only. Figure 7 indicates the pooled prevalence of depression during SARS-CoV-2 was 27.68%, with a 95%CI ranging from 24.67-31.06. A high heterogeneity of $I^2$ = 99.71% was identified.

Based on the analysis, MERS-CoV and SARS-CoV-2 appear to report the highest levels of depression based on the pooled prevalence of 27.64% and 33.65% respectively.

### *Post-traumatic stress disorder*

Twenty-seven studies reported post-traumatic stress disorder (PTSD) during the MERS-CoV outbreak. Figure 8 demonstrated a pooled prevalence of 35.97%, with a relatively moderate to high heterogeneity of $I^2$ = 75.2% and a 95%CI ranging between 29.60-43.72.

Sixty-four of the studies identified had reported on the prevalence of PTSD during SARS-CoV. Of these, 48 studies reported on the prevalence directly, whilst 17 demonstrated the mean score and the corresponding SD. Figure 9 shows the pooled prevalence of PTSD was 18.2% with a CI of 14.94-22.18 and an elevated heterogeneity of $I^2$ = 91.37%.

**Table 1 21 studies that are included in meta-analysis for Middle East respiratory syndrome**

| Study ID | Ref. | Study type | Sample size | Country | Exposure | Outcome | *P* value | Quality assessment (NOS) |
|---|---|---|---|---|---|---|---|---|
| 1 | Shin *et al*[36] | Quantitative | 63 | Korea | MERS patients | PTSD, Sleep problem, anxiety, depression, suicidality, phobic anxiety, addiction, aggression | Not specified | 7 |
| 2 | Um *et al*[37] | Quantitative | 64 | Korea | MERS patients and HCWs | PTSD, depression | Not specified | 7 |
| 3 | Abolfotouh *et al*[38] | Quantitative | 1031 | Saudi Arabia | HCWs | Level of Concern | Not specified | 7 |
| 4 | Jung *et al*[39] | Quantitative | 147 | Korea | HCWs | PTSD | Not specified | 6 |
| 5 | Ahn *et al*[40] | Quantitative | 63 | Korea | MERS Patients | Suicide, fatigue | Not specified | 6 |
| 6 | Lee *et al*[41] | Quantitative | 52 | Korea | MERS Patients | Depression, PTSD, fatigue | Not specified | 6 |
| 7 | Kim *et al*[42] | Quantitative | 112 | Korea | HCWs | PTSD, burnout | Not specified | 7 |
| 8 | Oh *et al*[43] | Quantitative | 313 | Korea | HCWs | Stress | Stress: 0.066 | 7 |
| 9 | Seo *et al*[44] | Quantitative | 171 | Korea | HCWs | Burnout | Not specified | 5 |
| 10 | Son *et al*[45] | Quantitative | 280 | Korea | HCWs and general public | PTSD | Not specified | 6 |
| 11 | Park *et al*[46] | Quantitative | 187 | Korea | HCWs | Stress | Not specified | 6 |
| 12 | Jeong *et al*[24] | Qualitative | 1692 | Korea | MERS patients and general public | Anxiety | Not specified | 7 |
| 13 | Al-Rabiaah *et al*[47] | Quantitative | 174 | Saudi Arabia | General public | Anxiety | Not specified | 7 |
| 14 | Park *et al*[48] | Quantitative | 63 | Korea | MERS Patients | PTSD, depression | Not specified | 7 |
| 15 | Cho *et al*[49] | Quantitative | 111 | Korea | General public | PTSD | PTSD: 0.3 | 7 |
| 16 | Kim *et al*[50] | Quantitative | 27 | Korea | General public | Depression | Not specified | 5 |
| 17 | Lee *et al*[51] | Quantitative | 359 | Korea | HCWs | PTSD | Not specified | 6 |
| 18 | Kim and Choi[52] | Quantitative | 215 | Korea | HCWs | Burnout, stress | Not specified | 6 |
| 19 | Bukhari *et al*[53] | Quantitative | 386 | Saudi Arabia | HCWs | Worry | Not specified | 6 |
| 20 | Mollers *et al*[54] | Quantitative | 72 | Netherlands | General public | PTSD | Not specified | 5 |
| 21 | Kim and Choi[52] | Quantitative | 215 | Korea | HCWs | PTSD: 0.017 | PTSD: 0.017 | 6 |

PTSD: Post-traumatic stress disorder; MERS: Middle East respiratory syndrome; HCW: Healthcare worker.

Nineteen studies reported the prevalence of PTSD during SARS-CoV-2. Figure 10 indicates a pooled prevalence of PTSD of 25.03% with a 95%CI ranging between 18.15-34.51. A high heterogeneity of $I^2$ = 99.58% was identified.

Based on the findings, PTSD appears to have been reported for SARS-CoV-2, MERS-CoV and SARS-CoV.

A comparative analysis was completed for each MH variable identified and reported, as demonstrated within Tables 3-5.

**Table 2 39 studies that are included in meta-analysis for severe acute respiratory syndrome**

| Study ID | Ref. | Study type | Sample size | Country/region | Exposure | *P* value | Quality assessment (NOS) |
|---|---|---|---|---|---|---|---|
| 1 | Kwek *et al*[20] | Cross-sectional | 360 | Singapore | SARS patients | PTSD: 0.79; Depression: 0.7; Anxiety: 0.51 | 7 |
| 2 | Fang *et al*[55] | Cross-sectional | 1278 | China | SARS patients | Anxiety: 0.291; Depression: 0.705; PTSD: 0.2 | 8 |
| 3 | Liang[56] | Prospective cohort | 769 | China, Taiwan | SARS patients | PTSD: > 0.05; Anxiety: > 0.05 | 7 |
| 4 | Dang *et al*[57] | Cross-sectional | 549 | China | General public | Anxiety: < 0.00001; Depression: 0.000361 | 7 |
| 5 | Yip[58] | Prospective cohort | 218 | China, Hong Kong | SARS patients | Not specified | 6 |
| 6 | Cheng *et al*[59] | Cross-sectional | 10 | China, Hong Kong | SARS patients | Anxiety: > 0.05; Depression: > 0.05 | 5 |
| 7 | Wu *et al*[60] | Cross-sectional | 286 | China, Hong Kong | SARS patients | PTSD: < 0.001; Depression: < 0.05; Anxiety: < 0.01 | 6 |
| 8 | MaK *et al*[61] | Retrospective cohort | 126 | China, Hong Kong | SARS patients | Not specified | 5 |
| 9 | Lee *et al*[62] | Cross-sectional | 10511 | China, Hong Kong | Were not HCWs | Not specified | 7 |
| 10 | Hong *et al*[63] | Cross-sectional | 1050 | China | SARS patients | PTSD: 0.0323 | 7 |
| 11 | Wang[64] | Prospective cohort | 22 | China | SARS patients | Not specified | 4 |
| 12 | Hu *et al*[65] | Cross-sectional | 763 | China | Attended hospital for other reasons | Not specified | 5 |
| 13 | Chen *et al*[66] | Prospective cohort | 325 | China, Taiwan | Non-infected HCWs in the largest obligatory SARS hospital, with high SARS contact | Anxiety: 0.55 Depression: 0.93 | 6 |
| 14 | Ko *et al*[67] | Cross-sectional | 72 | China, Taiwan | General public of outbreak area | Depression: 0.02 | 5 |
| 15 | Lee *et al*[21] | Cross-sectional | 114 | China, Hong Kong | General public of outbreak area | Not specified | 6 |
| 16 | Hawryluck *et al*[68] | Cross-sectional | 652 | Canada, Toronto | General public of outbreak area | Depression: 0.85; PTSD: 0.82 | 7 |
| 17 | Liu *et al*[69] | Cross-sectional | 96 | China, Beijing | Non-infected HCWs of SARS hospital | Depression: < 0.05 | 7 |
| 18 | Su *et al*[70] | Prospective cohort | 57 | China, Taiwan | Non-infected HCWs in SARS outbreak region with high exposure risk *vs* low exposure risk | PTSD: > 0.05; Depression: < 0.05 | 7 |
| 19 | Lam *et al*[71] | Retrospective cohort | 116 | China, Hong Kong | SARS patients | Not specified | 6 |
| 20 | Shi *et al*[72] | Prospective cohort | 87 | China, Beijing | SARS outbreak region | Not specified | 5 |
| 21 | Huang *et al*[73] | Cross-sectional | 4481 | China, Beijing | Were not HCWs | Not specified | 6 |
| 22 | Yu *et al*[74] | Prospective cohort | 180 | China, Hong Kong | General public of outbreak area | Not specified | 5 |
| 23 | Chang and Sivam[75] | Cross-sectional | 146 | Singapore | General public of outbreak area | Not specified | 5 |
| 24 | Moldofsky and Patcai[76] | Retrospective cohort | 107 | Canada, Toronto | SARS patients, who were HCWs | Not specified | 6 |
| 25 | Sun *et al*[77] | Prospective cohort | 1557 | China, Xianxi | SARS patients | PTSD: 0.67 | 7 |
| 26 | Lau *et al*[78] | Cross-sectional | 333 | China, Hong Kong | General public of outbreak area | Not specified | 5 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 27 | Reynolds *et al* [79] | Cross-sectional | 89 | Canada | General public of outbreak area, quarantined; non-infected HCWs in SARS outbreak region, quarantined | Not specified | 5 |
| 28 | Lancee *et al* [80] | Cross-sectional | 613 | Canada, Toronto | Non-infected HCWs in SARS outbreak region | Not specified | 6 |
| 29 | Lin *et al*[81] | Cross-sectional | 6280 | China, Taiwan, Taichung | Non-infected HCWs in in region without major SARS outbreak | Not specified | 6 |
| 30 | Gao *et al*[82] | Prospective cohort | 127 | China, Tianjin | SARS patients | Not specified | 5 |
| 31 | Xu *et al*[83] | Cross-sectional | 129 | China, Xianxi | Non-infected HCWs in SARS hospital | PTSD: > 0.05 | 6 |
| 32 | Wong *et al*[84] | Cross-sectional | 0 (?) | China, Hong Kong | Non-infected HCWs from SARS hospitals | Not specified | 4 |
| 33 | Sim *et al*[85] | Cross-sectional | 90 | Singapore | Non-infected HCWs in SARS outbreak region | Not specified | 5 |
| 34 | Wu *et al*[19] | Cross-sectional | 133 | China, Beijing | Non-infected HCWs in SARS hospital | Not specified | 6 |
| 35 | Chen *et al*[86] | Cross-sectional | 103 | China, Taiwan, Kaohsiung | Non-infected HCWs in SARS hospital, with high SARS contact; non-infected HCWs in SARS hospital; with low SARS contact | Not specified | 6 |
| 36 | Tham *et al*[87] | Cross-sectional | 90 | Singapore | Non-infected HCWs in SARS hospital with extra risk of exposure | Not specified | 5 |
| 37 | Maunder *et al* [88] | Cross-sectional | 90 | Canada, Toronto | Non-infected HCWs of outbreak area, unspecified (mix of SARS affected and non SARS affected hospitals | PTSD: < 0.01 | 7 |
| 38 | Mak *et al*[89] | Retrospective cohort | 126 | China, Hong Kong | SARS patient | Not specified | 6 |
| 39 | McAlonan *et al*[90] | Cross-sectional | 0 (?) | China, Hong Kong | Non-infected HCWs in SARS outbreak region with high exposure risk *vs* low exposure risk | Not specified | 3 |

PTSD: Post-traumatic stress disorder; MERS: Middle East respiratory syndrome; HCW: Healthcare worker; CI: Confidence interval; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

**Table 3 Pooled prevalence and confidence interval of anxiety across Middle East respiratory syndrome coronavirus, severe acute respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus-2**

| Anxiety | Prevalence (%) | 95%CI | Heterogeneity $I^2$ (%) |
|---|---|---|---|
| MERS | 17.35 | 8.36-36.02 | 95.62 |
| SARS-CoV-2 | 21.48 | 18.68-24.71 | 99.76 |
| SARS-CoV | 25.20 | 18.41-34.5 | 93.47 |

CI: Confidence interval; MERS: Middle East respiratory syndrome; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

**Table 4 Pooled prevalence and confidence interval of depression across three diseases**

| Depression | Prevalence (%) | 95%CI | Heterogeneity $I^2$ (%) |
|---|---|---|---|
| MERS | 33.65 | 22.02-51.42 | 69.86 |
| SARS-CoV-2 | 27.64 | 24.59-31.06 | 99.69 |
| SARS-CoV | 23.10 | 18.14-29.4 | 95.03 |

CI: Confidence interval; MERS: Middle East respiratory syndrome; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

### *Subgroup analysis*

Multiple subgroup analyses using age group, cohort and location were conducted as an aim to identify the causation of the heterogeneity reported throughout the meta-analyses.

### *Age*

**SARS-CoV-2:** The subgroup analysis of age includes 10-19, 20-29, 30-39, 40-49, 50-59, 60-69 (Supplementary Figure 1). In particular, it can be seen from Supplementary Figure 2 that the pooled prevalence for 10–19 year-olds who are likely to have depression due to SARS-CoV-2 is 24.42%. The pooled prevalence for 60–69 years old, on the other hand, was 7.75% with a lower prevalence of depression. Therefore, the details from these analyses demonstrate the statistically reported heterogeneity could be due to the inclusion of multiple age groups.

This is further demonstrated in Supplementary Figure 3, where similar results are indicated for those reporting PTSD among young people, which appears to be higher than the older population (for instance, 32.40% for 20-29 group compared while 5.38% for 50-59 group). However, this is still reflective of a high heterogeneity which could be attributed to the differences in body mass index or race, although, to make a conclusion, further research data is required.

**SARS-CoV:** The subgroup analysis based on age for the SARS-CoV indicate the prevalence of mental health issues in different age groups during SARS. Supplementary Figure 4 demonstrated that people from 50 to 59 years of age appear to have a higher risk of anxiety (51.62%) in comparison to those between 30-39 (27.4%) as indicated in Supplementary Figure 5. The prevalence of PTSD (Supplementary Figure 6) indicates people within the 30-39 age group report a relatively high risk (32.13%) of PTSD in comparison to those of 60-69 years of age. However, the age group of 60-69 years was based on a single study.

**Comparison:** Based on the comparison between the 3 meta-analyses, the following results associated with MH outcomes are as indicated within Tables 6-8.

### *Cohort*

**SARS-CoV-2:** Another facet of the subgroup analysis was based upon the cohorts included within this study, of HCPs, patients and the general public. The MH outcomes are demonstrated in Supplementary Figures 7-9. It is evident that healthcare workers (HCWs) have a higher prevalence of anxiety and depression compared to the general public. The exception to this appears to be the prevalence of PTSD, where the levels appear to be similar for the public and HCWs, at 24.83% and 25.16% respectively.

**MERS:** Supplementary Figure 10 demonstrates that the general public consists of a smaller pooled prevalence (6.04%) for the MH outcome of anxiety in comparison to patients who contracted MERS-CoV (33.95%), although some of these patients could very well be HCWs themselves. On the contrary, the pooled data for the general public and MERS-CoV survivors indicate a relatively high prevalence of depression (40.7% and 41.69%), while the HCWs appear less likely to have depression (20.52%), as indicated by Supplementary Figure 11. Mild heterogeneity was detected across these 2 groups, with $I^2$ scores of 41.71%, $I^2$ = 71.77%. Therefore, statistically, the data and subsequent results appear to be more conclusive and reliable. Supplementary Figure 12 indicated the prevalence of PTSD between HCWs and the general public. PTSD within the general public appears to be relatively low (19.02%) in comparison to depression. Additionally, depression amongst HCWs is more prevalent (49.87%). Moreover, the heterogeneity ($I^2$ = 0) of this subgroup analysis is negligible, which demonstrates the data are statistically reliable and the conclusions are therefore more conclusive.

**SARS-CoV:** The subgroup analysis within the SARS-CoV group demonstrated a much higher prevalence of anxiety within HCWs (98.44%) in comparison to the general public (26.19%), as indicated in Supplementary Figure 12. Supplementary Figure 13 indicates that HCWs have a higher prevalence of depression (25.42%) than general public (23.31%) and SARS-CoV patients (21.96%). In contrast, the prevalence of PTSD among HCWs appear to be relatively low (16.97%) in comparison to SARS-CoV patients (19.80%) as well as the general public (18.36%), as indicated in Supplementary Figure 14. However, the heterogeneity score $I^2$ remains high, thus there may be other potential factors that may affect the statistical findings.

**Comparison:** Based on the subgroup analysis above, Tables 9-11 showcase the prevalence of different MH outcomes among various cohorts. There are similarities and differences. The prevalence of anxiety within the general public during MERS (6.04%) is the lowest across the three outbreaks, while SARS-CoV demonstrates the largest prevalence of anxiety within general public (26.19%). Meanwhile, HCWs who experienced SARS-CoV were likely to have anxiety (98.44%). The prevalence of anxiety within MERS-CoV patients (33.95%) appear to be the most commonly reported MH outcome. MERS-CoV also demonstrates the highest prevalence of depression within the general public and patients, at 40.70% and 41.69% respectively. Based on the current data on SARS-CoV-2, HCWs are more likely to suffer from depression (37.97%). The highest levels of PTSD were found in HCWs during MERS-CoV and MERS-

**Table 5 Pooled prevalence and confidence interval of post-traumatic stress disorder across three diseases**

| PTSD | Prevalence (%) | 95%CI | Heterogeneity $I^2$ (%) |
|---|---|---|---|
| MERS | 35.97 | 29.6-43.72 | 75.2 |
| SARS-CoV-2 | 25.03 | 18.15-34.51 | 99.58 |
| SARS-CoV | 18.20 | 14.94-22.18 | 91.37 |

PTSD: Post-traumatic stress disorder; CI: Confidence interval; MERS: Middle East respiratory syndrome; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

**Table 6 Subgroup analysis on Middle East respiratory syndrome data based on different age groups**

| Subgroup-age | MERS | | | |
|---|---|---|---|---|
| | | Prevalence (%) | 95%CI | Heterogeneity $I^2$ (%) |
| Anxiety | 10-19 | - | - | - |
| | 20-29 | - | - | - |
| | 30-39 | - | - | - |
| | 40-49 | 18.51 | 8.11-42.23 | 96.43 |
| | 50-59 | - | - | - |
| Depression | 20-29 | - | - | - |
| | 30-39 | - | - | - |
| | 40-49 | 38.45 | 25.81-57.26 | 60.55 |
| | 50-59 | - | - | - |
| PTSD | 20-29 | 49.70 | 38.2-64.67 | 0 |
| | 30-39 | 19.32 | 14.82-25.18 | 0 |
| | 40-49 | 26.69 | 13.21-53.91 | 80.63 |
| | 50-59 | - | - | - |
| | 60-69 | 17.87 | 12.4-25.74 | 0 |

MERS: Middle East respiratory syndrome; PTSD: Post-traumatic stress disorder; CI: Confidence interval.

CoV patients (49.87% and 37.7%). SARS-CoV-2 appears to demonstrate that PTSD was experienced by 24.83% the general public.

From Supplementary Figures 15-17 we can see that people who experience MERS are more likely to have depression and PTSD than those who experience SARS-CoV-2 and SARS-CoV (the area of the MERS triangles in Supplementary Figures 15 and 17 are larger than the area of the SARS-CoV-2 and SARS-CoV triangles) while people who experience SARS-CoV may have a higher possibility to have anxiety than the other two (the area of the SARS-CoV triangle in Supplementary Figure 16 is larger the area of the MERS and SARS-CoV2 triangles).

### *Occupation*

**SARS-CoV-2:** Another facet of the subgroup analysis was based upon the occupation of the sample and the reporting of MH outcomes as demonstrated in Supplementary Figures 7-9. It is evident that HCWs have a higher prevalence of anxiety and depression compared to the general public. The exception to this appears to be the prevalence of PTSD, where the levels appear to be similar between the public and HCWs, at 24.83% and 25.16% respectively.

**MERS:** A subgroup analysis based upon the categories of HCWs, patients and the general public associated with the prevalence of MH outcomes further demonstrates variability. Supplementary Figure 10, for example, demonstrates that the general public is consistent with a smaller pooled prevalence (6.04%) for the MH outcome of anxiety in comparison to patients who contracted MERS-CoV (33.95%), although some of these patients could very well be HCWs themselves. On the contrary, the pooled data for the general public and MERS-CoV survivors indicate a relatively high level of

**Table 7 Subgroup analysis on severe acute respiratory syndrome coronavirus-2 data based on different age groups**

| Subgroup-age | SARS-CoV-2 | | | |
|---|---|---|---|---|
| | | Prevalence (%) | 95%CI | Heterogeneity $I^2$ (%) |
| Anxiety | 10-19 | 34.40 | 33.17-35.68 | 0 |
| | 20-29 | 25.70 | 19.38-34.08 | 99.25 |
| | 30-39 | 22.86 | 17.86-29.26 | 99.64 |
| | 40-49 | 15.59 | 9.65-25.17 | 99.66 |
| | 50-59 | 20.13 | 10.43-38.84 | 99.42 |
| | 60-69 | 7.75 | 0.79-76.29 | 99.47 |
| Depression | 10-19 | 43.91 | 42.12-45.77 | 0 |
| | 20-29 | 31.03 | 24.04-40.04 | 99.12 |
| | 30-39 | 30.4 | 25.15-36.74 | 99.48 |
| | 40-49 | 20.0 | 13.26-30.18 | 99.4 |
| | 50-59 | 19.98 | 15.84-25.19 | 92.68 |
| | 60-69 | 4.93 | 3.45-7.05 | 90.00 |
| PTSD | 20-29 | 32.40 | 6.54-160.49 | 98.29 |
| | 30-39 | 21.96 | 12.77-37.78 | 99.33 |
| | 40-49 | 27.72 | 19.88-38.66 | 97.59 |
| | 50-59 | 5.38 | 3.76-7.69 | 0 |
| | 60-69 | - | - | - |

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; PTSD: Post-traumatic stress disorder; CI: Confidence interval.

**Table 8 Subgroup analysis on severe acute respiratory syndrome coronavirus data based on different age groups**

| Subgroup-age | SARS-CoV | | | |
|---|---|---|---|---|
| | | Prevalence (%) | 95%CI | Heterogeneity $I^2$ (%) |
| Anxiety | 10-19 | - | - | - |
| | 20-29 | - | - | - |
| | 30-39 | 24.60 | 13.29-45.55 | 85.81 |
| | 40-49 | 15.63 | 10.97-22.26 | 60.57 |
| | 50-59 | 51.62 | 38.53-69.16 | 0 |
| Depression | 20-29 | - | - | - |
| | 30-39 | 27.47 | 16.09-46.9 | 89.58 |
| | 40-49 | 20.30 | 13.36-30.85 | 81.57 |
| | 50-59 | 22.49 | 14.8-34.17 | 0 |
| | 60-69 | 25.85 | 17.69-37.75 | 0 |
| PTSD | 20-29 | 24.43 | 15.53-38.44 | 72.18 |
| | 30-39 | 32.13 | 23.1-44.68 | 89.33 |
| | 40-49 | 11.68 | 8.45-16.15 | 86.20 |
| | 50-59 | 67.80 | 43.57-100 | 0 |
| | 60-69 | 7.54 | 2.64-21.54 | 53.28 |

SARS-CoV: Severe acute respiratory syndrome coronavirus; PTSD: Post-traumatic stress disorder; CI: Confidence interval.

**Table 9 Subgroup analysis on Middle East respiratory syndrome data based on different type of people**

| Subgroup-occupation | MERS | | | |
|---|---|---|---|---|
| | | Prevalence (%) | 95%CI | Heterogeneity $I^2$ (%) |
| Anxiety | General Public | 6.04 | 2.86-12.79 | 93.9 |
| | HCW | - | - | - |
| | Patient | 33.95 | 20.65-55.82 | 68.57 |
| Depression | General Public | 40.70 | 18.89-87.71 | 0 |
| | HCW | 20.52 | 11.81-35.67 | 41.71 |
| | Patient | 41.69 | 23.73-73.22 | 71.77 |
| PTSD | General Public | 19.02 | 14.01-25.81 | 0 |
| | HCW | 49.87 | 45.09-55.16 | 0 |
| | Patient | 37.70 | 27.47-51.74 | 0 |

MERS: Middle East respiratory syndrome; HCW: Healthcare worker; PTSD: Post-traumatic stress disorder; CI: Confidence interval.

**Table 10 Subgroup analysis on severe acute respiratory syndrome coronavirus-2 data based on different type of people**

| Subgroup-occupation | SARS-CoV-2 | | | |
|---|---|---|---|---|
| | | Prevalence (%) | 95%CI | Heterogeneity $I^2$ (%) |
| Anxiety | General Public | 21.18 | 17.88-25.09 | 99.82 |
| | HCW | 22.35 | 17.42-28.66 | 99.36 |
| | Patient | - | - | - |
| Depression | General Public | 27.6 | 23.36-32.24 | 99.8 |
| | HCW | 27.71 | 23.22-33.08 | 98.79 |
| | Patient | - | - | - |
| PTSD | General Public | 24.83 | 14.97-41.18 | 99.67 |
| | HCW | 25.16 | 16.62-38.08 | 99.33 |
| | Patient | - | - | - |

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; HCW: Healthcare worker; PTSD: Post-traumatic stress disorder; CI: Confidence interval.

prevalence (40.7% and 41.69%) of depression, while the HCWs appear less likely to have depression (20.52%), as indicated by Supplementary Figure 11. Mild heterogeneity was detected across these 2 groups, with $I^2$ scores of 41.71%, $I^2$ = 71.77%. Therefore, statistically, the data and subsequent results appear to be more conclusive and reliable. Supplementary Figure 12 indicated the prevalence of PTSD between HCWs and the general public. PTSD within the general public appears to be relatively low (19.02%) in comparison to depression. Additionally, depression is more prevalent in HCWs (49.87%). Moreover, the heterogeneity $I^2$ = 0 of this subgroup analysis is negligible, which demonstrates the data are statistically reliable and the conclusions are therefore more conclusive.

**SARS-CoV:** The subgroup analysis within the SARS-CoV group demonstrated a much higher prevalence of anxiety within HCWs (98.44%) in comparison to the general public (26.19%), as indicated in Supplementary Figure 13. Supplementary Figure 14 indicates that HCWs have a higher prevalence of depression (25.42%) than the general public (21.96%) and SARS-CoV patients (23.31%). In contrast, the prevalence of PTSD among HCWs appear to be relatively low (16.97%) in comparison to SARS-CoV patients (19.80%) as well as the general public (18.36%), as indicated in Supplementary Figure 15. However, the heterogeneity score $I^2$ remains high, thus there may be other potential factors that may affect the statistical findings.

It can be seen from Supplementary Figure 15 that it is less likely for people who experience SARS-CoV to have depression, while people who experience MERS are the most likely to suffer from depression. In particular, the general public and MERS patients have a greater risk of depression than

**Table 11 Subgroup analysis on studies under severe acute respiratory syndrome coronavirus data based on different type of people**

| Subgroup-occupation | SARS-CoV | | | |
|---|---|---|---|---|
| | | Prevalence (%) | 95%CI | Heterogeneity $I^2$ (%) |
| Anxiety | General Public | 26.19 | 11.93-57.48 | 98.22 |
| | HCW | 98.44 | 22.67-427.49 | 0 |
| | Patient | 24.21 | 17.34-33.79 | 85.16 |
| Depression | General Public | 23.31 | 14.64-37.11 | 97.97 |
| | HCW | 25.42 | 13.74-47.03 | 90.29 |
| | Patient | 21.96 | 16.86-28.6 | 78.1 |
| PTSD | General Public | 18.36 | 13.59-24.81 | 81.69 |
| | HCW | 16.97 | 12.28-23.45 | 91.8 |
| | Patient | 19.80 | 14.28-27.46 | 90.44 |

SARS-CoV: Severe acute respiratory syndrome coronavirus; HCW: Healthcare worker; PTSD: Post-traumatic stress disorder; CI: Confidence interval.

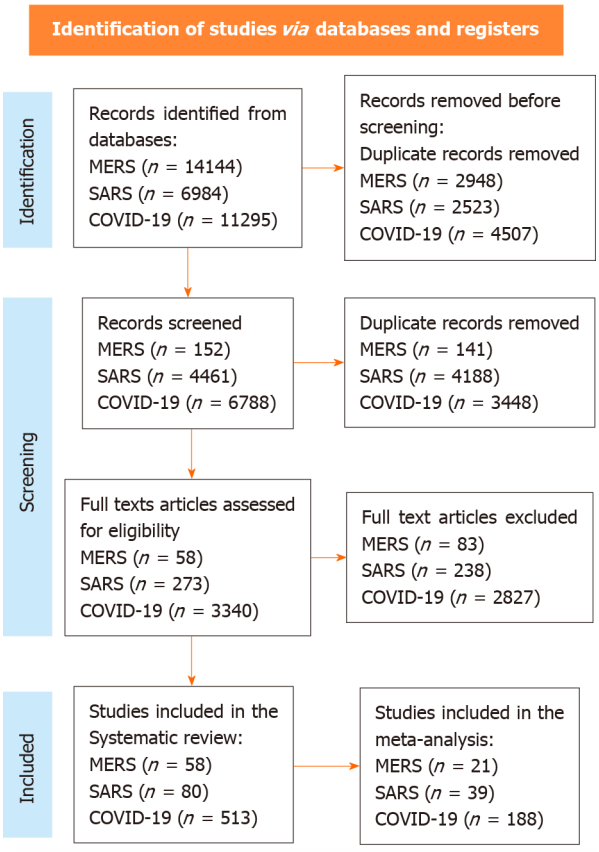


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**Figure 1 PRISMA flow diagram.** MERS: Middle East respiratory syndrome; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; COVID-19: Coronavirus disease 2019.

those who experience SARS-CoV-2 and SARS-CoV. However, people in the outbreak of SARS-CoV are more likely to have anxiety than people in the outbreak of MERS and SARS-CoV-2 (Supplementary Figure 16). Moreover, it can be noted from Supplementary Figure 16 that HCWs, during the outbreak of SARS-CoV, endured a very high risk of having anxiety. When it comes to PTSD, Supplementary Figure 17 shows that MERS leads to the highest prevalence of PTSD in almost all the mental health diseases across the three pandemics. In particular, HCWs and MERS patients suffer from a serious risk of PSTD after MERS. On the other hand, SARS-CoV seems to lead a relative low risk on the prevalence of PTSD.

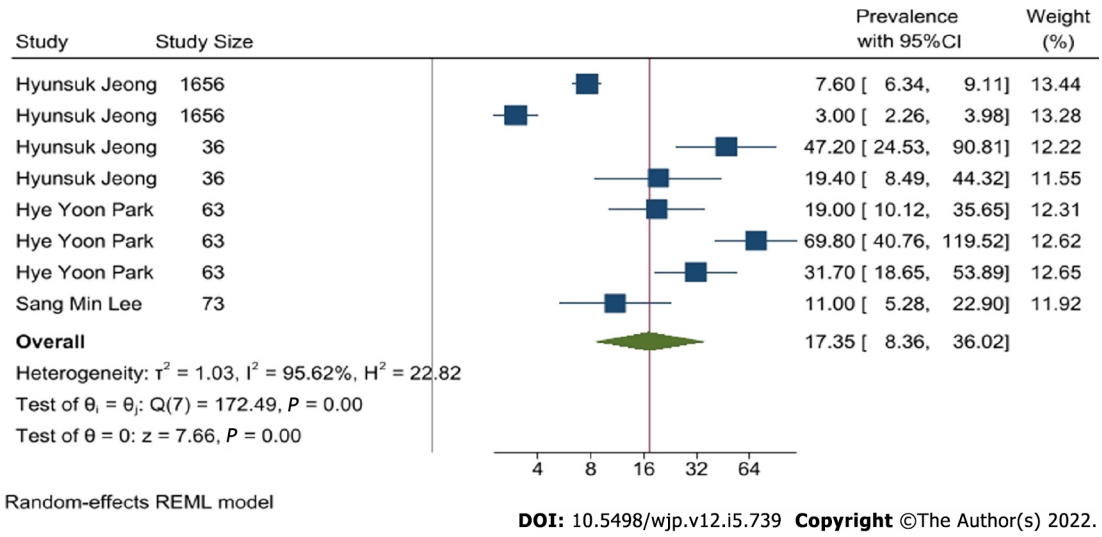


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**Figure 2 Forest plot of anxiety caused by Middle East respiratory syndrome.**

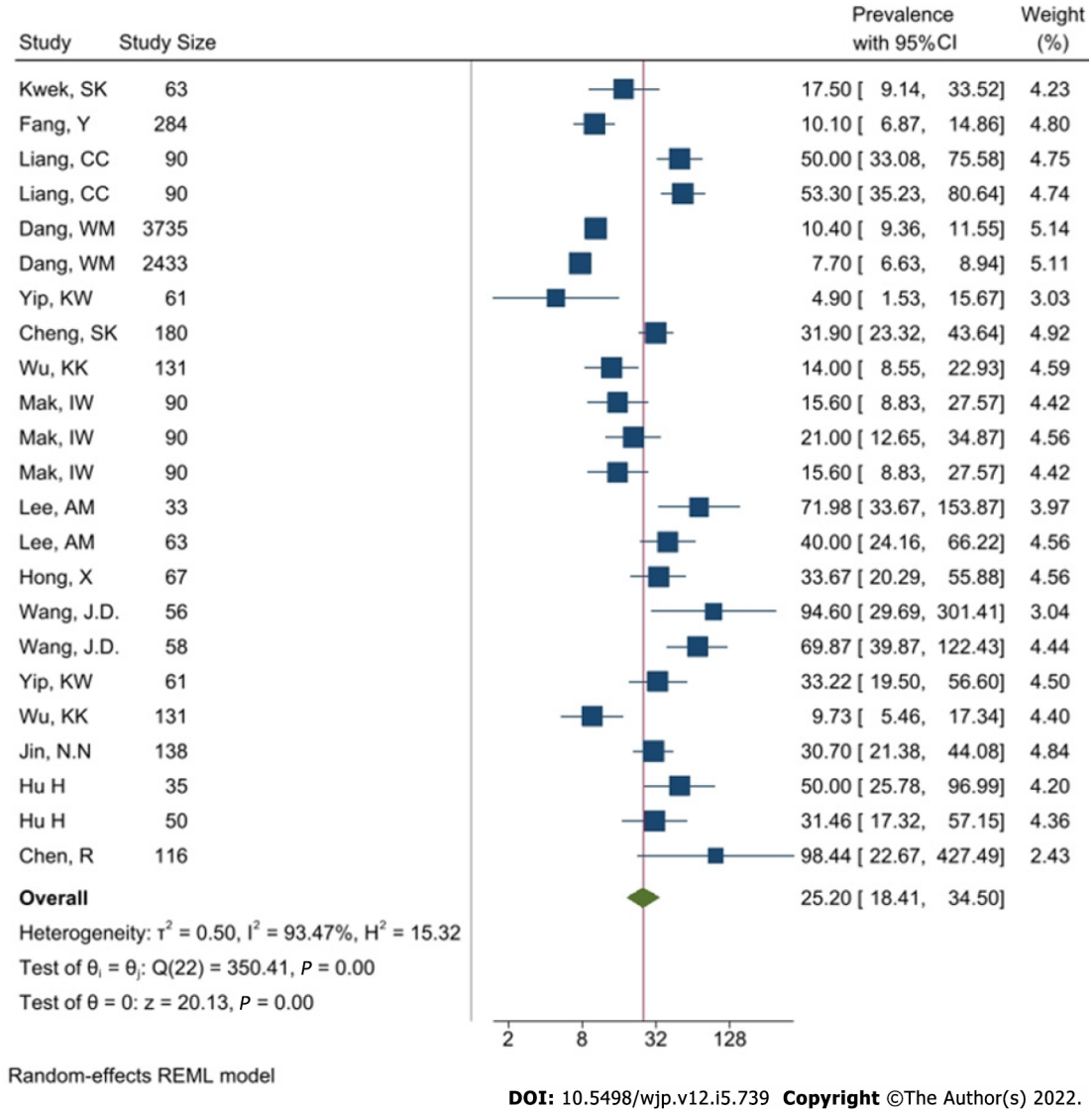


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**Figure 3 Forest plot of anxiety that is caused by severe acute respiratory syndrome coronavirus.**

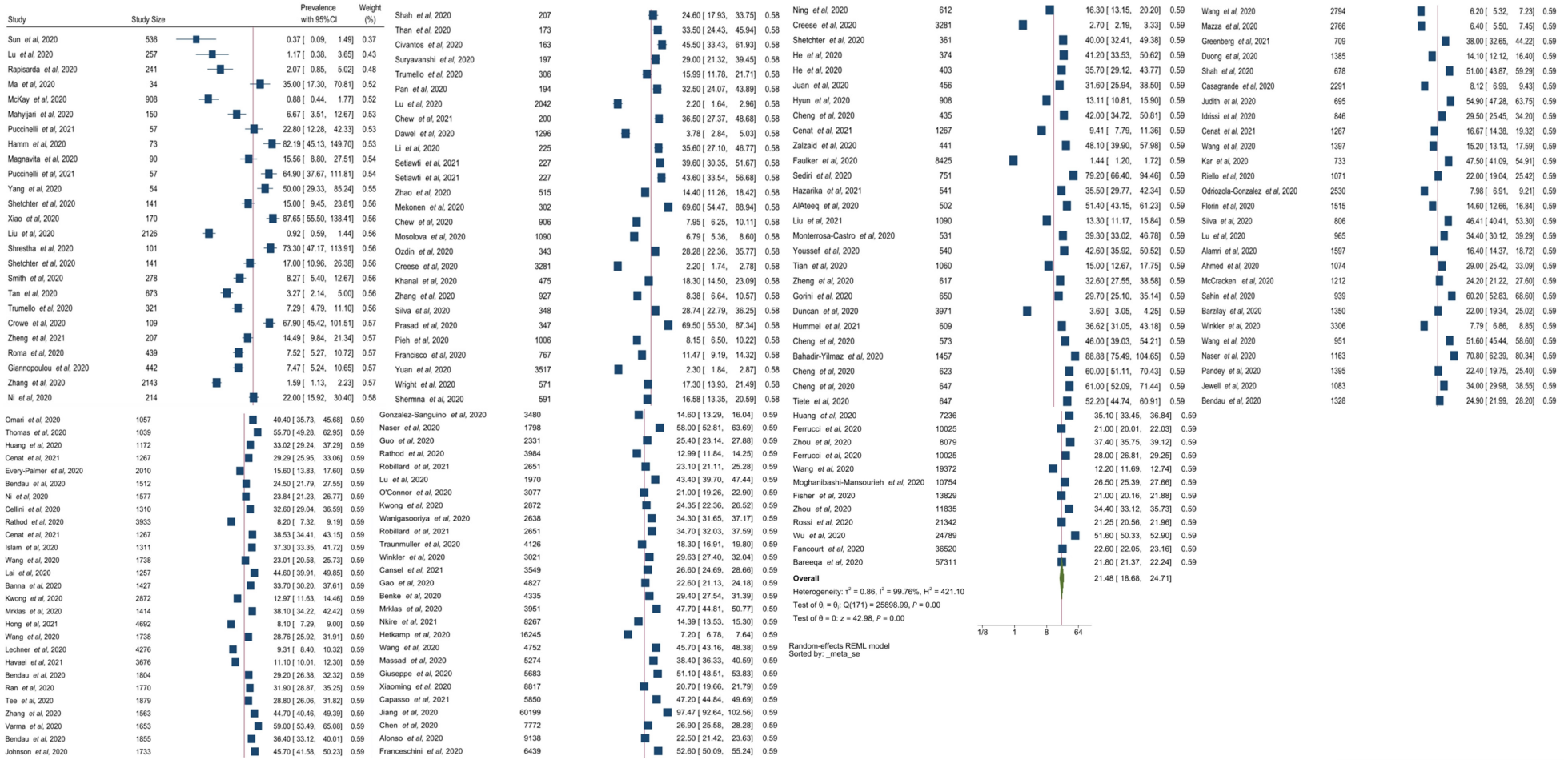


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**Figure 4 Forest plot of anxiety caused by severe acute respiratory syndrome coronavirus-2 forest plot.**

### *Geographical location*

**SARS-CoV-2:** From Supplementary Figure 18-20, we can see that people in Canada are more likely to have anxiety (80.85%) and PTSD (83.99%) when they experience SARS-CoV-2, and they also showcase a relative high possibility of having depression (57.90%), while people in Palestine suffer from the highest prevalence of depression (88.38%). On the other hand, people in the United Kingdom have the lowest prevalence of depression (1.44%) among all the countries. And people in the United States and Australia have the lowest prevalence of PTSD (5.38%) and anxiety (3.78%) respectively.

**Table 12 Sensitivity analysis for anxiety and depression studies under severe acute respiratory syndrome coronavirus-2**

| | Exposure | Outcome | Prevalence with 95%CI (before) | Prevalence with 95%CI (after) | *P* value |
|---|---|---|---|---|---|
| (g) | SARS-CoV-2 | Anxiety | 21.48 (18.66-24.71) | 25.82 (23.98-27.8) | < 0.05 |
| (h) | SARS-CoV-2 | Depression | 27.64 (24.59-31.06) | 29.3 (26.98-31.81) | > 0.05 |

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; CI: Confidence interval.

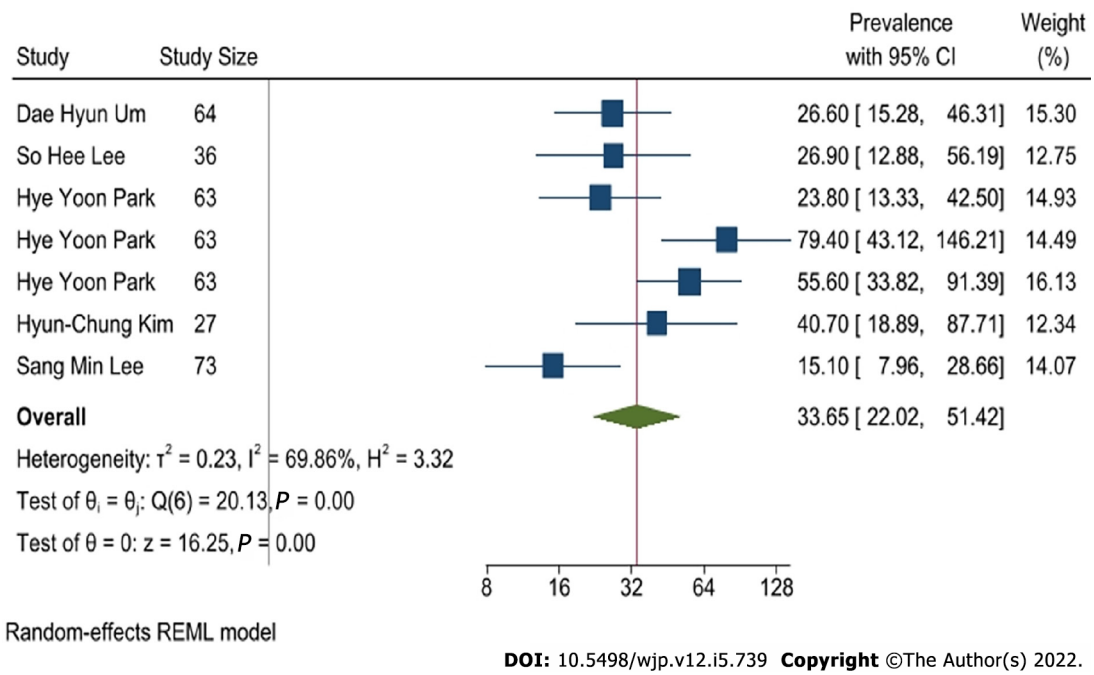


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**Figure 5 Forest plot of depression caused by Middle East respiratory syndrome.**

**MERS:** A subgroup analysis was not conducted due to the studies taking place in South Korea only.

**SARS-CoV:** Supplementary Figure 21-23 indicate Taipei shows the highest prevalence of depression (38.36%) and anxiety (52.91%) during SARS-CoV. Moreover, people in Kaohsiung/Southern Taiwan also suffer from the highest prevalence of PTSD (45.52%) during SARS-CoV. This indicates that people in the Taiwan area may experience a serious mental health issue due to the outbreak of SARS-CoV. On the other hand, people in Toronto, Singapore and Beijing have the lowest prevalence of PTSD (13.01%), anxiety (17.5%) and depression (21.80%) respectively.

### *Publication bias and sensitivity analysis*

The meta-analyses conducted indicate a high heterogeneity for depression, anxiety and PTSD. This could be due to differences in the reporting criteria and assessment tools used, geographical location and the difference in study designs, which had differing data collection time points. High heterogeneity could cause many studies to fall outside the 95%CI in the conventional funnel plot, which is based on the fixed effects model; therefore, we propose to use the funnel plot based on a random effects model. Both types of funnel plots were compared.

In the fixed effects model, the mean of the underlying model behind each study was fixed; therefore, the measure $\tau^2$ for heterogeneity was 0. Since the random effects model assumes that the mean of each study comes from a normal distribution, the DerSimonian and Laird estimates $\tau^2$ were calculated to show the heterogeneity between studies. The funnel plot based on the random effects model would include most of the studies and, therefore, make it easier to demonstrate publication bias. The pooled prevalence of the three mental health disorders and the 95%CI of the fixed (solid line) and random effects (dotted line) models were both plotted in Supplementary Figure 24 across all 3 pandemics.

When we looked at the funnel plots using the fixed effects model (solid line), most of the studies are located outside of the 95%CI. It is therefore difficult to find the sign of publication bias. They are masked by the widespread studies. By contrast, most of studies are well located within the 95%CI in the funnel plots using the random effects model (dotted line) except sub figs. Supplementary Figure 25A and B. Supplementary Figure 25C and D are typical examples. The large values of $\tau^2$, 1.1110 and 0.4574

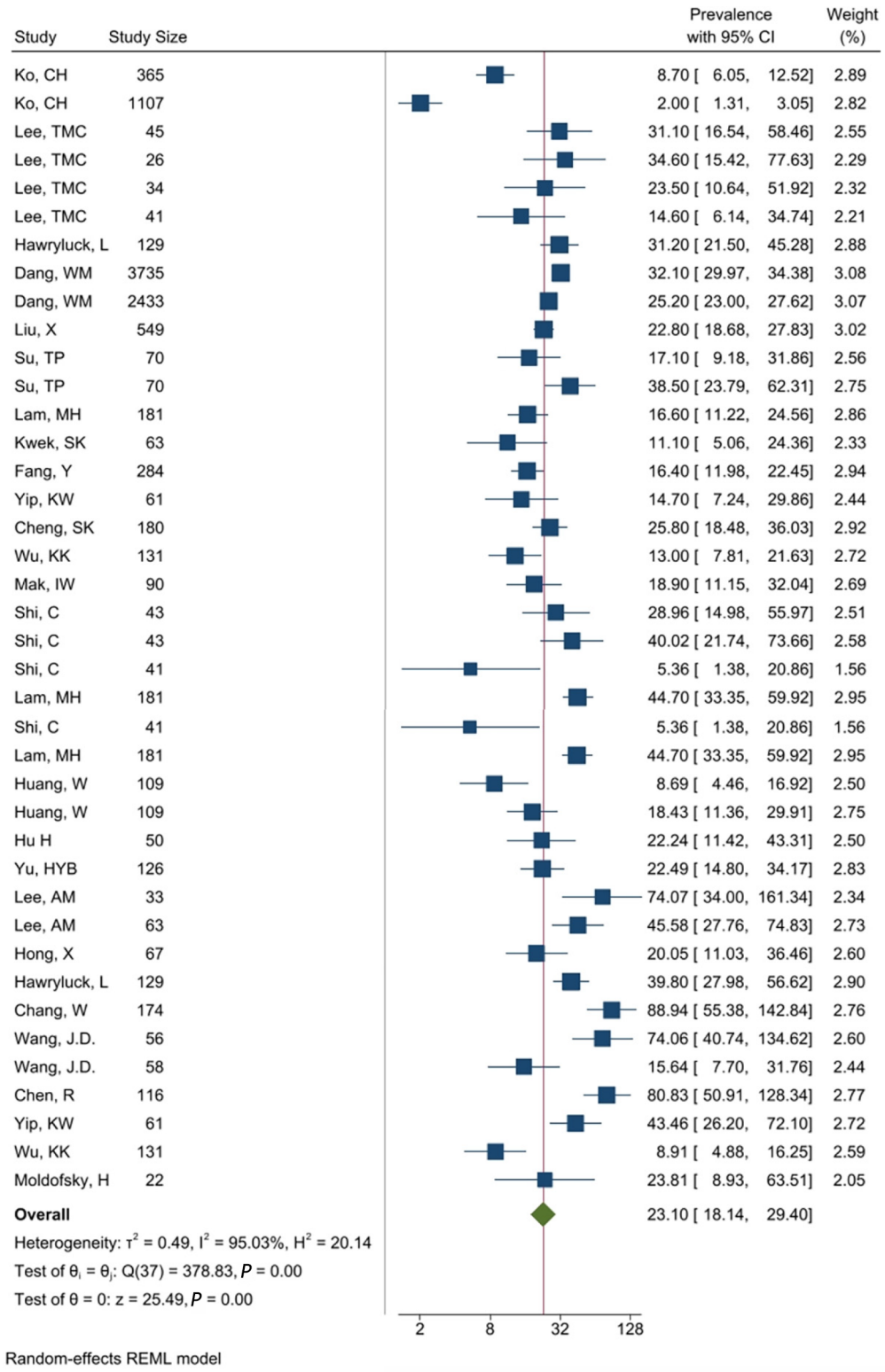


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**Figure 6 Forest plot of depression that is caused by severe acute respiratory syndrome coronavirus.**

confirm the severe heterogeneity, and the random effects model we used addresses this problem well. We can therefore focus on the problem of publication bias.

Based on the 95%CI of the random effects model (dotted line), there is little sign of publication bias in Supplementary Figure 25C-F; the *P* values of Egger's test of 0.082, 0.589, 0.146 and 0.539 echo the findings (Table 7). In Supplementary Figure 25G-I, however, there is a sign of publication bias and the *P* values of the Egger's test are all less than 0.05, confirming the findings (Table 11).

Even if we used the funnel plot based on the random effects model, many studies in Supplementary Figure 25A and B still fall outside the 95%CI, meaning the random effects model cannot address the problem of heterogeneity well. Further investigation is required. The sign of publication

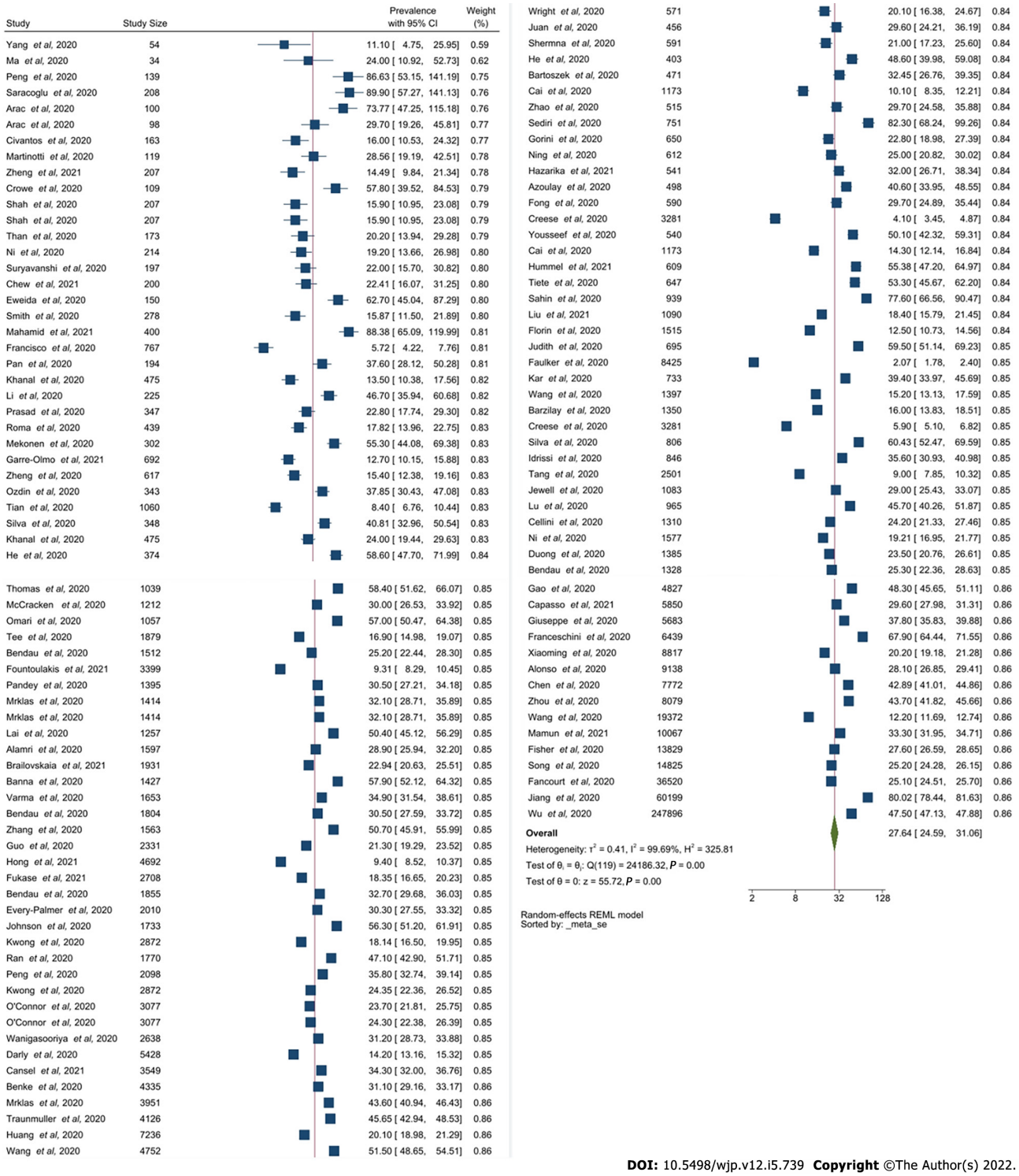


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**Figure 7 Forest plot of depression caused by severe acute respiratory syndrome coronavirus-2.**

bias is not clear; the *P* values of Egger's test are 0.085 and 0.000 respectively for Supplementary Figure 25A and B.

To reduce the unclear impact of studies that fall outside the 95%CI of random effects model in Supplementary Figure 25A and B, further sensitivity analyses, by removing the studies external to the 95%CI range, was demonstrated in Table 12.

The prevalence of anxiety and depression under SARS-COV-2 (Supplementary Figure 25A and B) are significantly higher after removing the studies external to the 95%CI, with the result changing from 21.44% (18.69-24.61) to 25.54% (23.28-28.02) and 27.68% (24.67-31.06) to 29.7% (27.25-32.39) respectively. It means that factors associated with heterogeneity, say, the design, population and quality of those studies, may have some impact on the conclusion and a further inspection of the study quality and other factors are needed.

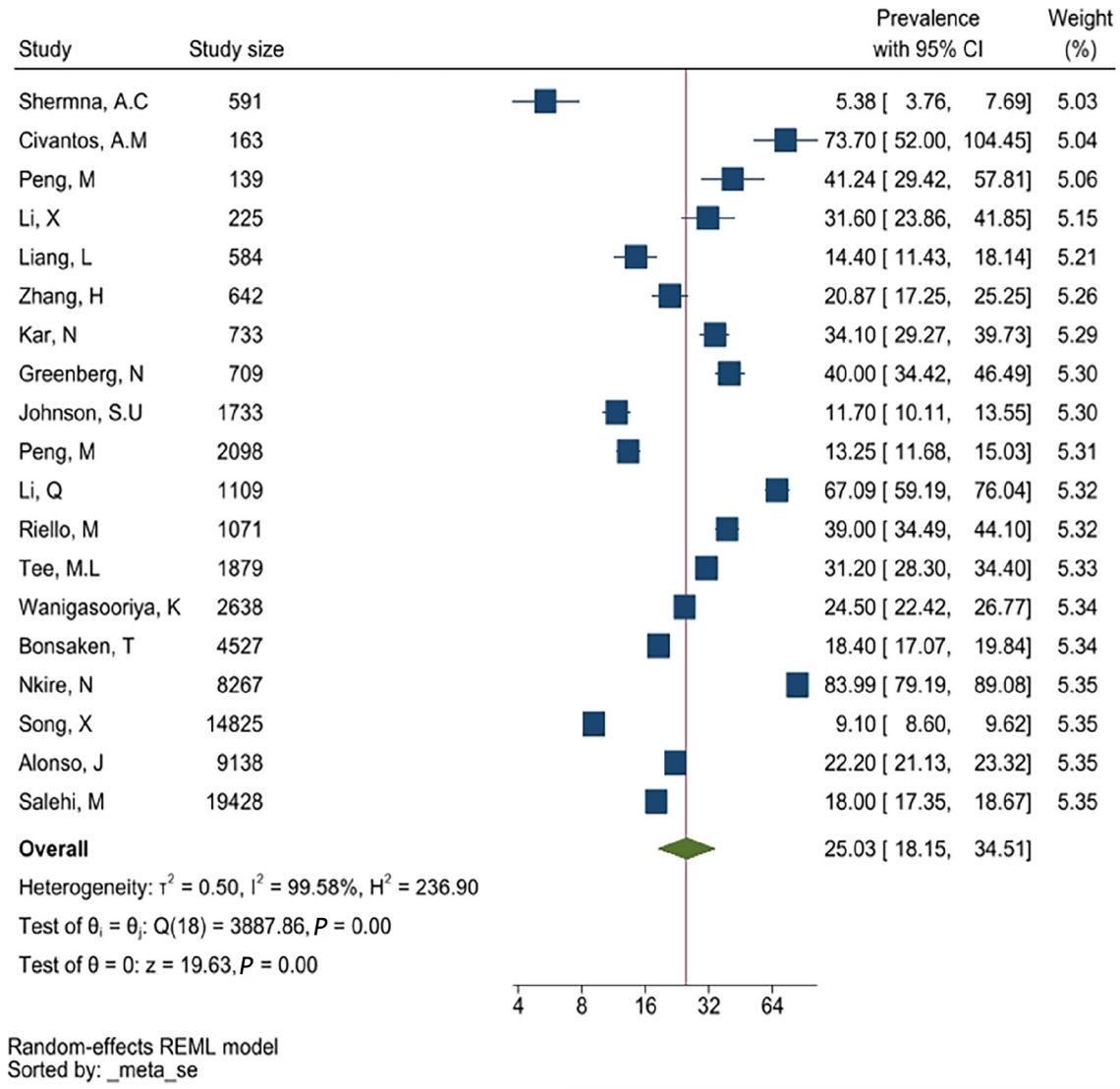


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**Figure 8 Forest plot of post-traumatic stress disorder that is caused by Middle East respiratory syndrome.**

## DISCUSSION

The prevalence of anxiety, depression and PTSD was common across HCWs, patients and the general public. It could be argued HCWs experience psychological burden more profoundly than patients and the general public given that the exposure to negative thoughts would be higher within their work environment. Patients equally could experience a high psychological burden with the exacerbation of their conditions due to a number of factors such as isolation. The general public could equally experience a decline in their mental health due to the lockdown situation in some parts of the world more extensively than others, especially with SARS-CoV-2 as a number of national level lock-downs were imposed in different countries.

The incidence of anxiety across all groups during SARS-CoV-2 (33.16%) was higher in comparison to MERS (17.35%) and SARS-CoV (25.2%). MERS and SARS-CoV-2 demonstrated higher depressive symptoms, at 33.65% and 31.35% respectively, in comparison to SARS-CoV, which reported 23.1%. PTSD was much higher during MERS (35.9%) than SARS-CoV-2 (25.03%) and SARS-CoV (18.2%).

The prevalence of PTSD among HCWs during MERS was 49.87%. The highest prevalence of anxiety for HCWs was during SARS-CoV at 98.44%. Among HCWs, the highest reported prevalence thus far during SARS-CoV-2 appear to be depression and insomnia, at 37.97% and 35.16% respectively. The identified prevalence rates could be influenced directly and indirectly by stigmatisation being an attributor. Stigmatisation within this context could include social processes to discriminate or separate the usual life changes and opportunities. This issue could present a significant barrier in managing access to equitable and quality services. Individual or social construct based beliefs and behaviours could promote social discrimination and moral discredit that may aggravate mental health implications to worsen health outcomes[27]. Interestingly, Dye and colleagues indicated HCWs were unlikely to follow social distancing protocols compared to non-HCWs. This could be associated with bullying as

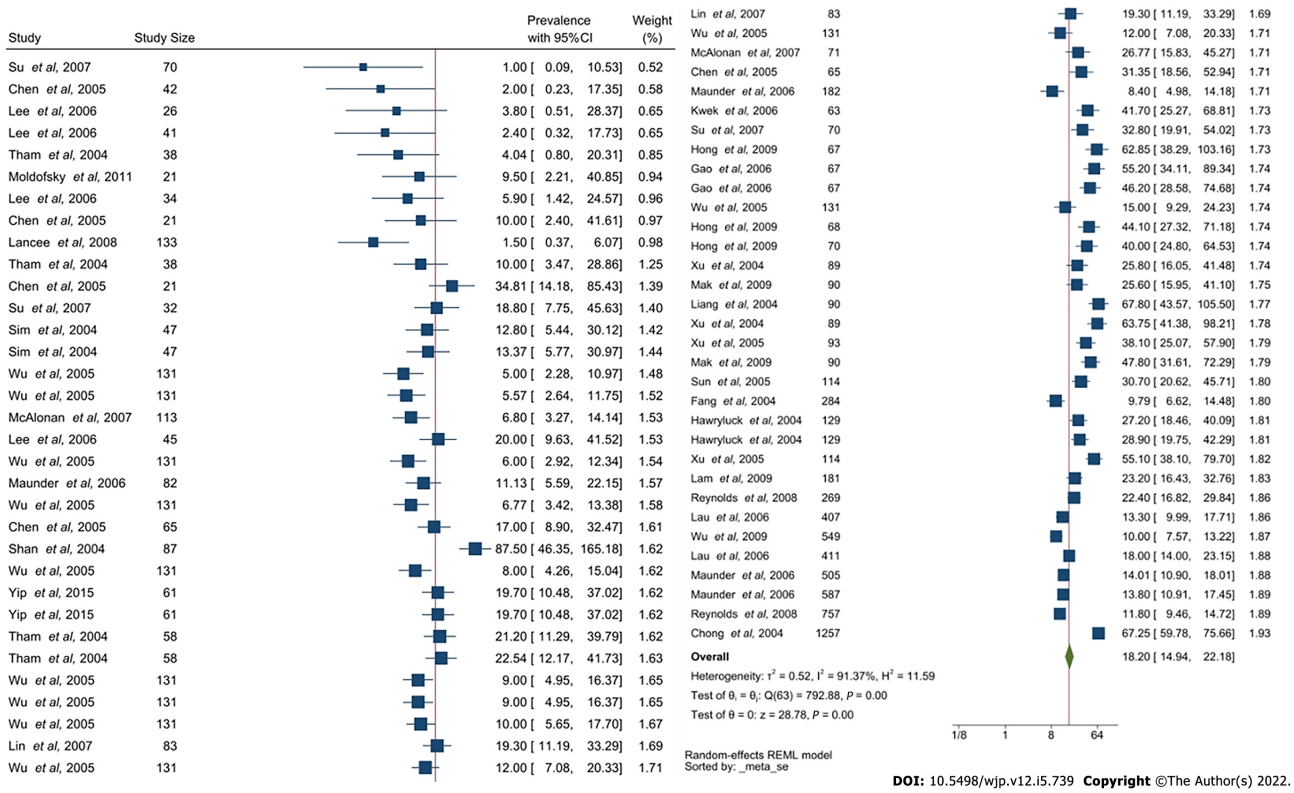


**Figure 9 Forest plot of post-traumatic stress disorder that is caused by severe acute respiratory syndrome coronavirus.**

demonstrated by Dye *et al*[27] Verbal and physical violence was also associated with bullying or harassment scenarios in comparison to MERS or SARS-CoV. This could be further purported with an influx of patients and workload that exacerbates fatigue and insomnia. This finding is consistent with MERS; therefore, it likely to occur with SARS-CoV-2.

Our results indicated age appear to play a role in mental illness manifestations during SARS-CoV-2, although there was insufficient data during MERS and SARS-CoV to conduct a comparative analysis. The pooled prevalence for ages between 20-29 years appear to demonstrate PTSD at 49.7% during MERS and 32.4% in SARS-CoV-2. Other mental illnesses during SARS-CoV-2 appear to be associated with 10 to 19 years of age with a significant prevalence of anxiety of 35.84% and insomnia (23.3%). In addition, depression was reported at 40.94% within the 30-39 age group.

The indirect influence of SARS-CoV-2 is widespread, especially among young people under 40 years old. For children and teenagers, the social isolation and loneliness of being unable to meet with friends will increase the anxiety. Students worry that the epidemic would limit their future choices and future education, employment and housing. Young workers have a higher rate of unemployment because of their immature skills. During MER-CoV, suicidality was reported at 16.62% with a 95%CI of 10.73-25.75, although the age range associated was non-specific.

Studies relating to SARS-CoV and MERs-COV are limited by several aspects, including the geographical constraints and sample sizes. The majority of studies were published in languages other than English. Psychological symptomatologies associated with depression, anxiety, distress, insomnia and fatigue, as well as comorbidities such as PTSD and neuro-psychiatric syndromes such as psychosis, have been reported in patients and HCWs more during the SARS-CoV-2 pandemic[28,29] which could be due to the scope and scale of the incidence and high transmission rates. The effects of mass lock-downs, economic downturns and mass uncertainty and fear within the general population are harder to characterise and assess, but early evidence suggests that rates of mental health disorders within the population will be higher during and following the pandemic[30,31]. More significant findings of severe psychological disorders including post-traumatic stress disorder and suicidal ideation amongst health care workers have been reported at levels greater than or expected to be seen in military veterans[32] or amongst victims of natural disasters[33]. Within the three groups there is likely to be variations in the levels of mental health disorders based on age, race and socio-economic status due to differences in the risk of mortality[34,35].

Non-specific use of MH interventions to support HCPs during each of the coronavirus disease outbreaks demonstrate the lack of preparedness global healthcare systems appeared to have had. Thereby, the ongoing SARS-CoV-2 will continue to impact their MH and overall well-being due to the lack of protective factors and assessments to identify specific risk factors. The available evidence demonstrates safeguarding measures should be considered by healthcare systems to better strategize

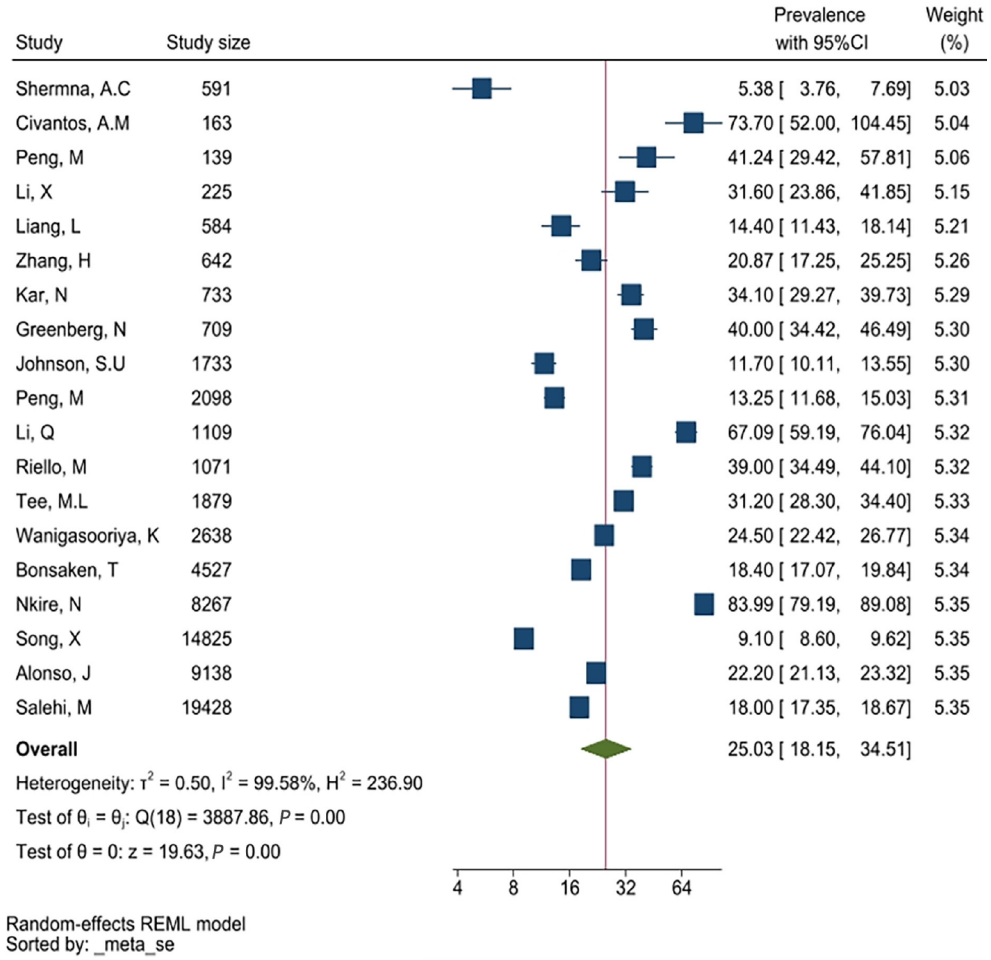


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**Figure 10 Forest plot of post-traumatic stress disorder caused by severe acute respiratory syndrome coronavirus-2.** CI: Confidence interval.

both collegial support and control steps to support all HCPs.

### *Limitations*

Several factors, including communication and country, as well as regional directives and their differences, were paramount to the inclusion and exclusion of the evidence within this study. All 3 cohorts included within this study reported their mental health impact differently. Multiple mental health assessments were used; thus, cut-off scores were used to better evaluate and inform the statistical analysis conducted. Unified approaches for the assessment of pandemic-specific or related mental health among HCPs, patients and the public should be considered in the future. This is another factor that led to the observations of high variation in outcomes and risks to medium- to long-term mental health impact.

## CONCLUSION

As vaccines are rolled out globally, it is hoped that pressures on acute medical services due to the SARS-CoV-2 will slowly improve. The aim of this study is to understand and build on our knowledge of the viruses' impact on mental health, both previously and now, so that we may better manage and prepare to deal with the hidden consequences of this and any future outbreaks. Whilst there are cultural, economic and environmental differences between the countries affected in each pandemic, drawing similarities between the lasting effects on mental health will be important in highlighting where resources and support are needed as we contemplate our recovery–physically, mentally and socially–from this pandemic. The mortality impact of seasonal influenza and a pandemic on the mental health of the general public, patients and HCPs vary.

This study analysed the prevalence of mental health outcomes during the MERS, SARS-CoV and SARS-CoV-2 across multiple cohorts. In terms of mental illness like anxiety, depression and PTSD, the prevalence of depression (33.65% with 95%CI: 22.02-51.42) and PTSD (35.97% with 95%CI: 29.6-43.72) is higher during MERS, while the prevalence of anxiety (33.16% with 95%CI: 25.99-34.5) is higher during

SARS-CoV-2. Patients and HCWs are the first and second most likely groups to suffer from mental health problems. Young people are more likely to be caught up in depressive and anxiety emotions than older people.

Developing evidence-based and cohort-specific MH interventions could be a useful way to optimise MH support. HCPs in particular may benefit from this as it could promote better well-being for staff, increasing the efficiency within the work environment.

## ARTICLE HIGHLIGHTS

### *Research background*

The severe acute respiratory syndrome (SARS) virus has been present for centuries in different forms. Whilst civilisation has evolved, so has the virus, including its' ability to transmit. Thus, the comparison of the three most recent severe acute respiratory syndrome coronavirus (SARS-CoV) viruses in terms of the mental health implications infused to patients, healthcare professionals (HCPs) and patients is an important facet both clinically and scientifically. As a result, our study explores an important component that hasn't been addressed from a potential disease sequalae perspective.

### *Research motivation*

Our motivation was to demonstrate the trends associated with the mental health prevalence in terms of specific conditions due to the last three virulent strands of SARS-CoV across patient, HCPs and the general public. The specified cohorts have specific behavioural patterns and differing levels of exposure to the virus, thus the risk of infection varies that influences the mental health impact. This would aid in assessing the true mental health impact that health care systems require to support those needing mental health support. The comparison also allows us to predict the trends in mental health impact due to infectious transmissions which ultimately should be addressed as a public health hazard, globally.

### *Research objectives*

The study has three primary aims of identifying and reporting: (1) Mental health conditions commonly observed across all three pandemics; (2) Impact of mental health outcomes across patients, the general public and HCPs associated with all 3 pandemics; and (3) The prevalence of the mental health impact and clinical epidemiological significance.

### *Research methods*

A systematic methodology was developed and published on PROSPERO (CRD42021228697). The databases PubMed, EMBASE, ScienceDirect and the Cochrane Central Register of Controlled Trials were used as part of the data extraction process, and publications from January 1, 1990 to August 1, 2021 were searched. MeSH terms and keywords used included *Mood disorders, PTSD, Anxiety, Depression, Psychological stress, Psychosis, Bipolar, Mental Health, Unipolar, Self-harm, BAME, Psychiatry disorders and Psychological distress*. The terms were expanded with a 'snowballing' method. Cox-regression and the Monte-Carlo simulation method was used in addition to $I^2$ and Egger's tests to determine heterogeneity and publication bias.

### *Research results*

The results indicated that there is a mental health impact observed among patients, HCPs and the general public at varying levels. This study analysed the prevalence of some mental health outcomes to the outbreaks of Middle East respiratory syndrome (MERS), SARS-CoV and SARS-CoV-2 and compared the prevalence of the participants and the prevalence of different occupational groups and age groups. In terms of mental illness like anxiety, depression and post-traumatic stress disorder (PTSD), the prevalence of depression [33.65% with 95% confidence interval (CI): 22.02-51.42] and PTSD (35.97% with 95%CI: 29.6-43.72) is higher during MERS, while the prevalence of anxiety (33.16% with 95%CI: 25.99-34.5) is higher during SARS-CoV-2. Patients and healthcare workers are the first and second most likely groups to suffer from mental health problems. Young people are more likely to be caught up in depressive and anxiety emotions than older people.

### *Research conclusions*

Developing evidence-based and cohort-specific mental health (MH) interventions could be a useful way to optimise MH support. HCPs in particular may benefit from this as it could promote better well-being for staff, increasing the efficiency within the work environment. As vaccines are rolled out globally, it is hoped that pressures on acute medical services due to the SARS-CoV-2 will slowly improve. The aim of this study is to understand and build on our knowledge of the viruses' impact on mental health, both previously and now, so that we may better manage and prepare to deal with the hidden consequences of this and any future outbreaks. Whilst there are cultural, economic and environmental differences between the countries affected in each pandemic, drawing similarities between the lasting effects on

mental health will be important in highlighting where resources and support are needed as we contemplate our recovery–physically, mentally and socially–from this pandemic. The mortality impact of seasonal influenza and a pandemic on the mental health of the general public, patients and HCPs vary.

### *Research perspectives*

Studies relating to SARS-CoV and MERS-CoV are limited by several aspects, including the geographical constraints and sample sizes. The majority of studies were published in languages other than English. Psychological symptomatologies associated with depression, anxiety, distress, insomnia and fatigue, as well as comorbidities such as PTSD and neuro-psychiatric syndromes such as psychosis, have been reported in patients and HCWs more during the SARS-CoV-2 pandemic which could be due to the scope and scale of the incidence and high transmission rates. The effects of mass lock-downs, economic downturns and mass uncertainty and fear within the general population are harder to characterise and assess, but early evidence suggests that rates of mental health disorders within the population will be higher during and following the pandemic. We need more comprehensive and longitudinal studies to be conducted to determine the mental health impact in multiple populations globally. This would also aid us to develop better pandemic preparedness frameworks and policies within healthcare systems.

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## FOOTNOTES

**Author contributions:** Delanerolle G and Phiri P developed the systematic review protocol and embedded this within the EPIC project's evidence synthesis phase; Delanerolle G and Goodison W wrote the first draft of the manuscript; The statistical analysis plan was developed by Delanerolle G and was conducted by Shi JQ, Yeng X and Zeng Y; The data was critically appraised by Shetty A, Phiri P, Zeng Y, Yeng X, Shi JQ, Goodison W, Ramakrishnan R, Ranaweera S and Raymont V; The SARS-CoV data was extracted by Chau SWH and his team; The SARS-CoV-2 data was extracted by Phiri P/Delanerolle G and their team; Yeng X and Zeng Y extracted the MERS dataset which was reviewed by Delanerolle G, Phiri P, Shetty S, Shi JQ and Shetty A; Yeng X, Zeng Y and Shi JQ conducted the analysis; Shetty S designed and developed the original illustration; Delanerolle G, Phiri P, Shetty A, Zeng Y, Yeng X, Shetty S, Shi JQ, Goodison W, Ramakrishnan R, Elliot K, Ranaweera S and Raymont V critically appraised and finalised the manuscript; All authors approved the final version of the manuscript.

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LETTER TO THE EDITOR

# COVID-19, mental health and Indigenous populations in Brazil: The epidemic beyond the pandemic

Jucier Gonçalves Júnior, Jucycler Ferreira Freitas, Estelita Lima Cândido

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## Abstract

The aim of this paper was to report on factors contributing to the deterioration of the mental health of Indigenous populations (IP) in Brazil. Five factors seem to have a direct impact on the mental health of IP in Brazil: (1) The absence of public policies; (2) Intellectual production; (3) Psychiatric medical care for remote areas (*e.g.*, telemedicine) aimed at promoting the mental health of Brazil's IP, which causes a huge gap in the process of assistance and social, psychological, economic and cultural valorization of native peoples; (4) The dissemination of fake news, which exposed, above all, older IP to risk behaviors in the pandemic, such as refusal of vaccination; and (5) The violence carried out on IP lands due to economic interests with mining/agribusiness.

**Key Words:** Brazil; COVID-19; Indigenous population; Mental health; Public health

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**Core Tip:** In Brazil, the mental health of the Indigenous population (healthy or with psychiatry disorders) suffers from several factors. Over the past 2 years, there has been growing violence against Indigenous people along with a considerable increase of fake news dissemination regarding the coronavirus disease 2019 pandemic currently afflicting them. These two factors, accentuated by the lack of public policies and scarce academic contribution in the area, make the mental health of the Indigenous population in Brazil an important public health problem.

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## TO THE EDITOR

With great interest we read the work of Diaz *et al*[1] commenting on how the coronavirus disease 2019 (COVID-19) pandemic affects psychiatric patients disproportionately compared to the general population. Of the highlighted minority groups, the Indigenous population (IP) draws our attention. We would like, therefore, to contribute to the discussion with some factors that in our opinion may further worsen the mental health of these populations in Brazil. A summary of the points we consider important about the topic are presented in Figure 1.

As the authors pointed out, there is a dearth of public policies that address the promotion of mental health in Indigenous patients with psychiatric illnesses (IPPI)[1]. Moreover, in Brazil, this situation is even more precarious. The most recent regulation on the mental health of the IPPI was only released by the Brazilian Ministry of Health in 2007 - the Policy of Comprehensive Mental Health Care for Indigenous Populations ("Política de Atenção Integral à Saúde Mental das Populações Indígenas")[2] (Figure 1). Besides that, academic production is limited. An integrative review carried out on the subject showed that of the 5510 articles found in 20 years of scientific publications, only 14 (0.2%) contemplated the mental health of the IPPI[3]. This factor reinforces their findings: That there is a lack in mental health care for IPPI[1]. However, in Brazil, in addition to the lack of mental health care, there is a gap between academic production and current legislation. At the same time, consecutive antibody seroprevalence surveys against COVID-19 conducted in urban areas in all regions of the Brazil reported a higher prevalence in IP than other ethnicities[4].

In Brazil, the spread of fake news is another important factor causing psychological distress in IPPI according to Figure 1. Studies have already demonstrated that advancement and dissemination of false information incite fear, anger, anguish and worsening of previous depressive and anxiety symptoms and can therefore be considered as an additional epidemic ("Infodemia") within the COVID-19 pandemic[5]. According to non-governmental organizations, which historically have been defending the health of IP, such as Articulação dos Povos Indígenas do Brasil and Conselho Indigenista Missionário, there is increasing fear and worry, especially by older members of IP, due to fake news. In fact, several news articles are aimed at promoting the ineffectiveness of vaccines for COVID-19 or associated nonexistent effects (*e.g.*, "those who took the vaccine would die in a fortnight" or "those who took the vaccine turn into an alligator")[6,7].

Another important factor with a negative impact on the mental health of the IPPI would be the rising rates of violence against IP during the COVID-19 pandemic (Figure 1). According to Conselho Indigenista Missionário, the cases of "invasions, illegal exploitation of resources and damage to property" in indigenous lands rose from 109 in 2018 to 256 in 2019. Occurrences of this type affected 151 indigenous lands and 143 peoples in twenty-three Brazilian states. There were also 35 cases of territorial conflicts, 33 cases of death threats, 34 cases of other types of threats, 13 cases of personal injury and 31 cases of deaths due to lack of assistance in the last year[7]. The continuous rise observed between 2018 and 2019 has possibly worsened during the pandemic.

Thus, the absence of telemedicine/internet services, prejudice and religious barriers are important factors that worsen the IPPI's mental health (Figure 1). In Brazil, in addition to these factors, the lack of knowledge of the epidemiological situation of mental illnesses in this population, the violence and the Infodemia are factors that increase psychological distress and make it difficult to draft and carry out public policies.

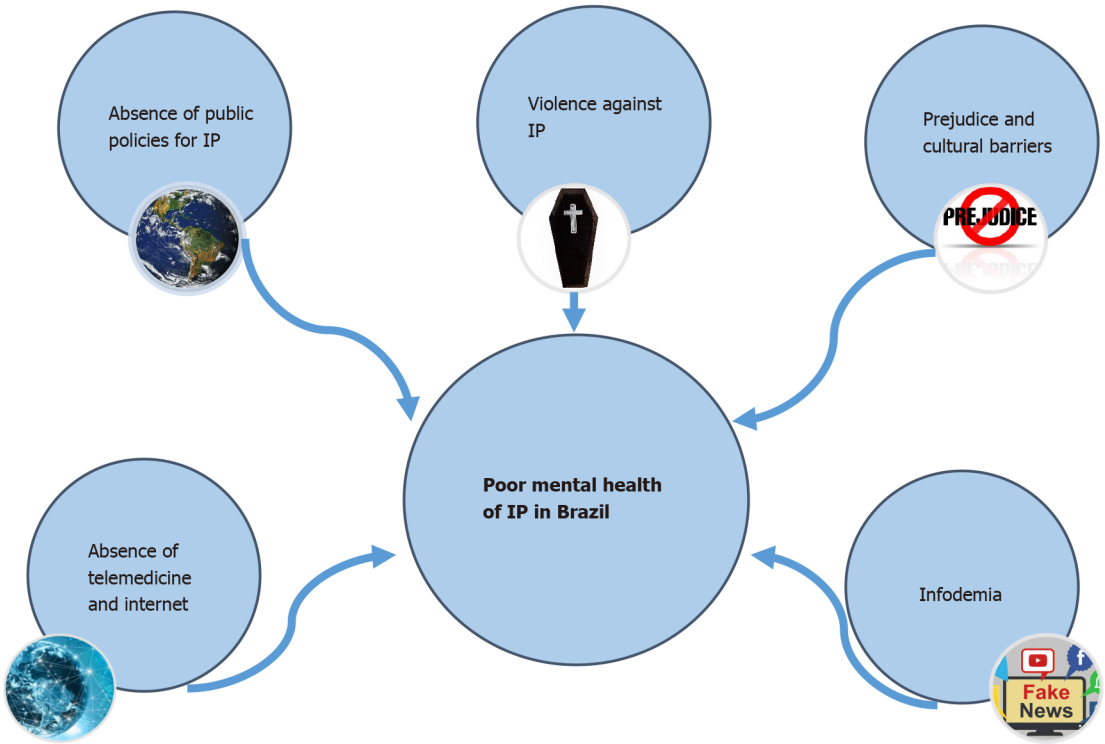


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**Figure 1 Factors that contribute to the worsening mental health of Indigenous peoples.** IP: Indigenous people.

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LETTER TO THE EDITOR

# Biological mechanisms and possible primary prevention of depression

Chih-Yun Kuo, Ivo Stachiv

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## Abstract

Individuals with unipolar depressive disorder (UDD) are having an increased risk of death and development of dementia in later life. It is widely expected that in a near future UDD would be the leading cause of death; therefore, a primary inexpensive prevention of UDD will be of a great importance to the society. Several studies provide evidences supporting the positive effect of Mediterranean diet on a reduced risk for development of depression.

**Key Words:** Unipolar depressive disorder; Mediterranean diet; Depression; Primary prevention; Dementia

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**Core Tip:** Dietary interventions, especially Mediterranean diet, may help to reduce the risk for development of depression. It is the high levels of various antioxidant compounds, adequate B-group vitamin and folate content which make the Mediterranean diet a possible candidate for an inexpensive primary intervention of depression. However, the long-term clinical trials on the large cohorts are still necessary to understand the relationship between dietary pattern and development of depression or dementia.

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## TO THE EDITOR

Unipolar depressive disorder (UDD) is characterized by an increased mortality in the general population. The healthy diet, especially Mediterranean diet, has been found being associated with the one`s health status including mental health. Unfortunately, up to date the exact relationship between the healthy diet and the risk for development of depression, biomarkers and overall improvements in the one`s quality of life is still not fully understood. With this in mind we read the narrative review by Pano *et al*[1] with a considerable interest. In their study, they have summarized the available evidences on the biological mechanisms of UDD and cardiometabolic diseases as well as the primary preventive strategies for depression such as dietary interventions. They have suggested that Mediterranean diet interventions could potentially be considered as an inexpensive strategy enabling to notably reduce the risk for depression, that is, Mediterranean diet can be viewed as the protective factor against depression. In addition, authors have also pointed out main advantages of this healthy diet (*i.e.*, Mediterranean diet) such as the high levels of various antioxidant compounds, adequate B-group vitamin and folate content.

We commend the authors for this important research and agree with their opinion and conclusions. Note that their data which are in a good agreement with other recently reported studies on association between dietary patterns and depression[2-4] or even dietary pattern and dementia in later life[5], are of great importance to public health. These recent studies provide evidences suggesting that oxidative stress, gut microbiota, the hypothalamic-pituitary-adrenal dysregulation and mitochondrial dysfunction are the possible driving mechanisms of depression. Despite the mechanisms associating the dietary interventions with depression are still not fully explained, there is a consensus among researchers that healthy diet, that is, particularly Mediterranean diet, can notably reduce the incidence of depression. In addition, Mediterranean diet has also been shown affecting depression *via* other chronical comorbid diseases such as diabetes mellitus or cardiovascular diseases. Pano *et al*[1] have also proposed that the systematic long-term clinical trials would be necessary to support the protective effect of dietary interventions. We foresee that these studies should also account for behavioral, biological and other factors such as sex and culture differences. Hence, the effect of other healthy diet and individual factors would be required to develop novel treatment strategies and clinical practice guidelines.

To conclude, we once again commend the authors on this interesting work and highly welcome their findings on this important topic. We emphasize here that research associating healthy lifestyle and depression should be of emergent importance, and a larger sample size and well-designed clinical trials are needed in the future studies.

## FOOTNOTES

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*MINIREVIEWS*

# Legacy of neuropsychiatric symptoms associated with past COVID-19 infection: A cause of concern

Domenico De Berardis, Francesco Di Carlo, Massimo Di Giannantonio, Mauro Pettorruso

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## Abstract

Although primarily affecting the respiratory system, growing attention is being paid to the neuropsychiatric consequences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Acute and sub-acute neuropsychiatric manifestations of coronavirus disease 2019 (COVID-19) disease and their mechanisms are better studied and understood currently than they had been when the pandemic began; however, many months or years will be necessary to fully comprehend how significant the consequences of such complications will be. In this editorial, we discuss the possible long-term sequelae of the COVID-19 pandemic, deriving our considerations on experiences drawn from past coronaviruses' outbreaks, such as the SARS and the middle east respiratory syndrome, and from the knowledge of the mechanisms of neurotropism and invasiveness of SARS-CoV-2. Acknowledging the global spread of COVID-19 and the vast number of people affected, to date amounting to many millions, the matter of this pandemic's neuropsychiatric legacy appears concerning. Public health monitoring strategies and early interventions seem to be necessary to manage the possible emergence of a severe wave of neuropsychiatric distress among the survivors.

**Key Words:** COVID-19; Neuropsychiatric symptoms; Neuropsychiatric sequelae; Mental health; Post-traumatic stress disorder; Depression

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**Core Tip:** While acute neuropsychiatric manifestations of coronavirus disease 2019 (COVID-19) are the object of study, far less is known about long-term neuropsychiatric sequelae of COVID-19 infection. Much of the knowledge about this topic can be drawn from past coronaviruses outbreaks and from the study of the mechanisms through which severe acute respiratory syndrome coronavirus 2 harms the central nervous system. A relevant wave of both psychiatric (anxiety and depressive disorders, post-traumatic syndromes) and neurological symptoms could be expected. There will be a vital need for monitoring and early intervention to minimize this potential burden of neuropsychiatric distress.

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## INTRODUCTION

Starting December 2019, several cases of pneumonia of unknown etiology were reported in Wuhan, China. A novel coronavirus was identified as the cause of such illnesses, and on January 12, China made public the gene sequence of the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus[1]. On January 30, 2020, the World Health Organization (WHO) declared the outbreak of coronavirus disease 2019 (COVID-19) a Public Health Emergency of International Relevance, and on March 11, 2020, the same organization proclaimed the beginning of the COVID-19 pandemic[1]. It was the start of the global crisis we are still struggling with[2].

Coronaviruses are single-stranded RNA viruses; in the past, they have been responsible for two well-known epidemics: (1) The 2002 SARS, caused by SARS-CoV-1; and (2) The 2012 Middle East Respiratory Syndrome (MERS). Like other coronaviruses, the newly identified SARS-CoV-2 affects the respiratory tract, usually causing mild and self-limiting symptomatology similar to the common cold. In susceptible individuals, the virus can reach the lower respiratory tract causing pneumonia and severe acute respiratory syndrome[3].

However, COVID-19 does not only induce a respiratory syndrome, but it can elude the immune response and spread to distant apparatuses, as the renal and cardiovascular[4] ones. In particular, like SARS and MERS, COVID-19 has been shown to be neuro-invasive[6]. A growing body of literature shows that 27% to 41% of COVID-19 patients may present neuropsychiatric complications during the acute stage of the illness[7]. The most reported ones are anosmia, ageusia, headache, confusion, agitation, cerebrovascular events, encephalopathies, anxiety, depressed mood, impaired memory and insomnia[8-10].

On the contrary, far less is known about long-term neuropsychiatric sequelae of COVID-19 infections [11]. The delayed effect of this pandemic, particularly that on the population's mental health, will require many months, or even years, to be fully acknowledged. Considering that many millions of people have been affected by COVID-19, this becomes a matter of deep concern. Given the aforementioned observations, this editorial aims at discussing the possible long-term effects of the COVID-19 pandemic on neuropsychiatric health.

## LONG-TERM NEUROPSYCHIATRIC SEQUELAE: A CAUSE OF CONCERN

Most of the hypotheses about COVID-19 long-term effects on the nervous system can be drawn from evidence on SARS-CoV-1 and MERS neuropsychiatric sequelae. As to SARS-CoV-1, high rates of depression (39%), pain disorders (36.4%), panic disorder (32.5%), and obsessive-compulsive disorder (15.6%) were reported among survivors. The mean time of onset of such complications ranged 31 mo to 50 mo post-infection[12]. According to another study, one year after the SARS-CoV-1 outbreak, 64% of the survivors showed some sign of psychiatric morbidity[13], while 30 mo after the outbreak, the prevalence of any psychiatric disorder was 33.3%[14]. A meta-analysis reported rates of neuropsychiatric sequelae in SARS-CoV-1 and MERS survivors raging 10% to 20%; the symptomology most often displayed was insomnia, anxiety, depression, fatigue, and memory impairment[7].

Moreover, an examination of the literature's data about the relationship between other non-epidemic coronaviruses and neuropsychiatric consequences can be helpful. Human coronavirus HCoV-NL63 infection was associated with mood disorders and suicide attempts[15]. Furthermore, exposure to viral infections, both in utero and during child development, has been linked to an increased risk for schizophrenia[16,17]. In this regard, when compared to controls, an increase in antibodies for four human coronavirus strains was found in patients with a recent psychotic onset[18]. In light of this, such data suggest a possible relation between coronavirus infection and psychosis that could emerge in the long

run from SARS-CoV-2.

Given the insight drawn from other coronaviruses and considering the mechanisms through which COVID-19 invades and damages the central nervous system (CNS), we can speculate on the long-term neuropsychiatric symptoms this virus may cause. Coronaviruses can spread to the CNS *via* retrograde axonal transport, from the olfactory nerve, or *via* the hematogenous route[19] (see Figure 1).

Once in the CNS, the latent virus can be hosted by both neural and immune cells, contributing to the onset of delayed neuropsychiatric complications. There are different pathways through which coronaviruses can affect the CNS, including damages through direct infections, immune or hypoxic damage, and direct binding to the ACE2 enzyme, which is highly expressed by neurons and glia[20]. These pathways were detected both in patients and in experimental animals affected by SARS-CoV-1 [21]. Several reports on SARS-CoV-1 and MERS discussing sub-acute demyelinating complications and neuromuscular and neurodegenerative diseases have been published[19,22,23]. Considering the neurotropism of all coronaviruses, we can imagine similar mechanisms and consequences also in COVID-19 patients.

However, SARS-CoV-2 has also shown different mechanisms of neuroinvasiveness. Besides from ACE-2, the neuropilin-1 protein was identified as an additional mediator, facilitating the virus entering the cells[24,25]. This protein is highly expressed in the brain, representing an element of concern, particularly for long-term cognitive sequelae of COVID-19 infections[26]. Early studies showed that cognitive impairment, frequently reported during acute infection, could also persist after recovery. A paper examining patients at a median of 85 d after acute illness showed that 78% of the group reported sustained cognitive difficulties. These deficits did not correlate with depressed mood, fatigue, hospitalization, type of treatment received, acute inflammation, or viremia. If these effects were to extend over time, the impact of SARS-CoV-2 on cognitive functioning might be of great concern[27]. Studies to shed light on SARS-CoV-2 specific neurotropism and its possible neurological consequences are still active [28].

The emergence of post-traumatic stress disorder (PTSD) associated with a prior COVID-19 infection should also be considered. This is because the experience of a potentially severe disease, such as COVID-19, is considered a traumatic event[29]. On the one hand, the infection can lead to brain vulnerabilities that could increase the risk of developing clinically relevant psychological distress. On the other hand, profound stressors linked to the infection, such as medical interventions or isolation, could play a critical role in the development of PTSD as seen for other diseases[30]. This was also demonstrated after the SARS-CoV-1 epidemic, with a 55% rate of PTSD detected among survivors[12]. There are many reports about the emergence of PTSD after a COVID-19 acute infection, and many more are probably yet to come[31,32].

## CONCLUSION

As said, long-term neuropsychiatric complications of COVID-19 infection will remain covert for several months or possibly even several years. Given the global spread of the COVID-19 infection, even if only a small part of the affected people will develop delayed neuropsychiatric sequelae the public health burden generated by these complications will be significant. Thus, we could expect a "crashing wave" [33] of COVID-19 neuropsychiatric consequences, with a plausible relevant impact on countries healthcare resources and on healthcare workers[34] as well. These consequences might be even more severe for those who were already suffering from a psychiatric or neurological disorder[35]. These consequences, hence, might be both psychiatric and neurological. Psychiatric long-term consequences could be observed in the form of an escalation in PTSD, depression and depressive symptoms, anxiety disorders, and perhaps even more severe mental illnesses such as psychosis. A variety of neurological sequelae have also been hypothesized.

This editorial will hopefully encourage many future considerations. Firstly, clinicians should be aware of the distant burden of neuropsychiatric distress that is potentially linked to COVID-19 infections. Careful attention should be given to survivors, in order to prevent or anticipate possible complications. It might be essential to mention an eventual wave of suicidality as the endpoint of unrecognized depressive syndromes or other severe mental distress. A patient's cognitive examination should also be included in long-term monitoring, exploring executive functions, memory, attention, and information processing.

As possible strategies of intervention against this wave, implementation of telehealth and digital medicine should be cited. Although these are promising and effective ways to deliver health assistance, mainly if applied for mental health purposes, they are still underused in many countries[36]. Research carried out during the pandemic's acute outbreak shows promising results in this field[37].

In the event of the likely impact of neuropsychiatric sequelae on the health system, it would be crucial to focus our efforts on strong-effectiveness interventions. Depression, anxiety, PTSD, and other emerging issues should be addressed with evidence-based and easy-delivered treatments. Besides from telehealth platforms, group interventions should also be implemented in response to the expected increase in psychological needs.

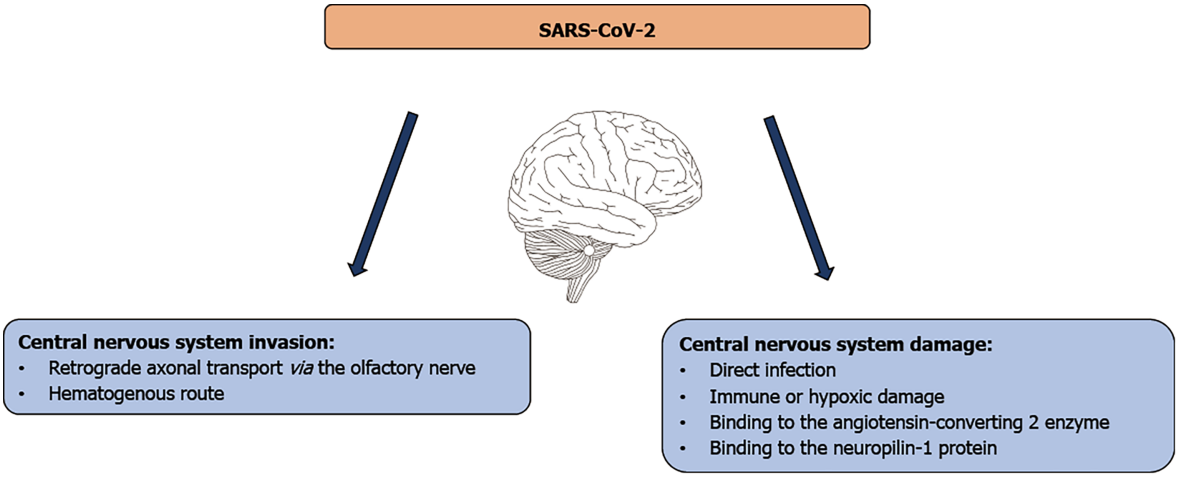


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**Figure 1 Summary of severe acute respiratory syndrome coronavirus 2 mechanisms of neuroinvasiveness and damage.**

As treatment approaches for COVID-19 neuropsychiatric consequences, we would imagine an important role for physical therapies and neuromodulation techniques, such as transcranial magnetic stimulation or transcranial direct current stimulation. Even if there is still no clear evidence, possible applications of neuromodulation techniques have been underlined[38]. Proposed pathways include regulating anti-inflammatory responses through dorsolateral prefrontal cortex stimulation and improving cognitive outcomes and fatigue. Moreover, the body of literature on the effectiveness of those techniques in many neuropsychiatric disorders has been growing, projecting a promising role for the management of long-term COVID-19 psychiatric sequelae[39,40].

In conclusion, all these considerations underline the need for a watchful follow-up on neuropsychiatric symptoms related to COVID-19 in order to understand the trajectories of possible neuropsychiatric outcomes in the future. Careful research, based mainly on longitudinal and prospective studies will be vital in this field, both for clinical and scientific purposes.

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*MINIREVIEWS*

# Role of high mobility group box protein 1 in depression: A mechanistic and therapeutic perspective

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## Abstract

As a common and serious psychiatric disorder, depression significantly affects psychosocial functioning and quality of life. However, the mechanism of depression is still enigmatic and perplexing, which limits its precise and effective therapeutic methods. Recent studies demonstrated that neuroinflammation activation plays an important role in the pathophysiology of depression. In this respect, high mobility group box 1 (HMGB1) may be a possible signaling inducer of neuroinflammation and can be a potential mechanistic and therapeutic target for depression. Herein, we review recent studies on the mechanistic and therapeutic targets of HMGB1 in depression and propose potential perspectives on this topic.

**Key Words:** Neuroinflammation; Depression; High mobility group box 1; Mechanism; Review; Perspective

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**Core Tip:** Limited reviews in the literature contributed to the high mobility group box 1 (HMGB1) in depression. This review provides a comprehensive mechanistic and therapeutic perspective on this topic and proposed that the future perspectives of HMGB1 in depression should be understanding the full signaling pathway of HMGB1 in depression, deeply investigating potential HMGB1 related therapeutic targets, and exploring the role of HMGB1 in depression and combined disease.

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## INTRODUCTION

Depression is one of the most common, serious, and costly psychiatric disorders that affect psychosocial functioning and quality of life[1]. The aggregate point, one-year, and lifetime prevalence of depression in the community is about 12.9%, 7.2%, and 10.8%, respectively[2]. Crucially, the number of people suffering from depression worldwide has increased from 172 million in 1990 to 258 million in 2017, with an increase of 49.86%[3,4]. The stress of the outbreak of coronavirus disease 2019 and interpersonal isolation makes it even more people suffer depression recently[5-7]. However, the mechanism of depression is still enigmatic and perplexing, which limits its precise and effective therapeutic methods [8,9]. Recent studies demonstrated that the activation of neuroinflammation might play an important role in the pathophysiology of depression[10]. High mobility group box 1 (HMGB1), a chromosomal protein, has been found to perform an essential job in the neuroinflammation of several central nervous system diseases, which might also be a potential therapeutic target[11-15]. Rana *et al*[11] proposed that HMGB1-mediated neuroinflammation in depression could have insights into the pathogenesis understanding and therapeutic promise. Herein, with recent studies concerning this topic, we review the role of HMGB1 in depression and propose several potential key mechanistic and future therapeutic perspectives.

## RESEARCH PROGRESS OF HMGB1 IN DEPRESSION

### *HMGB1: a potential mechanistic direction in depression*

HMGB1 is the most researched protein in the HMGB family for inflammation as innate immune responses[16]. Expressed in nearly all eukaryotic cells, HMGB1 is a kind of chromatin-binding molecule to function in chromatin remodeling in the nucleus under normal physiological situations[13]. Whereas in stressful situations or pathological situations, caused by immune and other cells or cell injury and death, HMGB1 secretes or translates from nuclei to the cytoplasm and eventually excretes or releases to the extracellular milieu, acting as a mediator of inflammation extracellularly[17]. Placing on extracellular milieu, HMGB1 is acknowledged by plenty of binding receptors, mainly including Toll-like receptors (TLRs) and receptors for advanced glycation end products (RAGE), resulting in the expression of proinflammatory response elements and eventually in the inflammatory cascade[18]. The TLRs and RAGE are transmembrane proteins, which are located in the membrane of several cells such as monocytes, macrophages, dendritic cells, and neural cells[12]. For the HMGB1-TLRs pathway (mainly including TLR2 and TLR4), MyD88 dependent and independent pathways were activated, resulting in the simulation of NF-κB and induction of pro-inflammatory response[19]. For MyD88-dependent pathway, MyD88 serves as a domain-containing adaptor for the cytoplasmic Toll/ interleukin (IL)-1 receptor[20]. Stimulated by ligands, MyD88 recruits IL-1 receptor-associated kinase-4 (IRAK-4) to TLRs; and IRAK-1 is phosphorylated and then associates with TRAF6, thereby activating the IKK complex and leading to activation of MAP kinases (JNK, p38 MAPK) and NF-κB[21,22]. The MyD88-independent pathway also mediates the immune response *via* TRIF and TRAF3, leading to recruitment of IKKε/TBK1, phosphorylation of IRF3, and expression of interferon-β[23,24]. A recent study also indicated that the HMGB1-TLR4 pathway could activate Nod-like receptor protein 3 (NLRP3) inflammasome and then enhanced the production of IL-1β[25]. For the HMGB1-RAGE pathway, the downstream signaling is propagated by the Akt, MAPK, ERK, JAK-STAT1, and Rac pathways, ultimately promoting the activation of NF-κB and expression of the proinflammatory cytokines and chemokines, which contributes in the immune cells' maturation and migration and surface receptors' expression[26,27]. Fully reduced HMGB1 (fr-HMGB1), which is a kind of three redox states (fr-HMGB1, disulfide HMGB1, and sulfonyl HMGB1), can act as a chemoattractant through connections with RAGE [28]. Furthermore, binding with C-X-C motif chemokine receptor 4, promotes chemotactic activity

(stimulates leukocyte recruitment)[29]. It should be noted that such inflammation activation can lead to inflammatory responses and cell injury and death, which promotes the further release of HMGB1 and upgrade of its receptors[30]. This may contribute to the aggravation and drug-resistance of HMGB1 related disease[15].

More recently, neuroinflammation has been proposed to play a significant role in several diseases including depression, epilepsy, stroke, traumatic brain injury, Parkinson's disease, and Alzheimer's disease[11-15]. HMGB1 is considered as an essential neuroinflammatory facilitator, which is released by glial cells and neurons upon inflammasome activation and acts as a pro-inflammatory cytokine[15]. Neurons are considered as a primary and necessary driver of neuroinflammation through release of HMGB1, with the subsequent amplification *via* recruitment of immunocompetent cells, including microglia and astrocytes[31]. HMGB1 has been proved that it releases from neurons in many central nervous system (CNS) diseases and then triggeres neuroinflammation as an upstream inflammatory mediator[15,32]. Activated by HMGB1, microglia functions as key contributor of the inflammatory processes sequentially influences neural cells, following by the activation of microglial NF-κB pathway and production of pro-inflammatory cytokines[33]. The study of Gao *et al*[34] using a Parkinson's disease model revealed that HMGB1 released from inflamed microglia and/or degenerating neurons, bound to microglial Mac1 and activated NF-κB pathway and nicotinamide adenine dinucleotide phosphate oxidase to stimulate production of multiple inflammatory and neurotoxic factors. Astrocytes are also a population of CNS cells with distinctive morphology and functions. Xiao *et al*[35] suggested that HMGB1 promoted the release of sonic hedgehog from astrocytes through signal pathway JNK, p38 and stat3 mediated by receptor RAGE in an animal model of multiple sclerosis, suggesting the important role of HMGB1-astrocytes medicated neuroinflammation. Also, some types of reactive astrocytes can also be induced by activated neuroinflammatory microglia and take parts in various human neurodegenerative diseases, formulating a complex immune network[36].

Depression is also found to closely link with neuroinflammation, which is mainly characterized by the increased mediators of inflammation and neurodegeneration[37]. Depressed patients have been found to have higher levels of proinflammatory cytokines, acute phase proteins, chemokines and cellular adhesion molecules, including IL-1β, IL-6, TNF-α and CRP[38,39]. Preclinical study based on animals also exhibited the activation of microglia together with enhanced inflammatory mediators. In a chronic mild stress (CMS) mouse model of depression, NLRP3-inflammasome/caspase-1/IL-1β axis microglia-mediated neuroinflammation was found being activated[40]. Another study suggested rats exposed to CMS exhibited a significant increase in inflammatory mediators, including TNF-α and IL-1β, activation of NF-κB signaling pathway in the hippocampus. Icariin, a flavonoid inhibiting neuroinflammation, could negatively regulated the activation of the NLRP3 inflammasome/caspase-1/IL-1β[41]. Chronic treatment with corticosterone and intraperitoneally administration of lipopolysaccharide depressed models also showed a higher expression level of pro-inflammatory phenotype characterized by IL-1β, IL-6, TNF-α and IκB-α[42,43]. These findings provide a powerful connection of neuroinflammation and depression.

Concerning HMGB1 medicates depression, recent studies suggested that HMGB1 might be a probable inducer of stress-mediated neuroinflammation in depression[11]. It has been proven that HMGB1 could activate neuroinflammatory reactions by inducing TNF-α to exhibit anhedonia-like behavior[44]. Based on the inescapable tail shock rats' model, Weber *et al*[45] indicated that HMGB1 in the brain is a probable inducer of stress-mediated microglial priming by acting on the NLRP3 inflammasome and pro-inflammatory cytokines. Based on recent studies, stress-mediated depression-like behaviors were found to be induced by HMGB1 and glycogen synthase kinase-3 dependent TLR4 signaling, resulting in the activation of NF-κB and NLRP3 inflammasome; and the HMGB1 was additionally promoted in mice[46]. This stress-induced neuroinflammation can further make it more susceptible to depression[47]. Based on rats' chronic unpredictable stress (CUS)-induced behavioral deficits, Franklin *et al*[48] discovered that CUS caused consistent upregulation of HMGB1 mRNA and RAGE mRNA in hippocampal microglia. They also found that HMGB1 infusion into the hippocampus caused anhedonic behavior and suggested that HMGB1-RAGE increased vulnerability to depressive-like behaviors long[10,48]. In addition, HMGB1 could also induce depressive behaviors by limiting the kynurenine pathway *via* suppression of activated enzymes[37]. Furthermore, based on preclinical studies, neuroinflammation induced by HMGB1 can mediate depressive behaviors such as reduction of locomotor activity and sucrose preference, which are analogs to the motivational deficits in depression [49,50].

### *HMGB1: a potential therapeutic target in depression*

Current studies proposed that interventions in the HMGB1 and related molecular in its neuroinflammation pathways have the potential to be a therapeutic target in several diseases like depression, epilepsy, cancers, stroke, and other local and systemic neuroinflammatory diseases[4,13,15]. The main potential therapeutic targets include anti-HMGB1 monoclonal antibody (mAb), HMGB1 inhibitors, and HMGB1 receptors and its related molecular in neuroinflammation pathway[15].

For depression, although several studies provided evidence on mediating HMGB1, this topic is still needing more effort. Traditionally commonly used anti-depression drugs based on the theory of serotonin-like selective serotonin reuptake inhibitors (SSRIs) as well as serotonin and norepinephrine

reuptake inhibitors may be complicated to treat motivational deficits symptoms, suggesting additional neurotransmitters like dopamine dysfunction might be involved[51,52]. Also, recent studies suggested the anti-inflammatory and anti-oxidative effects may be one of the potential mechanisms of these anti-depression drugs[53]. Only limited studies are based on animal models concerning the therapeutic target of HMGB1 in anti-depression. Liu *et al*[50] and Fu *et al*[54] indicated that the anti-depressive-like behavior compound Hesperidin and Baicalin reduced the CUS-induced model by inhibition of neuroinflammatory actions *via* HMGB1-TLR4-NF-κB pathway or HMGB1-RAGE-NF-κB pathway. The anti-HMGB1 mAb is highly specific for HMGB1, which shows the value of target validation but also has potential for the treatment of neuroinflammation diseases, including depression[14]. Hisaoka-Nakashima *et al*[55] used the model of partial sciatic nerve ligation to introduce neuropathic pain and anxiodepressive-like behaviors in mice. They observed increased HMGB1 and microglia activation in the frontal cortex. Anti-HMGB1 mAb and glycyrrhizic acid (HMGB1 inhibitor) can reduce microglia activation and anxiodepressive-like behavior[55]. HMGB1 inhibitors can be another possible anti-HMGB1 strategy. Based on the CUS-induced model both *in vivo* and *in vitro*, glycyrrhizic acid, the inhibitor of HMGB1, may restrain HMGB1 thus improving depressive-like behaviors through regulating the kynurenine pathway[47,56]. Encouragingly, a recent clinical trial found that depressive symptoms are relieved more in SSRI+ glycyrrhizic acid than SSRI+ placebo, proving anti-inflammatory agents is effective in clinical use[57]. The HMGB1 receptors and their related molecular in neuroinflammation pathway can also be a therapeutic target. Cheng *et al*[46] based on an inescapable tail shock model suggested that TLR4 knockout mice were resistant to learned helplessness and GSK3 (a TLR4 signaling dependent kinase) inhibitor TDZD-8 reduced the stress-induced increases of hippocampal cytokines and chemokines.

### *HMGB1: summarize of HMGB1 in depression*

Based on current studies, HMGB1 may be a possible signaling inducer of stress-mediated depression behaviors *via* HMGB1-TLRs signaling and HMGB1-RAGE signaling, followed by the activation of NF-κB and expression of the proinflammatory cytokines and chemokines, resulting in the neuroinflammation procedure[10]. This pathway suggests a possible mechanistic direction for depression. HMGB1 can also be a potential therapeutic target in depression by playing an important role in neurotransmitter-related anti-depression drugs, anti-HMGB1 mAb, HMGB1 inhibitors, and HMGB1 receptors[11]. However, there are still many challenges in further exploring HMGB1 as a potential mechanistic and therapeutic direction. The mechanistic illustration of HMGB1 in depression is provided as Figure 1.

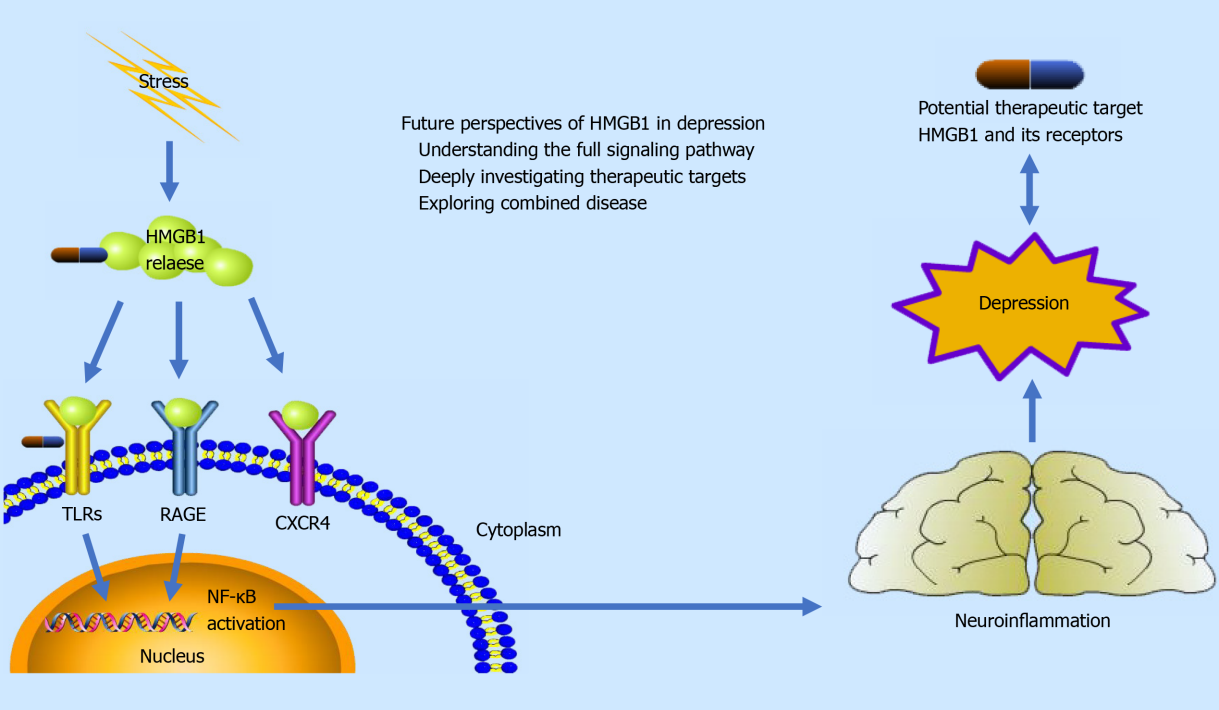
## PERSPECTIVES OF HMGB1 IN DEPRESSION

### *Focus on the complete signal pathway mechanism*

As a multifunctional protein, HMGB1 has been extensively researched. Encouragingly, cell stresses and plenty of disease processes are found related to this important inflammation facilitator[58]. HMGB1 needs to translate from nuclei to the cytoplasm and eventually release to the extracellular milieu for its inflammatory function[16]. Thus, location and translocation are the keys to function[59]. The potential mechanism of HMGB1 translocation, however, is still not clear and requires further exploration in depression. Furthermore, most current studies only focus on the release of HMGB1 in neuroglial cells (especially neuroimmune cells), which requires more studies on the role of other neuronal cells[11]. Another potential perspective is about HMGB1 receptors. The different functions, distribution, and potential relationship among various HMGB1 receptors emerge as a research focus in inflammation[60,61]. For depression, the mechanism of neurotransmitters and neuroinflammation may make this question more interesting and meaningful[53,62]. It has to be admitted that only limited studies explored some parts of the HMGB1 as a mechanism in depression. There still is a long way to understand the full signaling pathway of HMGB1 and the complete mechanism of depression introduced by the neuroinflammation.

### *A potential therapeutic target needs more evidence*

Although several studies indicated potential therapeutic targets as neurotransmitter-related anti-depression drugs, anti-HMGB1 mAb, HMGB1 inhibitors, and HMGB1 receptors, current researches are far from enough to provide evidence for potential therapy or clinical application[11]. The potential anti-inflammatory mechanisms and collaboration of neurotransmitter-related anti-depression drugs might be a clinically translational direction[53]. Furthermore, some anti-inflammatory and antiapoptotic compounds [such as (–)-Epigallocatechin-3-gallate and different microRNAs] can inhibit the HMGB1-NF-κB signaling pathway, which showed great potential in therapy of other HMGB1 related diseases [15]. These may also show effects in depression, which deserves further researches. The future need of the research is to deeply investigate potential HMGB1 related therapeutic targets using different animal models[63]. The ultimate goal is for contribution to human clinical applications, while the clinical study on glycyrrhizic acid (HMGB1 inhibitor) as an adjunctive treatment for depression is a meaningful attempt[57].




**DOI:** 10.5498/wjp.v12.i6.779 **Copyright** ©The Author(s) 2022.

**Figure 1 Illustration of mechanistic and therapeutic perspective of high mobility group box 1 in depression.** HMGB1: High mobility group box 1; TLRs: Toll-like receptors; RAGE: Receptors for advanced glycation end products; CXCR4: C-X-C motif chemokine receptor 4.

### *Combined disease: a future perspective*

It is commonly observed in clinical practice that depression may combine with other diseases, such as epilepsy, stroke, and heart disease[64-66]. HMGB1 is found widely participating in different inflammation-related diseases on the nervous system, circulatory system, and others[13]. Thus, HMGB1 may be at the crossroads of depression and other combined diseases. These diseases may have consistent or similar pathogenesis as HMGB1 and response to the same therapeutic target on HMGB1. The researches and discussion of HMGB1 as a potential common mechanistic and therapeutic direction in depression and combined inflammation-related disease may be meaningful and beneficial. Figure 1 shows an illustration of mechanistic and therapeutic perspective of HMGB1 in depression.

## CONCLUSION

Neuroinflammation activation plays an important role in the pathophysiology of depression. Playing an important role in neuroinflammation activation, HMGB1 may be a possible signaling inducer of depression. HMGB1 can also be a potential therapeutic target in depression by playing an important role in neurotransmitter-related anti-depression drugs, anti-HMGB1 mAb, HMGB1 inhibitors, and HMGB1 receptors. However, there are still many challenges in further exploring HMGB1 as a potential mechanistic and therapeutic direction. The future perspectives of HMGB1 in depression are understanding the full signaling pathway of HMGB1 in depression, deeply investigating potential HMGB1 related therapeutic targets, and exploring the role of HMGB1 in depression and combined disease.

## FOOTNOTES

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# Generalized structural equation modeling: Symptom heterogeneity in attention-deficit/hyperactivity disorder leading to poor treatment efficacy

Ruu-Fen Tzang, Yue-Cune Chang

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## Abstract

### *BACKGROUND*

Treatment efficacy for attention-deficit/hyperactivity disorder (ADHD) is reported to be poor, possibly due to heterogeneity of ADHD symptoms. Little is known about poor treatment efficacy owing to ADHD heterogeneity.

### *AIM*

To use generalized structural equation modeling (GSEM) to show how the heterogeneous nature of hyperactivity/impulsivity (H/I) symptoms in ADHD, irritable oppositional defiant disorder (ODD), and the presentation of aggression in children interferes with treatment responses in ADHD.

### *METHODS*

A total of 231 children and adolescents completed ADHD inattention and H/I tests. ODD scores from the Swanson, Nolan, and Pelham, version IV scale were obtained. The child behavior checklist (CBCL) and parent's satisfaction questionnaire were completed. The relationships were analyzed by GSEM.

### *RESULTS*

GSEM revealed that the chance of ADHD remission was lower in children with a combination of H/I symptoms of ADHD, ODD symptoms, and childhood aggressive behavior. ODD directly mediated ADHD symptom severity. The chance of reaching remission based on H/I symptoms of ADHD was reduced by

13.494% [= exp (2.602)] in children with comorbid ADHD and ODD [odds ratio (OR) = 2.602, 95% confidence interval (CI): 1.832-3.373, $P$ = 0.000] after adjusting for the effects of other factors. Childhood aggression mediated ODD symptom severity. The chance of reaching remission based on ODD symptoms was lowered by 11.000% [= 1 - exp (-0.117)] in children with more severe baseline symptoms of aggression based on the CBCL score at study entry [OR = -0.117, 95%CI: (-0.190)-(-0.044), $P$ = 0.002].

*CONCLUSION*

Mediation through ODD symptoms and aggression may influence treatment effects in ADHD after adjusting for the effects of baseline ADHD symptom severity. More attention could be directed to the early recognition of risks leading to ineffective ADHD treatment, *e.g.*, symptoms of ODD and the presentation of aggressive or delinquent behaviors and thought problems in children with ADHD.

**Key Words:** Attention-deficit/hyperactivity disorder; Oppositional defiant disorder; Aggression; Remission; Generalized structural equation modeling

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**Core Tip:** It is important to understand the factors that influence treatment outcomes for those with attention-deficit/hyperactivity disorder (ADHD). This generalized structural equation modeling pathway analysis studied heterogeneity in ADHD. We found that higher irritable oppositional defiant disorder (ODD) symptom levels mediated the treatment outcomes in children with ADHD. Treating children with ADHD is not only a matter of treating inattentive symptoms alone. Earlier recognition of risky hyperactivity/impulsivity ADHD symptoms + irritable ODD + childhood aggression as a particular subgroup and earlier provision of a more intensive combination of pharmacotherapy and cognitive behavior therapy modalities are essential.

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## INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder among children and adolescents, with a high prevalence ranging from 5.00% to 12.76%[1], and definitely needs early treatment. Although we know quite well the importance of early treatment of ADHD, approximately 25% to 30% of treated ADHD patients remain nonresponsive to treatment[2]. ADHD is a heterogeneous disorder in clinical presentation. The heterogeneity of ADHD in terms of clinical symptom profiles in children with co-occurring ADHD and oppositional defiant disorder (ODD) involves differentially higher levels of behavioral and emotional difficulties. ADHD comorbid with ODD is common and presents clinically in more than half of children with ADHD[3].

Another commonly seen clinical phenomenon is childhood aggression, which plays an essential role in the heterogeneity of ADHD. Clinically, childhood aggression commonly co-occurs in children with ADHD and ODD. As a result, these combinations of ADHD and other symptom comorbidities might further increase the highest levels of behavioral and emotional difficulties in children[4,5]. Furthermore, the treatment efficacy for ADHD in children with the commonly seen irritable subtype of ADHD presenting with childhood aggression remains ineffective. Indeed, many parents seek help from mental health experts due to irritability in children with ADHD, but they do not obtain proper treatment efficacy owing to undertreated emotional dysregulation problems associated with ADHD[6].

### *Prior studies*

In the real world, up to 80% of children with ADHD report an irritable subtype of ADHD[7]; here, we examined the heterogeneity of ADHD comorbid with ODD and aggression. As we reviewed studies on ODD, comorbidities between ADHD and ODD in children ranged from at least 40.6% to 60.0%[8,9]. Children with ADHD comorbid with ODD may have inattentive or hyperactivity/impulsivity (H/I) symptoms of ADHD and frequently have temper tantrums, excessive arguments with family, and uncooperative, deliberately annoying, or mean and spiteful behavior when younger[10], but the ODD

comorbidity problems in children with ADHD remain underdiagnosed[11]. The more irritable ODD symptoms noticed in children with ADHD, the more increased the risk of behavioral and emotional difficulties in these children with ADHD[12,13]. Clinically, there is more parental concern about this irritable mood associated with ADHD than inattentive symptoms of ADHD. Thus, ODD symptoms in ADHD may play mediating roles that impede treatment effects for ADHD, but little is known about these associations.

Additionally, when seeing the heterogeneity of ADHD from a childhood aggression perspective, child aggression is commonly seen in children with ADHD comorbid with ODD who have increased symptoms of irritable emotional difficulties associated with ODD[14-16]. Recently, childhood aggressive behavior was found to be closely associated with symptoms of ODD[17]. However, there is a gap in the study of childhood aggression in children with irritable ADHD because ODD commonly coexists with conduct disorder (CD)[18]. An earlier study focused more on childhood CD comorbid with ADHD. We know that any kind of childhood aggression may be a small part of the symptomatology of CD. However, in the real world, children with CD are not generally noticed in the clinic as more likely to have any kind of aggressive behavior. For example, the presentation of any kind of aggressive behavior was noticed to be as high as in 58% of preschool children[19]. A higher proportion of children with ADHD will present aggressiveness without meeting the full diagnostic criteria for CD[3]. Therefore, ODD plus aggression in children can be a bad predictor for children's future criminal behavior, social problems, and internalizing problems[20]. There is a lack of studies examining heterogeneity across symptom dimensions of ADHD + ODD + aggression. Here, we suggest that current child ADHD expertise should use updated latent class and factor analysis to account for all related levels of heterogeneity in ADHD.

### *Goal of this study*

To provide an evidence-based understanding of the heterogeneity of ADHD to optimally reflect real-world variation among children with ADHD, multiple symptoms should be simultaneously evaluated. Structural equation modeling (SEM) is necessary to show the theoretical relationships among symptom heterogeneity in ADHD and poor treatment outcomes with quite different implications. Because treatment responses are usually expressed as binary data (yes/no), the traditional SEM method is not appropriate to explore the pathway of how ODD and aggression interfere with treatment efficacy for ADHD. A new pathway analysis, called generalized SEM (GSEM), can use more normally distributed observed variables by adding the logistic regression model into the SEM (StataCorp., 2013). By using GSEM pathway analysis, we can fit logistic, probit, poisson, multinomial logistic, ordered logit, ordered probit, and other models. In other words, the observed variables used in GSEM can be continuous, binary, countable, categorical, and ordered variables. GSEM can detail the pathways by which ODD mutually increases the symptom severity of ADHD (expressed by inattentive and H/I symptoms) and problematic aggressiveness. Furthermore, using GSEM pathway analysis can be a good way to detail how ODD and aggressive behavior possibly interfere with the treatment efficacy for ADHD due to their interacting joint influence on ADHD symptom severity[21].

In this study, we hypothesized that when children and adolescents with ADHD and ODD also present with any kind of aggression, treatment efficacy is poor. Regarding inattention, H/I, and ODD symptom severity and any kind of aggression at study entry, it is expected that all these risks may affect the pathways influencing treatment efficacy for ADHD. Indirectly, we hypothesized that ODD with various aggressive symptoms in children might play a mediating role in treatment efficacy for ADHD.

We used GSEM to test the hypothesis that ODD is essentially an intermediate mediator of treatment effectiveness for ADHD (in terms of odds of reaching remission or the chance of remission) by direct and indirect pathway analysis. We hope that mental health professionals can regard the combination of ODD and aggression in children with ADHD as a warning risk for difficulty achieving remission in treating the ADHD and taking earlier steps to properly manage the symptoms of ODD and the presentation of any kind of aggressive behavior.

## MATERIALS AND METHODS

### *Participants and data collection*

Patients for this study were children recruited from the outpatient unit of Mackay Memorial Hospital, a major medical center in Taipei, Taiwan. The hospital's institutional review board approved the design of the study (Institutional Review Board No: MMH-I-S-489; name of project: Exploring the symptomatology on children with internet addiction and attention deficit hyperactivity disorder and their parent). After receiving a complete description of the study, potential participants (children and their parents) provided written informed consent in line with the institutional review board's guidelines. A total of 231 children (mean age ± standard deviation = 10.17 ± 2.59) with a clinical diagnosis of ADHD based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) were enrolled in this study. An experienced child and adolescent psychiatrist confirmed the clinical diagnosis of ADHD based on the DSM-IV criteria.

### Measurements

**ADHD and ODD symptoms:** The primary measures in this study reflected the core symptoms of ADHD (18 items) and ODD (8 items) as defined in the DSM-IV and included the inattention subscale, H/I subscale, and the ODD subscale of the Swanson, Nolan, and Pelham, version IV scale (SNAP-IV) [22]. Each item was scored by severity based on a 4-point scale (0-3 points, where 0: Not at all, 1: Just a little, 2: Quite a bit, and 3: Very much). The intraclass correlation coefficients for the three subscales of the Chinese-language SNAP-IV (SNAP-IV-C) ranged from 0.59 to 0.72 for the parent form and from 0.60 to 0.84 for the teacher form. All subscales of both the parent and teacher forms showed excellent internal consistency with Cronbach's α greater than 0.88[23].

**Remission rate measurements:** The remission criteria on the SNAP were defined as 0 (no) or equal to 1 (yes) for each of the symptoms or a total score that was < 9 (not at all-0 or just a little-1 for the ADHD symptoms) on the SNAP after treatment. More specifically, a patient was in remission with regard to inattention, hyperactivity, and ODD if after 6 wk of treatment, the three subscales of the SNAP-IV were ≤ 9, ≤ 9, and ≤ 8, respectively. Parents and investigators rated ADHD symptoms using the SNAP-IV-C at every follow-up session to measure remission after treatment.

**Aggressive behavior:** The child behavior checklist (CBCL) was designed to determine competencies and behavioral problems of children aged 4-18 years. The questionnaires, completed by the parents, contain 118 items to assess specific behavioral and emotional problems. The CBCL was translated into Chinese *via* a two-stage translation process[24]. The internal consistency and 1-mo test-retest reliability (all α values and reliabilities > 0.6, except for thought problems) of the Chinese version were satisfactory for Taiwanese patients[25]. The present study analyzed the following 6 scales: Aggressive behaviors (tpagbeh), attention problems (tpattpr), anxiety/depression (tpandep), social problems (tpsocpr), delinquent behaviors (tpdebeh), and somatic complaints (tpsoma).

**Caregiver satisfaction:** To assess the medication adherence of children with ADHD, parents/caregivers completed the caregiver's satisfaction form, which included the frequency of adverse events and the mean dose of methylphenidate (MPH), to understand the noncompliance risk. Parent/caregiver satisfaction with the current ADHD treatment was measured on a 5-point Likert scale as follows: (1) Completely dissatisfied; (2) Somewhat dissatisfied; (3) Neutral; (4) Somewhat satisfied; and (5) Completely satisfied. The only treatment was MPH (long- or short-acting formulations).

### Statistical analyses

In this study, we wanted to simultaneously explore the potential relationships among the remission odds (based on inattention, H/I, and ODD symptoms) and the aforementioned measurements. We used a typical multiple-indicators and multiple-causes model. The GSEM method was used to include the logistic regression model in the SEM first with Stata 13 for Windows to test the mediation model that specified the relationships between inattention, H/I, and ODD symptom severity, any kind of aggression, and remission (StataCorp., 2013). First, we used multiple logistic regression models using GSEM notations to understand the odds of remission based on each measure. The goodness-of-fit indices in this part were *P* values of the fitted coefficients, deviance, and McFadden's pseudo $R^2$. The second part was the (combined) mediation model, which combined those three multiple logistic regression models in the first part presented by GSEM notations. All statistical analyses were performed using STATA v.13.0 (StataCorp., 2013). Statistical significance was defined as a $P < 0.05$.

## RESULTS

Overall, 231 eligible patients with ADHD were enrolled. In terms of patient characteristics, 158 ADHD patients had a combined subtype (68.7%). The comorbidity rate was 73.0%. The remission rates with regard to inattention, H/I, and ODD symptoms were 30.7%, 53.7%, and 49.4%, respectively (Table 1).

As shown in Table 2, the results of the logistic regression showed that the chance of reaching remission based on inattentive symptoms of ADHD was significantly reduced by 22.7% [= 1 - exp (-0.258)] in those with more severe inattentive symptoms [odds ratio (OR) = -0.258, 95% confidence interval (CI): (-0.350)-(-0.167), $P < 0.001$] after adjusting for the effects of other factors. This means that the more severe the inattention problem at study entry, the poorer the ADHD treatment response. The chance of reaching remission was significantly reduced by 10.6% [= 1 - exp (-0.112)] in those with higher baseline CBCL aggression scores [OR = -0.112, 95%CI: (-0.186)-(-0.038), $P = 0.003$] after adjusting for the effects of other factors. The results of deviance, D (226) = 214.144 ($P = 0.704$), and McFadden's pseudo $R^2$ = 0.2485 indicated a very good model fit (Table 2, Figure 1).

Similarly, as shown in Table 3, the chance of reaching remission based on H/I symptoms of ADHD was significantly reduced by 9.7% [= 1 - exp (-0.102)] for each increase in the baseline CBCL aggression score [OR = -0.102, 95%CI: (-0.170)-(-0.073), $P = 0.004$) after adjusting for the effects of other factors. Moreover, for each increase in the parental satisfaction level, the chance of reaching remission based on H/I symptoms was significantly increased by 57.4% [= exp (0.579) – 1]. The results of goodness-of-fit

**Table 1 Sample characteristics and means and standard deviations of study measures**

| Characteristics | *N* | Mean, *n* (%) | SD |
|---|---|---|---|
| Age | 231 | 10.17 | 2.59 |
| Male (%) | 231 | 175 (75.8) | |
| Comorbidity | | | |
| Yes | 230 | 168 (73.0) | |
| No | 230 | 62 (27.0) | |
| Subtype | | | |
| Combined | 230 | 158 (68.7) | |
| Inattentive | 230 | 72 (31.3) | |
| Education | | | |
| Elementary school | 228 | 171 (75.0) | |
| Junior high school | 228 | 54 (23.7) | |
| Senior high school | 228 | 3 (1.3) | |
| ADHD | | | |
| Inattention | 231 | 17.19 | 4.50 |
| Hyperactivity | 231 | 12.43 | 6.46 |
| Disruptive child symptom | | | |
| Oppositional defiant disorder | 231 | 12.25 | 5.82 |
| Aggression | 231 | 13.32 | 7.23 |
| Remission | | | |
| Inattention | 231 | 71 (30.7) | |
| Hyperactivity | 231 | 124 (53.7) | |
| Disruptive child symptom | | | |
| Oppositional defiant disorder | 231 | 114 (49.4) | |
| SCL | | | |
| Somatization | 231 | 4.53 | 6.19 |
| Obsessive compulsive | 231 | 5.68 | 5.53 |
| Interpersonal sensitivity | 231 | 3.31 | 4.10 |
| Depression | 231 | 5.11 | 6.08 |
| Anxiety | 231 | 2.54 | 3.43 |

SCL: Symptom check list; ADHD: Attention-deficit/hyperactivity disorder; SD: Standard deviation.

indices, namely, deviance and McFadden's pseudo $R^2$, were D (224) = 242.862 ($P$ = 0.184) and pseudo $R^2$ = 0.2386, respectively, which indicated a very good model fit. The corresponding multiple logistic regression model presented by GSEM is shown in Figure 2.

The chance of reaching remission based on ODD symptoms decreased by 11.0% [= 1 - exp (-0.117)] with each increase in the baseline CBCL aggression score [OR = -0.117, 95%CI: (-0.190)-(-0.044), $P$ = 0.002] (Table 4). Again, the deviance and McFadden's pseudo $R^2$, D (226) = 255.740 ($P$ = 0.085) and pseudo $R^2$ = 0.2013, indicated that the model fit was good. The corresponding multiple logistic regression model of remission based on ODD symptoms presented by GSEM is shown in Figure 3.

Regarding the combined (mediation) model (Table 5), we first noted that the chance of reaching remission based on H/I ADHD symptoms was reduced by 13.494% [= exp (2.602)] in the children with ODD (OR = 2.602, 95%CI: 1.832-3.373, $P$ = 0.000) after adjusting for the effects of other factors. Moreover, the chance of reaching remission based on inattention ADHD symptoms was reduced by 29.785% [= exp (3.394)] in children with H/I ADHD symptoms (OR = 3.394, 95%CI: 1.862-4.927, $P$ = 0.000) and reduced by 5.094% [= exp (1.628)] in children with ODD symptoms (OR = 1.628, 95%CI: 0.600-2.656, $P$ = 0.002) after adjusting for the effects of other factors. The chance of reaching remission based on ODD

**Table 2 Results of the multiple logistic regression model in pathway to the remission of inattention of attention-deficit/hyperactivity disorder**

| | Coef | SE | *z* | *P* value | 95%CI |
|---|---|---|---|---|---|
| Remission I | | | | | |
| ADHD-I B | -0.258 | 0.047 | -5.53 | < 0.001 | (-0.350)-(-0.167) |
| Aggression_B | -0.112 | 0.038 | -2.96 | 0.003 | (-0.186)-(-0.038) |
| Delinquent B | 0.112 | 0.038 | 2.96 | 0.003 | 0.038-0.186 |
| Satisfaction | 0.402 | 0.147 | 2.74 | 0.006 | 0.114-0.689 |
| _cons | 3.065 | 0.834 | 3.68 | < 0.001 | 1.431-4.699 |

Pseudo-$R^2$ statistics assessed the predictive strength of the logistic regression model. The deviance and McFadden's pseudo $R^2$ were D (226) = 214.144 ($P$ = 0.704), pseudo $R^2$ = 0.2487, respectively. Remission I: Remission status of inattention; ADHD-I B: Attention-deficit/hyperactivity disorder baseline inattention; Aggression_B: Baseline aggressive behaviors; Delinquent B: Baseline delinquent behaviors; CI: Confidence interval; Coef: Coefficient; SE: Standard error.

**Table 3 Results of the multiple logistic regression model in pathway to the remission of hyperactivity/impulsivity of attention-deficit/hyperactivity disorder**

| | Coef | SE | *z* | *P* value | 95%CI |
|---|---|---|---|---|---|
| Remission H/I | | | | | |
| ADHD-H/I B | -0.132 | 0.030 | -4.39 | < 0.001 | (-0.191)-(-0.073) |
| Aggression_B | -0.102 | 0.035 | -2.92 | 0.004 | (-0.170)-(-0.033) |
| Anx/dep B | 0.075 | 0.046 | 1.64 | 0.101 | (-0.015)-0.164 |
| Social pro. B | -0.177 | 0.076 | -2.34 | 0.019 | (-0.325)-(-0.029) |
| Thought pro. B | 0.204 | 0.070 | 2.92 | 0.004 | 0.067-0.340 |
| Satisfaction | 0.579 | 0.133 | 4.34 | < 0.001 | 0.317-0.840 |
| _cons | 1.743 | 0.518 | 3.36 | 0.001 | 0.727-2.759 |

Pseudo-$R^2$ statistics assessed the predictive strength of the logistic regression model. The deviance and McFadden's pseudo $R^2$ were D (224) = 242.862 ($P$ = 0.184), pseudo $R^2$ = 0.2386, respectively, which indicated that the model fit was good. Remission H/I: Remission status of hyperactivity/impulsivity of attention-deficit/hyperactivity disorder; ADHD-H/I B: Attention-deficit/hyperactivity disorder baseline hyperactivity/impulsivity of attention-deficit/hyperactivity disorder; Aggression_B: Baseline aggressive behaviors; Anx/dep B: Baseline anxiety/depression; Social pro. B: Baseline social problems; Thought pro. B: Baseline thought problem; CI: Confidence interval; Coef: Coefficient; SE: Standard error.

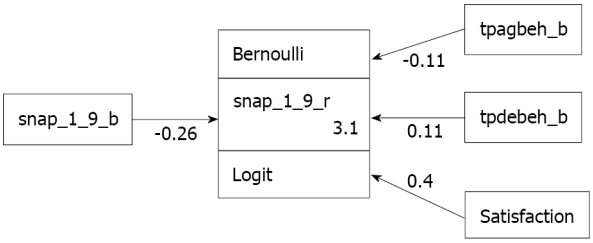


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**Figure 1 Results of the multiple logistic regression model of remission of inattention of attention-deficit/hyperactivity disorder presented by generalized structural equation modeling.** snap_1_9_b: Inattentive of attention-deficit/hyperactivity disorder baseline; snap _1_9_r: Inattentive of attention-deficit/hyperactivity disorder remission; tpagbeh_b: Aggressive behavior baseline; tpdebeh_b: Delinquent behavior baseline.

symptoms was lowered by 11.000% [= 1 - exp (-0.117)] in children with more severe baseline symptoms of aggression in the CBCL scores at study entry [OR = -0.117, 95%CI: (-0.190)-(-0.044), $P$ = 0.002]. The corresponding combined (mediation) model presented by GSEM is shown in Figure 4.

**Table 4 Results of the multiple logistic regression model in pathway to the remission of oppositional defiant disorder**

| | Coef | SE | *z* | *P* value | 95%CI |
|---|---|---|---|---|---|
| Remission ODD | | | | | |
| ODD B | -0.130 | 0.033 | -3.97 | < 0.001 | (-0.195)-(-0.066) |
| Aggression B | -0.117 | 0.037 | -3.15 | 0.002 | (-0.190)-(-0.044) |
| Delinquent B | 0.117 | 0.037 | 3.15 | 0.002 | 0.044-0.190 |
| Satisfaction | 0.505 | 0.127 | 3.98 | < 0.001 | 0.256-0.754 |
| _cons | 1.453 | 0.516 | 2.82 | 0.005 | 0.442-2.464 |

Pseudo-$R^2$ statistics assessed the predictive strength of the logistic regression model. The deviance and McFadden's pseudo $R^2$ were D (226) = 255.740 ($P$ = 0.085) and pseudo $R^2$ = 0.2013, respectively, which indicated that the model fit was good. Remission ODD: Remission status of oppositional defiant disorder; ODD B: Baseline oppositional defiant disorder; Aggression_B: Baseline aggressive behaviors; Delinquent B: Baseline delinquent behaviors; CI: Confidence interval; Coef: Coefficient; SE: Standard error.

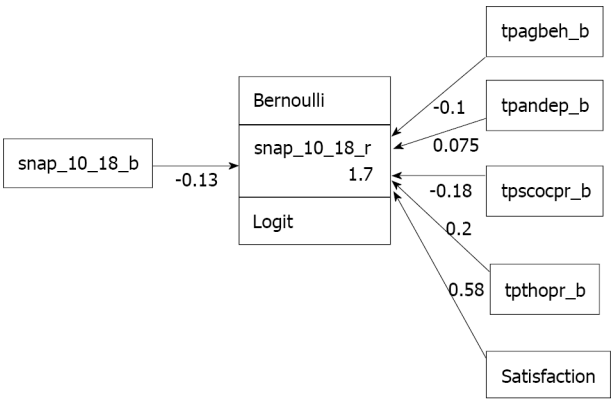


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**Figure 2 Results of the multiple logistic regression model of remission of hyperactivity/impulsivity of attention-deficit/hyperactivity disorder presented by generalized structural equation modeling.** Snap_10_18_b: Hyperactivity/impulsivity of attention-deficit/hyperactivity disorder baseline; snap_10_18_r: Hyperactivity/impulsivity of attention-deficit/hyperactivity disorder remission; tpagbeh_b: Aggressive behavior baseline; tpdebeh_b: Delinquent behavior baseline; tpscocpr_b: Social problem baseline; tpthorpr_b: Thought problem baseline.

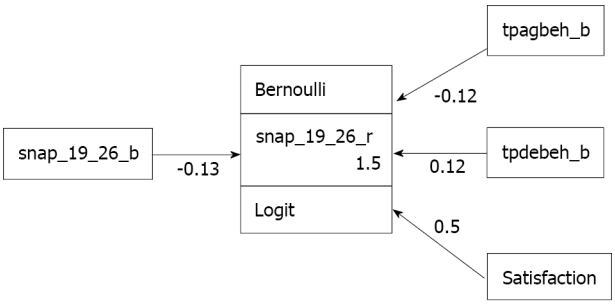


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**Figure 3 Results of the multiple logistic regression model of remission of oppositional defiant disorder presented by generalized structural equation modeling.** snap_19_26_b: Oppositional defiant disorder baseline; snap_19_26_r: Oppositional defiant disorder remission; tpagbeh_b: Aggressive behavior baseline; tpdebeh_b: Delinquent behavior baseline.

## DISCUSSION

This study examined the structure of ADHD symptoms in child adolescent samples using GSEM. This GSEM pathway analysis first supported that poor treatment outcomes in ADHD can be predicted as irritable ODD subtype of ADHD with aggressive behavior. This pathway analysis indicated higher ODD symptom levels mediated treatment outcomes for ADHD through enhancing inattentive and H/I

**Table 5 Results of the combined (mediation) model presented by the generalized structural equation modeling**

| | Coef | SE | z | *P* value | 95%CI |
|---|---|---|---|---|---|
| Remission I | | | | | |
| Remission H/I | 3.394 | 0.782 | 4.340 | 0.000 | 1.862-4.927 |
| Remission ODD | 1.628 | 0.524 | 3.100 | 0.002 | 0.600-2.656 |
| ADHD-I B | -0.234 | 0.058 | -4.050 | 0.000 | (-0.348)-(-0.121) |
| Aggression_B | -0.019 | 0.043 | -0.440 | 0.661 | (-0.104)-0.066 |
| Delinquent_B | 0.019 | 0.043 | 0.440 | 0.660 | -0.066-0.104 |
| Satisfaction | 0.216 | 0.173 | 1.250 | 0.212 | (-0.124)-0.556 |
| _cons | -1.433 | 1.196 | -1.200 | 0.231 | (-3.777)-0.910 |
| Remission H/I | | | | | |
| Remission ODD | 2.602 | 0.393 | 6.620 | 0.000 | 1.832-3.373 |
| ADHD-H/I B | -0.148 | 0.036 | -4.150 | 0.000 | (-0.218)-(-0.078) |
| Aggression_B | -0.050 | 0.039 | -1.270 | 0.205 | (-0.127)-0.027 |
| Anx/dep B | 0.093 | 0.054 | 1.710 | 0.087 | (-0.014)-0.200 |
| Social pro. B | -0.203 | 0.086 | -2.380 | 0.017 | (-0.371)-(-0.036) |
| Thought pro. B | 0.160 | 0.078 | 2.050 | 0.040 | 0.007-0.313 |
| Satisfaction | 0.431 | 0.153 | 2.810 | 0.005 | 0.130-0.731 |
| _cons | 0.567 | 0.607 | 0.930 | 0.350 | (-0.622)-1.756 |
| Remission ODD | | | | | |
| ODD B | -0.130 | 0.033 | -3.970 | 0.000 | (-0.195)-(-0.066) |
| Aggression_B | -0.117 | 0.037 | -3.150 | 0.002 | (-0.190)-(-0.044) |
| Delinquent B | 0.117 | 0.037 | 3.150 | 0.002 | 0.044-0.190 |
| Satisfaction | 0.505 | 0.127 | 3.980 | 0.000 | 0.256-0.754 |
| _cons | 1.453 | 0.516 | 2.820 | 0.005 | 0.442-2.464 |

Remission I: Remission status of inattention; ADHD-I B: Baseline inattention; Aggression_B: Baseline aggressive behaviors; Delinquent B: Baseline delinquent behaviors; Remission H/I: Remission status of hyperactivity/impulsivity of attention-deficit/hyperactivity disorder; ADHD-H/I B: Baseline hyperactivity/impulsivity of attention-deficit/hyperactivity disorder; Anx/dep B: Baseline anxiety/depression; Social pro. B: Baseline social problems; Thought pro. B: Baseline thought problem; Remission ODD: Remission status of oppositional defiant disorder; ODD B: Baseline oppositional defiant disorder; CI: Confidence interval; Coef: Coefficient; SE: Standard error.

symptoms. Treating children with ADHD is not only a matter of treating inattentive symptoms alone, but there is also a need to recognize and manage symptoms of ODD and the presented aggressive behavior, delinquent behavior, and thought problems in children with ADHD to improve ADHD treatment outcomes.

### *Comparison with prior work*

Hinshaw *et al*[26] suggested that only detailed pathway analysis can further assist clinicians in understanding the internal joint relationships among aggressive behavior, symptoms of ODD, and symptom severity of ADHD. Such pathway analysis might remind clinicians to recognize earlier risky irritable symptoms of ADHD + ODD + childhood aggression as a special subgroup and provide more effective therapeutic treatment modalities earlier.

Aggression in children and adolescents with irritable ADHD is a serious clinical and public health problem. Especially in the recent internet age, many children and adolescents present inattentive symptoms, externalizing behavior, or risk-taking behavior after excessive use of the internet[27,28]. We know that this unrecognized aggression in early childhood becomes more aggressive or violent behavior later in these irritable children[5,29]. Alternatively, the results of this study indicated that children with the irritable ODD subtype of ADHD characterized by symptoms of irritable ODD and aggressive behavior is harder to treat well. However, previous studies have focused more on conduct behavior (CD)[30,31] instead of any kind of aggression in children with ODD, which warrants more attention. Therefore, the implication of this study is that we suggest using a CBCL scale to identify

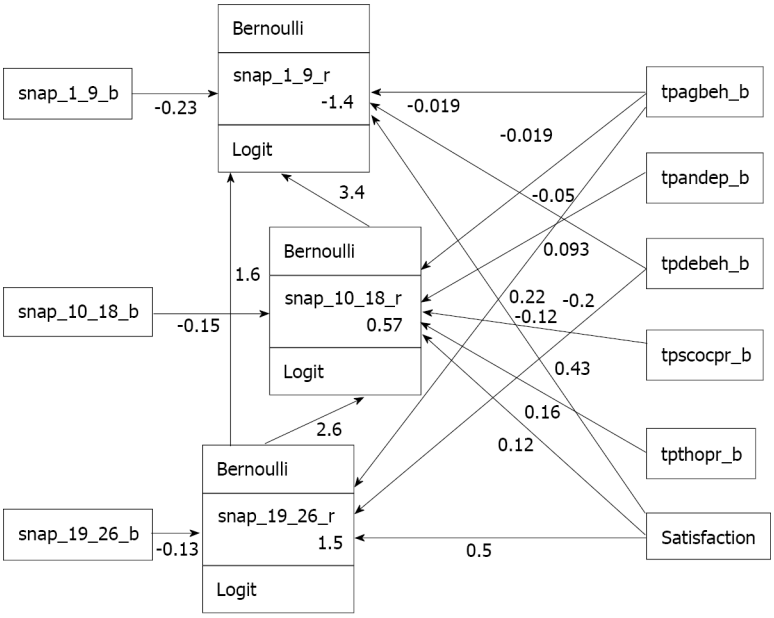


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**Figure 4 Results of the combined (mediation) model presented by generalized structural equation modeling.** snap_1_9_b: Inattentive of attention-deficit/hyperactivity disorder (ADHD) baseline; snap _1_9_r: Inattentive of ADHD remission; snap_10_18_b: Hyperactivity/impulsivity of ADHD baseline; snap_10_18 r: Hyperactivity/impulsivity of ADHD remission; snap_19_26_b: Oppositional defiant disorder baseline; snap_19_26_r: Oppositional defiant disorder remission; tpagbeh_b: Aggressive behavior baseline; tpdebeh_b: Delinquent behavior baseline; tpscocpr_b: Social problem baseline; tpthorpr_b: Thought problem baseline.

aggressive children and adolescents in child and adolescent clinics or internet gaming disorder clinics in the future. The presented aggressive behavior we derived from CBCL included relational aggression (argues a lot, bragging, boasting, demands much attention), disobedience at home, disobedience at school, easily jealous, screams a lot, showing off or clowning, stubborn, sullen or irritable, sudden changes in mood or feelings, talks too much, teases a lot, temper tantrums or hot temper, direct aggression (cruelty, bullying or meanness to others, destroys his or her own things, destroys things belonging to his or her family or others), and gets in many fights (physically attacks people, threatens other people), which can all be regarded as early recognition of any kind of aggression in children with ADHD and ODD. Earlier and effective treatment inventions for children with particular heterogeneous subtypes of ADHD should be provided by ADHD experts in these days with digital technology.

In the present study, the GSEM results found that ADHD symptom severity was determined by the joint effects between ODD, aggression, and delinquent behavior symptoms. With the under recognition and undertreatment of ODD and aggression in children with ADHD, there is always a significant risk that predicts poor treatment efficacy. Here, we suggest that children and psychiatrists should record a more extensive history of oppositional symptoms because one previous study indicated that there was an underdiagnosed ODD comorbidity problem in children with ADHD[11]. The treatment effects on ODD depend on how the underlying comorbid ADHD is treated. Usually, the core symptoms of ODD are not amenable to pharmacotherapy alone[32]. For children with ADHD with ODD, treatments with only pharmacotherapy for inattention alone always remains noneffective for these ODD symptoms[33,34]. The use of nonstimulant drugs such as atomoxetine was recently noticed to be effective in treating ODD symptoms in children with ADHD[35,36]. However, for children with ADHD with severe ODD and behavioral symptoms, there is still a need to use pharmacotherapy with stimulants (MPH), mood stabilizers such as sodium valproate (Depakin), and antipsychotics such as risperidone with concurrent behavioral therapy[37].

Cognitive behavior psychotherapy in children with ADHD is also essential to regulate emotion regulation circuitry by reducing reactive aggression[38]. Essentially, clinicians should provide effective combined pharmacotherapies with additional effective behavioral modification interventions, parenting programs, and cognitive behavioral therapy to improve treatment outcomes in this particular group of children with ADHD.

Based on the pathway analysis, both ODD and aggressive symptoms interacted as joint effects to exacerbate ADHD symptom severity, as a previous study had noticed[15,16]. We revealed the insight that aggression during childhood rarely occurs alone and is closely correlated with other symptoms of childhood psychopathology. Both ODD symptoms and aggression are important influences on the efficacy of ADHD treatment[39]. Clinicians should consider additional assessments to detect dimensional behavioral symptoms such as childhood aggressive or destructive behaviors to further provide effective treatment modalities to achieve remission of ADHD[40].

Regarding the childhood H/I symptoms of ADHD, previous findings showed that hyperactive ADHD symptoms had a role in predicting children becoming more socially immature, aggressive, and peer rejected[41]. Additionally, one recent meta-analysis indicated more severe symptoms of H/I, and children with ADHD were less likely to obtain better treatment outcomes[42]. In this GSEM, we found that childhood H/I symptoms resulted in a greater risk of increasing the inattention symptom severity, leading to subsequent poor treatment outcomes for ADHD. ODD symptoms and the presentation of aggressive behavior mediated an increase in inattentive and H/I symptom severity of ADHD. Nevertheless, children and adolescents need more attention regarding the diagnosing and managing of H/I symptoms of ADHD. ODD, aggression, and H/I symptoms of ADHD interactively increased the symptom severity of ADHD.

A previous study indicated that the coexistence of a diagnosis of ODD/CD, learning difficulties, anxiety, younger age, family dysfunction, and socioeconomic adversity were all risk factors for predicting poor treatment efficacy for ADHD[43]. This pathway analysis further focused on children with ADHD with ODD, and aggression led to poor treatment outcomes. ADHD is a heterogeneous disorder with complicated emotional and impulsivity deficits. From the Research Domain Criteria perspective, ADHD patients have deficits in the domains of cognition (specifically in working memory) and positive valence (in rewarding anticipation/delay/receipt)[44]. Emotional dysregulation defects may be highly associated with abnormal reward processing systems[45]. Therefore, for children with ADHD presenting symptoms of irritable ODD and aggression, our pathway analysis suggests that the children may have deficits in both cognition and reward domains. Thus, the children with symptoms of ADHD + ODD + aggression should be a clinically distinct emotional irritability subgroup, and clinicians should provide more specific treatment guidelines for these children with ADHD. Future DSM systems need to regard ODD as an essential risk for poor treatment effects for ADHD.

### *Limitations*

This study has the following limitations. First, the construction of the subscale of the SNAP and CBCL, without a direct interview with the parents, seems to be arbitrary. Additionally, the fact that most of the scale is provided by a main caregiver, mainly mothers and teachers, may lead to sampling bias. Another limitation is the cross-sectional design of the study, which may not necessarily represent the longitudinal relationships among ADHD, ODD, aggression, and remission rate. As the main purpose of this study was to explore the association among disruptive symptoms in children and remission rates, aggression scores from the CBCL were used to represent disruptive child behaviors instead of CD measures. This was a naturalistic observational study performed in Taiwan. Most patients from the outpatient department at that time received psychopharmacologic treatment, including short-term or long-acting MPH, or long-acting drugs such as atomoxetine rather than parenting behavior therapy. However, the thrust of this study was to predict poor treatment efficacy in the children with co-occurring ADHD, ODD, and aggressive symptoms by special GSEM statistical analysis. Therefore, we did not show the detailed treatment response after different kinds of drugs or other psychosocial interventions. Finally, the definitions of direct, indirect, and total effects in SEM have not yet been established in the GSEM. Although three out of four requirements for the mediation model were satisfied in our GSEM, it might not be appropriate to call the results in Figure 4 a mediation model. Here, we only borrowed the concept and spirit of the mediation model to emphasize the relationships among remissions based on ODD, H/I, and inattention symptoms for treating children with ADHD.

## CONCLUSION

Despite these limitations, to the best of our knowledge, this is the first study to determine mediators in reaching remission of ADHD. ODD is a categorical diagnosis, and aggressive behavior is a dimensional problem. Such interactive categorical and dimensional information provides an added dimension in the understanding of the etiology of heterogenicity of ADHD. This pathway study revealed additional insights into devising more efficacious pharmacotherapies and cognitive behavior therapies. Clinicians should regard ADHD + ODD + aggression comorbidity as a distinct entity that needs an early and combined intensive biopsychosocial model approach, as recent research demonstrated[46]. Future longitudinal and systemic research is needed to validate this as a potential obstacle, with the ODD symptoms dynamically interacting with childhood aggressive behavior symptoms.

### *Clinical significance*

GSEM pathway analysis was used to demonstrate that disruptive childhood symptoms, including categorical diagnoses such as ODD and dimensional problems such as aggressive symptoms before treatment, apparently lower the remission rate for those with ADHD. This paper suggests that clinicians should directly examine the joint effects of ADHD, ODD, and aggression to assess the risk for poor treatment outcomes. An early and more intensive combined biopsychosocial model approach for ADHD should be warranted for these children.

## ARTICLE HIGHLIGHTS

### *Research background*

Many parents seek help from mental health experts due to irritability in children with attention-deficit/hyperactivity disorder (ADHD). But treatment efficacy for irritable and aggressive ADHD in children remains ineffective. Therefore, the heterogeneity to ADHD treatment should be proposed by a specific mathematical method.

### *Research motivation*

Treating children with ADHD is not only a matter of treating inattentive symptoms alone. It is important to understand the factors that influence treatment outcomes for those with ADHD.

### *Research objectives*

This study used the generalized structural equation modeling (GSEM) pathway analysis to analyze heterogeneity in ADHD.

### *Research methods*

We used the GSEM to test the hypothesis that ODD is essentially an intermediate mediator of treatment effectiveness for ADHD (in terms of odds of reaching remission or the chance of remission) by direct and indirect pathway analysis.

### *Research results*

Higher irritable oppositional defiant disorder (ODD) symptom levels mediated the treatment outcomes in children with ADHD. Earlier recognition of risky hyperactivity/impulsivity ADHD symptoms + irritable ODD + childhood aggression as a particular subgroup and earlier provision of a more intensive combination of pharmacotherapy and cognitive behavior therapy modalities are essential.

### *Research conclusions*

Treating children with ADHD is not only a matter of treating inattentive symptoms alone, but there is also a need to recognize and manage symptoms of ODD and the presented aggressive behavior, delinquent behavior, and thought problems in children with ADHD to improve ADHD treatment outcomes.

### *Research perspectives*

Poor treatment outcomes in ADHD can be predicted as irritable ODD subtype of ADHD with aggressive behavior. An early and more intensive combined biopsychosocial model approach for ADHD should be warranted for these children. This study revealed additional insights into devising more efficacious pharmacotherapies and cognitive behavior therapies.

## FOOTNOTES

**Author contributions:** Tzang RF and Chang YC designed the study and wrote the protocol; Chang YC undertook the statistical analysis; and all authors contributed to and approved the final manuscript.

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ORIGINAL ARTICLE

Clinical Trials Study

# Randomized trial estimating effects of hypnosis *versus* progressive muscle relaxation on medical students' test anxiety and attentional bias

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## Abstract

### *BACKGROUND*

Test anxiety is prevalent among medical students and leads to impaired academic performance. Test-related attentional bias has been identified as an important maintaining factor in test-anxious individuals.

### *AIM*

To evaluate whether hypnosis and progressive muscle relaxation (PMR) could modify medical college students' test anxiety and attentional bias.

### *METHODS*

A total of 598 medical students were screened. The participants were divided into higher and lower test anxiety groups according to their scores on the test anxiety scale (TAS). Ninety medical college students with high TAS score were randomly assigned to a hypnosis or PMR group. Another 45 students with low TAS score

were included, forming a baseline control group. The intervention was conducted weekly for 6 wk, and each session lasted approximately 30 min. The total intervention time and the number of intervention sessions for the hypnosis and PMR groups were equal. Data were collected at the pretest, posttest, and 2-mo follow-up.

***RESULTS***

Hypnosis group participants had a significantly lower TAS score at posttest ($t$ = -21.827, $P$ < 0.001) and at follow-up ($t$ = -14.824, $P$ < 0.001), compared to that at pretest. PMR group participants also had a significantly lower TAS score at posttest ($t$ = -10.777, $P$ < 0.001) and at follow-up ($t$ = -7.444, $P$ < 0.001), compared to that at pretest. At the posttest level, the hypnosis group had a significantly lower TAS score than the PMR group ($t$ = -3.664, $P$ < 0.001). At the follow-up level, the hypnosis group also had a significantly lower TAS score than the PMR group ($t$ = -2.943, $P$ = 0.004). Clinically significant improvement was found in both the hypnosis and PMR groups (hypnosis = 64.0%; PMR = 62.22%). Hypnosis was more effective than PMR in reducing test anxiety among medical college students. Hypnosis could modify attentional bias toward threatening stimuli, but PMR could not.

***CONCLUSION***

These results suggest that attentional bias plays an important role in test anxiety treatment.

**Key Words:** Test anxiety; Hypnosis; Progressive muscle relaxation; Attentional bias; Randomized controlled trial

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**Core Tip:** We wanted to explore whether hypnosis and progressive muscle relaxation (PMR) could modify medical college students' test anxiety and related attentional bias toward threatening stimuli. We found that hypnosis was more effective than PMR in reducing test anxiety in medical students, and hypnosis could modify attentional bias toward threatening stimuli, but PMR could not. These results suggest that attentional bias plays an important role in the treatment of test anxiety.

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## INTRODUCTION

Medical education has always been regarded by students as a high-pressure environment[1], and the incidence rate of test anxiety among medical students is 25%-56%[2]. Research has demonstrated a series of adverse effects associated with test anxiety, such as impaired academic achievement and mental health problems[3,4]. Test anxiety comprises two interdependent factors: Emotionality (or physiology) and worry (or cognition)[5,6]. Emotionality, or physiology, involves awareness of physiological arousal associated with test situations: Increased heart rate, perspiration, muscle tension, and blood pressure[7]. Worry, or cognition, is a psychological phenomenon related to the overwhelming distress associated with testing situations[8].

There are different interventions for test anxiety that target either emotionality or cognition. For instance, progressive muscle relaxation (PMR) is a common behavioral approach to easing physiological reactivity to test situations. PMR targets emotionality/physiology rather than worry/cognition[9]. Several studies have suggested that PMR effectively reduces test anxiety in students[9,10]. Cognitive methods, on the other hand, aim at reducing the psychological detriments of test anxiety[11]. A recent study provided evidence for the utility of integrating integrated imagery work with cognitive-behavioral therapy for treating test anxiety[12]. Recently, a meta-analysis of the efficacy of interventions for test-anxious university students found that although interventions were superior to control conditions in reducing test anxiety, overall confidence should be tempered. The authors concluded that other psychological interventions for test anxiety are needed in future studies[13].

Hypnosis is "a state of consciousness involving focused attention and reduced peripheral awareness characterized by an enhanced capacity for response to suggestion"[14]. There are different types of

hypnosis, *i.e.*, waking or active-alert[15]. The present study employed the traditional definition of hypnosis. Hypnosis is a rapid and cost-effective intervention for anxiety and anxiety-related disorders [16]. During a hypnotic induction phase, a state of relaxation can be induced by maintaining eye fixation, following suggestions of calmness, closing the eyes, and imagery. A core component of hypnosis seems to involve facilitating a state of focused attention in a suggested direction that supports emotional well-being[17]. We therefore proposed that both the relaxation and cognitive components of hypnosis can make it effective in reducing test anxiety.

Attentional bias is believed to be associated with the onset and maintenance of anxiety[18]. Its effect is that anxious individuals tend to direct their attention toward and maintain attentional focus on threat-related stimuli, at the expense of attending to other more critical stimuli in the environment[19]. The same is true for test anxiety; highly test-anxious individuals demonstrate an attentional bias to threat and test-related information[20,21]. Recent research has shown that experimentally manipulating attentional bias away from a threat is effective for the individuals preparing for an exam[22]. Hypnosis also can treat individuals with test anxiety by modifying their attentional bias *via* hypnotic suggestion. For example, the participants received hypnotic suggestions to remain calm and relaxed when they received information related to the exam or got to the situation related to the exam. Further, they could no longer fixate their attention on the information. That is, they could no longer have attentional bias toward the information.

According to attention theory, visual memory is closely related to attentional bias[23], and attentional bias may reflect facilitated orienting of attention to negative information or slowed attentional disengagement from negative information[24]. Although various experimental paradigms have been used to evaluate attentional bias, most of them have not been able to differentiate its two mechanisms [9]. A recently-developed odd-one-out visual search task seems to have uncovered the specific processes underlying attentional bias[25]. In this paradigm, participants were presented with a matrix of stimuli and asked whether the matrix included one stimulus from a different category. The anxious participants demonstrated speeded detection of and slowed disengagement from the threatening stimuli[25].

Attentional bias may be considered an essential target in treating test anxiety. This study was designed as a pilot randomized clinical trial comparing the effects of hypnosis to PMR for test anxiety and the associated attentional bias. The hypnosis developed by this study was intended to target the two components of test anxiety: Emotionality/physiology and worry/cognition, while the PMR targeted only emotionality/physiology. PMR involves the voluntary stretching and relaxing of large muscle groups[26]. We hypothesized that both hypnosis and PMR would reduce anxiety symptoms. Yet, only hypnosis participants demonstrated a significant change in attentional bias to test-related stimuli, compared with those receiving PMR. To the best of our knowledge, this study is the first to use hypnosis to help individuals reduce test anxiety and attentional bias toward threatening stimuli. This is also the first study to use PMR to reduce attentional bias in students, although several studies have found that PMR effectively reduces test anxiety[10,27].

## MATERIALS AND METHODS

### Participants

The study was conducted at Anhui Medical University in China. The participants were college students. A total of 598 medical students were screened. The participants were divided into higher and lower test anxiety groups according to their scores on the test anxiety scale (TAS)[28]. The inclusion criteria were: Participants with a TAS score higher than 20 formed a high-anxiety group ($n$ = 102), while participants with a score lower than 12 formed a low-anxiety group ($n$ = 62). Twelve participants in the high-anxiety group refused to participate in the study. The remaining 90 participants were randomly assigned to either a hypnosis group or a PMR group, with 45 students in each group. Forty-five of 62 participants with low test anxiety scores were randomly selected for baseline comparisons (control group). The purpose of using the baseline control group was to explore whether the highly test-anxious individuals in both the hypnosis and PMR groups showed an attentional bias to test-related information at the pretest, compared to the participants with low test anxiety. Randomization was performed by the project leader using a computer-generated random list of numbers. Randomization information was sealed in sequentially numbered boxes that were identical in appearance.

The exclusion criteria were: The therapist (the first author) conducted a semi-structured interview to ensure that none of the participants had a history of psychiatric or neurological disease, medication use, or chronic illness, or a current major psychiatric disorder. The study was approved by Anhui Medical University's Human Ethics Committee (Trial Registration: ChiCTR1900025058). All participants provided written informed consent and were paid 180 Chinese Yuan for participating in the study. Participants, therapists, and independent evaluators were blinded to the study arm.

### Design

There were two groups with high test anxiety in this study: The hypnosis group and the PMR group. The low-test anxiety group served as a baseline control group. This was a randomized clinical trial in

which two treatment conditions (hypnosis and PMR) were compared with a baseline condition at a ratio of 1:1:1. A series of face-to-face assessments were performed at pretest and posttest, and a follow-up at 2 mo after the intervention (mailed responses). Given that group interventions on test anxiety reduction produced more significant effects than individual interventions[11], group interventions were conducted for the purposes of this study. Data was collected between February 2018 and May 2019.

### Intervention and therapists

The intervention sessions took place in a quiet classroom in the university. The intervention was conducted weekly for 6 wk, and each session lasted approximately 30 min. The total intervention time and number of intervention sessions for the hypnosis and PMR groups were equal.

**Hypnosis group:** An experienced hypnosis therapist conducted the hypnosis. Using a standard hypnotic induction procedure, the students were induced into a hypnotic state[29]. This procedure took approximately 15 min. The participants were then given hypnotic suggestions of mild to high test anxiety exposure, with imagery. In the meantime, the participants were given suggestions of relaxation and pleasant experiences. Suggestions were also made to change the participants' cognition and attention on the test (see more details in Supplementary material).

**PMR group:** The participants in the PMR group received PMR training with the guidance of a relaxation therapist. The procedure was initially developed by Jacobson[30] and was standardized by Bernstein and Borkovec[31]. Although several studies have attempted to combine PMR with guided imagery to expose patients to specific positive thoughts[32], this study utilized the PMR procedure based on Jacobson[30]'s theory and technique. The PMR technique mainly involved standardized and validated methods[31,33]. During the PMR exercises, the participants deliberately applied tension to specific muscle groups and then released it. The tension-relaxation response started with the hands, moved through the whole body, and ended with the feet.

**Control group:** Those with low TAS scores, who were included for baseline comparisons, received no intervention. Group hypnosis and group PMR were performed by a hypnosis specialist (Li XM) and a PMR therapist (Zhang Y). These individuals' mean duration of practice in psychiatry was 9 years. Each therapist received 20 h of additional training specific to the requirements of the study. To ensure adherence to the treatments, the therapists followed manuals for hypnosis and PMR and completed a checklist recording the techniques used in treatments.

### Outcome measures

**Primary outcome measure:** The TAS was designed to evaluate test anxiety[34]. The scale contains 37 true-false statements on test-taking, and the total number of "true" checks represents the TAS. The interpretation of TAS scores is as follows: 0 to 12 indicates no or mild test anxiety, 13 to 20 indicates moderate test anxiety, and > 20 signifies severe test anxiety. This study made use of an adapted Chinese version of the TAS that showed sufficient and comparable reliability and validity[28].

Attentional bias was evaluated by the odd-one-out search task adapted from the procedure used by Rinck *et al*[25]. The participant was seated approximately 50 cm from a 17-inch computer screen. Each trial started with a fixation cross (500 ms) in the screen center, followed by a 2 × 2 matrix of four words. The participant was instructed to determine whether there was a target word that belonged to a different category within the matrix by pressing 'A' (yes) or 'L' (no). The matrix contained four words with the same category or three words with the same category and a target word with a different category. The matrix remained on the screen until a response was given. The words represented three categories of emotional relevance: Threatening words related to the test ($n$ = 60), positive words related to positive emotion ($n$ = 60), and neutral words such as 'furniture' and 'natural environment' ($n$ = 120). Attentional bias was assessed: Accelerated detection and slowed disengagement. Eighty trials assessed speeded detection as follows: (1) Twenty trials presented the matrix containing three neutral words and one positive word; (2) Twenty trials showed the matrix containing three neutral words and one threatening word; and (3) Forty trials presented the matrix containing four neutral words. Eighty trials assessed slowed disengagement as follows: (1) Twenty trials showed the matrix containing three positive words and one neutral word; (2) Twenty trials presented the matrix containing three threatening words and one neutral word; (3) Twenty trials showed the matrix containing four positive words; and (4) Twenty trials presented the matrix containing four threatening words.

The location of the target word in each matrix was random for each trial and each participant. All participants engaged in both sessions, and the order of the sessions was counterbalanced across the participants. We conducted a pilot study on a sample of 45 college students to validate all words with a 9-point Likert scale assessing valence and arousal levels.

**Secondary outcome measures:** The state-trait anxiety inventory (STAI) consists of two sub-scales[35]. One scale assesses the temporary condition of state anxiety, while the other scale evaluates the long-standing quality of trait anxiety. Each scale contains 20 statements rated on a 4-point Likert scale ranging from 0 (almost never) to 3 (almost always). A higher score indicates higher anxiety. We used a validated Chinese version of the STAI with satisfying reliability and validity[36].

Before the intervention, the hypnotic susceptibility of participants, regarded as a control variable, was evaluated using the Stanford Hypnotic Susceptibility Scale (SHSS), Form C[29]. The scale consists of 12 motor items. The participant receives one score if they follow the motor suggestion and produce the movement. The total score is 12, and a higher score suggests greater hypnotic susceptibility.

### Sample size estimation

The power of the sample size was calculated using G*power software. We used an independent sample *t*-test between the hypnosis and PMR groups for sample size estimation with a power of 0.90 at $P = 0.05$ using a two-sided test. Moreover, we adjusted for any drop-outs at the rate of 15% during the follow-up test, resulting in the final sample size of 135 participants.

### Data analysis

Statistical analyses were conducted using SPSS 20.0. The intention-to-treat analyses were conducted on data from all participants who completed the pretest assessments. The missing data were treated using the last observation carried forward for those who did not complete the follow-up test. First, one-way analysis of variance (ANOVA) was conducted to test baseline differences among the three groups. At the pretest, planned comparisons were conducted between higher and lower test anxiety groups and the hypnosis and PMR groups. Then, the TAS measures were subject to a two-factor mixed design with treatment conditions as the between-group and time as the repeated measure factor. Differences in the TAS measures were compared using analysis of covariance (ANCOVA) with lysergic acid diethylamide *post hoc* comparisons on the adjusted means. Third, to test potential training effects, ANCOVA was performed to compare the hypnosis and PMR groups, using posttest scores as dependent variables and the corresponding pretest scores as covariate. Finally, a reliable change index (RCI) for TAS scores from pretreatment to posttest was computed using the formula reported by Jacobson and Truax[37]. Participants with an RCI score greater than a 1.96 reduction in TAS score at posttest were regarded as having a clinically significant improvement. Effect sizes were reported as partial eta squared ($\eta_p^2$), eta squared ($\eta^2$), Cohen's *d*, or Cramer's $\varphi$. Categorical data were analyzed using $\chi^2$ tests. Significance was defined at $P = 0.05$.

## RESULTS

### Demographic characteristics of samples and baseline comparison

The enrollment of participants and the study flow are shown in Figure 1. A total of 135 participants were assigned to three groups: Hypnosis, PMR, and control groups. Characteristics of the participants are presented in Table 1. The results of ANOVA conducted on the pretest scores in TAS, STAI, and attentional bias measures are shown in Table 1. For attentional bias measures on speeded detection trials, the speeded detection score is reaction time for neutral words - reaction time for threatening stimuli or positive words. On slowed disengagement trials, the slowed disengagement score is reaction time for threatening stimuli or positive stimuli - reaction time for neutral stimuli. One-way ANOVA was significant for: TAS ($F = 1008.808$, $P < 0.001$), STAI-trait ($F = 401.431$, $P < 0.001$), STAI-state ($F = 385.483$, $P < 0.001$), speeded detection to threatening stimuli ($F = 401.431$, $P < 0.001$), speeded detection to positive stimuli ($F = 401.431$, $P < 0.001$), slowed disengagement from threatening stimuli ($F = 401.431$, $P < 0.001$), and slowed disengagement from positive stimuli ($F = 401.431$, $P < 0.001$). There were significant differences between the higher and lower test anxiety groups in the planned comparisons, while there were no significant differences between the hypnosis and PMR groups at pretest. Given that test anxiety is a situation-specific disorder[13], this study also considered when assessments were made. The three groups did not differ in the number of days until the next exam at pretest ($F = 1.786$, $P > 0.05$), posttest ($F = 2.384$, $P > 0.05$), or follow-up ($F = 2.730$, $P > 0.05$).

### Intervention effects on TAS scores

The difference in TAS scores between the two groups was analyzed using 2 (group: Hypnosis and PMR) × 3 (time: Pretest, posttest, and follow-up) repeated measures ANOVA. Significant primary effects of time ($F = 334.444$, $P < 0.001$, $\eta_p^2 = 0.792$) and group ($F = 10.619$, $P = 0.002$, $\eta_p^2 = 0.108$), and the significant interaction effect between time and group ($F = 8.869$, $P = 0.002$, $\eta_p^2 = 0.092$) were revealed.

A simple effect analysis was conducted at each level of the group variable. The results are summarized as follows: (1) For the hypnosis group, a significant effect of time was revealed ($F = 304.878$, $P < 0.001$, $\eta_p^2 = 0.874$), and the paired *t*-test suggested that the participants had a significantly lower TAS score at posttest [$t = -21.827$, $P < 0.001$, Cohen's $d = 4.111$, 95% confidence interval (CI): 10.218-12.297] and at follow-up ($t = -14.824$, $P < 0.001$, Cohen's $d = 3.108$, 95%CI: 6.567-8.632), compared with that at pretest. The participants had a significantly higher TAS score at follow-up compared with posttest [$t = 10.551$, $P < 0.001$, Cohen's $d = 1.110$, 95%CI: (-4.356)-(-2.959)]; and (2) For the PMR group, a significant effect of time was revealed ($F = 93.195$, $P < 0.001$, $\eta_p^2 = 0.679$), and the paired *t*-test suggested that the participants had a significantly lower TAS score at posttest ($t = -10.777$, $P < 0.001$, Cohen's $d = 2.067$,

**Table 1 Characteristics of the participants and baseline comparison among three groups at pre-test**

| | Control (*n* = 45) | | Hypnosis (*n* = 45) | | PMR (*n* = 45) | | Hypnosis & PMR *vs* control | | | Hypnosis *vs* PMR | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *M* | *SD* | *M* | *SD* | *M* | *SD* | *t*/$\chi^2$ | *P* value | *Cohen's d*/Cramer's φ | *t*/$\chi^2$ | *P* value | *Cohen's d*/Cramer's φ |
| Female, *n* | 17 | | 27 | | 26 | | 5.35 | 0.02 | 0.19 | 0.05 | 0.83 | 0.02 |
| Age | 20.94 | 0.94 | 20.76 | 1.05 | 20.84 | 0.85 | 0.13 | 0.90 | 0.08 | -0.44 | 0.66 | 0.08 |
| Education | 14.71 | 0.84 | 14.80 | 1.14 | 14.96 | 0.82 | -0.97 | 0.33 | 0.18 | -0.76 | 0.45 | 0.16 |
| SHSS | 8.08 | 1.92 | 7.88 | 1.80 | 7.57 | 1.45 | 1.13 | 0.26 | 0.19 | 0.91 | 0.37 | 0.18 |
| TAS score | 8.66 | 1.33 | 23.74 | 1.63 | 23.97 | 2.42 | 45.03 | < 0.001 | 8.77 | 0.53 | 0.60 | 0.11 |
| STAI score | | | | | | | | | | | | |
| Trait | 36.78 | 1.75 | 49.38 | 3.14 | 50.20 | 2.47 | 28.14 | < 0.001 | 5.51 | 1.38 | 0.17 | 0.29 |
| State | 36.06 | 1.89 | 48.34 | 2.92 | 49.14 | 2.59 | 27.59 | < 0.001 | 5.33 | 1.37 | 0.17 | 0.29 |
| Speeded detection | | | | | | | | | | | | |
| Threatening words | -6.99 | 212.68 | -381.10 | 159.76 | -397.49 | 189.92 | -10.37 | < 0.001 | 1.89 | -0.94 | 0.35 | 0.19 |
| Positive words | -403.62 | 163.41 | -219.88 | 170.82 | -226.21 | 254.62 | 4.95 | < 0.001 | 0.94 | -0.14 | 0.89 | 0.03 |
| Slowed disengagement | | | | | | | | | | | | |
| Threatening words | 111.19 | 341.38 | 379.48 | 437.92 | 431.94 | 386.65 | 4.14 | < 0.001 | 0.78 | 0.62 | 0.55 | 0.13 |
| Positive words | 100.93 | 291.41 | -173.90 | 353.80 | -113.31 | 403.44 | -3.80 | < 0.001 | 0.72 | 0.76 | 0.45 | 0.16 |

False Discovery Rate correction for multiple comparisons was applied to the *P* values.
PMR: Progressive muscle relaxation; SHSS: Stanford hypnotic susceptibility scale; STAI: State-Trait Anxiety Inventory; TAS: Test anxiety scale.

95%CI: 6.620-9.665) and at follow-up ($t$ = -7.444, $P$ < 0.001, Cohen's $d$ = 1.408, 95%CI: 3.896-6.789), compared with that at pretest. The participants had a significantly higher TAS score at follow-up compared with posttest [$t$ = 22.164, $P$ < 0.001, Cohen's $d$ = 0.572, 95%CI: (-3.055)-(-2.545)].

The simple effect analysis at each level of time variable was conducted by planned $t$-test. At the posttest level, the hypnosis group had a significantly lower TAS score than the PMR group [$t$ = -3.664, $P$ < 0.001, Cohen's $d$ = 0.772, 95%CI: (-5.156)-(-1.530)]. At the follow-up level, the hypnosis group also had a significantly lower TAS score than the PMR group [$t$ = -2.943, $P$ = 0.004, Cohen's $d$ = 0.621, 95%CI: (-4.164)-(-0.807)] (Figure 2).

### *Intervention effects in the attentional bias and STAI*

The two higher test anxiety groups were compared with regard to their post-test scores of attentional bias and STAI, including pre-test scores as covariate. The results are displayed in Table 2. On speeded

**Table 2 Analysis of covariance comparing hypnosis and progressive muscle relaxation groups in post-test scores with pre-test as covariate**

| | Hypnosis ($n$ = 45) | | PMR ($n$ = 45) | | ANCOVA | | |
|---|---|---|---|---|---|---|---|
| | *M* | *SD* | *M* | *SD* | *F* | *P* value | $\eta^2$ |
| Speeded detection | | | | | | | |
| threatening words | -346.00 | 279.88 | -91.86 | 199.57 | 30.35 | < 0.001 | 0.26 |
| Positive words | -203.59 | 299.03 | -300.54 | 242.72 | 10.03 | 0.002 | 0.10 |
| Slowed disengagement | | | | | | | |
| threatening words | 260.04 | 398.21 | 387.18 | 420.11 | 3.36 | 0.070 | 0.04 |
| Positive words | -4.78 | 369.07 | -117.22 | 372.78 | 11.46 | 0.001 | 0.12 |
| STAI scores | | | | | | | |
| State | 35.11 | 2.53 | 36.32 | 1.92 | 6.04 | 0.02 | 0.07 |
| Trait | 38.21 | 2.51 | 38.39 | 2.34 | 0.12 | 0.73 | 0.001 |

PMR: Progressive muscle relaxation; STAI: State-Trait Anxiety Inventory; ANCOVA: Analysis of covariance.

detection trials, the hypnosis group was slower in detecting threatening stimuli and faster in detecting positive words than the PMR group. On slowed disengagement trials, the hypnosis group had a faster reaction time to threatening stimuli (one-tailed $P = 0.035$) or to positive words than the PMR group.

The average posttest scores on state anxiety and trait anxiety are presented in Table 2. The table shows that the hypnosis group had a lower state anxiety score than the PMR group, while there was no significant difference in the trait anxiety scores of the two groups. Additionally, we compared the differences in attentional bias and STAI scores between pretest and posttest. For the hypnosis group, there were significant differences between pretest and posttest in speeded detection of threatening words ($t = -9.143$, $P < 0.001$, Cohen's $d = 1.600$), speeded detection of positive words ($t = 3.010$, $P = 0.004$, Cohen's $d = 0.384$), slowed disengagement from threatening words ($t = -4.444$, $P < 0.001$, Cohen's $d = 0.285$), and slowed disengagement from positive words ($t = 3.865$, $P < 0.001$, Cohen's $d = 0.468$). However, for the PMR group, there were no significant differences in any of the above scores ($P > 0.05$). For the hypnosis group, there were significant differences between pretest and posttest in trait anxiety ($t = 608.99$, $P < 0.001$, Cohen's $d = 4.815$) and in state anxiety ($t = 150.83$, $P < 0.001$, Cohen's $d = 5.491$). For the PMR group, there were significant differences between pretest and posttest in trait anxiety ($t = 42.481$, $P < 0.001$, Cohen's $d = 3.969$) and in state anxiety ($t = 27.646$, $P < 0.001$, Cohen's $d = 4.864$).

### *Clinically significant change*

The results show that 39 participants in the hypnosis group (86.67%) and 28 participants in the PMR group (62.22%) met the criteria for clinically significant change (RCI score greater than 1.96 in TAS score at posttest; $\chi^2 = 7.07$, $P = 0.008$).

## DISCUSSION

This study investigated the efficacy of hypnosis and PMR for treating individuals with test anxiety. Both treatments appeared sound and demonstrated high within-group effect size in primary outcomes of test anxiety after intervention and at 2-mo follow-up. An important finding is that hypnosis was more effective than PMR in reducing attentional bias to threatening stimuli. For the group comparisons at pretest, the highly test-anxious individuals in both the hypnosis and PMR groups showed an attentional bias to threat and test-related information, consistent with previous studies[20,21]. Moreover, the higher test anxiety groups had significantly higher trait and state anxiety than the lower test anxiety group. Previous studies have also found positive correlations between the test anxiety score and STAI[4].

Compared with the pretest, the test anxiety of participants in both the hypnosis and PMR groups significantly decreased after 6-wk intervention and at 2-mo follow-up. Our data add to evidence from previous randomized controlled trials showing that hypnosis and PMR effectively reduce test anxiety [10,27]. Notably, the hypnosis group demonstrated lower test anxiety than the PMR group at posttest and at follow-up. This finding suggests that, in the present study, hypnosis was more effective than PMR in reducing test anxiety. Furthermore, analyses exploring clinically significant change showed that 86.67% of participants in the hypnosis group and 62.22% of those in the PMR group exhibited clinically significant reductions in test anxiety from baseline to posttest. This difference in response rates was

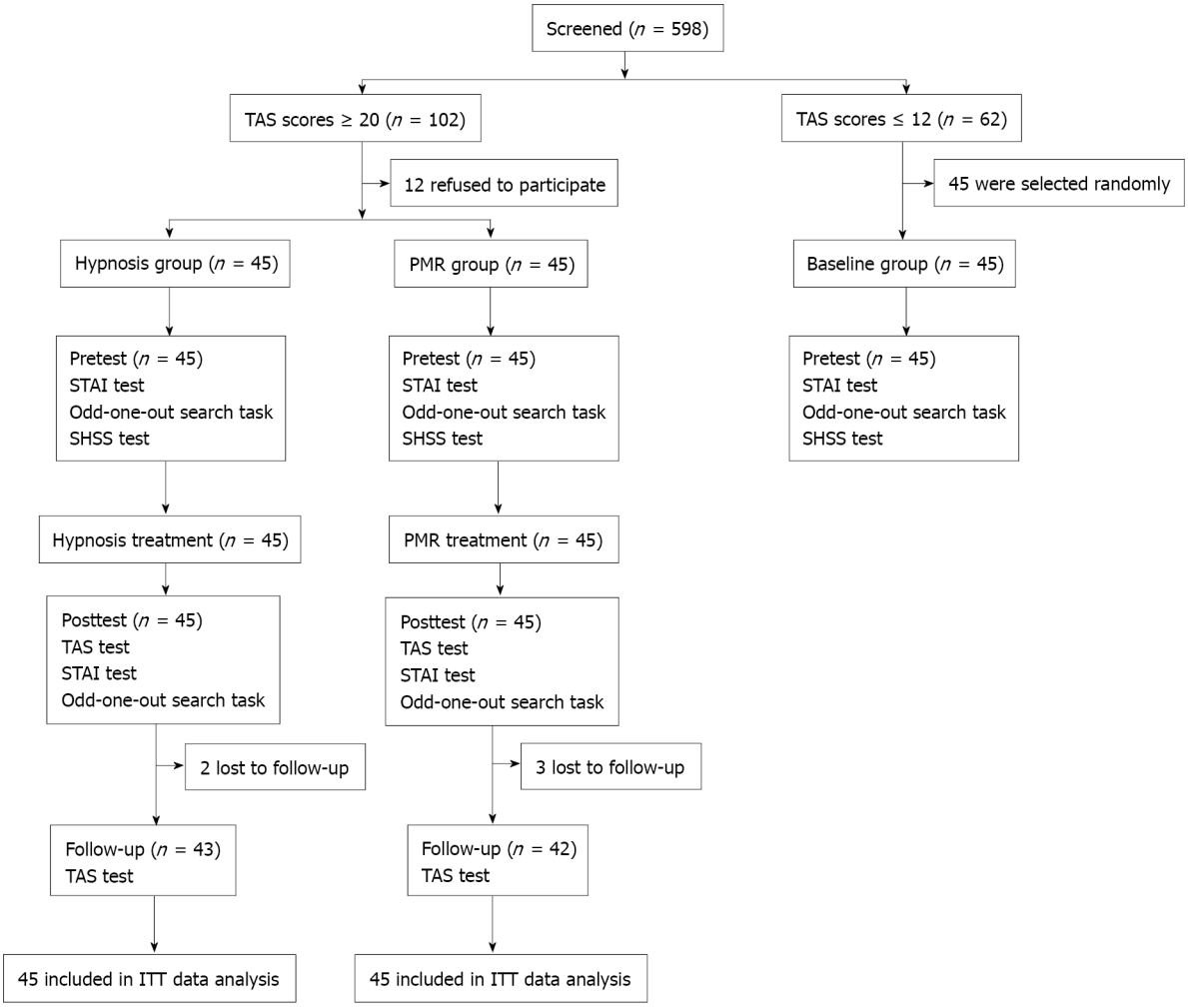


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**Figure 1 Enrollment and study flow.** PMR: Progressive muscle relaxation; TAS: Test anxiety scale; STAI: State-trait anxiety inventory; SHSS: Stanford hypnotic susceptibility scale; ITT: Intention-to-treat.

statistically significant, demonstrating that hypnosis outperformed PMR in test anxiety symptom reduction. In the hypnotic state, the participants were given suggestions of relaxation that produced positive and pleasant experiences. This method could help individuals reduce anxiety in a relaxed state and facilitate the link between anxious situations and pleasurable experiences. By establishing conditioning, individuals learn to anticipate pleasant experiences following threatening stimuli such as test situations. These findings have the important clinical implication that a combination of hypnosis and other psychotherapies would be more productive in treating anxiety disorders than hypnosis alone. Indeed, a previous study suggested that combined treatment using cognitive behavior therapy and hypnosis produces better effects than hypnosis alone[38].

Both the hypnosis and PMR groups demonstrated reduced trait anxiety and state anxiety at the posttest compared with the pretest, suggesting that test anxiety is relevant to both trait and state anxiety. Interestingly, state anxiety was reduced more in the hypnosis group than in the PMR group, while there was no significant difference in trait anxiety between the two groups at the posttest. State anxiety is unstable and specific to certain situations, which seems to make it more sensitive to training and intervention. This finding is consistent with previous studies reporting more beneficial effects from intervention on state anxiety than on trait anxiety[39].

Notably, this study investigated the attentional bias of test-anxious students by calculating two indices: Speeded detection and slowed disengagement. After the intervention, the individuals in the hypnosis group demonstrated reduced detection speed and slowed disengagement toward threatening stimuli. Significantly, the hypnosis group showed a reversed speeded detection of and delayed disengagement from positive stimuli after the intervention. Taken together, hypnosis appears to help individuals be less sensitive to threatening stimuli but more sensitive to positive stimuli, an effect more significant than PMR intervention.

These findings prove that hypnosis effectively reduced attentional bias to threatening stimuli and increased attentional bias to positive stimuli. In contrast, the PMR had little effect in lowering attentional bias to threatening stimuli. Hypnosis relies on hypnotic and posthypnotic suggestions to

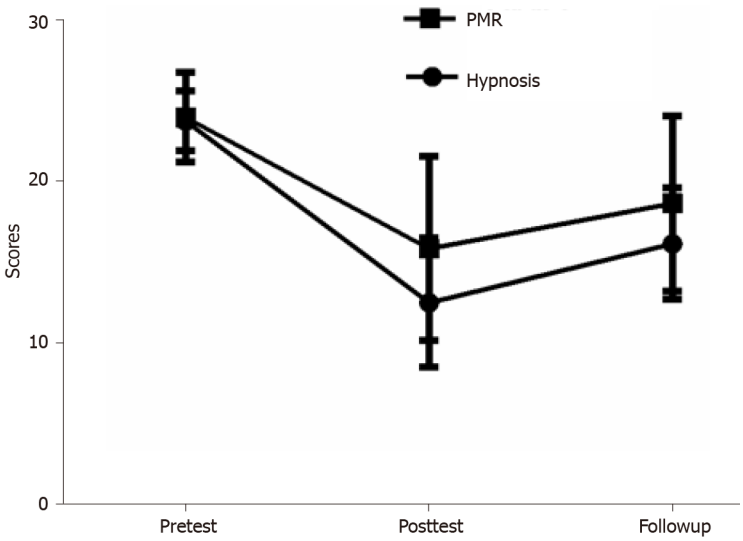


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**Figure 2 Test anxiety scores for two groups at pretest, posttest, and 2-mo follow-up test.** Error bars represent standard deviation. PMR: Progressive muscle relaxation.

modify participants' cognition and attention, whereas PMR is merely a relaxation technique that can affect the physiological and emotional components of test anxiety[5,6]. However, PMR may have little impact on cognition and attention. Two significant components of hypnosis are cognition and relaxation; combining those two components would be more effective in reducing anxiety[40].

General cognitive models of anxiety suggest that anxious individuals tend to direct their attention toward threatening information in the environment[41,42], thereby facilitating the development and maintenance of the anxious state[43]. Several studies have emphasized the vital influence of attentional bias on anxiety[44,45]. Mathews and MacLeod[46] further indicated that attentional bias has causal effects on vulnerability to anxiety. Therefore, attentional bias should be regarded as an essential target in treatment, and various training paradigms such as attentional bias modification have, in fact, been developed to target it, with promising effects in reducing test anxiety[22] and other disorders[47,48].

Our findings indicate that hypnosis, targeting both muscle relaxation and attentional bias, could decrease anxiety vulnerability to test-related stimuli and reduce attentional bias toward test-related stimuli. With hypnotic suggestions, the participants could remain calm and relaxed when facing information related to the exam, and thus they could cease fixating on the information. However, the PMR, which targeted muscle relaxation, could only change anxiety vulnerability and not attentional bias. All these suggest that it is crucial to look for an underlying mechanism as a target for prevention and treatment.

Hypnosis is not effective for everybody, because some patients respond quickly to hypnotic suggestions, while others are unaffected[49]. It appears that hypnotic susceptibility may affect the outcome, and it is an important control variable. Hypnotic susceptibility indicates proneness to accepting suggestions in and out of hypnosis[50]. Fortunately, there was no significant difference in hypnotic susceptibility among the three groups, and thus the influence of hypnotic susceptibility on the treatment can be ignored.

This study concluded that hypnosis is efficacious in treating test anxiety by reducing anxiety vulnerability and attentional bias to threatening stimuli. However, it had several limitations. First, we did not examine participants' physiological indices, such as skin conductance response, blood pressure, and heart rate. This would provide an objective measure more sensitive to the changes induced by the intervention. Moreover, a lack of physiological measures also makes it difficult to differentiate whether hypnosis did better than PMR due to better physical relaxation or attentional bias, or maybe some other factor. Second, the study did not evaluate the influence of the intervention on exam performance. Finally, we only considered a 2-mo follow-up, leaving the long-term effects of hypnosis in this context inconclusive.

## CONCLUSION

Hypnosis is more effective than PMR in reducing test anxiety in medical students; hypnosis could modify attentional bias toward threatening stimuli, but PMR could not. The reason for this may be that the hypnosis developed in this study targeted both anxiety symptoms and attentional bias, suggesting that targeting attentional bias is an important factor in treating test anxiety or other anxiety disorders.

Additionally, hypnosis integrated with some form of therapy may have enhanced effects on mental disorders.

## ARTICLE HIGHLIGHTS

### *Research background*

Test anxiety is prevalent among medical students and leads to impaired academic performance. Test-related attentional bias has been identified as an important maintaining factor in test-anxious individuals.

### *Research motivation*

The present study aimed to evaluate whether hypnosis and progressive muscle relaxation (PMR) could modify medical college students' test anxiety and attentional bias.

### *Research objectives*

This study was designed as an initial pilot randomized clinical trial comparing the effects of hypnosis to the effects of PMR on test anxiety and its associated attentional bias. This study is the first to use hypnosis to help individuals reduce test anxiety and attentional bias toward threatening stimuli, and is also the first to use PMR to reduce attentional bias in students.

### *Research methods*

A total of 598 medical students were screened. The participants were divided into higher and lower test anxiety groups according to their scores on the test anxiety scale (TAS). Ninety medical college students with high TAS scores were randomly assigned to a hypnosis or PMR group. Another 45 students with low TAS scores were included for baseline control group. The intervention was conducted weekly for 6 wk, and each session lasted approximately 30 min. The total intervention time and the number of intervention sessions were matched between the hypnosis and PMR groups. Data were collected at pretest, posttest, and 2-mo follow-up.

### *Research results*

Hypnosis group participants had a significantly lower TAS score at posttest ($t$ = -21.827, $P$ < 0.001) and at follow-up ($t$ = -14.824, $P$ < 0.001), compared with that at pretest. PMR group participants also had a significantly lower TAS score at posttest ($t$ = -10.777, $P$ < 0.001) and at follow-up ($t$ = -7.444, $P$ < 0.001), compared with that at pretest. At the posttest level, the hypnosis group had a significantly lower TAS score than the PMR group ($t$ = -3.664, $P$ < 0.001). At the follow-up level, the hypnosis group also had a significantly lower TAS score than the PMR group ($t$ = -2.943, $P$ = 0.004). Clinically significant improvement was found in both the hypnosis and PMR groups (hypnosis = 64.0%; PMR = 62.22%). Hypnosis was more effective than PMR in reducing test anxiety among medical college students. Hypnosis could modify attentional bias toward threatening stimuli, but PMR could not.

### *Research conclusions*

Hypnosis is more effective than PMR in reducing test anxiety in medical students; hypnosis could modify attentional bias toward threatening stimuli, but PMR could not. Additionally, hypnosis integrated with some form of therapy may have enhanced effects on mental disorders. Our findings have important implications for the design and optimization of hypnotic treatments for anxiety disorders.

### *Research perspectives*

This study concluded that hypnosis is efficacious in treating test anxiety by reducing anxiety vulnerability and attentional bias to threatening stimuli. The findings imply that attentional bias can be an important target in future research on treating test anxiety or other anxiety disorders.

## FOOTNOTES

**Author contributions:** Zhang Y, Yang XX, and Luo JY collected the data; Liang M, Li N, and Ma LJ undertook the statistical analysis; Tao Q modified the manuscript; Li XM designed the study and wrote the first draft of the manuscript; and all authors contributed to and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

# Composition of treatment alliance in bipolar disorder: A cross-sectional study of patients' perspectives

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## Abstract

### *BACKGROUND*

Treatment alliance has an impact on several key patient outcomes in all psychiatric disorders, including bipolar disorder (BD). It has been suggested that the construct of treatment alliance is different among patients from routine psychiatric settings compared to psychotherapeutic settings. However, research on the composition of treatment alliance in psychiatric disorders, such as BD, is relatively limited.

### *AIM*

To determine whether a broader construct of treatment alliance was prevalent among outpatients with BD.

### *METHODS*

This is a cross-sectional study, conducted in the psychiatric unit of a multi-specialty hospital in north India over 12 mo (September 2018 to September 2019). A consecutive sample of 160 remitted adult outpatients with BD on mood stabilizers for at least a year were selected. The principal instrument to assess treatment alliance was the Working Alliance Inventory-client version (WAI-Client). Other potential constituents of the alliance explored were perceived trust in clinicians assessed by the Trust in Physicians (TRIP) scale, perceived support from clinicians assessed by the Psychosocial Care by Physicians (PCP) scale, and perceived treatment satisfaction assessed by the Patient Satisfaction Questionnaire (PSQ). Associations between scores on all scales were determined by correlational and multiple regression analyses. Exploratory factor analysis of combined items of all scales was conducted using a principal components analysis.

### *RESULTS*

Scores on all the three WAI-Client subscales were significantly correlated with each other ($r$ = 0.66-0.81; $P$ < 0.0001). The total TRIP scores were associated with the total WAI-Client scores ($r$ = 0.28; $P$ < 0.01). The total TRIP scores and the total

PCP scores were also significantly associated with the WAI-Client scores on the Task subscale ($r$ = 0.28-0.29; $P < 0.01$). The total TRIP scores were significantly associated with the total PSQ scores ($r$ = 0.45; $P < 0.0001$). Factor analysis yielded two independent and coherent factors, which explained 69% of the variance in data. Factor-1 ("alliance and support"), which explained about 41% of the variance, was comprised of a combined WAI-Client goal-task-bond component as well as the PCP support items. Factor-2 ("trust and satisfaction"), which explained about 28% of the variance, consisted of all the TRIP trust and the PSQ treatment satisfaction items.

*CONCLUSION*

A broader construct of treatment alliance in BD was found. Apart from collaborative components, this construct included patients' perceptions regarding trust in clinicians, support from clinicians, and treatment satisfaction.

**Key Words:** Treatment alliance; Bipolar disorder; Composition; Factor-analysis

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**Core Tip:** Research on the composition of treatment alliance in bipolar disorder (BD) is relatively limited. This study examined its composition in 160 remitted adult outpatients with BD using four different scales. Factor analysis yielded two independent factors explaining 69% of the variance. Factor-1 comprised of a combined Working Alliance Inventory goal-task-bond component and perceived clinicians' support. Factor-2 consisted of items relating to the perceptions of trust in clinicians and satisfaction with treatment. This study suggested that in addition to collaborative components, treatment alliance among patients with BD also includes patients' perceptions of clinicians' trust, clinicians' support, and treatment satisfaction.

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## INTRODUCTION

Interest in the alliance between patients and clinicians has been gaining ground in mental health care because of its pivotal role in all aspects of psychiatric practice. Though the evidence is relatively scarce, stronger clinician-patient alliances appear to influence a variety of patient outcomes across different psychiatric disorders[1,2]. The principal benefit of an effective alliance is enhanced treatment adherence and engagement[1-5]. Other benefits for patients include reduced symptom severity, improved quality of life and functioning, favorable treatment attitudes, and greater treatment satisfaction[1-3]. The construct of treatment alliance in mainstream psychiatry has its roots in psychotherapy[1-3,6,7]. Of all the frameworks proposed, psychiatric practice in clinical settings has found Bordin's collaborative concept of working alliance the easiest one to adopt[1,2]. This model has a tripartite structure comprised of mutual agreements between clients and therapists on the goals and tasks of treatment, along with emotional bonds between them consisting of shared feelings of trust, acceptance, and confidence[8-11]. However, even this model is not readily transposed from psychotherapeutic to conventional psychiatric settings because of several discrepancies between the two treatment milieus[2-4,6,7]. These include the dissimilarities in nature, goals, and duration of treatment, the differences in types of patients, the diversities in treatment locations and professionals providing care, and the conflicts between the legal responsibilities of clinicians and their roles as therapists. Additionally, the notion of treatment alliance in psychiatry has also been influenced by other subsequent developments, such as the need for patient-centered care and shared decision-making (SDM), recovery-orientated approaches to care, and theories of clinician-patient communication[1,4,5,7,12]. This has led to proposals for enlarging the concept of treatment alliance in psychiatry by incorporating theoretical perspectives other than psychotherapeutic ones[2-4,6,7]. Focused research on the construct of alliance to determine its exact composition among patients from routine psychiatric settings has also been recommended[1,3,4,6,7]. However, despite such recommendations, research on the constituents of treatment alliance in psychiatric disorders has been limited[2,4,6,7].

Research on treatment alliance is particularly scarce for conditions such as bipolar disorder (BD) in spite of ample evidence suggesting that treatment alliance in BD has a similar impact on medication adherence and other patient outcomes[5,13-16]. This consideration prompted the current attempt at examining the composition of treatment alliance among outpatients with BD attending a hospital-based

psychiatric service. Factor analytic studies have been carried out in different groups of patients with psychiatric disorders using a variety of scales. These have shown that, particularly from the patient's perspective, collaborative aspects (task, goal, bond), trust in clinicians, cooperation, therapist support, and treatment satisfaction are the core components of the treatment alliance[17-20]. Additionally, existing studies of BD also indicate that apart from patients' views on collaboration with clinicians, their perceptions of trusting and supportive clinician-patient relationships, and their satisfaction with treatment is also associated with the strength and quality of alliances[21-25]. Thus, based on the existing evidence regarding treatment alliance, it was hypothesized that a broader construct of the alliance was more likely to exist among such patients. Therefore, in addition to collaborative aspects, other contributions to the construct of treatment alliance explored among patients of this study were perceived trust in clinicians, perceived clinicians' support, and treatment satisfaction.

## MATERIALS AND METHODS

### Participants

This was a part of a larger cross-sectional study which had examined the association of treatment alliance with medication adherence among outpatients with BD undergoing treatment at the psychiatry department of a multi-specialty hospital in north India. Sample size estimation, based on non-adherence rates of 30%, indicated that a minimum of 160 patients was required (alpha = 80%; $P < 0.05$).

Patients aged more than 18 years, with a Diagnostic and Statistical Manual of Mental Disorders-IV diagnosis of BD and on mood stabilizer treatment for at least a year before intake were selected. Patients with organic mental disorders, intellectual disabilities, acute illnesses, and potential for self-harm or violence were excluded. Patients had to be in remission during intake. Remission was defined as current scores of less than seven on the Hamilton Depression Rating Scale and less than six on the Young Mania Rating Scale. Finally, patients had to be accompanied by caregivers who were healthy adults involved in the patient's care.

Of the initial consecutive sample of 250 patients obtained over 12 mo (September 2018 to September 2019), 90 had to be excluded because they did not meet selection criteria. Thus, 160 patients formed the eventual sample of this study. The study was approved by the institutional review committees. Written informed consent was sought from the participants before inclusion and other ethical safeguards were also followed throughout the study.

### Assessments

The diagnoses were re-confirmed using the Mini International Neuropsychiatric Interview[26]. Clinical details were compiled using the Self-Rated Retrospective Life Chart Form of the National Institute of Mental Health[27]. Assessment of the collaborative components of treatment alliance was carried out using the Working Alliance Inventory-client version (WAI-Client)[8]. The WAI-Client has 36 items grouped into three subscales of goal, task, and bond, with a seven-point rating for each item. Higher scores (range 36-252) reflect more positive ratings of the alliance. Patients' perceptions of support from clinicians were assessed with the Psychosocial Care by Physicians (PCP) scale and their perceived trust in clinicians was measured with the Trust in Physicians-Short Form scale (TRIP)[28,29]. Both these scales are derived from the validated Cologne Patient Questionnaire and have a four-point item rating system. The 15-item PCP has four subscales of "Emotional Support", "Supportive Behavior" (subjective perceptions of support from physicians) "Informational Support", and "SDM". Higher scores (range 15-60) indicate greater levels of perceived support. Higher scores on the three-item TRIP (range 4-12) suggest greater levels of trust in physicians and their competence. Treatment satisfaction was examined using the Patient Satisfaction Questionnaire (PSQ)[30]. Higher scores on this four-item scale (range 0-12) denote greater satisfaction. To ensure uniformity of assessments, scale items were read out to all the patients and caregivers while eliciting their responses.

### Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences, version 23 for Windows. The nature of the distribution was ascertained by the Kolmogorov-Smirnov test. All continuous variables were normally distributed. Thus, Pearson's coefficients were used to determine the correlation between the scores on all scales and between the subscales of the WAI-Client. The Bonferroni correction was used to minimize chance associations. The significance level after the Bonferroni correction was set at 0.0003. Results from the stepwise multiple regression analyses, which were a part of the larger study were also used to determine associations between different scales. The composition of treatment alliance in BD was examined using exploratory factor analysis of items from all four scales. After the optimum number of factors was determined, a principal components analysis using orthogonal rotation with the varimax technique was conducted to determine the final factor solution. The analysis was approved by a biomedical statistician.

## RESULTS

### *Patient profiles*

The majority of the participants were middle-aged males who were married, literate, and employed, and came from rural, middle-class, nuclear families. Ratings of the course of their illness by patients and caregivers revealed indicators of favorable as well as adverse course and outcome. Though the patients had been ill for 18 years on average, they had also been on treatment for an average of 17 years. Moreover, their age of onset was relatively late, with episodes that were not frequent and were only of mild to moderate severity. At intake, the patients were in prolonged remission, with adequate insight and functioning, and low levels of residual symptoms. However, about half of them had predominantly manic episodes, episodes with psychotic symptoms, inadequate adherence, and multiple breakthrough episodes, relapses, or hospitalizations. Other indicators of poor outcome present in about 20%-30% of the patients included rapid-cycling course, comorbid physical or psychiatric disorders, and lifetime suicidal attempts. These details are included in Table 1.

### *Treatment alliance: Component scores and correlations*

The results of the treatment alliance component scores and their correlations are depicted in Table 2. The average total WAI-Client scores were high, suggesting that patients had predominantly positive views about their alliances with clinicians. Mean scores were significantly higher on the Bond subscale, followed by the Task and Goal subscales. The mean PCP scores were similarly high, indicating that patients' subjective perceptions were that their clinicians had been supportive of them. Weighted mean PCP scores were highest on the "Supportive behavior" subscale, followed by the subscales measuring emotional support, SDM, and informational support. The TRIP scores also revealed high levels of trust in the clinicians and their competence. The PSQ scores correspondingly indicated that patients were quite satisfied with the care they were receiving, including their access to clinicians and the competence displayed by them.

Scores on all the three WAI-Client subscales were significantly correlated with each other. The highest values of correlation coefficients were obtained for association between the Goal and Task subscale scores ($r = 0.81$; $P < 0.0001$), followed by the association between the Bond and Task subscale scores ($r = 0.69$; $P < 0.0001$), and the association between the Bond and Goal subscale scores ($r = 0.66$; $P < 0.0001$). The total TRIP scores were significantly associated with the total WAI-Client scores ($r = 0.28$; $P < 0.01$) and scores on the Task subscale ($r = 0.29$; $P < 0.01$). The total PCP scores were significantly associated with the WAI-Client Task subscale scores ($r = 0.28$; $P < 0.01$). The PCP-SDM subscale scores were significantly associated with the total WAI-Client scores ($r = 0.28$; $P < 0.01$) and scores on the goal subscale ($r = 0.28$; $P < 0.01$). However, the results of the stepwise multiple regression analyses (not included here) found that the PCP-SDM scores explained only about 3%-4% of the variance in the total WAI-Client and Goal subscale scores, while the TRIP scores contributed very little to the variance in the WAI-Client scores. Finally, the total TRIP scores were significantly associated with the total PSQ scores ($r = 0.45$; $P < 0.0001$).

### *Composition of treatment alliance: Results of the exploratory factor analysis*

The Bartlett's test of Sphericity and the Kaiser-Meyer-Olkin measure both indicated that factor analysis was appropriate for the combined data from all the scales. Only factors with eigenvalues > 1 were retained and loadings that were ≥ 0.4 were identified as significant loadings for each factor. The Scree plot also tailed off at two factors. Thus, the final factor solution that provided the best fit for the data consisted of two factors, which explained 69% of the variance in the data. Factor-1 or the "alliance and support" factor explained about 41% of the variance. It was made up of a combined WAI-Client component comprising of goals, tasks, and bonds as well as all the PCP support items. Factor-2 or the "trust and satisfaction" factor explained about 28% of the variance and consisted of all the TRIP trust items and the PSQ treatment satisfaction items. The results of the factor analysis are shown in Table 3.

## DISCUSSION

The existing literature suggests that a broader construct of treatment-alliance may be prevalent among patients from conventional psychiatric settings[2,4,6,7]. Nevertheless, studies of the composition of alliance among these patients are relatively few compared to studies among psychotherapy clients. The majority of studies among patients receiving psychotherapy have found a two-factor structure of treatment alliance, employing either the WAI or other measures[31-34]. These two factors have usually included a "relationship" or bond factor and another "collaborative" or combined task and goal factor[1,2,10,11], although the second factor has also included treatment satisfaction and help from therapists[17,18]. Others have found a single factor structure of alliance that incorporates the three dimensions of task, goal, and bond[31,35-38]. An equal number of studies have found separate factors for the three dimensions, but have noted a great deal of overlap between the task and goal components[39-41]. Among patients with psychiatric disorders, factor-analytic studies of the WAI or the Helping Alliance

**Table 1 Participants' profiles**

| Demographic & clinical variables | Patients with BD, *n* = 160 |
|---|---|
| Age (yr) | |
| mean ± SD (range) | 43.96 ± 13.51 (18-65) |
| Sex | |
| Male, *n* (%) | 107 (67) |
| Female. *n* (%) | 53 (33) |
| Marital status | |
| Currently single, *n* (%) | 27 (17) |
| Currently married, *n* (%) | 133 (83) |
| Year of education | |
| mean ± SD (range) | 11.85 ± 3.27 (5-18) |
| Occupation | |
| Not earning, *n* (%) | 43 (26) |
| Earning, *n* (%) | 117 (74) |
| Family income, in rupees per month | |
| mean ± SD (range) | 36977 ± 29385 (1500-131500) |
| Family type | |
| Nuclear, *n* (%) | 106 (66) |
| Non-nuclear, *n* (%) | 54 (34) |
| Residence | |
| Rural, *n* (%) | 128 (80) |
| Urban, *n* (%) | 32 (20) |
| Middle socioeconomic class, *n* (%) | 110 (69) |
| Diagnosis | |
| BD type I, *n* (%) | 157 (98) |
| BD type II, *n* (%) | 3 (02) |
| Most recent episode | |
| Manic or hypomanic[1], *n* (%) | 88 (55) |
| Depressive, *n* (%) | 72 (45) |
| Age of onset (yr) | |
| mean ± SD (range) | 26.11 ± 09.50 (12-60) |
| Duration of illness (mo) | |
| mean ± SD (range) | 210.88 ± 132.73 (12-600) |
| Duration of treatment (mo) | |
| mean ± SD (range) | 202.05 ± 129.01 (12-570) |
| Duration of current remission (mo) | |
| mean ± SD (range) | 19.82 ± 38.99 (4-456) |
| HDRS score | |
| mean ± SD (range) | 2.24 ± 1.18 (1-7) |
| YMRS score | |
| mean ± SD (range) | 1.56 ± 0.830 (1-6) |
| Insight-YMRS item 11 score | |

| | |
|---|---|
| mean ± SD (range) | 0.50 ± 0.56 (0-2) |
| Insight-HDRS item 17 score | |
| mean ± SD (range) | 0.55 ± 0.4 (0-2) |
| GAF score | |
| mean ± SD (range) | 69.04 ± 11.245 (48-92) |
| Total number of episodes | |
| mean ± SD (range) | 6.94 ± 5.77 (1-40) |
| Number of manic episodes[1] | |
| mean ± SD (range) | 3.68 ± 3.62 (0-30) |
| Number of depressive episodes | |
| mean ± SD (range) | 2.73 ± 2.71 (0-12) |
| Most recent episode polarity | |
| Manic or hypomanic[1], *n* (%) | 88 (55) |
| Depressive, *n* (%) | 72 (45) |
| Average severity of manic episodes[1,2], *n* (%) | 1.77 ± 0.62 (1-3) median 2 |
| Average severity of depressive episodes[2], *n* (%) | 1.49 ± 0.56 (0-3) median 1 |
| Patients with at least one episode of psychotic mania, *n* (%) | 107 (67) |
| Patients with at least one episode of psychotic depression, *n* (%) | 84 (53) |
| Rapid cycling affective disorder, *n* (%) | 30 (19) |
| Seasonal pattern, *n* (%) | 62 (39) |
| Lifetime suicidal attempts, *n* (%) | 34 (21) |
| Patients with any lifetime psychiatric comorbidity, *n* (%) | 43 (27) |
| Patients with comorbid substance use disorders, *n* (%) | 34 (21) |
| Patients with comorbid anxiety disorders, *n* (%) | 18 (12) |
| Patients with lifetime comorbid physical illness, *n* (%) | 54 (34) |
| Lifetime history of inadequate medication-adherence, *n* (%) | 77 (48) |
| Lifetime history of relapses or breakthrough episodes, *n* (%) | 85 (53) |
| Any history of hospitalization, *n* (%) | 82 (51) |
| On mood stabilizer prophylaxis, *n* (%) | 160 (100) |
| On lithium carbonate, *n* (%) | 116 (73) |
| Average dose | 720 ± 193 mg/d |
| On sodium valproate, *n* (%) | 42 (27) |
| Average dose | 1021 ± 284 mg/d |
| On antipsychotics, *n* (%) | 105 (66) |
| On antidepressants, *n* (%) | 40 (25) |

[1]Manic and hypomanic episodes have been clubbed together and referred to as mania/manic episodes.
[2]Severity was graded as 0-3 with 0 representing remission, 1 representing a mild episode, 2 representing a moderate episode, and 3 representing a severe episode.
BD: Bipolar disorder; GAF: Global Assessment of Functioning Scale; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale.

Questionnaire (HAQ) have also found alliance to consist of either two[17,18,32] or three factors[19,20]. Other studies have found a single factor structure of treatment alliance[18,42], including studies of those with BD[21,43].

The approach used in this study to determine the constituents of treatment alliance in BD was partly driven by the collaborative theory of alliance and partly by incorporating components of possible relevance to the alliance in BD, such as patients' perceptions of clinicians' trust, clinicians' support, and

**Table 2 Components of treatment alliance: Scores on the four scales**

| Scores | Patients with BD, *n* = 160, mean ± SD (range) |
|---|---|
| WAI-Client scores | |
| Total WAI-Client scores | 222.82 ± 20.14 (142-252) |
| Goal subscale | 72.24 ± 7.97 (45-84) |
| Bond subscale | 76.94 ± 7.97 (44-84) |
| Task subscale | 73.64 ± 7.55 (49-84) |
| PCP scores[1] | |
| Total PCP scores | 40.34 ± 5.86 (22-60) |
| Emotional support subscale | 14.45 ± 3.23 (8-33) |
| Informational support subscale | 6.5 ± 1.03 (4-8) |
| SDM subscale | 9.68 ± 1.57 (5-12) |
| Supportive behaviour (support) subscale | 9.69 ± 1.35 (4-12) |
| TRIP scores | |
| Total TRIP scores | 10.12 ± 1.45 (8-12) |
| I completely trusted my doctors | 3.40 ± 0.50 (2-4) |
| I had the impression that the doctors are very competent | 3.38 ± 0.51 (2-4) |
| With the doctors in this hospital one is in good hands | 3.40 ± 0.50 (2-4) |
| PSQ scores | |
| Total PSQ scores | 9.39 ± 1.99 (6-12) |
| Satisfied with places and times of appointment | 2.30 ± 0.59 (1-3) |
| Satisfied with time available for talking about problems | 2.31 ± 0.55 (1-3) |
| Feel confident that members of service are competent to deal with problems | 2.39 ± 0.49 (2-3) |
| Pleased with the care received from the service so far | 2.38 ± 0.50 (1-3) |
| Correlations between scores on different scales and subscales | Pearson's coefficients[2] |
| Goal and Task subscale scores of the WAI-Client | 0.81[a] |
| Bond and Task subscale scores of the WAI-Client | 0.69[a] |
| Bond and Goal subscale scores of the WAI-Client | 0.66[a] |
| Total TRIP scores and WAI-Client total scores | 0.28[b] |
| Total TRIP scores and WAI-Client Task subscale scores | 0.29[b] |
| Total PCP scores and WAI-Client Task subscale scores | 0.28[b] |
| PCP-SDM subscale scores and WAI-Client total scores | 0.28[b] |
| PCP-SDM subscale scores and WAI-Client Goal subscale scores | 0.28[b] |
| Total scores on the TRIP and the PSQ | 0.45[a] |

[a]$P < 0.0001$.
[b]$P < 0.01$.
[1]Weighted mean scores were highest on the "Supportive behavior" subscale (subjective perceptions of support by physicians), followed by the subscales measuring emotional support, shared decision-making and informational support.
[2]Only significant associations that persisted after the Bonferroni corrections are shown. Significant associations were also noted between the Working Alliance Inventory-client version (WAI-Client) total and subscale scores and the Trust in Physicians scores, between the WAI-Client total and subscale scores and the Psychosocial Care by Physicians total and subscale scores, but these did not cross the Bonferroni threshold.
BD: Bipolar disorder; PCP: Psychosocial Care by Physicians; PSQ: Patient Satisfaction Questionnaire; SDM: Shared decision-making; TRIP: Trust in Physicians; WAI-Client: Working Alliance Inventory-client version.

treatment satisfaction. In common with other studies from psychotherapeutic and clinical settings, two relatively independent factors were found to constitute the treatment alliance in BD based on patients' perceptions. The two-factor structure represented a statistically valid factor solution that accounted for a

**Table 3 Components of treatment alliance: Results of factor analysis**

| Components | Initial eigen values[1] | | | Rotation sums of squared loadings[1] | | |
|---|---|---|---|---|---|---|
| | Total | Percentage of variance | Cumulative percentage | Total | Percentage of variance | Cumulative percentage |
| 1 | 2.789 | 46.482 | 46.482 | 2.459 | 40.980 | 40.980 |
| 2 | 1.336 | 22.272 | 68.754 | 1.666 | 27.774 | 68.754 |
| Components[2] | Factor 1 | | | Factor 2 | | |
| WAI-Client Task scores | 0.913 | | | - | | |
| WAI-Client Goal scores | 0.903 | | | - | | |
| WAI-Client Bond scores | 0.850 | | | - | | |
| PCP total scores | 0.552 | | | - | | |
| TRIP total scores | - | | | 0.820 | | |
| PSQ total scores | - | | | 0.795 | | |

[1]Bartlett's Test of Sphericity - $\chi^2$ = 356.39; df = 15; $P$ < 0.001; Kaiser-Meyer-Olkin measure = 0.72 - this indicated that factor analysis was appropriate for the data.

[2]Only factors with Eigen values of > 1 were retained and loadings that were ≥ 0.4 were identified as significant loadings for each factor. The Scree plot tailed off at 2 factors.

PCP: Psychosocial Care by Physicians scale; PSQ: Patient Satisfaction Questionnaire; TRIP: Trust in Physicians; WAI-Client: Working Alliance Inventory-client version.

large proportion of variance in the data. The variance explained (69%) was comparable to earlier studies using a variety of instruments among clients from psychotherapeutic settings[31,32,38,39] or among patients from clinical settings[17], including those with BD[21]. Then again, the composition of factors obtained in this study was a little different from the existing studies. Factor-1 of this study consisted of a combined goal-task-bond component ("alliance") and perceived clinicians' support ("support"), while factor-2 consisted of patients' perceptions of trust in clinicians ("trust") and their satisfaction with the treatment received ("satisfaction").

The aggregation of goals, tasks, and bonds into a single component as a part of factor-1 was not unexpected given that there is a great deal of overlap between these dimensions. Significant correlations between the three WAI subscales found in this study have also been reported in several earlier ones and are commonly cited as evidence for this overlap[8,31,35,36,40]. Additionally, a similar integrated alliance factor combining goal, task, and bond items of the WAI has also been replicated across several factor-analytic studies[31,35,36,38,42]. It has been proposed that the integration of the three dimensions could be unique to patients' perceptions of the alliance[10,38,40]. Unlike therapists, patients do not differentiate between the three components of tasks, goals, and bonds and view them as a unified entity. The three dimensions may seem also indistinguishable to patients because they develop simultaneously during treatment. Moreover, it appears that for patients, the quality of their attachment with their clinicians is of primary importance[10,11,42]. Therefore, stronger bonds with clinicians are likely to enhance their agreement on goals and tasks of treatment. Nevertheless, the importance of collaboration as a part of the treatment alliance in BD is supported by several studies that have shown that patients assign a key role to the quality of interactions with their clinicians while rating alliance[23,25,44-46]. The presence of a "support" component as a part of factor-1 was also in keeping with the existing literature on the composition of alliances. One of the earliest concepts of treatment alliance formulated by Horvath and Luborsky[10] was based on patients' perceptions of their therapists as being supportive and helpful in addition to a sense of working together with them[11,17,18]. Since then many factor-analytic studies of the WAI, the HAQ, and other scales have consistently shown that perceived therapist supportiveness and helpfulness is an integral part of the alliance[17,31,36,39]. Additionally, these studies have found that the dimensions of perceived helpfulness and collaboration are highly correlated. This was similar to the association of the PCP support scores and the scores on the goal and tasks components of the WAI-Client in this study. It is also likely that perceived clinician support plays a greater role in patients' rather than clinicians' views of the alliance[36,46]. Moreover, quite a few studies of BD have shown that patients believe clinician support and helpfulness to be a central part of the treatment alliance[24,45-48].

The second factor consisted of a combination of trust in clinicians and treatment satisfaction among patients of this study. Although Bordin's concept of bonds includes feelings of mutual trust between patients and therapists[8-10], perceived trust in clinicians, favorable views about their competence, and treatment satisfaction could have emerged as independent constituents of treatment alliance in this

study simply because separate scales were used to measure these aspects. Moreover, cultural influences on alliance may have had some bearing in this study. The scores on various scales suggested the pre-eminence of trust, bonds, and emotional support as opposed to the goal and task dimensions of the alliance. This is in keeping with the suggestions that not only are Asian patients more likely to have a global view of treatment alliance, but they may also place a much higher value on their relationship with clinicians than on the collaborative aspects of treatment[38]. Consistent with this notion, studies of BD among Chinese patients have shown that patients' trust in clinicians and respect for their authority was far more influential in forging effective alliances than mutual agreements on tasks and goals[49,50]. However, the finding that trust in clinicians and positive beliefs regarding clinicians' competence is a necessary part of treatment alliance seems to be a universal finding[3,51]. Accordingly, the contribution of perceived trust to alliance formation found in this study has been noted by other factor-analytic studies with the WAI and other scales[17,31,32,52]. Studies of patients with BD have also shown that the trusted physician is regarded by them as a positive asset[22,23,44,53]. The treatment satisfaction component of factor-2 consisted of patients' satisfaction with the outcome of treatment, their confidence in the clinicians' abilities, and their access to the clinicians. Factor-analytic studies of the HAQ have shown that perceived satisfaction with treatment outcome is an essential component of alliances[18]. Similarly, patients' confidence in the clinician's competence has formed a part of the construct of alliance in other studies[31,32,52]. Moreover, these studies have also shown that there is considerable overlap between trust or bond, treatment satisfaction, and confidence in clinicians[18,31,52], which was similar to the significant association between the scores on the trust (TRIP) and the patient satisfaction (PSQ) components of this study. Finally, studies of BD have also found treatment satisfaction is associated with patients' perceptions of treatment alliances[21,25,49,50,53]. This suggests that the "trust and satisfaction" factor of this study was a conceptually valid component of treatment alliance in BD.

### *Limitations*

This exploratory study of treatment-alliance in BD had some limitations. Patients of this study had relatively higher total and subscale scores on the WAI-Client compared to other studies of BD using the same scale[54]. Moreover, unlike the other studies, scores on the bond subscale were significantly higher than the task and goal subscales in this study[35,36]. The precedence given to emotional support on the PCP was also different from other studies[28,29], but was in keeping with priority given to emotional bonds with clinicians. Apart from the cultural influences mentioned above, these differences could have been due to the favorable demographic attributes and the relatively stable course of illness among these patients, especially at the time they were assessed. Therefore, these findings will need to be replicated across different patient samples before they can be considered conclusive. This study focused exclusively on patients' perceptions of alliance in BD. Although the existing literature is somewhat inconclusive regarding differences between patients' and clinicians' perceptions of treatment alliance [55], it has to be acknowledged that patients' perceptions represent only one-half of the total picture. The cross-sectional design of this study could have been a limiting factor, though many studies have shown that factor structures remain stable over time[33,37,42]. Some scales used in this study, including the WAI, have not been validated in Indian patients. Finally, though factors like clinicians' support and treatment satisfaction have been considered as indicators of patient outcome, they are also included as a part of several alliance measures[3].

## CONCLUSION

Despite these limitations the findings of this study have provided preliminary evidence in favor of a broader concept of treatment alliance among outpatients with BD. The composition of alliance in these patients went beyond the usual collaborative elements to include perceptions of trust in clinicians, perceived support from them, and satisfaction with their treatment. Such an expanded concept of treatment alliance would also be congruent with the results of studies of BD, which have found that patients' views on collaboration with clinicians, clinicians' support, trust in clinicians and their expertise, and treatment satisfaction are associated with effective treatment alliances in BD[5,13-16]. The results emphasize the need for further research into the construct of treatment alliance in BD given its likely impact on adherence and other treatment outcomes. The findings of this study might also provide clinicians with insights into the kind of treatment relationships their patients seek from them. It appears that patients appreciate a collaborative and supportive relationship that promotes mutual trust and enhances perceived satisfaction. Therefore, treatment alliances that incorporate these components are more likely to help patients with BD.

## ARTICLE HIGHLIGHTS

### *Research background*

Treatment alliance has an impact on several key patient outcomes in all psychiatric disorders, including bipolar disorder (BD). It has been suggested that the construct of treatment alliance is different among patients from routine psychiatric settings compared to psychotherapeutic settings; however, research on the composition of treatment alliance in psychiatric disorders, such as BD, is relatively limited. The findings of this study might provide clinicians with insights into the kind of treatment relationships their patients seek from them. It appears that patients appreciate a collaborative and supportive relationship that promotes mutual trust and enhances perceived satisfaction. Therefore, treatment alliances that incorporate these components are more likely to help patients with BD.

### *Research motivation*

There is evidence to suggest that the concept of treatment alliance may differ among patients with psychiatric disorders seeking treatment in routine clinical settings. This study attempted to determine whether a broader construct of treatment alliance was prevalent among outpatients with BD. However, this was a preliminary exploratory study of treatment-alliance in BD that had some methodological limitations. The results emphasize the need for further, methodologically advanced research into the construct of treatment alliance in BD given its likely impact on adherence and other treatment outcomes.

### *Research objectives*

Based on the existing evidence regarding treatment alliance, it was hypothesized that a broader construct of the alliance was more likely to exist among such patients. Therefore, in addition to collaborative aspects, other contributions to the construct of treatment alliance explored among patients of this study were perceived trust in clinicians, perceived clinicians' support, and treatment satisfaction.

### *Research methods*

This was a cross-sectional study, conducted in the psychiatric unit of a multi-specialty hospital in north India over 12 mo (September 2018 to September 2019). A consecutive sample of 160 remitted adult outpatients with BD on mood stabilizers for at least a year were selected. The principal instrument to assess treatment alliance was the Working Alliance Inventory-client version (WAI-Client). Other potential constituents of the alliance explored were perceived trust in clinicians assessed by the Trust in Physicians (TRIP) scale, perceived support from clinicians assessed by the Psychosocial Care by Physicians (PCP) scale, and perceived treatment satisfaction assessed by the Patient Satisfaction Questionnaire (PSQ). Associations between scores on all scales were determined by correlational and multiple regression analyses. Exploratory factor analysis of combined items of all scales was conducted using a principal components analysis.

### *Research results*

Scores on all the three WAI-Client subscales were significantly correlated with each other ($r$ = 0.66-0.81; $P$ < 0.0001). The total TRIP scores were associated with the total WAI-Client scores ($r$ = 0.28; $P$ < 0.01). The total TRIP scores and the total PCP scores were also significantly associated with the WAI-Client scores on the task subscale ($r$ = 0.28-0.29; $P$ < 0.01). The total TRIP scores were significantly associated with the total PSQ scores ($r$ = 0.45; $P$ < 0.0001). Factor analysis yielded two independent and coherent factors, which explained 69% of the variance in data. Factor-1 ("alliance and support"), which explained about 41% of the variance, was comprised of a combined WAI-Client goal-task-bond component as well as the PCP support items. Factor-2 ("trust and satisfaction"), which explained about 28% of the variance, consisted of all the TRIP trust and the PSQ treatment satisfaction items.

### *Research conclusions*

A broader construct of treatment alliance in BD was found. Apart from collaborative components, this construct included patients' perceptions regarding trust in clinicians, support from clinicians, and treatment satisfaction.

### *Research perspectives*

More focused research is needed to determine the components of treatment alliance in BD. Future research should also determine the relative importance of the different components of alliance and their impact on key patient outcomes.

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## FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

# Disrupted leptin-fatty acid biosynthesis is an early manifestation of metabolic abnormalities in schizophrenia

Mohammad M Khan

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## Abstract

***BACKGROUND***

Insulin resistance (IR) and impaired energy expenditure (IEE) are irreparable metabolic comorbidities in schizophrenia. Although mechanism(s) underlying IR and IEE remains unclear, leptin and fatty acid signaling, which has profound influence on insulin secretion/sensitivity, glucose metabolism and energy expenditure, could be disrupted. However, no association of plasma leptin with erythrocyte membrane fatty acids, body mass index (BMI), and psychotic symptoms in the same cohort of untreated patients with first-episode psychosis (FEP) or medicated patients with chronic schizophrenia (CSZ) is presented before. These studies are crucial for deciphering the role of leptin and fatty acids in the development of IR and IEE in schizophrenia.

***AIM***

To determine the association between plasma leptin, erythrocyte membrane fatty acids, particularly, saturated fatty acids (SFAs), BMI and psychotic symptoms in patients with FEP and CSZ.

***METHODS***

In this study, twenty-two drug naive patients with FEP, twenty-one CSZ patients treated with atypical antipsychotic drugs, and fourteen healthy control (CNT) subjects were analyzed. Plasma leptin was measured using sandwich mode enzyme-linked immunosorbent assay. Erythrocyte membrane SFAs were measured using ultrathin capillary gas chromatography. BMI was calculated by using the formula: weight (kg)/height ($m^2$). Psychiatric symptoms were evaluated at baseline using brief psychiatric rating scale (BPRS), and positive and negative

syndrome scale (PANSS). The total BPRS scores, positive and negative symptom scores (PANSS-PSS and PANSS-NSS, respectively) were recorded. Pearson correlation coefficient ($r$) analyses were performed to find the nature and strength of association between plasma leptin, PANSS scores, BMI and SFAs, particularly, palmitic acid (PA).

*RESULTS*

In patients with FEP, plasma leptin not BMI was significantly lower ($P$ = 0.034), whereas, erythrocyte membrane SFAs were significantly higher ($P$ < 0.005) compared to the CNT subjects. Further, plasma leptin showed negative correlation with erythrocyte membrane SFAs-PA ($r$ = −0.4972, $P$ = 0.001), PANSS-PSS ($r$ = −0.4034, $P$ = 0.028), and PANSS-NSS ($r$ = −0.3487, $P$ = 0.048). However, erythrocyte membrane SFAs-PA showed positive correlation with PANSS-PSS ($r$ = 0.5844, $P$ = 0.0034) and PANSS-NSS ($r$ = 0.5380, $P$ = 0.008). In CSZ patients, plasma leptin, BMI, and erythrocyte membrane SFAs, all were significantly higher ($P$ < 0.05) compared to the CNT subjects. Plasma leptin showed positive correlation with BMI ($r$ = 0.312, $P$ = 0.032) but not with PANSS scores or erythrocyte membrane SFAs-PA. However, erythrocyte membrane SFAs-PA showed positive correlation with PANSS-NSS only ($r$ = 0.4729, $P$ = 0.031). Similar changes in the plasma leptin and erythrocyte membrane SFAs have also been reported in individuals at ultra-high risk of developing psychosis; therefore, the above findings suggest that leptin-fatty acid biosynthesis could be disrupted before the onset of psychosis in schizophrenia.

*CONCLUSION*

Disrupted leptin-fatty acid biosynthesis/signaling could be an early manifestation of metabolic comorbidities in schizophrenia. Large-scale studies are warranted to validate the above findings.

**Key Words:** Schizophrenia; Leptin; Fatty acids; Insulin resistance; Impaired energy expenditure

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**Core Tip:** Insulin resistance (IR) and impaired energy expenditure (IEE) are untreatable metabolic comorbidities in schizophrenia. Leptin and fatty acids have profound influence on insulin synthesis, secretion and energy metabolism. Although previous studies have measured plasma leptin and membrane fatty acids in schizophrenia, findings are very heterogeneous, and moreover, no single study has ever measured both plasma leptin and membrane fatty acids together in the same cohort of schizophrenia patients. These studies are crucial not only for analyzing the relationship between leptin and fatty acids in the same cohort of schizophrenia patients, but also for deciphering their role in the development of IR and IEE.

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## INTRODUCTION

Schizophrenia is a complex multisystem disorder, which apart from displaying psychotic symptoms and cognitive deficit also manifests a range of metabolic abnormalities including insulin resistance (IR) and impaired energy expenditure (IEE)[1-4]. Evidence suggests that IR and IEE may develop before the onset of psychosis and deteriorate further following antipsychotic intervention, prompting premature antipsychotic withdrawal, a leading cause of relapse in schizophrenia[5-9]. Deciphering the underlying mechanism(s) may help in developing appropriate therapies for minimizing IR and IEE and increasing treatment adherence and outcome in schizophrenia.

While several mechanisms may contribute in the development of IR and IEE, disrupted adipokine and fatty acid (FA) signaling could play a central role. Leptin is an important adipokine, which at physiologically elevated condition strongly inhibits insulin synthesis and secretion and causes weight gain by stimulating lipogenesis and adipogenesis while concurrently inhibiting fatty acid oxidation[10-12]. Removing leptin from blood circulation has been shown to normalize body weight and hyperglycemia in obese animals[13].

FAs, specially, saturated FAs (SFAs) stimulate insulin secretion from pancreatic β-cells[14], but inhibit both leptin synthesis and secretion from adipose tissue[15,16]. Since adipose tissue (adipocytes), like

erythrocytes, contain high percentage of SFAs; consequently, SFAs could be the main regulators of leptin synthesis and secretion from adipose tissue. Evidence suggests that elevated SFAs can impair glucose and FA metabolism by inducing endoplasmic reticulum stress and mitochondrial dysfunction [17]. Moreover, while intracellular accumulation of all FAs can provoke IR, effect of SFAs could be more detrimental and persistent due to the development of various inflammatory cues[18].

Although previous studies have measured plasma leptin and membrane SFAs in schizophrenia, findings are very conflicting and association between leptin, SFAs and body mass index (BMI) has not been studied. Moreover, no study has ever measured plasma leptin, membrane SFAs and BMI together in the same cohort of patients with schizophrenia. These studies are crucial not only for analyzing the relationship between leptin, SFAs, and BMI in schizophrenia, but also for deciphering their role in the development of IR, IEE, and other metabolic comorbidities.

In this study, association between plasma leptin, erythrocyte membrane SFAs, and BMI was determined in the drug-naive patients with first-episode psychosis (FEP), medicated patients with chronic schizophrenia (CSZ), and healthy control (CNT) subjects. While our group has published earlier preliminary data on the membrane FAs including SFAs, monounsaturated FAs and polyunsaturated FAs[19], data on the plasma leptin and BMI and its association with erythrocyte membrane SFAs, BMI and clinical symptoms in patients with FEP and CSZ is naive and is presented here. In addition, possible mechanisms delineating the role of leptin and SFAs in the development of IR and IEE are discussed.

## MATERIALS AND METHODS

### *Patients and control subjects*

A total of twenty-two ($n$ = 22) drug-naïve FEP patients, twenty-one ($n$ = 21) medicated patients with CSZ, and fourteen ($n$ = 14) male control (CNT) subjects were analyzed in this study. Patients with FEP were enrolled from consecutive admissions at the Department of Psychiatry, Dwight David Eisenhower Army Medical Center (DDEAMC), Fort Gordon, GA. The patients were mostly active duty army personal diagnosed with schizophrenia or schizophreniform disorder using DSM IV criteria, and after six months follow-up period during subsequent hospitalization. The BMI was calculated according to the formula BMI = kg/m$^2$, where kg is body weight in kilogram and m is the height in meters[20]. Clinical symptoms of the patients were evaluated at baseline using brief psychiatric rating scale (BPRS) and the positive and negative syndrome scale (PANSS)[21,22]. The total BPRS scores, positive symptoms scores (PANSS-PSS: sum of scores on conceptual disorganization, hallucination, delusions, unusual thoughts, contents, and suspiciousness), and negative symptom scores (PANSS-NSS: sum of scores on emotional withdrawal, blunted effect and motor retardation) were examined in this study. The mean age at the onset of psychosis was 22.40 ± 4.08 years. Patients with CSZ were enrolled at the outpatient clinic of Mental Health Service, VA Medical Center (VAMC), Augusta, GA. The clinical symptoms of these patients were analyzed using the same methodologies as used for patients with FEP. The CSZ patients were on treatment with various atypical antipsychotic drugs (AAD) including clozapine ($n$ = 14), olanzapine ($n$ = 4), or risperidone ($n$ = 3) for the past 1-5 years. It is important to point out that FEP patients after discharge from Army Medical Centers such as DDEAMC are admitted to the Psychiatry Services at the VA Medical Centers. Therefore, both patient groups in this study represent unique populations with demographic similarities except, the years of illness and treatment. The CNT subjects ($n$ = 14) consisted of healthy volunteers recruited *via* advertisements at the Medical College of Georgia (MCG), VAMC, and DDEAMC. The CNT subjects were matched for age and gender with the patients with FEP. The demographic and clinical characteristics of the patients are presented in the Table 1. Institutional Review Boards of DDEAMC and MCG, Augusta, GA approved the research protocol, and a signed consent was taken from all the patients and CNT subjects.

Regarding inclusion and exclusion criteria, all patients with FEP and CSZ were included in this study on the basis of the following criteria; they were medically healthy except psychosis, and none had a history of seizures or severe head injury with loss of consciousness or a history of substance abuse within the last one year. Patients with any of these complications were excluded from the study. Moreover, during the six months follow up period of patients with FEP, those patients who did not meet DSM IV criteria for diagnosis or who turned out to have primary bipolar or major depression were also excluded from the study. A total of 38 patients with FEP were followed up for six months, 29 patients (23 male and 6 female) were found to be eligible. Out of 29 patients, 6 female patients were excluded and 1 male patient plasma sample was not used due to turbidity, so only only 22 male patients with FEP were analyzed.

### *Analysis of erythrocyte membrane FAs and plasma leptin*

The procedures for measuring erythrocyte membrane FAs has been published earlier by our group, it is not discussed here for brevity[19,23]. For measuring plasma leptin, fasting blood was drawn in Lavender vaccutainer containing EDTA. The blood was centrifuged at 2500 rpm for 10 min at 5C. Plasma was carefully separated and stored at -20C before use. Sandwich mode enzyme-linked immunosorbent assay (ELISA) was used to measure plasma leptin using a commercially available Kit

**Table 1 Demographic and clinical characteristics of the study subjects**

| Characteristics | CNT | FEP | CSZ |
|---|---|---|---|
| Age (yr) | 25 ± 7.6 | 23.54 ± 4.65 | 42.23 ± 5.12 |
| Gender (M:F) | 14:0 | 22:0 | 21:0 |
| Age at onset of psychosis | | 22.80 ± 4.78 | 23.15 ± 6.35 |
| Years of Illness | | ≤ 5.0 d | 22.77 ± 7.21 |
| Total BPRS Total | | 45.18 ± 12.53 | 38.17 ± 6.96 |
| Total PANSS-PSS | | 21.03 ± 4.81 | 12.88 ± 4.10 |
| Total PANSS-NSS | | 20.91 ± 5.10 | 07.82 ± 2.31 |
| Plasma leptin (ng/mL) | 5.79 ± 0.80 | 4.77 ± 1.35 | 08.33 ± 1.25 |
| BMI (kg/m$^2$) | 25.1 ± 2.61 | 23.2 ± 2.14 | 29.86 ± 3.60 |
| Smoking | | 2/23 | 3/21 |
| Antipsychotic use | | | +++ |
| Tobacco | | | |
| Cannabis | | | |

CNT: Control subjects; FEP: First-episode psychosis; CSZ: Chronic schizophrenia; BPRS: Brief psychiatric rating scale; PANSS-PSS: Positive symptom scores; PANSS-NSS: Negative symptom scores; BMI: Body mass index.

from Signet Laboratories (Dedham, MA). The ELISA procedure was performed in accordance with the directions of the manufacturer in a sandwich mode using two monoclonal antibodies to leptin: a coating antibody and an HRP-conjugated antibody. The ELISA plates were supplied pre-coated with the coating antibody. All samples were diluted to 1:3000 (in PAT buffer provided with kits) before use. The plates were incubated in duplicates with 100 L of diluted samples overnight at 4C in dark. The wells were washed three times with 250 L of PT buffer (PBS-Tween 20 buffer provided with kit). Plates were then incubated with 100 L of diluted conjugate (HRP-conjugated leptin antibody) for 2 h at room temperature in the dark. The plates were then extensively (3-4 times) washed with 250 L of PT buffer followed by incubation with 150 L O-Phenylenediamine substrate for 20 min at room temperature in the dark to allow color formation. Reaction was stopped by the addition of 50 L of 5.0 M sulfuric acid and the color intensity was read at dual wavelengths using 492 nm as the test wavelength and 620 nm for the reference wavelength. All samples were analyzed twice simultaneously.

### *Statistical analysis*

All statistical analyses were performed using Prism software and the values are expressed as mean ± SE. The values of slope and intercept for the standard samples were calculated by the linear regression method. The data was further analyzed for significance between groups using Student's *t*-test (two-tailed variance) or One-Way ANOVA, and a $P$ value < 0.05 was considered significant. Pearson correlation coefficient ($r$) analysis was performed to find the nature and strength of association between different variables including SFAs, plasma leptin, BMI, and clinical symptoms including PANSS-PSS and PANSS-NSS.

## RESULTS

Table 1 shows the demographic and clinical characteristics of the patients and CNT subjects. Figure 1 shows statistical analyses of plasma leptin, BMI, erythrocyte membrane SFAs including palmitic acid (PA) and stearic acid (SA) in CNT subjects, FEP and CSZ patients. Average plasma leptin (Figure 1A) in FEP patients (4.77 ± 1.35 ng/mL) was significantly ($P$ = 0.028) lower than CNT subjects (5.79 ± 0.80 ng/mL), whereas, in CSZ patients, plasma leptin (8.33 ± 1.25 ng/mL) was significantly higher than FEP patients ($P$ = 0.006). The average BMI value (Figure 1B) of FEP patients (23.21 ± 2.14) was statistically similar to the BMI value of CNT subjects (25.10 ± 2.61, $P$ = 0.144). However, the average BMI value (Figure 1B) of AAD treated CSZ patients (29.86 ± 3.60) was significantly ($P$ = 0.012) higher than FEP patients, and the increase was in parallel with the increase in plasma leptin (Figure 1A). Regarding erythrocyte membrane SFAs, both PA (Figure 1C) and SA (Figure 1D) were significantly ($P$ < 0.005) higher in both FEP and CSZ patients compared to the CNT subjects suggesting that membrane SFA abnormalities in schizophrenia are untreatable.

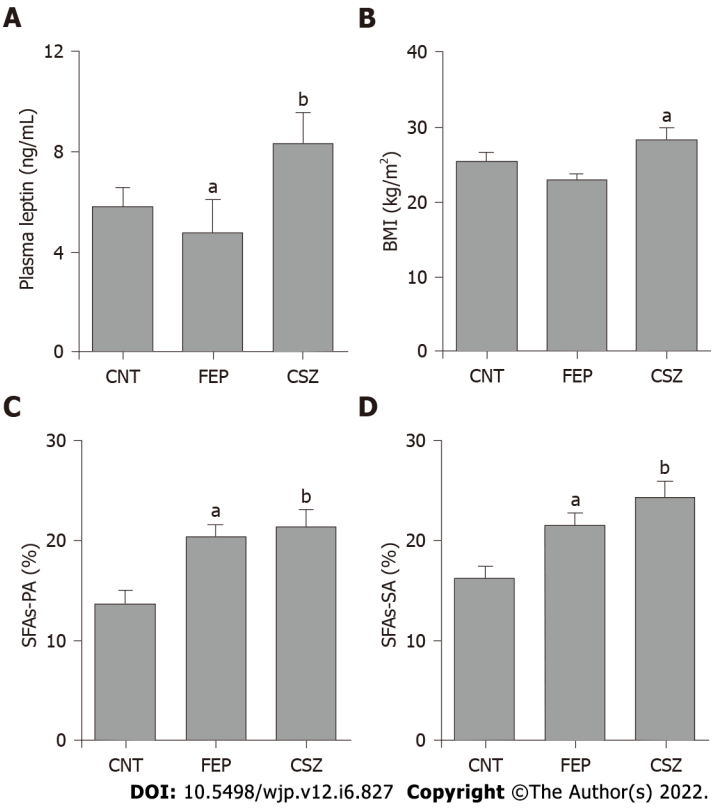


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**Figure 1 Statistical analyses of plasma leptin, body mass index, erythrocyte membrane saturated fatty acids in healthy control subjects, first-episode psychosis and chronic schizophrenia patients.** A: Average plasma leptin (Figure 1A) in first-episode psychosis (FEP) patients (4.77 ± 1.35 ng/mL) was significantly ($P$ = 0.028) lower than healthy control (CNT) subjects (5.79 ± 0.80 ng/mL). In chronic schizophrenia (CSZ) patients, plasma leptin (8.33 ± 1.25 ng/mL) was significantly higher than FEP patients ($P$ = 0.006); B: The average body mass index (BMI) value of FEP patients (23.21 ± 2.14) was statistically similar to the BMI value of CNT subjects (25.10 ± 2.61, $P$ = 0.144). The average BMI value of clozapine treated CSZ patients (29.86 ± 3.60) was significantly ($P$ = 0.012) higher than FEP patients; C and D: Erythrocyte membrane palmitic acid and stearic acid, respectively were significantly ($P$ < 0.005) higher in both FEP and CSZ patients compared to the CNT subjects. CNT: Healthy control; FEP: First-episode psychosis; CSZ: Chronic schizophrenia; BMI: Body mass index; SFAs: Saturated fatty acids; PA: Palmitic acid; SA: Stearic acid. $^{a}P$ < 0.05 and $^{b}P$ < 0.01.

Figure 2 shows the association of plasma leptin with clinical symptom scores. In patients with FEP, plasma leptin showed negative association with both PANSS-PSS (Figure 2A, $r$ = −0.4034, $P$ = 0.028) and PANSS-NSS (Figure 2B, $r$ = −0.3487, $P$ = 0.05). In CSZ patients, although negative association was observed between plasma leptin and either PANSS-PSS (Figure 2C, $r$ = −0.3055, $P$ = 0.18) or PANSS-NSS (Figure 2D, $r$ = −0.3001; $P$ = 0.13), it did not return significance. This could be due to treatment-induced alterations in both plasma leptin and PANSS scores compared to the drug-naive patients with FEP.

Figure 3 shows the association of erythrocyte membrane SFAs-PA with the clinical symptom scores. In patients with FEP, erythrocyte SFAs-PA showed positive correlation with both PANSS-PSS (Figure 3A, $r$ = 0.5844, $P$ = 0.0034) and PANSS-NSS (Figure 3B, $r$ = 0.5381, $P$ = 0.008). In AAD treated CSZ patients, erythrocyte SFAs-PA showed significant positive correlation with PANSS-NSS (Figure 3D, $r$ = 0.4729; $P$ = 0.031), but it was not significant in case of PANSS-PSS (Figure 3C, $r$ = 0.2485, $P$ = 0.28). These findings suggest that elevated erythrocyte SFAs could be associated more strongly with the negative symptoms in patients with both FEP and CSZ.

Since SFAs strongly inhibit leptin synthesis and secretion, therefore, association of leptin with erythrocyte SFAs-PA and BMI was also determined. In FEP patients, plasma leptin was negatively associated with SFAs-PA (Figure 4A, $r$ = −0.4335, $P$ = 0.0194) but not with BMI (Figure 4B, $r$ = 0.2169, $P$ = 0.3206), whereas, in patients with CSZ, plasma leptin showed positive association with BMI (Figure 4C, $r$ = 0.4135, $P$ = 0.0152) but not with erythrocyte SFAs-PA (Figure 4D, $r$ = 0.3331, $P$ = 0.1401). Moreover, SFAs-PA was elevated in both FEP and CSZ patients (Figure 1C and D), whereas, plasma leptin (Figure 1A) and BMI (Figure 1B) were elevated only in patients with CSZ suggesting that elevated plasma leptin could be involved in increasing BMI in CSZ patients.

## DISCUSSION

In this study, significant changes in plasma leptin, BMI, and erythrocyte membrane SFAs were observed in patients with FEP and CSZ compared to the CNT subjects. These changes were also significantly

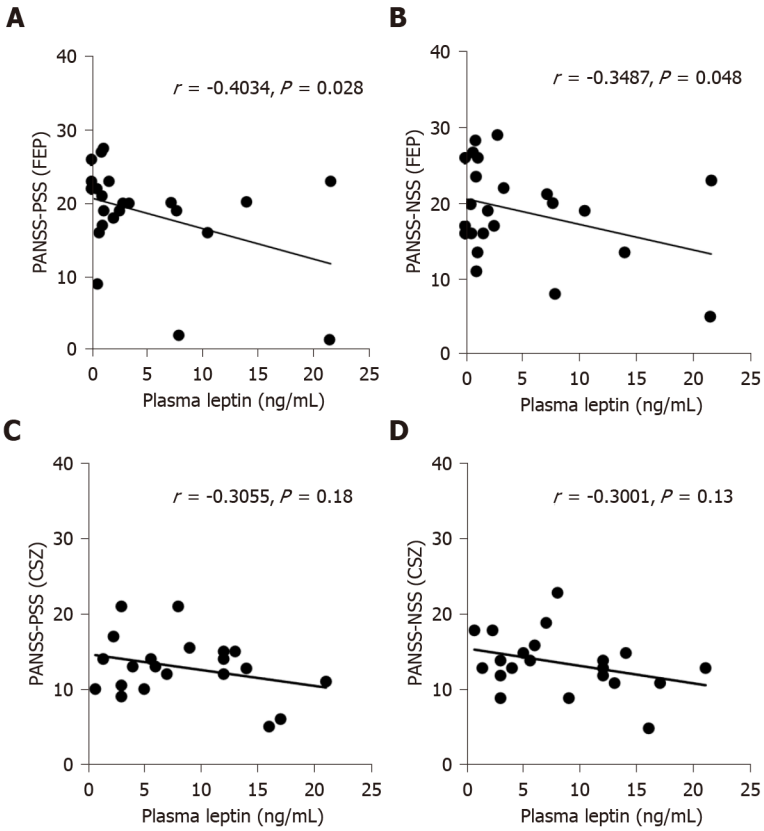


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**Figure 2 Association of plasma leptin with clinical symptom (positive and negative syndrome scale) scores.** A and B: In first-episode psychosis patients, plasma leptin showed negative correlation with both positive symptom score (PANSS-PSS) ($r$ = −0.4034, $P$ = 0.028) and negative symptom score (PANSS-NSS) ($r$ = −0.3487, $P$ = 0.05); C and D: In chronic schizophrenia patients, no significant negative correlation was observed between plasma leptin and either PANSS-PSS ($r$ = −0.3055, $P$ = 0.18) or PANSS-NSS ($r$ = −0.3001; $P$ = 0.13). PANSS-PSS: Positive and negative syndrome scale-positive symptom score; PANSS-NSS: Positive and negative syndrome scale-negative symptom score; FEP: First-episode psychosis; CSZ: Chronic schizophrenia.

associated with clinical symptoms in both groups of patients. The central message is that in patients with FEP, plasma leptin was significantly low and showed negative association with PANSS scores, whereas, SFAs were significantly higher and showed positive association with PANSS scores. Additionally, plasma leptin showed negative association with SFAs, which is in line with the negative effects of SFAs on leptin synthesis and secretion[15]. In AAD treated CSZ patients, plasma leptin, SFAs and BMI all were significantly higher, which is also in agreement with previous studies showing increased leptin synthesis, and weight gain after AAD treatment[24-26].

This is the first report that shows disrupted leptin and erythrocyte membrane SFA biosynthesis in the same cohort of drug-naive patients with FEP and ADD treated patients with CSZ. In addition, negative association between plasma leptin and erythrocyte SFAs has not been reported before. These findings together with the literature discussed below, suggest that leptin-fatty acid signaling, which plays a central role in insulin secretion, sensitivity, food-intake and energy metabolism, could be disrupted in schizophrenia.

Before discussing the role of leptin and SFAs in the development of IR and IEE, it can be argued that how elevated erythrocyte SFAs could relate to the changes in adipose tissue where leptin and other adipokines are synthesized[27]. Since both erythrocytes and adipose tissue share developmental relationship, and contain high percentage of SFAs[28,29], reduced leptin production in patients with FEP could be a result of increased SFA contents in the adipose tissue. And this effect should to be mediated, specifically, by the cytosolic pool of SFAs, accumulated either due to reduced FA oxidation or increased *de novo* FA biosynthesis or both because, studies have shown that SFAs circulating in the plasma or present in the extracellular space have no significant effect on leptin synthesis and secretion [15,30]. Further, like erythrocytes, SFAs could also be elevated in other tissues of FEP patients as a result of increased oxidative stress and inflammation, as both these conditions strongly stimulate *de novo* SFA biosynthesis[31-35]. Moreover, excess SFAs can be transported from intracellular space to the membrane and outside the cells by specific fatty acid transporter proteins[36].

### *Elevated SFAs in schizophrenia, and their role in the development of IR and IEE*

Over the past thirty years, extensive efforts have been made to understand the role of membrane FAs in the pathophysiology and psychopathology of schizophrenia and other psychiatric disorders. Regarding

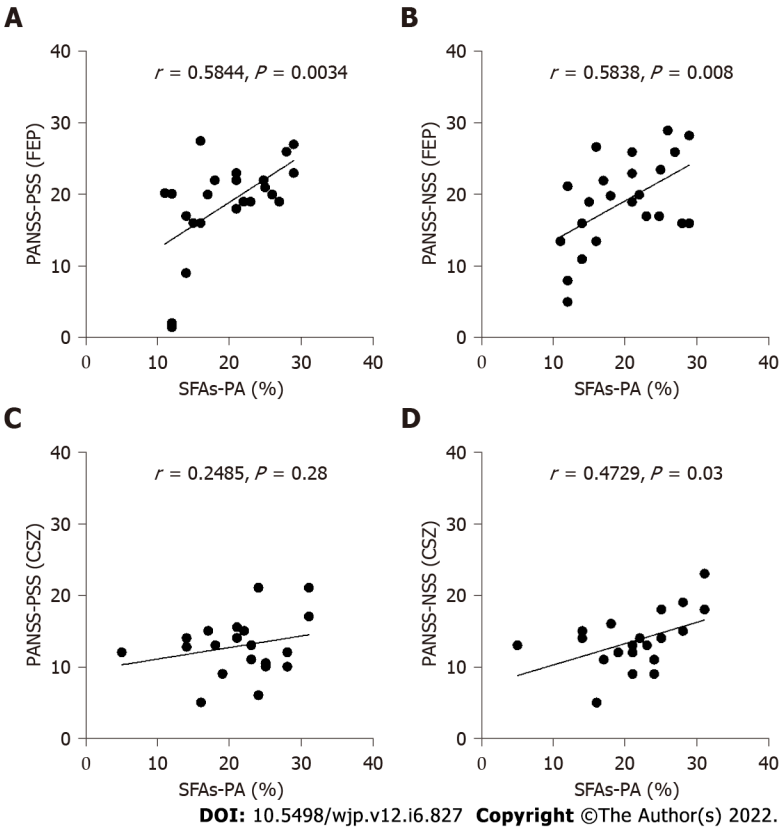


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**Figure 3 Association of erythrocyte membrane saturated fatty acids-palmitic acid with clinical symptoms (positive and negative syndrome scale) scores.** A and B: In first-episode psychosis patients, erythrocyte saturated fatty acids (SFAs)-palmitic acid (PA) showed positive correlation with both positive symptom score (PANSS-PSS) (A, $r$ = 0.5844, $P$ = 0.0034) and negative symptom score (PANSS-NSS) (B, $r$ = 0.5381, $P$ = 0.008); C and D: In chronic schizophrenia patients, erythrocyte SFAs-PA showed positive correlation with PANSS-NSS (D, $r$ = 0.4729; $P$ = 0.031), but it was not significant in case of PANSS-PSS (C, $r$ = 0.2485, $P$ = 0.28). Similar results were obtained with erythrocyte membrane stearic acid (data not shown). PANSS-PSS: Positive and negative syndrome scale-positive symptom score; PANSS-NSS: Positive and negative syndrome scale-negative symptom score; FEP: First-episode psychosis; CSZ: Chronic schizophrenia; SFAs: Saturated fatty acids; PA: Palmitic acid.

membrane FAs compositions, although there may be some contradictory findings, most studies including our own have shown that erythrocyte membrane PUFAs are reduced, whereas, SFAs are increased in drug-naive patients with FEP[19,37-39]. Similar alterations in PUFAs and SFAs have also been observed in the brain tissue from the patients with FEP[40]. Specially, prefrontal cortex regions have been shown to have deficit in various PUFAs, whereas, proportion of SFAs (particularly, PA) was increased in the specific phospholipid moieties[40]. Likewise, skin fibroblasts from patients with FEP have been shown to have abnormal membrane FA compositions[41].

Intriguingly, erythrocyte FA abnormalities have also been reported in individuals at ultra-high risk of developing psychosis. In a recent study, significant reduction in various PUFAs and increase in SFAs including PA in the erythrocyte membrane has been reported in individuals at ultra-high risk of developing psychosis[42]. These findings strongly support the observations that we reported nearly 20 years ago in FEP patients, and also corroborate findings published by other groups in recent years[15,40]. In conclusion, disrupted FA biosynthesis comprising of reduced PUFAs and increased SFAs could be an early manifestation of schizophrenia pathophysiology.

Regarding the cause of SFA elevation, hypoxia-induced oxidative stress, and inflammation appear to be the potential causative factors in schizophrenia. Hypoxia has been shown to induce *de novo* FA biosynthesis in embryonic neurons and potentiate pro-inflammatory effects of SFAs in macrophages[32,43]. In addition, recent studies have shown that elevated SFAs under hypoxic conditions may serve as hydrogen acceptors, an effect that favors a shift towards anaerobic glycolysis leading to increased lactate production, an indication of IEE[32,33]. Since glutamate/glutamine are required for the *de novo* SFA biosynthesis in neurons under hypoxia[32], increased SFA biosynthesis therefore also support the findings that have shown impaired glutamate/glutamine ratio in patients with FEP and CSZ[44].

Concerning the role of FAs in schizophrenia pathophysiology, although reduced membrane PUFAs have been linked with cognitive deficit and psychotic symptoms[19,38,45,46], consensuses have not reached on the role of elevated SFAs. Since SFAs are the major fuel for energy production and utilization during resting state, increased SFA levels in patients with FEP could be an indication of impaired resting state energy expenditure. Indeed, several recent studies have shown that FEP patients and their first-degree relatives display IEE[47-52]. Also, several lines of evidence suggest that elevated

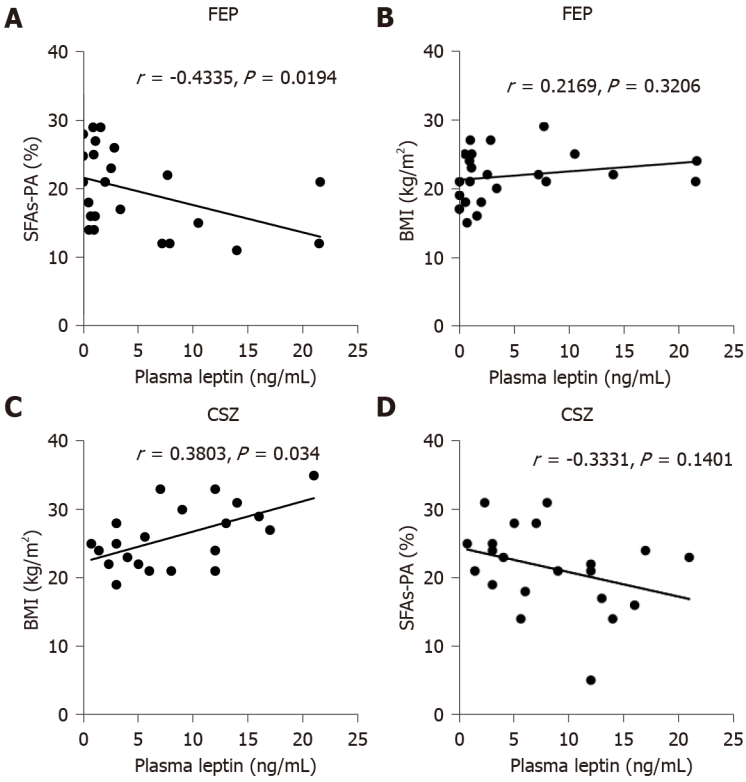


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**Figure 4 Association of plasma leptin with erythrocyte saturated fatty acids and body mass index.** A-D: In first-episode psychosis patients, plasma leptin showed negative correlation with saturated fatty acids (SFAs)-palmitic acid (PA) (A, $r$ = −0.4335, $P$ = 0.0194) but not with body mass index (BMI) (B, $r$ = 0.2169, $P$ = 0.3206), whereas, in chronic schizophrenia patients, plasma leptin showed positive correlation with BMI (C, $r$ = 0.4135, $P$ = 0.0152) but not with erythrocyte SFAs-PA (D, $r$ = 0.3331, $P$ = 0.1401). FEP: First-episode psychosis; CSZ: Chronic schizophrenia; BMI: Body mass index; SFAs: Saturated fatty acids; PA: Palmitic acid.

SFAs, particularly, PA could be a major risk factor for IR and IEE[53,54].

An overwhelming body of evidence suggests that most of the adverse effects including IR, IEE and increased lactate formation induced by SFAs occur as a result of increased oxidative stress and inflammation (see Figure 5 for detail mechanisms). It has been shown that SFAs, particularly, PA can cause abrupt release of $Ca^{2+}$ from endoplasmic reticulum (ER) thereby depleting ER $Ca^{2+}$ store, which in turn leads to a drastic increase in cytosolic and mitochondrial $Ca^{2+}$ concentration *via* entry through store-operated $Ca^{2+}$ channels[55-57]. This process stimulates reactive oxygen species (ROS) formation causing ER stress and mitochondrial dysfunctions (Figure 5). Evidence suggests that PA can induce ER stress in almost all the cellular systems including pancreas, cardiomyocytes, vascular smooth muscle cells, endothelial cells, skeletal muscle cells, glomerular podocytes, hepatocytes, adipose tissue, and brain by disrupting intracellular $Ca^{2+}$ homeostasis[58].

Additional toxicity of SFAs can be produced by their ceramide derivatives because; elevated SFAs have also been shown to stimulate ceramide synthesis[59,60]. Indeed, while studies analyzing skin fibroblasts from patient with schizophrenia have found reduced total ceramide concentration, SFAs (PA) based ceramide concentration was increased compared to the CNT subjects[61-63]. Similarly, altered production of ceramides, containing PA and other SFA, has also been reported in other tissues from patients with FEP and CSZ[61-63]. Although ceramides have many important functions, their increased production can be detrimental as they can induce inflammation, obesity-associated insulin resistance, abnormal FA oxidation and other toxic effects in various tissues by inducing ER stress, mitochondrial dysfunction, and ROS formation (Figure 5)[59,60,64].

Regarding pro-inflammatory effects, SFA accumulation has been shown to induce pro-inflammatory response in adipose tissue, skeletal muscle, and liver[34,57,65]. In these events, PA activated adipocytes as well as intercalated macrophages, particularly inflammatory type (M1 type) have been shown to play a major role by secreting several pro-inflammatory cytokines including IL-1b, IL-6, IL-8, and TNF-α[57-59,65]. These and other inflammatory cytokines have been found elevated in the brain and plasma of patients with FEP and CSZ[66]. Although treatment with AAD has been shown to reduce various cytokines, IL-1b, IL-6, IL-8 and TNF-α remained elevated despite years of treatment[66,67]. Since we observed that like drug-naive patients with FEP, erythrocyte PA and other SFAs were also elevated in AAD treated CSZ patients, therefore, accumulation of SFAs could be the major contributing factor to the elevated pro-inflammatory response throughout the course of schizophrenia illness.

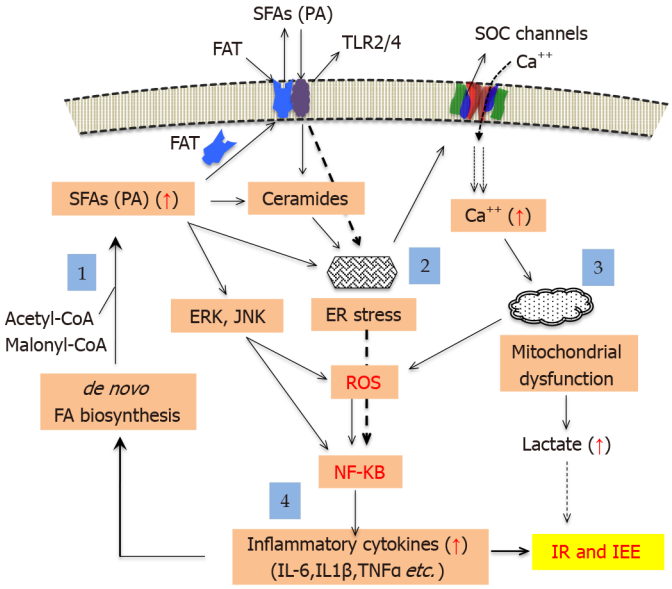


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**Figure 5 Mechanisms underlying saturated fatty acids-(palmitic acid)-induced insulin resistance and impaired energy expenditure.** Saturated fatty acids (SFAs) are synthesized *de novo* in the cytoplasm from acetyl-CoA and malonyl-CoA (light blue box 1), and are transported by fatty acid transporter proteins from intracellular space to the membrane and to the extra cellular space. Excess SFAs-palmitic acid (PA) can also be converted into ceramides, which together with PA can induce endoplasmic reticulum (ER) stress *via* depletion of stored calcium (light blue box 2). ER stress leads to increased calcium influx *via* plasma membrane-bound store operated calcium channels, resulting into the elevation of cytoplasmic and mitochondrial calcium and production of reactive oxygen species (ROS) as a result of mitochondrial dysfunction (light blue box 3). Both PA and ceramides can also activate plasma membrane TLR2/4 receptor resulting in the activation of MAPK/ERK and JNK pathways. Activation of these pathways leads to the production of ROS and NF-κB activation (light blue box 4), which enhances expression of inflammatory cytokine genes resulting into generation of inflammatory response and development of insulin resistance (IR) and impaired energy expenditure (IEE). SFA-induced mitochondrial dysfunction also stimulates anaerobic glycolysis leading to enhanced production of lactate, which also contributes in the development of IR and IEE. SFAs: Saturated fatty acids; PA: Palmitic acid; SOC: Store operated calcium; ROS: Reactive oxygen species; ER: Endoplasmic reticulum; IR: Insulin resistance; IEE: Impaired energy expenditure.

### *Altered leptin synthesis in schizophrenia and its role in the development of IR and IEE*

Although adipose tissue secretes several adipokines[68], leptin and adiponectin have generated huge interest in schizophrenia. However, here the discussion is limited only to leptin for two reasons. First, several studies have shown that leptin but not adiponectin production is reduced in patients with FEP [69]. Second, if elevated above the normal physiological concentration for longer duration, leptin inhibits insulin secretion, increases fat mass accumulation, and obesity *via* its pro-inflammatory and pro-adipogenic actions[11,13].

In schizophrenia, while previous studies have measured plasma leptin in patients with FEP, findings are very conflicting. For instance, a recent meta-analysis and clinical studies found that plasma leptin production was significantly reduced in antipsychotic-naïve FEP patients compared to the CNT subjects [69-71], whereas other studies found opposite results[72-74]. The reasons for these discrepancies are not clear; however, a number of factors including gender, sex hormones, age, eating behavior, duration of illness, smoking, and other medications may affect leptin production. For instance, plasma leptin levels have been found higher in women than men of the same age, and are also affected by smoking[72-75].

Regarding the role of leptin in the development of IR and IEE, animal studies have shown that leptin deficiency can lead to IR and hyperglycemia, whereas, leptin administration can reverse these abnormalities[76]. Thus, normal leptin concentration is required for maintaining glucose homeostasis. Although leptin is a potent regulator/inhibitor of insulin secretion from pancreatic β-cells under physiological condition[11], it can normalize blood glucose level both by insulin dependent and insulin independent mechanisms and with or without involving central nervous system (CNS). For instance, in a rat model of insulin deficiency diabetes, leptin infusion directly into the brain reversed hyperglycemia, suggesting involvement of CNS dependent mechanism[77,78]. Leptin administration in these model animals also normalized plasma levels of glucagon and corticosterone, which are potent hyperglycemic factors. Likewise in mouse model of type-2 diabetes with normal leptin but defect in insulin like growth factor-1 and leptin receptor signaling, leptin administration significantly prevented insulin resistance and hyperglycemia[79].

Leptin also has profound influence on FA metabolism and energy homeostasis both in adipose and non-adipose tissues. It stimulates FA oxidation and glucose uptake in skeletal and cardiac muscles, inhibits glucose output and lipogenesis in liver[80,81]. In white adipose tissue also, leptin has been shown to directly inhibit *de novo* FA biosynthesis, and increase the release and oxidation of FA[82]. Thus, low plasma leptin in patients with FEP that is observed in this study, could be one of the

contributing factors in the increased membrane SFA levels in patients with FEP.

In the present study, although leptin was significantly low in drug-naive patients with FEP, it was significantly elevated in AAD treated CSZ patients, which is in agreement with previous reports showing increased leptin production by AAD treatment[24,25,69]. Leptin elevation by AAD could be a result of their direct antagonistic action at various calcium channels leading to reduce calcium influx, as optimum intracellular calcium is crucial for optimal leptin synthesis and secretion[16,83]. Several lines of evidence suggest that elevated leptin can cause obesity by inducing pro-inflammatory, pro-lipogenic, and pro-adipogenic response[12,13,24]. Leptin has been shown to increase the production of pro-inflammatory cytokines including TNF-α, IL-10, and IL-6 from adipocytes[12]. Along with TNF-α, leptin can also activate macrophages, intercalated within the adipose tissue, to secrete pro-inflammatory cytokines leading to further amplification of inflammatory response[84-86]. It has been suggested that pro-inflammatory effects of leptin, directly or through TNF-α or both, may lead to the inflammation of the pancreas causing βb-cell dysfunction and reduced insulin secretion[10,11,84], which are typically seen in patients with schizophrenia after long-term treatment with AAD.

Pro-adipogenic effect of leptin is further potentiated by its pro-lipogenic and pro-inflammatory responses[12]. Leptin has been shown to increase the production of PLIN1, CAV-1, PPARγ, SREBP1C, and/or adiponectin during differentiation[12]. Together, these proteins orchestrate signaling mechanisms that increase transcription of various genes required for adipocyte differentiation. Further, leptin has been shown to induce lipid accumulation in adipocytes *via* an mTOR-dependent signaling[12], even in the absence of insulin, which plays a crucial role in pre-adipocyte differentiation. This suggests that leptin may induce adipocyte differentiation and lipogenesis even in the absence of insulin signaling. In support of this, a recent study has shown that removing circulating plasma leptin reduced body weight and normalized hyperglycemia in obese animals[13]. This is an important finding, which may help in designing leptin-based therapies for treating obesity and diabetes in schizophrenia and other psychiatric disorders.

This study has some strengths and limitations. Regarding the strengths: (1) The patients and CNT subjects had comparable socioeconomic and demographic characteristics; (2) FEP patients had shortest reported duration of illness (≤ 5 d); (3) no drug abuse; (4) no prior antipsychotic exposure; (5) minimum smoking (2/21); (6) no sedentary life style of FEP patients as all were active duty army personals; (7) no female hormone (estrogens) influence on plasma leptin and membrane FAs as all patients were male; and (8) restricted food diet. Regarding the limitations: (1) The sample size/number of patients were modest and therefore larger studies are needed to validate the above findings; (2) plasma insulin and IR were not measured in these patients; although, several studies have reported IR in drug-naive patients with FEP, and CSZ; and (3) first visit BMI data of CSZ patients was not available; however, these patients were included mainly for comparison purpose, and similar demographic characteristics of patients and CNT subjects.

## CONCLUSION

Over the years it has become increasingly clear that IR and IEE are irreparable metabolic comorbidities in schizophrenia. Although evidence suggests that IR and IEE may appear long before the onset of psychosis, antipsychotic intervention further deteriorates IR and IEE, prompting premature antipsychotic withdrawal, a leading cause of relapse in schizophrenia.

Although various signaling mechanisms could be involved in the development of IR and IEE, in schizophrenia these mechanisms seem to stimulate *de novo* FA biosynthesis leading to increased intracellular concentration of SFAs and their subsequent incorporation into the membrane. Elevated levels of erythrocyte SFAs have also been reported in individuals at ultra-high risk of developing psychosis, therefore, disrupted *de novo* FA biosynthesis could be an early manifestation and underlying cause of IR, IEE and other metabolic comorbidities in schizophrenia.

Antipsychotic drugs have been shown to further aggravate the severity of IR and IEE, which could be related to their ineffectiveness in reducing *de novo* SFA biosynthesis. In addition, all AAD have been shown to increase synthesis of leptin, which if elevated above physiological concentration, stimulates *de novo* FA biosynthesis and lipogenesis while concurrently suppressing lipolysis and FA oxidation. Consequently, leptin elevation by AAD may coincide with the onset of weight gain in schizophrenia. Further, as leptin has been shown to directly inhibit insulin secretion from pancreatic β-cells, its elevation could be a major risk factor associated with the reduced insulin secretion and hyperglycemia, which is typically observed in patients with CSZ during extended treatment with AAD.

One of the strongest evidence for the role of elevated SFAs in the development of IR and IEE is provided by a recent study, which showed that adipocytes overloaded with both SFAs and PUFAs provoked IR irrespective of the inflammatory response suggesting that intracellular accumulation of FAs is sufficient to induce IR whether it increases inflammatory cytokine secretion or not. However, unlike PUFAs, the effect of SFAs could be more detrimental and persistent due to the development of various inflammatory cues. Since oxidative stress and inflammation are potential stimulators of *de novo* FA biosynthesis, therapies aimed at reducing oxidative stress and inflammation or *de novo* FA biosyn-

thesis could be highly effective in reducing IR, IEE and other metabolic comorbidities in patients with schizophrenia and other psychiatric conditions. Additionally, therapies aimed at normalizing leptin level could also be highly effective in increasing insulin level and controlling weight gain during long-term treatment. Since calcium is a potential regulator of leptin synthesis and secretion in adipose tissue, use of calcium supplementation could normalize the plasma levels of both inulin and leptin during schizophrenia treatment.

## ARTICLE HIGHLIGHTS

### *Research background*

Apart from classical symptoms of psychosis, patients with first-episode psychosis and their first-degree relatives display a range of metabolic comorbidities including insulin resistance and impaired energy expenditure. One of the major hurdles in treating schizophrenia psychosis is that intervention with antipsychotic drugs further exacerbates the severity of metabolic comorbidities, which leads to premature antipsychotic withdrawal, a leading cause of relapse in schizophrenia. Finding the underlying mechanism(s) is crucial for designing effective therapies for minimizing the development or exacerbation of metabolic comorbidities during antipsychotic treatment in schizophrenia.

### *Research motivation*

Finding the mechanism(s) underlying metabolic comorbidities is crucial for enhancing treatment adherence and outcome in schizophrenia. Finding such mechanism(s) will also help in designing effective therapies for minimizing the development or exacerbation of metabolic comorbidities during antipsychotic treatment in schizophrenia.

### *Research objectives*

Since leptin and fatty acids together have profound influence on insulin secretion/sensitivity, and energy homeostasis, this study is directed to determine the association between plasma leptin, body mass index, and erythrocyte membrane fatty acids, particularly, saturated fatty acids (SFAs) in patients with first-episode psychosis (FEP).

### *Research methods*

Plasma leptin was measured using sandwich mode enzyme-linked immunosorbent assay; whereas, erythrocyte membrane SFAs were measured using ultrathin capillary gas chromatography. Body mass index was calculated by using the formula: weight (kg)/height ($m^2$). Psychiatric symptoms were evaluated at baseline using brief psychiatric rating scale, and positive and negative syndrome scale (PANSS). Pearson correlation coefficient ($r$) analyses were performed to find the nature and strength of association between plasma leptin, PANSS scores, body mass index (BMI) and SFAs, particularly, palmitic acid (PA).

### *Research results*

Plasma leptin not BMI was significantly lower, whereas, erythrocyte membrane SFAs were significantly higher in patients with FEP compared to the healthy control subjects. Further, plasma leptin showed negative correlation with erythrocyte membrane SFAs-PA, and PANSS scores. However, erythrocyte membrane SFAs-PA showed positive correlation with PANSS scores. Since, similar changes in the plasma leptin and erythrocyte membrane SFAs have also been reported in individuals at ultra-high risk of developing psychosis, the above findings suggest that leptin-fatty acid biosynthesis could be disrupted from the early stage of the illness in schizophrenia.

### *Research conclusions*

Disrupted leptin-fatty acid biosynthesis/signaling could be an early manifestation and underlying cause of metabolic comorbidities in patients with FEP.

### *Research perspectives*

Although large-scale studies are needed for validation of the above results, the data presented above will help in developing appropriate therapies for minimizing the development of insulin resistance and other metabolic comorbidities and increasing treatment adherence and outcome in schizophrenia. Since oxidative stress and inflammation are the major risk factors for the disrupted leptin-fatty acid biosynthesis/signaling, supplementation with calcium, anti-oxidant and/or anti-inflammatory agents will be highly effective in reducing the development or exacerbation of preexisting metabolic comorbidities in schizophrenia.

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## FOOTNOTES

**Author contributions:** Khan MM Designed and performed the research, and wrote the paper.

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**Informed consent statement:** A signed consent was taken from all the patients and CNT subjects.

**Conflict-of-interest statement:** Authors declare no conflict of interest.

**Data sharing statement:** No data are available.

**STROBE statement:** The authors have read the STROBE statement, and the manuscript was prepared and revised according to the STROBE statement.

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ORIGINAL ARTICLE

Observational Study

# Dimensions of emotional distress among Brazilian workers in a COVID-19 reference hospital: A factor analytical study

Marcos O Carvalho-Alves, Vitor A Petrilli-Mazon, Andre R Brunoni, Andre Malbergier, Pedro Fukuti, Guilherme V Polanczyk, Euripedes C Miguel, Felipe Corchs, Yuan-Pang Wang

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## Abstract

### *BACKGROUND*

The coronavirus disease 2019 (COVID-19) pandemic is an unprecedented challenge for public health and has caused the loss of millions of lives worldwide. Hospital workers play a key role in averting the collapse of the health system, but the mental health of many has deteriorated during the pandemic. Few studies have been devoted to identifying the needs of workers on frontline duty.

### *AIM*

To investigate dimensions of common emotional symptoms and associated predictors among Brazilian workers in a COVID-19 reference hospital.

### *METHODS*

This is an observational study of the mental health of professionals in a COVID-19 hospital in the city of São Paulo. We invited all hospital employees to respond to an online survey between July and August 2020, during the first peak of the pandemic. Data of 1000 participants who completed the survey were analyzed (83.9% were women and 34.3% were aged 30 to 40). Hospital workers self-reported the presence of symptoms of depression, anxiety, trauma-related stress, and burnout through the Patient Health Questionnaire-9, the Generalized Anxiety

Disorder-7, the Impact of Event Scale-Revised and the Mini-Z Burnout Assessment respectively. Responses were assembled and subjected to exploratory factor analysis to reveal workers' core emotional distress. Multiple linear regression models were subsequently carried out to estimate the likelihood of dimensions of distress using questions on personal motivation, threatening events, and institutional support.

***RESULTS***

Around one in three participants in our sample scored above the threshold of depression, anxiety, post-traumatic stress disorder, and burnout. The factor analysis revealed a three-factor structure that explained 58% of the total data variance. Core distressing emotional domains were avoidance and re-experience, depression-anxiety, and sleep changes. Regression analysis revealed that institutional support was a significant protective factor for each of these dimensions (β range = -0.41 to -0.20, $P < 0.001$). However, participants' personal motivation to work in healthcare service was not associated with these emotional domains. Moreover, the likelihood of presenting the avoidance and re-experience dimension was associated with having a family member or close friend be hospitalized or die due to COVID-19 and having faced an ethical conflict.

***CONCLUSION***

Distressing emotional domains among hospital workers were avoidance and re-experience, depression and anxiety, and sleep changes. Improving working conditions through institutional support could protect hospital workers' mental health during devastating public health crises.

**Key Words:** COVID-19; Pandemics; Health personnel; Mental health; Psychological distress; Occupational medicine

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**Core Tip:** Although the literature contains many reports on the deteriorating mental health of hospital workers during pandemics, few investigations have focused on the core mental health needs of this specific population. Hence, we subjected the common emotional symptoms of hospital workers to exploratory factor analysis. The main emotional dimensions were avoidance and re-experience, depression-anxiety, and sleep changes. Institutional support was found to be the most relevant protective factor for these emotional dimensions. This investigation could contribute to a better understanding of work-related distress from a dimensional perspective and has indicated comprehensive coping strategies in healthcare settings during a public health emergency.

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## INTRODUCTION

The coronavirus disease 2019 (COVID-19) is an infectious disease that emerged in Wuhan, China in late 2019, and rapidly spread worldwide. A dramatic loss of human life, economic disruption, unemployment, and food insecurity, all caused by the pandemic, have imposed a monumental challenge on communities. Millions of people are at risk of being infected by a life-threatening virus and falling into extreme poverty due to economic and social hardships. During the lockdown, to mitigate the spread of the epidemic, hospital workers (HWs) have played a key role in the fight against disease outbreaks, but without the privilege of confinement. Besides saving lives in exhaustive duties, HWs face an insurmountable burden of increased risk of infection, fear of infecting family members, increased workload, inadequate support, and discrimination[1]. The healthcare workforce is a particularly vulnerable population because the majority lack work protection and access to quality personal protection equipment (PPE). Thus, HWs are exposed to an overwhelmingly stressful environment, which contributes to the deterioration of their mental health, with subsequent development of multiple emotional symptoms.

Frontline HWs directly involved with patient care present greater vulnerability to developing disabling emotional symptoms, as shown in previous epidemics of Ebola virus disease and severe acute

respiratory syndrome[2,3]. Among different psychological reactions, symptoms of anxiety were the first to emerge in the early stages of epidemics. Although anxiety sometimes wanes over the course of the observation, symptoms of depression and distress may persist or intensify[4]. A recent cross-sectional study involving 1257 Chinese COVID-19 healthcare workers (HCWs) has indicated that 71.5% of the sample experienced symptoms of distress, 44.6% anxiety, 50.4% depression, and 34% insomnia[5]. Globally, a comprehensive review confirmed the high frequency of depression (24.3%), anxiety (25.8%), and stress (45%) among frontline HCWs caring for COVID-19 patients[6]. Likewise, a high frequency of symptoms of burnout was also reported in over one-third of Italian healthcare professionals[7]. Regarding the Brazilian context, a study composed of Brazilian HCWs from different regions also found high rates of anxiety (43.3%), depression (40.2%), trauma (36%), and insomnia (61.5%)[8]. Nevertheless, these rates present large fluctuations because data collection relies on individual and contextual aspects of vulnerability, such as socio-demographic characteristics, social support, time of data collection, institutional infrastructure, and public responses, among other factors. Thus, these quantitative rates are limited indicators for clarifying the psychological impact of the COVID-19 and the possibilities of coping with it.

Bearing in mind the plethora of observational studies describing the poor mental health of HWs during the pandemic, few studies have determined the symptomatic clustering of occupational distress during the pandemic. Because most of the emotional symptoms of HWs appear at the same time, we took advantage of a data reduction method of factor analysis to examine the structure of self-reported symptoms in this population. We estimated both individual and contextual factors that were potentially associated with dimensions of distress. The next logical step is to understand how to prevent or reduce emotional distress in healthcare settings. Hypothetically, we posited that core dimensions of emotional distress among HWs would manifest as a sound structure, and that protective or risk factors for this distress would indicate meaningful coping strategies.

The primary objective of the present study was to determine the structure of the mental health of HWs during the COVID-19 pandemic, as related to anxiety, depression, event-related stress, and burnout. Secondarily, we aimed to determine correlated factors of HWs' mental health. These findings could contribute to a greater understanding of the human capacity to face extreme working conditions during global sanitary crises. The implications of potential factors that could improve preventive and supportive strategies in pandemic contexts are discussed.

## MATERIALS AND METHODS

### *Study design*

Data of the current observational study were cross-sectionally collected between July 1 and August 28, 2020, using an online survey on the REDCap platform (https://www.project-redcap.org/). This is the baseline data of an ongoing longitudinal study on HWs' mental health.

At the time of data collection for this study, Brazil was one of the pandemic epicenters of the world, with high rates of new cases and deaths per day. The country had 2662485 confirmed cases, and 92475 deaths as of July 31, 2020[9]. Most of these cases were reported in the state of São Paulo, the most populous in Brazil. São Paulo had 542304 confirmed cases and 22997 deaths in the same period[9]. The Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP) became the main reference healthcare facility for COVID-19 care in the state. Wards of the HCFMUSP main building were entirely reconfigured into a full capacity of 900 beds for the exclusive care of COVID-19 patients. Between July and August of 2020 - around the decline of the first wave of the pandemic - the well-being of hospital professionals in this large care center was on the verge of collapse.

### *Participants*

The inclusion criterion was that participants had to be working at the hospital, in person or from home, at the time of data collection. Medical doctors, nurses, nursing assistants, dentists, speech therapists, psychologists, occupational therapists, dieticians, physical therapists, social workers, pharmacists, clinical laboratory technicians, radiological technologists, and administrative professionals were included as HWs. Professionals from all hospital sites were invited, including the emergency room, inpatient wards, intensive care units, outpatient care, operating room, pharmacy, and laboratory. There were few exclusions as current workers were all adults and able to respond to an online questionnaire. Potential participants did not present linguistic problems, but limited access to the internet from a computer or mobile phone could have been an obstacle to participation.

At the time of the baseline survey, 22056 employees were working in the hospital complex. The online invitation was sent to all HWs through the institutional e-mail, in addition to social media advertising and wall posters in the hospital. Moreover, participants were also encouraged to forward the online survey to eligible colleagues. Respondents could complete the survey, which took approximately 15 min to answer in its entirety, at any time. Using non-probabilistic sampling, data were gathered from 1377 respondents, but only 1000 provided complete data for inclusion in the analysis.

### *Measurement tools*

**The following instruments were used:** Socio-demographic questionnaire: This instrument consisted of questions about age, gender, marital status, educational level, occupational status, living with children or elderly adults, and time of direct contact with COVID-19 patients (hours per week, as an ordinal scale). Questions related to changes in daily routine and individual's ability to cope with distress were also included.

The Impact of Event Scale-Revised (IES-R) was used to screen and rate the severity of distress symptoms in the previous seven days, based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria of post-traumatic stress disorder (PTSD)[10]. The IES-R is a 22-item self-report scale, with a five-point ordinal scale from "not at all" (score 0) to "extremely" (score 4) for each item[10]. Total scores ranged from 0 to 88. Scores of 9, 26, and 44 are used as the cut-off points for mild, moderate, and severe post-traumatic symptoms, respectively[10]. The cut-off point ≥ 26 was adopted in this study, based on previous literature for a probable case of PTSD[5]. Cronbach's alpha coefficient of the IES-R was α = 0.96, indicating an adequate internal consistency.

The Patient Health Questionnaire-9 (PHQ-9) was used to screen and rate the severity of depressive symptoms in the previous two weeks, based on the DSM-IV[11]. The PHQ-9 is a nine-item self-report scale, with a four-point ordinal scale from "not at all" (score 0) to "nearly every day" (score 3) for each item[11]. The total score ranged from 0 to 27. Scores of 5, 10, 15, and 20 are used as the cut-off points for mild, moderate, moderately severe, and severe depression, respectively[11]. The cut-off point ≥ 10 has a sensitivity of 88% and a specificity of 88%, in comparison to the diagnosis of major depressive disorder [12]. Cronbach's alpha coefficient of the PHQ-9 was α = 0.90, indicating good internal consistency.

The Generalized Anxiety Disorder-7 (GAD-7) was used to screen and rate the severity of anxiety symptoms in the previous two weeks, based on DSM-IV criteria[13]. The GAD-7 is a seven-item self-report scale, with a four-point ordinal scale from "not at all" (score 0) to "nearly every day" (score 3) for each item[13]. The total score ranged from 0 to 21. Scores of 5, 10, and 15 are used as the cut-off points for mild, moderate, and severe anxiety, respectively[13]. The cut-off point ≥ 10 has a sensitivity of 89% and a specificity of 82%, in comparison to the diagnosis of generalized anxiety disorder[14]. Cronbach's alpha coefficient of the GAD-7 was α = 0.92, indicating appropriate internal consistency.

The validated single-item Mini-Z Burnout Assessment was used to evaluate the experience of burnout[15,16]. This question instructs respondents to define burnout for themselves: "Overall, based on your definition of burnout, how would you rate your level of burnout?". Responses are scored on a five-category ordinal scale and the threshold of burnout was indicated by a rating ≥ 3. Score 3 was applied to respondents who chose "I am definitely burning out and have one or more symptoms of burnout, such as physical and emotional exhaustion"; score 4 for those who chose "The symptoms of burnout that I'm experiencing won't go away. I think about frustration at work a lot"; and score 5 for those who chose "I feel completely burned out and often wonder if I can go on. I am at the point where I may need some changes or may need to seek some sort of help.". This single-item scale was validated against the exhaustion subscale of the Maslach Burnout Inventory, with a correlation of 0.64 ($P < 0.001$) [15], and previous studies have used it to evaluate burnout during the current pandemic[17].

Psychoactive substance use: Straightforward questions about increased consumption of alcohol and tobacco were included to assess changes in substance use patterns. Answers were recorded as dichotomous yes/no answers.

Threatening events: HWs were asked about the following three self-reported items, with dichotomous yes/no answers, to assess COVID-19 related threatening events: having had a confirmed COVID-19 diagnosis, having had a close family member or friend hospitalized or dying due to COVID-19, and having experienced an ethical conflict during COVID-19 patient care. Ethical issues covered a broad array of extreme contexts such as lack of PPE, disagreement with clinical decisions, overwork, mandatory work despite belonging to a risk group for COVID-19, use of public transportation, *etc.*

Personal motivation: To evaluate contextual variables in the occupational setting, questions about personal motivation and stressors were formulated based on previous literature[2,4,18]. All answers were scored on a five-point Likert scale: "I feel my family, friends or colleagues recognize me for the work I am doing during the COVID-19 pandemic"; "I feel like I'm gaining new knowledge while I am working on the COVID-19 pandemic"; "I feel that my work on the COVID-19 pandemic helps people"; "I am willing to accept the risks because I want to help infected people"; "I feel like I'm developing myself by working on the COVID-19 pandemic"; "I feel motivated to work on the COVID-19 pandemic"; and "I feel part of a movement in my community to take care of infected people".

For statistical analysis, the cumulative score of each of the seven items was calculated, generating a total score labeled "personal motivation". Cronbach's alpha coefficient of personal motivation questions was α = 0.85, indicating appropriate internal consistency.

Institutional support: Based on previous studies[2,4,18], support related to the organizational environment was evaluated using questions on a five-point Likert scale: "I have access to adequate PPE in situations where this is required"; "I have access to equipment and resources needed to provide adequate care to patients"; "I feel that I received adequate training to carry out my work in the COVID-19 pandemic"; "I feel supported by my bosses and by the institution"; "I feel supported by my work team"; "I feel that the patient care protocols are clear in the institution, and I know what must be done"; "If I get infected, I will receive care at my institution"; "If I get infected, my family will receive support";

and "I feel that I have enough rest to continue my job as long as it is necessary".

For statistical analysis, the cumulative score for each of these items was calculated, leading to a total score labeled as "institutional support". These items yielded a Cronbach's alpha coefficient of 0.85, indicating adequate internal consistency.

### Statistical analysis

All analyses were performed using R software, version 4.0.4 (https://www.r-project.org/), and corresponding packages detailed below. The significance level was set at $\alpha = 0.05$ for 2-tailed tests. Because data were not normally distributed according to the Shapiro-Wilk test ($P < 0.05$), a descriptive analysis of participant socio-demographic characteristics was presented as percentage (%) for categorical variables and medians with interquartile ranges for continuous variables.

To investigate the factorial structure of mental health in our sample, an exploratory factor analysis (EFA) was performed. All 39 items of the PHQ-9, the GAD-7, the IES-R, and the single-item Mini-Z Burnout Assessment were assembled in a single dataset to determine the underlying latent constructs of separate items. Before factor extraction, the factorability of the data was checked using the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity. The data were considered adequate for performing EFA because Bartlett's test of sphericity $\chi^2$ value was 31085.35 ($P < 0.001$) and the KMO value was 0.98. The between-item correlation was examined in a matrix containing all 39 individual items of the scales. Factors were extracted using the principal axis factoring method. We used criteria such as Kaiser's eigenvalues > 1[19,20], Cattell's scree plot inspection[19,20], and clinical interpretability of the resulting factor structure to determine the number of factors to be extracted[19,20]. To aid in factor interpretation, the initial solution was subjected to oblique (Oblimin) rotation, assuming that extracted factors would be correlated to reflect the structure of HWs' emotional distress[19,20]. Items presenting factor loadings above 0.40 were retained in each factor, due to their substantial contribution to data variance. The EFA was run with *psych* and *GTArotation* packages in R.

A collinearity analysis was subsequently conducted using the *polycor* package to rule out the correlation between independent variables. All analyzed variables had a Variance Inflation Factor below 3 (for more details, see Supplementary Table 1), suggesting that multicollinearity was not a problem in our data. Two multiple linear regression models were carried out to identify potential predictors for each of the retained factors, using the *beta.lm* function. Factor scores of each of the retained factors were used as dependent variables. After checking for independence, homoscedasticity, normality, and linearity, two regression models were run for each retained factor. First, a crude model included predictor questions on threatening events, personal motivation, and institutional support. Second, the final adjusted model was controlled for sociodemographic variables such as gender, age, marital status, educational level, and occupation. Results were reported as β, 95% confidence interval, and *P* value. Model fit was estimated in terms of $R^2$.

The statistical methods were reviewed by Wang YP from the Department of Psychiatry, School of Medicine, University of Sao Paulo.

### Ethics

The online survey was anonymous and participant confidentiality was assured. Due to social isolation, data were collected by means of an online survey which included an informed consent form explaining the study design, its purpose, and the responsible researcher of the study. This study was approved by the Institutional Board of Research Ethics, protocol # 30710620.2.0000.0068.

## RESULTS

### Demographic and mental health characteristics

Considering Table 1, out of 1000 participants who completed the survey, 83.9% were women, 34.3% were aged 30 years old to 40 years old, 57.4% were married or living with a partner, and 72.9% had an educational level of university graduate or higher. In terms of occupational characteristics, 74.1% were HCWs directly involved in patient care and the remaining 25.9% had no direct contact with patients infected with COVID-19 (office workers and clinical clerks). Regarding participant occupations, 14% were medical doctors, 34.8% were nurses or nursing assistants, and 25.3% were other healthcare professionals. Although participants were recruited using a non-probabilistic strategy, the distribution of socio-demographic characteristics was similar to the total sample of employees in the institution, in terms of gender, age, and occupation. Regarding threatening events directly related to COVID-19 care, 79.6% had direct contact with COVID-19 patients and 32.8% reported having had COVID-19 themselves. An additional 38.6% reported having had a close family member or friend hospitalized or dying due to COVID-19. Approximately one in five participants reported having had to deal with an ethical conflict related to COVID-19 patient care. Regarding the previous history of mental disorders, 28% reported previous psychiatric or psychological treatment and 13.8% reported psychological or psychiatric treatment after the onset of the pandemic.

**Table 1 Sociodemographic and clinical characteristics of participants (*n* = 1000)**

| Characteristics | *n* (%) |
|---|---|
| Age bracket | |
| 18-30 | 211 (21.1) |
| 30-40 | 343 (34.3) |
| 40-50 | 252 (25.2) |
| > 50 | 194 (19.4) |
| Gender | |
| Female | 839 (83.9) |
| Male | 159 (15.9) |
| Other | 2 (0.2) |
| Marital status | |
| Unmarried | 426 (42.6) |
| Married | 574 (57.4) |
| Educational level | |
| < University graduate | 271 (27.1) |
| ≥ University graduate | 729 (72.9) |
| Living with elderly (> 60 yr) | |
| Yes | 233 (23.3) |
| No | 767 (76.7) |
| Living with children | |
| Yes | 450 (45.0) |
| No | 550 (55.0) |
| Occupation | |
| Medical doctor | 140 (14.0) |
| Nurse and nursing assistants | 348 (34.8) |
| Other healthcare professionals[1] | 253 (25.3) |
| Administrative workers[2] | 259 (25.9) |
| Work sector | |
| Emergency room | 60 (6.0) |
| Inpatient ward | 176 (17.6) |
| Intensive care unit | 157 (15.7) |
| Outpatient care | 128 (12.8) |
| Operating room | 44 (4.4) |
| Pharmacy | 36 (3.6) |
| Laboratory | 84 (8.4) |
| Other sectors | 163 (16.3) |
| Direct contact with COVID-19 patient (h/wk) | |
| 0 | 204 (20.4) |
| 1-20 | 311 (31.1) |
| 21-40 | 285 (28.5) |
| > 40 | 200 (20.0) |
| Had COVID-19 (self-reported) | |

| | |
|---|---|
| Yes | 328 (32.8) |
| No | 672 (67.2) |
| Close family or friend hospitalized or who died due to COVID-19 | |
| Yes | 386 (38.6) |
| No | 614 (61.4) |
| Changes in daily routine due to pandemic | |
| Financial failure | 387 (38.7) |
| Lack of public safety | 199 (19.9) |
| Lack of public transport | 297 (29.7) |
| Lack of medical care | 292 (29.2) |
| Distancing from family and friends | 620 (62.0) |
| Previous psychiatric or psychological treatment | |
| Yes | 280 (28.0) |
| No | 720 (72.0) |
| Previous self-reported diagnoses | |
| Anxiety | 91 (9.1) |
| Depression | 78 (7.8) |
| PTSD | 6 (0.6) |
| Previous psychotherapy treatment | 199 (19.9) |
| Previous pharmacological treatment | 177 (17.7) |
| Psychological or psychiatric treatment after pandemic beginning | 138 (13.8) |
| Protective health actions | |
| Physical activities | 274 (27.4) |
| Meditative practices | 182 (18.2) |
| Leisure activities/hobbies | 320 (32.0) |
| Religious practices | 310 (31.0) |
| I'm not doing anything in this sense | 354 (35.4) |
| Ethical conflict | 119 (11.9) |

[1]Other healthcare professionals: dentists, speech therapists, psychologists, occupational therapists, dieticians, physical therapists, social workers, pharmacists, clinical laboratory technicians, and radiological technologists.
[2]Administrative workers: receptionist, information technicians, secretary, security guard.
COVID-19: Coronavirus disease 2019; PTSD: Post-traumatic stress disorder.

Table 2 shows the range and frequency of the scores of the rating scales IES-R, PHQ-9, GAD-7, and Mini-Z Burnout Assessment. The score was categorized into severity levels, according to the established cut-offs. With reference to clinically significant levels of assessed psychiatric categories, 46.8% of participants scored above the level for a probable case of PTSD, 37.9% for depression, 32.5% for anxiety, and 34.9% for burnout. An additional 7.6% of participants reported increased tobacco consumption and 17.1% reported increased alcohol consumption.

### *Factor analysis*

Table 3 shows the rotated pattern matrix of the EFA solution. The initial solution for the 39 items yielded two factors meeting Kaiser's eigenvalue > 1 criterion. Nevertheless, the scree test suggested a three- or four-factor solution, according to Cattell's criterion. Taking into account these two criteria and the clinical interpretability of the resulting factorial structure, a three-factor solution was chosen as the optimal model, in view of the balance between parsimony and comprehensiveness.

After oblique rotation, salient factor loadings (≥ 0.40) for 38 items were observed in a single factor. Cross-loading occurred with the item "trouble falling or staying asleep, or sleeping too much?" (PHQ-9 #3), which contributed to both factors 2 and 3. All three factors accounted cumulatively for 58% of the total data variance. The correlation between factor 1 and factor 2 was 0.64, 0.56 between factor 1 and

**Table 2 Frequency of categories of distress symptoms (*n* = 1000)**

| Scale and severity categories | *n* (%) |
|---|---|
| The Patient Health Questionnaire-9 | 7 (4-13)[1] |
| Minimal (< 5) | 312 (31.2) |
| Mild (5-9) | 309 (30.9) |
| Moderate (10-14) | 177 (17.7) |
| Moderately severe (15-19) | 116 (11.6) |
| Severe (≥ 20) | 86 (8.6) |
| The Generalized Anxiety Disorder-7 | 6 (3-12)[1] |
| Minimal (< 5) | 347 (34.7) |
| Mild (5-9) | 328 (32.8) |
| Moderate (10-14) | 154 (15.4) |
| Severe (≥ 15) | 171 (17.1) |
| The Impact of Event Scale-Revised | 24 (11-42)[1] |
| Minimal (< 9) | 197 (19.7) |
| Mild (9-25) | 335 (33.5) |
| Moderate (26-43) | 225 (22.5) |
| Severe (≥ 44) | 243 (24.3) |
| Mini-Z Burnout Assessment (≥ 3)[2] | 349 (34.9) |
| Increased tobacco consumption | 76 (7.6) |
| Increased alcohol consumption | 171 (17.1) |

[1]Interquatile range.
[2]Participants with a score above the cut-off point for burnout.

factor 3, and 0.55 between factor 2 and factor 3. Cronbach's alpha coefficient for factors 1, 2, and 3 was α = 0.96, 0.94, and 0.87, respectively, indicating adequate internal consistency of each extracted factor.

The first dominant factor explained 28% of the total variance and included 20 items from the IES-R but excluded #15 - "I had trouble falling asleep" - and #2 - "I had trouble staying asleep". The second factor explained 24% of the total variance and included all the items from the GAD-7, 8 items from the PHQ-9 (except #3 - "Trouble falling or staying asleep, or sleeping too much?"), and the Mini-Z Burnout Assessment. The third factor explained an additional 6% of the total variance and included two items from the IES-R (#15 and #2) and one item from the PHQ-9 (#3).

We consistently examined how each item loaded in each factor to label each one of the latent factors. The first factor was composed of all the IES-R items, except two items related to sleep ("I had trouble falling asleep" and "I had trouble staying asleep"). The following three items presented the highest loadings: "I tried to remove it from my memory", "I found myself acting or feeling as though I was back at that time" and "I was aware that I still had a lot of feelings about it, but I didn't deal with them". These items are related to major PTSD-associated symptom clusters, namely avoidance, and re-experiencing.

The second factor was composed of all the items from the GAD-7, almost all the items from the PHQ-9 (except one item related to sleep, "trouble falling or staying asleep, or sleeping too much?"), and the Mini-Z Burnout Assessment. The following three items presented the highest loadings: "Feeling down, depressed, or hopeless?", "Feeling tired or having little energy?" and "Little interest or pleasure in doing things?". These items mostly relate to major symptoms associated with depression. Hence, the second factor was labeled Depression-anxiety. Lastly, the third factor was composed of three items associated with sleep, two of which loaded 0.7 or higher: "I had trouble falling asleep" and "I had trouble staying asleep". The third factor was labeled Sleep changes.

### *Predictors of the mental health dimensions*

Table 4 shows crude and adjusted multiple linear regression models which were built to evaluate potential predictors for each of the emotional dimensions retained from the EFA. First, models were carried out using the following independent variables: direct contact with a COVID-19 patient, previous psychiatric and psychological treatment, had COVID-19, close family or friend hospitalized or died due to COVID-19, ethical conflict, personal motivation, and institutional support. The fitness of all three

**Table 3 Pattern matrix of rotated Oblimin solution as extracted through principal axis factoring**

| Description | Item | Avoidance and re-experience | Depression-anxiety | Sleep changes | Communality |
|---|---|---|---|---|---|
| I tried to remove it from my memory | IES-R-17 | **0.81** | -0.10 | 0.05 | 0.60 |
| I found myself acting or feeling as though I was back at that time | IES-R-14 | **0.79** | 0.03 | -0.01 | 0.66 |
| I was aware that I still had a lot of feelings about it, but I didn't deal with them | IES-R-12 | **0.79** | -0.13 | 0.02 | 0.53 |
| I tried not to think about it | IES-R-11 | **0.78** | -0.12 | 0.04 | 0.53 |
| Pictures about it popped into my mind | IES-R-9 | **0.76** | 0.10 | 0.01 | 0.70 |
| I was jumpy and easily startled | IES-R-10 | **0.75** | 0.12 | 0.02 | 0.71 |
| I tried not to talk about it | IES-R-22 | **0.75** | -0.06 | -0.03 | 0.48 |
| My feelings about it were kind of numb | IES-R-13 | **0.72** | -0.02 | -0.02 | 0.48 |
| I thought about it when I didn't mean to | IES-R-6 | **0.70** | 0.14 | 0.09 | 0.73 |
| I had waves of strong feelings about it | IES-R-16 | **0.68** | 0.12 | 0.12 | 0.71 |
| I stayed away from reminders about it | IES-R-8 | **0.68** | -0.10 | 0.03 | 0.40 |
| I felt watchful or on-guard | IES-R-21 | **0.65** | 0.19 | 0.01 | 0.62 |
| I felt as if it hadn't happened or wasn't real | IES-R-7 | **0.62** | 0.05 | -0.02 | 0.42 |
| I avoided letting myself get upset when I thought about it or was reminded of it | IES-R-5 | **0.62** | 0.05 | 0.07 | 0.48 |
| Other things kept making me think about it | IES-R-3 | **0.61** | 0.12 | 0.22 | 0.70 |
| Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart | IES-R-19 | **0.60** | 0.20 | 0.03 | 0.59 |
| Any reminder brought back feelings about it | IES-R-1 | **0.59** | 0.19 | 0.07 | 0.59 |
| I had dreams about it | IES-R-20 | **0.49** | 0.12 | 0.10 | 0.41 |
| I had trouble concentrating | IES-R-18 | **0.45** | 0.32 | 0.12 | 0.61 |
| I felt irritable and angry | IES-R-4 | **0.45** | 0.34 | 0.09 | 0.60 |
| Feeling down, depressed, or hopeless | PHQ-9-2 | 0.01 | **0.84** | -0.05 | 0.68 |
| Feeling tired or having little energy | PHQ-9-4 | -0.15 | **0.78** | 0.15 | 0.60 |
| Little interest or pleasure in doing things | PHQ-9-1 | -0.07 | **0.75** | 0.09 | 0.58 |
| Feeling nervous, anxious, or on edge | GAD-7-1 | 0.06 | **0.74** | 0.02 | 0.63 |
| Feeling bad about yourself - or that you are a failure or have let yourself or your family down | PHQ-9-6 | 0.05 | **0.74** | -0.09 | 0.52 |
| Not being able to stop or control worrying | GAD-7-2 | 0.16 | **0.72** | -0.01 | 0.69 |
| Becoming easily annoyed or irritable | GAD-7-6 | 0.11 | **0.72** | -0.03 | 0.61 |
| Trouble concentrating on things, such as reading the newspaper or watching television | PHQ-9-7 | 0.04 | **0.68** | 0.07 | 0.55 |
| Worrying too much about different things | GAD- | 0.13 | **0.68** | 0.03 | 0.62 |

| | | | | | |
|---|---|---|---|---|---|
| | 7-3 | | | | |
| Trouble relaxing | GAD-7-4 | 0.01 | **0.68** | 0.22 | 0.69 |
| Overall, based on your definition of burnout, how would you rate your level of burnout | Mini-Z | -0.05 | **0.67** | 0.05 | 0.45 |
| Moving or speaking so slowly that other people could have noticed | PHQ-9-8 | 0.18 | **0.62** | -0.08 | 0.49 |
| Poor appetite or overeating | PHQ-9-5 | 0.04 | **0.56** | 0.13 | 0.45 |
| Feeling afraid as if something awful might happen | GAD-7-7 | 0.31 | **0.56** | -0.12 | 0.53 |
| Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual | PHQ-9-9 | 0.02 | **0.49** | -0.08 | 0.21 |
| Being so restless that it's hard to sit still | GAD-7-5 | 0.27 | **0.46** | -0.06 | 0.41 |
| I had trouble falling asleep | IES-R-15 | 0.21 | -0.03 | **0.81** | 0.85 |
| I had trouble staying asleep | IES-R-2 | 0.17 | 0.05 | **0.74** | 0.77 |
| Trouble falling or staying asleep, or sleeping too much | PHQ-9-3 | -0.16 | **0.46** | **0.53** | 0.60 |
| Eigenvalue; Explained variance (%) | | 10.76; 28.00 | 9.22; 24.00 | 2.50; 6.00 | |
| Total explained variance (%) | | 28.00 | 52.00 | 58.00 | |

Loadings above 0.40 are typed in bold. PHQ-9: The Patient Health Questionnaire-9; GAD-7: The Generalized Anxiety Disorder-7; IES-R: The Impact of Event Scale-Revised; Mini-Z: Single-item Mini-Z Burnout Assessment.

**Table 4 Multiple linear regressions between predictable variables and each of the emotional dimensions of hospital workers (*n* = 1000)**

| | Avoidance and re-experience | | Depression-anxiety | | Sleep changes | |
|---|---|---|---|---|---|---|
| | β (95%CI) | β (95%CI)[1] | β (95%CI) | β (95%CI)[1] | β (95%CI) | β (95%CI)[1] |
| Direct contact with COVID-19 patient (h/wk) | 0.05 (-0.01 to 0.11) | 0.02 (-0.04 to 0.09) | 0.08 (0.02 to 0.13)[b] | 0.02 (-0.04 to 0.09) | 0.03 (-0.03 to 0.08) | -0.02 (-0.08 to 0.05) |
| Previous psychiatric or psychological treatment (self-reported) | 0.33 (0.2 to 0.46)[c] | 0.33 (0.21 to 0.46)[c] | 0.38 (0.27 to 0.5)[c] | 0.38 (0.26 to 0.49)[c] | 0.26 (0.13 to 0.38)[c] | 0.25 (0.12 to 0.38)[c] |
| Had COVID-19 (self-reported) | 0.14 (0.02 to 0.26)[a] | 0.09 (-0.03 to 0.21) | -0.03 (-0.14 to 0.08) | -0.07 (-0.18 to 0.04) | 0.09 (-0.03 to 0.21) | 0.05 (-0.07 to 0.17) |
| Close family or friend hospitalized or who died due to COVID-19 | 0.14 (0.03 to 0.26)[a] | 0.13 (0.02 to 0.25)[a] | 0.06 (-0.06 to 0.16) | 0.06 (-0.04 to 0.17) | 0.14 (0.02 to 0.26)[a] | 0.13 (0.01 to 0.24)[a] |
| Ethical conflict | 0.21 (0.03 to 0.39)[a] | 0.26 (0.08 to 0.44)[b] | 0.08 (-0.09 to 0.25) | 0.12 (-0.04 to 0.29) | 0.02 (-0.16 to 0.2) | 0.03 (-0.15 to 0.21) |
| Personal motivation | -0.03 (-0.11 to 0.04) | -0.02 (-0.09 to 0.06) | -0.03 (-0.1 to 0.04) | -0.02 (-0.09 to 0.05) | -0.01 (-0.09 to 0.06) | 0.01 (-0.07 to 0.08) |
| Institutional support | -0.26 (-0.34 to -0.18)[c] | -0.26 (-0.33 to -0.18)[c] | -0.41 (-0.49 to -0.33)[c] | -0.41 (-0.48 to -0.34)[c] | -0.2 (-0.28 to -0.12)[c] | -0.2 (-0.28 to -0.13)[c] |

[1]Adjusted for age, gender, marital status, educational level, and occupation.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
All models were statistically significant ($P < 0.001$). CI: Confidence interval.

crude models was statistically significant ($P < 0.001$). Likewise, the adjusted $R^2$ for each of the models was 0.14, 0.25, and 0.08 respectively. Second, three final models were adjusted for age, gender, marital status, educational level, and occupation, yielding an adjusted $R^2$ of 0.18, 0.29, and 0.09, respectively. All adjusted models were statistically significant ($P < 0.001$) by $F$ test, considering the Bonferroni test for multiple models.

The analysis revealed that institutional support presented a negative association with all dimensions of emotional distress (β = -0.26, $P < 0.001$; β = -0.41, $P < 0.001$; β = -0.22, $P < 0.001$). Personal motivation was not a significantly correlated variable with dimensions of emotional distress. Moreover, the final sociodemographic adjusted models indicated that participants with previous psychiatric or psychological treatments presented a significant likelihood of manifesting the three mental health dimensions ( β = 0.33, 0.38, and 0.25, $P < 0.001$, respectively). Chi-squared tests were carried out to evaluate the association between this variable and scores of each used scale, showing a $P$ value < 0.001 for all tests, which points out that pre-pandemic psychopathology was associated with higher rates of mental health outcomes (data not shown, available upon request).

In terms of events related to COVID-19 care, the dimension of avoidance and re-experience also presented a significant association with those HWs who had a close family member or friend who was hospitalized or died due to COVID-19 (β = 0.13, $P < 0.05$) and had experienced an ethical conflict during COVID-19 patient care (β = 0.26, $P < 0.01$). Furthermore, direct contact with COVID-19 patients was positively associated with the depression-anxiety dimension (β = 0.08; $P < 0.01$) and having had COVID-19 (β = 0.14; $P < 0.05$) was associated with avoidance and re-experience in the non-adjusted crude model.

Regarding sociodemographic predictors as data not shown, high educational level was negatively associated with all factors ($P < 0.01$; $P < 0.01$; $P < 0.05$). Age presented a negative association with factors 1 and 2 ($P < 0.01$; $P < 0.001$). Being a nurse was a significant factor associated with the first dimension ($P < 0.01$) when compared with being a medical doctor.

## DISCUSSION

The mental health status of 1000 workers in a large COVID-19 reference hospital was assessed through self-reporting scales as applied online during the 2020 pandemic peak, a hectic period for HWs when exhausted professionals needed to continue to fight to stop the frightening level of deaths caused by COVID-19. Unsurprisingly, the results indicated a high frequency of depression, anxiety, stress, and burnout, as well as increased consumption of tobacco and alcohol, which were in line with reported rates found in previous studies[21-23]. Over one in four participants reported previous psychological or psychiatric treatment and an additional 14% of participants reported that they started treatment after the beginning of the pandemic. This incremental figure of HWs in need of care confirmed the vulnerability of this population to emotional distress during a demanding global health crisis. We showed a three-factor structure as a well-fit model for data variance of multiple co-occurring symptoms among HWs. Avoidance and re-experience, depression-anxiety, and sleep changes represent core dimensions of their prevalent emotional symptoms. Moreover, our findings suggested that the support of the organizational environment was the preventive intervention most associated with workers' emotional reactions. Also, professionals who had a close relative or friend present severe COVID-19 or had experienced an ethical challenge also presented a significant likelihood of association with the PTSD-like dimension of avoidance and re-experience. These results only include the suffering experience of a sample of HWs; however, their relevance should be examined in light of their fundamental role in the battle against the COVID-19 pandemic. Protecting their mental health by providing sufficient institutional support could make a difference to HWs' well-being.

Although the method of factor analysis used for examining underlying dimensions of psychopathologies is a well-known technique for data reduction in psychiatry, we are aware of only one factorial study on the mental health of HWs during the pandemic. Chatterjee *et al*[24] conducted a factor analysis of distress among 140 Hindu HCWs and observed a four-factor structure: sleeplessness, anxiety, irritability, and hopelessness. In line with our findings, they also found that symptoms of sleep, anxiety, and depression play an important role in HWs' distress. Unlike them, however, we found that stress-related responses were the most relevant dimension for data variance and sleep changes had the lowest impact. While our second factor included symptoms of depression and anxiety, symptoms such as hopelessness prevailed over irritability or anxiety. The difference could be explained by the fact that they selected a smaller sample size of participants, collected data in different stages of the pandemic course, and used specific instruments to assess only insomnia and perceived stress. Direct comparison between factorial models and their generalizability is not feasible.

Our dominant factor was the stress-related Avoidance and re-experience dimension, which was correlated with the depression-anxiety and sleep changes dimensions. This finding might support the argument that the current pandemic is considered a stressor event capable of triggering PTSD-like responses as well as worsening other related mental health problems such as depression and anxiety [25]. Furthermore, depressive, anxiety and burnout symptoms could be more associated with chronic stressors not directly related to COVID-19 care. Regarding externalizing behaviors, our questionnaire indicated that HWs increased their consumption of psychoactive substances, namely 7.6% tobacco and 17.1% alcohol. However, we did not include these variables in the analysis because of their weak contribution to the factorial model (communality < 0.10, data not shown). Hypothetically, HWs might be using more psychoactive substances to alleviate their distress[26]. This increased consumption is one of the aspects that might be bi-directionally related to their sleep problems[27], disturbing their sleep, or

being a way of dealing with distress caused by inefficient rest. However, a more consistent investigation is warranted.

This study was conducted during the peak of the first wave of COVID-19 in Brazil, which was associated with the highest level of hospitalization of infected patients and produced an overwhelmingly stressful environment for HWs[28]. Our frequency of symptoms of traumatic events (46.8%) was similar to the rate of 49.4% found during the contagion peak in Italy[29]. The current data revealed that while working as a nurse was associated with the likelihood of presenting the avoidance and re-experience dimension, being a HW of older age and higher education level were both protective factors. These findings are in accordance with a recent systematic review that revealed that nurses facing pandemic crises experienced more stress when compared to doctors and that having more experience in healthcare work was a protective factor[30]. We also found that having had a close family member or friend hospitalized or die due to COVID-19 and having experienced an ethical conflict related to COVID-19 patient care had a significant positive association with this dimension. In this regard, recent studies have indicated that the loss of colleagues and dealing with ethical challenges in a time of acute resource shortages were associated with an increased risk of mental disorders[31-33]. Our results suggested that stress-related symptoms like avoidance and intrusive traumatic thoughts are a part of hospital professionals' emotional response to demanding conditions and adverse settings. Hence, it is recommended that hospital providers and administrators pay special attention to the occurrence of these symptoms among workers.

The second factor was labeled Depression-anxiety and the included items were taken from the PHQ-9, the GAD-7, and the burnout assessment. Previous studies have reported high levels of depression, anxiety, and burnout among HWs dealing with the pandemic[31,34,35]. Our findings were in accordance with these studies, showing that the retained dimension accounted for a substantial 24% of the data variance, with symptoms of hopelessness, anhedonia, and anergia being more represented than complaints of anxiety and burnout. A possible explanation for this dimension may be the important role of chronic stress in the workplace and decreased protective health actions for the development of psychological conditions among those professionals, such as high workload, changes in daily routine, reduced physical activity, scarcity of resources, and lack of rest[36-38]. Corroborating this proposition, our analysis did not find a significant correlation between acute threatening events and this dimension, which is also consistent with the suggestion that the association between direct contact with COVID-19 patients and anxiety and depression is based on weak evidence[23].

The third factor, Sleep changes, included three sleep-related items from the IES-R and the PHQ-9. Although no specific scale for screening sleep disorders was employed in this study, our factor analysis suggested an independent and unobservable sleep pattern, with the difficulty of falling or staying asleep having a high impact. This is consistent with previous studies[30,39,40] that have demonstrated an increased level of sleep problems among such professionals, with a frequency reaching 45%. A study describing the experience of supporting HWs in the current pandemic also reported a high frequency of sleep complaints and suggested specific support be provided for this condition[41]. Several aspects may be associated with these sleep changes, including physical exhaustion, quarantine, sleeping in unfamiliar places, separation from family, concerns about getting infected or infecting close contacts, and long work shifts[42,43]. Therefore, this sleep factor represents a neurovegetative dimension and may be triggered by other aspects apart from trauma-related stress, depression, anxiety, and burnout, which might justify its inclusion in a different emotional distress dimension.

Regarding coping strategies, the strongest finding was that aspects related to the organizational environment had a protective effect on overall emotional dimensions, which is in line with previous literature[44,45]. Amid a paucity of information on specific psychological interventions that could be useful to cope with the current pandemic[46], our findings provide some support to interventions that have already been applied in practice[47-51], such as providing adequate PPE and receiving adequate training, implementing an adequate and clear protocol for dealing with possible ethical conflicts, supporting HWs' families, and providing enough rest time for workers to continue their job. For the purposes of the present paper, we only evaluated the institutional support during the peak of the first wave in Brazil. However, several studies have demonstrated concerns about chronic COVID-19 sequelae, which could be associated with mental health outcomes among other clinical conditions, requiring specific treatments and continuous aid[52,53]. Moreover, although altruistic acceptance of risk and support from family and friends have been considered protective coping factors in previous studies [30], our results did not confirm this relationship, showing any association between motivational coping strategies and emotional distress. However, this finding corroborates a recent study that did not find an association between adaptive coping strategies and symptoms of anxiety, depression, and stress[54]. A possible explanation for this is that we analyzed these aspects together as a personal motivation predictor, including items feeling recognized, motivated, and altruistic, which may enable a more consistent assessment of the role of all these variables in preventing the worsening of HWs' well-being.

This study has some limitations. First, although our sample size was large enough, it was not representative of our institutional HWs, with a low response rate of 4.5%, and might be vulnerable to self-selection and response bias. Nevertheless, a good fit factorial model does not require a representative sample, but a large enough size with correlated items[19]. Second, self-reported online questionnaires were used, hence response bias may have occurred, where over or underreporting could not be ruled

out. Third, considering the study design, we could not distinguish preexisting mental health symptoms from new-onset symptoms. Many participants self-reported previous history of mental disorders and treatment, but our rates clearly surpass the pre-pandemic level. Finally, because data were cross-sectionally collected in the baseline wave of an ongoing longitudinal study, causal relationships with predictors should not be stated definitively.

## CONCLUSION

This factor analytical study of common psychological symptoms among HWs during the first wave of the current pandemic revealed that avoidance and re-experience, depression-anxiety, and sleep changes were the core reported manifestations. Institutional support was the most relevant protective aspect of the workers' well-being. Mental health professionals, health service administrators, and policy-makers should be mindful of the core dimensions of emotional distress of frontline workers and implement sound safeguarding measures. In the future, interventions should be tailored to improve occupational well-being in health services during subsequent waves of COVID-19 as well as possible forthcoming pandemic crises. Moreover, tracking the longitudinal course of HWs' reactions may help clarify their coping mechanisms for adversity.

## ARTICLE HIGHLIGHTS

### *Research background*

The current pandemic has generated a dramatic challenge to public health, in a set of contextual changes throughout the world, including millions of deaths, the collapse of health systems, economic disruption, and food insecurity. During frontline service, hospital workers (HWs) were exposed to an increased risk of becoming infected, fear of infecting family members, ethical conflicts, overwhelming workload, among other stressors. Facing these stressors may contribute to a decline in their psychological well-being. Supporting this suggestion, high rates of depression, anxiety, stress, burnout, and insomnia have been reported among hospital professionals.

### *Research motivation*

Several observational studies have described rates of common psychological responses of HWs facing the current pandemic. Nevertheless, few studies have examined the structure of multiple co-occurring symptoms through exploratory factor analysis. The data reduction approach is a potential asset to expand our understanding of how to prevent or reduce emotional distress in healthcare settings using a smaller number of variables.

### *Research objectives*

We aimed to show core dimensions of common psychological symptoms as well as their associated predictors among HWs in a coronavirus disease 2019 (COVID-19) reference hospital.

### *Research methods*

This is an observational study, and the data were cross-sectionally collected using an online survey during the first peak of the pandemic in Brazil. Data of 1000 HWs who completed the survey were analyzed (83.9% women and 34.3% aged 30 to 40). Self-reported symptoms of depression, anxiety, trauma-related stress, and burnout were subjected to exploratory factor analysis. Multiple linear regression models were then carried out to estimate predictors for each of the factors retained using questions on personal motivation, threatening events, and institutional support as independent variables.

### *Research results*

HWs presented high rates of depression, anxiety, stress, and burnout during their frontline duty, as well as increased tobacco and alcohol consumption. The following three factors were the main dimensions of HWs' distress: avoidance and re-experience, depression-anxiety, and sleep changes. Institutional support was the most significant protective factor for each of these dimensions. Furthermore, scores of the avoidance and re-experience dimension were associated with having a family member or a close friend with severe COVID-19 and having dealt with an ethical challenge. Contrary to expectation, participants' personal motivation to work with COVID-19 patients was not associated with these factors.

### *Research conclusions*

This factor analytic study revealed distressing dimensions of avoidance and re-experience, depression-

anxiety, and sleep changes as the core psychological reactions of a sample of Brazilian HWs during the pandemic. It also highlighted the importance of institutional support in preventing a worsening of hospital professionals' mental health during their pandemic service. These findings have implications for tailoring interventions to maintain HWs' mental health.

### *Research perspectives*

Data reduction methods, such as exploratory factor analysis, contribute to enlarging our understanding of the core psychological reactions of hospital professionals during a sanitary crisis. Multiple co-occurring symptoms can be clustered in a sound dimensional structure. In the future, institutional strategies based on these unobservable patterns could be planned to improve occupational well-being in health settings, either during subsequent waves of COVID-19 or during other future pandemic crises. Lastly, analyzing the longitudinal trajectory of the HWs' reactions could help to elucidate coping mechanisms in similar stressful periods.

## FOOTNOTES

**Author contributions:** Carvalho-Alves MO, Brunoni AR, Malbergier A, Fukuti P, Polanczyk GV, Miguel EC and Corchs F contributed to the study design, data acquisition and interpretation, and revised the manuscript; Wang YP conceived the statistical analysis; Carvalho-Alves MO, Petrilli-Mazon VA, Corchs F and Wang YP conducted the statistical analysis and wrote the preliminary draft; all authors reviewed and approved the manuscript in its final version.

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*REVIEW*

# Influencing factors, prediction and prevention of depression in college students: A literature review

Xin-Qiao Liu, Yu-Xin Guo, Wen-Jie Zhang, Wen-Juan Gao

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## Abstract

The high prevalence of depression among college students has a strong negative impact on individual physical and mental health, academic development, and interpersonal communication. This paper reviewed the extant literature by identifying nonpathological factors related to college students' depression, investigating the methods of predicting depression, and exploring nonpharmaceutical interventions for college students' depression. The influencing factors of college students' depression mainly fell into four categories: biological factors, personality and psychological state, college experience, and lifestyle. The outbreak of coronavirus disease 2019 has exacerbated the severity of depression among college students worldwide and poses grave challenges to the prevention and treatment of depression, given that the coronavirus has spread quickly with high infection rates, and the pandemic has changed the daily routines of college life. To predict and measure mental health, more advanced methods, such as machine algorithms and artificial intelligence, have emerged in recent years apart from the traditional commonly used psychological scales. Regarding nonpharmaceutical prevention measures, both general measures and professional measures for the prevention and treatment of college students' depression were examined in this study. Students who experience depressive disorders need family support and personalized interventions at college, which should also be supplemented by professional interventions such as cognitive behavioral therapy and online therapy. Through this literature review, we insist that the technology of identification, prediction, and prevention of depression among college students based on big data platforms will be extensively used in the future. Higher education institutions should understand the potential risk factors related to college students' depression and make more accurate screening and prevention available with the help of advanced technologies.

**Key Words:** Depression; Prediction; Prevention; Artificial intelligence; Big data; Machine learning

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**Core Tip:** This study reviewed the extant literature by identifying nonpathological factors related to college students' depression, investigating the methods of predicting depression, and exploring nonpharmaceutical interventions for depression among college students. The influencing factors can be categorized into students' demographic characteristics, college experience, lifestyle, and social support. For the prediction of depression, methods such as machine algorithms and artificial intelligence have been employed together with the traditional psychological scales. This study summarizes general and professional measures that can be taken for the prevention and treatment of college students' depression.

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## INTRODUCTION

The prevalence of depression among college students has gradually increased in recent years, even exceeding that of the general public, which has become a global phenomenon[1]. Mounting research has focused on the topic, and the consensus is that the high prevalence of depression among college students cannot be ignored. For instance, in Asia, a follow-up survey and analysis based on 1401 undergraduates in China over four consecutive years showed that approximately 20% to 40% of undergraduates suffered from depression, anxiety and stress to different degrees, and approximately 35% of them had higher depression levels than the normal population[2]. An online survey based on 7915 freshmen students at Hong Kong University in China showed that 21%, 41% and 27% of individuals had moderate or higher levels of depression, anxiety and stress, respectively, far exceeding the average in the general population[3]. The median prevalence rate for depression among 15859 college students in six ASEAN countries (Cambodia, Laos, Malaysia, Myanmar, Thailand and Vietnam) was 29.4%, and 7% to 8% of students committed suicide; despite the high prevalence of mental illness, their willingness to seek professional help was relatively low[4]. Among 642 college students in Saudi Arabia, the proportions of moderate depression, anxiety and stress were 53.6%, 65.7% and 34.3%, respectively[5]. In Africa, among 1206 Nigerian college students, 5.6% had mild depression, and 2.7% suffered severe depressive disorder[6]. In North America, 53% of 1455 American college students reported that they had experienced depression since the beginning of college, and 9% said they had considered suicide since the beginning of college[7]. Thirty percent of 7800 Canadian undergraduates reported that their psychological stress increased, and the degree of depression was significantly higher than that of the general population[8]. In Europe, more than one-third of college students from three higher education institutions in the United Kingdom suffered from long-term mental health diseases, the prevalence rate of which was higher than the average level of national surveys, and the scores of the eight dimensions of mental health, measured by the MOS 36-item short-form health survey, were all significantly lower than those of local peers aged 18 to 34[9]. In Oceania, 21.8% of 751 Australian college students reported depression, and their depression scores were higher than the standard scores of the general Australian population[10].

The global outbreak of the coronavirus disease 2019 (COVID-19) pandemic in 2020 brought in additional pressure and challenges for the prevention and treatment of depression among college students. Many reports worldwide voiced that college students had a greater probability of struggling with higher levels of depression after the pandemic. The data show that after the outbreak of the pandemic, acute stress, anxiety, and depressive symptoms were widespread among Chinese college students, and the incidence rate was significantly higher than before[11]. The prevalence rates of moderate depression and suicide-related symptoms among 212 Japanese college students were 11.7% and 6.7%, respectively[12]. Among 2031 American college students, 48.14% suffered from moderate to severe depression, 38.48% experienced moderate to severe anxiety, 18.04% had suicidal thoughts, and 71.26% reported that their stress/anxiety levels increased during the pandemic[13]. More than a quarter of Swiss university students had depressive symptoms during the pandemic, which was much higher than that of the general population and higher than that before the pandemic[14].

The transition from high school to university is full of tension and adaptation. It is a critical period for the shift from late adolescence to adulthood or emerging adulthood, which is neither adolescence nor young adulthood but theoretically and empirically distinct from both periods[15]. Arnett stressed that

this is a stage full of self-exploration, instability, possibility, self-focus, and something in between[16]. At this phase, individuals will face the challenges of identity and role transformation and more diversification and complexity from families and institutions. Specifically, compared with middle schools, universities put forward higher requirements for freshmen's independence and self-regulation, such as the independence of living in a new place, the autonomy of learning patterns, and the complexity of social networks. However, confronted with these challenges, college students entering the campus for the first time often wander between independence and dependence. On the one hand, they are eager to enjoy new freedoms; on the other hand, it is difficult to eliminate their attachment and economic dependence on their parents; thus, they are often in a state of "pseudo independence"[17].

In summary, compared with teenagers and adults, college students are the key group at significantly higher risk of poor mental health. A series of factors, including family, college, studies, and social interactions, are likely to induce college students' depression. However, few publications have reviewed the literature on risk factors for college students' depression. Given that most studies examined individual risk factors based on samples from a certain country or region, this paper reviewed the extant literature related to college students' depression and aimed to systematically present the nonpathological factors, predictions and nonpharmaceutical interventions for college students' depression to provide a reference for stakeholders worldwide.

## NONPATHOLOGICAL INFLUENCING FACTORS OF DEPRESSION

The related factors can be roughly divided into four categories: biological factors, personality and psychological state, college experience, and lifestyle. The literature review presented the specific risk factors under four categories in Table 1. Subsequently, this paper explained certain factors with controversial research conclusions.

### *Sex*

Some studies have asserted that the risk of depression in female college students is significantly higher than that in male students[24,26,40,41]. The possible mechanism lies in physiological differences between the sexes (such as genetic vulnerability, hormone, and cortisol levels), differences in self-concept, and different role expectations from society leading to different emotional responses and behavior patterns. Females are more likely to internalize their negative feelings, whereas males resort to externalizing behaviors such as smoking and alcoholism[42-44]. However, some analyses did not find significant sex differences[28,45,46]. Other studies have shown that men have a higher prevalence of depression[20,47]. This may be ascribed to their conservative attitudes toward mental health counseling and treatment under certain social expectations. For instance, women are more help-seeking than men and therefore tend to have more diagnoses and treatment. In particular, gregarious women are more likely to discuss their difficulties with others, such as family and friends, as a form of coping. Nevertheless, considering that societal expectations for men might be different, with those who express vulnerable emotions being regarded as weak, the depressive symptoms of men may manifest as anger and excessive indulgence in smoking and drinking, which are more acceptable masculine expressions in society[43,44].

### *Year of study*

Most studies have found significant differences in the depression level of college students in different years of their education, although some found the difference to be insignificant[28]. Some research has suggested that undergraduates with lower grades suffer more from depression, which can be attributed to separation from relatives and friends, social adaptation, academic pressure, and increased investment in social activities. A survey of Chinese students showed that the highest scores for depression, anxiety and stress all appeared in the first three years of college, and students' mental health status was relieved in the fourth year with the passage of time[48]. A survey of medical students in Saudi Arabia found that students' depression levels continued to rise from the first year of enrollment, reached maximum intensity in the third year, and then dropped significantly with graduation in the last year[22]. However, other studies found that compared with other undergraduates, senior students had a higher risk of depression. The graduation year is a critical period for individuals to further their studies or go into society, and students are faced with many new stressors, such as graduation pressure, pressure from grades and applications to other institutions, difficulties in future career planning and employment discrimination in the labor market[49]. Compared with undergraduates, postgraduates may be exposed to greater pressure in obtaining financial security, stable employment, getting married and other aspects of life, which results in a higher risk of depression[19,41].

### *Lifestyle*

The depression issues of college students can largely be attributed to their lifestyles. First, the lack of regular physical activities increases the risk of depression[11,14], particularly for individuals whose amount of weekly physical activity fails to meet the standards of the World Health Organization[20].

**Table 1 Factors related to depression in college students**

| Category | Specific variable | Factor positively correlated with high levels of depression |
|---|---|---|
| Biological factors | Sex | Inconclusive |
| | Nationality | Ethnic minorities[18], international student[14,19] |
| | Family | Low family socioeconomic status[14,18,26,27] |
| | | Non-only child[19], too many siblings[6] |
| | | Parents divorced or having mental problems[29,30], family dysfunction[11] |
| | | Adverse childhood experiences such as injury, physical violence, psychological abuse and lack of family care [30,31] |
| | | Insufficient social support especially family support[11,14,36,39] |
| Personality and psychological state | | Neuroticism[20] |
| | | Presence of psychological illness[21,22] |
| | | High level of psychological stress (including value, aspiration, deprivation, or coping)[23] |
| | | Low self-efficacy[14,24] |
| | | Solitude[25] |
| College experience | Year of study | Inconclusive |
| | Academic performance | Poor academic performance[21,30] |
| | Financial support | Lack of financial resources and support[21] |
| | Living arrangement | Do not have own room[6,26] |
| | College satisfaction | Low satisfaction with teachers and low satisfaction with college major[26], low satisfaction with university facilities[22] |
| Lifestyle | Physical exercise | Lack of physical exercise[11,14,20] |
| | Substance abuse | Smoking and drinking[6,12,21] (especially alcohol intake[32,33]) |
| | Sleep | Daytime drowsiness[20,34], poor sleep quality[21], sleep too short[35] or too long[10] |
| | Diet | Unhealthy food intake[30], gluttony[14], skipping breakfast[10], malnutrition[36] |
| | Network usage | Social networking sites, online game addiction[37,38] |

Second, substance abuse, such as excessive smoking, alcohol abuse[6,12,21], or alcohol intake[33], can cause depressive disorders, and it should be noted that their relationship might be bidirectional. Studies have shown that individuals with depression are more likely to drink obsessively to relieve their negative emotions due to their poor self-control, which will in turn trap them in a vicious cycle between excessive drinking and depressive disorders[32]. Third, unhealthy sleeping habits such as daytime sleepiness[20,34], poor sleep quality[21], and short[35] or long sleep duration[10] may lead to depressive symptoms. Fourth, unhealthy nutritional habits are also among the crucial factors that are strongly correlated with depression[36]. From the perspective of dietary structure and nutritional habits, individuals with depression often report excessive intake of high-fat snacks and margarine/butter/meat fat and inadequate intake of fruits, vegetables, and lean protein[30]. Overeating[14] and skipping breakfast[10], especially for males, are also related to depressive disorders.

### *Network usage*

Relevant studies have indicated that depression in college students is associated with their time spent on the internet[50,51]. Those who suffer from internet addiction and dependence are more likely to struggle with depression[52], and phubbing (a portmanteau of the words "phone" and "snubbing") has been proven to be a mediator of the relationship between depression and problematic internet use[53], mainly focusing on social networking and entertainment[54].

### *Social software*

Some researchers believe that social software, as a complementary mode of providing social support, can provide more help for people with low social support, thus reducing the occurrence of depression [55]. However, there is increasing recognition that social networks, especially the excessive use of social media, are closely related to depression[56-60]. Regarding the possible contributing factors, first, individuals who frequently use social software are more likely to have a fear of missing out, and they

are always worried that they will miss some important information if they do not refresh the social platform dynamics frequently. This persistent social anxiety will increase the risk of depression[61]. Second, college students who are addicted to social media are more likely to have a comparison mentality when checking the status updates of others on social network platforms, especially when they feel that others' lives are better than their own, which can result in symptoms of depression[62]. Third, it is quite impossible for those who struggle with depressive disorders to establish satisfactory interpersonal relationships in virtual space since they usually maintain poor relationships in the real world. The lack of expected support from social networks undoubtedly aggravates their depression[63].

In addition, because the COVID-19 pandemic has aggravated the depression of college students worldwide, we further analyzed the influencing factors of college students' depression against the background of the COVID-19 pandemic, apart from the general factors mentioned above: (1) Given that COVID-19 is highly contagious and uncertain, the higher risk of becoming infected with COVID-19 is closely related to individuals' level of depression. Research has indicated that individuals who live in high-risk areas for COVID-19, have close contact with the COVID-19 virus, or have acquaintances or relatives infected with COVID-19[19,41] often have a higher prevalence of depression; (2) Considering that the internet serves as the main channel for college students to obtain information about COVID-19, those who browse the internet for a short time will not suffer from too much anxiety because of the small amount of information they receive. Meanwhile, students surfing the internet for a long time will be able to obtain more accurate details about COVID-19, which can prevent misunderstanding relevant information. Nevertheless, individuals with shorter browsing times often have a higher risk for depression given that they may be easily misled by the rumors and have limited time to verify the authenticity of relevant information[64]; (3) Academic stress increases the degree of depression of college students with the closure of schools, the challenges of online courses and the risk of graduation delay[13,65]; (4) Financial pressures include the impact of the pandemic on family economic resources [49] and the increasing uncertainty of individuals about future employment[13]; (5) Environmental changes, home study, self-isolation, isolation from relatives and friends, decreased exercise frequency, uncertainty of school reopening, regular temperature measurement, wearing masks for a long time, cancellation of package deliveries and take-out supplies and other forced changes in daily study and living habits all increase the risk of depression among college students[13,49]; (6) There is less family support, social support and deteriorating family relations[65]; and (7) Social confidence wanes. Research has shown that the prevalence of depression also increases when individuals lack confidence in the government[66].

## PREDICTING DEPRESSION

Traditional depression prediction methods are based on various self-rated psychological scales, such as the 21-item depression, anxiety and stress scale (DASS-21) and the self-rating depression scale (SDS). A growing body of research on the reliability and validity of the DASS-21 scale has been published from throughout the world (such as in Britain, Portugal, The Netherlands, Italy, the United States, and Nepal), all of which show that the DASS-21 is a mature tool that can accurately measure the symptoms of depression, anxiety and stress in adult clinical and nonclinical samples and identify and screen people at high risk of depression[67-70]. Similar to the DASS-21, the prediction reliability and validity of the SDS scale for depression have also been confirmed and recognized by relevant studies[71-73]. These are screening tools, and when elevated scores are detected, further evaluation is needed by a clinician. Moreover, the measurement often needs to rely on the patient's own active consultation and cooperation, which is costly, time-consuming, and inaccurate, and there is a risk of social stigma for patients. In recent years, with the progress of science and technology, a series of more advanced methods of depression risk prediction and identification, such as machine learning and artificial intelligence, has emerged, which can deeply learn all types of social and behavioral characteristics of people with potential mental illness risk based on big data and then accurately simulate, identify and predict who they are. Typical methods include support vector machines, decision trees, naïve Bayes classifiers, K-nearest neighbor classifiers and logistic regression[74]. More specifically, support vector machines are applied to classify handwritten digits and organize cancer tissue samples using microarray expression data[75,76]. Decision trees serve as a hierarchical classifier, employing certain rules to divide the predictor space. The naïve Bayes classifier is based on Bayes' theorem and is employed to predict class membership probabilities. K-nearest neighbor classifiers are instance-based learning classifiers that compare a new datapoint with the k nearest sample datapoints, regarding the class with the nearest neighbors to the new datapoint as the class of the datapoint. Logistic regression, as a probabilistic linear classifier, directly estimates class probabilities with the logit transform[74].

The gait feature analysis method based on machine learning has been developed as a supplementary tool to identify depression among college students. Relevant research found that the gait of depressed and nondepressed college students showed significant differences. The specific gait performance of depressed patients included reduced walking velocity, arm swing, vertical head movement and stride length, increased body sway and a slumped head posture. When the above series of features were

applied to classifiers with different machine learning algorithms, the accuracy of depression screening and recognition reached 91.58%[77]. A study collected 121 campus behaviors of college students, including basic personal information, academic achievements, poverty subsidies, consumption habits, daily life, library behaviors, and eating habits, and found that 25 campus behaviors are related to depression, such as failing exams, having bad eating habits, increasing night activities, decreasing morning activities, and seldom participating in social activities (such as eating with friends). On this basis, a depression recognition method was developed by combining machine learning algorithms[78]. There is also research and development of a machine learning method to identify depression based on college students' smartphone and fitness tracker data (*e.g.*, Bluetooth, calls, location, campus map, phone usage, steps, sleep), which extracts many features that can effectively identify depression, such as long-term inactivity and restless sleep at night; the recognition accuracy of this method for college students' depression can reach over 80%[79].

In addition, it is worth noting that social software has increasingly become a nonpathological risk factor for depression among college students. Addiction to social software is often more likely to induce depression, while college students at high risk of depression are more inclined to vent their negative emotions and relieve stress on various online social platforms. In this way, social network behavior analysis was developed based on machine learning as another effective way to identify and predict depression[80,81]. Through mining, emotion analysis and emotion recognition of personal user information data on social network platforms, we can capture the abnormal behavior patterns of people with depression, among which the most frequently used communication methods are text, emoticons, user log-in information and pictures. The selected research usually uses classic off-the-shelf classifiers to analyze the available information and combines words, such as National Research Council Canada (NRC) Word-Emoticon Association Lexicon, WordNet-Affect, Anew, and Linguistic Inquiry and Word Count tool. It is challenging to analyze the combination of temporal information and different types of information[82]. For example, some studies have conducted text analysis on the Sina Weibo data of Chinese college students. First, the behavioral differences between depressed and nondepressed individuals in language style, emoji usage, number of Weibos, followers and so on were obtained. Then, a deep neural network was applied to feature extraction and dimension reduction for college students with depression, and input data suitable for the classifier were constructed. Finally, a deeply integrated support vector machine was introduced to classify the input data, and more stable and accurate depression identification was realized[83]. Some studies collected historical behavior data of American college students using Google search and YouTube during the COVID-19 pandemic and found that there were strong correlations between depression and the following online behavior changes: long use sessions (multiple comprehensive activities with short time intervals), more online activities in the middle of the night or even staying up late, and searching for more authentic and realistic topics related to work, money or death, which verifies the feasibility of building a machine learning model based on individual behavior signals to predict college students' depression[84].

Generally, machine learning has been widely used in a series of mental health risk predictions about college students' depression, stress[85] and suicidal behavior[86,87]. Big data brings many benefits to the prediction of psychological states by reducing the subjectivity of human judgment or human operations to a certain extent and relieving the concerns of patients about possible social stigma and discrimination. In other words, big data and machine learning result in no prejudice in predictions. Thus, confirming depression through data and behavioral performance may be the developing trend in identifying and predicting depression among college students and an even broader population in the future. However, issues such as data privacy and data protection are unavoidable. The government needs to set stricter privacy protection policies, while a more extensive collection of personal data needs to be confirmed and approved by the collectors.

## NONPHARMACEUTICAL PREVENTION OF DEPRESSION

Both general and professional measures for the prevention and treatment of depression were explored in this study. The former emphasizes the importance of multi-subject participation in the prevention and treatment of depression among college students, while the latter focuses on measures with the theoretical support of professional disciplines such as psychology.

### *General intervention measures*

The general interventions are summarized in Table 2 and can be coarsely categorized into support from family, interventions by colleges and universities, cultivation of personal lifestyles, and resilience therapy.

### *High level of family support*

A high level of family support can be used as a buffer against the influence of a high-stress reaction to prevent the development of depression[91]. In a study of 62 patients who recovered from depression, a high level of perceived emotional support from their families indicated that family support, especially

**Table 2 General intervention measures**

| General intervention | Specific measures |
|---|---|
| High level of family support | Emotional support from family |
| Interventions by colleges and universities | Mental health services from the faculty, peers, and psychological counseling centers |
| Cultivation of healthy lifestyles | Proper physical exercise, healthy sleep and diet, and regular sun exposure |
| Resilience therapy | Self-healing for positive emotional and cognitive outcomes, and increasing life satisfaction and resilience[88-90] |

emotional support, was very important for the relief and even rehabilitation of depression[92]. However, it should be noted that family support and perfect family functioning depend more on objective characteristics related to family socioeconomic status, such as parents' level of education[93]. In addition, some studies have found that the role family support plays in the prevention and treatment of depression also depends on the levels of perceived stress reactivity of individuals. Specifically, family emotional support can significantly alleviate the symptoms of depression when the perceived stress reactivity is low, but when the individual shows a high level of the perceived stress response, the effect of family emotional support in preventing depression will be greatly reduced[94].

### *The intervention from colleges and universities*

Prior literature has shown that the faculties, peers, and social clubs on campus can help alleviate the negative effects of online games on depression. Students may seek social support from their teachers, peers, or psychological counseling centers to prevent addiction to online video games that may lead to depressive disorders[38]. Therefore, colleges and universities should build mental health services involving faculty, students, and psychological counseling centers. In addition, some studies have indicated that the implementation of related courses and projects in universities, such as resilience programs (including goal-building, mindfulness, and resilience skills), might be effective in improving college students' mental health[95].

### *Cultivation of healthy lifestyles*

Apart from external support from family and intervention by higher education institutions, the prevention of depression also needs to rely on the patient's own efforts. Studies have shown that healthy lifestyles, including proper physical exercise, healthy sleep and diet, and regular sun exposure, can help prevent or reduce the occurrence of depression in college students[96]. For instance, students with a consistent sleep schedule and sufficient sleep duration are less likely to suffer from depression. Meanwhile, regular sun exposure aids in the synthesis of vitamin D in the body, which is crucial to release fatigue and change the negative moods that individuals with mild or moderate depression may experience[46]. Proper physical activities are also important for stress and depression relief among college students[97,98]. Additionally, improving diet and overall nutrition is also an effective way to treat depression[99]. In particular, eating breakfast on time helps reduce the risk of depression[46]. Certain nutrients, including zinc, magnesium, B vitamins, and cooking fats, have also been proven to be associated with depressive symptoms[100-102]. Therefore, colleges and universities can help prevent the occurrence of depression in college students by providing a regular diet with an adequate intake of vitamins and nutrients[103].

### *Resilience therapy*

Some research has shown that resilience therapy can help individuals maintain mental health in the face of negative emotions and stressful events, thereby reducing the occurrence of depression[104]. Others have also found that it can reduce depressive symptoms by modulating the effects of timing and sleep quality on depression[105].

### *Professional intervention measures*

Cognitive behavioral therapy, which aims to change individual thoughts and behaviors, has been the most widely used treatment method for depression thus far[106-110,113-115]. Mindfulness intervention programs[111] based on cognitive behavioral therapy and dialectal behavior group therapy[112] can effectively alleviate the depressive symptoms of college students.

In recent years, a growing number of online technologies have been applied to the treatment of depression among college students thanks to the rapid development of internet technology and mobile terminal devices[116-120], and some of the technologies were even skillfully combined with cognitive behavioral therapy[121,122]. For example, there are many apps that incorporate elements of cognitive behavioral therapy and mindfulness. A study from Switzerland revealed that apps such as MoodKit, MoodMission and MoodPrismying can successfully deliver ecological momentary interventions (EMIs) based on cognitive behavioral therapy principles to users through smartphones, thereby improving their well-being and effectively reducing the symptoms of depression. The study also noted that EMI

has been generally accepted by users of different ages, sex, educational backgrounds and occupations and is expected to provide scalable global mental health solutions[123]. Compared with behavioral cognitive therapy and online interventions, the efficacy of traditional educational/personalized feedback interventions in the past has been slightly inferior. Some projects have evaluated the effectiveness of mailing personalized standardized alcohol surveys for college students' depression prevention, but unfortunately, there is no obvious improvement[124].

## LIMITATIONS

Limitations of this study include the following. First, this paper analyzed relevant literature written in English, but research in other languages, such as Chinese, Japanese, German, and Italian, was not included. Second, the paper is a narrative review of extensive studies including the influencing factors, prediction, and prevention of depression in college students. We did not undertake explicit methods such as systematic reviews, nor did we involve substantial clinical results and corroborate the evidence in prior literature such as retrospective reviews. The study merely presents studies in the pertinent field by summarizing their main conclusions, which cannot be directly applied to clinical treatment.

## CONCLUSION

This paper reviewed the extant literature by identifying nonpathological factors related to depression among college students, investigating methods of predicting their depressive symptoms, and summarizing nonpharmaceutical interventions. The nonpathological related factors of college students' depression mainly fell into four categories: biological factors, personality and psychological state, college experience, and lifestyle. The outbreak of COVID-19 exacerbated the severity of depression among college students worldwide and posed grave challenges to the prevention and treatment of depression, given that the coronavirus spread quickly with high infection rates, changing the daily routines of college life and creating financial stress, academic stress, and long-term home isolation. Regarding the prediction of vulnerability to depression, machine algorithms and artificial intelligence based on big data have emerged in addition to the commonly used psychological scales. A series of big data, such as text, pictures, video and audio, based on individual social network behaviors was widely discussed and applied to identify and predict college students' depression. Regarding preventive measures, both general measures and professional interventions were discussed for the prevention and treatment of college students' depression, which required not only help from family, professionals, and institutions (cognitive behavioral therapy and online therapy) and society but also the individuals themselves through the cultivation of healthy habits.

Technology based on the internet and big data platforms will become more widely used in the future to identify, predict, and prevent depression among college students. Higher education institutions should clearly understand the potential risk factors related to college students' depression and employ advanced technology for more accurate screening and prevention. They should also work on increasing access to resources and clinical support considering the common difficulties in making appointments and long-term waits for psychological consultation.

Furthermore, this paper proposed two prospects for the future development of nonpharmaceutical interventions for college students' depression. First, the risk of stigma should be minimized. Many traditional precautionary measures are used to help students identify whether they suffer from depression, including e-mail, posters, campus activities, pamphlets, and first aid training courses about mental health. However, these measures may result in further concerns about the risk of stigmatization and psychological worries of students[125]. Therefore, in the future, we should avoid stigmatizing issues in the prevention of depression among college students and pay more attention to personalization and privacy in the development and application of precautionary measures. Second, the importance of general measures for the prevention and treatment of college students' depression should be combined with professional interventions such as cognitive intervention therapy and other evidence-based treatment. A meta-analysis showed that apart from cognitive behavioral therapy and mindfulness-based interventions, other measures, such as art, exercise, and peer support, are also effective in relieving depressive symptoms in college students[126].

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*MINIREVIEWS*

# SARS-CoV-2 consequences for mental health: Neuroinflammatory pathways linking COVID-19 to anxiety and depression

Anna Julie de Mello, Morgana Moretti, Ana Lúcia S Rodrigues

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## Abstract

The coronavirus disease 2019 (COVID-19) pandemic has been linked to an increased prevalence of mental health disorders, particularly anxiety and depression. Moreover, the COVID-19 pandemic has caused stress in people worldwide due to several factors, including fear of infection; social isolation; difficulty in adapting to new routines; lack of coping methods; high exposure to social media, misinformation, and fake reports; economic impact of the measures implemented to slow the contagion and concerns regarding the disease pathogenesis. COVID-19 patients have elevated levels of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α, and other inflammation-related factors. Furthermore, invasion of the central nervous system by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may potentially contribute to neuroinflammatory alterations in infected individuals. Neuroinflammation, a consequence of psychological stress due to the COVID-19 pandemic, may also play a role in the development of anxiety and depressive symptoms in the general population. Considering that neuroinflammation plays a significant role in the pathophysiology of depression and anxiety, this study investigated the effects of SARS-CoV-2 on mental health and focused on the impact of the COVID-19 pandemic on the neuroinflammatory pathways.

**Key Words:** Anxiety disorders; COVID-19 pandemic; Depression; Mental health; Neuroinflammation; Stress

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**Core Tip:** The coronavirus disease 2019 pandemic has impacted the mental health of the population worldwide. This review summarizes the evidence of the role of neuroinflammation, either as a result of chronic stress caused by the pandemic or severe acute respiratory syndrome coronavirus 2 infection, in the development of anxiety and depressive disorders.

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## INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared the outbreak of the coronavirus disease 2019 (COVID-19) as a pandemic[1]. More than two years have passed since the emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and its ramifications have changed human lives worldwide. In response to the COVID-19 outbreak, the scientific community has collaborated to provide information on all aspects of the disease, including the devastating sequelae in survivors. The pandemic has directly affected people through infections and resulted in increased psychological stress in the general population.

Several factors contributed to the psychological consequences of the pandemic in the affected population, such as poor knowledge about the disease, previously undiagnosed mental health disorders, lack of a healthy lifestyle, no prior mental health assessment, economic problems, changes in eating and sleeping habits, difficulty in adapting to new routines, lack of coping methods, high exposure to social media, misinformation and fake reports, and social isolation during quarantine[2,3]. Quarantine and lockdowns have severely impacted everyday life worldwide, ranging from student education to the immense workload on health professionals[4]. Social distancing has isolated people inside their houses and significantly impacted the economy[5-7]. People with an infected household or a close contact with COVID-19 patients or those with a history of chronic illnesses have been shown to a higher risk of developing psychiatric distress[8,9].

Another concern is related to patients hospitalized due to COVID-19. Hospitalized patients are at risk of experiencing depression, anxiety, insomnia, and delirium[10]. Among all sequelae resulting from the disease, those of psychopathological nature can be induced either directly through the invasion of the virus in the central nervous system (CNS) or indirectly as a consequence of systemic inflammation and immune response[11]. Neuroinflammatory alterations have been postulated to cause depression and anxiety[12]. Although there are several comprehensive literature reviews on the impact of SARS-CoV-2 on human health, in this minireview, we have discussed how neuroinflammation caused by chronic stress or SARS-CoV-2 infection can lead to anxiety and depression. We hypothesized that the neuroinvasion of SARS-CoV-2 in the brain, peripheral pro-inflammatory cytokines that may enter the brain after SARS-CoV-2 infection, and psychological stress associated with the pandemic, alone or in combination, could cause neuroinflammation and contribute to the development of anxiety and depression disorders.

## COVID-19-RELATED STRESS AND THE HIGH PREVALENCE OF DEPRESSION AND ANXIETY

The increase in depression and anxiety during the COVID-19 pandemic has become a major health concern[2-4]. Depression and anxiety frequently co-occur and are prevalent and burdensome psychiatric disorders[13]. Depression was the second largest cause of disease burden in 2020[14-16] and has been projected to take precedence by 2030[17]. The most recent Atlas of Mental Health published by the WHO in 2020 revealed the indicators of mental health and Comprehensive Mental Health Action Plan, which has been extended till 2030 to assist individuals whose mental health has been affected by the COVID-19 pandemic[17]. Generally, anxiety disorders have a high annual prevalence at approximately 14%, with the United States and Europe presenting a higher rate than other areas[18,19]. One in four individuals is likely to develop or has already developed anxiety disorders[20]. Of note, the risk of developing anxiety and depression has been closely associated with exposure to chronic stress[21] such as that in the COVID-19 pandemic[22].

Coronaphobia, or excess anxiety about COVID-19, is strongly associated with elevated reports of depression, general anxiety, a lack of hope, and suicidal ideation[14,15,23]. A systematic review and

meta-analysis of 13 studies with a total of 33062 participants indicated a 23.2% and 22.8% prevalence of anxiety and depression, respectively, in healthcare workers in China during the beginning of the pandemic, with a higher prevalence in female nurses[4]. In addition, the prevalence of depression and anxiety has increased in the general population, especially in young adults. During the initial stages of the COVID-19 pandemic in the United States, at least one-third of participants in a cross-sectional study reported high levels of depression (43.3%), anxiety (45.4%), and post-traumatic stress (31.8%)[24]. These rates were higher than those found in a previous study conducted in 2009 using the same assessment tools, showing a prevalence rate of 6.2% among young adults aged 18–24 years and 13.1% among those aged 25–34 years[25]. These symptoms were also associated with loneliness and low resilience to stress, whereas a higher tolerance to stress was associated with lower anxiety. Family support has been previously associated with lower levels of depression and post-traumatic stress disorder[24].

Another Chinese study conducted in 2020 reported a four times higher prevalence of depression, anxiety, or both, than a study published in 2019 (20.4% in 2020 *vs* 4% in 2019)[26,27]. This study associated the development of depressive and anxiety symptoms with some common pandemic stressors, including worrying about oneself or loved ones being infected; concerns about income, jobs, school, and ability to pay loans; and hardships involving home quarantine in everyday life[26]. Depression and anxiety reported by Bangladeshi University students during the pandemic were associated with uncertainty about their academic or professional future and financial instability[28]. Early reports between mid-February and mid-March 2020 showed an increase of 34.1% in the demand for anxiolytic drugs, followed by 18.6% for antidepressants and 14.8% for sleep medications[29].

Studies on youth population have suggested that children and adolescents have also been affected by the pandemic. During the first year of the pandemic, one in four young adults experienced a clinical increase in depressive symptoms, with older children being the most affected. In addition, one in five children and adolescents had clinically elevated anxiety levels. The prevalence rates of depression and anxiety in children and adolescents increased over time and doubled compared to estimates before the pandemic according to a recent meta-analysis[30]. Further, the global prevalence of depression and anxiety increased by 25% and 27.6% due to the COVID-19 pandemic in 2020, indicating the negative impact of COVID-19 on the mental health of people of all ages worldwide[31].

## NEUROINFLAMMATION AND PSYCHOLOGICAL MANIFESTATIONS

Several studies have shown that inflammation plays a key role in the pathophysiology of depressive disorders[12]. Preclinical studies have provided consistent evidence that exposure of rodents to chronic unpredictable and/or inescapable stress situations induces depressive-like behavior accompanied by peripheral and central activation of the immune, inflammatory, and oxidative and nitrosative stress pathways. Furthermore, chronic administration of antidepressants attenuates these effects[32]. Chronic stress can also induce neurotoxic effects on specific brain regions, either directly or indirectly, through the kynurenine pathway[33], causing a reduction in brain-derived neurotrophic factor with consequent impairment of adult hippocampal neurogenesis[32].

Individuals with depression present with high serum levels of pro-inflammatory cytokines and acute-phase proteins and an increased expression of adhesion molecules and chemokines[34-38]. These protein alterations suggest an association between depression and activation of pro-inflammatory responses. Depression has been associated with increased levels of peripheral and central tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, and C-reactive protein[34,37,39]. Furthermore, studies have reported an increase in the levels of other acute-phase proteins (*i.e.*, α-1-acid glycoprotein, α -1-antichymotrypsin, and haptoglobin) in the plasma of patients with depression[37,40-42]. Elevated levels of human macrophage chemoattractant protein-1, soluble intracellular adhesion molecule-1, and E-selectin have also been reported[43]. An apparent association between the severity of depressive symptoms and level of inflammatory mediators in the plasma of patients has also been shown[34,44]. In addition, functional variants of alleles of IL-1β and TNF-α genes influence different factors, either elevating the risk of depression or reducing the response to antidepressants[40,45,46].

Despite the frequent co-occurrence of anxiety and depression and their common association with cardiovascular[47] and metabolic diseases[48], the role of neuroinflammation in the pathophysiology of anxiety disorders has not been studied as extensively as that in depression[49]. Neuroinflammation may cause alterations in the structure or function of anxiety-related brain circuits (mainly the limbic and prefrontal regions), priming the brain to become vulnerable to anxiety disorders[33]. Studies have reported increased inflammation in patients of both sexes with late-onset anxiety disorder; however, they were unable to confirm it as an etiological factor[49]. Other studies have linked the immune system and CNS through key interactions that can influence behavioral changes; however, a causal relationship between anxiety and inflammation needs extensive investigation[49]. In preclinical studies, activation of the nucleotide-binding oligomerization domain-like receptor pyrin domain-containing-3 (NLRP3) inflammasome has been associated with anxiety-like behavior[50,51]. Clinical findings have suggested that increased cytokine levels affect neurotransmitters, such as monoamines and glutamate, in the amygdala, insula, and anterior cingulate cortex, which are brain regions related to anxiety[52].

Accordingly, inhibition of neuroinflammation has been accompanied by anxiolytic effects[51].

Increased levels of TNF-α, a cytokine important for cellular regulation and apoptosis, have been consistently associated with depression and anxiety in humans[53]. Similarly, central administration of TNF-α in mice resulted in depressive-like behavior, whereas TNF-α receptor 1 knockout mice exhibited antidepressant-like behavior in the forced swimming test and tail suspension test[54]. In addition, administration of TNF-α induced anxiety-related behavior in mice[55]. Administration of etanercept, a TNF-α blocker, reduced anxiety and depressive-like behavior in db/db mice exhibiting type-2 diabetes-related inflammation and mood alterations[56]. TNF-α blockade also caused an anxiolytic effect in mice with experimental autoimmune encephalomyelitis[55] and mice subjected to peripheral immune challenge with lipopolysaccharide[57]. Furthermore, administration of the TNF-α-neutralizing antibody infliximab in the basolateral amygdala reversed anxiety-like behaviors in mice with persistent inflammatory pain[58].

During the initial phases of inflammation, IL-6 is induced along with TNF-α and may represent a key inflammatory mediator in patients with COVID-19[59-61]. Similarly, IL-1β is the major cytokine (in association with IL-18) produced by the activation of the NLRP3 inflammasome and increases in depression. These cytokines modulate the neuroimmune pathways that regulate critical brain circuits involved in cognition, mood, and reward[62-64]. Notably, SARS-CoV-2 is postulated to directly activate the NLRP3 inflammasome, and patients with dysregulated NLRP3 inflammasome activity may develop COVID-19 with severe tissue damage and a cytokine storm[65].

Increased levels of pro-inflammatory cytokines such as IL-6 may repress brain-derived neurotrophic factor, contributing to the development of depressive behavior[66,67]. IL-6 is also associated with lymphocyte exhaustion, and its role in COVID-19 inflammation has propelled the use of IL-6 inhibitors, corticosteroids, antimalarial drugs, and intravenous immunoglobulin to oppose the effects of cytokine storms in individuals with COVID-19[68]. Therefore, a strong inflammatory response can be related to disease severity and death in patients with COVID-19[68]. In severely affected patients, increased levels of peripheral cytokines can cause lymphopenia and invasion of mononuclear cells in the heart, lungs, lymph nodes, spleen, and kidneys[69]. A study on COVID-19 survivors revealed elevated depression, anxiety, insomnia, post-traumatic stress disorder, and obsessive–compulsive symptoms one month after hospitalization[70]. These findings are consistent with those reported during the previous coronavirus outbreaks, in which 10%-35% patients in the post-disease recovery stage presented psychiatric comorbidities[10]. These psychiatric outcomes may be a consequence of neuroinflammation caused by COVID-19. Moreover, neuroimaging and CSF marker elevations in patients with COVID-19 have suggested that SARS-COV-2 causes CNS inflammation[71].

## NEUROINVASION BY SARS-COV-2

Individuals infected with SARS-CoV-2 can remain asymptomatic or develop COVID-19 symptoms. Hospitalized patients with COVID-19 commonly present with clinical sequelae that appear up to three months after discharge[72]**.** These sequelae are not limited to respiratory issues because patients can manifest cardiovascular, neurological, and psychosocial symptoms after discharge[11,72,73].

The neurological symptoms after COVID-19 may be associated with direct SARS-CoV-2 invasion of the CNS, where the virus has a high potential for replication, causing significant neuronal death[74]. Patient autopsies have revealed neuronal loss[75], often associated with an immune response against the virus in the CSF. Few reports showed that patients who tested positive for SARS-CoV-2 in their CSF but did not have any significant risk factors or a history of neurological diseases manifested neurological symptoms, such as seizures and loss of consciousness[76].

Most *in vitro* and *in vivo* experiments support the hypothesis that neuroinvasion by SARS-CoV-2 causes neurological symptoms in patients with COVID-19. The presence of the virus within neurons in multiple brain areas of infected animals resulted in a neuropathology similar to that observed in hospitalized patients[77]. Importantly, these alterations are not limited to adult patients; children also manifest the same critical developments after COVID-19, including thrombosis, inflammation, and secondary tissue ischemia[78,79]. Severe COVID-19 is rarely reported in children; however, there have been reports of children who developed acute fulminant cerebral edema, severe encephalopathy, and ischemic stroke despite being previously healthy[80,81].

Animal experiments have provided detailed information regarding the neuroinvasive potential of SARS-CoV-2. A study by Song *et al*[74] revealed that SARS-CoV-2 infects animal lungs at early time points, while it infects the brain much later. In the same study, electron microscopy to identify viral particles sprouting from the endoplasmic reticulum indicated that the virus could use cellular machinery for replication. Unlike other neurotropic viruses such as Zika, SARS-CoV-2 causes metabolic changes in the brain, as demonstrated using human brain organoids[74].

The literature further suggests SARS-CoV-2 neuroinvasion occurs through the trans-neuronal route, especially during the early stages of infection, in which SARS-CoV-2 invades the brain *via* the cranial nerve pathways such as the olfactory, gustatory, and trigeminal nerves[77]. This infiltration route is also associated with the severity of infection and neurological manifestations that lead to a higher risk of

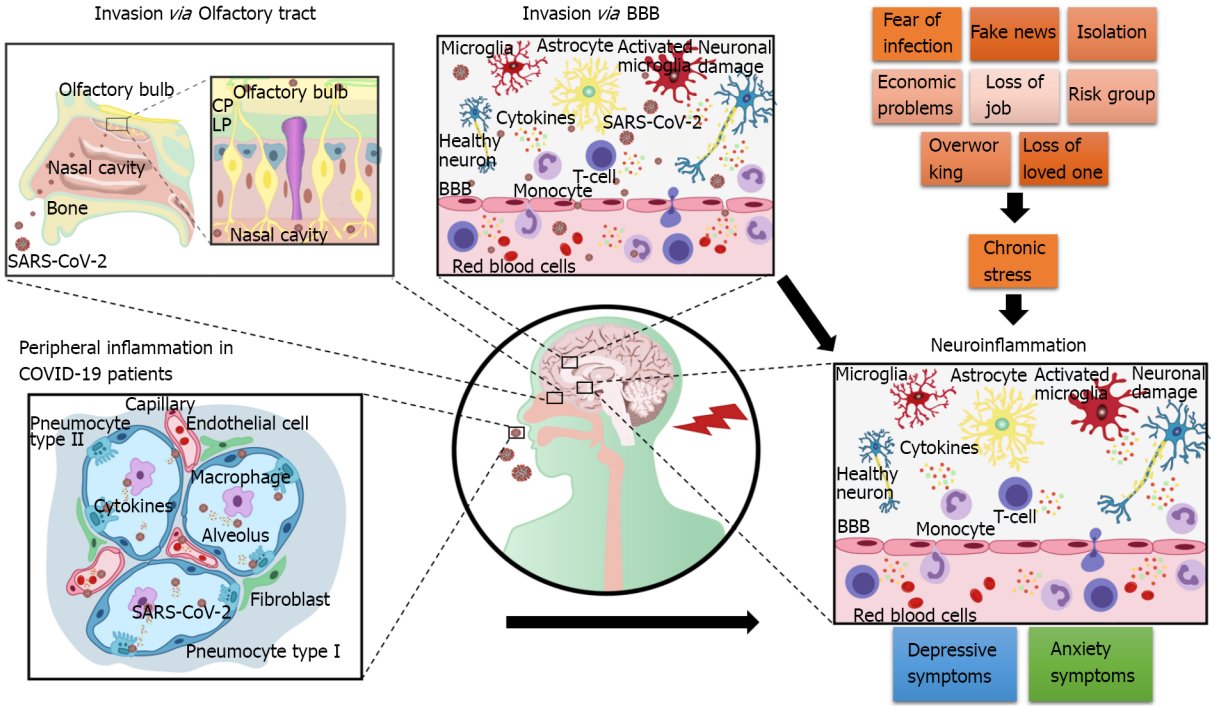


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**Figure 1 Role of neuroinflammation in the development of anxiety and depressive disorders due to coronavirus disease 2019.** Peripheral inflammation experienced by patients with coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome coronavirus 2 neuroinvasion, either *via* the olfactory tract or blood-brain barrier, contribute to neuroinflammatory alterations in infected individuals. Chronic stress resulting from several factors associated with the COVID-19 pandemic can also induce neuroinflammation. By activating astrocytes and microglia, causing neurotoxicity, and affecting synaptic plasticity and neurogenesis, neuroinflammatory alterations may play a role in the development of anxiety and depression. BBB: Blood-brain barrier; COVID-19: Coronavirus disease 2019; CP: Cribriform plate; LP: Lamina propria; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

mortality in patients with COVID-19. Liu *et al*[77] reported that death occurred only in infected animals with neurological deficits, suggesting that disease progression is associated with the severity of neurological impairment.

Involvement of the trans-neuronal route suggests that SARS-CoV-2 enters the CNS through the olfactory nerves *via* angiotensin-converting enzyme 2 (ACE2; a part of the renin-angiotensin-aldosterone system) present on the cell membrane. The virus then migrates through the neuroepithelium and reaches the brain, consistent with the loss of smell observed in patients with COVID-19[82,83]. This route of SARS-CoV-2 neuroinvasion has been demonstrated by Song *et al*[74] in mice overexpressing human ACE2[74]. Accordingly, COVID-19 respiratory distress has been associated with increased nasopharyngeal expression of ACE2 and transmembrane serine protease 2[84]. In addition, clinical studies and *post-mortem* analyses have reported the presence of viral antigens in the olfactory tract[85-88]. Magnetic resonance imaging examination of patients with COVID-19 revealed structural changes throughout the olfactory pathway, including the nerve, bulb, and cerebral cortex, and supports the olfactory bulb route hypothesis[83,89,90]. Immunostaining for SARS-CoV-2 in animal models has revealed extensive staining in these regions[91,92].

Another plausible entry route for SARS-CoV-2 could be through the blood-brain barrier (BBB) by binding to ACE2 on endothelial cells[82]. This route, previously linked to infected individuals with high fever, may cause cytokine storms and increase the BBB permeability[93,94], thereby facilitating the access of SARS-CoV-2 to the brain[95]. As a consequence of BBB impairment, peripheral immune cells can enter the brain, increase the release of pro-inflammatory cytokines by microglial cells and sustain neuroinflammation[96].

Finally, *post-mortem* studies have reported the presence of ischemic damage and microinfarcts in brain samples of patients with COVID-19, supporting the assumption of SARS-CoV-2 neuroinvasion into the CNS[74].

## CONCLUSION

As illustrated in Figure 1, the increased prevalence of depression and anxiety during the COVID-19 pandemic may be attributed to SARS-CoV-2 neuroinvasion and its harmful consequences on the CNS. Depression and anxiety may also occur because of peripheral inflammation caused by the virus and

indirect negative effects on the brain function. Moreover, long-lasting social stressors linked to the pandemic may contribute to neuroinflammation and, consequently, to the development of these psychiatric symptoms. Therefore, anxiety and depression can affect the infected individuals and general population exposed to long-lasting pandemic stress. In the future, epidemiological studies should be conducted to elucidate the COVID-19 psychiatric burden, and public health control measures to help manage this burden must be provided.

## FOOTNOTES

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*MINIREVIEWS*

# Genetic variables of the glutamatergic system associated with treatment-resistant depression: A review of the literature

Estela Saez, Leire Erkoreka, Teresa Moreno-Calle, Belen Berjano, Ana Gonzalez-Pinto, Nieves Basterreche, Aurora Arrue

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## Abstract

Depression is a common, recurrent mental disorder and one of the leading causes of disability and global burden of disease worldwide. Up to 15%-40% of cases do not respond to diverse pharmacological treatments and, thus, can be defined as treatment-resistant depression (TRD). The development of biomarkers predictive of drug response could guide us towards personalized and earlier treatment. Growing evidence points to the involvement of the glutamatergic system in the pathogenesis of TRD. Specifically, the N-methyl-D-aspartic acid receptor (NMDAR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

(AMPAR), which are targeted by ketamine and esketamine, are proposed as promising pathways. A literature search was performed to identify studies on the genetics of the glutamatergic system in depression, focused on variables related to NMDARs and AMPARs. Our review highlights *GRIN2B*, which encodes the NR2B subunit of NMDAR, as a candidate gene in the pathogenesis of TRD. In addition, several studies have associated genes encoding AMPAR subunits with symptomatic severity and suicidal ideation. These genes encoding glutamatergic receptors could, therefore, be candidate genes for understanding the etiopathogenesis of TRD, as well as for understanding the pharmacodynamic mechanisms and response to ketamine and esketamine treatment.

**Key Words:** Genetics; N-methyl-D-aspartic acid receptor; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Treatment-resistant depression; Ketamine; Esketamine

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**Core Tip:** Depression is a common mental disorder and one of the leading causes of disability worldwide. Up to 15%-40% of cases are considered treatment-resistant depression, which seems to be conditioned by environmental and genetic factors. The glutamatergic system, specifically N-methyl-D-aspartic acid receptor (NMDAR) dysfunction, has been proposed to be involved in the pathogenesis of treatment-resistant depression (TRD). A literature search was performed to identify studies on the genetics of the glutamatergic system in depression, focused on NMDAR and the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor. Our review highlights *GRIN2B*, which encodes the NR2B subunit of NMDAR, as a candidate gene in the pathogenesis of TRD.

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## INTRODUCTION

### *Depression: An overview*

Depression is characterized by sustained low mood, anhedonia, psychomotor inhibition and, frequently, somatic alterations that significantly affect an individual's functioning and, as such, poses a social and economic problem, as well as a health problem. It is, according to the World Health Organization, a common, recurrent mental disorder and one of the leading causes of disability and global burden of disease worldwide[1]. Thus, it has been highlighted as one of the priority conditions covered by the Mental Health Gap Action Programme. The 12-mo prevalence of major depressive disorder (MDD) is estimated to be approximately 6%[2], whereas the lifetime risk of depression is between 15% and 18%[3]. Thus, MDD is common, with almost one in five people experiencing one episode at some point in their lifetime. Between 2005 and 2015, the incidence of depression increased by 18.4% worldwide[4]. Regarding gender differences, the lifetime-incidence of a major depressive episode in females has been reported to be twice that of males[5].

Depression significantly affects family, social, and occupational functioning and is, therefore, a health, social and economic problem. A recent review calculated that the direct costs of depression, due to the higher use of healthcare services, may be up to 24,069€ *per* patient/year, depending on the jurisdiction wherein the analyses were performed[6]. Productivity losses, for their part, were estimated to be between 1963€ and 27364€ *per* person *per* year[6]. It is among the leading causes of loss of disability-adjusted life years, mainly in the age range between 10 and 49 years[7], and is the most frequently identified diagnosis in people who have died by suicide[8]. Thus, in recent years, depression has become a major target of public health policies[9,10] due to the consequences that both depression itself, as well as associated events such as suicide, have on society.

If depression is untreated or inadequately treated, it is associated with higher rates of medical morbidity, lower productivity, decreased life expectancy, higher rates of suicide, and higher rates of functional disability. However, sometimes, despite evidence-based treatment, the patient may not respond favorably to treatment. Even though we have a growing number of therapeutic alternatives available to treat depression, approximately half of patients do not respond, and up to two-thirds do not achieve remission after first-line treatment[11]. In this context, the development of biomarkers

predictive of drug response, which could guide us towards personalized treatment for each patient, is a challenge for the future.

## TREATMENT-RESISTANT DEPRESSION

Although there is no consensus on the definition of treatment-resistant depression (TRD), it is a useful concept to characterize a group of patients with MDD that do not respond to traditional monoaminergic antidepressants. The European Medicines Agency considers TRD to be that which has not responded to two antidepressants of different classes, prescribed at adequate doses (within a therapeutic range), for the appropriate time (> 6 wk) and ensuring correct adherence to the protocol[12,13]. Some authors add that potentiation strategies, such as lithium, neuroleptic drugs, or electroconvulsive therapy, also need to have been used.

According to the well-known Sequenced Treatment Alternatives to Relieve Depression study, one-third of patients with depression could be classified as TRD, as they do not respond to two different antidepressant treatments[11]. Along the same lines, other works have described that 15%-40% of patients with MDD do not respond to multiple pharmacological treatments[14].

Patients with MDD are more likely to make attempts and/or complete suicide, as well as to experience more frequent relapses and hospitalizations, and to have a worse overall prognosis. In other words, they form a subgroup of depressive patients characterized by clinical severity and higher health and social costs[15].

Resistance to treatment seems to be conditioned by genetic and environmental factors[16]. The underlying genetic factors of individuals cannot be modified, but genetic information could be used to predict response and tailor treatments to the idiosyncrasies of each patient. Emerging evidence has shown that genetic variations associated with antidepressant responses appear to cluster in families, supporting the importance of these variations in the underlying mechanism of depression, especially in TRD[17].

Identifying biomarkers that can predict the antidepressant response could be helpful in designing the initial treatment, decreasing the need for trial-and-error testing, and also avoiding suffering and possible chronicity. Single nucleotide polymorphisms (SNPs) have been suggested to be a decisive factor in the antidepressant response; numerous genetic polymorphisms have been described as possible risk factors for MDD and TRD[18-21].

## GENETICS OF DEPRESSION

Albeit a clinically heterogeneous pathology, there is consistent evidence, based on twin and adoption studies, that there is a heritability of 29%-49% in MDD (reviewed in[22]). Research has also been performed to identify more genetically homogeneous groups of MDD, indicating that clinical severity, the need for certain therapeutic strategies, recurrent episodes, and postpartum depression show differences in heritability[23,24].

It is a polygenic disease caused by the combined effect of polymorphisms, common to the general population, in different genes[25]. The genetics of depression has been studied for years *via* a candidate gene approach, mainly focusing the study on genes involved in the serotonergic, noradrenergic, and dopaminergic pathways, targets of the usual treatments[26-28]. A recent literature review of 18 candidate genes showed that most of the studies performed lacked sufficient statistical power and, thus, questioned previous depression candidate gene findings[29]. More recent work has begun to focus on the glutamatergic pathway as a candidate in the study of genetic factors involved in depression[30].

In recent years, genome-wide association studies (GWAS) have proliferated in an attempt to identify genes involved in various pathologies, including depression. A recent GWAS identified 102 independent variants, 269 genes, and 15 gene-sets associated with depression, including both genes and gene pathways associated with synaptic structure and neurotransmission, providing further evidence of the importance of prefrontal brain regions. A previous GWAS implicated voltage-gated calcium channels, the D2 dopamine receptor and, interestingly, glutamate receptors[31]. The authors stated that all humans carry a lesser or greater number of genetic risk factors for MDD.

Along this line, many authors have investigated the interaction between genetics and environment in the pathogenesis of depression. Recent reviews concluded that various genetic polymorphisms in the serotonergic system moderate the association between adverse childhood experiences and depression [32], and that early-life stress produces transcriptomic changes that are moderated by the female sex[33].

Finally, postmortem studies have also been conducted to investigate differential gene expression in human brains. *GluR* gene expression in the dorsolateral prefrontal cortex has been studied in small postmortem cohorts of MDD subjects and controls, with inconclusive results to date[34,35]. Nonetheless, the data seemed to indicate a fundamental dysfunction of the glutamatergic system in the frontal cortex in MDD[36].

## THE GLUTAMATERGIC SYSTEM AND TRD

The neurotransmitter systems most studied in the etiopathogenesis of depression have been the serotonergic, noradrenergic, and dopaminergic systems, which are targeted by the most commonly used antidepressant drugs. However, another system involved is the glutamatergic system. Glutamate exerts its action *via* ionotropic receptors [N-methyl-D-aspartic acid receptor (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), and 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine kainate receptors (KAR)] and metabotropic receptors. In the last two decades, the glutamatergic system, specifically NMDAR dysfunction, has been shown to be involved in the pathogenesis of TRD[37]. In particular, NMDAR antagonism has been highlighted, marking it a target of numerous drugs indicated for TRD[38], such as ketamine and esketamine[39,40].

Intravenous ketamine and intranasal esketamine, rather than inhibiting, activate glutamate release [41], resulting in a rapid antidepressant effect, a prompt disappearance of suicidal ideation[42,43], and a reduction of anhedonic symptoms[44]. This emerging hypothesis suggests that NMDAR antagonism in GABAergic interneurons (the mechanism of action of ketamine and esketamine) leads to glutamate release[45]. Regarding this gamma-amino butyric acid (GABA)-glutamate neurotransmitter system, animal and human studies have described that intravenous ketamine administration reduces GABA concentration in several brain areas, such as the frontal cortex[45-47].

Treatment with ketamine and esketamine has proven particularly useful in cases of TRD[48], thus their mechanism of action in glutamatergic pathways, being the major difference with respect to usual antidepressant treatments, is an interesting starting point for understanding the etiopathogenesis of TRD.

Central glutamatergic activity is measured at the peripheral level *via* plasma levels of glutamate (pGlu) and GABA (pGABA). pGlu and pGABA levels have been described to significantly correlate with cerebrospinal fluid glutamate levels[49,50], indicating that, although the plasma levels assessed derive from both the brain and the periphery, the plasma levels of these amino acids reflect brain concentrations[51]. Previous studies reported altered levels of pGlu in blood, cerebrospinal fluid, and prefrontal, frontal, and occipital cortical areas of patients with depression compared with healthy volunteers[52-55].

In relation to GABA, as a neurotransmitter system closely related to the glutamatergic, a recent meta-analysis indicated a decrease in pGABA levels in patients with depression compared with healthy controls, although the heterogeneity was significant[56].

All these findings indicate that alterations in the glutamatergic system may play a key role in the development of TRD. Therefore, it has been proposed that genes involved in glutamatergic transmission could be candidate genes to explain the neurobiological basis of TRD, *i.e.*, genetic risk factors for the development of depression, especially TRD[55,57].

## GENETIC VARIABLES OF THE GLUTAMATERGIC SYSTEM ASSOCIATED WITH TRD

### *Literature search*

A literature search was performed to identify studies regarding the genetics of the glutamatergic system in depression. A total of 118 articles, published up to October 15, 2021, were retrieved from the PubMed and Reference Citation Analysis (https://www.referencecitationanalysis.com/) databases using broad search terms in order to identify as many potentially eligible studies as possible: [(NMDA receptor OR AMPA receptor) AND gene* AND depression]. An age filter was added: "Adults: 19+ years". Studies were included according to three criteria: (1) They investigated the influence of genetics/epigenetics on glutamate receptors in depression; (2) They were systematic reviews, meta-analyses, narrative reviews, or original research studies; and (3) They were written in English or Spanish. The reference lists of the selected studies and reviews were also checked to identify additional relevant articles using a snowballing approach. Finally, 46 papers were included in the review.

This is not a systematic review, but a narrative one; it summarizes the findings described in the selected reports and, in this way, provides an overview of the subject. The main results are summarized in Table 1.

### *NMDA receptor*

NMDAR, indicated as a therapeutic target in TRD[58], consists of four subunits (Figure 1). Two of them must be the NR1 subunit, mandatory for the receptor to be functional, while the other two subunits can be any of the four NR2 subunits (NR2A-D), or two NR3[59]. The NR2A-D subunits bind glutamate[60]. These subunits are encoded by the *GRIN1*, *GRIN2A-D*, and *GRIN3* genes[61,62].

### *NR2B subunit: The GRIN2B gene*

Associations between the functionality of these subunits and depression or response to antidepressant molecules were mostly found with the NR2B subunit. This is encoded by the *GRIN2B* gene, which is located on chromosome 12p12 and consists of 13 exons. Three potentially functional SNPs have been

**Table 1 Summary of studies on main candidate genes of the glutamatergic system related to depression**

| Receptor | Gene | Marker | Ref. | Result |
|---|---|---|---|---|
| NMDA | *GRIN2A* | rs16966731 | Chen *et al*[79], 2021 | T allele associated with antidepressant effect of ketamine |
| | *GRIN2B* | rs1805502 | Zhang *et al*[69], 2014 | G allele associated with TRD |
| | | | Arnold *et al*[70], 2009 | GT haplotype increased risk of TRD |
| | | rs890 | Zhang *et al*[69], 2014 | C allele associated with TRD |
| | | | Arnold *et al*[70], 2009 | |
| | | rs2268115 | Sokolowski *et al*[72], 2013 | Associated with suicide attempts |
| | | rs220557 | Sokolowski *et al*[72], 2013 | Associated with suicide attempts |
| AMPA | *GRIA2* | rs4302506 | Chiesa *et al*[91], 2012 | C allele associated with a lower age of onset in MDD |
| | | rs4400397 | Chiesa *et al*[91], 2012 | C allele associated with a lower age of onset in MDD |
| | *GRIA3* | rs4825476 | Laje and McMahon[17], 2007 | G allele associated with suicidal ideation |
| Kainate | *GRIK4* | rs1954787 | Horstmann *et al*[94], 2010 | CC haplotype associated with response to antidepressants |
| | | | Serretti *et al*[95], 2012 | No significant associations |
| | | rs12800734 | Horstmann *et al*[94], 2010 | GG haplotype associated with response to antidepressants |
| | | | Serretti *et al*[95], 2012 | No significant associations |

NMDA: N-methyl-D-aspartic acid; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; TRD: Treatment-resistant depression; MDD: Major depressive disorder; T: Thymine; G: Guanine; C: Cytosine.

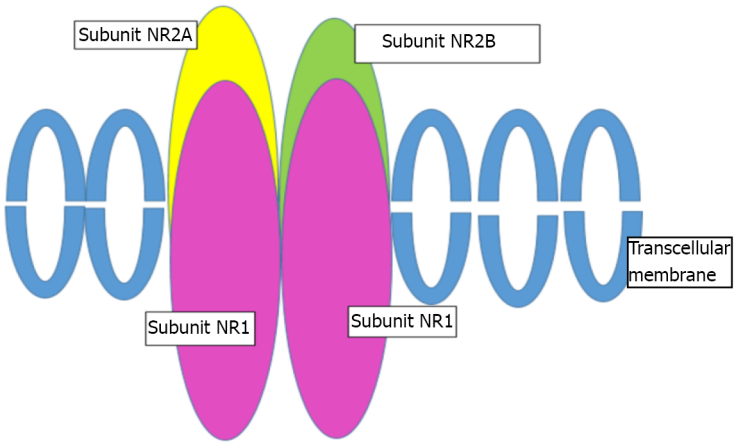


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**Figure 1 Structure of the N-methyl-D-aspartic acid receptor, which consists of four subunits [NR1, and either two of the four NR2 subunits (NR2A-D) or two NR3].**

identified in this gene, all located in the 3'-untranslated region (UTR) that governs gene expression: rs1805502 (A to G), rs1806201 (T to C), and rs890 (A to C). They may contribute to the regulation of *GRIN2B* gene expression and influence glutamate release activity in the brain.

Ketamine users have also been reported to have a higher frequency of the rs1806201 TT genotype and a lower frequency of the CC genotype than controls, suggesting that this polymorphism may play a role in ketamine abuse[63]. Clinical trials report the superior therapeutic efficacy of NMDAR NR2B subunit antagonists over conventional antidepressants in patients with TRD[64,65].

Different GWAS have revealed a relationship between SNPs in the *GRIN2B* gene and depression[38,66,67]. *In vivo* studies evaluating glutamatergic activity at the brain level have shown that carriers of the rs1805502 G, rs1806201 T, or rs890 C allele have decreased glutamate concentrations in the anterior cingulate cortex. These alleles have been related to several psychiatric disorders[68-70], suggesting that they be a risk factor (genetic predictor) for TRD[69] in MDD patients. Recently, in a preclinical study in

transgenic mice with selective mutations in the NR2B subunit in GABAergic interneurons, deletion of NR2B was found to block the antidepressant action of ketamine[71].

These *GRIN2B* gene polymorphisms have been described both as risk variables for MDD and predictors of TRD. An association was reported between the GT haplotype (rs1805502-rs890) and increased TRD risk compared with controls, as well as between the rs1805502 G allele and TRD (compared with non-resistant depression)[69].

A GWAS-based study reported a significant association between GRIN2B and suicide attempts, as well as a gene-environment relationship with a history of physical abuse in childhood and adolescence, which also increases the risk of suicide[72]. Indeed, they found that *GRIN2B* and *ODC1* (encoding ornithine decarboxylase, a rate-limiting enzyme of the polyamine synthesis pathway) seem to be associated with severe suicide attempts, as well as with serious physical assault in childhood and adolescence[73,74], which in turn increases the risk of suicide attempts, thereby configuring a gene-by-environment interaction.

Finally, human postmortem studies found *GRIN2B* expression to be higher in suicidal MDD patients, compared with non-suicidal MDD patients[36], and in the locus coeruleus of depressed individuals[75]. It is therefore postulated that *GRIN2B* mRNA level may be a biomarker of suicide; indeed, *GRIN2B* genetic polymorphisms in MDD have been reported to predict treatment resistance, suicide attempts, and reasoning ability[72].

Based on the data described, *GRIN2B* is considered a promising candidate gene for MDD susceptibility, and more specifically for TRD, supporting the contention that TRD can be classified as a specific subtype of MDD[69].

### *Other NMDAR subunits: GRIN1, GRIN2A, C, and D, and GRIN3*

Regarding other NMDAR subunits, postmortem studies in rodents using depression models have observed that chronic stress, besides increasing NR2B subunit mRNA, also increases NR1 and NR2A in several brain regions[76,77]. Postmortem studies in humans reported higher expression levels of GRIN1 and GRIN2A in the brains of depressed patients than in controls, and of GRIN2B in suicidal compared with non-suicidal MDD patients[36,78]. Likewise, the *GRIN2A* rs16966731 polymorphism (T to C, intron area) has been associated with the rapid and persistent antidepressant effect of ketamine[79]. Chandley *et al*[75] also reported altered expression of the *GRIN2C* gene at the locus ceruleus in depressed patients [75]. Finally, one paper reported that women with MDD had higher expression levels of all the NMDAR subunit genes; the only one not reaching statistical significance was GRIN3A[36].

From a gene-environment interaction perspective, an epigenetic study showed that *GRIN1* methylation was a significant predictor of depression in a sample of abused children[80]. In one study, *GRIN2A* hypermethylation in the hippocampus and prefrontal cortex in postmortem studies was related to overexpression of the GluN2A subunit[81,82]. Interestingly, maternal separation increases the expression of this subunit in the hippocampus of adult rats, but not of subunit 2B. Numerous rat stress models have evaluated GRIN1A, GRIN2B, and GRIN2A with results similar to those described above [77,83,84].

### *AMPA receptor: The GRIA2 and GRIA3 genes*

AMPARs are transmembrane ionotropic glutamatergic receptors and the main receptors mediating rapid synaptic neurotransmission in the brain. They consist of four subunits (GluR1-4) encoded by four genes (*GRIA1-4*)[85] (Figure 2). Evidence also suggests that the antidepressant mechanism of action of ketamine and esketamine involves the activation of AMPARs, with a subsequent increase in brain-derived neurotrophic factor levels (usually reduced in patients with depression)[45], as has been observed in rodent models[86]. Therefore, AMPARs have been proposed to play a key role in the antidepressant effect associated with ketamine[87].

Ketamine and its enantiomer, esketamine, lead to the disinhibition of glutamatergic neurons that modulate AMPARs by antagonizing the NMDAR of GABAergic interneurons[45,88]. In addition, ketamine metabolites such as hydroxynorketamine seem to exert their antidepressant effect *via* AMPAR activation[84,89].

In mouse models reproducing depression and stress, increased expression of AMPARs has been observed[76,90]. Postmortem studies described increased GRIA2-4 expression in the prefrontal cortex of MDD patients *vs* controls[36], and of GRIA3 in suicidal *vs* non-suicidal patients with MDD. As regards the *GRIA2* gene, several authors have observed an association between carriers of the C allele (rs4302506; C to T, located in the coding exon) and carriers of the T allele (rs4400397; C to T, 3'-UTR), and a lower age of MDD onset[91]. Also, the G allele (rs4825476; G to A, intron 3) of the *GRI3A* gene has been associated with suicidal ideation in patients with major depression treated with monoaminergic antidepressants[17]. The AMPAR subunits GluA2-4 had significantly higher expression in female MDD patients[36].

### *Other glutamatergic receptors associated with treatment response*

Animal studies have suggested that ionotropic glutamate receptors play a role in the action of antidepressant drugs[92,93]. Another widely investigated gene is *GRIK4*, which encodes subunit 4 of the ionotropic glutamate KAR. Here, an association was observed between the rs1954787 polymorphism

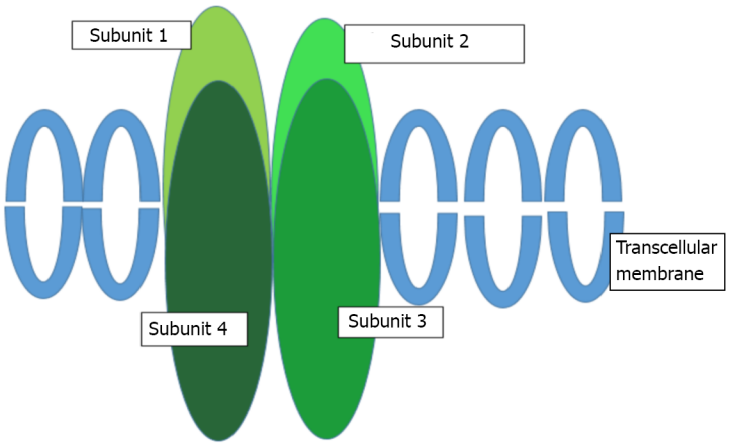


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**Figure 2 Structure of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, which consists of four subunits (GluR1-4).**

and antidepressant response[94]; however, the *GRIK4* polymorphism with the highest predictive value for treatment outcome was rs12800734. Nonetheless, these findings have not been replicated in other studies, probably due to design differences[95]. Existing data also revealed increased expression of the KAR subunits, GluK1 and GluK2. In addition, the strongest predictor of suicide was GRIK3 (GluK3) expression in both sexes[36]. KARs appear to regulate L-glutamate release by functioning as facilitatory or inhibitory autoreceptors during repetitive synaptic activation. The KAR activity may contribute to excitotoxic cell death; however, the role of these receptors in the dorsolateral prefrontal cortex of MDD subjects remains to be elucidated. Genetic variation in *GRIK3* has been associated with recurrent MDD [36].

In addition to ionotropic glutamatergic receptors, metabotropic receptors have also been involved in the genesis of MDD. Increased expression of *GRIN1, GRIN2A-D, GRIA2-4, GRIK1-2, GRM1, GRM4, GRM5*, and *GRM7* has been observed in female MDD patients. In contrast, *GRM5* expression was lower in male MDD patients relative to male controls. When suicidal MDD patients were compared with non-suicidal patients, *GRIN2B, GRIK3,* and *GRM2* were expressed at higher levels in suicidal patients[36]. Recent studies showed that mGluR4 regulation is altered in male suicidal individuals, leading to higher expression of mGluR. Higher expression levels of the mGluR2 encoding gene, *GRM2*, were also detected; *GRM2* has been proposed as a biomarker of suicide[36].

Repeated stress in male rats has been reported to be associated with lower expression of AMPARs and NMDARs, and, also, with a lower activity of these receptors. In contrast, in female rats exposed to stress, the expression of AMPARs and NMDARs was normalized *via* the activation of estrogen receptors, resulting in a neuroprotective and procognitive effect[96]. The authors proposed that, in female patients, estrogenic activity may lead to a differential response to ketamine; it should be noted that two-thirds of MDD patients are women.

Finally, there is downregulation of metabotropic receptors in mice reproducing models of depression, especially in the mGlu2 subunit, which is completely restored by ketamine administration[97].

## LIMITATIONS AND STRENGTHS

The main limitation of this review is the scarcity and heterogeneity of the literature available on the topic. Few studies have employed similar methodology and, thus, there is limited replication of the described findings. Due to the small number of studies, all research conducted in humans and animals has been included in the review, although the extrapolation of the results, in this case, is limited. As we have noted, this is a narrative review, and limitations inherent to this type of review should also be mentioned: Study selection, data extraction, and synthesis were not protocol-based and, thus, could be prone to bias.

Nonetheless, it should also be noted that this is the first review, to our knowledge, of this specific topic, making it possible to summarize the current state of the art, highlighting the need to advance research in this field.

## CONCLUSION

Patients with TRD often experience long periods of therapeutic trials with different antidepressant

medications, resulting in a worse outcome, a delay in symptomatic remission, and an increased risk of fatal events, such as suicide. Therefore, the management of TRD with appropriate therapy could be facilitated by the identification of biological markers of TRD, which could guide treatment choice from the outset.

Although the serotonergic, noradrenergic, and dopaminergic pathways were those historically studied, more recent work indicates the involvement of the glutamatergic pathway. This proposal is consistent with new therapeutic strategies in TRD, such as ketamine and esketamine, which act mainly on glutamatergic receptors.

Our review highlights *GRIN2B*, which encodes the NR2B subunit of NMDAR, as a candidate gene in the pathogenesis of TRD. In addition, several studies have associated genes encoding AMPAR subunits with symptomatic severity and suicidal ideation. These genes encoding glutamatergic receptors could, therefore, be candidate genes for understanding the etiopathogenesis of TRD, as well as for understanding the pharmacodynamic mechanisms and response to ketamine and esketamine treatment. However, further empirical work is required to replicate the observed associations and to confirm the involvement of these genes in the pathogenesis of TRD.

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*MINIREVIEWS*

# Social media and schizophrenia: An update on clinical applications

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## Abstract

Social media has redesigned the landscape of human interaction, and data obtained through these platforms are promising for schizophrenia diagnosis and management. Recent research shows mounting evidence that machine learning analysis of social media content is capable of not only differentiating schizophrenia patients from healthy controls, but also predicting conversion to psychosis and symptom exacerbations. Novel platforms such as Horyzons show promise for improving social functioning and providing timely access to therapeutic resources. Social media is also a considerable means to assess and lessen the stigma surrounding schizophrenia. Herein, the relevant literature pertaining to social media and its clinical applications in schizophrenia over the past five years are summarized, followed by a discussion centered on user feedback to highlight future directions. Social media provides valuable contributions to a multifaceted digital phenotype that may improve schizophrenia care in the near future.

**Key Words:** Social media; Schizophrenia; Digital phenotype; Facebook; YouTube; Instagram

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**Core Tip:** Recent literature demonstrates that social media data analysis guided by machine learning can differentiate users with schizophrenia from healthy controls as well as predict conversion to psychosis and symptom exacerbations. Novel platforms such as Horyzons can improve social functioning in schizophrenia patients, but long-term engagement is a challenge that may be addressed by streamlining the user experience.

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## INTRODUCTION

Although the increased prevalence of social media has already transformed daily life, these platforms are poised to further improve the management of various medical conditions. Schizophrenia presents a unique opportunity for advancement in diagnosis and management. Prior studies have established the feasibility and acceptability of social media in patients with schizophrenia[1-3], and the recent research discussed within this article demonstrate that potential benefits are within reach.

The intrinsic sociality of social media platforms such as Facebook and YouTube offers the capability to not only assess and reform the stigma surrounding the condition, but also provides a manner of communication and community that may be more agreeable to individuals with schizophrenia who are likely to self-isolate.

The aim of this article is to review the recent literature on social media with a focus on clinical applications in schizophrenia. A literature search for (social media) AND [(psychosis) OR (schizophrenia)] was conducted on PubMed and Reference Citation Analysis (https://www.referencecitationanalysis.com/) from 2017 to present, and the most relevant articles were selected for discussion. The contributions of the subsequent studies to schizophrenia diagnosis and clinical management will be reported, followed by a discussion on future directions that details necessary changes and further avenues of research that may augment the promising advances in schizophrenia management.

## SOCIAL MEDIA

### *Diagnosis*

The content of several social media platforms was analyzed, and findings will be organized by platform in consideration of the inherent differences between media types (*i.e.*, typed posts on Facebook, Twitter, Reddit; visual content on Instagram). These findings are summarized in Table 1.

Kelly *et al*[4] performed a study that offers insight into the clinical utility of Facebook posts. Blinded clinical raters assessed eight participants with schizophrenia, seven with depression, and eight health controls using symptom severity scales, including the Brief Psychiatric Rating Scale for psychotic symptoms and the Community Assessment of Psychotic Experiences for global functioning. The clinical raters included psychiatrists and other mental health clinicians, who rated participants on the corresponding scales by both de-identified Facebook posts and in-person assessments. The ratings for the Facebook posts were significantly correlated with in-person assessments across all three categories of psychotic symptoms, depressive symptoms, and global functioning. These results validate the clinical relevance of social media posts.

Birnbaum *et al*[5] analyzed Twitter posts by combining clinical appraisals with machine learning and found significant linguistic differences between individuals who self-disclosed as having schizophrenia from healthy controls. The clinicians evaluated the self-disclosed Twitter users' posts to determine authenticity of the diagnosis. Their appraisals were used to strengthen the machine learning algorithm to achieve an accuracy of 88% in identifying users with schizophrenia. In addition, the schizophrenia group were found to have significantly greater use of interpersonal pronouns, decreased attention on friendship, and increased preoccupation with biological processes. In other studies, machine learning analysis of Twitter posts have also revealed that users with schizophrenia are more likely to tweet about depression, anxiety, and suicidality than control groups, which highlights the importance of social media as a facet of digital phenotyping that may lead to earlier detection of symptoms[6,7].

Machine learning has been found to be similarly capable of identifying users with schizophrenia with up to 93% accuracy in Rezaii *et al*[8], in which 30000 Reddit posts were analyzed. The authors emphasize that low semantic density and content about voices and sounds were essential factors in predicting conversion to psychosis. Although outside the scope of the present discussion, the study used a

**Table 1 Summary of findings across social media platforms related to schizophrenia diagnosis**

| Ref. | Social media platform | Findings |
|---|---|---|
| Kelly *et al*[4] | Facebook | Blinded clinical raters assessed Facebook posts using standardized symptom scales that correlated with in-person assessments |
| Birnbaum *et al*[5] | Twitter | Combined clinical appraisals with machine learning to achieve accuracy of 88% differentiating users with schizophrenia from controls |
| Hswen *et al*[6, 7] | Twitter | Users with schizophrenia tweet more frequently about depression, anxiety, and suicidality |
| Rezaii *et al*[8] | Reddit | Low semantic density and content about voices and sounds in users' posts were core variables in differentiating users with schizophrenia |
| Bae *et al*[9] | Reddit | Machine learning differentiated users with schizophrenia through increased third person plural pronouns, negative emotion words, and symptom-related topics |
| Kim *et al*[10] | Reddit | Machine learning able to analyze users' posts and categorize into range of psychiatric diagnoses |
| Hänsel *et al*[11] | Instagram | Users with schizophrenia spectrum disorders found to have significantly lower saturation, colorfulness, and decreased number of faces in posted images |

mathematical method called vector unpacking that breaks down the meaning of a sentence into a simplified set of core ideas. Further expanding on linguistic features, Bae *et al*[9] used machine learning and Reddit posts focusing on schizophrenia to highlight significant differences from the control group, including increased frequency of third person plural pronouns, words representing negative emotions, and topics related to their symptoms. Lastly, Kim *et al*[10] was likewise able to use machine learning to tie the contents of user posts in Reddit mental health communities with schizophrenia, but expanded its classification to include a range of diagnoses including depression, schizophrenia, borderline personality disorder, and autism. All the above studies demonstrate that social media posts can be used to differentiate schizophrenia patients from healthy controls, forming the foundation for diagnostic relevance in the future.

In addition to the linguistic features of social media posts, the clinical utility of visual content on Instagram has also been explored. Hänsel *et al*[11] extracted image features such as color composition and the number of faces depicted from nearly 12000 Instagram posts from 68 individuals with schizophrenia spectrum disorders and 34 healthy controls. The study found that users with schizophrenia posted images with significantly lower saturation, colorfulness, and number of faces. Individuals with schizophrenia also had significantly lower ratios of followers to the number of accounts being followed compared to the control group. The study proves that visual Instagram data can be another clinically relevant component that can ultimately contribute to a digital phenotype with a diagnostic signature.

### *Management*

One of the most researched benefits offered by social media may be found in their characteristic ability to provide users with an alternative form of socializing. Several studies have evaluated the capacity of these platforms to encourage social behaviors in the schizophrenia population, who commonly tend to self-isolate.

Although not in schizophrenia patients, a study by Alvarez-Jimenez *et al*[12] sets the stage for the discussion by investigating social media interventions in young people considered high risk for transition to psychosis. Researchers developed a platform called MOMENTUM, which highlights mindfulness, personal strengths, and self-efficacy. Thirteen of the fourteen participants reported that the platform was helpful, and data showed significant improvements in social functioning and subjective wellbeing, as well as significant increases in mindfulness skills and use of strengths that were both highlighted by the intervention. Thus, the platform MOMENTUM was not only used widely by participants, but also led to measurable improvements in sociality.

Alvarez-Jimenez *et al*[13] also led the first intervention in first-episode psychosis patients *via* a similar platform called Horyzons, which aims to incorporate social networking, psychotherapy, moderation by experts and peers, and the aforementioned emphasis on mindfulness and personal strengths[13]. The primary outcome was social functioning, using the Personal and Social Performance Scale at the final follow-up at 18-mo. The study recruited 170 participants between the ages of 16 and 27, who were randomly assigned to the Horyzons intervention in addition to treatment as usual (TAU) or solely TAU, which consisted of generic medical and mental health services.

While no significant effects were found, participants in the intervention group demonstrated a 5.5 times greater increase in their odds of finding employment or furthering their education compared to the control group. Participants can choose from a selection of activities, and topics related to occupational preparation were among the most selected. This included activities such as "Nailing the interview," "How to write a resume," and "Getting your public persona ready." This content likely

contributed to the improved vocational and educational attainment compared to the TAU group, in which vocational/educational measures declined over the length of the study. Likewise, 13% of the Horyzons group were hospitalized due to psychosis compared to 27% of the control group, but again this difference was not significant. The level of engagement with the Horyzons platform may play a role, as 55.5% of intervention participants logged on for at least 6 mo, and 47% logged on for at least 9 mo[14]. Although medication adherence was not a target measure in these studies, it is likely that the reduced hospitalization rates and other benefits are in part due to treatment adherence reinforced through platform participation. The awareness of symptom exacerbations to both participants and moderators may identify medication nonadherence and allow for timely dose adjustments as well. Overall, the Horyzons platform continues to hold promise as a feasible opportunity to prevent relapse and bridge patients from early psychosis treatment to multiple fundamental resources[14,15]. The study was originally developed and performed in Australia, but has since expanded to several other countries as well[15-17], further supporting the accessibility of social media interventions.

From a clinical perspective, Birnbaum *et al*[18] used machine learning models to analyze over 50000 Facebook posts from 51 patients with first-episode psychosis. The study captured behavioral and linguistic markers associated with predicting relapse, including significant differences in the wording of Facebook posts that preceded relapse hospitalization by one month. These differences included increased use of first and second person and more frequent use of words related to swearing, anger, and death. The related posts showed significantly less mentions of work, health, and friends, yet also involved more frequent co-tagging of friends. The study demonstrates the predictive value that social media can offer in identifying patients most susceptible to relapse. Similarly, patients who displayed increased, above-median Twitter posts related to schizophrenia had a 15% increase in mental health episodes[19]. Temporal analyses showed a seven-day pattern of positively associated Twitter posts and mental health fluctuations on day 1, negative association by day 4, and a return to negative association at day 7. The identified pattern illustrates the potential predictive value of Twitter posts on the symptomatic course of schizophrenia and may be valuable in identifying individual risks for symptom exacerbation.

Lastly, social media can provide additional benefits that improve patients' daily life in unique ways. Pertaining to physical health improvements, Naslund *et al*[20] investigated the role of a Facebook group to support health goals in patients with severe mental illness (SMI). Group participants who achieved weight loss of at least 5% of body weight or improved physical activity had contributed increased Facebook interactions, though this relationship neared but did not surpass the threshold for significance. Nevertheless, when participants posted about their personal successes and challenges, it generated significantly more platform interactions in comparison to motivational content, health information, and program reminders. This study exemplifies the impact that social media can have on patients' medical health outside of psychiatric care.

On a similar note, social media can be used to identify habits detrimental to health, such as smoking. Hswen *et al*[21] found that Twitter users with schizophrenia had significantly more posts containing tobacco-related keywords, which parallels the reality that smoking is more common in the schizophrenia community relative to the general population. Thus, these two studies demonstrate the capability of social media to not only identify areas to improve physical health, but also provide a reasonable intervention buffered by social support. Apart from physical health benefits, Sangeorzan *et al*[22] found that patients with SMI who vlog through YouTube receive peer support, increased self-efficacy, and diminished self-stigma. These benefits are likely to contribute to an improved sense of well-being, as would reducing overall stigma through public health education.

### *Public health education*

While not a directly clinical application, it is worthwhile to briefly note the impact of social media in removing stigma through educational efforts targeting the general population. Robinson *et al*[23] examined over one million tweets and found schizophrenia to be the most stigmatized condition among mental health illnesses. Likewise, 68.3% of Turkish Twitter posts containing schizophrenia were deemed stigmatizing[24]. Several efforts have been made to assess public perception and improve awareness through Twitter[23-25], YouTube[26-28], Facebook[29,30], Instagram[30,31] and Weibo[32] (a Chinese social media platform). Social media has demonstrated potential to reduce stigma of schizophrenia, which may indirectly benefit patients' daily interactions and sense of well-being.

## FUTURE DIRECTIONS

Although the above results are undoubtedly promising, one concern that must be addressed is whether these benefits apply to all age groups. Rekhi *et al*[33] reported the results of a survey of 265 individuals with schizophrenia to determine the characteristics of social media users. 52% of individuals used social media in the past week. However, patients that more frequently used social media were of younger age, higher family income, decreased symptom severity, and education above secondary school. Similarly, in a survey of patients from early psychosis and recovery units, age accounted for differences in use and

access of technology[34]. The use of technology and interest in internet-based interventions were nevertheless primarily positive, suggesting that with improvements, the interventions can become even more appealing to the broader population. These statistics are also improved compared to a 2015 survey that reported on 80 patients of ages 18-70 with schizophrenia, in which only 27% of individuals used social media[35]. At that time, participants reported that social media assisted them in increasing socialization, further supporting that the underlying interest is present and growing, but peak usage may depend on improvements in appeal and functionality.

To better understand what these improvements may be, a suitable starting point is patient feedback. Twelve participants with a mean age of 23 years were interviewed from the original Horyzons study. While some participants reported that the strengths of the intervention were on-demand support and flexibility, others felt overwhelmed by the options available to them that resulted in decreased motivation to engage with the platform[36]. Additional feedback was given by 26 participants involved in an open trial of the Horyzons platform in the United States. These users recommended the development of a smartphone application, the functionality to allow users to send private messages to each other, and the expansion of the Horyzons community to incorporate a greater number of users[15]. Integrating user suggestions such as simplifying the users' choices and increasing ease of use with a smartphone application may increase motivation to engage with the platform and ultimately expand the diversity of the userbase. Lastly, future updates to the Horyzons platform may benefit from employing artificial intelligence to automate delivery of therapy content tailored to users by analysis of individual data, further streamlining the user experience[37].

The negative effects of platforms such as Horyzons should also be taken into consideration for future research. Social media users with SMI report various concerns about privacy vulnerabilities. Specifically, these concerns involve the fear of stigma and judgment by others, impact on personal relationships, hostility towards participants, being hurt, and endangering employment. In a survey of 90 social media users with SMI, approximately one-third reported being concerned about privacy[38]. These concerns are legitimate, and platform developers should continue to involve participants in the development of their systems and ensure that privacy is prioritized. Likewise, enrolled participants should be educated on how to protect themselves from the potential risks related to stigma, self-disclosure, and other related concerns. These platforms must also take precautions to prevent spreading misinformation, worsening participant symptoms, and delaying professional help when necessary[38]. Lastly, the aforementioned improvement in vocational and educational outcomes seems to be dependent on user engagement, as those in the top quartile of logins (greater than 77 times over the course of the study) demonstrated significantly greater effects compared to those in the bottom quartile of logins (less than 9 times)[14]. Since these improvements seem to follow a dose-response relationship, platforms should screen for participants in this lower quartile of engagement, as they are not receiving the intended intervention effects, but may benefit from additional one-on-one time with moderators or specifically designed interventions.

## CONCLUSION

Social media has transformed daily life and is on the cusp of extending an equal impact to psychiatric diagnosis and management. Studies have consistently shown the capability of machine learning to distinguish users with schizophrenia through social media data, whether it be typed language or visual content. These technologies showcase the emerging predictive value in first-episode psychosis and episodes of symptom exacerbation. Novel platforms such as Horyzons improve social functioning and increase timely access to resources such as peer support and psychotherapy. With platform improvements that streamline the user experience and augment patient engagement, all users stand to benefit from the contribution of social media to a multifaceted digital phenotype.

## FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

# *ABCB9* polymorphism rs61955196 is associated with schizophrenia in a Chinese Han population

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## Abstract

***BACKGROUND***

Schizophrenia (SCZ) is a complex disease which can be affected by both genetic and environmental factors. Prenatal famine exposure may cause changes in DNA methylation levels of genes. Meanwhile, maternal nutrition during pregnancy is a pivotal environmental factor in the development of SCZ. DNA methylation may be an intermediate factor mediating exposure to famine during pregnancy and SCZ, and DNA methylation quantitative trait loci might serve as a promising tool for linking SCZ and prenatal famine.

***AIM***

To analyze the association between prenatal famine exposure and SCZ risk in Northeast Han Chinese through analysis of DNA methylation related loci.

***METHODS***

A total of 954 Han Chinese from Northeast China were recruited, including 443 patients with SCZ and 511 healthy controls. The participants were further divided into famine (born in 1960-1962) and non-famine (born in 1963-1965) groups to investigate the effect of prenatal famine exposure. Four single-nucleotide polymorphisms (SNPs) selected according to the relevant literature were genotyped, namely, rs11917047 in *PTPRG*, rs2239681 in *IGF2*, rs3842756 in *INSIGF*, and rs61955196 in *ABCB9*. DNA were extracted from peripheral blood samples, and the genotypes of these SNP loci were detected using the improved Multiple Ligase Detection Reaction multiple SNP typing technique. The associations of the DNA methylation related SNPs with SCZ risk and prenatal famine,

and their interactions were analyzed using logistic regression analysis and generalized multifactor dimensionality reduction (GMDR) software.

***RESULTS***

Based on the sequencing data, genotype distributions and allele frequencies of the four selected SNPs were determined. All genotype frequencies of the four SNPs in the healthy control group were tested for deviation from Hardy-Weinberg equilibrium ($P > 0.05$). Logistic regression analysis showed that rs61955196 was significantly associated with SCZ risk in the log-additive model [odds ratio (OR): 1.22; 95% confidence interval (CI): 1.01-1.48; $P = 0.040$]. We also found that the rs61955196 allele was related with an enhanced risk of SCZ (G>C, OR: 1.22; 95%CI: 1.01-1.47; $P = 0.042$). However, no associations were observed between rs11917047, rs2239681, or rs3842756 and SCZ risk. Under the optimal genetic model, no significant association of famine with the four SNPs was seen. Though the gene–gene interactions between rs2239681 and rs61955196 were found in GMDR analysis, none of the gene-gene interactions and gene-famine interactions were associated with the risk of SCZ.

***CONCLUSION***

Our study suggested that rs61955196 in *ABCB9* is associated with SCZ susceptibility in Northeast Han Chinese, providing insight into genetic effects on SCZ.

**Key Words:** Schizophrenia; Prenatal famine; rs61955196; DNA methylation; *ABCB9* polymorphism

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**Core Tip:** Prenatal famine exposure may cause changes in DNA methylation levels of genes, while maternal nutrition is a pivotal environmental factor for schizophrenia (SCZ). To analyze the association between prenatal famine exposure and SCZ risk, we recruited 443 SCZ patients and 511 healthy controls with four single-nucleotide polymorphisms genotyped, which were previously identified as DNA methylation quantitative trait loci. Our study observed significant differences in rs61955196 genotype distribution and allele frequency between SCZ patients and healthy controls for the first time, suggesting that rs61955196 in *ABCB9* was associated with SCZ susceptibility among the Northeast Han Chinese population.

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## INTRODUCTION

Schizophrenia (SCZ) is a complex disease affected by both genetic and environmental factors, which is often characterized by symptoms such as hallucinations, social withdrawals, delusions, and cognitive dysfunction[1,2]. The global point prevalence of SCZ was estimated to be 0.28% (0.24%–0.31%) in 2016 which contributes 13.4 (95% uncertainty interval: 9.9–16.7) million years of life lived with disability to burden of disease globally[3]. And China was assessed to show the highest prevalence of 0.42% among global countries, which raises necessity to conduct research enrolling local Chinese participants to reveal the practical status and underlying biological mechanisms of SCZ for its management and treatment.

DNA methylation is a heritable epigenetic modification which alters gene expression[4]. Studies have demonstrated that overall DNA hypomethylation is evident in SCZ patients, while treatment with haloperidol might increase methylation[5,6]. In other words, DNA methylation, which can regulate gene expression, is closely associated with the risk of SCZ [7-10].

Although the peak incidence rate of SCZ appears in adolescence and early adulthood, many believe that its etiological origin exists much earlier in one's life, which includes exposure to environmental and genetic factors. The exposure occurring in the early stages of life development along with a cumulative effect during the later stages may eventually lead to the appearance of symptoms[11]. Among the environmental factors, maternal nutrition during pregnancy plays an early and vital role in the occurrence and development of SCZ[12,13]. Studies have shown that prenatal famine exposure may

cause changes in DNA methylation levels of genes. Malnutrition during pregnancy, especially the lack of maternal protein and folic acid, seriously affects fetal development which will result in changes in DNA methylation[14]. Empirical studies of the Great Famine of China in 1959-1961 and the Dutch famine in 1944-1945 both showed that prenatal famine exposure led to an obviously increased risk of SCZ[15-17]. It was found that those who were born during the famine are twice as likely to have SCZ in their later years as normal people[16]. Therefore, we proposed that prenatal nutritional deficiencies may increase the risk of SCZ by altering DNA methylation status.

In recent years, genome-wide association studies (GWAS) have been effectively used for studying genetic variation associated with SCZ[18,19]. As DNA methylation tends to be sensitive to environmental factors, DNA methylation quantitative trait loci (meQTL) seems more promising. They can be derived by GWAS mapping levels of DNA methylation in genotyped individuals and define loci at which DNA methylation is influenced by genetic variation[20], with a superiority of higher consistency throughout one's life than DNA methylation itself. There have already been reports revealing the role of meQTLs in SCZ risk, which promote the feasibility of them serving as a useful tool for SCZ-related research[21,22]. However, the results from GWAS studies are often not repeatable due to the enormous number for detection and heterogeneity of genetic information regarding people from different races and regions[23]. Given the high SCZ prevalence in China and current lack of available genetic data covering native patients, we find it necessary to conduct research collecting genetic data among Chinese individuals.

Here we intended to analyze the associations between single-nucleotide polymorphisms (SNPs) identified as meQTLs with the risk of SCZ and prenatal famine exposure among a Han population in Northeast China. We recruited SCZ patients and healthy controls (HCs) with comparable age including individuals born between 1959 and 1961 with prenatal famine exposure, and collected their peripheral blood samples for genotyping. We selected four SNPs which were previously reported as meQTLs, and determined their associations with SCZ and prenatal famine along with their interactions. We hope our work may provide more practical reference in management of SCZ.

## MATERIALS AND METHODS

### Study subjects

A desired sample size of 417 patients was calculated using the software Quanto with a proper power before the recruitment of participants, with a unmatched case-control rate of 1.2, an estimated population risk of 1% for SCZ, a log-additive model gene with allele frequency of 0.1, genetic effect of 1.5, and a type I error rate of 0.05 by two-sided test. According to the desired sample size and the inclusion and exclusion criteria, a total of 954 Han Chinese from Northeast China were finally recruited between 2010 and 2012, including 443 SCZ patients and 511 healthy people. The patients were recruited from the Siping Psychiatric Hospital and Sixth Hospital of Changchun City (Jilin, China). Each patient was diagnosed according to the Tenth Revision of International Classification of Diseases-10 for SCZ and confirmed by at least two experienced psychiatrists. Those with neurological disorders, severe organic lesions, and drug dependence were excluded. Subjects in the HC group matching the patients by gender and age were recruited from the Changchun Municipal Centre for Disease Control and Prevention, in order to get a comparable proportion of famine-exposed individuals between two groups and a similar ratio of gender. The healthy subjects were required to have no history of mental illness and were in good health without any known disease at the time of recruitment. Furthermore, subjects who were in uterus between 1959 and 1961 were regarded to be exposed to famine. And then they were divided into two groups, namely, famine group (born in 1960-1962) and non-famine group (born in 1963-1965), according to whether they were exposed to famine before birth. All methods were performed in accordance with the relevant guidelines and regulations. The study adhered to the tenets of the Declaration of Helsinki, and was approved by the Ethics Committee of the School of Public Health of Jilin University (Approval No: 2014-03-11). All participants provided informed consent.

### Genomic DNA extraction and genotyping

In the first step, we collected peripheral blood samples from the participants and extracted genomic DNA. Then, DNA content and purity were determined based on the ratio of $OD_{260}/OD_{280}$. Combining the feasibility of the detection method and the previous publications, we selected four SNPs (rs11917047 in *PTPRG*, rs2239681 in *IGF2*, rs3842756 in *INSIGF*, and rs61955196 in *ABCB9*) which have been confirmed as meQTLs, and the SNPs themselves or the genes that they belong to were assessed to be associated with SCZ[21,24-26].

Then, the genotypes of these SNP locus were detected using the improved Multiplex Ligase Detection Reaction multiple SNP typing technique (Shanghai Tian Hao Biological Technology Co. Ltd.). Using the Assay Design software 3.1, we successfully designed primers for the four meQTL SNPs. And the primer sequences for each SNP are as follows: rs11917047-F, AGATGAAAGATTGGGGTGTGGGTA and rs11917047-R, GCTGGTACCCAACCAGGAACAC; rs2239681-F, ATGGGCAAATCAGCCTGAAGAG and rs2239681-R, GTGTGCAAGAGGGGTGAAAGGT; rs3842756-F, TCCACAGGGACTCCAT-

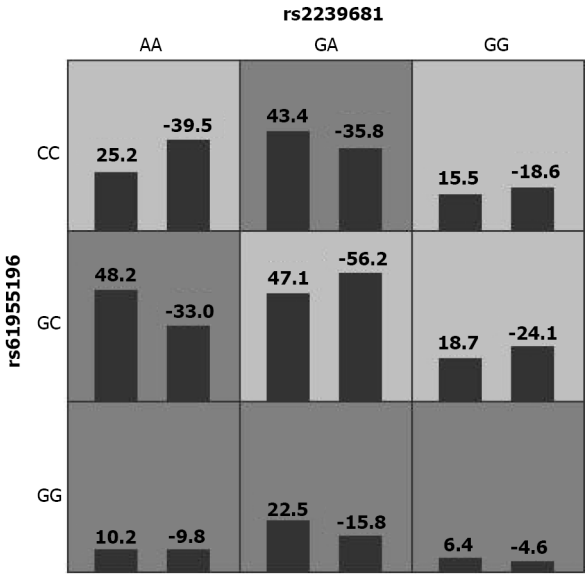


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**Figure 1 Generalized multifactor dimensionality reduction 2D interaction model in rs2239681 and rs61955196.** The left bar represents the positive score and the right bar represents the negative score.

CAGAAA and rs3842756-R, CCTGTGGCTCAGGGTCCAGTAT; and rs61955196-F, GCTGCAAGGTCG-GAGCTGAG and rs61955196-R TGGGAGGAGTTTGCCACAGG.

### *Statistical analysis*

Deviation of the genotypes from Hardy-Weinberg equilibrium (HWE) between the SCZ patients and healthy individuals was assessed using a $\chi^2$ goodness-of-fit test. Logistic regression analysis was used to examine the relationship between SNPs and the risk of SCZ as well as the association of famine with SNPs with age and sex adjusted as covariates. The online genetic analysis software, SNPStats, was used to select the optimal genetic model according to the Akaike information criterion (AIC) and Bayesian information criterion. Generalized multifactor dimensionality reduction (GMDR) analysis was conducted to analyze the gene-gene interactions, which are rather critical in investigating genetic information for multifactorial diseases, and the gene-environment interactions were analyzed by crossover analysis based on logistic regression analysis. Except for the above specified, all statistical analyses were performed with SPSS 24.0 software. A $P$-value < 0.05 was considered statistically significant.

## RESULTS

Based on the SNP sequencing data, the genotype distributions and allele frequencies of the four selected SNPs in SCZ patients ($n$ = 443) and HCs ($n$ = 511) were determined and the detailed data are shown in Table 1. All genotype frequencies of the four SNPs in the HC group were in accordance with HWE ($P$ > 0.05). Logistic regression analysis showed that, compared with those carrying the wild-type homozygote (CC) of rs61955196, subjects carrying the mutant homozygote (GG) had a higher risk of SCZ [odds ratio (OR): 1.54; 95% confidence interval (CI): 1.03-2.30; $P$ = 0.037]. We also found that the rs61955196 allele was related with an enhanced risk of SCZ (OR: 1.22; 95%CI: 1.01-1.47; $P$ = 0.042). The frequency of the rs61955196 G allele was 40.5% in the case group, which was significantly higher than that of the control group (36.6%; $P$ < 0.05). No associations were observed between SCZ patients and HC subjects regarding different genotypes or alleles of the rest three SNPs.

Based on the findings, we dug into the association between genotypes of rs61955196 and SCZ risk using multiple genetic models. As shown in Table 2, a significant association between rs61955196 and SCZ in the log-additive model was revealed (OR: 1.22; 95%CI: 1.01-1.48; $P$ = 0.040). In the codominant model, we also found the association of rs61955196 with SCZ in the GG *vs* CC genotype comparison. No obvious effect of rs61955196 on the risk of SCZ was found in other models ($P$ > 0.05).

To investigate the relationship of meQTLs and prenatal famine exposure, we analyzed the associations of the four SNPs with famine. Totally, 492 subjects were exposed to prenatal famine, including 220 SCZ patients and 272 HC subjects. As shown in Table 3, based on the AIC, the inheritance model was recessive for rs11917047 and rs2239681, codominant for rs3842756, and overdominant for rs61955196. SCZ patients and HCs were further divided into a famine group and a non-famine group.

**Table 1 Association analysis for four target single-nucleotide polymorphisms and schizophrenia risk, *n* (%)[1]**

| SNP | Genotype/allele | SCZ (*n* = 443) | HC (*n* = 511) | *P* value | OR (95%CI) | HWE test for controls |
|---|---|---|---|---|---|---|
| rs11917047 (*PTPRG*) | AA | 219 (49.4) | 259 (50.7) | | 1.00 (ref) | 0.151 |
| | AG | 183 (41.3) | 200 (39.1) | 0.431 | 1.12 (0.85-1.47) | |
| | GG | 41 (9.3) | 52 (10.2) | 0.713 | 0.92 (0.58-1.45) | |
| | A | 621 (70.1) | 718 (70.3) | | 1.00 (ref) | |
| | G | 265 (29.9) | 304 (29.7) | 0.885 | 1.02 (0.83-1.24) | |
| rs2239681 (*IGF2*) | AA | 156 (35.2) | 177 (34.6) | | 1.00 (ref) | 0.104 |
| | AG | 211 (47.6) | 232 (45.4) | 0.667 | 1.07 (0.80-1.43) | |
| | GG | 76 (17.2) | 102 (20.0) | 0.447 | 0.87 (0.59-1.26) | |
| | A | 523 (59.0) | 586 (57.3) | | 1.00 (ref) | |
| | G | 363 (41.0) | 436 (42.7) | 0.567 | 0.95 (0.79-1.14) | |
| rs3842756 (*INSIGF*) | CC | 405 (91.4) | 475 (93.0) | | 1.00 (ref) | 0.409 |
| | CT | 38 (8.6) | 36 (7.0) | 0.319 | 1.28 (0.79-2.08) | |
| | TT | - | - | - | - | |
| | C | 848 (95.7) | 986 (96.5) | | 1.00 (ref) | |
| | T | 38 (4.3) | 36 (3.5) | 0.329 | 1.27 (0.79-2.04) | |
| rs61955196 (*ABCB9*) | CC | 157 (35.4) | 202 (39.5) | | 1.00 (ref) | 0.513 |
| | CG | 213 (48.1) | 244 (47.7) | 0.297 | 1.16 (0.88-1.55) | |
| | GG | 73 (16.5) | 65 (12.7) | 0.037[a] | 1.54 (1.03-2.30) | |
| | C | 527 (59.5) | 648 (63.4) | | 1.00 (ref) | |
| | G | 359 (40.5) | 374 (36.6) | 0.042[a] | 1.22 (1.01-1.47) | |

[a]$P < 0.05$.

[1]Adjusted for gender.

SCZ: Schizophrenia; HC: Healthy control; OR: Odds ratio; HWE: Hardy-Weinberg equilibrium; SNP: Single-nucleotide polymorphism.

Logistic regression analysis indicated that under the optimal genetic model, there was no significant association of famine with the four SNPs in either the SCZ group or HC group ($P > 0.05$).

In this study, GMDR was used to import and analyze the interactions between rs11917047, rs2239681, rs3842756, and rs61955196. The impact of gene–gene interaction on the risk of SCZ is summarized in Table 4. The multifactor model 2 (rs2239681 × rs61955196) presented the best cross-validation consistency, which had a testing-balanced accuracy of 55.8%. Figure 1 shows the interaction model of this gene–gene interaction between rs2239681 and rs61955196. However, no significant association of gene-gene interaction with the risk of SCZ was found in this model.

Crossover analysis based on a multiplicative model of logistic regression was conducted to determine the interactions between the SNPs and famine in SCZ patients (Table 5). None of the interactions between the genotypes of the four loci of rs11917047/rs2239681/rs3842756/rs61955196 with the risk of famine were statistically significant ($P > 0.05$).

## DISCUSSION

Based on existing reports, we selected four susceptibility loci of SNPs related to SCZ as the starting point for analysis, which are rs11917047 in *PTPRG*, rs2239681 in *IGF2*, rs3842756 in *INSIGF*, and rs61955196 in *ABCB9*, respectively. This study analyzed genetic data from representative samples of Northeastern Chinese using meQTL SNPs, and found the difference of rs61955196 genotype distribution with allele frequency between SCZ patients and HC subjects for the first time. rs61955196 is located in the 5' untranslated region of the *ABCB9* gene, encoding the ABCB9 protein which belongs to the ATP-binding cassette (*ABC*) transporter family. The *ABC* gene can be divided into seven different subfamilies (*MRP, ABC1, OABP, ALD, GCN20, MDR/TAP,* and *White*)[27], and the ABCB9 protein is a member of the *MDR/TAP* subfamily. *ABC* family and *ABCB9* are reported to be involved in progression of multiple malignant tumors and chemoresistance[28-31], but little research has been done on the relationship

**Table 2 Associations between rs61955196 and schizophrenia based on multiple models, *n* (%)[1]**

| Model | Genotype | SCZ (%) | HC (%) | OR (95%CI) | *P* value | AIC | BIC |
|---|---|---|---|---|---|---|---|
| Codominant | CC | 157 (35.4) | 202 (39.5) | 1.00 | | 1279.8 | 1299.2 |
| | GC | 213 (48.1) | 244 (47.8) | 1.16 (0.88-1.55) | 0.297 | | |
| | GG | 73 (16.5) | 65 (12.7) | 1.54 (1.03-2.30) | 0.037[a] | | |
| Dominant | CC | 157 (35.4) | 202 (39.5) | 1.00 | 0.120 | 1279.7 | 1294.3 |
| | GC + GG | 286 (64.6) | 309 (60.5) | 1.24 (0.95-1.62) | | | |
| Recessive | CC + GC | 370 (83.5) | 446 (87.3) | 1.00 | 0.068 | 1278.9 | 1293.5 |
| | GG | 73 (16.5) | 65 (12.7) | 1.41 (0.97-2.04) | | | |
| Overdominant | CC + GG | 230 (51.9) | 267 (52.2) | 1.00 | 0.810 | 1282.1 | 1296.7 |
| | GC | 213 (48.1) | 244 (47.8) | 1.03 (0.80-1.34) | | | |
| Log-additive | - | - | - | 1.22 (1.01-1.48) | 0.040[a] | 1278 | 1292.6 |

[a]$P < 0.05$.
[1]Adjusted for gender.
SCZ: Schizophrenia; HC: Healthy control; OR: Odds ratio; AIC: Akaike information criterion; BIC: Bayesian information criterion.

**Table 3 Association analysis for famine and single-nucleotide polymorphisms, *n* (%)[1]**

| Group | SNP | Genotype | Famine | Non-famine | *P* value | *OR* (95%CI) |
|---|---|---|---|---|---|---|
| SCZ | rs11917047 | AA + GA | 204 (92.7) | 198 (88.8) | 0.150 | 1.00 |
| | (Recessive) | GG | 16 (7.3) | 25 (11.2) | | 1.62 (0.84-3.13) |
| | rs2239681 | AA + GA | 185 (84.1) | 182 (81.6) | 0.550 | 1.00 |
| | (Recessive) | GG | 35 (15.9) | 41 (18.4) | | 1.16 (0.71-1.91) |
| | rs3842756 | CC | 198 (90) | 207 (92.8) | 0.270 | 1.00 |
| | (Codominant) | CT | 22 (10) | 16 (7.2) | | 0.68 (0.35-1.34) |
| | rs61955196 | CC + GG | 117 (53.2) | 113 (50.7) | 0.610 | 1.00 |
| | (Overdominant) | GC | 103 (46.8) | 110 (49.3) | | 1.10 (0.76-1.60) |
| HC | rs11917047 | AA + GA | 249 (91.5) | 210 (87.9) | 0.160 | 1.00 |
| | (Recessive) | GG | 23 (8.5) | 29 (12.1) | | 1.50 (0.84-2.68) |
| | rs2239681 | AA + GA | 222 (81.6) | 187 (78.2) | 0.330 | 1.00 |
| | (Recessive) | GG | 50 (18.4) | 52 (21.8) | | 1.24 (0.80-1.92) |
| | rs3842756 | CC | 257 (94.5) | 218 (91.2) | 0.150 | 1.00 |
| | (Codominant) | CT | 15 (5.5) | 21 (8.8) | | 1.65 (0.83-3.27) |
| | rs61955196 | CC + GG | 144 (52.9) | 123 (51.5) | 0.750 | 1.00 |
| | (Overdominant) | GC | 128 (47.1) | 116 (48.5) | | 1.06 (0.75-1.50) |

[1]Adjusted for gender.
SCZ: Schizophrenia; HC: Healthy control; OR: Odds ratio; SNP: Single-nucleotide polymorphism.

between *ABCB9* gene and SCZ. Recent evidence suggests that *ABCB9* is positively associated with the risk of SCZ[32], which is in accordance to our findings to some extent.

Increasing studies have shown that epigenetic modifications are associated with the pathogenesis of SCZ, and DNA methylation is a crucial one regulating gene expression, which may be a key factor in the process[33,34]. Our results showed that the methylation locus rs61955196 increased the risk of SCZ in the log-additive model. However, we did not observe the association between the methylation loci located in the other three genes and SCZ, which is inconsistent with existing studies. For example, Cressant *et al*[35] discovered that the *PTPRG* gene containing the rs11917047 locus was associated with SCZ. The receptor protein tyrosine phosphatase PTPRG is a ligand for members of the contact protein

**Table 4 Generalized multifactor dimensionality reduction analysis for best interaction combination models**

| No. | Best combination | CVC | Te-BA | *P* value |
|---|---|---|---|---|
| 1 | rs61955196 | 9/10 | 0.5097 | 0.8281 |
| 2 | rs2239681 × rs61955196 | 10/10 | 0.5582 | 0.0547 |
| 3 | rs11917047 × rs2239681 × rs61955196 | 10/10 | 0.5341 | 0.1719 |
| 4 | rs11917047 × rs2239681 × rs3842756 × rs61955196 | 10/10 | 0.5449 | 0.1719 |

CVC: Cross validation consistency; Te-BA: Testing-balanced accuracy.

**Table 5 Crossover analysis of interactions between rs11917047/rs2239681/rs3842756/ rs61955196 and famine factor with schizophrenia**

| SNP | Genotype | Famine | SCZ | HC | OR (95%CI) | *P* value |
|---|---|---|---|---|---|---|
| rs11917047 | AG + GG | + | 121 | 119 | 1.21 (0.85-1.72) | 0.294 |
| | AG + GG | - | 103 | 133 | 0.92 (0.65-1.31) | 0.646 |
| | AA | + | 102 | 120 | 1.01 (0.70-1.45) | 0.958 |
| | AA | - | 117 | 139 | 1.00 (ref) | |
| rs2239681 | AG + GG | + | 144 | 157 | 1.13 (0.78-1.65) | 0.519 |
| | AG + GG | - | 143 | 177 | 1.00 (0.69-1.45) | 0.986 |
| | AA | + | 79 | 82 | 1.19 (0.77-1.83) | 0.432 |
| | AA | - | 77 | 95 | 1.00 (ref) | |
| rs3842756 | CT | + | 16 | 21 | 0.99 (0.50-1.95) | 0.974 |
| | CT | - | 22 | 15 | 1.90 (0.96-3.77) | 0.064 |
| | CC | + | 207 | 218 | 1.23 (0.95-1.61) | 0.123 |
| | CC | - | 198 | 257 | 1.00 (ref) | |
| rs61955196 | CG + GG | + | 147 | 145 | 1.35 (0.94-1.95) | 0.109 |
| | CG + GG | - | 139 | 164 | 1.13 (0.78-1.63) | 0.513 |
| | CC | + | 76 | 94 | 1.08 (0.71-1.64) | 0.724 |
| | CC | - | 81 | 108 | 1.00 (ref) | |

SCZ: Schizophrenia; HC: Healthy control; OR: Odds ratio; SNP: Single-nucleotide polymorphism.

family, which are linked to autism spectrum disorders. The interpretation for these disagreements may be due to the disparity in the target population as what we studied is the Han population in Northeast China, which is different from other studies in race, sample size, and geographic location.

It is a pity that we did not find the association of prenatal exposure to famine with DNA methylation loci. A recent study also reported that maternal risk alleles for neurodevelopmental disorders, primarily attention-deficit/hyperactivity disorder, were associated with prenatal exposures, but nor for SCZ or autism spectrum disorder[36]. Nevertheless, there have been much supportive evidence regarding the positive relationship between SCZ and prenatal famine exposure. Waterland[37] discovered that maternal nutritional deficiency may result in permanent abnormal DNA methylation with the potential to affect gene expression. In addition, since human is unable to synthesize folic acid which is necessary for normal DNA methylation, the lack of folic acid which hinders the production of methyl donors might affect gene expression related to neurodevelopmental processes. Prenatal famine leads to undernutrition during fetal development, which is believed to further promote the risk of SCZ in offspring[38]. Wang and Zhang[39] also used data from a nationally representative sample to analyze the association of prenatal famine exposure with the risk of SCZ. The results showed that famine population had a higher risk of SCZ compared to the non-famine cohorts. This pattern was found throughout different subsamples, such as the urban/rural population[40]. Therefore, we still believe that it is vital to continue exploring the association of prenatal famine exposure with DNA methylation and SCZ in the future. Meanwhile, this study had several limitations. First, we only adjusted for gender as we mainly focused on the genetic variants, and we were not able to explore some underlying

confounders such as medication as we have directly excluded those who had any medical treatment in the past 3 mo before enrollment. Second, as we did not collect sufficient information from the patients regarding illness-related parameters such as the severity or duration of disease, we could not rule out the possibility that the SNPs could be associated with SCZ under some specific conditions although we got negative results. Third, this is a case-control study and the patients were recruited from hospitals, resulting in inevitable selection bias. Finally, limited by the feasibility and applicability of the detection method, we only selected four SNPs in this study, and the constrained selection may leave out other crucial SNPs related to DNA methylation.

## CONCLUSION

Our study suggested that rs61955196 in *ABCB9* could be associated with SCZ susceptibility among the Han population in Northeast China. No association was found between the four meQTL SNPs and prenatal famine. These findings provide insight into genetic effects on SCZ. Future research should be devoted to validating the results, and gathering comprehensive information for additional subgroup analyses may help to reveal the association between prenatal famine and SCZ risk.

## ARTICLE HIGHLIGHTS

### *Research background*

Schizophrenia (SCZ) is a severe mental disorder bringing heavy burden, which is closely related with genetic and environmental factors. The effect of prenatal exposure of famine on SCZ risk has been reported with intense interest. DNA methylation may be an intermediate factor mediating prenatal famine and SCZ, and DNA methylation quantitative trait locus (meQTLs) can serve as a promising tool.

### *Research motivation*

The lifetime prevalence of SCZ is approximately 1% around the world, and study has reported the highest age-standardized prevalence of SCZ in China. Meanwhile, the Chinese famine of 1959-1961 is a proper source of study subjects to investigate the effect of prenatal famine on SCZ with little available genetic data. As a result, we intended to conduct analyses for SCZ and prenatal famine using native subjects with collected genetic information, which may provide insights specifically for Chinese researchers and patients.

### *Research objectives*

To investigate the associations of four single-nucleotide polymorphisms (SNPs) identified as meQTLs with the risk of SCZ and prenatal famine exposure along with their interactions among Northeast Han Chinese.

### *Research methods*

We recruited 954 Han Chinese from Northeast China including 443 patients with SCZ and 511 healthy controls, and their peripheral blood samples were collected. Among them, 492 born in 1960-1962 were further allocated to a famine group. Four SNPs were selected and genotyped, namely, rs11917047 in *PTPRG*, rs2239681 in *IGF2*, rs3842756 in *INSIGF*, and rs61955196 in *ABCB9*. The associations of the meQTLs with SCZ risk and prenatal famine, and their interactions were analyzed using logistic regression analysis and generalized multifactor dimensionality reduction software.

### *Research results*

The genotype distributions along with allele frequencies of the four SNPs were determined among the Chinese participants. We found that rs61955196 was significantly associated with SCZ risk in the log-additive model [odds ratio (OR): 1.22; 95% confidence interval (CI): 1.01-1.48; $P = 0.040$], and rs61955196 allele was related with an enhanced risk of SCZ (G>C, OR: 1.22; 95%CI: 1.01-1.47; $P = 0.042$). However, the other three SNPs were not associated with SCZ risk. No association was observed between the SNPs and prenatal famine. Gene-gene interactions were seen between rs2239681 and rs61955196, while no gene-gene or gene-famine interactions were associated with the risk of SCZ.

### *Research conclusions*

Our results suggested that rs61955196 in *ABCB9* might be involved in SCZ susceptibility among Northeast Han Chinese.

### *Research perspectives*

Our study provides a potential functional variant rs61955196 for SCZ susceptibility, and we recommend

further research to extend the findings to different populations and verify its function. Although no evidence between SCZ and prenatal famine was found, we believe that gathering comprehensive information for analyses regarding subgroups may help to reveal the association in the future.

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## FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

# Predicting South Korea adolescents vulnerable to depressive disorder using Bayesian nomogram: A community-based cross-sectional study

Haewon Byeon

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## Abstract

*BACKGROUND*

Although South Korea has developed and carried out evidence-based interventions and prevention programs to prevent depressive disorder in adolescents, the number of adolescents with depressive disorder has increased every year for the past 10 years.

*AIM*

To develop a nomogram based on a naïve Bayesian algorithm by using epidemiological data on adolescents in South Korea and present baseline data for screening depressive disorder in adolescents.

*METHODS*

Epidemiological data from 2438 subjects who completed a brief symptom inventory questionnaire were used to develop a model based on a Bayesian nomogram for predicting depressive disorder in adolescents.

*RESULTS*

Physical symptoms, aggression, social withdrawal, attention, satisfaction with school life, mean sleeping hours, and conversation time with parents were influential factors on depressive disorder in adolescents. Among them, physical symptoms were the most influential.

*CONCLUSION*

Active intervention by periodically checking the emotional state of adolescents and offering individual counseling and in-depth psychological examinations when necessary are required to mitigate depressive disorder in adolescents.

**Key Words:** Depressive disorder; Nomogram; Adolescents; Risk factor; Community-based

cross-sectional study; Brief symptom inventory

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**Core Tip:** The early detection and prevention of depressive disorder in adolescents is important because it not only adversely affects interpersonal relationships and academic achievement but also increases the probability of other related mental illnesses such as panic disorder. We developed a nomogram for screening depressive disorder using epidemiological data on 2438 adolescents. Physical symptoms, aggression, social withdrawal, attention, satisfaction with school life, mean sleeping hours, and conversation time with parents were influential factors on depressive disorder in adolescents.

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## INTRODUCTION

Depressive disorder causes an emotional response that can make a person feel a sense of failure, a sense of loss, and/or a sense of worthlessness as a result of a negative perception of him/herself[1]. It is defined as a persistent feeling of sadness or hopelessness to the extent of not being able to maintain daily activities for 2 wk in the past year[1]. It has been reported that South Koreans experience depressive disorder most frequently during adolescence compared to other stages of life[2]. A national survey of South Korean adolescents reported that one in four males and one in three females were diagnosed with depressive disorder[3]. In particular, it has been reported that depression during adolescence increases rapidly after middle school[3,4], suggesting that the mental health of adolescents is at risk during this period.

Adolescence involves the most physical, mental, and social changes that occur in a human lifetime [5]. Adolescents experiencing depressive disorder are highly likely to self-torture and/or express delinquent and aggressive behavior[5]. Moreover, if depressive disorder is not identified and managed early, it may progress to become a chronic illness with depression likely to recur during a person's lifetime[6]. The early detection and prevention of depressive disorder in adolescence is an important social issue because it not only adversely affects interpersonal relationships and academic achievement but also increases the probability of developing other mental illnesses such as panic disorder[7].

Although South Korea has developed and carried out evidence-based intervention and prevention programs to mitigate depressive disorder in adolescents[2], the number of adolescents with depressive disorder has increased every year for the past 10 years[2]. Consequently, it is necessary to identify the influential factors causing depression and develop a predictive model with high accuracy that can identify groups highly vulnerable to depressive disorder as soon as possible.

Recently, the naïve Bayesian nomogram has been used as a method for predicting groups at high risk of developing diseases[8,9]. One of the advantages of this method is that it presents the risk probability according to multiple risk factors of a disease visually so that clinicians can easily understand the results [10]. In this study, a nomogram based on a naïve Bayesian algorithm using epidemiological data on adolescents in South Korea was developed and baseline data for screening depressive disorder in adolescents is presented.

## MATERIALS AND METHODS

### *Data source*

This is a secondary data analysis study using raw data from the 2019 Korean Children Youth Panel Study (KCYPS) survey from March to June 2019 provided by the National Youth Policy Institute. The study was approved by the Research Ethics Review Board of the National Youth Policy Institute (No. KCYPS-2018).

The survey method for KCYPS is presented in Cho *et al*[11] (2018). Briefly, the KCYPS sampled 7$^{th}$-grade students attending 162 middle schools across South Korea using a stratified multi-stage cluster sampling method. Schools were selected according to the probability proportional to the size sampling method for 27 clusters across 16 metropolitan cities, small and medium-sized cities, and rural areas. After checking the information on the number of 7$^{th}$-grade classes and the number of students in each

**Table 1 Measurements of explanatory variables**

| Classification | Variable | Characteristics |
|---|---|---|
| Sociodemographic factors | Gender | Male or female |
| | Number of siblings (including the subject) | 1 person, 2 people, 3 people, or 4 people or more |
| Environmental factors | Mean conversation time with parents *per* day | < 30 min, ≥ 30 min and < 1 h, ≥ 1 h and < 2 h, ≥ 2 h and < 3 h, or ≥ 3 h |
| Personal factors | Satisfaction with academic achievement | Dissatisfied, not dissatisfied or satisfied, or satisfied |
| | Satisfaction with school life | Dissatisfied, not dissatisfied or satisfied, or satisfied |
| | Mean sleeping hours *per* day | < 5 h, 6 h, 7 h, 8 h, 9 h, or ≥ 10 h |
| | Social withdrawal | Continuous variable |
| | Aggression | Continuous variable |
| | Attention | Continuous variable |
| | Physical symptoms | Continuous variable |

class at each school, samples were extracted by randomly selecting classes. The KCYPS collected data using a tablet-assisted personal interview method to compensate for the quality deterioration caused by existing questionnaire input errors or logical errors and to increase the accuracy and efficiency of the survey. In the present study, we analyzed 2438 subjects after excluding 152 cases with missing values in the depressive disorder screening part among 2590 people who completed the KCYPS questionnaire in 2019.

### Measurements

Depression, the outcome variable, was defined by using ten items for measuring depression in the brief symptom inventory (BSI) (1984)[12], which was adapted for the South Korean population by standardizing the Symptom Checklist-90-Revision[13]. The BSI is a self-reporting test with each item being measured on a 4-point scale. Moreover, the total score ranges from 10 to 40 points. A higher score indicates more severe depression. Referring to Byeon *et al*[14] (2015), the threshold for depression in this study was 24 points, corresponding to 1 standard deviation (less than the 16$^{th}$ percentile). *AORN J* reported that Cronbach's α (a measurement of reliability) for the BSI was 0.904 (0.882 in the present study)[15].

Explanatory variables included gender, environmental factors (number of siblings and mean conversation time with parents during weekdays), and personal factors (satisfaction with academic achievement, satisfaction with school life, mean sleeping hours during weekdays, social withdrawal, aggression, attention, and physical symptoms). The definitions of the explanatory variables are provided in Table 1.

Social withdrawal was measured by using five items from the Behavior Problem Scale for Children and Adolescence (BPSCA) developed by Kim and Kim[16] (1998) after excluding items overlapping with other sub-domains. Each item was measured on a 4-point scale with the total score ranging from 5 to 20 points. A higher score indicates more severe social withdrawal. *AORN J* reported that Cronbach's α for the tool was 0.850 (0.894 in the present study)[15].

Aggression was measured by using the Emotional or Behavioral Problems Scale (EPS) developed by Cho and Lim[17] (2003). Six items were used and each item was measured on a 4-point scale with the total score ranging from 6 to 24 points, and a higher score indicates a more aggressive condition. Cho and Lim[17] (2003) reported that the Cronbach's α of the tool was 0.760 (0.809 in the present study).

Attention problems were measured by using 7 items in the EPS[17]. Each item was measured on a 4-point scale with the total score ranging from 7 to 28 points. A higher score indicates more severe attention problems. Kim and Song[18] (2014) reported Cronbach's α for the tool was 0.791 (0.813 in the present study).

Physical symptoms are when a person perceives that he or she is frequently ill or tired such as chest tightness or stomach discomfort without a pathological cause. These were measured by using eight items in the EPS[17]. Each item was measured on a 4-point scale with the total score ranging from 8 to 32 points. A higher score indicates more severe physical symptoms. Choi *et al*[19] (2017) reported Cronbach's α for the tool was 0.87 (0.858 in the present study).

### Developing the naïve Bayes nomogram for predicting adolescents vulnerable to depressive disorder

A nomogram is used to visually present complex functions or calculations[20,21]. In particular, it is used as a method to visually present the diagnosis, recurrence, and survival prediction of a disease[20,21]. It is expressed graphically (Figure 1) in which a line is assigned to each attribute used as an input item and the possible value of the attribute is displayed on the line[22]. The score corresponding to the position of

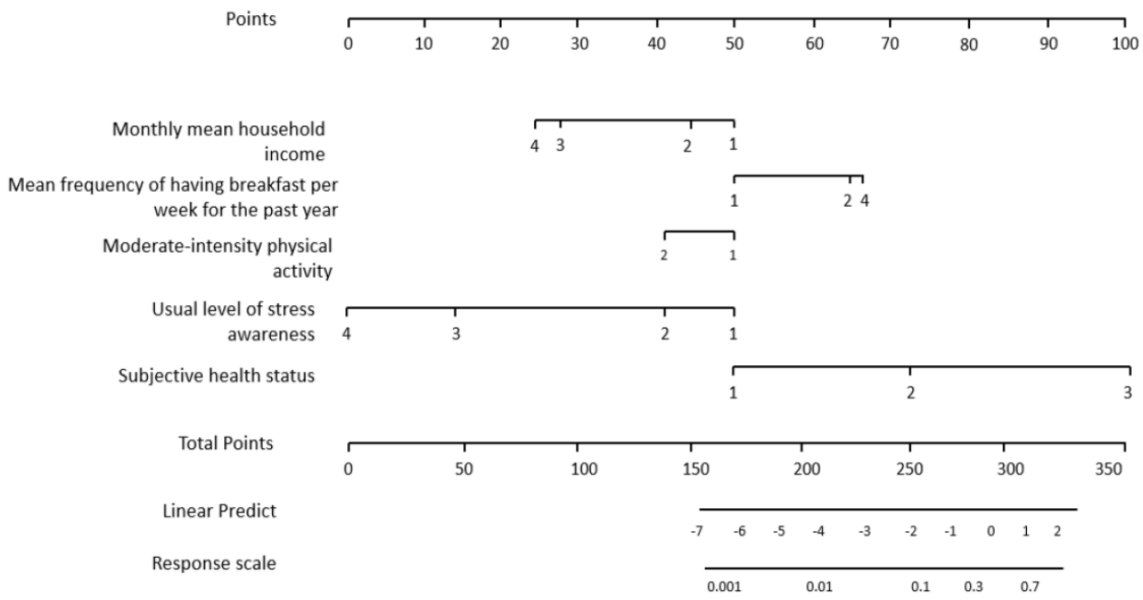


**Figure 1 An example of a nomogram[22].** Citation: Byeon H. Developing a nomogram for predicting the depression of senior citizens living alone while focusing on perceived social support. *World J Psychiatry* 2021; 11: 1314-1327. Copyright ©The Authors 2021. Published by Baishideng Publishing Group Inc.

the attribute value becomes the individual score of the point displayed at the top.

We used a naïve Bayes classifier as the algorithm to develop the nomogram. A naïve Bayes classifier model determines the probability for a specific class by applying the Bayesian theorem under the assumption that the attributes of data and events are independent of each other. When the attributes are assumed to be independent, the posterior probability indicating the probability that an object (belongs to class *C* can be expressed as follows:

$$P(c|X) = \frac{P(a_1, a_2, ..., a_m|c)P(c)}{P(X)} = \frac{P(c)\prod_i P(a_i|c)}{P(X)} \quad (1)$$

Where $c$ is the target class of the nomogram. However, if it is a class other than $c$, and $P(|X)$ represents the probability that object $X$ does not belong to class c[9], then the odds ratio (OR) for these two probabilities can be calculated as:

$$OR = \frac{P(c|X)}{P(\bar{c}|X)} = \frac{P(c)\prod_i P(a_i|c)}{P(\bar{c})\prod_i P(a_i|\bar{c})} \quad (2)$$

We calculated the general accuracy, precision, recall, F-1 score, the area under the curve (AUC), and calibration plot using leave-one-out cross-validation (LOOCV) of the developed Bayesian algorithm-based nomogram to validate its predictive performance.

Precision is defined as the proportion of classifications that are true actually being true:

$$(Precision) = \frac{TP}{TP + FP}$$

Recall is defined as the ratio of the number of model predictions that are true over the number that are actually true:

$$(Recall) = \frac{TP}{TP + FN}$$

Accuracy is an evaluation index that can most intuitively indicate the performance of a model:

$$(Accuracy) = \frac{TP + TN}{TP + FN + FP + TN}$$

However, since using accuracy alone to overcome bias due to data imbalance is limited, it is necessary to present the F-1 score as an additional predictive performance indicator to overcome bias.

The F-1-score is the harmonic mean of Precision and Recall; *i.e.*

$$(F1 - score) = 2 \times \frac{1}{\frac{1}{Precision} + \frac{1}{Recall}} = 2 \times \frac{Precision \times Recall}{Precision + Recall}$$

AUC is an indicator used to evaluate the performance of a binary classifier. The maximum value is 1, and a value close to 1 means that the performance of the model is good (*i.e.*, the recall is larger than the

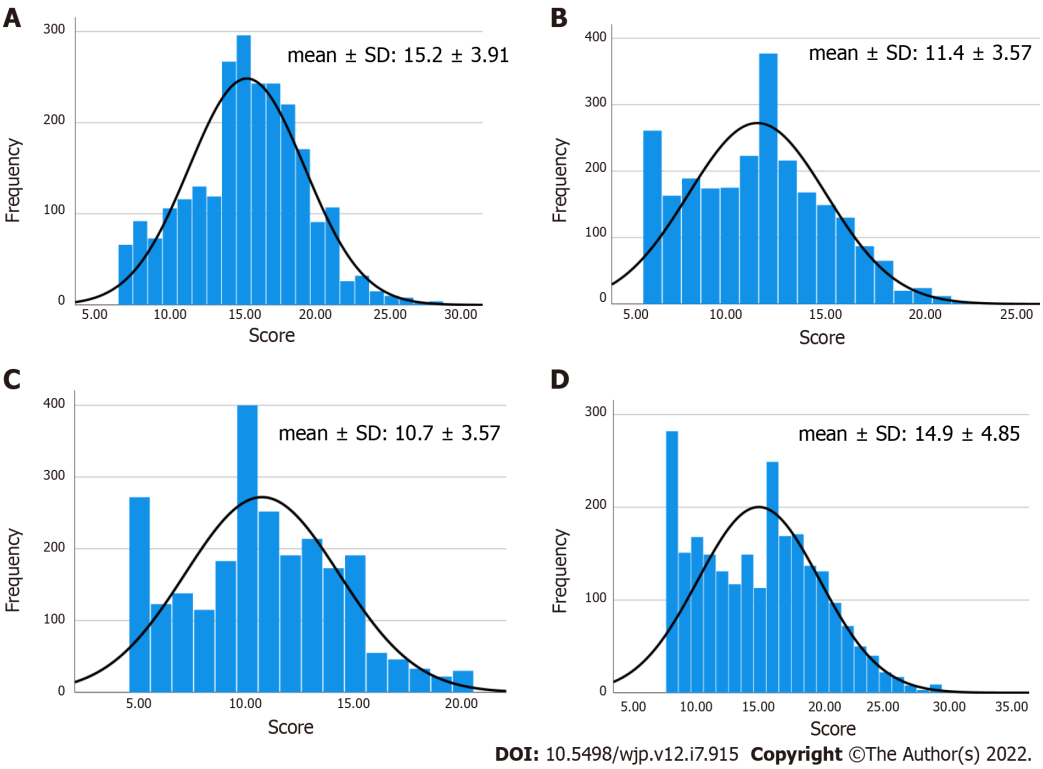


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**Figure 2 Test results.** A: Subject's attention test; B: Subject's aggression test; C: Subject's social withdrawal test; D: Subject's physical symptoms test.

fall-out). All analyses were performed by using Python version 3.10.0 (https://www.python.org/downloads; accessed on November 28, 2021).

## RESULTS

### General characteristics of the subjects

Of the 2438 subjects, the majority were male (54.1%) in a family with two siblings including the subject (61%); 32.0% had 30 minutes or more but less than 1 h of mean conversation time with their parents during weekdays; 37.2% were neither satisfied nor dissatisfied with last semester's school performance, 44.2% were satisfied with last semester's school life, and 40.4% slept for an average of 8 h *per* day during weekdays (Table 2). Their aggression, attention problems, physical symptoms, and social withdrawal are presented in Figure 2.

### General sample characteristics and prevalence of depressive disorder

The results of Chi-square tests showed significant differences ($P < 0.05$) between the groups with and without depressive disorder in gender, mean sleeping hours *per* day, mean conversation time with parents *per* day, satisfaction with academic achievement, satisfaction with school life, attention, aggression, social withdrawal, and physical symptoms (Table 3).

### Correlations between variables

Correlation analysis results between the major variables used in this study are presented in Figure 3. Depressive disorder was significantly and positively correlated with attention, aggression, social withdrawal, and physical symptoms ($P < 0.05$).

### Predicting the group of adolescents vulnerable to depressive disorder by using the Bayesian nomogram

Figure 4 shows the Bayesian nomogram for predicting the adolescent group vulnerable to depressive disorder. We developed a nomogram comprising seven variables with high importance: Physical symptoms, aggression, social withdrawal, attention, satisfaction with school life, mean sleeping hours, and conversation time with parents were the major influential factors associated with depression in adolescents. Physical symptoms comprised the most influential factor for predicting depression in this high-risk group. We predicted the depression risk of South Korean adolescents by using the developed nomogram (Figure 4). The high-risk group comprised those who received 15.5 points for physical

**Table 2 General characteristics of subjects (mean ± SD)**

| Characteristic | *n* | % |
|---|---|---|
| **Depressive disorder** | | |
| No | 1999 | 82.0 |
| Yes | 439 | 18.0 |
| **Gender** | | |
| Male | 1318 | 54.1 |
| Female | 1120 | 45.9 |
| **Number of siblings (including the subject)** | | |
| 1 person | 358 | 14.7 |
| 2 people | 1487 | 61.0 |
| 3 people | 515 | 21.1 |
| 4 people | 78 | 3.2 |
| **Mean sleeping hours *per* day** | | |
| < 5 h | 63 | 2.6 |
| 6 h | 236 | 9.7 |
| 7 h | 600 | 24.6 |
| 8 h | 986 | 40.4 |
| 9 h | 454 | 18.6 |
| ≥ 10 h | 99 | 4.1 |
| **Mean conversation time with parents *per* day** | | |
| < 30 min | 456 | 18.7 |
| ≥ 30 min and < 1 h | 781 | 32.0 |
| ≥ 1 h and < 2 h | 644 | 26.4 |
| ≥ 2 h and < 3 h | 351 | 14.4 |
| ≥ 3 h | 206 | 8.4 |
| **Satisfaction with academic achievement** | | |
| Dissatisfied | 577 | 23.9 |
| Not dissatisfied or satisfied | 906 | 37.6 |
| Satisfied | 928 | 38.5 |
| **Satisfaction with school life** | | |
| Dissatisfied | 144 | 5.9 |
| Not dissatisfied or satisfied | 616 | 25.4 |
| Satisfied | 1666 | 68.7 |
| Attention | 15.2 ± 3.9 | |
| Aggression | 11.4 ± 3.5 | |
| Social withdrawal | 10.6 ± 3.5 | |
| Physical symptoms | 14.9 ± 4.8 | |

symptoms (EPS test), 11.5 points for aggression (EPS test), 10.5 points for social withdrawal (BPSCA test), and 17.5 points for attention (EPS test) and were dissatisfied with their school life, slept 10 h or more *per* day on average, and talked with parents less than 30 min (84% of developing depression).

The predictive performance of the developed nomogram for predicting the adolescent group highly vulnerable to depressive disorder was validated by using AUC, F-1 score, accuracy, and a calibration plot. The results of the LOOCV evaluation show that the model had an AUC of 0.90 (Figure 5), F-1 score of 0.86, general accuracy of 0.85, precision of 0.88, and recall of 0.86. Adolescents with and without

**Table 3 Characteristics by prevalence of depressive disorder, *n* (%) (mean ± SD)**

| Characteristic | Depressive disorder | | *P* value |
|---|---|---|---|
| | No (*n* = 1999) | Yes (*n* = 439) | |
| **Gender** | | | < 0.001 |
| Male | 1119 (84.9) | 199 (15.1) | |
| Female | 880 (78.6) | 240 (21.4) | |
| **Number of siblings (including the subject)** | | | 0.671 |
| 1 person | 301 (84.1) | 57 (15.9) | |
| 2 people | 1217 (81.8) | 270 (18.2) | |
| 3 people | 419 (81.4) | 96 (18.6) | |
| 4 people | 62 (79.5) | 16 (20.5) | |
| **Mean sleeping hours *per* day** | | | <0.001 |
| < 5 h | 44 (69.8) | 19 (30.2) | |
| 6 h | 191 (80.9) | 45 (19.1) | |
| 7 h | 512 (85.3) | 88(14.7) | |
| 8 h | 841 (85.3) | 145 (14.7) | |
| 9 h | 350 (77.1) | 104 (22.9) | |
| ≥ 10 h | 61 (61.6) | 38 (38.4) | |
| **Mean conversation time with parents *per* day** | | | < 0.001 |
| < 30 min | 240 (74.6) | 116 (25.4) | |
| ≥ 30 min and < 1 h | 645 (82.6) | 136 (17.4) | |
| ≥ 1 h and < 2 h | 539 (83.7) | 105 (16.3) | |
| ≥ 2 h and < 3 h | 293 (83.5) | 58 (16.5) | |
| ≥ 3 h | 182 (88.3) | 24 (11.7) | |
| **Satisfaction with academic achievement** | | | < 0.001 |
| Dissatisfied | 434 (75.2) | 143 (24.8) | |
| Not dissatisfied or satisfied | 735 (81.1) | 171 (18.9) | |
| Satisfied | 812 (87.5) | 116 (12.5) | |
| **Satisfaction with school life** | | | < 0.001 |
| Dissatisfied | 63 (43.8) | 81 (56.3) | |
| Not dissatisfied or satisfied | 470 (76.3) | 146 (23.7) | |
| Satisfied | 1457 (87.5) | 209 (12.5) | |
| Attention | 14.6 ± 3.8 | 17.7 ± 3.1 | < 0.001 |
| Aggression | 10.6 ± 3.1 | 15.1 ± 3.1 | < 0.001 |
| Social withdrawal | 10.0 ± 3.3 | 13.6 ± 2.9 | < 0.001 |
| Physical symptoms | 13.7 ± 4.2 | 20.2 ± 3.7 | < 0.001 |

depressive disorder were compared by using a calibration plot (Figure 6) and Chi-square tests based on the predicted and observed probability, between which there was no significant difference ($P$ = 0.683).

## DISCUSSION

This study was conducted to present baseline data for preventing depressive disorder in adolescents by identifying multiple influential risk factors. The results reveal that physical symptoms, aggression, social withdrawal, attention, satisfaction with school life, mean sleeping hours, and conversation time

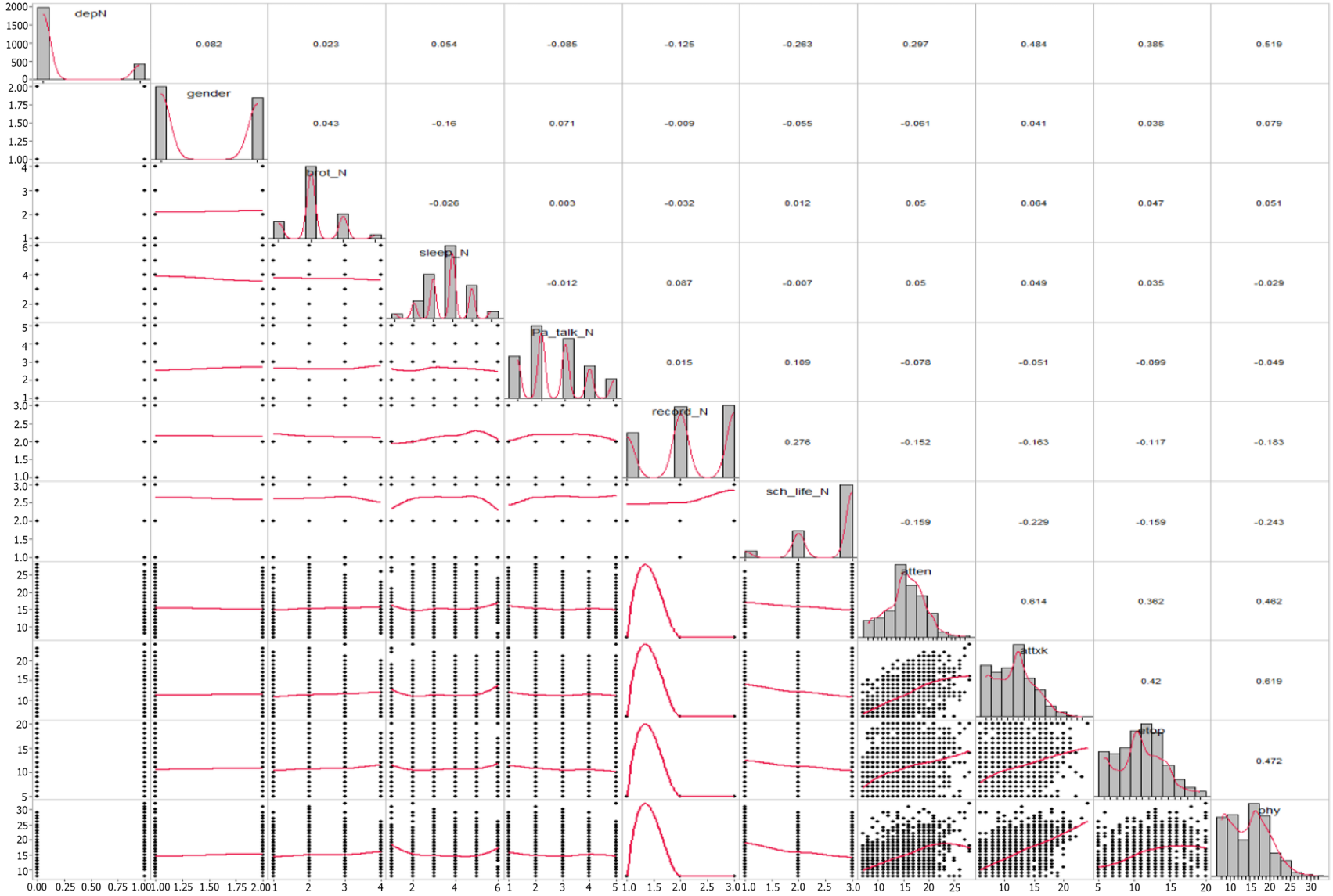


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**Figure 3 Correlation between variables: Scatter matrix.** depN: Depressive disorder; brot_n: Number of siblings; sleep_N: Mean sleeping hours *per* day; Pa_talk_N: Mean conversation time with parents *per* day; record_N: Satisfaction with

academic achievement; sch_life_N: Satisfaction with school life; atten: Attention; attxk: Aggression; etop: Social withdrawal; phy: Physical symptoms.

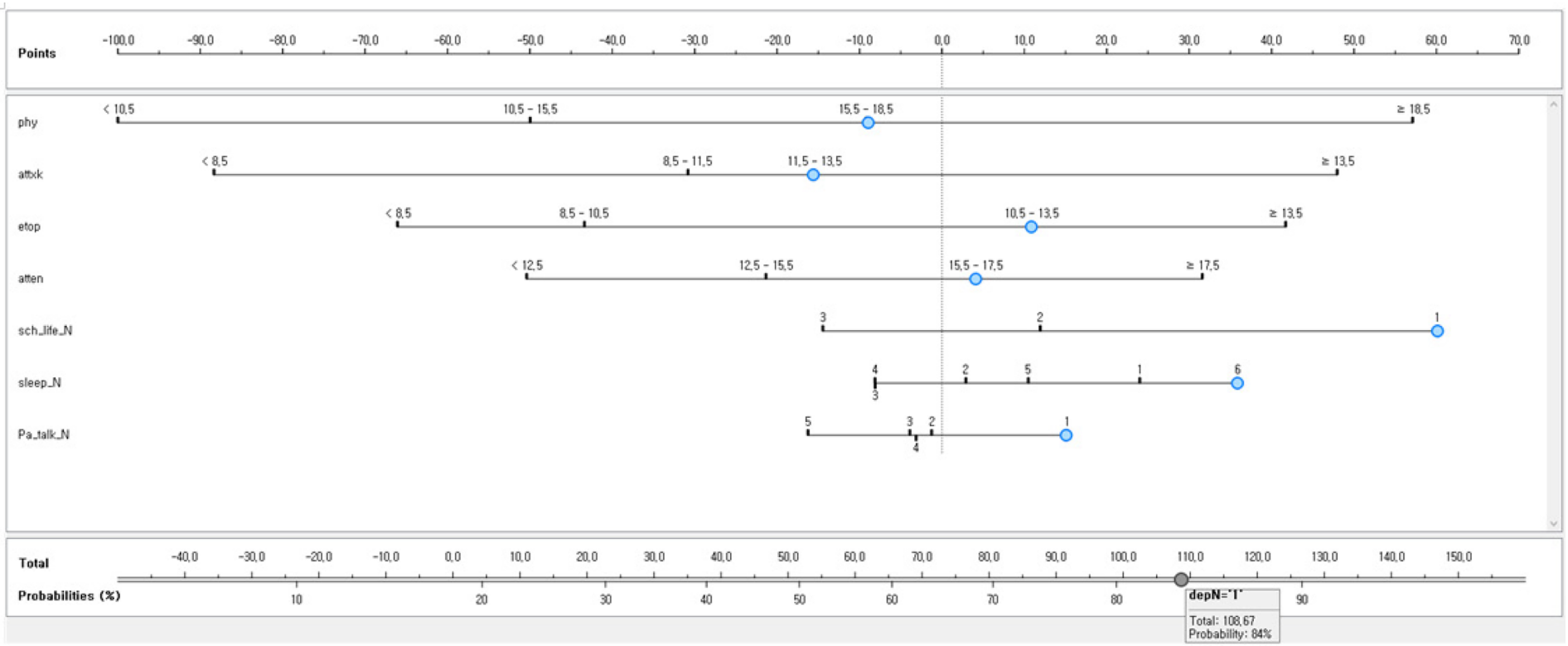


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**Figure 4 A model for predicting adolescent groups vulnerable to depressive disorder by using Bayesian nomograms.** phy: Physical symptoms; attxk: Aggression; etop: Social withdrawal; atten: Attention; sch_life_N: Satisfaction with school life (1 = dissatisfied, 2 = not dissatisfied or satisfied, 3 = satisfied); Pa_talk_N: Mean conversation time with parents *per* day (1: < 30 min, 2: ≥ 30 min and < 1 h, 3: ≥ 1 h and < 2 h, 4: ≥ 2 h and < 3 h; 5: ≥ 3 h).

with parents were significant predictors. Among them, physical symptoms had the greatest influence on the depressive disorder of adolescents. The outcomes of numerous previous studies on variables associated with depression in adolescents identify peer relationships, the home environment, and the school environment as significant risk factors[23-26], which supports the findings of the present study.

From the perspective of the socioecological model, family, peer group, and school are three major domains directly affecting the mental health of adolescents[27,28]. Since risk and protective factors are generated in these three domains[27,28], the viewpoint of the socioecological model is useful for

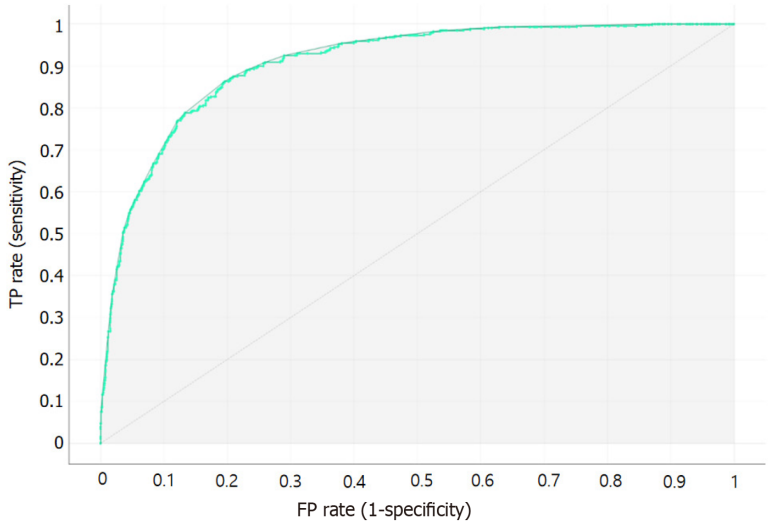


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**Figure 5 Receiver operating characteristic analysis result of the developed model.**

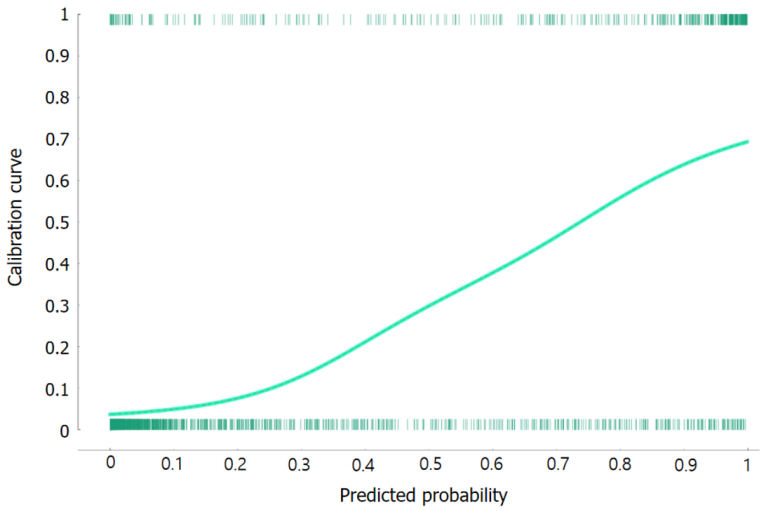


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**Figure 6 Calibration plot comparing predicted to actual probability of depressive disorder.**

explaining the depressive disorder of adolescents as the outcome of multiple risk factors. Nevertheless, there were limitations in previous studies about explaining the relationship between multiple risk factors and depressive disorder[2,25]. First, researchers mainly used regression models as the method of exploring the risk factors associated with depressive disorder in adolescents. Although calculating ORs by using regression analysis is useful for identifying individual risk factors, its ability to identify complex multiple risk factors is limited. Second, only sociodemographic and environmental factors as risk factors associated with depressive disorder were identified in previous studies[23,25]. Indeed, comprehensive analysis of risk factors associated with depressive disorder in adolescents by using individual factors such as difficulty with attention, social withdrawal, as well as environmental factors, has still not been sufficiently conducted. Third, as normality and independence between the variables are assumed in regression analysis, it is difficult to draw accurate conclusions because the data on many diseases such as depressive disorder are unbalanced, thereby violating the normality assumption.

In summary, there are limitations when utilizing depression prediction models for adolescents based on regression analysis in the primary medical care environment because it is difficult to identify the complex relationships between multiple risk factors solely relying on ORs based on regression models. Thus, we identified an adolescent group highly vulnerable to depressive disorders by using multiple risk factors based on a Bayesian nomogram to overcome these limitations. Our results predicted that adolescents who received 15.5 points in physical symptoms, 11.5 points in aggression, 10.5 points in social withdrawal, and 17.5 points in attention and who were dissatisfied with their current school life, slept for 10 h or more *per* day on average, and talked with their parents less than 30 min have a

depression risk of 84%. Therefore, communities and schools must continually monitor the high-risk group for the early identification and prevention of depressive disorder in adolescents with these multiple risk factors.

Another important finding of the present study is that physical symptoms in adolescents comprised the most influential risk factor in predicting depressive disorder. Ryu and Hong[29] (2019) also explored factors affecting depressive disorder in 1881 middle school students and confirmed that physical symptoms of adolescents comprised the main risk factor influencing depressive disorder. Choi *et al*[19] (2017) also revealed that physical symptoms and depressive disorder had a positive correlation in fourth graders.

Physical symptoms in adolescents, which are related to mental activities and the psychological state, are generally overlooked as an early symptom of depressive disorder because they cannot be found by internal or neurological examination, or even when a physical abnormality is found, the symptoms are insufficient for disease diagnosis. However, although depressive disorder of adolescents is similar to the adult psychopathology, unlike in adults, clinical characteristics are often accompanied by physical symptoms (*e.g.*, fatigue, insomnia, muscle pain, and headache) and aggression[30]. In particular, Jung *et al*[31] (2004) reported that depressed people excessively focus on physical symptoms or amplify their bodily sensations. Therefore, frequent complaints by adolescents of physical symptoms without a known medical cause are likely to be early signs of depressive disorder, even when the physical symptoms seem superficially less severe. Consequently, the community and school must pay attention to them and actively intervene by periodically checking the emotional state of adolescents, as well as providing individual counseling and in-depth psychological testing.

The strength of the present study is that it identified the group at high risk of developing depressive disorder based on multiple risk factors by using epidemiological data on South Korean adolescents and provided evidence for the early screening and management of depression. However, it does have some limitations, with the first being that there could be more potential variables for depressive disorder in addition to the explanatory variables used in this study because we analyzed secondary data. Second, the results cannot be generalized for all high school students because we identified a high-risk group for depressive disorder in seventh graders only. Third, the variables used (including depressive disorder) were measured based on a self-report questionnaire. Thus, future studies are needed to identify groups at high risk of depressive disorder by integrating qualitative research methods such as Delphi analysis and in-depth interviews in addition to self-report questionnaires. Fourth, since the results were based on a cross-sectional approach, it is difficult to determine causal relationships. Hence, additional prospective cohort studies should be conducted to prove causality between the depressive disorder high-risk group and depressive disorder found in the present study.

## CONCLUSION

We showed that physical symptoms, aggression, social withdrawal, attention, satisfaction with school life, mean sleeping hours, and conversation time with parents are influential factors associated with depressive disorder in adolescents. Among them, physical symptoms comprise the most influential factor in the prediction of depressive disorder. Therefore, periodically checking on the emotional state of adolescents is required, along with providing individual counseling and conducting in-depth psychological examinations when necessary. Moreover, longitudinal studies based on clinical depressive disorder data targeting depressive disorder in the high-risk group confirmed in this study should be conducted.

## ARTICLE HIGHLIGHTS

### *Research background*

Although South Korea has developed and carried out evidence-based intervention and prevention programs to mitigate depressive disorder in adolescents, the number of adolescents with depressive disorder has increased every year for the past 10 years. Consequently, it is necessary to identify the influential factors causing depression and develop a predictive model with high accuracy that can identify groups highly vulnerable to depressive disorder as soon as possible.

### *Research motivation*

Recently, the naïve Bayesian nomogram has been used as a method of predicting groups at high risk of developing diseases. One of the advantages of this method is that it presents the risk probability according to multiple risk factors of a disease visually so that clinicians can easily understand the results.

### Research objectives
In this study, a nomogram based on a naïve Bayesian algorithm using epidemiological data on adolescents in South Korea was developed and baseline data for screening depressive disorder in adolescents was presented.

### Research methods
We used a naïve Bayes classifier as the algorithm to develop the nomogram. Also, we calculated the general accuracy, precision, recall, F-1 score, the area under the curve, and calibration plot using leave-one-out cross-validation of the developed Bayesian algorithm-based nomogram to validate its predictive performance.

### Research results
We showed that physical symptoms, aggression, social withdrawal, attention, satisfaction with school life, mean sleeping hours, and conversation time with parents were influential factors associated with depressive disorder in adolescents.

### Research conclusions
Periodically checking on the emotional state of adolescents is required, along with providing individual counseling and conducting in-depth psychological examinations when necessary.

### Research perspectives
Longitudinal studies based on clinical depressive disorder data targeting depressive disorder in the high-risk group confirmed in this study should be conducted.


## FOOTNOTES


**Author contributions:** Byeon H designed the study, interpreted the data, preformed the statistical analysis, and wrote the article.

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**Informed consent statement:** All patients gave informed consent prior to study participation.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Data sharing statement:** Technical appendix, statistical code from the corresponding author at bhwpuma@naver.com.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.



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ORIGINAL ARTICLE

Observational Study

# Believing processes during the COVID-19 pandemic in individuals with bipolar disorder: An exploratory study

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## Abstract

*BACKGROUND*

Believing or "credition" refers to psychological processes that integrate the cognitions and emotions that influence our behavior. In the credition model by Angel and Seitz, four parameters are postulated: proposition, certainty, emotion and mightiness. It is assumed that believing processes are influenced by both the individual as well as socio-cultural factors and external circumstances. External or environmental circumstances can include threatening situations such as the ongoing pandemic. It has been hypothesized that believing processes related to the pandemic differ between individuals with bipolar disorder (BD) and healthy controls (HC).

*AIM*

To investigate credition in individuals with BD during the coronavirus disease 2019 (COVID-19) pandemic.

*METHODS*

Psychiatrically stable individuals with BD ($n$ = 52) and age- and sex matched HC (

*n* = 52) participated in an online survey during the first lockdown of the COVID-19 pandemic. The survey took place between April 9th and June 4th, 2020, in Austria. Participants completed the Brief Symptom Inventory-18, the Beck Depression Inventory-II, the Altman Self-Rating Mania Scale, the Pittsburgh Sleep Quality Index and a dedicated Believing Questionnaire assessing four parameters of credition (proposition, certainty, emotion and mightiness). The MAXQDA software was used to analyze the qualitative data. Statistical analyses included analyses of variance, a multivariate analysis of variance and a multivariate analysis of co-variance.

***RESULTS***

Individuals with BD reported significantly more negative propositions [$F$ (1,102) = 8.89, $P$ = 0.004, $\eta^2_p$ = 0.08] and negative emotions [Welch´s $F$ (1,82.46) = 18.23, $P$ < 0.001, $\eta^2_p$ = 0.18], while HC showed significantly more positive propositions [$F$ (1,102) = 7.78, $P$ = 0.006, $\eta^2_p$ = 0.07] and emotions [$F$ (1,102) = 14.31, $P$ < 0.001, $\eta^2_p$ = 0.12]. In addition, individuals with BD showed a higher incongruence between their propositions and their emotions [$F$ (1,102) = 9.42, $P$ = 0.003, $\eta^2_p$ = 0.08] and showed strong correlations between the parameters of the Believing Questionnaire and their psychiatric symptoms ($r$ = 0.51-0.77, all $P$ < 0.001). Positive as well as negative emotions and propositions were associated with scores measuring symptoms of depression, anxiety and sleep quality.

***CONCLUSION***

Believing parameters were associated with psychiatric symptoms in BD during the pandemic. Findings broaden knowledge about the susceptibility of believing processes for ambient challenges in individuals with BD.

**Key Words:** COVID-19; Bipolar disorder; Cognition; Emotions; Judgement; Evaluation study

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**Core Tip:** Research concerning believing processes ("creditions") in individuals with bipolar disorder (BD) during the coronavirus disease 2019 pandemic showed that patients reported more negative emotions and propositions than healthy controls who reported more positive emotions and propositions. Individuals with BD had a higher incongruence between their propositions and their emotions and strong correlations between the parameters of the Believing Questionnaire and psychiatric symptoms. These findings provide insight into the attitudes and beliefs of people with BD during a crisis.

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## INTRODUCTION

Believing is a fundamental cognitive process involving belief formation, updating and evaluation[1,2]. Importantly, beliefs determine an individual's behavior by allowing predictions of future events[3]. In the past century, believing has widely been neglected as an object of scientific interest since it was associated with spirituality or considered as abnormal[4]. Recently, however, there is growing interest in the processes of believing and beliefs in evolutionary biology, cognitive neuroscience, psychology and psychiatry[5]. This is corroborated by neuroimaging evidence revealing underlying neural correlates of believing[6-10]. To contextualize this research within the realm of cognition and emotion, the term "credition" is derived from the Latin word "credere" (which means "to believe"). This term highlights psychodynamic activities which underpin the believing processes resulting in stable but still modifiable states of belief[4].

Creditions are understood as dynamic processes that can activate at any time and influence existing states of belief which were constructed by a person's prior experiences[4]. Accordingly, creditions are an important part of our lives as they influence our thinking, feeling and acting and vice versa[11]. Sacks and Hirsch[12] postulated that people tend to accept something as reality until they are proven wrong and that belief formation can be understood as the result of perceptual and affective information processing. Supporting this notion, prior work demonstrates that integration of cognition and emotion

occurs in the lateral prefrontal cortex[13]. In the credition model, four characteristic parameters are differentiated: proposition, certainty, emotion and mightiness[1]. "Proposition" represents the content of the statement. "Certainty" reflects the person's inclination to believe the proposition. "Emotion" reflects the affective valence of the proposition for a person. "Mightiness" reflects the degree of relevance of the proposition. It is assumed that believing processes are influenced by the individual themself as well as by socio-cultural factors and external circumstances[14]. Such external or environmental circumstances can include threatening situations including the ongoing pandemic.

The coronavirus disease 2019 (COVID-19) pandemic has deeply influenced the lives of the global population. Caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it was labelled as a pandemic by the WHO on March 11th, 2020[15]. Since its outbreak, the virus has infected over 274 million and claimed the lives of more than five million people (December 2021)[16]. To contain the virus spread, several periods of lockdown have been implemented across the world contributing to far-reaching effects of the pandemic on the environment[17], economy, social life[18] and mental health [19]. The psychological consequences have been numerous[20], particularly for individuals with pre-existing psychiatric disorders including affective disorders[21].

Bipolar disorder (BD) is a neuropsychiatric affective disorder characterized by severe changes in mood ranging from depression to mania. Typically emerging in early adulthood, bipolar spectrum disorders have a prevalence of 1% to 6%[22,23]. Stressful events and exposure to life stress increase the recurrence of affective episodes in BD[24], making individuals with BD a vulnerable group during the COVID-19 pandemic[25]. Increased depressive symptoms, fatigue[26], psychological distress[27,28], post-traumatic stress symptoms[29], fear and sleeping problems[29,30] have all been shown in this population during this period. An increase in subjective cognitive dysfunction has also been found in this population and was associated with negative symptoms and poor quality of life[31].

In Beck's cognitive model of depression[32], dysfunctional cognitive schemata are assumed to be the basis for the development of a depressive episode. This leads to a cognitive bias in information processing as attention is selectively directed towards negative aspects and experiences while positive events and memories are blocked[32,33]. Regarding the COVID-19 pandemic, the specific believing processes possibly contributing to the development of a depressive episode remain largely unknown.

The aims of the current study were: (1) To analyze believing processes, in particular the four parameters of proposition, certainty, emotion and mightiness in individuals with BD during the COVID-19 pandemic compared with healthy controls (HC); and (2) to investigate correlations between these parameters and psychiatric symptoms in BD.

Due to the still lacking empirical evidence in this field, this study utilized an exploratory approach. However, based on the literature, it was expected that in accordance with Beck's cognitive theory of depression[32], individuals with BD would show more negative propositions and emotions in their verbalized believing processes than HC. Further, it was expected that HC would show more positive propositions and emotions in their verbalized believing processes compared to individuals with BD. Additionally, it was hypothesized that current psychiatric symptoms would be related to possible differences in parameters between the two groups.

## MATERIALS AND METHODS

### Participants

In total, 260 individuals were recruited; 208 of these had complete data sets. After matching for sex and age, the final sample was comprised of 52 stable, medicated individuals diagnosed with BD (29 males and 23 females) and 52 HC. The individuals with BD were previously diagnosed at the outpatient center for BD at the Medical University of Graz, Department of Psychiatry and Psychotherapeutic Medicine, using the Structured Clinical Interview for DSM-IV[34]. Exclusion criteria for HC were any psychiatric diagnosis, taking psychiatric medication or first-degree relatives with psychiatric disorders. Inclusion criteria for all participants were voluntary participation and e-mail access. All participants with BD and the majority of HC were recruited from the pool of the ongoing BIPLONG study which assesses lifestyle, metabolism and cognitive function in individuals with BD compared to HC. Additional HC were recruited by word of mouth and social media.

### Procedure

An online survey was sent out *via* the survey tool LimeSurvey (Version 3.27.4, Limesurvey GmbH) between April 9th and June 4th, 2020, starting 3 wk after the beginning of the first lockdown in Austria. Participants were thus experiencing travel restrictions, social distancing measures, and the closure of institutions such as schools, leisure venues and nonessential shops while completing measures for this study.

Participants gave informed consent before pseudo-anonymously responding to questionnaires. This study was approved by the local ethics committee in accordance with the current revision of the Declaration of Helsinki, ICH guideline for Good Clinical Practice and current regulations (Medical University of Graz, Austria; individuals with BD were from the BIPLONG study, EK-number: 25-335 ex

12/13; data was collected in the course of a new study, EK number: 32-363 ex 19/20).

### Psychological inventories

Analyses in the current study were conducted on the following psychological inventories:

The Brief Symptom Inventory-18 (BSI-18) was constructed by Derogatis and Fitzpatrick[35], a short version of the Symptom-Checklist-90-Revised (SCL-90-R) by Derogatis and Savitz[36]. The BSI-18 was used to measure psychological symptoms during the last week. This measure yields a Global Severity Index (GSI) and three subscales: anxiety, depression and somatization, each with acceptable internal consistency (Cronbach's alpha: GSI $\alpha = 0.93$, anxiety $\alpha = 0.84$, depression $\alpha = 0.87$, and somatization $\alpha = 0.82$).

The Beck Depression Inventory (BDI-II) by Beck *et al*[37] assessed the severity of depressive symptoms within the last week with a score of 18 or higher indicating clinically relevant depression. Assessed quality criteria were Cronbach's alpha ($\alpha \geq 0.84$) and reliability ($r \geq 0.75$)[38].

The Altman Self-Rating Mania Scale (ASRM) is a 5-item questionnaire that determines the extent of manic symptoms in the course of 1 wk[39]. Assessing self-confidence, mood, speech, activity level and need to sleep, each item is rated on a five-point scale (0-4). A score of five or more is considered clinically relevant.

The Pittsburgh Sleep Quality Index (PSQI) was constructed by Buysse *et al*[40] and measures sleep quality in the last month. The 19 items constitute seven components: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication and daytime sleepiness. The sum score has a range of 0-21, with a higher score indicating worse sleep quality. A total score > 5 has diagnostic sensitivity of 89.6% and specificity of 86.5% ($\kappa = 0.75$, $P < 0.001$) when differentiating between poor and good sleepers.

The Believing Questionnaire (BQ) was created by JWS and ND of the Department of Psychiatry and Psychotherapeutic Medicine in consultation with HFA and RS. The BQ assessed the characteristic credition parameters (proposition, certainty, emotion, mightiness) during the COVID-19 pandemic. Consisting of six open-ended questions, the BQ was developed to gain insight in believing processes during such a precarious and challenging situation:

*When I think of the current, very special situation, I believe*;
*When I think of my body, I believe*;
*When I think of my mental/emotional situation, I believe*;
*When I think of the coronavirus, I believe*;
*When I think of what the future holds 3 mo from now, I believe*;
*When I think of what the future holds 6 mo from now, I believe*.

Participants were asked to answer as spontaneously and honestly as possible. Each question was then rated on a scale from 0 (= not sure) to 100 (= very sure) regarding the certainty of belief. Additionally, participants were asked to identify the emotion that arose for them in the context of that belief using an "Emotion Wheel" consisting of three concentric circles. The innermost circle showed the six basic emotions according to Ekman[41]: fear, anger, joy, sadness, disgust and surprise. The surrounding two circles provided options to further differentiate the basic emotion. The intensity of the emotion (sense of mightiness) was rated on a scale from 0 (= not sure) to 100 (= very sure) as well.

### Statistical analysis

To analyze the qualitative data of the BQ in a standardized and transparent manner, MAXQDA 2020[42] software was used; this has previously proven useful in research of BD in clinical settings[43,44]. The process of analysis consisted of two independent raters categorizing individuals' propositions and emotions into the three categories positive, negative and indifferent, generating six codes (positive propositions, negative propositions, indifferent propositions, positive emotions, negative emotions and indifferent emotions). The interrater reliability of $\kappa = 0.92$ was satisfactory.

To make data suitable for analysis with the Statistical Package for Social Sciences (SPSS version 26, IBM), six new variables were calculated to reflect the frequency of each code. Additionally, a variable reflecting the frequency of incongruencies between the valence of a person's proposition and the identified emotion was created.

A multivariate analysis of variance (MANOVA) with group (BD *vs* HC) as the independent variable was calculated to test for between-subject differences in the credition parameters. Positive propositions, negative propositions and positive emotions were included in the MANOVA as variables because they were moderately intercorrelated ($r = 0.64$-$0.78$, all $P < 0.001$). Not all credition parameters were intercorrelated; as such, single ANOVAs were utilized for indifferent propositions, negative emotions, indifferent emotions, incongruence, certainty and mightiness. A multivariate analysis of co-variance with the same design but controlling for psychiatric symptomatology was then conducted. The psychiatric symptomatology consisted of the individual total scores in the BSI-18 (GSI), BDI-II and PSQI. The total score of the ASRM was not included because the two groups did not differ in their manic symptomatology. Spearman correlation analyses were used to test for associations between credition parameters and psychological test scores (BSI-18, BDI-II, ASRM and PSQI). Bonferroni correction ($P < 0.003$) was used to correct for conducting multiple tests. To test for normal distribution for the psychological test scores and credition parameters of both groups, Shapiro-Wilk tests were run and skewness

and kurtosis were calculated. All data met the assumed criteria of linearity. The criterion of normality was not met for several variables (sex, negative propositions, positive emotions, negative emotions, indifferent emotions, and certainty) however, the sample size was adequate ($n \geq 30$) and thus, normal distribution could be assumed, according to the central limit theorem. The criterion of variance was also not met for several variables (GSI, BDI-II, PSQI, negative propositions, positive emotions, negative emotions). However, the analyses were continued given that MANOVAs are relatively robust to violations of equality of variance[45] and for ANOVAs the Welch-ANOVA could be interpreted[46,47].

In addition, word clouds in MAXQDA were used to present propositions and emotions for each item of the BQ. Word clouds are a useful method to simultaneously visualize the actual words as well as their frequency[48]. The word clouds show the most frequently used words for each BQ item. Prepositions and conjunctions were ignored and added to a stop list in MAXQDA. The word clouds were translated from German into English for the present paper. It is noted that a loss of information may occur due to translation.

## RESULTS

### Sample characteristics

Each group consisted of 29 males and 23 females. Mean age was 50.2 years (individuals with BD; *SD* = 14.5) and 49.0 years (HC; *SD* = 13.3). The individuals with BD showed higher scores of psychiatric symptoms than the HC group [$F$ (3,100) = 11.53, $P < 0.001$, Roy's Largest Root = 0.346, $\eta^2_p = 0.257$; see Table 1 for statistics].

### Differences in believing parameters between the individuals with BD and HC

The MANOVA testing for group differences in the believing parameters showed significant differences for the combined dependent variables of positive propositions, negative propositions and positive emotions [$F$ (3,100) = 4.93, $P = 0.003$, $\eta^2_p = 0.13$, Roy´s Largest Root = 0.15]. Specifically, the HC group showed more positive propositions and emotions in their verbal believing processes than the individuals with BD. In contrast, the individuals with BD revealed more negative propositions and emotions compared with HC (Table 1). The individuals with BD showed a stronger incongruence between the valence of their propositions and the valence of their emotions. Furthermore, HC were more certain about their propositions than were individuals with BD. However, this difference did not remain significant after Bonferroni correction. No statistically significant differences emerged between the two groups in indifferent propositions and emotions or in mightiness.

After controlling for psychiatric symptoms (GSI score of the BSI-18, total scores of BDI-II and PSQI), the group differences in credition parameters were no longer significant.

### Word clouds

Figures 1-3 show word clouds for the six BQ items. Results of item 2 (“When I think about my body, I believe”) and item 3 (“When I think about my mental/emotional situation, I believe”) are presented in more detail because there were significant differences between the two groups for both the valence of propositions [item 2: $\chi^2(2) = 12.45$, $P = 0.002$, Cramér's V = 0.22 item 3: $\chi^2(2) = 8.03$, = 0.018, Cramér's V = 0.27] and the valence of emotions [item 2: $\chi^2(2) = 10.44$, $P = 0.004$, Cramér's V = 0.31; item 3: $\chi^2(2) = 9.61$, $P = 0.005$, Cramér's V = 0.30]. For item 2, individuals with BD used a total of 352 words and the HC 273 words. For item 3, individuals with BD used a total of 486 words and the HC 292 words. The word frequencies of the different words for the two items are shown in Tables 2 and 3.

For item 2 (Figure 2, Table 2), both groups used the word “I” most often, followed by positive emotional words. The HC predominantly used positive words about their body, such as “fit”, “fitter” and “healthy”. In contrast, the individuals with BD, predominantly used the word “fat” for their body. In addition, the individuals with BD often used negative emotion words such as “fearful” and “unhappy”. For item 3 (Figure 2, Table 3), both groups again used the word “I” most frequently. However, the individuals with BD more frequently utilized self-centered words, such as “me” and “myself”, followed by positive emotion words, such as “good” and “content”. The HC used positive emotion words most often, such as “content”, “good”, “balanced” and “calm”.

For item 4 (“When I think of the coronavirus, I believe") and item 6 (“When I think of what the future holds 6 mo from now, I believe"), it was notable that individuals with BD used the word “I” and the HC the word “We” most frequently (see Figures 1 and 3).

### Correlations between believing parameters and psychiatric symptoms

Spearman correlation analyses between the believing parameters and psychiatric symptoms showed significant correlations in individuals with BD ($P < 0.001$ after Bonferroni correction; Table 4) for both positive as well as negative propositions and psychiatric symptoms. Specifically, there were significant negative correlations between the positive propositions and emotions and the BSI-18 scales GSI, depression and anxiety, the BDI-II and the PSQI sum score. Positive correlations were found between

**Table 1 Differences in the psychiatric symptoms and the credition parameters between the bipolar individuals and controls**

| | Bipolar | | Control | | *F* | *P* value | $\eta^2_p$ |
|---|---|---|---|---|---|---|---|
| | M | SD | M | SD | | | |
| BSI-18 | 13.21 | 13.45 | 3.83 | 4.23 | 23.05 | **< 0.001** | 0.18 |
| BDI-II | 12.08 | 10.92 | 2.77 | 3.54 | 34.22 | **< 0.001** | 0.25 |
| ASRM | 1.52 | 2.73 | 0.94 | 1.60 | 1.73[1,2] | 0.192 | |
| PSQI | 7.08 | 4.26 | 4.12 | 2.34 | 19.30 | **< 0.001** | 0.16 |
| Positive propositions | 3.15 | 1.80 | 4.08 | 1.57 | 7.78 | **0.006** | 0.07 |
| Negative propositions | 1.63 | 1.70 | 0.81 | 1.10 | 8.89 | **0.004** | 0.08 |
| Indifferent propositions | 1.23 | 1.17 | 1.12 | 1.00 | 0.29 | 0.590 | |
| Positive emotions | 3.10 | 2.31 | 4.54 | 1.49 | 14.31 | **< 0.001** | 0.12 |
| Negative emotions | 2.65 | 2.34 | 1.06 | 1.34 | 18.23[2,3] | **< 0.001** | 0.18 |
| Indifferent emotions | 0.25 | 0.65 | 0.38 | 0.75 | 0.96 | 0.329 | |
| Incongruence[4] | 2.13 | 1.39 | 1.38 | 1.09 | 9.42 | **0.003** | 0.08 |
| Certainty[5] | 80.49 | 15.67 | 86.35 | 10.44 | 5.03 | 0.027 | 0.05 |
| Mightiness[5] | 78.11 | 13.91 | 77.20 | 15.98 | 0.10 | 0.757 | |

[1]Welch´s *F*.
[2]$df_{error}$ = 82.46.
[3]$df_{error}$ = 80.98.
[4]Incongruence between the propositions and the emotions.
[5]In percent.
Bold letters: Bonferroni corrected significant differences. $df$ = 1; $df_{error}$ = 102; BSI-18: Brief-Symptom Inventory-18; BDI-II: Beck Depression Inventory; ASRM: Altman Self-Rating Mania Scale; PSQI: Pittsburgh Sleep Quality Index.

the negative emotions and the BSI-18 scales GSI, depression and anxiety, the BDI-II and the PSQI sum score. Additionally, a negative correlation was found between negative propositions and depression while GSI, the BDI-II and the PSQI sum score were positively correlated. No correlations were found with the scores in the ASRM.

In HC, there was only one negative correlation between certainty about the proposition and the BSI-18 GSI score ($r$ = -0.48, $P$ < 0.001, after Bonferroni correction).

### *Correlations between the believing parameters in the Believing Questionnaire*

Spearman correlation analyses were used to examine the extent to which the believing parameters depend on each other (Tables 5 and 6). The analyses were calculated for both groups separately. After Bonferroni correction, both groups showed significant correlations between propositions and emotions with a positive and negative valence. There was another significant correlation between certainty and mightiness. Furthermore, the controls showed significant correlations between the positive and negative propositions and incongruence.

## DISCUSSION

In this study, creditions of individuals with BD were investigated using questionnaires tapping into beliefs and believing processes during the first wave of the COVID-19 pandemic. Findings showed that individuals with BD differed from controls in the believing parameters of propositions and emotions. Results confirmed our hypothesis that individuals with BD would show more negative propositions and emotions in their verbalized believing processes than HC. This corresponds to Beck's cognitive theory about negative dysfunctional cognitive schemata in depressive disorders[32]. Accordingly, a cognitive bias in information processing renders depressive individuals likelier to focus their attention more on negative aspects of life and to block positive aspects. This change in perception can result in negative believing processes. In addition, we found that individuals with BD showed greater incongruence between the valence of their propositions and the valence of their emotions compared to HC. Carl Rogers[49] has suggested incongruence as the root cause for the development of mental disorders. According to this concept, the actual experience does not match one´s own self-image. Recently, it was proposed that incongruence stems from a mismatch between the internal and external

**Table 2 Word frequencies for item 2 ("When I think about my body, I believe") in the Believing Questionnaire for the two groups**

| BD | | | HC | | |
|---|---|---|---|---|---|
| **Word** | **Frequency** | **%[1]** | **Word** | **Frequency** | **%[1]** |
| I | 31 | 8.8 | I | 28 | 10.3 |
| Optimistic | 8 | 2.3 | Good | 10 | 3.7 |
| More | 7 | 2.0 | Content | 8 | 2.9 |
| My | 7 | 2.0 | Body | 6 | 2.2 |
| Not | 6 | 1.7 | Everything | 6 | 2.2 |
| Should | 6 | 1.7 | Healthy | 6 | 2.2 |
| Content | 5 | 1.4 | More | 6 | 2.2 |
| Could | 5 | 1.4 | Exercise | 5 | 1.8 |
| Happy | 5 | 1.4 | My | 5 | 1.8 |
| Much | 5 | 1.4 | Optimistic | 5 | 1.8 |
| Thick | 5 | 1.42 | Fit | 4 | 1.47 |
| Better | 4 | 1.14 | Fitter | 4 | 1.47 |
| Expectant | 4 | 1.14 | Myself | 4 | 1.47 |
| Good | 4 | 1.14 | Should | 4 | 1.47 |
| Age | 3 | 0.85 | Unconcerned | 4 | 1.47 |
| Always | 3 | 0.85 | Worried | 4 | 1.47 |
| Confident | 3 | 0.85 | Calm | 3 | 1.10 |
| Fearful | 3 | 0.85 | Could | 3 | 1.10 |
| Fits | 3 | 0.85 | Fits | 3 | 1.10 |
| Make | 3 | 0.85 | Self-confident | 3 | 1.10 |
| Me | 3 | 0.85 | Sports | 3 | 1.10 |
| Myself | 3 | 0.85 | | | |
| Okay | 3 | 0.85 | | | |
| Quite | 3 | 0.85 | | | |
| Unhappy | 3 | 0.85 | | | |
| Very | 3 | 0.85 | | | |
| Yr | 3 | 0.85 | | | |

[1]Shows what percentage of the total words the word represents. BD: Individuals with bipolar disorder; HC: Healthy controls.

experiences and a person's self-concept, resulting in a state of tension[50]. The high incongruence we found in individuals with BD could therefore reflect an experiential incongruence within the individuals with BD themselves.

Furthermore, we observed that believing parameters were strongly related to psychiatric symptoms in the bipolar group. The correlations were particularly strong between the propositions or emotions and the total scores in the BSI-18, BDI-II and PSQI. The believing parameters related to propositions and emotions were more negative as psychiatric symptoms were more severe and more positive as psychiatric symptoms were less severe. In contrast, only a moderate negative association between GSI and the believing parameter of certainty was observed. One possible explanation for the fact that psychiatric symptoms and believing parameters were highly correlated in individuals with BD could be that individuals with BD generally experienced more psychiatric symptoms during the COVID-19 pandemic. Another possible explanation is that individuals with BD ruminate more on emotional experiences, both negative and positive[51-53]. Consequently, cognitions and emotions appear to have a profound impact on mental health in individuals with BD.

An interesting result of this study was that after controlling for psychiatric symptoms, *i.e.* total scores in BSI-18, BDI-II and PSQI, the differences in believing parameters between the two groups

**Table 3 Word frequencies of item 3 ("When I think about my mental/emotional situation, I believe") in the Believing Questionnaire for the two groups**

| BD | | | HC | | |
|---|---|---|---|---|---|
| **Word** | **Frequency** | **%[1]** | **Word** | **Frequency** | **%[1]** |
| I | 55 | 11.3 | I | 32 | 11.0 |
| Good | 12 | 2.5 | Content | 13 | 4.5 |
| Me | 11 | 2.3 | Good | 11 | 3.8 |
| Myself | 11 | 2.3 | Balanced | 7 | 2.4 |
| Content | 10 | 2.1 | Calm | 7 | 2.4 |
| Not | 8 | 1.7 | Me | 7 | 2.4 |
| Better | 7 | 1.4 | Myself | 7 | 2.4 |
| Everything | 7 | 1.4 | Optimistic | 7 | 2.4 |
| Completely | 6 | 1.2 | Stable | 7 | 2.4 |
| Happy | 6 | 1.2 | Very | 6 | 2.1 |
| My | 6 | 1.23 | Reassured | 5 | 1.71 |
| Like | 5 | 1.03 | Carefree | 4 | 1.37 |
| Can | 4 | 0.82 | Everything | 4 | 1.37 |
| Confident | 4 | 0.82 | Expectant | 4 | 1.37 |
| Depressed | 4 | 0.82 | Happy | 4 | 1.37 |
| Much | 4 | 0.82 | Not | 4 | 1.37 |
| Optimistic | 4 | 0.82 | Better | 3 | 1.03 |
| Sad | 4 | 0.82 | Confident | 3 | 1.03 |
| Stable | 4 | 0.82 | Psychologically | 3 | 1.03 |
| Balanced | 3 | 0.62 | Self-confident | 3 | 1.03 |
| Currently | 3 | 0.62 | Strong | 3 | 1.03 |
| Feel | 3 | 0.62 | | | |
| Now | 3 | 0.62 | | | |
| Room | 3 | 0.62 | | | |
| Still | 3 | 0.62 | | | |
| Time | 3 | 0.62 | | | |

[1]Shows what percentage of the total words the word represents. BD: Bipolar disorder; HC: Healthy controls.

disappeared. This finding suggests that believing processes reflect important aspects of life that are also represented by the questionnaire for psychological symptoms. This could be explained by an intrinsic *modulator function* that is accounted for by the credition model[1]. On the molecular level, the modulator function may be linked to the dopamine system which plays an important role in believing processes[54, 55] as well as for abnormal believing processes in psychiatric disorders[56-58].

The word clouds we created showed that the individuals with BD used words of emotion with negative connotations more often compared to the control group. Moreover, those with BD used more self-centered language than HC. We, therefore, assume that individuals with BD tend to consider the self in the focus of their believing processes more often than the HC. Interestingly, individuals with BD more frequently answered the two items "When I think of the coronavirus, I believe" and "When I think of what the future holds 6 mo from now, I believe" from an individual perspective using the word "I", whereas HC more often answered from a group perspective with "We". Perhaps individuals with BD depend more upon the self in the context of coping while healthy individuals are more likely to refer to social reasoning. Another explanation for this finding is that individuals with BD could be the disorder itself and the associated introspection processes and self-awareness, possibly learned in psychotherapy, as all patients were treated at the outpatient center for BD at the Medical University of Graz.

**Table 4 Bipolar group: Bonferroni adjusted Spearman correlations between the parameters of the Believing Questionnaire and the psychiatric symptoms**

| | BSI-18 | Somatization[2] | Depression[2] | Anxiety[2] | BDI-II | ASRM | PSQI |
|---|---|---|---|---|---|---|---|
| Positive propositions | **-0.66**[c] | -0.38[b] | **-0.72**[c] | **-0.56**[c] | **-0.56c** | 0.20 | **-0.51**[c] |
| Negative propositions | **0.54**[c] | 0.38[b] | **-0.60**[c] | 0.42[b] | **0.63c** | -0.21 | **0.54**[c] |
| Indifferent propositions | 0.28[a] | 0.11 | 0.25 | 0.32[a] | -0.05 | -0.02 | 0.06 |
| Positive emotions | **-0.70**[c] | -0.47[b] | **-0.71**[c] | **-0.62**[c] | **-0.79**[c] | 0.09 | **-0.59**[c] |
| Negative emotions | **0.66**[c] | 0.44[b] | **0.68**[c] | **0.58**[c] | **0.77**[c] | -0.14 | **0.62**[c] |
| Indifferent emotions | 0.07 | -0.04 | -0.04 | 0.19 | -0.10 | 0.10 | -0.22 |
| Incongruence[1] | 0.28[a] | 0.18 | 0.31[a] | 0.18 | 0.20 | -0.16 | 0.17 |
| Certainty | -0.20 | -0.21 | -0.17 | -0.12 | -0.17 | 0.03 | -0.16 |
| Mightiness | 0.03 | -0.05 | 0.08 | 0.07 | 0.09 | 0.05 | 0.08 |

[1]Incongruence between the propositions and the emotions.
[2]Subscales of the BSI-18.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
Bold letters: Bonferroni corrected significant correlations. BSI-18: Brief-Symptom Inventory-18; BDI-II: Beck Depression Inventory; ASRM: Altman Self-Rating Mania Scale; PSQI: Pittsburgh Sleep Quality Index.

**Table 5 Bipolar group: Bonferroni adjusted Spearman correlations between the parameters of the Believing Questionnaire**

| | Pos. Pro. | Neg. Pro. | Ind. Pro. | Pos. Emo. | Neg. Emo. | Ind. Emo. | Incongruence[1] | Certainty | Mightiness |
|---|---|---|---|---|---|---|---|---|---|
| Pos. Pro. | | | | | | | | | |
| Neg. Pro. | **-0.78**[c] | | | | | | | | |
| Ind. Pro. | -0.44[b] | -0.15 | | | | | | | |
| Pos. Emo. | **0.67**[c] | **-0.61**[c] | -0.10 | | | | | | |
| Neg. Emo. | **-0.68**[c] | **0.63**[c] | 0.10 | **-0.96**[c] | | | | | |
| Ind. Emo. | 0.00 | -0.14 | 0.19 | -0.09 | -0.11 | | | | |
| Incongruence | -0.37[b] | 0.04 | **0.55**[c] | -0.31[a] | 0.29[a] | 0.11 | | | |
| Certainty | 0.23 | -0.19 | 0.04 | 0.26 | -0.26 | -0.04 | -0.07 | | |
| Mightiness | -0.05 | 0.12 | 0.01 | -0.01 | 0.02 | -0.18 | -0.04 | **0.66**[c] | |

[1]Incongruence between the propositions and the emotions.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
Bold letters: Bonferroni corrected significant differences. Pos.: Positive; Neg.: Negative; Ind.: Indifferent; Pro.: Propositions; Emo.: Emotions.

### *Limitations*

The present study had several limitations. Due to the lockdown in Austria at the time of study, testing was limited to online questionnaires precluding face-to-face interactions with study participants. Nevertheless, scores from self-report did allow us to capture and control for current symptoms. Another potential problem of this, as well as other online studies, is that of sampling bias. Only data from individuals who were motivated to participate in the survey were collected. Thus, results may not apply to the general population. Furthermore, believing processes themselves could not be studied, as only the verbalized expressions could be directly assessed. It may be inferred that believing processes were influenced by the introspective ability of the subjects; however, introspective ability was not measured in the present study. A further limitation of the current study is that the qualitative data of the BQ had to be transformed into positive, negative and indifferent categories, that is, the data were reduced profoundly and may thus miss some important information. Lastly, as this was a cross-sectional study, causality cannot be determined.

**Table 6 Control group: Bonferroni adjusted Spearman correlations between the parameters of the Believing Questionnaire**

| | Pos. Pro. | Neg. Pro. | Ind. Pro. | Pos. Emo. | Neg. Emo. | Ind. Emo. | Incongruence[1] | Certainty | Mightiness |
|---|---|---|---|---|---|---|---|---|---|
| Pos. Pro. | | | | | | | | | |
| Neg. Pro. | **-0.74**[c] | | | | | | | | |
| Ind. Pro. | **-0.77**[c] | 0.16 | | | | | | | |
| Pos. Emo. | **0.61**[c] | -0.40[b] | **-0.50**[c] | | | | | | |
| Neg. Emo. | **-0.56**[c] | **0.52**[c] | 0.35[a] | **-0.86**[c] | | | | | |
| Ind. Emo. | -0.20 | -0.06 | 0.33[a] | **-0.51**[c] | 0.11 | | | | |
| Incongruence | **-0.58**[c] | 0.33[a] | **0.55**[c] | -0.34[a] | 0.44[b] | 0.01 | | | |
| Certainty | 0.11 | 0.01 | -0.10 | 0.12 | -0.13 | -.12 | -0.18 | | |
| Mightiness | 0.26 | -0.12 | -0.22 | 0.26 | -0.19 | -0.15 | -0.16 | **0.60**[c] | |

[1]Incongruence between the propositions and the emotions.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
Bold letters: Bonferroni corrected significant differences. Pos.: Positive; Neg.: Negative; Ind.: Indifferent; Pro.: Propositions; Emo.: Emotions.

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**Figure 1 Word clouds showing the most frequently used words of individuals with bipolar disorder and healthy controls for items 2 and 3 concerning their beliefs during the first lockdown of the COVID-19 pandemic.**

### *Practical Implications*

Our findings offer practical implications for the treatment of individuals with BD. Because differences in believing parameters were no longer present after controlling for psychiatric symptoms, the credition model could contribute to a better understanding of negative or even positive dysfunctional schemata in psychiatric individuals, as well as be adopted into the psychotherapeutic context. Since humans tend to believe their perceptions to be true and beliefs can be updated by confirming or disproving new evidence[57], dysfunctional cognitive schemata could presumably be changed if they were revealed. It is hypothesized that belief evaluation is one approach to help with this and could be used as a tool for cognitive treatment approaches in psychotherapy.

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**Figure 2 Word clouds showing the most frequently used words of individuals with bipolar disorder and healthy controls for items 1 and 4 concerning their beliefs during the first lockdown of the COVID-19 pandemic.**

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**Figure 3 Word clouds showing the most frequently used words of individuals with bipolar disorder and healthy controls for items 5 and 6 concerning their beliefs during the first lockdown of the COVID-19 pandemic.**

## CONCLUSION

The present study showed that the model of credition is applicable in the clinical context regarding the postulated believing processes. Individuals with BD differed in their believing processes regarding the COVID-19 pandemic from healthy persons. Thus, this study provides a deep insight into the attitudes and beliefs of particularly vulnerable people during a global crisis. Believing parameters should be examined in other clinical groups in future studies.

## ARTICLE HIGHLIGHTS

### *Research background*

Believing, or "credition," refers to psychological processes that integrate the cognitions and emotions influencing our behavior. Angel and Seitz created a model consisting of four credition parameters: proposition, certainty, emotion and mightiness. Believing processes are postulated to be influenced by external or environmental circumstances, such as the coronavirus disease 2019 (COVID-19) pandemic.

### *Research motivation*

As empirical evidence about believing processes is lacking, studies examining this field of research are needed. Investigating credition during a crisis, such as the COVID-19 pandemic, will hopefully provide valuable insight into the mind of individuals with bipolar disorder (BD) and might be able to offer implications for treatment.

### *Research objectives*

The purpose of this study was to explore credition in individuals with BD as well as healthy controls (HC) during the COVID-19 pandemic.

### *Research methods*

Euthymic individuals with BD ($n$ = 52) and age- and sex matched HC ($n$ = 52) from Austria participated in an online survey taking place from April 9$^{th}$ to June 4$^{th}$, 2020. The following questionnaires were completed: Brief Symptom Inventory-18, Beck Depression Inventory-II, Altman Self-Rating Mania Scale, Pittsburgh Sleep Quality Index and a Believing Questionnaire assessing four parameters of credition (proposition, certainty, emotion and mightiness). The MAXQDA software was used to analyze data about believing processes. Statistical analyses included analyses of variance, a multivariate analysis of variance and a multivariate analysis of co-variance.

### *Research results*

Individuals with BD showed significantly more negative propositions and negative emotions, whereas HC reported significantly more positive propositions and emotions. Moreover, individuals with BD showed a higher incongruence between their propositions and emotions. Positive as well as negative emotions and propositions were associated with scores measuring symptoms of depression, anxiety and sleep quality.

### *Research conclusions*

During the COVID-19 pandemic, believing parameters were associated with psychiatric symptoms in BD and differed from HC. Results demonstrate the sensitivity of believing processes to external influences in individuals with BD.

### *Research perspectives*

Believing processes should be further examined in future studies, especially regarding cognitive treatment approaches in psychotherapy.

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study procedure; Wagner-Skacel J, Angel H-F, Ratzenhofer M, Fellendorf FT, Körner C, Reininghaus EZ, Seitz RJ and Dalkner N edited the manuscript and gave important intellectual input.

**Institutional review board statement:** The study was reviewed and approved by the local ethics committee in accordance with the current revision of the Declaration of Helsinki, ICH guideline for Good Clinical Practice and current regulations (Medical University of Graz, Austria; individuals with BD were from the BIPLONG study, EK-number: 25-335 ex 12/13; data was collected in the course of a new study, EK number: 32-363 ex 19/20).

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ORIGINAL ARTICLE

Observational Study

# Treatment outcome, cognitive function, and psychopathology in methamphetamine users compared to other substance users

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## Abstract

### *BACKGROUND*

The rising number of people using methamphetamine leads to an increasing need for treatment options for this patient group. Evidence-based research on the efficacy of treatment programs for methamphetamine users is limited. Due to specific characteristics of methamphetamine users, the question arises whether established treatment methods for individuals using other substances can be effective for the treatment of methamphetamine dependence as well. We hypothesize that there are significant differences between the two groups that may affect the effectiveness of treatment and worsen the prognosis of treatment outcomes for methamphetamine users compared to consumers of other substances.

### *AIM*

To investigate potential differences in cognitive functioning and psychopathology between methamphetamine users and other substance users and possible correlations with treatment outcomes.

***METHODS***
A total of 110 subjects were recruited for an observational, longitudinal study from a German inpatient addiction treatment center: 55 patients with methamphetamine dependence and 55 patients with dependence of other substances ("OS group"). Both groups were examined at beginning (baseline) and end of treatment (after 6 mo) with regard to treatment retention, craving, cognitive functioning, psychosocial resources, personality traits, depression, and other psychiatric symptoms. Instruments used were Raven's IQ test, Mannheimer craving scale, cognitrone cognitive test battery, NEO personality factors inventory, Hamilton depression scale, Becks depression inventory, and a symptom checklist. The statistical methods used were $\chi^2$-test, *t*-test and multiple mixed ANOVAs.

***RESULTS***
A total drop-out rate of 40% (methamphetamine-group: 36.4%; OS-group: 43.6%) was observed without significant differences between groups. At baseline, methamphetamine-group subjects significantly differed from OS-group individuals in terms of a lower intelligence quotient, fewer years of education, slower working speed, and decreased working accuracy, as well as less cannabinoid and cocaine use. Methamphetamine-group subjects further showed a significantly lower score of conscientiousness, depressive, and psychiatric symptoms than subjects from the OS-group. In both groups, a reduction of craving and depressive symptoms and an improvement of working speed and working accuracy was noted after treatment.

***CONCLUSION***
There are differences between methamphetamine users and users of other drugs, but not with regard to the effectiveness of treatment in this inpatient setting. There are differences in cognitive function and psychopathology between methamphetamine and other drugs users. The existing treatment options seem to be an effective approach in treating methamphetamine dependence.

**Key Words:** Treatment outcome; Cognitive function; Psychopathology; Methamphetamine; Substance use; Comparison

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**Core Tip:** There are differences between methamphetamine users and users of other drugs, but not with regard to the effectiveness of treatment in this inpatient setting. The existing treatment options seem to be an effective approach in treating methamphetamine dependence.

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## INTRODUCTION

The United Nations estimated that about 27 million people worldwide regularly abuse amphetamine-type stimulants (ATS) in 2018[1]. The rising number of people using methamphetamine has been considered the "next addiction crisis"[2] and causes growing concern[1]. Accordingly, there is a growing need for evidence-based treatment options for methamphetamine users[2,3]. Evidence-based research on the efficacy of treatment programs for methamphetamine users is still limited[4], with no established pharmacotherapy available[2,5]. The question arises whether established treatment methods for individuals using other substances can be effective for the treatment of methamphetamine dependence as well. This question is important since – until a few years ago – methamphetamine use played a minor role in German substance treatment services, and therefore, most methamphetamine users are treated in institutions having a focus on other drugs of abuse, such as alcohol, opioids, amphetamine, or cocaine. However, representative studies comparing the characteristics of methamphetamine users to users of other substances are limited. A study based on expert interviews and focus groups on characteristics of methamphetamine consumers showed that they differ from users of other stimulants with respect to higher levels of dissocial behavioral (*e.g.*, aggressiveness, impuls-

iveness, egoism, or irritability), as well as emotional instability, unreliability, and other comorbidities [6]. The authors also reported that the therapy of methamphetamine users is substantially affected by their comorbidities and stated, that the provided rehabilitation for methamphetamine users in Germany is inadequate, resulting in a need to adapt the treatment concepts for this group[6]. Another study also showed that methamphetamine use seems to be associated with co-occurring substance use and mental illness[8]. This may be of relevance as reviewed comorbidities were frequently associated with worse treatment outcomes[9]. The available data demonstrate that the rise in methamphetamine use is intimately linked to the ongoing opioid crisis. The concurrent use of opioids and methamphetamines may decrease adherence to short-term residential treatment. Accordingly, effective strategies should be identified to retain individuals who use opioids and methamphetamines concurrently in treatment[10, 11]. In addition, there are also data suggesting methamphetamines cause neural damage and persistent forms of cognitive impairment, including deficits in attention, memory, and executive function[12]. These results are in line with other studies also indicating that methamphetamine users may differ from other substance users with respect to cognitive function[13,14]. This may be important in terms of treatment outcome, since for example Bernhardt *et al*[15] reported correlations between methamphetamine treatment outcome and the recovery of cognitive impairment.

Another study found an association between a low level of perceived social support and methamphetamine dependence[16]. However, the authors also found an association between moderately (and not distinct) pronounced personality factors (agreeableness, neuroticism, extraversion, conscientiousness, and openness) and methamphetamine use[16]. A systematic review of psychological treatments for methamphetamine use disorders states that focusing more on the helping-relationship categories is a key approach for increasing the efficacy of treatments for methamphetamine use[17].

These studies have been mostly of exploratory in nature and were exclusively investigating methamphetamine users without direct comparison to other drug users. In this study, we focus on factors such as cognition, personality traits, comorbidities, psychiatric symptoms, and psychosocial resources and their implication on treatment outcome. Based on limited previous research, one may assume that methamphetamine users have more neuropsychiatric symptoms compared to users of other substances. Specifically, a higher rate of comorbid psychiatric symptoms and disorders, a lower level of cognitive functioning, limited psychosocial resources and lower retention rates in treatment in methamphetamine users can be postulated. This exploratory study focuses on these possible differences in primary methamphetamine users compared to users of other substances. We hypothesize that there are significant differences between the two groups that may affect the effectiveness of treatment and worsen the prognosis of treatment outcomes for methamphetamine users compared to consumers of other substances.

## MATERIALS AND METHODS

### *Participants and treatment program*

All participants were inpatients at a hospital specialized for treatment of substance use disorders (MEDIAN Klinik Mecklenburg) and were recruited by psychologists and physicians during the first 2 wk to 4 wk after admission. Participation was voluntary. The treatment was set up for 6 mo and the interventions were applied as individual and group therapy, with the main focus on group sessions (five times per week). Table 1 shows details about the treatment concept. Main treatment goals were the analysis of triggers for craving and the development of new behavioral strategies for coping with craving and other substance related problems. The 2-wk initial phase aimed at completion of diagnostics, establishment of self-reflection and motivational support, and defining therapy goals. During the 22-wk core treatment phase, interventions such as psychoeducation, situation and trigger analyses, mindfulness strategies and assertiveness training were applied. The last 2 wk focused on relapse prevention and aftercare. For further details see also Soyka *et al*[18].

Inclusion criteria were a history of methamphetamine abuse or addiction (meeting the respective ICD-10 criteria) for the primary methamphetamine user group and a history of abuse or dependence of other substances for the other substances group ("OS group"). Because polydrug use is very common [19] methamphetamine-group participants were included when having a history of previous use of other substances, but methamphetamine had to be the primary drug of abuse and the main reason for admission to treatment. See Table 2 for information about the history of substance use in both groups.

Minimum age was 18 years. Exclusion criteria were acute psychotic symptoms, intoxication on test days, and insufficient comprehension of study materials or procedure. Informed written consent was obtained from all participants after a complete and extensive description of the study protocol. The study protocol was approved by the Ethics Committee of the Ludwig-Maximilians-University of Munich. All participants were financially reimbursed with 15 Euro after completion of assessments. Routine urine samples and breath alcohol tests were collected to verify substance use. These tests were part of the usual hospital practice and were conducted by the clinic staff on a sample basis and in case of suspected substance use.

**Table 1 Phases of the therapeutic treatment concept**

| Therapy phase | Content and therapy frequency | Duration |
|---|---|---|
| Admission | Checking the entry requirements, *e.g.*, recent drug use | Admission day |
| Entry phase | Diagnostics, self-reflection, strengthen and increasing motivation, defining therapy goals, treatment planning | 2 wk |
| Main phase | Change-, testing and stabilization phase: psychoeducation (2x/wk), mindfulness-based relapse prevention (1x/wk), trigger analysis (1x/wk), individual psychotherapy (50 min/wk), sports (1x/wk), further offers according to the results of diagnostics *e.g.*, nutrition counseling (1x/wk), body therapy (1x/wk), ergotherapy (1x/wk), assertiveness training (1x/wk) | 22 wk |
| Discharge, planning aftercare | Follow-up plan, relapse prevention, arrangement of further care management *e.g.*, contact to job center and clarified housing situation | 2 wk |

**Table 2 Substance use in both groups**

| Substance class | *n* | | *P* |
|---|---|---|---|
| | MA-group | OS-group | |
| Alcohol | 16 | 21 | 0.31 |
| Cannabis | 32 | 42 | 0.04 |
| Cocaine | 5 | 19 | 0.001 |
| Hallucinogens | 0 | 1 | 0.3 |
| Opioids | 3 | 7 | 0.18 |
| Sedativa | 2 | 3 | 0.65 |
| Tobacco | 49 | 42 | 0.07 |
| Volatile solvents | 1 | 0 | 0.3 |
| Stimulants | 55 (methamphetamine) | 31 (amphetamine) | - |

MA: Methamphetamine; OS: Other substances.

### Study design

The observational longitudinal study was designed to capture within and between group differences at two time points: "T0" Baseline at the beginning of treatment and "T1" at the end of treatment, after approximately 24 wk. The T1 assessment took place during the last 3 wk before discharge, but the exact time point varied individually. Both surveys were conducted by trained staff. Data were collected between November 2016 and June 2018 for the Methamphetamine-group and between June 2018 and February 2019 for the OS-group. See Figure 1 for details.

### Outcome measures and instruments

The main outcome of interest was the completion of treatment as scheduled (regular discharge). Individuals stopping treatment prematurely (at own request or as a disciplinary decision) were defined as dropouts. A positive urine test result was classified as a non-reported relapse, which led to a disciplinary dismissal.

Further outcomes of interest were differences between methamphetamine- and OS-group and between time points T0 and T1. These differences include craving, cognitive functioning, psychosocial resources, depression, and other psychiatric symptoms, as well as personality traits (only measured at baseline). Table 3 displays the used instruments at the respective assessment.

### Statistical analyses

Continuous variables were summarized by their mean (m) and standard deviation (SD), categorical variables by absolute ($n$) and relative frequencies (%). Group comparisons were performed using $\chi^2$-test (for categorial variables, or in case of small cell numbers, Fisher's exact test) and $t$-test (continuous variables). Multiple mixed ANOVAs were calculated to compare mean differences between substance groups taking into account both time points (T0 and T1). Since $t$-tests and ANOVAs are regarded as robust statistical procedures, both methods were also used for variables potentially deviating from the

**Table 3 Study instruments**

| Instrument | Description | Assessment |
|---|---|---|
| Becks Depression Inventory-II (BDI-II) (Hautzinger *et al*[29], 2006) | 21-question multiple-choice self-report inventory measuring the severity of depression. Raw scores were used for analyses | T0, T1 |
| Cognitrone (Wagner and Karner[30], 2003) | Computer administered Test of cognitive working speed and working accuracy (comparisons of geometrical figures). Scores were standardized into *T*-values according to test norms | T0, T1 |
| Documentation standards III for the evaluation of the treatment of dependent individuals (German Society for Addiction and Therapy [31], 2001) | Defined items to assess substance use and related factors (*e.g.*, years of substance use, age at use onset, number of withdrawals) | T0 |
| Hamilton Depressive Rating Scale (HAMD)(Hamilton[32], 1960) | Clinician-administered depression assessment scale, containing 17 items of symptoms of depression. Time period: past week. Assessed as a semi structured interview. Raw scores were used for analyses | T0, T1 |
| Inventory of personal psychosocial resources(Küfner *et al*[33], 2006) | Self-report questionnaire measuring psychosocial resources in the past and at present based on different scales, *e.g.*, relationship, friends, financial and work situation. A total raw score of all scales measuring the present situation was built and used for analyses | T0, T1 |
| Mannheimer Craving Scale (Nakovics *et al*[34], 2009) | Self-report questionnaire with 12 multiple choice items and 4 additional items measuring Craving within the last 7 d. Raw scores from the main 12 items were used for analyses | T0, T1 |
| NEO-Five-Factor-Inventory (NEO-FFI)(Borkenau and Ostendorf[35], 2008) | Self-report questionnaire with 60 items for the measurement of the so-called "big five" personality traits (neuroticism, extraversion, openness, agreeableness, consciousness). Scores were standardized into *T*-values according to test norms | T0 |
| Raven's Standard Progressive Matrices(Raven *et al*[36], 2016) | Nonverbal intelligence test, Computer version. Scores were standardized into IQ values according to test norms | T0 |
| Structured Clinical Interview for DSM-IV Axis I (Wittchen *et al*[37], 1997) | Diagnostic structured interview to determine the presence of DSM-IV Axis I disorders | T0 |
| Symptom Checklist 90-R (SCL-90R) (Franke [38], 1995) | Self-report questionnaire assessing symptoms of psychopathology on different scales. For this study two scales were use: intensity of depressive symptoms scale and "Positive Symptom Distress Index" (PSDI), a measure of intensity of present symptoms. Scores of both scales were standardized into T-values according to test norms | T0, T1 |
| Wender Utah Rating Scale -short Version (Wursk) (Retz-Junginger *et al*[39], 2002) | Short version (25 items including 4 control items) of a self-report questionnaire assessing retrogradely childhood symptoms of attention deficit hyperactivity disorder. Raw Scores were built from the 21 core items and used for analyses | T0 |

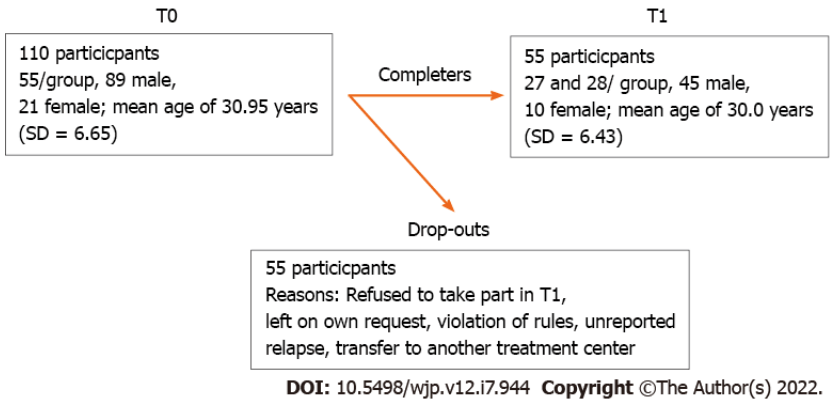


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**Figure 1 Characteristics of participants at each time point (T0 and T1).**

normality assumption. Univariable logistic regression models were applied to investigate the effect of independent factors on treatment drop-out. Odds ratios (OR) are reported together with their 95% confidence intervals (CI). The significance level was set at $P = 0.05$ and no $P$ value adjustment for multiple testing was applied in this explorative study. All statistical analyses were conducted in SPSS version 24.

## RESULTS

### *Participants' flow and treatment completion*

A total of 110 participants (55 in each group, 89 men and 21 women) with a mean age of 30.95 years (SD = 6.65) were included in the first assessment at T0. There were no statistically significant differences in age (30.0 years *vs* 32.0 years, $P = 0.12$) or sex distribution (76.4% *vs* 85.5% males, $P = 0.23$) between methamphetamine- and OS-groups. Out of this original sample, 18 subjects refused to take part in further assessments after T0 and 55 subjects (27 from methamphetamine, 28 from OS-group) participated again in the second measurement T1 with a mean age of 30.0 years (SD = 6.43). Again, the majority of T1 subjects was male (45 men, 10 women) and there was no significant difference in sex distribution ($P = 0.50$).

From the baseline sample, 66 subjects (60%) completed the treatment while 44 individuals (40%) dropped-out of treatment. Comparison of the methamphetamine-group and the OS-group revealed no significant difference in drop-out rates (36.4% *vs* 43.6%, $P = 0.44$). In addition, there was neither a significant difference in age ($P = 0.19$) nor in sex distribution ($P = 0.84$) between drop-outs and completers.

The most common reason for treatment drop-out was at own request (42.2%), followed by violation of institution rules (26.7%), unreported relapse during treatment (24.4%), and transfer to another treatment center (6.7%). There was no significant association in the reasons for drop-out between methamphetamine and OS-group ($P = 0.21$).

Participants remained in treatment for a mean time of 147 d (SD = 68). There was a trend towards a longer treatment retention in the methamphetamine-group compared to OS-group, but this difference failed to reach statistical significance [159 (SD = 60) *vs* 135 d (SD = 73), $P = 0.07$]. The OS group attended a slightly higher mean number of group sessions [OS: 103 (SD = 57); methamphetamine: 87 (SD = 35), $P = 0.07$], while the methamphetamine-group had a slightly higher mean number of individual therapy sessions [methamphetamine: 27 (SD = 18); OS 22 (SD = 13), $P = 0.08$]. However, both differences were not statistically significant. A mean treatment duration of 93 d (SD = 57) was found among the patients dropping out of treatment.

### *Baseline comparisons of methamphetamine and OS-group characteristics*

Methamphetamine-group subjects had fewer years of education than OS-group subjects ($P = 0.048$) and showed a significantly lower mean intelligent quotient (Raven`s IQ = 93.7) at baseline than the OS-individuals (IQ = 100.1, $P = 0.02$, see also Table 4). Methamphetamine-group participants also performed worse on both measures of the cognitive test battery Cognitrone, resulting in a significantly decreased working speed ($P = 0.002$) and working accuracy ($P = 0.03$) compared to OS-subjects. Methamphetamine- and OS- subjects showed no significant differences with respect to employment ($P = 0.19$) or partnership during the last 6 mo prior to admission ($P = 0.46$).

Participants from the methamphetamine-group showed a significantly lower score of the personality trait conscientiousness (measured by the NEO-Five-Factor-Inventory) compared with subjects from the OS-group ($P = 0.04$). No other personality traits differed significantly between both groups. The OS group showed significantly higher Hamilton Depressive Rating Scale (HAMD) ($P = 0.04$) and Symptom Checklist (SCL) depression ($P = 0.03$)but not Beck Depression Inventory-II (BDI- II) ($P = 0.17$) mean scores at T0 than the methamphetamine-group. The OS-group also had a higher mean score of the SCL "Positive Symptom Distress Index" (PSDI), a measure of intensity of present symptoms, compared to the methamphetamine-group ($P = 0.02$). There were no statistically significant differences in attention deficit hyperactivity disorder (ADHD) scores ($P = 0.56$), craving ($P = 0.87$), or psychosocial resources ($P = 0.69$) at baseline.

As explained, methamphetamine-group subjects may have had a history of other drug use, but methamphetamine had to be the prior substance. The majority of all subjects also used cannabinoids, but the number of cannabinoid users was significantly higher in the OS-group than in the methamphetamine-group ($P = 0.04$, see Table 2). The OS-group also included a significantly higher number of individuals that used cocaine ($P = 0.001$), while there were no differences in the use of other substances. There was no significant difference between groups concerning the number of previous substance abuse treatments ($P = 0.98$)

Regarding the number of comorbid psychiatric diagnoses (measured by ICD-10), a significantly higher rate of anxiety disorders ($P = 0.03$) and somatoform disorders ($P < 0.0001$) was found in methamphetamine-group patients, while there was a higher rate of other psychotic disorders in OS-group participants ($P = 0.04$, see Table 5).

### *Comparisons of groups over time*

Mixed ANOVAs were used to compare the cognitive functioning over time and between groups. The working speed significantly improved from T0 to T1 in both groups ($P < 0.001$, see also Table 6) and there was a significant group effect for both measurements, showing a better performance in the OS- than in the methamphetamine group in working speed ($P < 0.001$, see Figure 2). There was no interaction effect ($P = 0.94$). Regarding working accuracy, there also was a significant improvement of

**Table 4 Comparison between MA- and OS-group at baseline T0**

| | MA-group | OS-group | *P* |
|---|---|---|---|
| *n* | 55 | 55 | |
| Male | 42 (76.4%) | 47 (85.5%) | 0.23 |
| Age | 30.0 (± 5.3) | 32.0 (± 7.7) | 0.12 |
| Number of withdrawals (*n* = 48) | 3.0 (± 4.1) | 3.0 (± 4.1) | 0.98 |
| Raven's IQ (MA *n* = 50, OS *n* = 54) | 93.7 (± 13.5) | 100.1 (± 13.6) | 0.02 |
| Cognitrone working speed (MA *n* = 53, OS *n* = 54) | 49.1 (± 8.0) | 54.3 (± 9.0) | 0.002 |
| Cognitrone accuracy (MA *n* = 53, OS *n* = 54) | 43.0 (± 8.9) | 47.1 (± 9.8) | 0.03 |
| Personality factors | *n* = 37 | *n* = 42 | |
| Neuroticism | 22.8 (± 6.7) | 25.1 (± 9.7) | 0.24 |
| Extraversion | 25.0 (± 6.0) | 25.2 (± 7.5) | 0.89 |
| Openness | 26.3 (± 5.6) | 28.6 (± 6.7) | 0.11 |
| Agreeableness | 26.6 (± 4.2) | 27.9 (± 6.8) | 0.33 |
| Conscientiousness | 29.0 (± 5.6) | 31.9 (± 6.6) | 0.04 |
| BDI-II Score (MA *n* = 42, OS *n* = 54) | 13.6 (± 10.8) | 16.8 (± 11.3) | 0.17 |
| HAMD Score (MA *n* = 46, OS *n* = 42) | 5.3 (± 4.8) | 8.3 (± 7.9) | 0.04 |
| SCL-PSDI Score (MA *n* = 39, OS *n* = 40) | 53.5 (± 11.1) | 59.3 (± 10.1) | 0.02 |
| Wursk Score (MA *n* = 36, OS *n* = 40) | *n* = 3628.6 (± 16.7) | *n* = 4030.8 (± 15.1) | 0.56 |
| Craving (MA *n* = 39, OS *n* = 40) | 13.9 (± 9.5) | 14.2 (± 8.0) | 0.87 |
| Years of education | *n* = 52 | *n* = 50 | 0.048 |
| ≤ 9 yr | 35 | 24 | |
| ≥ 10 yr | 17 | 26 | |
| Employment | *n* = 51 | *n* = 48 | 0.19 |
| Unemployed | 43 | 33 | |
| Employed | 4 | 7 | |
| Other (*e.g.*, retiree) | 4 | 8 | |
| Ever injected | *n* = 49 | *n* = 40 | 0.75 |
| | 7 | 4 | |

Data displays means ± standard deviation or number of participants (education and employment). Different *n* result from missing values. BDI-II: Becks Depression Inventory-II; HAMD: Hamilton Depressive Rating Scale; MA: Methamphetamine; OS: Other substances; SCL: Symptom Checklist; Wursk: Wender Utah Rating Scale-short Version.

performance over time in both groups ($P < 0.001$). The OS-group showed a higher working accuracy at both times, but this effect was not statistically significant ($P < 0.43$). Again, there was no interaction effect ($P < 0.79$, see Figure 2). Both groups showed a significant reduction of the intensity of psychiatric burden, as measured by the SCL-90-R PSDI score, over time ($P < 0.001$). The OS-group showed a greater decrease than the Methamphetamine-group (see Figure 3), but the interaction effect failed to reach statistical significance ($P = 0.07$). The groups no longer differed significantly in this regard over time ($P = 0.29$). SCL-90-R depression scores ($P < 0.001$) and HAMD depression scores ($P = 0.001$) were significantly decreased over time in both groups. However, taking baseline and T1 assessment together, the difference between the OS- and methamphetamine-groups was no longer significant (SCL depression score: $P = 0.09$; HAMD: $P = 0.09$). Again, no interaction effects were found (SCL depression score: $P = 0.97$; HAMD: $P = 0.66$, see Figure 4). Analyzing the BDI-II depression scores also revealed a significant reduction of depression scores over time ($P < 0.001$), but without interaction ($P = 0.81$) or group effect ($P = 0.56$). Similar results were seen regarding craving scores with a significant reduction over time ($P < 0.001$), without interaction ($P = 0.94$), and without group effect ($P = 0.86$). We found a significant increase of psychosocial resources over time ($P = 0.048$), but again, no significant differences between both groups ($P = 0.99$) and no interaction effect ($P = 0.71$).

**Table 5 Number of comorbid diagnoses**

| | MA group, *n* = 54 | OS group, *n* = 55 | *P* |
|---|---|---|---|
| Depression | 11 | 15 | 0.40 |
| Anxiety disorder | 5 | 0 | 0.03 |
| Eating disorder | 0 | 2 | 0.49 |
| Obsessive-compulsive disorder | 0 | 0 | - |
| Posttraumatic stress disorder | 15 | 12 | 0.47 |
| Personality disorder | 11 | 11 | 0.96 |
| ADHD | 6 | 7 | 0.80 |
| Psychotic disorder | 3 | 10 | 0.042 |
| Somatoform disorder | 18 | 0 | < 0.001 |

Data displays number of participants diagnosed with the respective comorbidity. ADHD: Attention deficit and hyperactivity disorder; MA: Methamphetamine; OS: Other substances.

**Table 6 Comparison over time and between groups (ANOVA results)**

| | | MA-group | *n* | OS-group | *n* | *P* |
|---|---|---|---|---|---|---|
| BDI | T0 | 15.31 (± 11.55) | 26 | 16.36 (± 12.39) | 33 | $P_{time}$[b]; $P_{group}$ NS; $P_{time \times group}$ NS |
| | T1 | 7.27 (± 7.20) | | 8.97 (± 8.98) | | |
| Cognitrone accuracy | T0 | 43.62 (± 7.84) | 26 | 44.93 (± 9.85) | 28 | $P_{time}$[b]; $P_{group}$ NS; $P_{time \times group}$ NS |
| | T1 | 50.50 (± 8.63) | | 52.54 (± 10.16) | | |
| Cognitrone speed | T0 | 48.81 (± 7.68) | 26 | 57.18 (± 9.05) | 28 | $P_{time}$[b]; $P_{group}$[b]; $P_{time \times group}$ NS |
| | T1 | 54.08 (± 10.04) | | 62.61 (± 10.88) | | |
| HAMD | T0 | 6.52 (± 5.36) | 25 | 9.59 (± 9.14) | 27 | $P_{time}$[b]; $P_{group}$ NS; $P_{time \times group}$ NS |
| | T1 | 3.60 (± 4.77) | | 5.81 (± 5.98) | | |
| IPR | T0 | 204.43 (± 36.47) | 21 | 201.78 (± 33.84) | 27 | $P_{time}$[a]; $P_{group}$ NS; $P_{time \times group}$ NS |
| | T1 | 215.48 (± 38.71) | | 217.78 (± 54.15) | | |
| MaCS | T0 | 14.39 (± 9.81) | 23 | 14.59 (± 6.69) | 27 | $P_{time}$[b]; $P_{group}$ NS; $P_{time \times group}$ NS |
| | T1 | 8.57 (± 5.71) | | 8.96 (± 8.04) | | |
| SCL 90R Depression Score | T0 | 58.14 (± 9.09) | 21 | 62.70 (± 10.52) | 27 | $P_{time}$[b]; $P_{group}$ NS; $P_{time \times group}$ NS |
| | T1 | 50.71 (± 8.19) | | 55.19 (± 11.55) | | |
| SCL 90 R PSDI | T0 | 55.90 (± 10.51) | 21 | 61.26 (± 11.40) | 27 | $P_{time}$[b]; $P_{group}$ NS; $P_{time \times group}$ NS |
| | T1 | 51.71 (± 8.33) | | 52.61 (± 10.66) | | |

[a]$P < 0.05$.

[b]$P \leq 0.001$.

Data displays means and standard deviations. BDI: Becks Depression Inventory; BDI-II: Becks Depression Inventory-II; HAMD: Hamilton Depression Rating Scale; IPR: Inventory of personal resources; MaCS: Mannheimer Craving Scale; NS: Not significant; *P*group: Group effect; *P*time: Effect of time; *P* timexgroup: Interaction effect; SCL: Symptom Checklist.

### *Predictors of treatment drop-out*

Neuroticism measured at baseline was a significant predictor for treatment drop-out in the whole sample, showing decreasing odds for drop-out with increasing neuroticism scores [OR = 0.93, 95%CI: (0.87, 0.99), $P = 0.03$]. No other baseline personality variables predicted treatment drop-out. Higher scores in Cognitrone working accuracy, measured at baseline, also significantly predicted a treatment drop-out [OR= 1.05, 95%CI: (1.0, 1.09), $P = 0.04$], while working speed was not a significant predictor ($P = 0.20$). Raven's IQ ($P = 0.90$), craving at baseline ($P = 0.99$), and SCL depressive scores ($P = 0.10$) were also not significant predictors of drop-out.

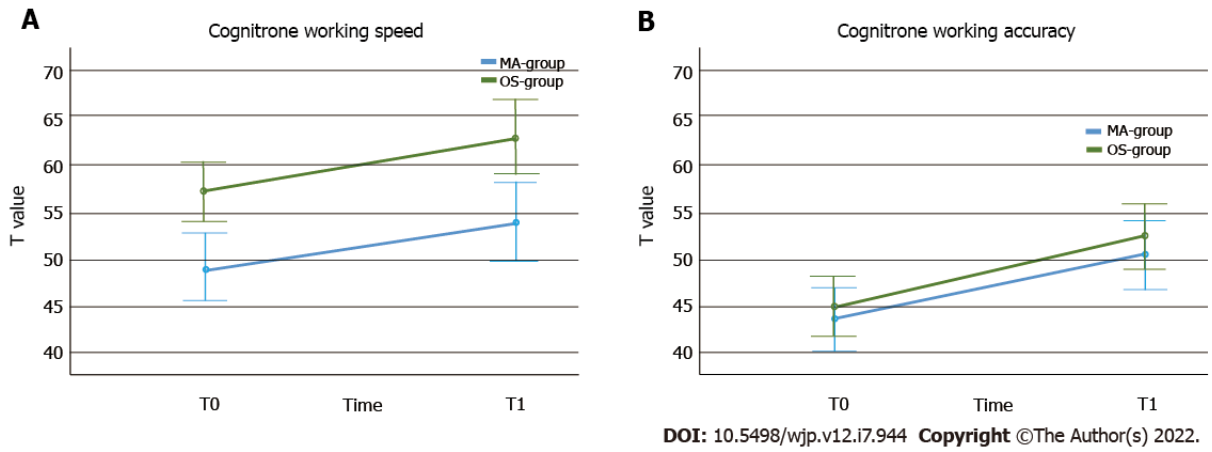


**Figure 2 Working speed (A) over time and between groups (error bars represent 95% confidence interval) and working accuracy (B) over time and between groups (error bars represent 95% confidence interval).** MA: Methamphetamine; OS: Other substances.

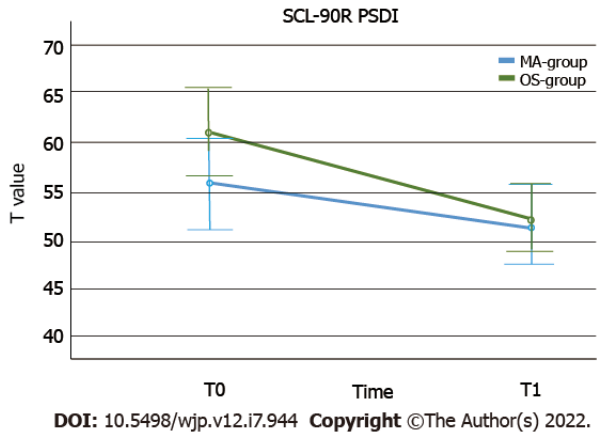


**Figure 3 Positive Symptom Distress Index over time and between groups (error bars represent 95%CI).** MA: Methamphetamine; OS: Other substances; SCL-90-R: Positive symptom distress index.

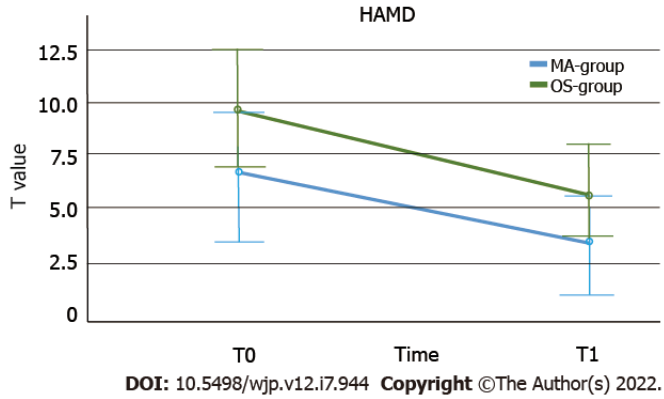


**Figure 4 Hamilton Depressive Rating Scale scores over time and between groups (error bars represent 95% confidence interval).** HAMD: Hamilton Depression Rating Scale; MA: Methamphetamine; OS: Other substances.

## DISCUSSION

The present study found differences between methamphetamine and other drug users in terms of cognitive function, psychiatric comorbidities, and personality traits, but not regarding treatment outcome and retention. The latter finding suggests that despite the encountered differences between

methamphetamine users and other drug users, methamphetamine users do not perform worse than other drug users in currently provided treatments. This result raises the question if there is need for new and specialized treatment options for methamphetamine users. For example, patients may have reported methamphetamine related situations or consequences when reflecting their use patterns and for example possible relapse situations. Previously, in another longitudinal study, we compared the methamphetamine group from this study with another methamphetamine user group that received a more stimulant specific treatment[20]. We found no differences in treatment retention or long-term relapse rates between both groups, which supports the hypothesis that methamphetamine users may not benefit automatically from a more stimulant specific treatment. Study results reveal that a high number of methamphetamine users use other substances, too. These patients may benefit from existing treatments.

Interestingly, the present study revealed a trend (although not statistically significant) towards longer treatment duration of approximately 20 d in the methamphetamine group, which may indicate that methamphetamine users may have a greater benefit from the investigated treatment. However, with regards to all other treatment outcome measures, we did not find any relevant interaction, which suggests that both groups overall benefited from treatment. For example, both groups showed a reduction of craving, depression scores and overall psychiatric burden (measured by SCL-90R) and an improvement in working speed and working accuracy, as well as an increase of psychosocial resources at the end of the treatment compared to its initiation. Therefore, it can be concluded that a current "treatment as usual" inpatient addiction program is helpful for methamphetamine users and users of other substances, and that both user groups do not differ from each other in their response to the treatment.

Nevertheless, this study did reveal differences between methamphetamine users and other substance users; for example, differences were found between the two groups with respect to cognitive function. Neurotoxic effects of metamphetamine use are well established[2]. As we hypothesized, methamphetamine users had significantly lower baseline intelligence quotient, slower working speed, and decreased working accuracy compared to users of other drugs. This finding confirms results from other studies indicating that methamphetamine use can impair cognitive functions[13,14]. However, years of school education were fewer in the methamphetamine-group, raising the question of whether impaired cognitive function in the methamphetamine-group is a reason for, or rather a consequence of, methamphetamine use. Unfortunately, there are no longitudinal data to further explore this point. A previous study failed to show improvement of cognitive impulsivity deficits in metamphetamine users after short term abstinence of 6 wk[21]. Furthermore, the performance of the methamphetamine user group was still in the average range, when applying the test norms (*t*-values), and we had no matched control group without drug users to clarify the differences between both groups. Interestingly, and contrary to our hypothesis, higher scores in working accuracy at baseline were associated with a higher likelihood for treatment drop-out. Other studies that have examined ADHD patients have found lower accuracy scores as significant predictors of drop out and mild cognitive deficits, which is in contrast to the results of this study[22]. Furthermore, we did not find an effect of working speed and IQ on treatment retention, which makes it difficult to generalize the impact of cognitive performance on drop-out rates.

Again, as assumed, methamphetamine-patients had a higher rate of comorbid anxiety and somatoform disorders. But contrary to this result, OS- group participants showed a higher rate of psychotic disorders, and there were no differences between both groups in terms of other comorbidities. Therefore, different substance use patterns may be associated with different comorbidities, but not in this study.

Another unexpected result was the negative association between neuroticism and treatment drop-out which found that the higher the score for neuroticism, the lower the odds of treatment drop-out. Other studies conclude, contrary to our results, that emotional instability and high neuroticism scores are risk factors for relapse, at least in alcohol users[23]. Treatment dropouts in a program for cocaine addiction showed a higher score on histrionic and antisocial scales compared to completers[24]. Since it can be assumed that histrionic, as well as antisocial personality traits, tend to be associated with higher neuroticism, this result is also not consistent with our finding. We are not aware of any studies that specifically examined neuroticism as a predictor of addiction treatment dropout.

Our study has several limitations. For example, we did not correct the analyses for multiple testing, as this study was designed to generate hypotheses for future research on possible differences between methamphetamine- and OS patients.

Furthermore, in the group that used other substances, amphetamine use was not an exclusion criterion. Even though the two substances are very similar, it has been suggested that methamphetamine has a stronger effect on the dopamine transporter mediated cell physiology than methamphetamine; therefore, the latter has a higher addictive potential[25].

Beyond that, the reported treatment effects are limited to the sample of treatment completers. Regarding the therapeutic outcome of the drop-out patients, there were no available data for T1, and therefore, the treatment effects for the drop-out sample remain unclear. In particular, there is not enough information on patients who stopped treatment at their own request. The present study showed that the average time patients spend in treatment before they dropped out is still quite high (around 3

mo). It remains unclear why they did not continue the treatment. Future investigations covering the whole treatment process may help gaining further information on characteristics of later drop-outs with focus on craving, treatment satisfaction and value of therapeutic relationship[26-28].

## CONCLUSION

There are differences between methamphetamine users and users of other drugs, but not with regard to the overall effectiveness of a 6-mo inpatient addiction treatment. Both groups showed a reduction in psychiatric symptoms over time and improved cognitive function after treatment. Methamphetamine users, therefore, seem to benefit from existing, stimulant nonspecific treatment options in a similar way than other drug users do.

## ARTICLE HIGHLIGHTS

### *Research background*

Over the last years the misuse of methamphetamine has risen, leading to an increased need for treatment options for this group of patients. To date, it remains elusive whether treatment programs for methamphetamine users are effective. One question arises whether established treatment methods for individuals using other substances can effectively target individuals with methamphetamine dependence.

### *Research motivation*

The present study aims to investigate the potential differences in cognitive functioning and psychopathology between methamphetamine users and other substance users and possible correlations with treatment outcomes.

### *Research objectives*

In order to provide effective therapy for the subgroup of methamphetamine users, differences to the group of other substance abusers need to be identified.

### *Research methods*

For this observational longitudinal study from a German inpatient addiction treatment center a total of 110 subjects were recruited. Of those, 55 patients had methamphetamine dependence and 55 patients had dependence of other substances ("OS group"). Both groups were examined at beginning (baseline) and end of treatment (after 6 mo) with regard to treatment retention, craving, cognitive functioning, psychosocial resources, personality traits, depression, and other psychiatric symptoms. Instruments used were Raven's IQ test, Mannheimer craving scale, Cognitrone cognitive test battery, NEO personality factors inventory, Hamilton depression scale, Becks depression inventory and symptom checklist. The statistical methods used were $\chi^2$-tests, *t*-tests, and multiple mixed ANOVAs.

### *Research results*

Over the period of 6 mo, a total drop-out rate of 40% (methamphetamine-group: 36.4%; OS-group: 43.6%) was observed without significant differences between groups. At baseline, methamphetamine-group subjects significantly differed from OS-group individuals in terms of a lower intelligence quotient, fewer years of education, slower working speed and lower working accuracy as well as less cannabinoid and cocaine use. Methamphetamine-group subjects further showed a significantly lower score of conscientiousness, depressive, and psychiatric symptoms than subjects from the OS-group. In both groups a reduction of craving and depressive symptoms and an improvement of working speed and working accuracy were noted after treatment.

### *Research conclusions*

The existing treatment options for substance abuse seem to be an effective approach in treating methamphetamine dependence.

### *Research perspectives*

Future studies should investigate specific programs that aim to improve cognitive function and psychopathology in methamphetamine dependent patients.

## FOOTNOTES

**Author contributions:** Koller G and Soyka M were responsible for the study concept and design; Behle N and Kamp F wrote the manuscript; Behle N, Kamp F, Proebstl L, Hager L, Riebschläger M, Schacht-Jablonowsky M, Hamdorf W, and Neumann S performed the research and data collection; Behle N, Kamp F and Manz K performed data analysis; Behle N, Kamp F, and Krause D interpreted the analyses outcomes; Koller G, Soyka M, Franke AG, and Krause D reviewed and edited the manuscript; All authors critically reviewed content and approved final version for publication.

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ORIGINAL ARTICLE

Observational Study

# Clinical characteristics of pediatric patients with treatment-refractory Tourette syndrome: An evidence-based survey in a Chinese population

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## Abstract

*BACKGROUND*

Tourette syndrome (TS) is a complex neurodevelopmental condition marked by tics, as well as a variety of psychiatric comorbidities, such as obsessive-compulsive disorders (OCDs), attention deficit hyperactivity disorder (ADHD), anxiety, and self-injurious behavior. TS might progress to treatment-refractory Tourette syndrome (TRTS) in some patients. However, there is no confirmed evidence in pediatric patients with TRTS.

*AIM*

To investigate the clinical characteristics of TRTS in a Chinese pediatric sample.

*METHODS*

A total of 126 pediatric patients aged 6-12 years with TS were identified, including 64 TRTS and 62 non-TRTS patients. The Yale Global Tic Severity Scale (YGTSS), Premonitory Urge for Tics Scale (PUTS), and Child Behavior Checklist (CBCL) were used to assess these two groups and compared the difference between the TRTS and non-TRTS patients.

*RESULTS*

When compared with the non-TRTS group, we found that the age of onset for TRTS was younger ($P < 0.001$), and the duration of illness was longer ($P < 0.001$). TRTS was more often caused by psychosocial ($P < 0.001$) than physiological factors, and coprolalia and inappropriate parenting style were more often present in the TRTS group ($P < 0.001$). The TRTS group showed a higher level of premonitory urge ($P < 0.001$), a lower intelligence quotient (IQ) ($P < 0.001$), and a higher percentage of family history of TS. The TRTS patients demonstrated more problems ($P < 0.01$) in the "Uncommunicative", "Obsessive-Compulsive", "Social-Withdrawal", "Hyperactive", "Aggressive", and "Delinquent" subscales in the boys group, and "Social-Withdrawal" ($P = 0.02$) subscale in the girls group.

*CONCLUSION*
Pediatric TRTS might show an earlier age of onset age, longer duration of illness, lower IQ, higher premonitory urge, and higher comorbidities with ADHD-related symptoms and OCD-related symptoms. We need to pay more attention to the social communication deficits of TRTS.

**Key Words:** Treatment-refractory Tourette syndrome; Yale Global Tic Severity Scale; Child Behavior Checklist; Premonitory Urge for Tics Scale; Social withdrawal; Obsessive-compulsive disorder

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**Core Tip:** This study provides important evidence of treatment-refractory Tourette syndrome (TS) among Chinese patients due to the current shortage of studies based on Chinese samples. We found that the onset age of pediatric patients with treatment-refractory TS (TRTS) might be younger, and they might have a longer duration of illness, a lower intelligence quotient, and a higher premonitory urge, which often fluctuate due to psychosocial factors. Moreover, TRTS children might suffer more emotional and behavioral problems including social communication deficits (such as uncommunicative and social withdrawal), attention deficit hyperactivity disorder-related symptoms (hyperactive, aggressive, and delinquent), and obsessive-compulsive symptoms. These were the basic clinical characteristics of TRTS based on Chinese pediatric patients. Unravelling these clinical characteristics is beneficial for the early diagnosis and treatment of TRTS.

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## INTRODUCTION

Tourette syndrome (TS) is a complex neurodevelopmental condition marked by tics, as well as a variety of psychiatric comorbidities, such as obsessive-compulsive disorders (OCDs), attention deficit hyperactivity disorder (ADHD), anxiety, and self-injurious behavior[1,2]. The worldwide prevalence of tic disorders (TDs) ranges from 0.4 to 1.5%[3]. In a recent report, the prevalence of TS in children and adolescents in China was 0.4%[4]. Some patients with TS fail to respond to traditional treatment, and this condition is referred to as "treatment-refractory Tourette syndrome" (TRTS)[5]. To the best of our knowledge, being refractory to "traditional treatments" (*i.e.*, medicine treatment or behavioral treatment) implies failure to respond to (or have severe side effects from) alpha-adrenergic agonists, typical and atypical antipsychotics, and benzodiazepine, as well as behavioral therapies (*i.e.*, habit-reversal training and exposure type therapy)[6]. It should be noted that one of the unresolved issues is the definition of what constitutes treatment-refractory TS; the most likely reason is the lack of the robust clinical features of TRTS, especially the features associated with the co-occurring other mental disorders [7].

However, different criteria are used to define TRTS in different countries[8]. The most commonly used criterion for TRTS was from the International Deep Brain Stimulation Registry and Database for Gilles de la Tourette Syndrome[9]. It recommended that TRTS should be the major source of disability, with a Yale Global Tic Severity Scale (YGTSS) score of 35/50, failure of conventional therapies (medications from 3 pharmacologic classes), and a trial of CBIT if feasible. European clinical guidelines for Tourette syndrome also reported the criteria of TRTS for European countries[10]. However, no Chinese version of the TRTS criteria has been described. The most likely reason is the lack of confirmed evidence related to TRTS, especially for Chinese patients. Moreover, the different criteria for TRTS were established mostly based on the clinical characteristics of adult patients with Tourette syndrome[8,9]. However, there is no evidence focusing on pediatric patients with TRTS.

Therefore, we need more confirmatory evidence about the clinical characteristics of TRTS. There are some reasons why we need to investigate the clinical characteristics of TRTS. First, TS is frequently encountered by both psychiatrists and neurologists, indicating that TS holds a unique status as a quintessentially neuropsychiatric condition at the interface between neurology (movement disorder) and psychiatry (behavioral condition)[11]. However, few studies have focused on the behavioral and emotional components of TRTS. Second, TS onset occurs between the ages of six and eight years; tics typically start simple and become more complex toward the teenage years[12,13]. Identifying the "indicators" of TRTS in the early stage may help in the treatment of these patients[14]. However, few studies have focused on these potential "indicators" of TRTS. For example, premonitory urge was

suggested as an indicator for the severity of tic symptoms[15-17], and confirmatory evidence is required to ascertain if it is also an important sign for TRTS. Third, OCD, ADHD, anxiety, and depression disorders were the top four comorbidities of TS[11], especially TRTS[18], but no evidence links these comorbidities to pediatric TRTS. Fourth, some authors suggested that there might be different subtypes of TS[19,20]. Whether TRTS is different from "pure TS" (only tic symptoms without comorbidities) is unknown. More evidence is needed to explore these differences, especially at the early stage of TRTS. Taken together, we might need more evidence about the clinical characteristics of TRTS, especially in pediatric patients.

In addition, the Child Behavior Checklist (CBCL) is one of the most important tools to identify the emotional and behavioral profiles of different mental disorders[21]. It has been suggested that the CBCL can be used to identify ADHD-related[22], obsessive-compulsive[23], anxiety[24], and depression symptoms[25]. It might provide different dimensions of clinical characteristics for TRTS, which can distinguish it from other types of TS.

Therefore, this study aimed to examine the clinical characteristics of TRTS in a Chinese pediatric population. We will compare the clinical characteristics (*i.e.*, the onset of tic age, duration of illness, intelligence quotient (IQ), and behavioral and emotional problems) of patients with TRTS and non-TRTS patients. Furthermore, the locations and the frequency of tic onset in TRTS will be reported. The CBCL will be used to present the different dimensions of mental problems between TRTS and non-TRTS. We hypothesized that TRTS patients might show more severe behavioral and emotional problems, especially in the dimensions of obsessive-compulsive, ADHD-related (*i.e.*, hyperactive, aggressive, and delinquent), and depression symptoms. This study will provide important information for a Chinese version of the TRTS criteria, especially for pediatric patients.

## MATERIALS AND METHODS

### Participants

All participants were recruited from the Department of Psychiatry, Beijing Children's Hospital, China from October 1, 2018 to January 1, 2021. Both inclusion and exclusion criteria for TS patients were developed. The inclusion criteria were as follows: (1) Aged from 6 to 12 years; and (2) Met the diagnostic criteria for Tourette syndrome according to the Diagnostic and Statistical Manual of Mental Disorders, 5$^{th}$ Edition (DSM-5)[26]. The exclusion criteria were as follows: (1) Epilepsy or any known comorbid brain medical conditions; (2) IQ less than 80; and (3) Serious physical illness.

The criteria for TRTS were as follows: (1) Nonresponsive to trials of medications from dopamine antagonists (typical and atypical) or other medications (*i.e.*, alpha-adrenergic or benzodiazepine) at adequate dosage for at least 6 mo; (2) YGTSS severity total score greater than 35; and (3) Failure following 12 sessions of habit reversal training (if the included TS patients did not meet the criteria for TRTS, they were identified as a non-TRTS group).

The ethics committee of the Beijing Children's Hospital of Capital Medical University approved this study, and we also obtained written informed consent from the parents or guardians of the enrolled children and adolescents.

### Measures

**Basic clinical information:** A basic information list was used to identify the baseline clinical information, including age, sex, age of onset, duration of illness, factors associated with the fluctuation of tic symptoms (psychosocial factors, *i.e.*, negative emotion or stress; physiological factors, *i.e.*, respiratory tract infection or allergy symptoms), locations of onset of tic, coprolalia frequency, and inappropriate parenting style, among others.

**Yale Global Tic Severity Scale:** The YGTSS is a semi-structured scale rated by a clinician or trained interviewer. It was developed for assessing the tics observed within 1 wk before the assessment[27,28]. The five dimensions included in the YGTSS are the number, frequency, intensity, complexity, and interference. The total YGTSS score (range: 0-100) is derived by summing the tic severity ranging between 0 and 50 (motor tics range = 0-25 and vocal tics range = 0-25) and the impairment rating score (range = 0-50). The YGTSS is a widely used scale with excellent reliability and validity for assessing children and adolescents with TD[29].

**Premonitory Urge for Tics Scale:** The Premonitory Urge for Tics Scale (PUTS) is a nine-item self-report questionnaire measuring premonitory sensations in individuals with tics[30]. Each item is scored from 1 (not at all true) to 4 (very much true). The total score is computed by summing the nine items. Total scores range from 9 to 36, where higher scores represent greater severity of premonitory urges. The PUTS has demonstrated good internal consistency, test-retest reliability, and construct validity among adolescents between 11 and 16 years of age[31].

**Child Behavior Checklist:** The CBCL is a widely used questionnaire to assess behavioral and emotional problems. It is often used as a diagnostic screener. The Chinese version of the CBCL contains 118

specific behavioral and emotional problem items and two open-ended items. Each symptom question in the CBCL was scored 0 (not true, as far as you know), 1 (somewhat or sometimes true), or 2 (very true or often true). Liu completed a regional survey in Shandong and reported that the 2-wk test-retest reliability was 0.90 in 30 children, and the internal consistency as measured by Cronbach's α was 0.93 [32,33]. Cronbach's α was also calculated in the present study, and it was 0.87 for the total scale. The CBCL was completed by the parents or other caregivers for a given child or adolescent. In young patients, the CBCL included eight subscales in the boys' group (including the Schizoid, Depressed, Uncommunicative, Obsessive-Compulsive, Somatic Complaints, Social-Withdrawal, Hyperactive, Aggressive and Delinquent) and 9 subscales in girls' groups (including the Depressed, Social-Withdrawal, Somatic Complaints, Schizoid-Obsessive, Hyperactive, Sex Problem, Delinquent, Aggressive, and Cruel).

In addition, the Wechsler Intelligence Scale for Children-4$^{th}$ Edition (WISC-IV) was used to calculate the full IQ[34]. All the included participants were outpatients. The assessments were performed by child psychiatrists after diagnosis was completed.

### Statistical analysis

We used the Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago, IL, United States, v25.0) to perform the statistical analyses. Descriptive statistics were performed to identify the basic clinical information, and *t* tests or $\chi^2$ tests were used to compare the different variables of different TS groups. A *P*-value of 0.05 was set as the significance threshold.

## RESULTS

### Basic information of the whole sample

The total sample comprised 126 patients diagnosed with TS, with a male percentage of 73.02%. The mean age of the included patients was 9.24 ± 2.06 years (range, 6-12 years), and the mean duration of illness was 3.83 ± 2.52 years. A total of 64 patients with TS were identified as having TRTS, while 62 non-TRTS patients were also included (Figure 1).

### Clinical characteristics of TRTS

After comparing the basic clinical characteristics of the TRTS group with those of the non-TRTS group, we found that in the TRTS group, the onset age was lower ($P < 0.001$), and the duration of illness was longer than those in the non-TRTS group ($P = 0.02$). Children in the TRTS group self-reported more fluctuations in conjunction with psychosocial rather than physiological factors ($P < 0.001$); coprolalia was more often present in the TRTS group than in the non-TRTS group ($P < 0.001$); and the TRTS group showed more severe functional impairment ($P < 0.001$). More patients with TRTS showed a positive family history of TS ($P = 0.02$). The TRTS group showed a lower level of premonitory urge ($P < 0.001$) and a higher level of tic symptoms ($P < 0.001$) than the non-TRTS group. Lower IQ was identified in the TRTS group ($P < 0.001$). In addition, the TRTS group showed more severe tic symptoms and premonitory urges ($P < 0.001$) (Table 1).

### Locations of first-onset tic symptoms in TRTS group

We listed the locations of the first onset of tic symptoms, and the order was the face (48.44%), throat (18.75%), shoulder (12.50%), abdomen (10.93%), and upper/lower limbs (9.38%) (Figure 2).

### Most frequent tic symptoms in TRTS group

We listed the top five motor and vocal tic symptoms that were frequently present in TRTS patients. The top five motor tic symptoms included head shaking/nodding, blinking, shrugging, hand moving, and mouth moving, while the vocal tic symptoms included clearing the throat, coprolalia, repetitive speech, imitating speech, and cough (Figure 3).

### Emotional and behavioral profiles in TRTS group

We found that the total CBCL score was higher in the TRTS group ($P < 0.001$). We also found that the TRTS patients demonstrated more problems in the "Uncommunicative" ($P < 0.001$), "Obsessive-Compulsive" ($P = 0.001$), "Social-Withdrawal" ($P < 0.001$), "Hyperactive" ($P < 0.001$), "Aggressive" ($P = 0.002$), and "Delinquent" ($P < 0.001$) subscales of the CBCL in the boys group and "Social-Withdrawal" ($P = 0.02$) in the girls group (Tables 2 and 3).

**Table 1 Basic clinical characteristics of patients with treatment-refractory Tourette syndrome and non-treatment-refractory Tourette syndrome patients**

| Related variable | TRTS (*n* = 64) | Non-TRTS (*n* = 62) | $t/\chi^2$ | *P* value |
|---|---|---|---|---|
| Sex (male percentage) | 48 (75.0%) | 44 (71.0%) | 0.26 | 0.61 |
| Age | 9.64 ± 3.01 | 8.82 ± 2.63 | 1.63 | 0.11 |
| Onset age | 5.12 ± 2.81 | 7.29 ± 3.67 | -3.73[c] | < 0.001 |
| Duration of illness | 4.39 ± 2.17 | 3.27 ± 2.93 | 2.43[a] | 0.02 |
| Caused by psychosocial factors | 34 (53.1%) | 16 (25.8%) | 9.82[c] | < 0.001 |
| Caused by physiological factors | 32 (50.0%) | 24 (38.7%) | 1.63 | 0.20 |
| Coprolalia | 30 (46.9%) | 10 (16.1%) | 13.74[c] | < 0.001 |
| Function impairment | 46 (71.9%) | 28 (45.2%) | 9.27[c] | < 0.001 |
| Family of TS history | 16 (25%) | 6 (9.7%) | 5.13[a] | 0.02 |
| YGTSS total | 66.35 ± 4.61 | 39.58 ± 3.97 | 34.88[c] | < 0.001 |
| YGTSS severity total | 40.41 ± 3.51 | 21.32 ± 2.78 | 33.77[c] | < 0.001 |
| Impairment | 25.94 ± 3.89 | 18.26 ± 2.21 | 13.57[c] | < 0.001 |
| PUTS | 26.23 ± 3.28 | 18.33 ± 2.76 | 14.61[c] | < 0.001 |
| IQ | 92.42 ± 7.63 | 101.05 ± 10.03 | 5.45[c] | < 0.001 |

[a]$P < 0.05$.
[c]$P < 0.001$.
TRTS: Treatment-refractory Tourette syndrome; YGTSS: Yale Global Tic Severity Scale; PUTS: Premonitory Urge for Tics Scale; IQ: Intelligence quotient.

**Table 2 Behavioral and emotional characteristics of treatment-refractory Tourette syndrome and non-treatment-refractory Tourette syndrome in the boys group**

| Subscales of CBCL | TRTS (*n* = 48) | Non-TRTS (*n* = 44) | *t* | *P* value |
|---|---|---|---|---|
| Schizoid | 3.75 ± 0.67 | 3.51 ± 0.84 | 1.52 | 0.13 |
| Depressed | 6.17 ±1.24 | 5.81 ± 0.93 | 1.56 | 0.12 |
| Uncommunicative | 3.52 ± 0.89 | 2.81 ± 0.73 | 4.75[c] | < 0.001 |
| Obsessive-compulsive | 7.69 ± 0.74 | 6.97 ±1.25 | 3.40[c] | 0.001 |
| Somatic complaints | 3.24 ± 0.68 | 3.44 ± 0.71 | -1.38 | 0.17 |
| Social-withdrawal | 3.78 ± 0.91 | 2.96 ± 0.54 | 5.20[c] | < 0.001 |
| Hyperactive | 6.59 ± 0.87 | 5.64 ± 1.13 | 4.54[c] | < 0.001 |
| Aggressive | 14.87 ± 2.01 | 13.55 ± 1.94 | 3.20[b] | 0.002 |
| Delinquent | 3.49 ± 0.66 | 2.81 ± 1.02 | 3.83[c] | < 0.001 |
| Total Score | 50.72 ± 6.19 | 43.13 ± 7.16 | 5.45[c] | < 0.001 |

[b]$P < 0.01$.
[c]$P < 0.001$.
CBCL: Child Behavior Checklist; TRTS: Treatment-refractory Tourette syndrome.

## DISCUSSION

In the present study, we found that pediatric patients always developed TRTS at an earlier age, had a longer duration of illness, had a lower IQ, and had a higher premonitory urge, which often fluctuated due to psychosocial factors. In addition, the incidence of coprolalia seemed higher in the TRTS group. The locations of tics often occur at the face, followed by the throat and shoulder in TRTS; the most common motor tics were nodding or shaking the head, blinking, or shoulder shrugging, while the vocal tics commonly included clearing the throat, coprolalia, and repeated speech. These were the basic

**Table 3 Behavioral and emotional characteristics of treatment-refractory Tourette syndrome and non-treatment-refractory Tourette syndrome in the girls group**

| Subscale of CBCL | TRTS (*n* = 16) | Non-TRTS (*n* = 18) | *t* | *P* value |
|---|---|---|---|---|
| Depressed | 8.75 ± 1.67 | 7.65 ± 1.84 | 1.82 | 0.08 |
| Social-withdrawal | 6.23 ± 1.17 | 5.24 ± 1.22 | 2.41[a] | 0.02 |
| Somatic complaints | 3.22 ± 1.03 | 3.05 ± 0.93 | 0.51 | 0.62 |
| Schizoid-obsessive | 2.19 ± 0.44 | 2.07 ± 0.35 | 0.89 | 0.38 |
| Hyperactive | 6.29 ± 1.27 | 5.94 ± 1.13 | 0.85 | 0.40 |
| Sex problem | 0.59 ± 0.17 | 0.56 ± 0.21 | 0.45 | 0.65 |
| Delinquent | 2.79 ± 0.66 | 2.61 ± 0.72 | 0.76 | 0.46 |
| Aggressive | 8.17 ± 1.25 | 7.55 ± 1.04 | 1.58 | 0.12 |
| Cruel | 2.13 ± 0.67 | 2.07 ± 0.47 | 0.31 | 0.76 |
| Total Score | 41.06 ± 5.17 | 36.80 ± 4.65 | 2.53[a] | 0.02 |

[a]$P < 0.05$.

CBCL: Child Behavior Checklist; TRTS: Treatment-refractory Tourette syndrome.

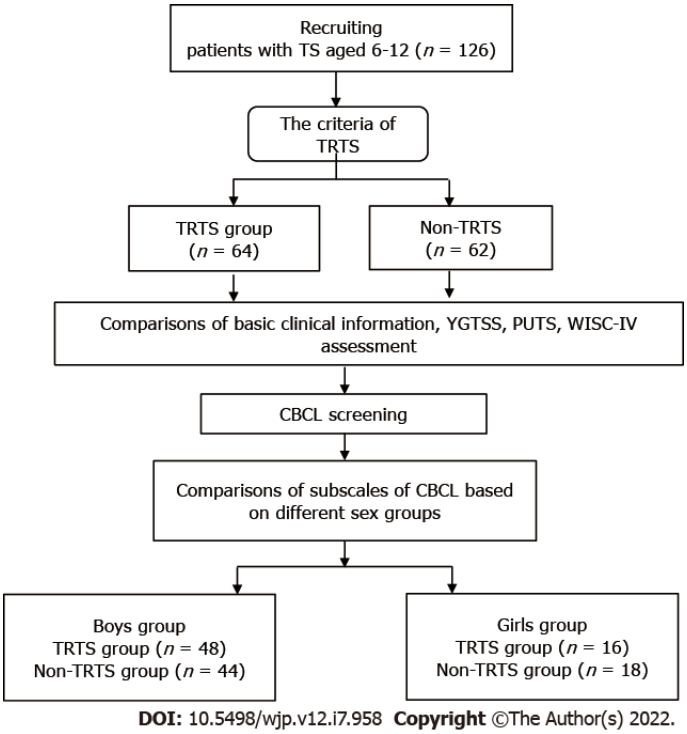


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**Figure 1 Flowchart of identification of included participants.** TRTS: Treatment-refractory Tourette syndrome; YGTSS: Yale Global Tic Severity Scale; PUTS: Premonitory Urge for Tics Scale; WISC-IV: Wechsler Intelligence Scale for Children-4th Edition.

clinical characteristics of TRTS based on Chinese pediatric patients. Unraveling these clinical characteristics is beneficial for the early diagnosis and treatment of TRTS.

Based on the results of this study, psychiatric components might be robust features of TRTS. Cavanna *et al*[11] performed a review of the psychopathological spectrum of TS and reported that the psychiatric components of TS included OCD, ADHD, and affective disorders. A large cross-sectional survey including 1001 TSs found that 85.7% of TSs had at least one psychiatric disorder, and 57.7% had two or more psychiatric disorders[35]. It seems that the most common psychiatric disorders were ADHD and OCD[6].

In this study, we found that children diagnosed with TRTS might suffer more emotional and behavioral problems than non-TRTS children. These included social communication deficits (such as uncommunicative and social withdrawal), ADHD-related symptoms (hyperactive, aggressive, and

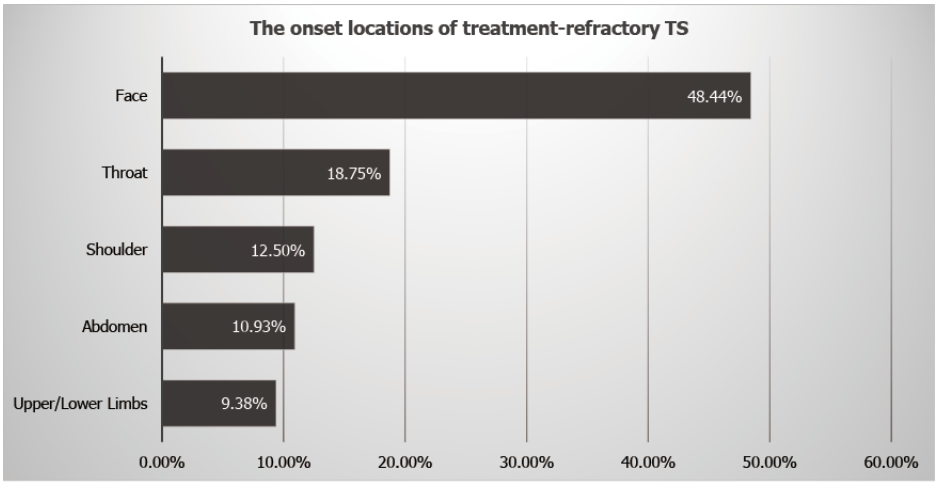


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**Figure 2 Percentage of onset locations of tic symptoms in treatment-refractory Tourette syndrome.**

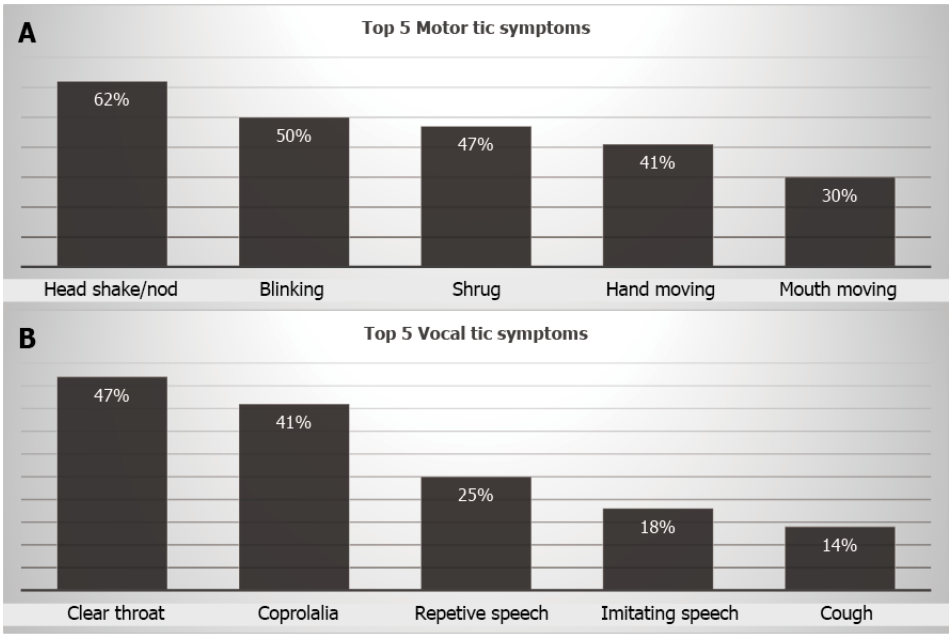


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**Figure 3 Percentage (top 5) of high frequency motor and vocal tic symptoms in treatment-refractory Tourette syndrome.** A: Top 5 high frequency motor tic symptoms in treatment-refractory Tourette syndrome (TRTS); B: Top 5 high frequency vocal tic symptoms in TRTS.

delinquent), and obsessive-compulsive symptoms. The high levels of ADHD-related symptoms and obsessive-compulsive symptoms in TRTS suggest that the comorbid psychiatric conditions of ADHD and OCD seem to be the main clinical characteristics of TRTS. Comorbid ADHD might increase the risk of impulsive behavior (such as running the red light)[36], and these might develop into new psychosocial factors that can cause fluctuations in tic symptoms in TS. Comorbid ADHD might also result in the failure of psychotherapeutic interventions for TS[37]. Moreover, the severity of obsessive-compulsive symptoms in TS was one of the most important predictors of the severity of tic symptoms [38]. Taken together, the comorbid ADHD and OCD might make the traditional treatment of TS harder, which is the most likely reason for the treatment refractoriness of TS.

In addition, in the present study, we found that premonitory urge might be one of the indicators of TRTS. Indeed, obsessive-compulsive symptoms also showed an association with premonitory urge in TS [39]. It seemed that premonitory urge could predict the severity of tic symptoms[40]. This finding suggested that we need to pay attention to the assessment of premonitory urge at the early stage of treatment of TS, which might be an indicator of potential progression to TRTS.

However, we hypothesized that patients diagnosed with TRTS might have more depressive symptoms, but the opposite result was found. Notably, two aspects of social communication,

uncommunicative and social withdrawal, were prominent among children diagnosed with TRTS. Regarding the social communication deficits of TS, a recent study reported that TS showed significantly higher mean Social Communication Questionnaire (SCQ) scores than the general population[41]. These results suggested that more attention should be given to social communication deficits in TS.

Based on the clinical characteristics of TRTS, a younger onset age of tics, a longer duration of illness, comorbidities and social communication deficits may be indicators for TRTS. Up to 70% of the troubles caused by nontic-related functional impairment result from ADHD or OCD[42]. The functional impairment could be caused by both the tics and the comorbidities. Moreover, psychiatric comorbidities might lead to less effective medical treatment or psychotherapeutic treatment[6]. It is indicated that practitioners should pay more attention to early screening and properly treat the comorbidities of patients with TRTS. This could improve the global function and prognosis of TRTS patients with comorbidities. In addition to medicine and psychotherapeutic treatment, there are also some other treatment options. Repetitive transcranial magnetic stimulation can significantly relieve tic and obsessive-compulsive symptoms in TS patients in a meta-analysis[43]. Deep brain stimulation was carefully recommended to patients with TRTS for more consideration of its efficacy and tolerability[44].

In this study, we investigated the clinical characteristics of TRTS, which will provide conforming evidence to the definition of the Chinese version of the criteria for TRTS. According to our study, TRTS might be an important subtype of TS, which differs from "pure TS". The following aspects might be indicators of pediatric TRTS: An earlier age of onset, longer duration of illness, higher incidence rates of complicated tics such as coprolalia, higher premonitory urge, lower IQ, and more severe functional impairment than other "pure TSs". Moreover, TRTS is more frequently associated with ADHD-related symptoms, obsessive-compulsive symptoms, and social communication deficits. Cumulatively, these clinical characteristics provide important information for the definition of TRTS in China, especially for pediatric patients.

What may account for the social communication deficits in children diagnosed with TRTS? There might be the following three factors. First, both motor and vocal tic symptoms last longer and are more severe in TRTS than in other types of TS. For example, we found that the incidence rates of coprolalia were higher, which brought self-stigma pressure to the patients upon receipt of negative comments such as being called "freak" by peers. A study reported that stigma, social maladjustment, social exclusion, bullying, and discrimination are considered to be caused in large part by misperceptions of the disorder by teachers and peers[45]. Second, psychosocial factors have a huge impact on TRTS. The high comorbidity with ADHD makes children with TRTS suffer poorer test performance and rejections from peers or teachers at school[46]. Moreover, we found that children with TRTS might experience more negative parenting styles, indicating that they might suffer lower self-esteem and become socially withdrawn[47]. Third, it has been confirmed that social cognition deficits can also influence the social communication function of TS[48]. Overall, it indicated the importance of social communication deficit-related symptoms for TRTS.

However, in previous studies, we focused more on ADHD and obsessive-compulsive symptoms in TRTS, and social communication-related problems seemed to be neglected. It should be noted that social communication deficits are crucial signs of functional impairment[45], suggesting that we also need to assess social communication deficits during the assessment of function in TRTS. Therefore, we should pay more attention to social communication deficits in TRTS regardless of the assessment or the treatment.

Some of the following limitations existed in this study. First, the sample size should be larger to increase the effect size. Second, the evaluation tool was limited to the CBCL. Although the CBCL can assess the emotional and behavioral problems associated with TS, more specific tools should be included to evaluate TS comorbidities. Third, this study was a cross-sectional study, and a longitudinal follow-up study will provide more confirmatory evidence in the future.

## CONCLUSION

Pediatric TRTS might show an earlier age of onset age, longer duration of illness, lower IQ, higher premonitory urge, and higher comorbidities with ADHD-related symptoms and OCD-related symptoms than 'pure TS'. Moreover, TRTS shows more social communication deficits that need to be covered in both the assessment and treatment of TRTS. TRTS might be one of the subtypes of TS. We need to develop a proper Chinese version definition of the TRTS in the future, especially for pediatric patients.

## ARTICLE HIGHLIGHTS

### *Research background*

Tourette syndrome (TS) is a complex neurodevelopmental condition marked by tics, as well as a variety

of psychiatric comorbidities, such as obsessive-compulsive disorders (OCDs), attention deficit hyperactivity disorder (ADHD), anxiety, and self-injurious behavior. However, no Chinese version of the TRTS criteria has been described. Moreover, the different criteria for TRTS were established mostly based on the clinical characteristics of adult patients with Tourette syndrome.

### Research motivation

We need more confirmatory evidence about the clinical characteristics of TRTS. However, few studies have focused on the behavioral and emotional components of TRTS. Identifying the "indicators" of TRTS in the early stage may help in the treatment of these patients. Whether TRTS is different from "pure TS" (only tic symptoms without comorbidities) is unknown. More evidence is needed to explore these differences, especially at the early stage of TRTS.

### Research objectives

This study aimed to examine the clinical characteristics of TRTS in a Chinese pediatric population, compare the clinical characteristics (*i.e.*, the onset of tic age, duration of illness, intelligence quotient (IQ), and behavioral and emotional problems) of patients with TRTS and non-TRTS patients, and report the locations and the frequency of tic onset in TRTS.

### Research methods

A total of 126 pediatric patients aged 6-12 years with TS were identified, including 64 TRTS and 62 non-TRTS patients. The Yale Global Tic Severity Scale (YGTSS), Premonitory Urge for Tics Scale (PUTS), and Child Behavior Checklist (CBCL) were used to assess these two groups and compared the difference between the TRTS and non-TRTS groups. Descriptive statistics were performed to identify the basic clinical information, and $t$ tests or $\chi^2$ tests were used to compare the different variables of different TS groups.

### Research results

When compared with the non-TRTS group, we found that the age of onset for TRTS was younger ($P < 0.001$), and the duration of illness was longer ($P < 0.001$). TRTS was more often caused by psychosocial ($P < 0.001$) than physiological factors, and coprolalia and inappropriate parenting style were more often present in the TRTS group ($P < 0.001$). The TRTS group showed a higher level of premonitory urge ($P < 0.001$), a lower intelligence quotient (IQ) ($P < 0.001$), and a higher percentage of family history of TS. The TRTS patients demonstrated more problems ($P < 0.01$) in the "Uncommunicative", "Obsessive-Compulsive", "Social-Withdrawal", "Hyperactive", "Aggressive", and "Delinquent" subscales in the boys group, and "Social-Withdrawal" ($P = 0.02$) subscale in the girls group.

### Research conclusions

Pediatric TRTS might show an earlier age of onset age, longer duration of illness, lower IQ, higher premonitory urge, and higher comorbidities with ADHD-related symptoms and OCD-related symptoms than 'pure TS'. Moreover, TRTS shows more social communication deficits that need to be covered in both the assessment and treatment of TRTS. TRTS might be one of the subtypes of TS. We need to develop a proper Chinese version definition of the TRTS in the future, especially for pediatric patients.

### Research perspectives

In previous studies, we focused more on ADHD and obsessive-compulsive symptoms in TRTS, and social communication-related problems seemed to be neglected. It should be noted that social communication deficits are crucial signs of functional impairment, suggesting that we also need to assess social communication deficits during the assessment of function in TRTS. Therefore, we should pay more attention to social communication deficits in TRTS regardless of the assessment or the treatment.

## FOOTNOTES

**Author contributions:** Li Y and Yan JJ contribute equally to this study; Cui YH and Li Y took the initiative; Yan JJ participated in the data collection; Li Y performed the data analysis; Yan JJ finished the draft; all authors have read and approved the manuscript.

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ORIGINAL ARTICLE

Observational Study

# Effect of distinct psychological interventions on changes in self-reported distress, depression and loneliness among older adults during COVID-19

Stav Shapira, Daphna Yeshua-Katz, Orly Sarid

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## Abstract

***BACKGROUND***

Older adults have been considered a primary at-risk population during the coronavirus disease 2019 (COVID-19) pandemic, and many efforts have been and still are directed toward supporting them and enhancing their capacity to cope with the pandemic. Evidence shows that by enhancing proactive coping abilities through psychological interventions, in which cognitive-behavioral and mindfulness techniques are taught and practiced effectively, these interventions have supported older adults throughout the pandemic. However, the underlying mechanisms by which specific intervention components affect various mental states such as distress, depression and loneliness among older adults remain unclear and warrant investigation.

***AIM***

To determine the effect of an intervention using cognitive-behavioral and mindfulness techniques on changes in distress, depression and loneliness.

***METHODS***

We performed a secondary analysis on data from a previous study in which community-dwelling older adults attended a short-term, internet-based intervention during the first COVID-19 wave in Israel. The intervention included seven sessions during which various cognitive-behavioral and mindfulness techniques were learned and practiced. In-session changes in psychological distress were measured using the Subjective Units of Distress Scale (SUDS), which participants rated at the beginning and end of each session. Participants also filled out questionnaires that evaluated levels of depression [Patient Health Ques-

tionnaire (PHQ-9)] and loneliness (UCLA loneliness Scale) prior to and after the entire intervention process. The effect of in-session changes in the SUDS on changes in post-intervention depression and loneliness levels were assessed, as a proxy for distinct technique effectiveness.

***RESULTS***

The findings indicated in-session differences in terms of a decrease in psychological distress (SUDS). Sessions that included relaxation exercises and guided imagery, as well as sessions that included cognitive restructuring and mindfulness meditation, demonstrated the largest decreases in in-session psychological distress (≥ 35%). Two multivariate regression models, one for levels of post-intervention depression (PHQ-9 score) and the other for levels of post-intervention loneliness (UCLA loneliness score), were fitted. The results revealed two statistically significant explanatory variables for depression: The SUDS difference for sessions in which cognitive restructuring and mindfulness meditation were practiced, beta = -0.25, 95%CI: -1.23 to -0.1, and the pre-intervention level of depression, beta = 0.62, 95%CI: 0.37-0.75. The second model for loneliness revealed only one significant explanatory variable: The SUDS difference for sessions in which relaxation and guided imagery were practiced, beta = 0.41, 95%CI: 0.14-0.65.

***CONCLUSION***

Different psychological techniques seem to have different effects on distress, loneliness and depression. Understanding the pathways by which distinct techniques affect negative mental symptoms has implications for future intervention design.

**Key Words:** COVID-19; Depression; Loneliness; Aged; Cognitive behavioral therapy; Subjective Units of Distress Scale; Intervention studies

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**Core Tip:** The present study explored how distinct cognitive, behavioral and mindfulness interventions affect depression and loneliness *via* changes in psychological distress among older adults. This study is, to the best of our knowledge, the first to explore underlying mechanisms of change in aspects of mental health against the unique backdrop of the coronavirus disease 2019 pandemic among older adults. The results provide both theoretical and clinical insights into future intervention design and in regard to ways of supporting older adults during times of change and uncertainty.

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## INTRODUCTION

Ever since the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, a vast number of studies have investigated the effects of protective measures such as social distancing, quarantining and self-isolating on those individuals defined as comprising the primary at-risk population–older adults. Indeed, much evidence has pointed to elevated levels of psychological distress, depressive symptoms and loneliness among quarantined older adults, especially during the first 6 mo of the pandemic[1-4]. Conversely, later studies have suggested a much more nuanced picture with evidence indicating that the mental health of older adults remained roughly stable through the pandemic[5] and that, in fact, older adults have been more resilient to the negative mental health repercussions of the pandemic compared with younger individuals who have suffered greater economic losses[6] and struggled with managing childcare and work commitments[7]. In an effort to trace the protective factors that contributed to older adults' resilience during the pandemic, several studies have pointed to the importance of maintaining close and meaningful social connections[8], of implementing proactive coping[9] and of being able to use technology and function well in digital environments in these regards [10].

Digital environments and tools can be used not only as a means of staying connected with loved ones but also as powerful platforms to deliver designated psychological interventions to support older adults' mental health and well-being throughout the pandemic and promote proactive coping[11-13].

Indeed, remotely-delivered programs which have been developed during the pandemic have mainly focused on increasing social connectedness and combating the consequences of social isolation, as well as in augmenting coping skills[14]. One of the widespread and common therapeutic approaches used for adapting and enhancing coping abilities involves cognitive-behavioral tools (which include a wide range of techniques) in combination with other modalities such as mindfulness meditation. Previous evidence found that internet-based cognitive and behavioral interventions combined with peer support, such as interventions conducted in a group format, can effectively reduce depression[15] and loneliness [16].

Cognitive-behavioral interventions, as well as mindfulness interventions, are currently very much in use by therapists to help individuals combat depression[17] and loneliness[18]. Theoretically, these interventions focus on several mental pathways. Examples include: (1) Targeting the autonomic nervous system and sympathetic-parasympathetic responses[19,20]; by using techniques such as relaxation, breathing exercises, guided imagery and mindfulness meditation, which share key components of body-based exercises and mind-based practice, therapists aim to retrieve stressful autobiographical memories and alter those memories to be less alarming; and (2) focusing on high-order cognitive processes such as identifying maladaptive thinking patterns, altering them on a moment-to-moment basis and restructuring self-supportive talk[21]. These "bottom-up" and "top-down" processes, respectively, are of great relevance to different populations with whom therapists work. Although older adults are considered to have better regulatory emotional responses compared to younger people[22], it is important to understand which interventions are most effective in reducing distress, depression and loneliness among this cohort, as well as in different stressful situations.

We previously reported the results of a short-term, internet-based intervention which was found to alleviate symptoms of loneliness and depression among older adults during the initial COVID-19 outbreak and the first general lockdown in Israel[23-26]. Our intervention protocol aimed to provide participants with the skills to facilitate effective coping with the dire circumstances and uncertainty that typified that period-resulting from high infection and mortality rates, increasing economic pressures, along with reduced social connections and contact. Whereas we focused then on the effectiveness and acceptability of the intervention as a whole, we did not explore whether the mechanisms of change in psychological distress, loneliness and depression were related to the use of those specific techniques that constituted the full protocol. The process of developing the intervention protocol had been based on previous evidence that highlighted the importance of addressing older adults' own thoughts and emotions[27] and deficits in social cognition, as primary components of programs aiming to support older adults through times of change and uncertainty[28]. Furthermore, multifaceted interventions that incorporate a collection of therapeutic techniques, such as cognitive, behavioral and mindfulness techniques, as well as elements of social interaction and peer support through guided group discussions, have been found to be effective in assisting older adults' coping with various health conditions and stressful events[29-31]. The specific techniques that were incorporated into the intervention protocol were chosen on the basis of previous and solid evidence regarding their effectiveness in reducing depression, loneliness and distress. These included relaxation and guided imagery [32], cognitive restructuring[33,34] and mindfulness meditation[35]. Yet the specific mechanism of change for each of these techniques when delivered and practiced online has not previously been explored among older adults in the context of the pandemic.

We hypothesized that the above-mentioned online intervention would reduce psychological distress, depressive symptoms and loneliness among older adults during the initial COVID-19 outbreak. Furthermore, we explored the links between the different techniques that were learned in terms of changes in psychological distress during sessions, as well as the effect of these changes (in distress) on post-intervention depressive symptoms and loneliness.

## MATERIALS AND METHODS

The analysis described here was performed on data obtained from a randomized controlled trial pilot study. The initial study aimed to evaluate the effectiveness of a short-term, internet-based group intervention to alleviate mental health difficulties among community-dwelling older adults during the pandemic's first lockdown in Israel. The intervention protocol and findings regarding its effectiveness were previously described elsewhere[24,26]. Briefly, the intervention included seven guided online sessions over 3.5 wk *via* the videoconferencing app Zoom, for small groups of up to seven participants. Each session lasted approximately 60-90 min. During the intervention, participants learned and practiced cognitive-behavioral and mindfulness techniques such as the use of repeated self-talk mantras, cognitive restructuring, breathing exercises, guided imagery and mindfulness meditation (Figure 1). The group moderators were clinical social workers trained to guide the intervention; additionally, they received ongoing supervision by a senior clinical social worker from the research team.

### *Study participants*

Between March and June 2020, following approval by the institutional review board of Ben-Gurion

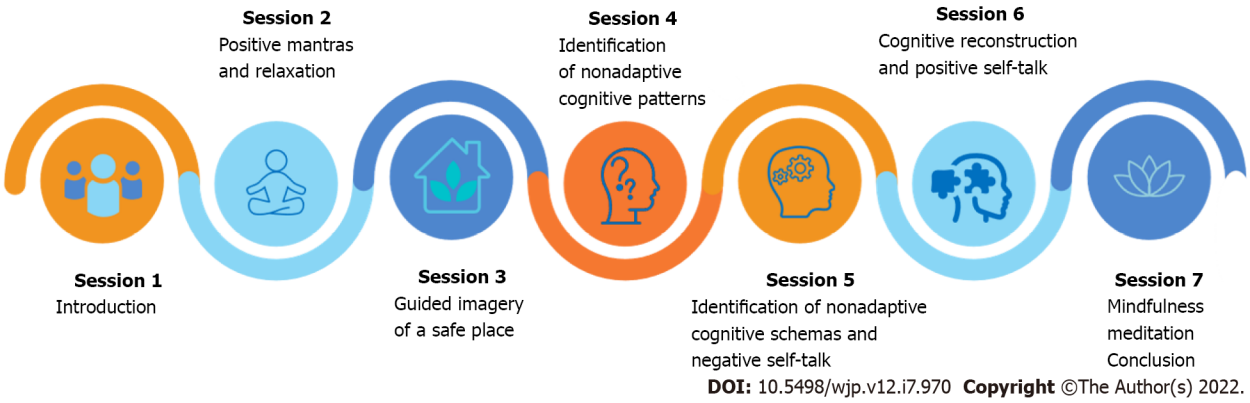

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**Figure 1 Intervention protocol: Skills and techniques learned in each session.**

University of the Negev, an online invitation to participate in the study was circulated to prospective participants. The invitation was distributed *via* WhatsApp groups of a local non-governmental organization that focuses on promoting digital literacy among seniors, as well as through welfare departments of several local municipalities in Israel. Eligible participants were community-dwelling older adults (aged 65+) who were: (1) Proficient in Hebrew; and (2) Could provide informed consent. Additional inclusion criteria were: (1) Having an active internet connection; (2) Possessing at least one device that enables online communication (*i.e.* a computer or smartphone); and (3) Having a minimal ability to operate this device (*i.e.* switching it on and off). A total of 124 applicants applied and were screened for eligibility: 37 applicants were excluded due to age (< 65) (21) or non-response (16), and one applicant withdrew from the study for personal reasons, leaving 86 eligible participants. The participants were then randomized *via* a 4:1 ratio into either the intervention or the waitlist control group. We used this allocation instead of an even ratio for ethical reasons; we wanted to provide mental support as quickly as possible to the greatest number of people who were, at the time (during the initial months of the pandemic), confined to their homes for an unknown period. The current analysis will focus on data obtained solely from the intervention group ($n$ = 64). For detailed information on drop-out reasons and rates see Shapira *et al*[26] (2021).

### Procedure

Participants filled out pre- and post-intervention online questionnaires (web-based survey, https://www.qualtrics.com) that had been sent to them by the group moderator *via* email or mobile phone in accordance with their preference. Additionally, at the beginning and immediately at the end of each session, all participants rated their level of subjective mental distress (see in detail in the section below); these data were collected *via* the use of Google Forms. At the end of the study, each participant provided two measurements (pre- and post-intervention) of the study questionnaire, in addition to 14 measurements of subjective distress (two measurements at the beginning and end of each of the seven sessions).

### Measurement

**Pre- and post-intervention questionnaire:** Dependent variables: The dependent variables were depression and loneliness. Depression was assessed using a 9-item measure, which is part of the Patient Health Questionnaire (PHQ-9). The PHQ-9 is a commonly used self-administered measure of depression containing nine items that map each of The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria for major depression[36]. The items assess the frequency of depressive symptoms over the past 2 wk and are rated on a four-point Likert-type scale: 0 (not at all) to 3 (nearly every day). The responses were summed, with a range of 0–27. The PHQ-9 was previously translated into Hebrew and tested among the Israeli population with good reliability (α ranged between 0.88 to 0.93)[37]. Loneliness was assessed using the short 3-item version of the UCLA loneliness Scale [38]. The items in this scale are related to lack of companionship, social exclusion and social isolation. Participants rated their feeling of loneliness on a 3-point Likert-type scale: (1) Hardly ever; (2) Some of the time; and (3) Often. Scores for the three items were summed with a possible score of 3–9. Higher scores indicated greater loneliness. This scale was previously translated into Hebrew and used among the Israeli population with good reliability (α = 0.87)[39].

Independent variables: The independent variables included sociodemographic data and evaluation of subjective health. Sociodemographic data included age, sex, educational level (dichotomized: Tertiary education *vs* non-tertiary education) and household composition [dichotomized: Live alone *vs* live with other(s)]. *Subjective* Health was assessed *via* one item from Israel's Central Bureau of Statistics survey of health indicators[40]. The participants were asked to rate their perception of personal health on a 4-

point Likert-type scale: 1 (poor) to 4 (excellent). Higher scores indicated better self-rated health.

**In-session evaluation of subjective mental distress:** Psychological distress was assessed using The Subjective Units of Distress Scale (SUDS)[41], at the beginning and end of each session. The SUDS provides a quick and simple way to measure distress in a given moment. The respondents were asked to estimate the severity of their emotional distress by providing a numerical value ranging from 0 (no distress) to 10 (highest distress you ever felt). The SUDS is a common tool for measuring the effect of therapeutic interventions[42] and has been previously used among older individuals[43,44].

### Statistical analysis

Data were analyzed in three steps. First, the differences between the SUDS start score and the SUDS end score for each session were calculated, resulting in seven new variables *per* participant that represented their changes in mental distress (SUDS) during each session (SUDS1 to SUDS7). Pearson's correlations were used to assess the intercorrelations between the seven SUDS differences. If the correlation coefficient between two values was higher than 0.65, a mean score was calculated for those values to avoid possible multicollinearity and potential bias in the following stages of analysis. The second analysis step included bivariate analyses to evaluate associations between the two dependent variables (post-intervention loneliness and depression levels), SUDS differences and other study variables using Pearson's correlations and Mann-Whitney U-test. Finally, two multivariate linear regression models were developed to identify significant associations between the explanatory variables that were found significant in the bivariate analyses and each outcome measure: Post-intervention depression and loneliness levels. A $P$ value of ≤ 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS (version 26, SPSS Inc., Chicago, IL, United States).

## RESULTS

### Descriptive statistics

Out of the 86 participants who met the inclusion criteria, a total of 64 participants completed the intervention program and provided data for the current analysis. The baseline characteristics of those participants were as follows: sex, 52 female participants (81%) and 12 male participants (19%); age, M = 72.1 (SD = 5.3) years; household composition, 24 residing alone (37.5%) and 40 residing with other(s) (62.5%); education, 48 had a tertiary education (76%) and 16 had a non-tertiary education (24%). In terms of subjective health, 33% reported their health to be "very good" or "excellent," 44% reported their health to be "fair," and the rest (23%) reported their health as "not so good" or "poor." The PHQ-9 score (depression) was 6.6 (SD = 5.2) at baseline and decreased to 5.2 (SD = 4.7) post-intervention. The score on the UCLA loneliness scale was 5.4 (SD = 2) at baseline and decreased to 4.7 (SD = 1.6) post-intervention. For detailed information on study participants and changes in outcome measures, see previous publications[25,26].

### Subjective mental distress

Subjective mental distress was evaluated by measuring the SUDS rating (on a scale from 0-10) at the beginning and end of each session. Figure 2 presents the mean values of the SUDS measure for each of the seven sessions in the program and the average percentage of change in each session.

The findings indicate that the sessions in which the average decrease in subjective mental distress was highest (≥ 35%) were sessions 2, 3, 6, and 7. Further analysis estimated the intercorrelations between the seven variables representing the delta differences in SUDS ratings. The results revealed a strong correlation (defined as $r > 0.6$) between the delta values of sessions 2 and 3 ($r = 0.65$, $P < 0.001$) and between the delta values of sessions 6 and 7 ($r = 0.69$, $P < 0.001$). Given these results, the variables were merged by calculating a mean value for each of the two pairs.

### Bivariate analysis

The associations between levels of post-intervention depression and loneliness, and SUDS difference scores, were assessed. Significant associations were observed between levels of depression and the SUDS difference of sessions 2 + 3 ($r = -0.36$, $P = 0.003$) and of sessions 6 + 7 ($r = -0.4$, $P = 0.001$). Only one significant association was detected between levels of loneliness and the SUDS difference of sessions 2 + 3 ($r = -0.33$, $P = 0.009$). An additional association was found between levels of depression and age ($r = -0.3$, $P = 0.03$). Other personal characteristics did not reach statistical significance. Table 1 presents the intercorrelations between study variables.

### Multivariate analysis

Two multivariate regression models were fitted to identify statistically significant associations between the study variables: (1) Levels of post-intervention depression (PHQ-9 score); and (2) Levels of post-intervention loneliness (UCLA loneliness score). The variables entered into each model were selected on the basis of the bivariate analysis results; in addition, we controlled for levels of pre-intervention

**Table 1 Correlation matrix of study variables (*n* = 64)**

| | Loneliness | Depression | SUDS1 | SUDS_2_3 | SUDS4 | SUDS5 | SUDS_6_7 | Age | Subjective health |
|---|---|---|---|---|---|---|---|---|---|
| Loneliness | 1 | | | | | | | | |
| Depression | -0.01 | | | | | | | | |
| SUDS1 | 0.12 | -0.18 | 1 | | | | | | |
| SUDS_2_3 | -0.33[b] | -0.36[b] | 0.57[b] | 1 | | | | | |
| SUDS4 | 0.21 | -0.30 | 0.21 | 0.52[b] | 1 | | | | |
| SUDS5 | -0.02 | -0.20 | -0.09 | 0.24 | 0.31[a] | 1 | | | |
| SUDS_6_7 | 0.07 | -.40[b] | 0.26 | 0.48[b] | 0.42[b] | 0.50[b] | 1 | | |
| Age | -0.16 | -.27[a] | 0.14 | 0.03 | -0.13 | -0.10 | -0.08 | 1 | |
| Subjective health | 0.02 | -0.13 | 0.27 | 0.20 | 0.14 | 0.07 | 0.10 | -0.15 | 1 |

[a]$P < 0.05$.
[b]$P < 0.001$.
All Subjective Units of Distress Scale variables are delta differences.

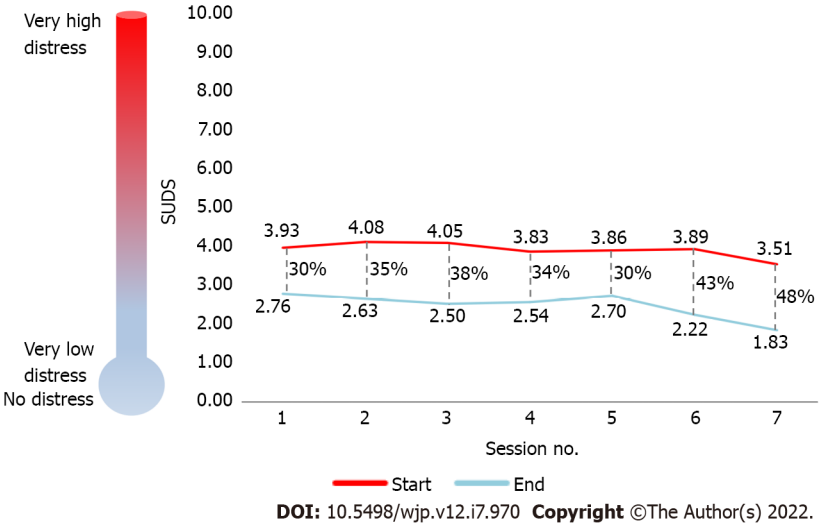

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**Figure 2 Mean values for the Subjective Units of Distress Scale measure at the start and end of the intervention sessions for the entire study sample (*n* = 64).** The dashed lines and accompanying values represent the mean percentage of change in Subjective Units of Distress Scale scores for each session. SUDS: Subjective Units of Distress Scale.

depression/loneliness. Both models employed a standard linear regression analysis. The results revealed two statistically significant explanatory variables for depression: The SUDS difference for sessions 6 + 7, beta = -0.25, 95%CI: -1.23 to -0.1, and the level of pre-intervention depression, beta = 0.62, 95%CI: 0.37-0.75. The second model for loneliness revealed only one significant explanatory variable: The SUDS difference for sessions 2 + 3, beta = 0.41, 95%CI: 0.14-0.65 (Tables 2 and 3).

## DISCUSSION

This study examined the effectiveness of a short-term group intervention using cognitive-behavioral and mindfulness interventions for alleviating psychological distress, depression and loneliness among older adults during the first wave of the COVID-19 pandemic and a national lockdown in Israel. The findings indicated in-session differences in terms of decreases in psychological distress. Sessions during which the techniques of relaxation exercises and guided imagery were learned, and sessions during which cognitive restructuring and mindfulness meditation were learned, led to the highest reduction in distress and these reductions were related to significant changes in levels of post-intervention loneliness and depression, correspondingly. These results suggest that specific techniques may have different

**Table 2 Multivariate regression (with post-intervention Patient Health Questionnaire-9 score as dependent variable)**

| | Unstandardized coefficients | | Standardized coefficients | | 95% confidence interval for β | | *P* value |
|---|---|---|---|---|---|---|---|
| | β | Std. Error | β | t | Lower bound | Upper bound | |
| (Constant) | 8.248 | 7.321 | | 1.127 | -6.417 | 22.913 | 0.265 |
| Age | -0.099 | 0.094 | -0.110 | -1.057 | -0.287 | 0.089 | 0.295 |
| Sex | -0.655 | 1.239 | -0.055 | -0.529 | -3.136 | 1.826 | 0.599 |
| SUDS_2_3 | 0.040 | 0.317 | 0.014 | 0.127 | -0.594 | 0.675 | 0.899 |
| SUDS_6_7 | -0.666 | 0.281 | -0.255 | -2.367 | -1.230 | -0.102 | 0.021 |
| PHQ_SUM_1 | 0.563 | 0.095 | 0.626 | 5.948 | 0.374 | 0.753 | 0.000 |

$n$ = 62, adjusted $r^2$ = 52.2%, F = 14.138, $P$ < 0.001.

**Table 3 Multivariate regression (with post-intervention UCLA loneliness score as dependent variable)**

| | Unstandardized coefficients | | Standardized coefficients | | 95% confidence interval for β | | *P* value |
|---|---|---|---|---|---|---|---|
| | β | Std. Error | β | t | Lower bound | Upper bound | |
| (Constant) | 7.805 | 3.237 | | 2.411 | 1.323 | 14.287 | 0.019 |
| Age | -0.045 | 0.041 | -0.147 | -1.100 | -0.126 | 0.037 | 0.276 |
| Sex | -0.071 | 0.540 | -0.017 | -0.132 | -1.152 | 1.010 | 0.896 |
| SUDS_2_3 | -0.399 | 0.129 | -0.416 | 3.092 | -0.657 | -0.140 | 0.003 |
| Lonely_1 | 0.155 | 0.109 | 0.195 | 1.427 | -0.063 | 0.373 | 0.159 |

$n$ = 62, adjusted $r^2$ = 11%, F = 2.847, $P$ = 0.03.

effects on the mental constructs that were examined (*i.e.* depression and loneliness). Possible explanations for these results are elaborated upon below.

First, the associations between psychological distress, measured by SUDS, and loneliness and depression, have been established previously[45,46]. Changes in SUDS scores have also previously been used to evaluate the effectiveness of psychological interventions and of specific intervention components[47]. The current findings strengthen the notion that changes in SUDS scores can be used as an indicator reflecting adjustments attained by a specific intervention component, and thus make an important methodological contribution to the design and evaluation of psychological interventions.

Furthermore, in relation to the specific effect of distinct cognitive-behavioral and mindfulness intervention components, the different mechanisms underlying the abovementioned therapeutic techniques and their impact on mental health outcomes should be discussed. The need to consider the underlying mechanisms involved in the effects of psychological interventions has been previously identified[28,48]. These mechanisms are not yet well understood, and some evidence suggests that observed positive changes are likely to occur *via* several pathways, such as changing maladaptive cognitive biases[18], improving emotion self-regulation[49] and shifting the sympathetic/parasympathetic balance[50]. The current findings which point to body-oriented, behavioral interventions such as relaxation through breathing and guided imagery as effective in decreasing distress (and consequently loneliness), but not in decreasing depression, contradict some previous findings but align with others. The same can be said for the finding which indicated that relatively more complex techniques such as cognitive restructuring and mindfulness meditation effectively reduced distress and depression but not loneliness. It should be noted that a meta-analysis study concluded that interventions that address maladaptive social cognitions present the greatest potential for reducing loneliness[28]. This notion was partially supported by the current results, in that the study's entire protocol was indeed found to reduce loneliness[25], although the specific techniques that addressed social cognitions (*e.g.*, cognitive restructuring) were not necessarily found to do so. It is therefore possible to assume that the latter techniques indeed contributed to reducing loneliness in the specific context of the current intervention (the first COVID-19 wave in Israel) and population (older adults isolated in their homes) but that their contribution was smaller compared to that of other techniques identified. Previous evidence has indicated the effectiveness of mindfulness-based[51] as well as cognitive restructuring techniques[52,53] in interventions treating depression. The current findings align with this evidence and highlight the importance of combining these two techniques together in

programs to treat depression, specifically among older individuals.

Finally, it is also worth mentioning once again the unique setting of the current group intervention–which was internet-based, short-term and guided–and discussing the abovementioned insights in this context. Indeed, the current program was not designed as a classic therapeutic intervention, but rather as a study program aimed to provide participants with a toolkit that would be available to them, and which would be at their disposal during a period marked by social isolation, lockdowns, and other dire circumstances. As such, the effect of learning and practicing new skills in a digital environment may also have contributed to the beneficial changes observed *via* empowering the participants, perhaps by increasing their self-efficacy[54] and enhancing social inclusion[55]. Future research should explore the effects of online learning as an independent mechanism that enhances older adults' coping capacity during periods of crisis and uncertainty.

The current study had several limitations. First, as the intervention was delivered in a group setting, thus enabling discussion between participants during sessions, we cannot rule out a possible effect of participants' interactions on the outcomes obtained. Second, the effectiveness of the techniques learned was evaluated through a proxy measure: Changes in levels of psychological distress. It is possible that this measure does not fully reflect the effect of the intervention on the participants as it was self-reported and subjected to potential bias. Future studies should incorporate objective measures, such as monitoring facial expressions, as part of online interventions[56,57]. Third, the present study examined the group effect of the techniques learned and did not focus on individual-level preferences. Fourth, the small sample size may also compromise the study's conclusions. Larger studies in the future would allow for subgroup analyses and enable the determination of effectiveness for different program elements in a more robust manner.

## CONCLUSION

The current study examined in depth the mechanisms underlying the beneficial changes in mental health outcomes among older individuals who participated in an internet-based group intervention during the early part of the COVID-19 pandemic. Findings indicated that different intervention components had different effects on psychological distress, loneliness and depression, and that each component may enhance the proactive coping abilities of older individuals in different ways. From a theoretical perspective it is important to understand the specific pathways by which distinct techniques affect mental capacities[49]. The frameworks of cognitive-behavioral and mindfulness interventions need to be dissected into segments as a way to better understand the role of each interventional strategy. Doing so would support the design of more concise and efficient interventions tailored to the needs of different populations and mental states. From a clinical perspective, the findings shed light on potential paths by which different therapeutic techniques might affect mental health outcomes among older adults specifically, and thus have implications for future intervention design. These insights may help in the enhancement of older individuals' resilience during future outbreaks, as well as during other large public health emergencies.

## ARTICLE HIGHLIGHTS

### *Research background*

Older adults have been considered a primary at-risk population during the coronavirus disease 2019 (COVID-19) pandemic. Recent evidence has shown that enhancing proactive coping abilities through psychological interventions can support older adults throughout the pandemic. However, the underlying mechanisms by which specific intervention components affect various mental states among older adults remain unclear and warrant investigation.

### *Research motivation*

We previously reported the results of a short-term, internet-based intervention which was found to alleviate symptoms of loneliness and depression among older adults during the initial COVID-19 outbreak and the first general lockdown in Israel. We focused then on the effectiveness and acceptability of the intervention as a whole, but did not explore whether the mechanisms of change in mental states were related to the use of those specific techniques that constituted the full protocol. We believe that a better understanding of the role of each interventional strategy can support the design of more concise and efficient interventions tailored to the needs of different populations and mental states.

### *Research objectives*

To determine the effect of an intervention using cognitive-behavioral and mindfulness techniques on changes in distress, depression and loneliness. Furthermore, we explored the links between the different techniques that were learned in terms of changes in psychological distress during sessions, as well as the

effect of these changes (in distress) on post-intervention depressive symptoms and loneliness.

### *Research methods*

We performed a secondary analysis on data from the original intervention described above. The intervention included seven sessions during which various cognitive-behavioral and mindfulness techniques were learned and practiced. In-session changes in psychological distress were measured using the Subjective Units of Distress Scale (SUDS) which participants rated at the beginning and end of each session. In addition, levels of depression (Patient Health Questionnaire) and loneliness (UCLA Loneliness Scale) were assessed prior to and after the entire intervention process. The effect of in-session changes in the SUDS on changes in post-intervention depression and loneliness levels were assessed as a proxy for distinct technique effectiveness.

### *Research results*

The findings indicated in-session differences in terms of decreases in psychological distress. Sessions during which the techniques of relaxation exercises and guided imagery were learned, and sessions during which cognitive restructuring and mindfulness meditation were learned, led to the highest reduction in distress, and these reductions were related to significant changes in levels of post-intervention loneliness and depression, correspondingly.

### *Research conclusions*

Different psychological techniques seem to have different effects on the specific mental states that were assessed in the current study. The findings shed light on potential paths by which different therapeutic interventions might affect mental health outcomes among older adults specifically, and thus have implications for future intervention design. These insights may help in the enhancement of older individuals' resilience during future outbreaks and other emergencies.

### *Research perspectives*

Larger studies are needed to allow for subgroup analyses that would enable the determination of effectiveness for different program elements in a more robust manner.

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## FOOTNOTES

**Author contributions:** Shapira S, Yeshua-Katz D and Sarid O designed and performed the research; Shapira S and Sarid O analyzed the data; Shapira S wrote the first draft of the manuscript; all authors have read and approved the final manuscript.

**Institutional review board statement:** The study protocol was approved by the institutional review board of Ben-Gurion University of the Negev, No. 1885-1.

**Informed consent statement:** All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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SCIENTOMETRICS

# Mapping the landscape and structure of global research on binge eating disorder: Visualization and bibliometric analysis

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## Abstract

### *BACKGROUND*

Binge-eating disorder (BED) is a clinical syndrome and is considered the most common type of eating disorder. However, our understanding of the global performance and progress of BED research is limited.

### *AIM*

To describe and perform a bibliometric analysis of the state of BED research.

### *METHODS*

The term 'Binge eating' was searched in the title throughout the previous year's up to December 31, 2020. We searched the Scopus and Reference Citation Analysis for publications on Binge eating. The VOSviewer software version 1.6.17 was used to produce the network visualization map of the most frequent author, collaborative relationships between countries/regions, and to determine the hotspots related to binge eating research. In addition, conventional bibliometric indicators were generated.

***RESULTS***

The search strategy found 2713 total articles and an average of 62 articles *per* year. Among them, 'Article' represented 82.49% of the publications ($n$ = 2238 articles) and was the most frequent type, followed by reviews ($n$ = 243; 8.96%). The number of publications increased steadily during the last decade of the study period. One hundred and thirty-two countries contributed to binge eating research, with 1495 (55.11%) articles published in the United States, followed by Italy with 256 (9.44%), the United Kingdom with 183 (6.75%), and Germany with 182 (6.71%). Currently, the main hot topics related to BED are 'type of treatment and management and treatment provided to BED"; "processes and pathways to binge eating"; and 'diagnosis, signs and symptoms, comorbidities and prevalence and associated factors with BED'.

***CONCLUSION***

The number of publications has increased noticeably during the previous decade. There are indeed relatively few publications on BED from low-and middle-income nations, so much is to be learned from the experience of all countries. Studies on this topic are critical in all countries to discover risk factors and effective intervention measures. Although our findings are preliminary, they imply that the future prospects for interventions aimed at BED management are bright, focusing on complex models of care and long-term maintenance of therapeutic gains.

**Key Words:** Binge-eating disorder; Scopus; Bibliometric; VOSviewer; Eating disorders.

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**Core Tip:** Over the last decade, research on binge eating disorder (BED) has focused on various issues. A review of the published literature would aid in determining the density and gaps of research. The number of publications related to BED has significantly increased over the last decade. Research on this topic is critical for identifying risk factors and developing effective intervention strategies in all countries. Although our findings are preliminary, they suggest that the future of BED management interventions is bright, emphasizing complex models of care and long-term maintenance of therapeutic gains.

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## INTRODUCTION

Disordered eating is a common condition that is often comorbid, especially when associated with obesity. Patients may suffer from various forms of eating disorders, including anorexia nervosa, bulimia nervosa, and binge eating disorder (BED). In the general population, almost 1%–3% of individuals will develop BED during their lifetime, making this form the most common eating disorder[1-3]. Psychiatrist Albert Stunkard first identified BED in 1959[4]. Stunkard outlines an eating habit characterized by eating large amounts of food at irregular intervals in his study "*Eating Patterns and Obesity*"[4].

BED is characterized by recurrent episodes in which people eat larger amounts of food than most people could eat simultaneously and under similar circumstances while experiencing feelings of loss of control and the absence of compensatory behaviors such as vomiting. Individuals suffering from BED can experience rapid eating in the absence of hunger, uncomfortable fullness, and afterward feelings of disgust, guilt, or sadness[5-9].

Several studies reported that many factors could facilitate binge eating, including impulsivity, inability to control emotions, and negative mood conditions[10-13]. In 2015, a meta-analysis of 33 studies found that negative mood conditions increase food intake in patients with BED compared to

those who do not suffer from BED, suggesting a strong relationship between negative mood conditions and binge eating behaviors[14].

However, despite the significant physical and psychological impairment, a higher percentage of binge-eaters did not seek treatment or receive any treatment[15,16]. Therefore, current treatments for BED primarily focus on behavioral, psychological, and physical outcomes that include cognitive behavioral therapy (CBT) and behavioral weight loss therapy (BWLT)[15,17]. CBT is considered the most effective approach for BED episodes, while BWLT is more effective in weight loss[18].

Over the last decades, research on BED has focused on a variety of topics. An examination of the published literature would aid in determining the density of research and the gaps. We found some bibliometric publications related to certain nutritional subjects[19-22], but none related to BED; therefore, this article is a novelty in this field. This study investigates the global performance and progress of BED research and maps the research patterns and trends using a visualization tool to address this gap. A bibliometric study of previous publications could serve as a foundation for a comprehensive understanding of existing research on BED and highlight some future research topics.

## MATERIALS AND METHODS

### Data source

The Scopus database was used to perform a descriptive bibliometric evaluation of BED publications. The Scopus database has a wider coverage of health and biomedical disciplines than the Web of Science and PubMed and has a higher coverage of citation reports[23,24]. It is also simple to access various legitimate analytical tools, making it an ideal choice for our research[23,24]. Scopus has also been used and validated in bibliometric analyses published in the previous two years[25-29].

### Search strategies

On October 1, 2021, the search and download procedure was completed in order to avoid significant mistakes caused by daily database changes. The data was immediately retrieved from the Scopus database and Reference Citation Analysis (RCA) (https://www.referencecitationanalysis.com/). "Binge eating" was used as a search term in the Scopus database for the whole preceding year, up to December 31, 2020. This search term included 'Binge eating', 'Binge-eating', 'Binge eating disorder', and 'Binge-eating disorder'. We used the keyword 'binge-eating' because we are concerned with binge-eating *per se* rather than related terminology. The search method for phrases relevant to binge-eating was confined to title alone to gain higher accuracy in the findings since when other search fields such as Abstract and Keywords were widened; numerous publications were found that were not connected to binge-eating ( *i.e.*, false-positive data). According to the researchers' experience[30-32], including search elements in the title rather than a topic search (title, abstract, and keywords) substantially improves specificity with minimal loss of sensitivity.

### Bibliometric indicators

Document types, yearly number of publications, author names, journal names, country names, institution names, funding agency names, and number of citations were included in the data exported from the Scopus. The impact index *per* article for the top ten most-cited publications based on RCA was calculated. RCA is an open, multidisciplinary citation analysis database owned by Baishideng Publishing Group Inc. (Pleasanton, CA 94566, United States)[33].

### Network visualization maps

The VOSviewer 1.6.17 software produced the network visualization map of the most frequent author, collaborative relationships between countries/regions, and the hotspots related to binge-eating research. The size of the nodes on the network visualization map is proportional to the number of occurrences, while the distance between words reflects the strength of the relationship between countries, authors, and terms, with a closer distance suggesting a stronger relationship[34].

### Ethical approval

Because all data were collected from previously published articles, there was no ethical approval requirement for this bibliometric study.

## RESULTS

### General description of the retrieved publications

The search strategy found 2713 total documents and an average of 62 documents *per* year. Among them, 'Article' represented 82.49% of the publications ($n$ = 2238 articles) and was the most frequent type,

followed by reviews (*n* = 243; 8.96%). The remaining publication types were 232 documents (8.54%).

### Annual growth of publications

The oldest paper was written by Wilson[35] in 1976 entitled 'Obesity, binge eating, and behavior therapy: Some clinical observations' in *Behavior Therapy*. After this, the number of publications grew slowly from 1976 to 1990, with little fluctuation. Figure 1 shows the publication trend related to BED from 1976 to 2020. Clearly, the number of relevant publications has increased sharply since 2011, while 2020 netted the largest amount of binge eating research (195 published documents).

### Active countries

One hundred and thirty-two countries contributed to binge eating research, with 1,495 (55.11%) articles published in the United States, followed by Italy with 256 (9.44%), the United Kingdom with 183 (6.75%), and Germany with 182 (6.71%) (Table 1). Figure 2 shows the collaboration of the international network. Countries with a minimum contribution of ten articles (*n* = 26) were included in the network. The map is divided into eight clusters of varying colors, each representing one of eight different cross-country network collaborations. The United States and Canada had the strongest cross-country collaboration, as indicated by the thickness of the connecting line.

### Active institutions

Table 2 lists the top ten core institutions publishing the most documents on the BED. The most active institutions in this field were those associated with American colleges. The top 10 active institutions contributed 835 articles (30.77%). Ten of the top active institutions were located in North America. *The Yale School of Medicine* came in first with 172 articles, followed by *Yale University* with 116, the *University of Minnesota Twin Cities* with 91, and the *Neuropsychiatric Research Institute, Fargo* with 85.

### Contributions of funding agencies

Table 3 includes the top ten core funding agencies with the most documents in the BED. Among them, nine agencies were from the United States, and one agency was from the United Kingdom. The *National Institutes of Health* came first, with 562 studies that the *Department of Health* supported. The *US Department of Health and Human Services* came second (*n* = 537). In contrast, the *National Institute of Diabetes and Digestive and Kidney Diseases* came third (*n* = 319), and the *National Institute of Mental Health* came fourth (*n* = 289).

### Active authors

The total number of authors who published on BED was 6223, of whom 40 (0.64%) published more than 20 documents for each author. Figure 3 shows the map of the co-authorship network of authors with at least ten publications. The authors with the largest node size contributed the most and included Grilo CM; Masheb RM; Mitchell JE; Crosby RD; White MA; McElroy SL; Crow SJ; Peterson CB; Wilfley DE; and Bulik CM.

### Active journals

Table 4 shows the top ten active journals for the literature related to BED. The *International Journal of Eating Disorders* (*n* = 398, 14.57%) was first ranked, followed by Eating *Behaviors* (*n* = 139, 5.12%), *Appetite* (*n* = 94, 3.46%), and the *European Eating Disorders Review* (*n* = 85; 3.13%).

### Citation analysis

According to citation analysis, the retrieved articles got 99491 citations, with an average of 36.7 *per* article and an h-index of 137. The number of citations ranged from 0 to 1454. Two hundred and fifty of the articles retrieved had zero citations, while 248 received 100 or more citations. The top 10 most-cited papers received 7126 citations in all. The total citations of these articles that quoted the research on BED research ranged from 458 to 1454 (Table 5). Furthermore, the ten most cited articles have an impact index *per* article of 0.7 to 64.4 (Table 5).

### Research themes

Three clusters emerged from the mapping of terms in the titles and abstracts of the retrieved literature, reflecting three major research themes in this field (Figure 4). The first group (blue) signifies a research theme on the management and treatment provided for BED (psychotherapy, CBT, interpersonal psychotherapy, and pharmacotherapy). The second cluster (green) is a research theme that focuses on processes and pathways to binge eating (dietary restriction theory, cognitive models of binge eating, cognitive behavior model of BED, and emotional regulation theory). Finally, the third theme (red) is the largest topic and discusses diagnosis, signs and symptoms, comorbidities, and prevalence and associated factors with BED.

**Table 1 List the top ten core countries publishing the most documents on binge-eating disorder**

| Ranking | Country | Number of documents | % |
|---|---|---|---|
| 1st | United States | 1495 | 55.11 |
| 2nd | Italy | 256 | 9.44 |
| 3rd | United Kingdom | 183 | 6.75 |
| 4th | Germany | 182 | 6.71 |
| 5th | Canada | 157 | 5.79 |
| 6th | Australia | 127 | 4.68 |
| 7th | Brazil | 101 | 3.72 |
| 8th | Spain | 59 | 2.17 |
| 9th | Switzerland | 58 | 2.14 |
| 10th | France | 57 | 2.10 |

**Table 2 List the top ten core institutions publishing the most documents on binge-eating disorder**

| Ranking | Institution | Country | *n* | % |
|---|---|---|---|---|
| 1st | *Yale School of Medicine* | United States | 172 | 6.34 |
| 2nd | *Yale University* | United States | 116 | 4.28 |
| 3rd | *University of Minnesota Twin Cities* | United States | 91 | 3.35 |
| 4th | *Neuropsychiatric Research Institute, Fargo* | United States | 85 | 3.13 |
| 5th | *The University of North Carolina at Chapel Hill* | United States | 70 | 2.58 |
| 6th | *Harvard Medical School* | United States | 67 | 2.47 |
| 7th | *University of Cincinnati College of Medicine* | United States | 65 | 2.40 |
| 8th | *Columbia University* | United States | 60 | 2.21 |
| 9th | *University of North Dakota* | United States | 56 | 2.06 |
| 10th | *Stanford University School of Medicine* | United States | 53 | 1.95 |

**Table 3 List the top ten core funding agencies that have the most documents on binge-eating disorder**

| Ranking | Funding agencies | Country | *n* | % |
|---|---|---|---|---|
| 1st | *National Institutes of Health* | United States | 562 | 20.72 |
| 2nd | *U.S. Department of Health and Human Services* | United States | 537 | 19.79 |
| 3rd | *National Institute of Diabetes and Digestive and Kidney Diseases* | United States | 319 | 11.76 |
| 4th | *National Institute of Mental Health* | United States | 289 | 10.65 |
| 5th | *National Institute on Drug Abuse* | United States | 71 | 2.62 |
| 6th | *Eunice Kennedy Shriver National Institute of Child Health and Human Development* | United States | 39 | 1.44 |
| 7th | *National Institute of Alcohol Abuse and Alcoholism* | United States | 36 | 1.33 |
| 8th | *Shire* | United Kingdom | 32 | 1.18 |
| 9th | *National Center for Advancing Translational Sciences* | United States | 31 | 1.14 |
| 9th | *National Institute of Heart, Lung, and Blood Institute* | United States | 31 | 1.14 |

## DISCUSSION

The present study used a bibliometric methodology to analyze global research publications on BED. In addition to reviewing current research on BED, this study identifies hot topics in this field and suggests future study options. The interest in global research in BED has increased significantly in recent years.

**Table 4 List the top ten core journals that have the most documents on binge-eating disorder**

| Ranking | Journal | *n* | % | IF[1] |
|---|---|---|---|---|
| 1st | *International Journal of Eating Disorders* | 398 | 14.67 | 3.668 |
| 2nd | *Eating Behaviors* | 139 | 5.12 | 2.156 |
| 3rd | *Appetite* | 94 | 3.46 | 3.608 |
| 4th | *European Eating Disorders Review* | 85 | 3.13 | 3.560 |
| 5th | *Eating and Weight Disorders* | 67 | 2.47 | 3.634 |
| 6th | *Behaviour Research and Therapy* | 48 | 1.77 | 4.500 |
| 7th | *Journal of Consulting and Clinical Psychology* | 45 | 1.66 | 4.632 |
| 8th | *Obesity* | 40 | 1.47 | 3.742 |
| 9th | *Comprehensive Psychiatry* | 35 | 1.29 | 2.567 |
| 10th | *Eating Disorders* | 33 | 1.22 | 2.013 |
| 10th | *Journal of Clinical Psychiatry* | 33 | 1.22 | 4.204 |
| 10th | *Physiology and Behavior* | 33 | 1.22 | 2.826 |
| 10th | *Psychiatry Research* | 33 | 1.22 | 2.118 |

[1]Impact factor (IF) from 2020 Journal Citation Reports (Clarivate Analytics).

**Table 5 List of the top 10 cited articles for studies related to binge-eating disorder**

| Ranking | Ref. | Year | Source title | Cited by | Impact index *per* article[1] |
|---|---|---|---|---|---|
| 1st | Heatherton and Baumeister[6] | 1991 | *Psychological Bulletin* | 1454 | 7.4 |
| 2nd | Gormally *et al*[6] | 1982 | *Addictive Behaviors* | 1292 | 29.1 |
| 3rd | Spitzer *et al*[6] | 1993 | *International Journal of Eating Disorders* | 686 | 17.2 |
| 4th | Spitzer *et al*[6] | 1992 | *International Journal of Eating Disorders* | 659 | 17.3 |
| 5th | Kessler *et al*[1] | 2013 | *Biological Psychiatry* | 602 | 64.4 |
| 6th | Stice *et al*[6] | 2002 | *Health Psychology* | 531 | 23.3 |
| 7th | Stice *et al*[6] | 2000 | *Psychological Assessment* | 506 | 0.7 |
| 8th | Telch *et al*[70] | 2001 | *Journal of Consulting and Clinical Psychology* | 473 | 19.4 |
| 9th | Halmi *et al*[7] | 1981 | *Psychological Medicine* | 465 | 34.2 |
| 10th | Fairburn *et al*[7] | 2000 | *Archives of General Psychiatry* | 458 | 16.7 |

[1]The impact index *per* article is presented based on Reference Citation Analysis [Source: Baishideng Publishing Group Inc. (Pleasanton, CA 94566, United States)].

Furthermore, it is clear that the output in this field has risen steadily as the risk of BED has been better understood. In addition, there is a shift from surgical to preventative techniques for BED management, including lifestyle interventions such as physical therapy or pharmacological treatment[36-40].

The United States, Italy, the United Kingdom, Germany, and Canada had the most binge eating research published in the literature, accounting for 83.8% of all publications in the study. Although no bibliometric study on BED has been published on BED, some studies have been conducted on nutrition research productivity in various fields[41,42], as measured by publications, and found that the United States, the United Kingdom, and Europe countries were the top producers of binge eating publications during this time. Eating disorders are more common in western societies than in non-western societies, although the incidence appears to be increasing[43,44]. Furthermore, the burden of eating disorders is likely to increase in low- and middle-income countries as they grow and experience cultural change [44]. As a result, the rising prevalence of eating disorders among Western cultures or in low- and middle-income countries and the scarcity of research documents published in these areas point to an urgent need for more research on this subject.

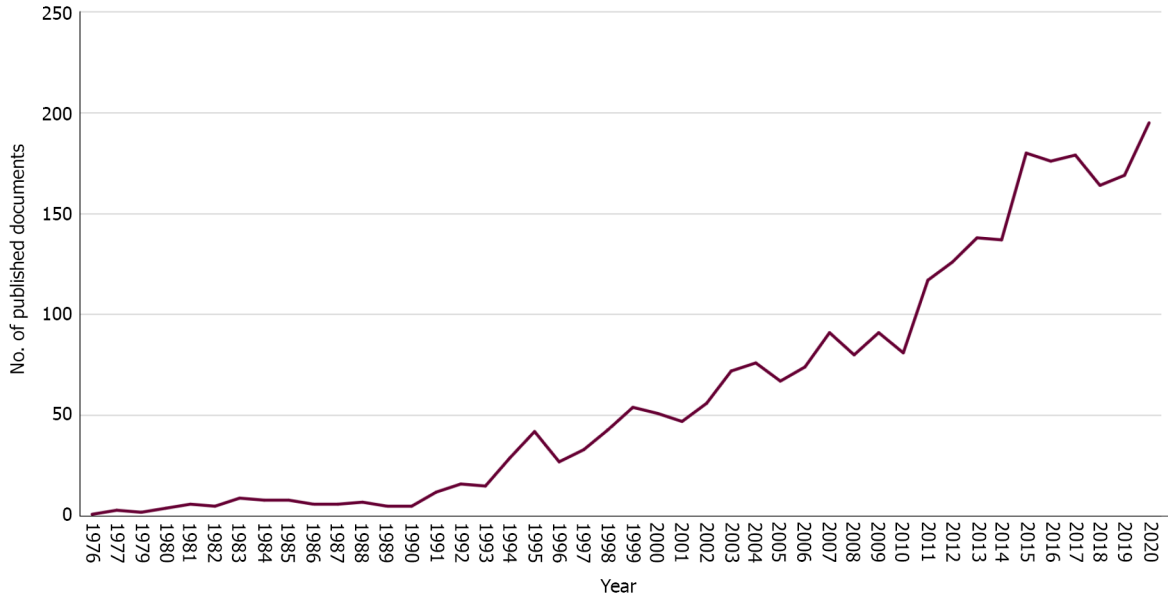


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**Figure 1 Annual growth of publications in the field of binge-eating.** The publication trend related to binge-eating disorder from 1976 to 2020. Clearly, the number of relevant publications has increased sharply since 2011, while 2020 netted the largest amount of binge eating research (195 published documents). There is zero publication in the year 1978.

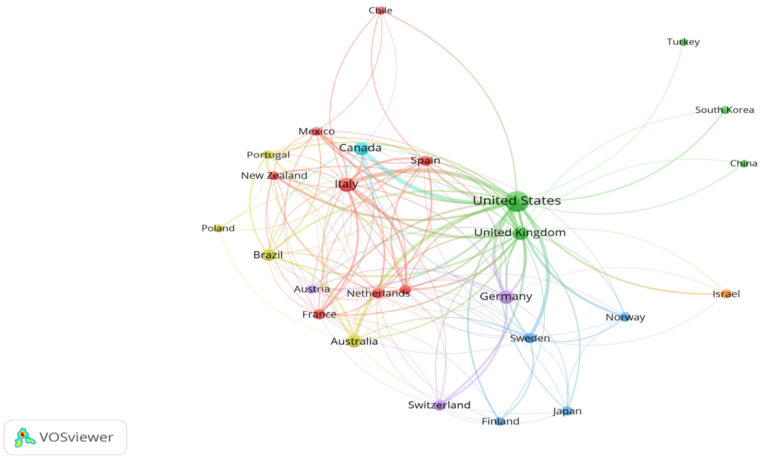


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**Figure 2 Network visualization map of country collaboration in the field of binge-eating with a minimum contribution of 10 documents *per* the country was set as a threshold (*n* = 26).**

Based on the analysis of terms and specific domains of research interest, three significant research themes were identified in binge-eating research. This study identified the terms most often used terms in the scientific literature and showed how they appeared in various publications. One of the main hot topics in the current study was the 'type of treatment and management provided for BED'. The most well-known psychotherapy treatment for BED is cognitive-behavioral therapy. In addition, interpersonal psychotherapy has been investigated as an alternative treatment for BED by targeting these individuals' social and interpersonal impairments[45]. BED's remission rates for the CBT and interpersonal psychotherapy have been higher than remission rates for anorexia nervosa and bulimia nervosa[46].

Other pharmacological treatment methods that are effective for BED include antidepressants, antiepileptic drugs, anti-obesity medications, and central nervous system stimulants. These treatments show modest short-term efficacy in reducing binge eating, and fewer eating compulsions without losing weight than patients experienced when using antidepressants, while topiramate showed a greater weight reduction[47]. However, the use of pharmacological treatment is limited due to potential adverse effects and harms, which are reported in 80% of studies and lead to higher rates of discontinuation[48].

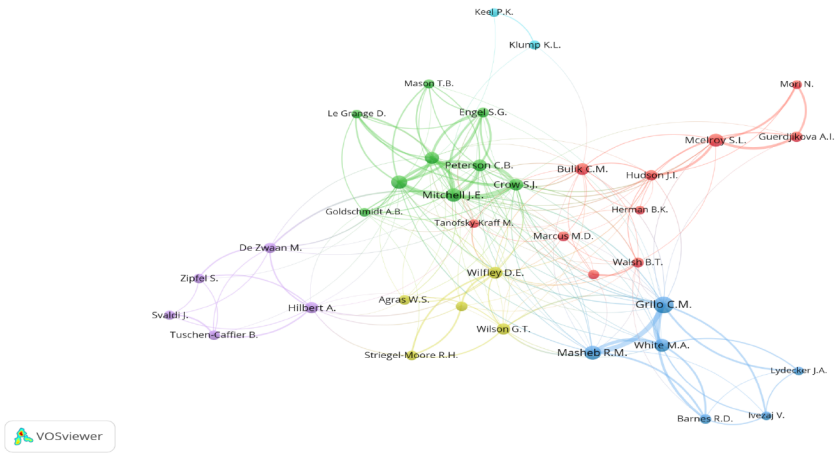


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**Figure 3 Network visualization map of authors in the field of binge-eating with a minimum contribution of 20 documents.**

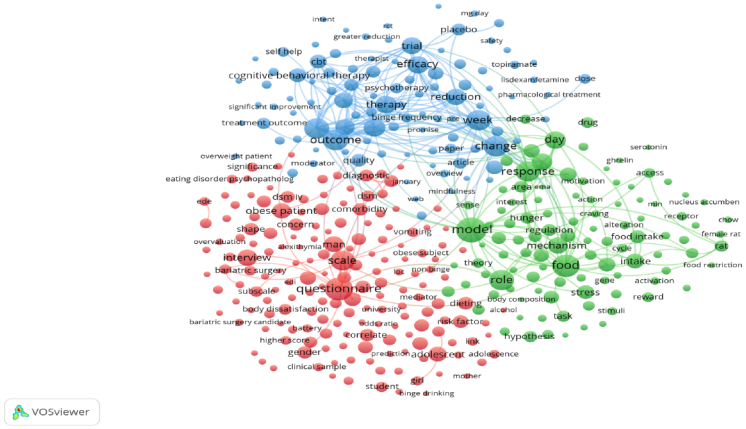


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**Figure 4 Network visualization map of terms related to the field of binge eating with minimum occurrence of 30 in the titles/abstracts of the retrieved publications.**

In 2015, the United States Food and Drug Administration approved lisdexamfetamine dimesylate (LDX) as the first and only drug for BED. LDX was previously approved as a central nervous system stimulant for treating Attention Deficit Hyperactivity Disorder and is now considered the only currently approved drug for BED[49].

Another subject that has received much attention has focused on processes and pathways to binge eating, including concepts related to dietary restriction theory, cognitive models of binge eating, the cognitive-behavioral model of BED, and emotional regulation theory. Most research on cognitive models of binge eating has concentrated on limiting or dieting behavior, negative affect, emotional control and behavioral dysregulation, preoccupations with body, shape, and weight, and low self-esteem[50,51]. Dietary restriction and body image or weight worries may cause the development and/or maintenance of binge eating behavior in certain people. However, for others, highly processed meals may induce neuroplastic changes in the brain, resulting in an addictive process[52]. Some theoretical advances have focused on investigating the persistence of beliefs or schemas that can contribute to the high rate of post-treatment relapse found in the binge eating group[53,54].

Another hot topic is the diagnosis, signs and symptoms, comorbidities, prevalence, and associated factors with BED. Furthermore, BED has a major burden on psychiatric and physical health[55]. Almost 80% of individuals with BED have suffered from mood disorders, such as major depressive disorder, anxiety, suicidal tendency, and bipolar disorder, as well as physical comorbidities, such as hypertension, obesity, chronic types of pain, and chronic diabetes[1,55,56].

Several studies estimate the prevalence, incidence, and sex differences in BED in adolescents and children and found that the prevalence rates are the same as those of adults and count between 1 and 3%, with almost double the number of girls compared to boys, which are similar to the results in adults [57]. Late adolescence to early adulthood was the age of onset of BED and is also associated with physical and psychological impairments[58]. BED was found to be strongly associated with diabetes

and metabolic syndrome. Furthermore, those with obesity and BED have a higher risk of respiratory and gastrointestinal diseases than those without obesity and BED[59]. This makes people with BED suffer from a lower quality of life-related to health[60,61].

Citation analysis is one of the most important ways to evaluate the influence or importance of a specific publication for some time or determine its level of recognition. The most cited articles can determine which study topic has received the most attention from the scientific community[62,63]. The findings of our analysis show that the most widely cited articles on BED focused on a number of subtopics in cooccurring terms that are close to the study hotspots, including "type of treatment and management provided to BED"; "processes and pathways to binge eating"; and "diagnosis, signs and symptoms, comorbidities and prevalence and associated factors with BED".

The most cited article was by Heatherton and Baumeister[64] and published in the *Psychological Bulletin*. This study put a hypothesis for BED to break away from self-awareness. Specifically, binge eaters tend to avoid the surrounding stimuli and significant ideas that will result in disinhibition of eating. The second most cited article was by Gormally *et al*[65] and published in *Addictive Behaviors*. Using two tools to assess binge eating among obese individuals, the study found a varied degree of binge disorder. It should be noted that those with severe binge eating were more likely to plan rigorous eating habits that are difficult to follow and maintain. The third most cited article was Spitzer *et al*[66], published in the *International Journal of Eating Disorders*. This study discussed the deep associations of certain characteristics with binge eating problems, including, but not limited to, the frailty of social and working life, inappropriate feelings toward body weight, and having psychological problems or substance abuse. The fourth most cited article was by Spitzer *et al*[67] and was published in *International Journal of Eating Disorders*. The researchers in this article have tested the criteria for the diagnosis of binge disorder. They found that this problem is prevalent in women and people who follow hospital weight control programs, and it was correlated with the degree of obesity of individuals. The fifth most cited article was by Kessler *et al*[1] and published in *Biological Psychiatry*. A public survey reported a prevalence of binge eating problems, which is slightly closer to bulimia nervosa. The binger begins in late adolescence, and its risk increases in females. However, the study identified the clinical value of asking patients about eating abnormalities.

The sixth most cited article was undertaken in 2002 by Stice *et al*[68]. This publication concluded a list of biological and psychological variables that predict BED. For example, the need to be thin, modeling of eating disorder, exaggerated appearance, body shape umbrage, depression, body weight, and low self-confidence were potential risk factors for binge eating. The seventh most cited article was published in 2000 by Stice *et al*[69]. This study established a self-diagnostic tool for binge eating problems, tested for reliability and validity, and showed acceptable levels for both tests. Consequently, the researchers recommend that this instrument be used clinically and for research purposes.

The eighth article most cited was the study by Telch *et al*'s using dialectical behavioral treatment in women with BED[70]. It found a great improvement in binge eating measures, and most of them curbed this diet problem compared to the control group. However, factors related to changes in mood and weight were not found to be significant. The ninth most cited article was carried out in 1981 by Halmi *et al*[71]. This research was conducted to characterize BED among college students. It was found that 13% of students had main symptoms of eating disorder, with the main skewed toward the female gender. Additionally, people with a history of increased weight were associated with symptoms of eating disorders. Lastly, the tenth most cited article was published in 2000 by Fairburn *et al*[72]. This article explained the natural sequence of BED in young women (aged 16 to 35 years) for five years. In general, a great improvement was initially observed, and then the improvement gradually became gradual. The percentage with any form of the clinical eating problem was decreased to 18% at the end of the study. However, the weight increased in thirty-nine percent of this population.

### *Strengths and limitations*

This is the first study to use bibliometrics to report and evaluate global trends in binge eating research. In addition, this study will assist researchers seeking to find hotspots and issues in need of investigation in this subject and those seeking to identify influential articles and the most prolific authors in this research niche. The present study has some limitations. Only one database (Scopus) was used to obtain bibliometric data; some binge-eating-related publications might have been missed. On the other hand, Scopus remains the finest accessible database for analyzing research activity and locating research hotspots on a certain topic. Another limitation is the possibility of errors in ranking institutions or authors due to differing spelling in various publications. Furthermore, publications that do not include the binge-eating term in the title might not be considered for our analysis. Despite these limitations, the findings of this investigation were sufficient to provide an accurate picture of the situation in binge-eating-related publications.

It's interesting and perhaps worthy of comment that there are few articles on the neurobiology or cognitive neuroscience of BED. This is truly a 'hot topic' in the field of eating disorders in general, and it is possible that less has been published on BED than on other eating disorders or that these types of articles are more often based on transdiagnostic dimensional features or underlying constructs (*i.e.*, RDoC) that do not map neatly onto diagnoses such as BED and would be detected by a methodology as that employed herein.

## CONCLUSION

This timely bibliometric review examines the findings of the BED, which could help advance the discipline and establish the basis for future research. Over the last decade, the amount of global research output on BED has expanded substantially, accounting for most publications in relevant journals. The United States and the United Kingdom have made significant contributions to the number of publications. Furthermore, research institutions from the United States have contributed to the centrality of publications. There are indeed relatively few publications on BED from low-and middle-income nations, so there is much to be learned from the experience of all countries.

Studies on this topic are critical in all countries to discover risk factors and effective intervention measures. Currently, the main hot topics related to BED are "type of treatment and management provided to BED"; "processes and pathways to binge eating"; and "diagnosis, signs and symptoms, comorbidities and prevalence and associated factors with BED". Although our findings are preliminary, they imply the future prospects to identify some of the currently most important categories of studies, such as randomized clinical trials.

## ARTICLE HIGHLIGHTS

### *Research background*

Binge-eating disorder (BED) is associated with various psychological and non-psychological issues that impair daily life to varying degrees, with a few severe impairments. Diabetes, obesity, chronic pain, and hypertension are some of its comorbid conditions.

### *Research motivation*

A growing body of evidence shows that the BED appears to impact human health significantly. We discovered some bibliometric publications on specific nutritional topics, but none on BED; thus, this article is novel in this field.

### *Research objectives*

This study aims to analyze research publications on the BED and identify global hotspots on this topic.

### *Research methods*

A comprehensive research technique was undertaken using the SciVerse Scopus database to meet the study's goal.

### *Research results*

This is the first bibliometric analysis of trends in BED publications. The interest in global research in BED has increased significantly in recent years. It is clear that the output in this field has risen steadily as the risk of BED has been better understood.

### *Research conclusions*

In conclusion, based on our timely examination and analysis of hotspots and research trends, we found that the main hot topics related to BED are "type of treatment and management provided to BED"; "processes and pathways to binge eating"; and "diagnosis, signs and symptoms, comorbidities and prevalence and associated factors with BED".

### *Research perspectives*

This study explores the global performance and advancement of BED research and maps the research patterns and trends using a visualization tool to fill this knowledge gap. In addition, a bibliometric analysis of prior articles could lay the groundwork for a full understanding of existing research on BED and indicate some potential future research subjects.

## FOOTNOTES

**Author contributions:** Zyoud SH conceptualized and designed the research project, took care of data management and analysis, generated figures, made significant contributions to the manuscript's existing literature search and interpretation of the manuscript, and drafted the manuscript; Shakhshir M, Abushanab AS, Al-Jabi SW, Jairoun AA, Shahwan M and Koni A were involved in the interpretation of the data, contributed to the manuscript writing, and made revisions to the initial draft; all authors provided a critical review and approved the final manuscript before submission.

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**S-Editor:** Fan JR
**L-Editor:** A
**P-Editor:** Fan JR

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LETTER TO THE EDITOR

# COVID-19 survivors: Multi-disciplinary efforts in psychiatry and medical humanities for long-term realignment

Henriette Löffler-Stastka, Monika Pietrzak-Franger

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## Abstract

The coronavirus disease 2019 pandemic represents an enduring transformation in health care and education with the advancement of smart universities, telehealth, adaptive research protocols, personalized medicine, and self-controlled or artificial intelligence-controlled learning. These changes, of course, also cover mental health and long-term realignment of coronavirus disease 2019 survivors. Fatigue or anxiety, as the most prominent psychiatric "long coronavirus disease 2019" symptoms, need a theory-based and empirically-sound procedure that would help us grasp the complexity of the condition in research and treatment. Considering the systemic character of the condition, such strategies have to take the whole individual and their sociocultural context into consideration. Still, at the moment, attempts to build an integrative framework for providing meaning and understanding for the patients of how to cope with anxiety when they are confronted with empirically reduced parameters (*e.g.*, severe acute respiratory syndrome coronavirus type 2) or biomarkers (*e.g.*, the FK506 binding protein 5) are rare. In this context, multidisciplinary efforts are necessary. We therefore join in a plea for an establishment of 'translational medical humanities' that would allow a more straightforward intervention of humanities (*e.g.*, the importance of the therapist variable, continuity, the social environment, *etc*) into the disciplinary, medial, political, and popular cultural debates around health, health-care provision, research (*e.g.*, computer scientists for simulation studies), and wellbeing.

**Key Words:** Long COVID; Resilience; Multi-disciplinarity; Medical Humanities; Psychiatric sequelae

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**Core Tip:** Recovery from coronavirus disease 2019 demands that multidisciplinary efforts be brought together to inquire, assess, and learn from various strategies of resilience we have witnessed in this context. Extant studies into individual, communal, and social-environmental aspects of (multisystemic) resilience can thus be expanded and validated; in effect, novel interventions may ensue.

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## TO THE EDITOR

We read with interest the narrative review by Putri C *et al*[1], who presented various biological factors contributing to psychiatric sequelae of coronavirus disease 2019 (COVID-19). We agree with the authors' insights concerning both the screening and the prevention of the COVID-19 psychiatric sequelae. They suggested such measures as music therapy, strengthening of social support, and self-management to foster resilience in long-COVID-19 patients. As a complement to this perspective, we would propose (following Wolf and Erdos[2]), a multidisciplinary patient-oriented approach that is directed towards a better (e-Health) infrastructure (including a precise, reliable data-protection-conform privacy framework[3]), investment in (digital) media literacy, and an emphasis on transcultural competence in doctor-patient communication.

The COVID-19 pandemic represents an enduring transformation in health care and education with the advancement of smart universities, telehealth, adaptive research protocols, personalized medicine, self-controlled or artificial intelligence-controlled learning, and flexible approaches to achieve solutions. But attempts to build an integrative framework for providing meaning and understanding for the patient when he or she is confronted with empirically reduced parameters or biomarkers are rare and are lacking in Putri *et al*[1]. A parallel development has spotlighted the role of multidisciplinary efforts, such as Medical/Health Humanities, in the understanding, learning, and overcoming the (psychological) effects of the pandemic. Kirsten Ostherr[4] has called for the establishment of 'translational medical humanities' that would allow a more straightforward intervention of humanities scholars into the disciplinary, medial, political, and popular-cultural debates around health, health-care provision, and wellbeing.

Understanding the factors contributing to resilience is key when designing interventions to support the improvement or development of resilience. Meta-analyses have shown that in longitudinal studies investigating protective factors in children exposed to traumata, the most robust factors were self-regulation, self-efficacy, and socioenvironmental support (supportive communities, family, peers, school). Investigations on resilience vis-à-vis adversary events show that mutual support and sharing capacity are based on social capital as a buffer to deal with poverty and vulnerability. However, when shocks are systemic or last longer, these traditional coping mechanisms fail, especially in households with low incomes or human resources. On an individual level, features associated with personality functioning have been shown to be very relevant. In medical doctors the personality traits associated with better resilience and well-being are maturity, taking responsibility, optimism, perseveration, and cooperation[5,6]. Hartmann's theory of different boundary types gives a way of understanding individual differences in terms of thick or thin boundaries (boundaries between inner and outer experience, past and present, and so on). Boundaries are necessary for well-being; what is even more important is an efficient management of these boundaries (self-regulation, self-awareness) dependent on the context and situation (responsibility of setting, maintaining professional boundaries). Acceptance of boundaries relies on a contented, sound development and is linked to psychic maturity with the establishment of a supporting balanced and trusting super-ego function. Epistemic trust[7] is established in early childhood together with secure attachment; shared knowledge is valued as "trustable." However, in cases of early adversity, credulity and mistrust may develop, with associations of insecure attachment, deficits in mentalizing, affect-, and self-regulation, unstable relationships, and poor resilience.

In order to establish resilience, in the psychiatric-psychotherapeutic relationship, empathy and adequate management of this relationship including authentic acknowledgement of biographically important relationship experiences are important for the outcome on an individual and group level. Further, clinicians' therapeutic attitudes affect regulation capacities and socialization correlated with relationship factors and therefore with the effectiveness of treatment[8]. Resilience depends on affect regulation abilities; resilient individuals recover from negative experiences by buffering against stress and distressing triggers with positive emotions (positive reappraisal, giving positive meaning, problem-focused coping, and so on). The pandemic has led to a variety of foundational transformations in the

very definition of mental health and mental disorder with a significant shift towards more liberal understandings of values implicated under COVID 19 (*e.g.*, values comprising coherence and quality of life). Social and environmental conditions[5] have to be taken into consideration in order to inquire into an individual's resilience, recovery, and containment possibilities. Putting the subject(ive)[9] more into the forth in the form of public-patient-involvement research designs and in the interdependence with the mentioned surrounding is of particular importance in understanding (psycho)pathoplastic dynamics. An integration of intrapersonal, interpersonal, and person-environmental dimensions of resilience on a personal, communal, and social-environmental level will lead to a more systemic approach doing justice to the dynamics of interactions with the outer world[10].

Consequently, as a way of establishing epistemic trust, it is necessary to focus on training programs for individuals and their microsystems. Interventions will have to be directed to the exo- and macrosystem and to formal and informal structures containing or indirectly influencing the target group (*e.g.*, people with mental health problems). Psychiatry has a long tradition in this field[11]. Instruments with known social impact like education and culture (music, art, poetry) should be applied based on the existing knowledge concerning the processes and contexts of resilience and individual and communal adaptability.

Against this backdrop, it is of importance to include Medical/Health Humanities in the discussion on resilience. With their "interdisciplinary, inclusive, applied, democratizing, and activist approach … in informing and transforming health care, health, and well-being"[12], Medical/Health Humanities have gone far beyond the concern with training medical practitioners by using arts and humanities. Instead, their proponents have asserted the complicated and not always linear or one-directional (expert – public) models of such application and have stressed the importance of bringing "the public to therapeutic uses of the arts and humanities"[12]. With these goals in mind, Medical/Health Humanities strive to emphasize "co-design, co-creativity, and co-learning"[12]. In view of these developments and vis-à-vis recent trends in Humanities, current tendencies in Medical/Health Humanities encompass a series of thematic, theoretical, and methodological innovations, all of which have received even a greater impetus from the pandemic. In this context, extant research into pandemic narratives, blame allocation strategies, discriminatory discourse, and resultant exacerbation of inequalities is central to future interventions.

Combining such multi- and transdisciplinary efforts is also helpful in a critical rethinking both of the positive (and negative) sides of the resilience in its individual, communal, and social-environmental levels as well as in tracing their dependencies with suggesting practical interventions.

## FOOTNOTES

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# Underlying reasons for the decline in physical activity during COVID-19

Yang-Fen Zhang, Li-Ke Qiu, Zhi-Peng Li, Lian-Ping He, Ling-Ling Zhou

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## Abstract

The article not only successfully evaluated regular physical activities can improve mental well-being during self-isolation and social distancing policies related to the coronavirus disease 2019 (COVID-19), but also concluded that the COVID-19 pandemic may lead to augmented levels of angiotensin-converting enzyme-2. By reading the article of Walid Kamal Abdelbasset, we have some questions and put forward some suggestions on the content of the article.

**Key Words:** Angiotensin-converting enzyme-2; COVID-19; Mental health; Physical activity

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**Core Tip:** During the coronavirus disease 2019, physical activity declined. There are many reasons behind this phenomenon. And the surveys in the article don't attach survey area. Additionally, the mutually affected relationship between physical activity and mental health is not clearly elaborated. The above are the areas that need to be improved in the article, and we also put forward some suggestions for improvement.

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## TO THE EDITOR

We were happy to read the ingenious article by Abdelbasset *et al*[1], in which they illustrated the effect of physical activity on mental well-being during the coronavirus

disease 2019 (COVID-19). The author not only elaborate the impact of physical activity on mental health through three sections: Mental health and community, neurological manifestations related to COVID-19, physical activity and mental health, but also conclude that the COVID-19 pandemic is correlated with angiotensin-converting enzyme-2, leading to related diseases. The article has had a significant impact on the current world that is still affected by the epidemic, but there are still some issues that need further consideration.

There are many reasons for the decline in physical activity from COVID-19. On the one hand, the COVID-19 itself can affect the body's metabolic process, directly causing musculoskeletal symptoms, such as muscle pain and numbness, and joint swelling and soreness[2]. On the other hand, the disease can affect the patient's respiratory system, digestive system and circulatory system and indirectly cause symptoms of physical decline. In the acute stage, patients often have respiratory symptoms such as dry cough and dyspnea, resulting in insufficient oxygen intake. At this time, patients often have fever symptoms. Fever will accelerate the body's metabolic process, thereby increasing oxygen consumption and further reducing blood oxygen content, and even acidosis may occur[3]. The patient is in such a state of oxygen imbalance that it is very easy for the patient to feel decreased physical strength or muscle weakness. Gastrointestinal symptoms can also occur in the acute phase, causing the patient to lose appetite. Studies have also shown that the COVID-19 may cause anosmia in patients[4]. In short, the effects of COVID-19 on patients with eating disorders will weaken the body's intake of food, thereby weakening the body's energy conversion. Without sufficient energy intake, patients often feel muscle soreness and weakness, because at this time the body has more the glycolysis pathway is used to generate adenosine-triphosphate, and the muscles use more creatine phosphate to maintain muscle activity[5]. The lactate and creatine phosphate metabolites produced by the glycolysis pathway take a longer time to complete metabolic consumption, so it accumulates in the muscles for a long time and causes muscle soreness. Therefore, we suggest that the authors supplement the reasons for the above-mentioned physical decline in order to make the theory of this review more complete and richer. What's more, not everyone's physical activity has decreased during the COVID-19 period, and some people are still able to maintain regular exercise as usual, which suggests that we need to think more deeply. During the period of the COVID-19, measures such as increasing people's ownership of sports equipment, developing interesting sports software or games, and converting ordinary sports into online sports competitions will greatly promote people's enthusiasm for physical exercise. This is something we should strive to do in the future.

In addition, the author detailed many surveys on the relationship between physical activity and mental health. However, the COVID-19 appeared in China and spread around the world, affecting populations worldwide and causing thousands of deaths[6,7]. If the survey area can be attached to the table, and if the survey areas are diverse and extensive, then it can highly increase the reliability of the results, as well as widen the applicability of the conclusions. Thus, we suggest that the author should include the survey area in the table, so that the results of each survey area can be clearly seen, and the conclusion that physical activity affects mental health can be more convincing and reliable.

One of the conclusions of the article is that exercise training for a long time does not indicate good mental well-being, but it may be a predictor of developing mood disorders[8]. But nothing is absolute, and so is the conclusion, which applies to people who are physically active for a long time, especially during lockdown periods when their need for exercise can not be met. The definition of prolonged exercise varies from person to person. Therefore, we suggest that the author should add a conditional supplement to this conclusion to increase the rigor of the article. It would be better if the author could give a general definition of exercise training for a long time in the article.

The terms exercise and physical activity are often used interchangeably, but by definition they are two different things. Physical activity is a process in which people use their skeletal muscles to consume energy to achieve human movement. Exercise is part of physical activity, and if someone runs once on a whim and then doesn't continue that activity, it's not exercise. Exercise is a subcategory of physical activity that is planned, structured, repetitive, and purposefully focused on improvement or maintenance of one or more components of physical fitness[9]. People who run in the park every morning, young people who play basketball two or three times a week, old women who dance in the square every evening, they have well integrated exercise into their lives. But not everyone can exercise consistently. Many people just do physical activity and call it exercise. This is the phenomenon of combining exercise and physical activity. Doing housework at home, walking, running and so on are just physical activities that are more common than exercise. In the future, provided that different levels of exercise are proposed to improve people's mental health, the distinction between physical activity and exercise should not be ignored.

Nevertheless, as the author wrote, anxiety and depression may lead to negative effects on various quality of life domains, such as being physically inactive[10]. This shows that not only does physical activity affect mental health, but mental health can also affect physical activity. In other words, physical activity and mental health are closely related and mutually affected.

## FOOTNOTES

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EDITORIAL

# Meeting employees where they are: The rise of workplace mental health services

Gaddy Noy, Ravi Navin Shah

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## Abstract

Many key organizations have called attention to the importance of addressing workplace mental health. In this Open Forum piece, two academic psychiatrists present recommendations from their experiences providing psychiatric care in a corporate setting. A literature review using the PubMed database was performed. The search found no peer review articles that discuss the topic of employer-sponsored mental health services outside of traditional employee assistant programs. Based on first-hand experience, the authors of this forum describe key issues and best practices to ensure employer-sponsored mental health services are a successful treatment for patients and mental health providers alike.

**Key Words:** Employer sponsored mental health; Employee mental health; Psychiatry; Corporate wellness; Workplace mental health; Mental health

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**Core Tip:** The importance of mental health has been ever present in our society and has been highlighted during the stress of the coronavirus disease 2019 pandemic. As corporations continue to recognize the value of a mentally healthier workforce for their employees, their business and their bottom line, it would behoove corporate business to implement embedded psychiatric services with integrated models and enhance the wellness of their community; providing easy access, affordable and timely mental health services. Our experience sheds light on the benefits these services can offer.

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## INTRODUCTION

Many key organizations, including the Centers for Disease Control, World Health Organization, and American Psychiatric Association have called attention to the importance of addressing workplace mental health[1-3]. Employers recognize the toll of mental illness on their employees (less productivity, increased absenteeism, increased substance use, increased medical comorbidities)[4]. As the idea that a mentally well workforce is good for the bottom line has gained more traction, a growing cadre of corporations are contracting with mental health companies like Modern Health (valued at > $1 billion), Lyra Health (valued at > $2 billion), Ginger (valued at > $1 billion), Spring Health (valued at $200-500 million), and others to provide mental health services directly on-site or *via* telehealth as an employee benefit[5]. These employer-sponsored mental health services create a platform in which corporations link employees to mental health providers (therapists and/or prescribers) *via* either employee assistance programs or in-network service providers.

## CONCLUSION

The importance of mental health has been ever present in our society and has been highlighted during the stress of the coronavirus disease 2019 pandemic. As corporations continue to recognize the value of a mentally healthier workforce for their employees, their business and their bottom line, it would behoove corporate business to implement embedded psychiatric services with integrated models and enhance the wellness of their community; providing easy access, affordable and timely mental health services. Our experience sheds light on the benefits these services can offer.

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*REVIEW*

# Does COVID-19 related symptomatology indicate a transdiagnostic neuropsychiatric disorder? - Multidisciplinary implications

Sari Goldstein Ferber, Gal Shoval, Gil Zalsman, Aron Weller

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## Abstract

The clinical presentation that emerges from the extensive coronavirus disease 2019 (COVID-19) mental health literature suggests high correlations among many conventional psychiatric diagnoses. Arguments against the use of multiple comorbidities for a single patient have been published long before the pandemic. Concurrently, diagnostic recommendations for use of transdiagnostic considerations for improved treatment have been also published in recent years. In this review, we pose the question of whether a transdiagnostic mental health disease, including psychiatric and neuropsychiatric symptomology, has emerged since the onset of the pandemic. There are many attempts to identify a syndrome related to the pandemic, but none of the validated scales is able to capture the entire psychiatric and neuropsychiatric clinical presentation in infected and non-infected individuals. These scales also only marginally touch the issue of etiology and prevalence. We suggest a working hypothesis termed Complex Stress Reaction Syndrome (CSRS) representing a global psychiatric reaction to the pandemic situation in the general population (Type A) and a neuropsychiatric reaction in infected individuals (Type B) which relates to neurocognitive and psychiatric features which are part (excluding systemic and metabolic dysfunctions) of the syndrome termed in the literature as long COVID. We base our propositions on multidisciplinary scientific data regarding mental health during the global pandemic situation and the effects of viral infection reviewed from Google Scholar and PubMed between February 1, 2022 and March 10, 2022. Search inclusion criteria were "mental health", "COVID-19" and "Long COVID", English

language and human studies only. We suggest that this more comprehensive way of understanding COVID-19 complex mental health reactions may promote better prevention and treatment and serve to guide implementation of recommended administrative regulations that were recently published by the World Psychiatric Association. This review may serve as a call for an international investigation of our working hypothesis.

**Key Words:** Mental health; Symptoms; Comorbidity; Long COVID; Fatigue; Transdiagnostic

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**Core Tip:** This Review asks a question shown in its title and hidden to date in the scientific literature on coronavirus disease 2019 (COVID-19) pandemic. It integrates the immense COVID-19 and long COVID literature on psychiatric and neuropsychiatric reactions to the pandemic in the general population. It also derives a working hypothesis on Type A and Type B of a hypothesized syndrome to be termed Complex Stress Reaction Syndrome. This working hypothesis is elaborated in the manuscript and supports the need to ask the transdiagnostic question in a timely manner based on a novel interdisciplinary and genuine integration of the relevant scientific literature.

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## INTRODUCTION

Since the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, increasing evidence revealed several psychiatric diagnoses suspected as being involved in the reaction of the general population to the pandemic and its related stressors. The majority of the studies investigated the comorbidity of depression and anxiety[1-4] and others added stress[5-9] and posttraumatic stress disorder (PTSD)[10-14]. However, many others found a significant incidence of other symptoms that are not clearly related to these comorbidities as outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and International Classification of Diseases (ICD-11): Latent infection phobia[15], OCD symptoms[16-19], somatization[20], health anxiety[19,21], internet gaming disorder[22,23], reports of repeated nightmares with virus-related narratives and intrusive thoughts, change in dream recall frequency[24], addictive social media use[25,26], thoughts of self-injury or suicide[27-31], emotional eating and binge eating[32], antisocial behavior, and substance abuse to relieve stress or boredom[33].

Thus, as the COVID-19 pandemic evolved, the psychiatric symptomatology reportedly progressed from single disorders to mixtures of diagnoses. These mixtures could be found even within the same patient, while a complex of symptoms derived from several diagnostic categories was found in many individuals[34-36]. This multiplicity of diagnoses is in accordance with the recent concern that multiple diagnoses are given to single patients and that the term "comorbidity" is excessively used, thus undermining treatment focus and prevention efforts[37].

A more accurate diagnosis could further reduce individual and organizational challenges, including, *e.g.*, the risk for stigmatization[38]. It is of relevance also that the World Psychiatric Association produced an ethical protocol aimed at treatment of psychiatric patients during the COVID-19 era. This protocol is relevant for new patients and those with previous psychiatric diagnoses and for both infected and non-infected people[39]. However, how can we apply administrative regulations and provide and allocate appropriate treatment without an available accurate diagnosis? If changes are recommended, research efforts for a valid diagnosis are warranted.

In this review, we ask whether a new mental health disease has emerged since the onset of the pandemic, if its main characteristic is its transdiagnostic feature of symptomatology, and whether this new suspected syndrome may be related to the neuropsychiatric manifestation included in the general term "Long COVID". This latter term contains neurological, psychiatric, and systemic symptoms in a manner which makes it difficult to differentiate for deriving appropriate treatment by different medical specialists.

An accurate diagnosis has always been the starting point for the development of appropriate psychotherapeutic and pharmacological treatments and for clinical trials examining their effectiveness. This developmental process within the professional field of psychiatry is expected to reach the identification of precise therapeutic components for further benefit of the diagnosed individuals. This potential for an

accurate diagnosis may also emerge as the initial stage for the implementation of new institutional regulations for in- and out-patients with psychiatric reactions to the pandemic and with residual syndromes of the infection. It must be noted that accurate diagnosis has been only recently recognized as a professional need[40].

## THE PSYCHIATRIC AND NEUROPSYCHIATRIC REACTIONS TO COVID-19 IN THE GENERAL POPULATION: AN INTERDISCIPLINARY APPROACH

### *The psychiatric COVID syndrome in the general population*

The psychiatric consequences of COVID-19 have been reported according to ICD or DSM illness codes in many studies to date. These studies have reported greater depression and anxiety levels compared to pre-pandemic prevalence of depressive- and anxiety-related syndromes[3,4]. Intolerance to uncertainty has been related to COVID-19 related anxieties due to the inherent uncertainty in the pandemic situation[41]. In addition, the literature reports on specific pandemic-related psychopathology. Several reports show that the severity of diverse symptoms across diagnostic categories are correlated during the pandemic and suggest that a link exists among these symptoms[17,42-45]. The reports of COVID-19 related symptoms evolved from single diagnostic categories to combinations of ICD-10 and DSM-5 diagnoses, often within a single patient, and altogether many individuals present a complex symptomatology across several diagnostic disorders[34-36]. The reports are worldwide and related to all ages, and includes even pregnant mothers[46].

Several tools have been suggested in the literature following investigation and validation for identifying a mental health disorder particular to the pandemic situation. Following research, construction, and validation of the COVID Stress Scales[47], Taylor *et al*[45] proposed COVID Stress Syndrome[45]. The main aspect of this syndrome is worry about the dangers of the pandemic with four additional concerns: (1) Worry regarding the impact of the pandemic on one's personal socioeconomic situation; (2) Xenophobic worries regarding spread of the virus; (3) Nightmares or intrusive thoughts related to COVID-19; and (4) Compulsive checking and reassurance seeking. These researchers have also described a second set of beliefs, termed COVID-19 Disregard Syndrome. It is centered around the conviction that the viral threat is exaggerated. This belief is associated with disregard for social distancing, poor hand hygiene, and anti-vaccination attitude, also termed as "pandemic related adjustment"[33,48]. Persian[49], Turkish[50], and Singaporean versions[51] added to the overall validation of the study in these cultures. Another transdiagnostic scale (containing 12 sub-scales) is the self-reported COVID-19 Pandemic Mental Health Questionnaire, which includes patterns of contamination anxiety, paranoid ideations, and several additional beliefs, behaviors, and sources of resilience[52]. The COV19-quality of life scale assesses quality of life regarding mental health[53]. The COVID-19 phobia scale measures "corona phobia"[15]. Multidimensional Assessment of COVID-19-Related Fears assess related concerns[54]. Another group has suggested two additional scales: The Coronavirus Anxiety Scale (CAS) and Fear of COVID-19 Scale[55-57]. This group demonstrated how the levels of anxiety and fear, measured by these scales, co-varied with gender, age, cohabitation status, educational levels, and the presence of positive cases or pandemic-related deaths. The CAS has been shown to have cross-cultural validity in 12 Latin American countries[58]. A different anxiety scale, validated in England, is the COVID-19 Anxiety Syndrome Scale[59]. In China, COVID-19 Related Psychological Distress has been assessed[60]. The COVID-19 Stressor Scale assesses stressor exposure and appraisal with demonstrated convergent and discriminant validity, from an online survey of a national sample ($n$ = 437) in the United States[61]. Combined scales for anxiety, depression and stress also exist. However, neither of these versions distinguished patients diagnosed with depression and anxiety from each other or from other psychiatric conditions when studied during the COVID-19 quarantine period in Saudi Arabia[62]. A Chinese distress scale (used in a nationwide survey) is the COVID-19 Peritraumatic Distress Index[63]. Another approach to studying trauma in COVID-19 is to use the Impact of Event Scale with modifications for COVID-19[64].

The COVID-19 literature indicates high correlations among several symptoms in a manner that shows that the architecture of the pandemic-related mental health reactions spans over the conventional DSM-5/ICD-11 criteria[8,65]. A recent narrative review of the psychometric qualities of scales noted that the heterogeneous and insufficient description of methods used to assess the psychometric characteristics of these scales may limit their usefulness for clinical and research purposes[66]. A systematic review focusing on the quality of data collection addressing 37 relevant mental health cross-sectional surveys of the general public (average sample size = 5137) noted a high risk of selection bias[67].

Regarding etiology, there are limited data and research. Most of the studies assumed that the COVID situation is combined from different stressors but have not shown the personality structure covariance with a specific stressor or more than one stressor. Recently it had been mentioned that the investigation of stressors is a challenge because of the independence between different stressors when they impact the elicitation of a syndrome and because of their dependency on premorbid psychiatric conditions and earlier predispositions of personality traits[61,68]. Therefore, to date, we still do not know in a causative manner if the COVID-19 situation is a global source for a new psychiatric disorder or a transient

stressful condition that should be dealt with from the level of personal coping perspective and coping accepted theories.

### *The neurological component of the COVID infection as a newly suspected mental health disease*

Another insufficiently studied issue is the mental health problems associated with the viral infection following recovery, often referred to as "long COVID". The syndrome recognized as "long COVID" has been described with heterogeneous symptomatology, including psychiatric, neurological, and systemic symptoms[69-73]. These symptoms include loss of smell and/or taste, fatigue, cough, aching pain, "brain fog", insomnia, shortness of breath, and tachycardia[74-78]. The prevalence of long COVID as found in modest and large samples is around 40% of recovering individuals with different manifestations and not necessarily with all symptoms in a patient[79]. A wide range of prevalence and of prevalence over time were reported for the different symptoms[74,80]. The syndrome has been recognized 12 wk to 6 mo following recovering from the acute COVID-19 infection[79,81].

The long COVID syndrome has been related to the identification of the COVID virus as a multi-organ infection with differential damages to each cell type in many organs[74,82,83]. The assumed underlying mechanisms are complex. They include dysregulation of mitochondria, which results in systemic decrease in metabolic activity and bioenergetics at the cellular level within the nervous system. The factors underlying brain fog may also produce additional pathogenic insults. It has been suggested that these pathological insults can progress to repetitive viral and bacterial propagation cycles[84]. The mental health symptoms have been suggested to be connected to increased susceptibility to infection due to a compromised immune system[84]. Others suggested a list of pathologies, *i.e.*, production of inflammatory cytokines, cellular damage, and pro-coagulant state that underlie long-lasting COVID-19 symptomatology[85].

We suggest that mental health problems following recovery from COVID-19 infection result directly from damage to redox and antioxidative defenses of the cell, as well as the neural basis for the fatigue manifestation, which has been identified as the most common symptom included in the long COVID term[79,86-90]. This fatigue may be the basis for the cognitive impairment reported too. We note that the psychiatric components of long-COVID may be secondary effects of the immense fatigue and neurological symptom's impact on emotional regulation and may not result from direct damage to neural cells. As there are conflicting results on the association of severity in the acute phase and the manifestation of long COVID syndrome, it is unclear whether there is one or more underlying mechanisms underlying this syndrome and whether there is a cascade of deteriorating effects of one or more cellular damages caused by the infection. There are only scarce research efforts to disentangle the long COVID syndrome from its psychiatric, neurological, and systemic components[28,82].

## COMPARISONS OF MENTAL HEALTH SYMPTOMATOLOGY BETWEEN INFECTED AND NON-INFECTED INDIVIDUALS: IS THERE A DIFFERENCE?

The pattern of findings appears mixed and inconsistent. While most studies reported more severe mental health disorders in infected compared to non-infected individuals, some studies did not reveal this pattern. Some representative findings from the majority of studies are as follows: (1) Prevalence of post-traumatic stress symptoms was more severe in COVID-19 survivors compared to healthy controls [91]; (2) Anxiety and depression were more prevalent in infected compared to non-infected people in a large Chinese sample[92]; (3) "Prevalence of stress, anxiety, depression, intrusion, hypervigilance, and avoidance among infected health care workers (HCWs) were significantly higher in comparison to non-infected HCWs"[93]; and (4) Suicidal ideation was more prevalent in infected *vs* non-infected individuals, in the United States[27]. Even months after recovery from the infection, depression, anxiety, and PTSD were prevalent[94]. In contrast, the prevalence of psychological distress among healthcare workers in Quebec was not associated with COVID infection status[95]. Furthermore, surprisingly, in a geriatric sample, the risk for depression symptoms was lower in infected (and recovering from COVID-19) individuals compared to non-infected controls[96]. A study using a different approach compared the transcriptome and data on immune factor transcription (from peripheral blood mononuclear cells) between infected patients and individuals with psychiatric disorders[97]. COVID-19 infected patients had a transcriptional profile prominently presenting inflammatory cytokine and interferon response genes, a profile fitting with a pro-inflammatory state. The authors also reported 39 dysregulated genes shared by COVID-19 and bipolar disorder, 22 shared with schizophrenia, and 19 with PTSD. The profile of the common genes is dominated by pro-inflammatory and cytokine factors. Finally, infected patients showed profiles of the peripheral (blood) immune system with considerable correspondence with those among the patients with the psychiatric conditions[97]. In a small sample of infected patients, a neuroradiological severity clinical index was correlated significantly with injury to the CNS (measures: Glial fibrillary acidic protein, total-tau, ubiquitin carboxyl-terminal hydrolase L1), and inflammation (C-reactive protein)[98]. A recent Cochrane review reported that stroke, paralysis, and altered mental status were the most frequent neurological disorders associated with COVID-19 infection[99]. The authors also suggested that COVID-19 could potentially induce new-onset of seizures, Guillain-Barre Syndrome,

encephalitis, and other neurological disorders. Additionally, in a large sample of infected individuals, in 55% of the people at least one neurological symptom was observed; the prevalence was greater in people with high body mass index and older age[100]. In this study, headaches and loss of smell and taste were prevalent, while seizures and stroke were the least common neurological symptoms.

We conclude the following two risks based on this mixed clinical picture as it arises from the extensive COVID literature: (1) The COVID-19 situation is a multiple stressor condition posing risks to mental health in the general population; and (2) Being infected poses an additional neuropsychiatric risk, implying that the two risks should be investigated and dealt with from psychiatric and neuropsychiatric perspectives for better diagnosis and treatment.

## THE COMPLEX STRESS REACTION SYNDROME (TYPE A AND TYPE B)

### *Diagnostic considerations*

COVID-19 has been shown to elicit transdiagnostic psychiatric symptomatology[65,101,102]. Beyond peripheral somatic effects, COVID-19 also affects the brain, as shown in neurocognitive impaired functions of recovering individuals. Therefore, we propose two sub-categories of this new perspective/syndrome. In principle, the two types are not mutually exclusive. Thus, we suggest including psychiatric and neuropsychiatric components in the newly suspected syndrome while excluding systemic and metabolic manifestations.

The first type is found in non-COVID-19 infected people, who present with psychopathology similar to that described above. We hypothesize that the etiology of this "Type A" follows exposure to pandemic stressors, including quarantine and social isolation, fear of infection, and both social and physical distancing. "Type B" is manifested in infected individuals. We suggest that it includes neurological and psychiatric characteristics which emerge from the resulting effects of the viral infection, *e.g.*, coagulopathy-related strokes and cranial nerve injury[103], and sensory impairment[104, 105]. It may be diagnosed as a part (excluding systemic and metabolic dysfunctions) of the heterogeneous syndrome, currently termed in the literature as long COVID.

It has been reported in a large sample ($n$ = 84285) of COVID-19 infection survivors that those chronic neurocognitive impairments persisted, even when gender, age, racial-ethnic group, income, education level, and previously experienced medical conditions were considered. This study supported the authors' conclusion that COVID-19-related symptoms are induced by the virus acting at multi-system levels, affecting the brain beyond the effects on other organs[106]. Bi-directional associations between psychiatric disorders and COVID-19 infection have been suggested, based on retrospective analysis of data from a large sample[107]. Specifically, survivors of COVID-19 infection presented an increased risk of psychiatric outcomes, and an existing psychiatric diagnosis was a risk factor for COVID-19 infection.

Thus, a clinical neurological evaluation is needed in addition to assessing psychopathology to provide a comprehensive clinical picture of COVID-19-related symptoms. The etiology of Type A is hypothesized to be linked to the multiplicity of COVID-19 situational stressors. The etiology of Type B is suggested to be mainly the consequence of the infection itself, including the neuropsychiatric effects of the virus. This approach may provide an overarching framework for future studies (see Figure 1).

### *Differential diagnosis*

In contrast to traditional diagnoses, mental disorders associated with COVID-19 are different as follows: (1) PTSD diagnosis includes exposure to a frightening stressor, resulting in nightmare and over-generalization to other situations. However, the COVID-19 reactions include extended exposure to complex stressors, diffused anxiety regarding infection and disease, without repeated nightmares, flashbacks or over-generalization as recently reported[47]; (2) Diagnosis of Adjustment Disorder rules out PTSD and bereavement, and it displays a short stressor to symptoms onset. In contrast, during COVID-19, several months may elapse before symptom onset; (3) Diagnosis of Acute Stress Disorder implies a simpler stressor and a specific symptom response. In contrast, the pandemic stressors and the pattern of response are complex, as detailed above; (4) Obsessional thoughts are ego-syntonic by definition. During the pandemic, fear of contamination and associated behaviors are justified by the objective situation (*e.g.*, need for masks, extra hygienic guidelines, social distancing); the behaviors related to these guidelines are clearly not part defined by Obsessive Compulsive Disorder; (5) The criteria for defining Generalized Anxiety Disorder list excessive worrying (on diverse issues) and shifting back and forth among them. In contrast, COVID-19-related mental health reports include anxiety that is clearly related to the several pandemic-relevant stressors[47]; and (6) The diagnosis of Major Depression Disorder includes anhedonia, low affect, psychomotor agitation, unfitting guilt feelings, diminished drive and energy, trouble concentrating, and indecisiveness. Some of these symptoms, along with others, are to be found in COVID-19-related mental health reports. Future studies should address all these issues.

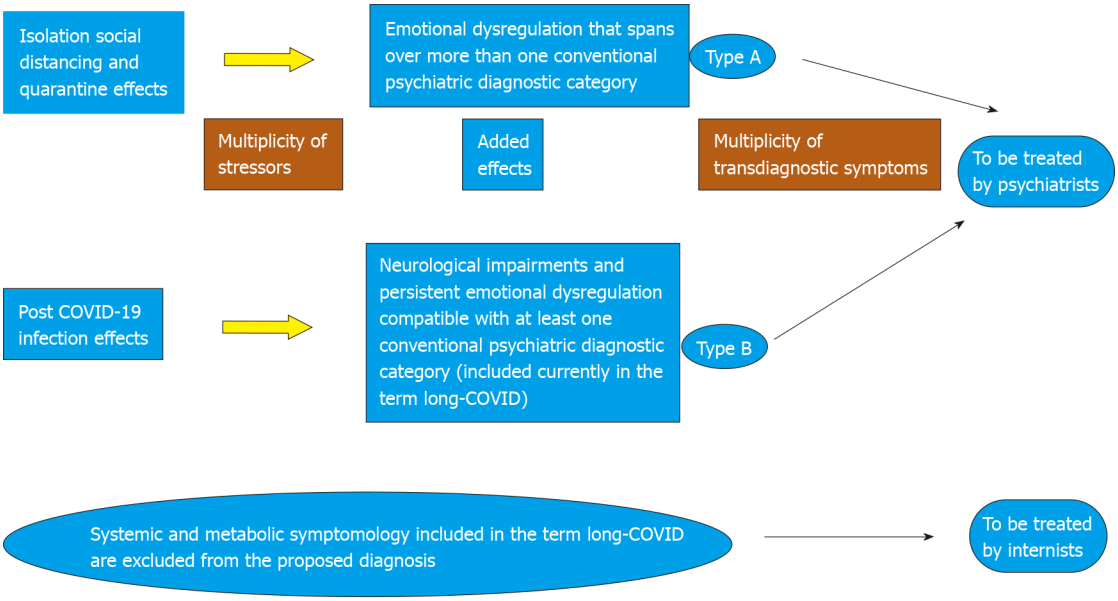


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**Figure 1 Outline of the Complex Stress Disorder Syndrome hypothesis and pathways for future treatment as a diagnosis-derived expected development.** COVID-19: Coronavirus disease 2019.

### *Life span considerations*

There is no agreement in the literature on the neuropsychiatric impacts of the pandemic on children, adolescents, and youth and especially on the prevalence of the post-infection syndrome termed long COVID[108-110]. According to available data, both psychiatric and neuropsychiatric effects are shown in young ages[110-112]. Regarding the elderly, a population with greater risk for infection and severe conditions, we suggest that premorbid psychiatric and neurological problems related to older ages may be involved in the older population's reactions to the pandemic. Some reports support our transdiagnostic CSRS understanding, even in elderly[74,113].

Therefore, further studies are warranted to evaluate the applicability of our working hypothesis across the life span. As an elaboration of our working hypothesis, we suggest that on the axis between Type A and Type B of the proposed diagnosis, Type A may be more prevalent in younger ages, Type B may be more prevalent in older ages, and the variability in the incidence of Type A, Type B or both together may be greater during adulthood than in younger or older ages.

## CONCLUSIONS

The clinical presentation of mental health symptomatology during the pandemic in infected and non-infected individuals implies many "comorbidities," *i.e.*, a transdiagnostic manifestation as arising from the literature. In the available diagnostic manuals, there are no transdiagnostic categories as yet, while the study of the mental health reactions to the pandemic shows such a pattern. Additionally, the suspected mental health disorder, as we suggest diagnosing it, implies the effect of multiplicity of co-occurring stressors, which result in a mixed clinical picture. Such a stress syndrome may be valid for post-pandemic days as well. Therefore, our outline for the suggested new diagnosis may be termed as CSRS, Type A, Type B. The validation of this hypothesis may relate the psychiatric and neuropsychiatric symptomatology to be treated by professional psychiatrists while other types of systemic and metabolic symptoms remain to be treated by internal medicine professionals (see Figure 1). This hypothesis has the potential to secure appropriate treatments for the suffering patients. This review may serve as a call for a meta-analysis and systematic reviews of the literature as well as for an international investigation of our working hypothesis.

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## FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

# Antidepressants combined with psychodrama improve the coping style and cognitive control network in patients with childhood trauma-associated major depressive disorder

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## Abstract

*BACKGROUND*

The use of antidepressant therapy alone has a limited efficacy in patients with childhood trauma-associated major depressive disorder (MDD). However, the effectiveness of antidepressant treatment combined with psychodrama in these patients is unclear.

*AIM*

To evaluate the effectiveness of antidepressant treatment combined with psychodrama.

*METHODS*

Patients with childhood trauma-associated MDD treated with antidepressants were randomly assigned to either the psychodrama intervention (observation group) or the general health education intervention (control group) and received combination treatment for 6 mo. The observation group received general health education given by the investigator together with the "semi-structured group intervention model" of Yi Shu psychodrama. A total of 46 patients were recruited, including 29 cases in the observation group and 17 cases in the control group. Symptoms of depression and anxiety as well as coping style and resting-state functional magnetic resonance imaging were assessed before and after the intervention.

*RESULTS*

Symptoms of depression and anxiety, measured by the Hamilton Depression Scale, Beck Depression Inventory, and Beck Anxiety Inventory, were reduced after the intervention in both groups of patients. The coping style of the observation group improved significantly in contrast to the control group, which did not. In addition, an interaction between treatment and time in the right superior parietal gyrus node was found. Furthermore, functional connectivity between the right superior parietal gyrus and left inferior frontal gyrus in the observation group increased after the intervention, while in the control group the connectivity decreased.

*CONCLUSION*

This study supports the use of combined treatment with antidepressants and psychodrama to improve the coping style of patients with childhood trauma-associated MDD. Functional connectivity between the superior parietal gyrus and inferior frontal gyrus was increased after this combined treatment. We speculate that psychodrama enhances the internal connectivity of the cognitive control network and corrects the negative attention bias of patients with childhood trauma-associated MDD. Elucidating the neurobiological features of patients with childhood trauma-associated MDD is important for the development of methods that can assist in early diagnosis and intervention.

**Key Words:** Major depressive disorder; Childhood trauma; Yi Shu psychodrama; Cognitive control network; Coping style

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**Core Tip:** Antidepressant therapy alone has limited efficacy in patients with childhood trauma-associated major depressive disorder. In our study, we treated patients with childhood trauma-associated major depressive disorder with antidepressants combined with psychodrama. After treatment, the internal connectivity of the cognitive control network increased in patients with childhood trauma-associated depression. Antidepressants combined with psychodrama were more effective in improving patients' coping styles and cognitive control network than combined with a general health education intervention.

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## INTRODUCTION

Major depressive disorder (MDD) is a common psychiatric condition and leads to significant physical, psychological, and economic distress in individuals, families, and society[1,2]. Traumatic experiences during childhood, as shown by a meta-analysis[3], are significant psychosocial risk factors for MDD, and their presence represents a major reason for the refractory and recurrent nature of depression[1,4,5]. Childhood trauma, also known as early life stress, early life adverse life events, childhood adversity, and early negative events, generally refers to a variety of adverse life events that occurred in childhood or adolescence that the child or adolescent was unable to cope with; these include experiences such as abuse, neglect, parental divorce, and parental death. In China, the depression associated with childhood trauma is estimated to be as high as 55.5%[6].

The psychologist A. T. Beck proposed a cognitive model of depression in which it was proposed that early negative events can lead to the formation of a negative cognitive schema and can thus have a significant impact on cognitive functions such as information processing, interpretation, attention, and memory[7]. Cognitive function plays an important role in coping with environmental changes and in guiding problem-solving, decision-making, and behavioral responses in new situations[8]. Therefore, the coping style can reflect the cognitive function of individuals to some extent. As a continuing stressor for the individual, childhood trauma may affect the coping style. Some studies have pointed out that depressed patients with childhood trauma have inappropriate coping styles[9]. Patients with depression were also found to pay more attention to negative stimuli when presented with external environmental stimuli such as visual space than patients without depression[10]. More attention to negative information may hinder the regulation of emotion and the use of positive coping strategies in patients

with depression[11]. Furthermore, depressed patients with a history of childhood trauma were more likely to pay attention to negative information (such as facial expression) than those without childhood trauma[12].

Resting-state functional magnetic resonance imaging (MRI) is helpful for researchers to understand the activity and neural functions of brain neurons. Functional connectivity (FC) is defined as the correlation between spatially nonadjacent brain regions in neurophysiological activities and is often used to evaluate information transmission by different brain regions[13]. Childhood is a critical period in human brain development[14], and the experience of childhood trauma may be sufficiently stressful to cause changes in both brain structure and function. Several studies have found that connectivity changes in the cognitive control network (CCN) may be the basis of cognitive impairment in patients with depression[15]. The CCN is located in the frontal and parietal lobes, primarily in the dorsolateral prefrontal cortex, dorsal anterior cingulate cortex, posterior parietal lobe, and posterior cingulate cortex [16]. It has been observed that compared with healthy controls, there was reduced internal connectivity in the CCN in patients with depression[17-19]. A study of multiple brain networks in patients with childhood trauma-associated MDD also found similar changes[20].

Antidepressants alone appear to have limited effectiveness in treating patients with depression resulting from childhood trauma. It has been found that psychotherapy is more effective in these patients compared with those without childhood trauma[21]. An intervention study on patients with chronic childhood traumatic depression found that the remission rate of clinical symptoms after treatment with antidepressants combined with psychotherapy was higher than that with antidepressants alone[22]. Brain imaging studies have pointed out that the internal connectivity of the CCN in patients with depression after receiving antidepressant medication is still lower than that in healthy controls[18,23]. However, the inferior frontal gyrus (IFG) connection in the CCN in depression patients increased after psychotherapy[24], which suggests that antidepressant therapy and psychotherapy may have different effects on the CCN in patients with depression. However, research on the effects of psychotherapy on CCN connectivity in patients with childhood trauma-associated MDD is limited.

At present, cognitive behavioral therapy (CBT) is the most effective form of psychotherapy for treating depression[25]. However, researchers have pointed out that because CBT is a psychotherapeutic model developed by A. T. Beck, an American psychologist, patients suffering from symptoms of depression from other cultures and non-English speaking countries may not be as responsive to CBT intervention[26].

Psychodrama is a type of group psychotherapy founded by J. L. Moreno, a psychiatrist and psychotherapist. Studies have shown that the symptoms of depression in patients were significantly improved after psychotherapy and that the levels of cortisol, a marker related to stress, were also significantly decreased. These findings suggest that psychodrama may significantly improve depression and effectively reduce the physical and mental distress caused by stressors[27].

The winner of the American Group Psychotherapy and Psychodrama Society's Lifetime Achievement Award, and trainer, educator, and practitioner certified by The American Board of Examiners in Psychodrama, Sociometry and Group Psychotherapy, Chinese-American Dr. Gong Shu integrated the five elements of Eastern philosophy, the psychological theory of traditional Chinese medicine, and the balance of Yin and Yang in Taoist culture with classic psychodrama and explored and developed Yi Shu psychodrama in line with Chinese culture. Patients have reported significant improvement and the relief of physical and emotional distress following the use of Yi Shu psychodrama, which healed both emotions and the body together[28].

We hypothesized that the combination of first-line antidepressants and psychodrama therapy, or general health education, would improve the clinical symptoms and coping styles of patients with childhood trauma-associated MDD. We also hypothesized that the internal connectivity of the CCN would be altered after the combination therapy. Therefore, MDD patients with childhood trauma were selected after taking first-line antidepressants in the acute phase (8 wk) treatment and randomly divided into two groups, namely the observation group in which antidepressants were combined with Yi Shu psychodrama and the control group in which antidepressants were combined with general health education. The effects on clinical symptoms, coping style, and the CCN were then observed. It is hoped that these findings will enrich empirical research on the clinical treatment of childhood traumatic depression and will provide scientific data for the specific application of psychodrama in clinical practice.

## MATERIALS AND METHODS

### *Participants and grouping*

Participants were recruited from the Department of Psychiatry outpatients in the First Affiliated Hospital of Chongqing Medical University from July 2017 to July 2019. Inclusion criteria: all participants were between the ages of 18 and 50, with a minimum of 9 years of education, right-handed, and had received only first-line antidepressants (selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors). The prospective participants received structured clinical

interviews with ICD-10 (International Classification of Diseases-10) conducted by two different licensed clinical psychologists who did not participate in the study. All the participants were required to meet the ICD-10 criteria for a current episode of MDD. According to the questionnaire survey of childhood trauma experience and standardized interview of childhood experience, the MDD patients should have had at least one experience of childhood trauma. Exclusion criteria: (1) MDD accompanied by severe physical diseases; (2) MDD accompanied by mental retardation or dementia, obvious psychotic symptoms, bipolar disorder, post-traumatic stress-related disorders, or severe personality disorders; (3) Patients with serious suicide risk and self-injury behavior within the previous 3 mo; (4) Patients addicted to alcohol or other substances; (5) Patients who had undergone major surgery, received electric shock, or transcranial magnetic therapy within the previous 3 mo; (6) Patients receiving other systematic psychotherapy at the same time; (7) Patients being treated with hormonal drugs; (8) Pregnant or lactating women; and (9) Patients with MRI taboos or claustrophobia.

The patients were divided into 2 groups using computer-generated random numbers: an observation group and a control group. Imaging data that could not be analyzed or the data of patients who were unwilling to participate in the intervention study or who had dropped out during the observation period were excluded. All patients provided written informed consent, and the study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

### Intervention process

**General health education:** During the 6-mo observation period, the investigator provided general health education to the control group through the distribution of the health manual for depression and providing and explaining information about depression either in the outpatient setting or on the phone.

**Psychodrama:** Yi Shu psychodrama intervention was conducted in small, closed groups (6-10 patients in each batch) in batches by Er-Dong Wang, who is a Clinical Practitioner certified by The American Board of Examiners in Psychodrama, Sociometry and Group Psychotherapy and was supervised by Dr. Gong Shu. The intervention frequency for each group was 4 d for each intervention, once every 2 mo for a total of three times lasting for 6 mo. There were several psychiatric medical staff who had been trained in psychodrama as professional auxiliary egos and could deal with possible clinical crises.

In this study, we applied the "semi-structured group intervention model" of Yi Shu psychodrama for depression (Figure 1). This included the three classic "structure" stages of psychodrama: the warm-up phase, the enactment/action phase, and the sharing/integration phase. The protagonist is allowed to go from the "now" back to the "past" to explore the influence of past experiences, then to return to the present to "integrate self" and experience the possibility of the future in surplus reality, and finally return to anchoring in the present.

Since the enrolled depression patients had all experienced childhood trauma, we added a stabilization process. The structural stabilization work was carried out during the half day at the beginning and the half day at the end, running through the whole process. In the warm-up phase, the use of music, dancing, painting, body feelings, and dreams, amongst others, assisted patients to become aware of implicit or body memories often associated with traumatic events. In the enactment or action phase, the impacts of traumatic events were explored, and the patients' negative cognition was corrected through typical psychodrama techniques such as role-playing, role reversal, double, mirroring, and soliloquy, amongst others. In addition, energy blockages in both the body and emotions were released simultaneously. In the sharing or integration phase, patients shared their own stories related to the protagonist during the psychodrama enactment.

### General information and assessment indicators

All subjects completed the Hamilton Depression Scale (HAMD-17), 13-item Beck Depression Inventory (BDI-13), 21-item Beck Anxiety Inventory (BAI-21), and Trait Coping Style Questionnaire (TCSQ) twice, at the beginning and at the end of the 6-mo observation period. In addition, the Childhood Trauma Questionnaire-Short Form was used to quantitatively assess the type and degree of childhood trauma. The sociodemographic information form was designed to acquire the patient's general information before the experiment. All the observation indicators are described below.

**Sociodemographic information form:** This part of the questionnaire contained general information on the participant's age, sex, years of education, and the types of antidepressants taken.

**Childhood Trauma Questionnaire-Short Form:** The Childhood Trauma Questionnaire-Short Form, with modifications by Bernstein *et al*[29] in 2003 was used; this has validity in diverse clinical and nonreferred populations. This questionnaire has a total of 28 items (25 items plus the 3-item validity scale) and divides childhood trauma into five dimensions: emotional neglect, physical neglect, sexual abuse, emotional abuse, and physical abuse. The internal consistency coefficient of the questionnaire was 0.73.

**HAMD-17:** The HAMD-17 was used to evaluate the severity of depressive symptoms. Two psychiatrists or postgraduates who had received consistent training were given HAMD joint examinations, and the prescribed guidelines were used at the same time. After the examination, the scores were determined by

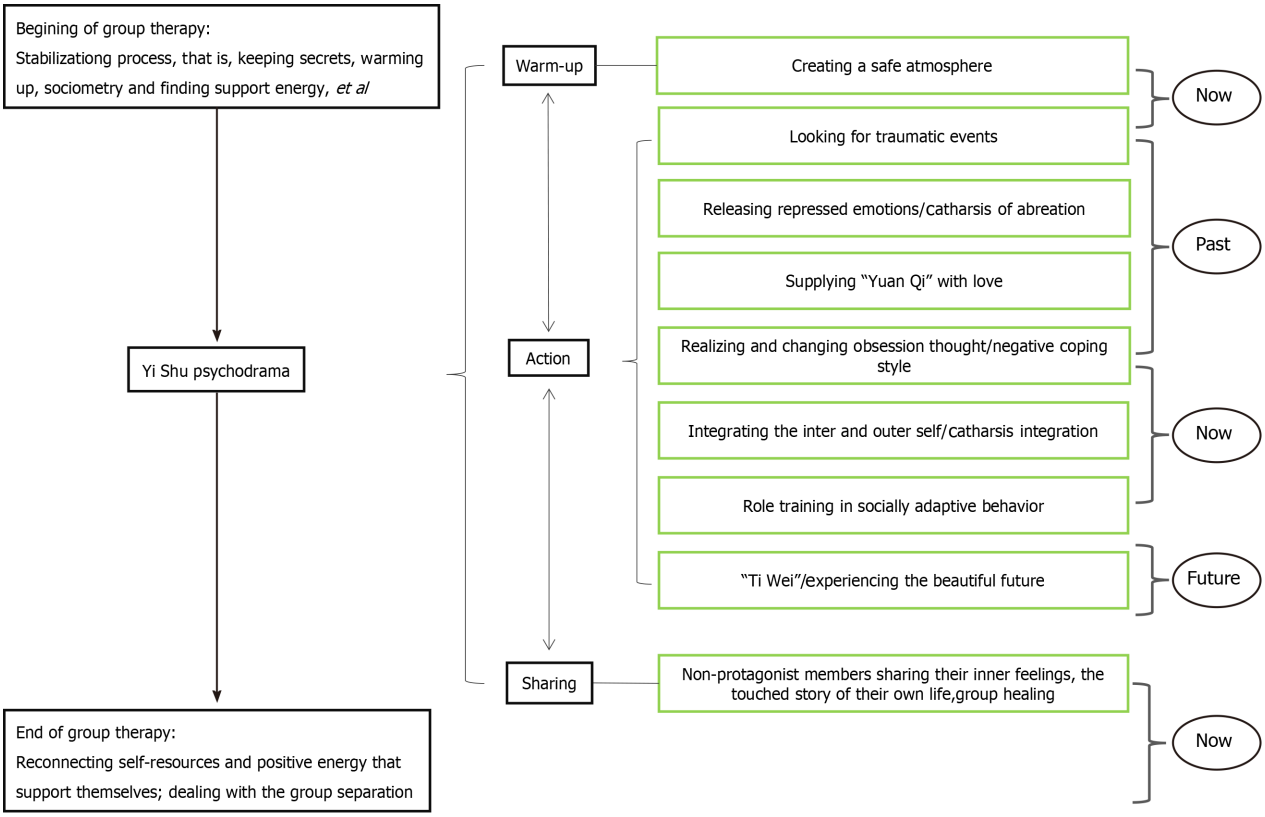


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**Figure 1 Model of Yi Shu psychodrama for patients with major depressive disorder.**

two independent examiners who were unaware of the grouping of the patients to avoid subjective scoring. This questionnaire has passed the reliability and validity tests in China, and its internal consistency coefficient was 0.714. The total score for no depression was 0-7, and the total score for mild depression was 8-17. Patients with moderate depression scored between 18 and 24, and patients with severe depression scored over 25. Reductions in the HAMD-17 score of ≥ 75% or a total score of ≤ 7 points after the intervention indicated significant effectiveness. A HAMD-17 score reduction rate ≥ 50% was defined as effective, a 25% ≤ score reduction rate < 50% was defined as improvement, and a score reduction rate < 25% was defined as invalid.

**BDI-13:** The degree of depression of the patients was assessed at the same time by the BDI-13, which was translated into Chinese. The questionnaire had passed the Chinese test of reliability and validity, and its internal consistency coefficient was 0.86. Each item of the BDI-13 was rated as 0-3, with a total score of 0-4 for no depression, 5-7 for mild depression, 8-15 for moderate depression, and more than 16 for severe depression.

**BAI-21:** The degree of anxiety was assessed by the BAI-21. Each item was scored by 1-4 grades. The higher the total score, the more serious the anxiety level of the patients. The internal consistency coefficient of the questionnaire was 0.95.

**TCSQ:** The TCSQ for Chinese was used for direct measurement of coping style and indirect assessment of cognitive schema. This questionnaire includes two dimensions of positive and negative coping. Each dimension comprised 10 items, with the score of each item ranging from 1 (absolutely no) to 5 (absolutely yes). The higher the score on a given subscale, the more an individual tends to adopt the respective coping style. The validity and reliability of the TCSQ have been established, and the Cronbach's alpha coefficients for positive coping and negative coping were 0.790 and 0.776, respectively [30,31].

### *Data collection and analysis*

**Questionnaire data acquisition and analysis:** The subjects completed the questionnaires online through the QuestionStar Internet platform (https://www.wjx.cn/) by scanning a two-dimensional code before and after the intervention. The researchers confirmed the submissions immediately and evaluated the questionnaire results in the background on the same day. SPSS 25.0 was used to process and analyze the questionnaire data. The *t* test was used for normally distributed measurement data, and the results were

expressed as mean ± standard deviation. Nonparametric tests were used to compare measurement data that did not conform to the normal distribution, and the results were expressed by *M* (Q). The count data were compared by the $\chi^2$ test, and the results were expressed as percentages.

**MRI data acquisition:** All imaging data (baseline and after intervention) were acquired using a Signa 3.0 Tesla MRI system (GE Medical Systems, Waukesha, WI, United States) at the First Affiliated Hospital of Chongqing Medical University. At the baseline scan, T1-weighted and BOLD data were collected. In addition, T2-Flair image data of all the participants were also collected at the baseline scan because if any brain illnesses were found the participant would be removed from the study and examined by the Neurology Department. Both the T1-weighted and BOLD scan sequences were described in our previous article[32]. Participants were instructed to keep their eyes closed but be awake during the scan, and head motion during scanning was restricted by restraining the head using foam pads inserted on each side.

**Resting-state functional MRI data preprocessing:** The resting-state functional MRI data preprocessing were carried out using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) and the GRETNA toolbox[33] (http://www.nitrc.org/projects/gretna/), which are based on MATLAB. The first 10 volumes were excluded, and the remaining 230 volumes were corrected for head motion. In this step, the middle slice was used as the reference slice. If the participant's head motion exceeded 3 mm in distance or a 3° angle during scanning, whether at baseline or after the intervention, all the patient's data were excluded. Individual 4D volumes were then spatially normalized to the Montreal Neurological Institute space, retaining a voxel of size 3 mm× 3 mm× 3 mm (originally acquired at 3.75 mm× 3.75 mm× 3.75 mm), using diffeomorphic anatomical registration through exponentiated lie algebra[34] and were then spatially smoothed with a 6-mm full width at half-maximum Gaussian kernel. It is worth mentioning that a smooth step only exists in the preprocessing step of voxel-wise functional connection analysis based on the node efficiency result. Next, linear trends were removed to account for scanner drift, and temporal band-pass filtering (0.01–0.1 Hz) was performed. Finally, multiple linear regression was performed on the Friston-24 parameters of head motion[35] and the signals of the white matter and cerebrospinal fluid.

**Functional brain network construction and node efficiency analysis:** All networks are composed of nodes and connected edges. In the functional brain network, nodes refer to the brain regions with internal consistency and external independence, and the edge connection between nodes can be regarded as the temporal behavioral consistency between the two spatially independent nodes. From a statistical point of view, the meaning of the edge is statistically dependent on the time series of two brain regions.

In this study, we constructed a functional brain network for each subject according to the automated anatomical labeling template[36] that divides the brain into 90 anatomical regions, with each region defined as a node. Then, positive Pearson's correlation coefficients between the time series of two nodes (xi, xj) were computed as the edges to produce a 90 × 90 correlation matrix for each subject.

Then, the correlation matrix was transformed into a binary matrix according to the preset threshold value, that is, when Rij is greater than the threshold value, the corresponding element of the binary matrix is 1; otherwise it is 0. In this study, sparsity was used to set a series of continuous thresholds to construct a brain network in a threshold space. Sparsity is defined as the ratio of the number of edges in the network to the maximum number of edges that may exist in the network. The sparsity range in this study was $S \in (0.01, 0.5)$. Within this range, binary brain networks for all subjects were constructed under all sparsity degrees with a step size of 0.1.

When the brain network is constructed, the node efficiency of each node in each sample under all selected thresholds is calculated. In this case, a graph of node efficiency can be constructed for each node, and the area under the curve can be calculated to characterize the overall characteristics of node efficiency within the selected threshold. The area under the curve was used in the subsequent statistical analysis.

Statistical analysis using the MATLAB statistical toolkit, NBS statistical method[37], and repeated measurement analysis of variance was carried out on the node efficiency area under the curves of 90 nodes in the two groups of patients. The results were not corrected by multiple comparisons, and the significance level was set as 0.001.

**Functional connection analysis based on node efficiency result:** Based on the results of node efficiency, the brain regions of the two groups with node efficiency interacting with treatment and time were selected as seed points for voxel-wise FC analysis of the whole brain. SPM was used for statistical analysis and flexible design was used for treatment time interaction analysis. SPSS was used for *t* tests, covariate regression was used for sex and age, and multiple comparison correction was performed by Gaussian random field correction with a voxel level of 0.001 and a mass level of 0.05.

## RESULTS

### Comparative results of demographic information

Both questionnaire and MRI data, before and after the intervention, were collected from 46 subjects between July 2017 and July 2019. There were 29 cases in the observation group and 17 cases in the control group (complete questionnaire and MRI data were collected from 33 cases in the observation group, with 4 cases dropping out, and from 27 cases in the control group, with 10 cases dropping out). There were no statistically significant differences between the two groups of patients in terms of demographics and medication information ($P > 0.05$) (Table 1).

### Changes in the clinical and psychological questionnaire information after intervention

**Comparison of the clinical efficacy of two intervention methods:** The $\chi^2$ test was used to analyze the clinical efficacy of HAMD-17 between the two groups. In the observation group, the number of significantly effective scores was 23 (79.31%), the number of effective scores was 1 (3.45%), and there were 2 improvements (6.90%). In the control group, the number of significantly effective scores was 12 (70.59%), with 2 effective (11.76%) and 3 improvements (5.89%). No significant differences in clinical efficacy were observed between the two groups ($P > 0.05$) (Table 2).

**Comparison of HAMD, BDI, BAI, and coping style scores before and after interventions:** The HAMD, BDI, BAI, positive coping style, and negative coping style scores were analyzed by the generalized estimation equation. There were statistically significant differences in the time effect and interaction effect on HAMD, BDI, and BAI between the two groups ($P < 0.01$). There were also statistically significant differences in the between-group effects, time effect, and interaction effect between the two groups of patients in the positive coping style and negative coping style ($P < 0.05$) (Table 3).

**Simple effect analysis of HAMD, BDI, BAI, and coping style scores before and after interventions:** We conducted a further analysis based on the results shown in Table 3. The HAMD, BDI, BAI, positive coping style, and negative coping style scores between and within the two groups were tested by independent-sample *t* tests or Mann Whitney *U* tests with two independent samples and paired-sample *t* tests. There were no significant differences in the baseline scores of each scale between the two groups before the intervention ($P > 0.05$). After the intervention, while there were no significant differences in the HAMD, BDI, and BAI scores between the two groups ($P > 0.05$), the score for positive coping style in the observation group was significantly higher than that in the control group ($P < 0.05$), and the score for negative coping style in the observation group was significantly lower than that in the control group ($P < 0.01$). The HAMD, BDI, BAI, and negative coping style scores in the observation group were significantly lower than those before the intervention ($P < 0.01$), while the scores for positive coping style were significantly increased ($P < 0.01$). The HAMD, BDI, and BAI scores in the control group after intervention were lower than those before intervention ($P < 0.05$), while the scores for positive coping style and negative coping style were not statistically significant ($P > 0.05$) (Table 4).

### The results of node efficiency and FC

The results of this part of the study found that only the node efficiency of the right superior parietal gyrus (SPG) in brain area 60 showed an interaction between treatment and time (Figure 2). It was found that the node efficiency of brain area No. 60 increased after intervention in the observation group and decreased in the control group.

Based on these results, brain area No. 60 was subsequently used as a seed point to conduct a whole-brain voxel-wise FC connection analysis. The results showed that after the intervention, the change in the FC strength of a mass in the right SPG and the left IFG was associated with a significant interaction between treatment and time. Further post-examination analysis found that compared with before the intervention the connection between the right SPG and the left IFG of the observation group was enhanced after the intervention, while the connection in the control group was weakened (Table 5, Figure 3).

## DISCUSSION

Emotional and physical neglect account for a high proportion of childhood traumatic experiences in MDD patients[6]. Chinese parents have paid a great deal of attention to education over the past 40 years, with many Chinese parents pushing their children to study hard and succeed to the possible detriment of the children's emotional and physical well-being. Both emotional and physical neglect can play significant roles in the development of depression. Depressive patients who have experienced childhood trauma often have negative coping styles[9], an aspect that should receive more attention in psychological intervention.

We found that while both interventions produced similar clinical effects in decreasing the levels of depression and anxiety among patients diagnosed with MDD with childhood trauma, the combination

**Table 1 Baseline demographic comparison between the two groups**

| Item | Observation group, *n* = 29 | Control group, *n* = 17 | $t/\chi^2$ | *P* value |
|---|---|---|---|---|
| Age, yr | 25.970 ± 7.189 | 28.120 ± 6.214 | -1.029 | 0.309 |
| Sex, F/M | | | 0.405 | 0.525 |
| Female | 22 (76) | 15 (88) | | |
| Male | 7 (24) | 2 (12) | | |
| Education, yr | 15.030 ± 2.179 | 13.710 ± 2.443 | 1.909 | 0.063 |
| Med, SSRIs/SNRI | | | 0.423 | 0.515 |
| SSRIs | 24 (83) | 16 (94) | | |
| SNRI | 5 (17) | 1 (6) | | |
| CTQ | 50.210 ± 9.715 | 48.880 ± 8.908 | 0.460 | 0.648 |

Data are mean ± SD or *n* (%). Due to rounding, the total % might be more than 100%. SSRIs: Selective serotonin reuptake inhibitors; SNRI: Serotonin noradrenaline reuptake inhibitors; CTQ: Childhood Trauma Questionnaire; F: Female; M: Male.

**Table 2 Comparison of clinical efficacy between the two groups**

| Item | Total cases | General improvement | Invalid |
|---|---|---|---|
| Observation group | 29 | 26 (89.66) | 3 (10.34) |
| Control group | 17 | 15 (88.24) | 2 (11.76) |
| $\chi^2$ | | | 0.022 |
| *P* value | | | 0.881 |

Data are *n* (%). Due to rounding, the total % might be more than 100%.

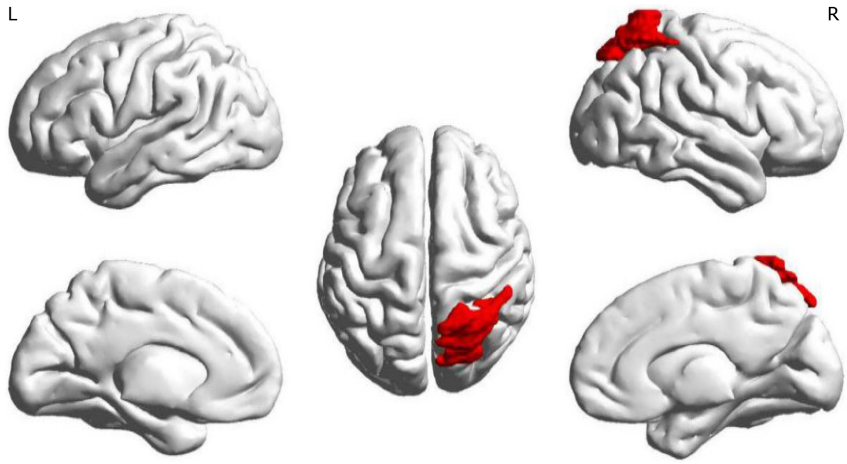


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**Figure 2 Location of brain regions with interactions of node efficiency.** The red brain area marked in the figure is the right superior parietal gyrus, the brain region where the node efficiency interacts after intervention in the two groups.

of first-line antidepressants and psychodrama was found to be more effective than that of the combination of first-line antidepressants and general health education in reducing the passive coping styles and enhancing the positive coping styles of patients, which is similar to the conclusion of Stanisławski's study[38]. Other studies have also found that positive support can reduce the impact of childhood traumatic experiences on depressive symptoms[39]. Perceived social support has been identified as a classic coping strategy[9]; however, it has been observed that individuals with childhood trauma have difficulty seeking support[40]. Furthermore, depressed patients' disproportionate preferences for negative information has been found to affect their coping strategies[11].

**Table 3 Comparison of the scores of each scale between the two groups before and after the intervention**

| Item | Group | Pre-intervention | Post-intervention | Wald $\chi^2$ | | |
|---|---|---|---|---|---|---|
| | | | | Between-group effect | Time effect | Interaction effect |
| HAMD | Observation group | 19.690 ± 6.887 | 6.240 ± 7.342 | 0.000 | 125.683[b] | 137.316[b] |
| | Control group | 18.410 ± 9.625 | 7.590 ± 7.246 | | | |
| BDI | Observation group | 14.000 ± 5.898 | 4.480 ± 5.096 | 0.004 | 97.162[b] | 105.231[b] |
| | Control group | 13.120 ± 8.455 | 5.590 ± 5.269 | | | |
| BAI | Observation group | 38.380 ± 10.584 | 31.100 ± 9.828 | 0.142 | 19.415[b] | 20.096[b] |
| | Control group | 36.350 ± 8.536 | 31.290 ± 9.225 | | | |
| P-coping style | Observation group | 22.000 ± 5.988 | 26.790 ± 7.379 | 3.898[a] | 8.635[b] | 12.891[b] |
| | Control group | 20.760 ± 5.663 | 21.650 ± 6.800 | | | |
| N-coping style | Observation group | 32.030 ± 7.580 | 22.140 ± 4.875 | 4.017[a] | 18.020[b] | 60.931[b] |
| | Control group | 30.350 ± 8.775 | 31.240 ± 7.164 | | | |

[a]$P < 0.05$.
[b]$P < 0.01$.
Data are mean ± SD or *n* (%). Due to rounding, total % might be more than 100%. HAMD: Hamilton Depression Scale; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; P-coping style: Positive coping style; N-coping style: Negative coping style.

**Table 4 Simple effect analysis of each scale in two groups before and after intervention**

| Item | Comparison between the two groups before intervention | Comparison between the two groups after intervention | Comparison of before and after intervention in the observation group | Comparison of before and after intervention in the control group |
|---|---|---|---|---|
| HAMD | 0.523 | -0.481 | -8.985[b] | -6.614[a] |
| BDI | 0.416 | -0.586 | -8.453[b] | -5.035[b] |
| BAI | 0.671 | -0.114 | -3.517[b] | -2.619[a] |
| P-coping style | 0.689 | -2.211[a] | 3.003[b] | 0.642 |
| N-coping style | 0.685 | -5.124[b] | -6.744[b] | 0.436 |

[a]$P < 0.05$.
[b]$P < 0.01$.
The value in the table is the statistical value *t*/*Z* (where *t* is the *t*-value of the test two independent samples or paired-samples *t* test and *Z* is the statistical value of the Mann-Whitney *U* test). HAMD: Hamilton Depression Scale; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; P-coping style: Positive coping style; N-coping style: Negative coping style.

The Yi Shu psychodrama group provided emotional support for its members. For example, "action performance" and "love hugs" during the Yi Shu psychodrama sessions could nourish the body and mind. With Yi Shu psychodrama "the trauma treatment and self-integration intervention structure" allows patients to receive corrective emotional experiences for their childhood trauma by altering their negative cognition, reconnecting internal and external resources, and integrating themselves, leading to improved coping style and the ability to adapt to environmental change. Therefore, we speculate that Yi Shu psychodrama is more effective than general health education in influencing the coping style. This may be because psychodrama can correct the patient's perception of distress by altering the disproportionate attention to negative information in depression patients with childhood trauma, and the psychodrama groups can provide individual physical and mental support.

We found that after 6 mo of intervention, the node efficiency of the right SPG increased and the connection with the left IFG increased in the group receiving first-line antidepressants combined with psychodrama, while the node efficiency in the other group that received first-line antidepressants combined with general health education decreased and the connection with the left IFG decreased. Node efficiency is a measure of the ability of a node to transmit information to other nodes. The higher

**Table 5 Connections to the brain area interacting with the right superior parietal gyrus after intervention**

| Brain region | Voxels | MNI Coordinate (X, Y, Z) (mm) | Peak intensity | $t_A$ ($p_A$) | $t_B$ ($p_B$) |
|---|---|---|---|---|---|
| Inferior frontal gyrus | 39 | (-54, 27, 0) | 28.3857 | 2.492 (0.019) | -2.156 (0.047) |

X, Y, Z: Coordinates of primary peak locations in the Montreal Neurological Institute space. MNI: Montreal Neurological Institute. Peak intensity: The statistical value of the interactive brain region that passes the Gauss random field corrected $P < 0.05$. $t_A$ ($p_A$): Comparison of after intervention and before intervention in the observation group; $t_B$ ($p_B$): Comparison of after intervention and before intervention in the control group. A positive value for $t$ indicates a stronger connection after treatment, and a negative value for $t$ indicates a weaker connection after the intervention.

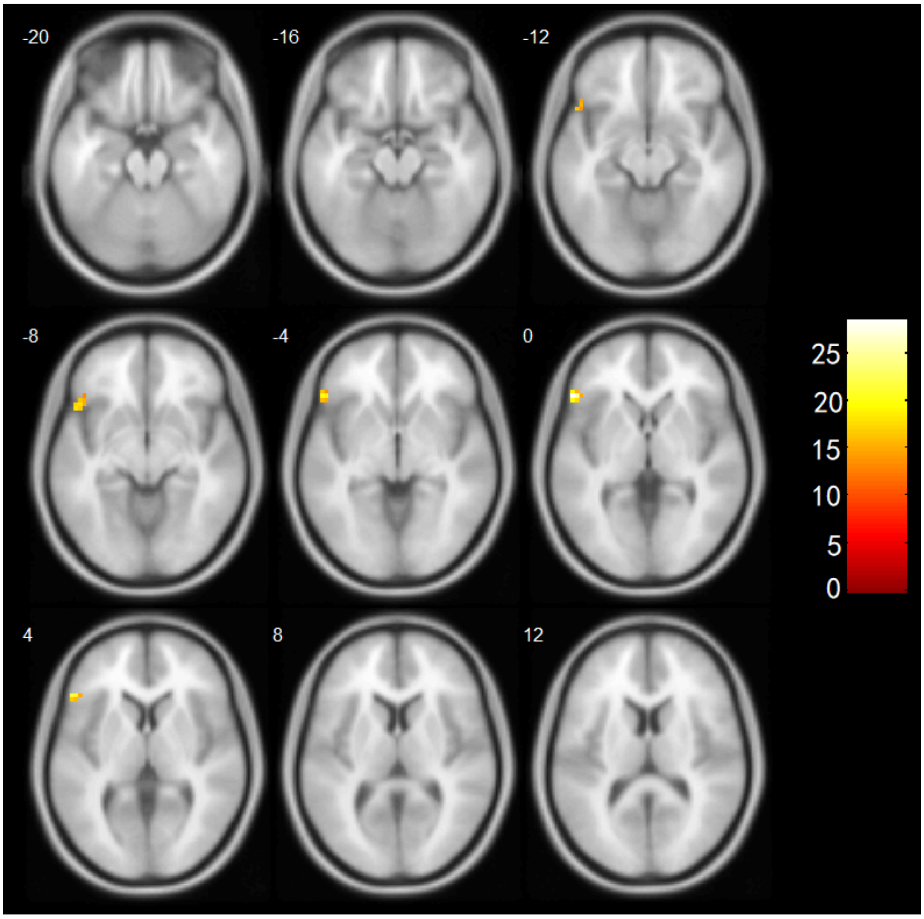


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**Figure 3 Increased connectivity with the right superior gyrus after intervention.** The numbers in the figure represent the axial coordinates of the brain profile in Montreal Neurological Institute space, and the brightness of the color represents the significance level of the interaction, with brighter color indicating higher significance.

the node efficiency, the greater the importance of the node in the network, and the easier it spreads information to other nodes, resulting in greater integration in the brain[41]. SPG, as an important brain region integrating multi-channel information of visual, auditory, and sensory movements, participates in the processes of attention control and target selection[42].

In our study, Yi Shu psychodrama aimed to reverse the negative effects of childhood trauma on the individual through various channels such as vision, hearing, and kinesthetic sense. Therefore, we suggest the use of the SPG as the functional MRI target when using psychodrama as a treatment. Some studies have observed significantly lower activation of the bilateral frontal lobe and right SPG than in healthy controls[43], which may be the reason depression patients tend to pay more attention to negative information[44]. It has been pointed out that CCN abnormalities in depression patients are usually manifested as an inability to effectively transmit information between the parietal lobe and the frontal lobe. As a result, depression patients cannot adjust the parietal lobe attentional bias in a way that is beneficial to individual development. This may be the general mechanism underlying impairments in cognitive performance in patients with depression[45]. Our study found that the two intervention

methods had different effects on the right SPG.

The IFG participates in response inhibition[46], that is to say, it inhibits the individual's spontaneous response to a specific environmental stimulus[47]. Some studies have also pointed out that the IFG may be involved in individual monitoring of the external environment to establish or maintain attention to a certain objective of the current external environment[48,49]. The activation of the IFG in individuals with childhood trauma may be related to their high vigilance against the external environment[50]. Our research found that the SPG, which is responsible for integrating visual information in the CCN, and the IFG, which has the function of reflecting inhibition or monitoring the external environment, showed increased connectivity after the intervention in the observation group, while such connections appeared reduced in the control group after intervention. These results are similar to those of previous studies that found a decrease in the internal connectivity of the CCN after antidepressant treatment, while there was increased internal connectivity of the CCN after psychotherapy[23,24,51].

Other studies have found that the frontal lobe controls the area of attention of the parietal lobe through top-down regulation[52]. The impairment of CCN function in patients with depression leads to reduced control over the hyperactivation of the limbic system (*i.e.* the higher cognitive level areas cannot effectively regulate the activities of lower cognitive level areas), and its top-down regulation of attention and emotion is reduced[53-56]. Our study suggests that the enhanced internal connectivity of the CCN after the intervention of first-line antidepressants combined with psychodrama may be due to an enhanced top-down attention control from the IFG to the SPG. The cognitive control capability of the whole network was restored, and the negative attention bias was corrected. However, the treatment of first-line antidepressants combined with general health education did not restore the cognitive control capability of the network, and the negative attention bias of the patients was not corrected. This is similar to the finding that even if patients with depression recover from a depressive episode, their attention is still negatively biased[57]. We further speculate that psychodrama can enhance the internal connectivity of the CCN and correct the patient's negative attentional bias better than general health education.

It has been pointed out that psychotherapy works through a top-down mechanism[58]. Top-down cognitive control by the CCN has been found to overcome hyperactivity of the limbic system[59]. The ability of the individual to regulate the response to negative stimuli depends on the attention to negative stimuli when facing the visual spatial environment[57]. Based on this indirect evidence and our own research evidence, we speculate that psychodrama may restore the cognitive control capability of the CCN in depressive patients from the top-down, inhibiting overactivity of the limbic system and thus reducing the patient's negative attentional bias. Then, like CBT, it could weaken the patient's perception of negative cognitive schemas[60] and improve their coping styles.

## CONCLUSION

This study provides initial support for the use of antidepressants combined with psychodrama to improve the coping style of MDD patients with childhood trauma, which was found to increase the functional connectivity between the SPF and IFG. However, antidepressants combined with general health education did not produce these effects. We speculate that psychodrama can enhance the internal connectivity of the CCN and can thus correct the negative attention bias of patients.

In conclusion, we preliminarily found that antidepressant drugs combined with Yi Shu psychodrama therapy have better short-term effects in improving the coping style of these patients than antidepressant drugs combined with general health education, which provides a new option for clinical intervention with childhood traumatic depression. This study shows that psychodramas enhanced characteristics of cognitive network connectivity will be beneficial for the development of methods for early diagnosis and treatment of such patients. In the future, we will combine more abundant clinical psychological indicators and neurobiological indicators to conduct joint exploration to lay a foundation for the early diagnosis of depression with childhood trauma and the exploration of effective intervention targets.

## ARTICLE HIGHLIGHTS

### *Research background*

The use of antidepressant therapy alone has a limited efficacy in patients with childhood trauma-associated major depressive disorder. However, the effectiveness of antidepressant treatment combined with psychodrama in these patients is unclear.

### *Research motivation*

To evaluate the effectiveness of antidepressant treatment combined with psychodrama.

### *Research objectives*

Patients with childhood trauma-associated major depressive disorder treated with antidepressants.

### *Research methods*

Patients with childhood trauma-associated major depressive disorder treated with antidepressants were randomly assigned to either the psychodrama intervention (observation group) or the general health education intervention (control group) and received combination treatment for 6 mo. The observation group received general health education given by the investigator together with the "semi-structured group intervention model" of Yi Shu psychodrama. A total of 46 patients were recruited, including 29 cases in the observation group and 17 cases in the control group. Symptoms of depression and anxiety as well as coping style and resting-state functional magnetic resonance imaging were assessed before and after the intervention.

### *Research results*

Symptoms of depression and anxiety, measured by the Hamilton Depression Scale, Beck Depression Inventory, and Beck Anxiety Inventory, were reduced after the intervention in both two groups of patients. The coping style of the observation group improved significantly in contrast to the control group, which did not. In addition, an interaction between treatment and time in the right superior parietal gyrus node was found. Furthermore, functional connectivity between the right superior parietal gyrus and left inferior frontal gyrus in the observation group increased after the intervention, while in the control group the connectivity decreased.

### *Research conclusions*

This study supports the use of combined treatment with antidepressants and psychodrama to improve the coping style of patients with childhood trauma-associated major depressive disorder. Functional connectivity between the superior parietal gyrus and inferior frontal gyrus was increased after this combined treatment. We speculate that psychodrama enhances the internal connectivity of the cognitive control network and corrects the negative attention bias of patients with childhood trauma-associated major depressive disorder.

### *Research perspectives*

Elucidating the neurobiological features of patients with childhood trauma-associated major depressive disorder is important for the development of methods that can assist in early diagnosis and intervention.


## FOOTNOTES


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ORIGINAL ARTICLE

Case Control Study

# Can the prediction model using regression with optimal scale improve the power to predict the Parkinson's dementia?

Haewon Byeon

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## Abstract

### *BACKGROUND*

Efficiently detecting Parkinson's disease (PD) with dementia (PDD) as soon as possible is an important issue in geriatric medicine.

### *AIM*

To develop a model for predicting PDD based on various neuropsychological tests using data from a nationwide survey conducted by the Korean Centers for Disease Control and Prevention and to present baseline data for the early detection of PDD.

### *METHODS*

This study comprised 289 patients who were 60 years or older with PD [110 with PDD and 179 Parkinson's Disease-Mild Cognitive Impairment (PD-MCI)]. Regression with optimal scaling (ROS) was used to identify independent relationships between the neuropsychological test results and PDD.

### *RESULTS*

In the ROS analysis, Korean version of mini mental state ex-amination (MMSE) (KOREAN version of MMSE) (b = -0.52, SE = 0.16) and Hoehn and Yahr staging (b = 0.44, SE = 0.19) were significantly effective models for distinguishing PDD from PD-MCI ($P < 0.05$), even after adjusting for all of the Parkinson's motor symptom and neuropsychological test results. The optimal number of categories (scaling factors) for KOREAN version of MMSE and Hoehn and Yahr Scale was 10 and 7, respectively.

### *CONCLUSION*

The results of this study suggest that among the various neuropsychological tests conducted, the optimal classification scores for KOREAN version of MMSE and Hoehn and Yahr Scale could be utilized as an effective screening test for the early discrimination of PDD from PD-MCI.

**Key Words:** Hoehn and Yahr staging; Optimal scale; Parkinson's dementia; Mini mental state ex-amination; Montreal Cognitive Assessment

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**Core Tip:** Although a general linear model can be constructed if all of the variables used in the analysis are numeric, it is difficult to fit the data when the variables are nominal. We build a regression model using the transform variables obtained by iteratively using alternating least squares to compute the optimal scaling. We developed a predictive model to discriminate Parkinson's disease with dementia from Parkinson's Disease-Mild Cognitive Impairment based on the results of nine neuropsychological tests and found that only Korean version of mini mental state examination and Hoehn and Yahr Scale could be successfully employed to this end.

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## INTRODUCTION

As the longevity of the South Korean population increases, so does the proportion of advanced-aged individuals[1] along with the incidence of chronic degenerative diseases[1]. For this reason, the importance of prevention and early treatment of degenerative dis-eases in old age should be emphasized. Parkinson's disease (PD) is a representative neurodegenerative disease caused by damaged nerve cells that secrete dopamine in the sub-stantia nigra. However, researchers have paid less attention to PD than dementia or stroke in terms of health science because its incidence rate is only 1% in the older adult population (≥ 65 years old) and its prevalence rate is lower than for dementia or stroke. However, the number of PD patients is steadily increasing in the aged population. The Health Insurance Review and Assessment Service (HIRAS) (2019)[2] reported that the number of patients diagnosed with PD steadily increased from 61565 in 2010 to 100716 in 2018 and predicted that the number of PD patients will double in 2030 compared to 2005 at this rate. In particular, the number of older adults with PD is expected to increase even more in South Korea considering that by 2050, the proportion of the older adult population in South Korea will be 35.9%, the second-highest after Japan (40.1%)[3]. Consequently, the effective early detection of PD is an important topic in the field of geriatric medicine.

PD is a motor disorder comprising a combination of weakness, tremor, and rigidity. However, over the past 20 years, other symptoms including autonomic nerve disorder, affective and sensory disorders such as depressive disorders, and cognitive impairment have been reported[1-7]. Many previous studies [8-10] have reported that 20%-57% of patients develop mild cognitive impairment (MCI) within 5 years from the date of being diagnosed with PD. MCI refers to a state in which cognitive decline is observed without accompanying a decline in activities of daily living (ADL). It is a pre-clinical state of PD with dementia (PDD) and it is an intermediate stage from normal to PDD. Previous follow-up studies also have revealed that approximately 10% to 15% of MCI patients transited to dementia every year[7]. It means that they are highly vulnerable to dementia and it was much higher than the annual dementia incident rate of healthy older adults (65 years or older)[7]. It is the earliest stage of dementia that can be detected in clinical examination, and it is clinically very important because it is possible to maximize the therapeutic effect[7]. Neuropsychological screening battery, cognitive assessment, autonomic function, and other tests have been carried out to objectively assess the clinical status of PD accompanying MCI [11]. However, it is difficult to distinguish MCI from aging or mild dementia only using these screening tests[11]. To make it more challenging, it can be misdiagnosed with progressive supranuclear palsy-parkinsonism (PSP-P) when a patient suffers from PD and cognitive deficit at the same time[12,13].

Compared to the United States and Europe, South Korea currently has insufficient epidemiological data on cognitive impairment in old age. Although community-based studies on PD conducted in South Korea have focused on patients in small and medium-sized cities, prediction models based on a nationwide epidemiological survey have not yet been developed[14-17]. Although a general linear model (GLM) for PD can be constructed if all of the variables used in the analysis are numeric, it is difficult to fit the data when the variables are ordinal or nominal. An alternative method to overcome this limitation is to build a regression model with an optimal scale (optimal regression).

Optimal scaling is based on the prediction theory (also known as the quantification theory) developed by considering how to quantify qualitative variables to enable optimal data analysis rather than simply ranking them and interpreting the results. Optimal scaling has been mainly used in social science fields

such as psychology when proving causality is important[18-20]. However, it has only been used in a small number of studies in the cognitive science field. Identifying neuropsychological tests (*e.g.*, cognitive and de-pression tests) and Parkinson's motor symptom tests that are effective in discriminating PDD from PD-MCI by using regression with optimal scaling (ROS) and checking the optimal classification scores of the tests is clinically meaningful. However, it has only been used in a small number of studies in the cognitive science field. The objectives of the present study were to develop a model for predicting PDD based on various neuropsychological tests using data from a National Biobank of Korea data.

## MATERIALS AND METHODS

### Data source

Approval for the study was received from the Distribution Committee (No. KBN-2019-1327) and the Research Ethics Review Committee of the National Biobank of Korea under the Korean Centers for Disease Control and Prevention (No. KBN-2019-005). Epidemiologic data on patients with PD were collected from 14 tertiary care providers nationwide from January to December 2015 under the supervision of the Korean Centers for Disease Control and Prevention. PDD has been designated as idiopathic Parkinson's dis-ease according to the diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank[21]. The diagnostic criteria for probable PDD have been suggested by the Movement Disorder Society Task Force[22]. When causes of cognitive impairment other than PD (*e.g.*, hydrocephalus and vascular Parkinsonism) were found in magnetic resonance imaging scans, the subject was excluded from the study (see Byeon[23] for more details). PD-MCI was diagnosed by neuropsychologists according to the criteria of the International Working Group on MCI[24]. Health surveys were conducted by using computer-assisted personal interviews. We analyzed the PD epidemiologic data comprising demographic information, any family history of PD, health-affecting behaviors ( *e.g.*, smoking), disease history (*e.g.*, diabetes), and Parkinson's motor symptoms (*e.g.*, rigidity) and neuropsychological characteristics (*e.g.*, cognitive level). The variables and their values are reported in Table 1. Thus, data on 289 patients with PD (110 PDD and 179 PD-MCI) who were 60 years or older were used in the study.

### Variable measurement

The label was defined as PDD confirmed by medical diagnosis. To understand the difference in the general characteristics of subjects according to the demographic variables (*e.g.*, age, sex, and education level), medical history (*e.g.*, hypertension), and family history [*e.g.*, PD and Alzheimer's disease (AD)].

Explanatory variables (neuropsychological tests) included scores from the Hoehn and Yahr (H&Y) staging[25], Global Clinical Dementia Rating (CDR)[26], Schwab and England Activities of Daily Living [27], the Korean Instrumental ADL (K-IADL)[28], the Unified PD Rating Scale (UPDRS) total[22], the UPDRS motor[22], the Korean Mini-Mental State Examination (KOREAN version of MMSE)[29], and the Korean-Montreal Cognitive Assessment (K-MoCA)[30]. Hoehn and Yahr Scale[25] is a screening test to determine the stage of PD and is measured by clinicians. The score ranges from 1 to 5, and a higher score indicates that the symptoms of PD are more severe.

CDR[26] is a screening test to determine the stage of dementia and is measured by clinicians. The possible outcomes are 0, 0.5, 1, 2, 3, 4, and 5 points, and a higher score means more severe dementia. Schwab and England ADL[27] is a screening test for physical impairment. It is evaluated by clinicians to measure indices regarding independent performance in the daily activities of PD patients. The score ranges from 0 to 100, and a higher score is interpreted as a lower functional impairment. K-IADL[28] is a cognitive screening test that measures skills and behaviors necessary for social life such as "money management" and "phone use". It consists of eleven items that can score between 0 and 3, and a higher score means higher functional impairment. UPDRS[22] is an overall evaluation scale for the symptoms of PD and consists of four segments (mentation/behavior/mood, ADL, motor examination, and dyskinesia). The test is conducted by a clinician, and a higher score is interpreted as a higher degree of disability. KOREAN version of MMSE[29] is a test for screening cognitive disorders such as dementia and consists of time orientation, spatial orientation, memory registration (input), calculation and attention, memory recall, and language items. The total score is 30 points, and the cut-off score is 24 points. A lower score indicates more severe cognitive impairment. K-MoCA[30] is a test for screening MCI. The total score is 30 points, and people with 22 points and above are interpreted as normal. A lower score is understood as more severe cognitive impairment.

### Regression with optimal scale

If all the variables (*e.g.*, Independent variables, dependent variables, and confounding variables) used in the analysis are numeric variables (quantitative variables), the GLM can be used. However, if it is an ordinal or nominal variable, it is difficult to use the general linear regression model because these variable types do not meet the assumptions of the regression models and error terms. Therefore, analysis can be con-ducted by deriving an optimized linear regression equation of transformed variables

**Table 1 Measurement of variables**

| Factors | Measurement | Characteristics |
|---|---|---|
| Demographic factors | Sex | Male or female |
| | Age | 60-74, 75+ |
| | Mainly used hand | Left hand or right hand |
| | Education level | Middle school graduate and below or high school graduate and above |
| Family history of the disease | Parkinson's disease; Alzheimer's disease | Yes or no; Yes or no |
| Health behaviors | Pack-years (smoking) | Non-smoking, 1-20, 21-40, 41-60, or ≥ 61 pack-years |
| | Coffee-drinking | Yes or no |
| | Mean coffee intake per day (cups/d) | No, ≤ 1, 2-3, or ≥ 4 cups |
| | Coffee drinking period (yr) | No, ≤ 5, 6-9, or ≥ 10 |
| Disease history | Carbon monoxide poisoning | Yes or no |
| | Diabetes | Yes or no |
| | Alcoholism | Yes or no |
| | Hyperlipidemia | Yes or no |
| | Traumatic brain injury | Yes or no |
| | Hypertension | Yes or no |
| Exercise characteristics related to Parkinson's disease relatedmotor signs | Tremor | Yes or no |
| | Rigidity | Yes or no |
| | Akinesia/bradykinesia | Yes or no |
| | Postural instability | Yes or no |
| | Late motor complications | Yes or no |
| Neuropsychological test | K-MoCA | Continuous variable |
| | K-MMSE | Continuous variable |
| | Global CDR score | Continuous variable |
| | Sum of boxes in CDR | Continuous variable |
| | Hoehn and Yahr staging | Continuous variable |
| | UPDRS (Total UPDRS score) | Continuous variable |
| | UPDRS (Motor UPDRS score) | Continuous variable |
| | K-IADL | Continuous variable |
| | Schwab and England ADL | Continuous variable |

K-MoCA: Korean version of montreal cognitive assessment; K-MMSE: Korean version of mini mental state examination; CDR: Clinical dementia rating; UPDRS: Untitled parkinson disease rating; K-IADL: Korean version of instrumental activities of daily living; Schwab and England ADL: Schwab and England avtivities of daily living scale.

by repeatedly performing optimal scaling based on the alternating least squares method.

It is a way to estimate parameters for the linear relationship between independent and dependent variables using data on each variable. The estimated general linear regression model is presented as follows[19]:

$Yi = \alpha + \beta X_i + \varepsilon_i$

*Yi = dependent variable*

*Xi = independent variable* (Equation 1)

*εi = error term*

*α,β = parameter to estimate*

When the assumptions for the error term, such as "the expected value of the error term shall be 0" and "it shall follow a normal distribution and all observations shall have the same variance", parameters are estimated by using the least-squares and other methods to determine the relationship between the

independent and dependent variables. The least-squares method is used to obtain parameter estimates ( $\alpha\hat{}$ and $\beta\hat{}$) that minimize the sum-of-squared residuals, where the residual ($\varepsilon_i$) is equal to the difference between the actual observations ($Y_i$) and the predicted values of the dependent variables (($Y_i$)$\hat{}$ (($Y_i$)$\hat{}$ $=\alpha\hat{} +\beta\hat{} X_i$)).

In this study, ROS consisted of three stages. The first is the data transformation stage. After normalizing k categorical indicators for the nth variable by vectorizing them, all of the variables are treated as numeric variables. Subsequently, they are optimized repeatedly by using the calculated categorical quantification values and regression coefficients. The second stage is updating the categorical quantification vector by considering the scale level (*i.e.*, whether the variables are nominal, ordinal, or numeric) and calculating the regression coefficient vector. The third stage is to establish convergence by repeatedly calculating the categorical quantification vector and the regression coefficient vector until they satisfy the predetermined convergence condition[19].

ROS transforms each variable appropriately by considering its scale in the GLM. When dependent variable $Y$ is transformed to $\theta(Y)$ and independent variable $X$ to $\sigma(X)$, the resulting parameters are the intercept and slope of a GLM (linear regression) equation formed by minimizing the sum-of-squares ( $SSQ$) of the error[19] as follows: $minSSQ[\theta(Y)-\beta\sigma(X)]$ (Equation 2).

The conversion variable has a standardization constraint. Minimizing the $SSQ$ error is achieved by least-squares regressing the transformed variables [*e.g.*, $\theta(Y)$, $\sigma_1(X_1)$, …, $\sigma_n(X_n)$)]. The ROS analysis with standardization constraints is written as

$$minSSQ(\theta(Y) - \sum_{i=1}^{n} \beta_i \sigma_i(X_i)) \text{ (Equation 3).}$$

ROS was used to identify the independent relationship between each test and PDD. The analysis results were presented with a regression coefficient, odds ratio, 95% confidence interval (CI), quantification index, and standard error by bootstrap ($n$ = 999). General characteristics of the subjects and the prevalence of PD were analyzed using the Chi-square test.

When independent significance was confirmed in the ROS, the Cochran-Armitage (CA) trend test was used to determine whether the p values had a linear trend based on the reference group as follows [31]:

$$T = \frac{\sum_{i=1}^{R} n_{i1}(R_i - \bar{R})}{\sqrt{p_{.1}(1-p_{.1})s^2}} s^2 = \sum_{i=1}^{R} n_{i.}(R_i - \bar{R})^2 \text{ (Equation 4).}$$

The analysis of ROS was conducted by using CatReg Software version 3.0 (the Data Theory Scaling System Group, Leiden, The Netherlands).

## RESULTS

### Characteristics of the participants and the prevalence of PD

The results of $\chi^2$ tests show that age, handed, PD family history, gender, the highest level of education, AD family history, hypertension, traumatic brain injury history, stroke history, carbon monoxide poisoning history, hyperlipidemia, and diabetes were not significantly different between PDD and PD-MCI (Table 2). Therefore, the subjects in this study did not have statistically significant demographic or health differences between the groups.

Table 3 reports the data and Figure 1 shows a bag plot for visualizing the spread, location, outliers and skewness.

The neuropsychological test results of PD-MCI and PDD are compared (Table 4). As a result of the independent $t$-test, KOREAN version of MMSE, K-MoCA, Total UPDRS score, CDR (sum of boxes), K-IADL, Hoehn and Yahr staging, Motor UPDRS score, and Schwab and England ADL were not significantly different between PDD and PD-MCI ($P < 0.05$).

### The analysis results of ROS

The analysis results of ROS are summarized in Table 5. Hoehn and Yahr Scale (b = 0.44, SE = 0.19) and KOREAN version of MMSE (b = -0.52, SE = 0.16) were significantly effective for distinguishing PDD from PD-MCI even after adjusting for all of test results ($P < 0.05$). The regression model was adjusted for demographic factors, family disease history, health-affecting behaviors, dis-ease history, Parkinson's motor symptoms, and neuropsychological test.

Quantification scores for KOREAN version of MMSE and Hoehn and Yahr Scale are reported in Tables 6 and 7, respectively, and presented in Figures 2 and 3, respectively. The results show that the optimal number of categories (scaling factors) for KOREAN version of MMSE and Hoehn and Yahr Scale was 10 and 7, respectively. The odds ratios (ORs) and 95%CIs for the optimal categories of KOREAN version of MMSE and Hoehn and Yahr Scale are reported in Table 8. When distinguishing PDD from PD-MCI, PD-MCI patients who had 23 or 24 points for KOREAN version of MMSE had a 4.5-fold higher risk of PDD than those who had 25 or higher. Moreover, those who scored 21 or 22, 19 or 20, 15 to 18, and 3 to 14 points had a 2.7-fold, 13.3-fold, 22.4-fold, and 55-fold higher risk of developing PDD, respectively, than those who had 25 or higher. The results of the CA Trend test show a significant relationship ($P$ for Trend < 0.001) between the increase in OR and the KOREAN version of MMSE score (optimal categories score).

**Table 2 General characteristics of the subjects based on Parkinson's disease with dementia, *n* (%)**

| Variables | PD-MCI (*n* = 179) | PDD (*n* = 110) | *P* value |
|---|---|---|---|
| Age | | | 0.168 |
| 60-74 | 117 (65.0) | 63 (35.0) | |
| 75+ | 62 (56.9) | 47 (43.1) | |
| Sex | | | 0.550 |
| Male | 78 (63.9) | 44 (36.1) | |
| Female | 101 (60.5) | 66 (39.5) | |
| Education level | | | 0.072 |
| Middle school graduate and below | 110 (58.2) | 79 (41.8) | |
| High school graduate and above | 69 (69.0) | 31 (31.0) | |
| Family history of the Parkinson's disease | | | 0.600 |
| No | 144 (64.3) | 80 (35.7) | |
| Yes | 12 (70.6) | 5 (29.4) | |
| Family history of the Alzheimer's disease | | | 0.285 |
| No | 130 (63.4) | 75 (36.6) | |
| Yes | 8 (80.0) | 2 (20.0) | |
| Carbon monoxide poisoning | | | 0.743 |
| No | 158 (62.5) | 95 (37.5) | |
| Yes | 10 (66.7) | 5 (33.3) | |
| Traumatic brain injury | | | 0.277 |
| No | 158 (62.0) | 97 (38.0) | |
| Yes | 10 (76.9) | 3 (23.1) | |
| Diabetes | | | 0.508 |
| No | 144 (64.0) | 81 (36.0) | |
| Yes | 35 (59.3) | 24 (40.7) | |
| Hypertension | | | 0.304 |
| No | 110 (65.5) | 58 (34.5) | |
| Yes | 69 (59.5) | 47 (40.5) | |
| Hyperlipidemia | | | 0.220 |
| No | 155 (61.8) | 96 (38.2) | |
| Yes | 24 (72.7) | 9 (27.3) | |

## DISCUSSION

In this study, KOREAN version of MMSE and Hoehn and Yahr Scale could independently differentiate PDD from PD-MCI even after adjusting for all of the PD's test results. Moreover, when the ROS (optimal classification scores) were calculated, the increase in OR according to all of the categories showed a significant proportional trend.

It is not easy to accurately detect and diagnose PSP-P by identifying the pattern of PD-MCI in PDD by using neuropsychological tests[26]. First, it is difficult to determine whether dementia is the cause of a patient's cognitive impairment symptoms[27] because patients with PD often take a variety of medications (*e.g.*, anticholinergics, amantadine, anxiolytics, and sedatives) and can experience temporary cognitive decline or confusion (easily mistaken for dementia) as side effects of the medications[32]. Second, cognitive impairment can occur temporarily due to endocrine imbalance due to depression, electrolyte imbalance, and/or dehydration; systemic diseases; or infection[22]. Third, even if dementia is diagnosed, it is necessary to effectively differentiate it from other types of irreversible dementia such as Alzheimer's disease or, especially, dementia with Lewy bodies[22]. Hence, it is necessary to develop predictive models that can more efficiently discriminate PDD from PD-MCI as

**Table 3 Results of the neuropsychological profiles**

| Results | K-MMSE | K-MoCA | Global CDR score | Sum of boxes in CDR | K-IADL | Total UPDRS | Motor UPDRS | H&Y staging | ADL |
|---|---|---|---|---|---|---|---|---|---|
| Mean | 22.73 | 16.27 | 0.67 | 2.80 | 1.90 | 43.56 | 25.33 | 2.45 | 74.40 |
| Standardized mean error | 0.32 | 0.44 | 0.03 | 0.22 | 0.26 | 2.02 | 0.77 | 0.04 | 1.42 |
| Standard deviation | 5.51 | 6.33 | 0.56 | 3.49 | 4.08 | 23.77 | 12.59 | 0.78 | 18.30 |
| Minimum | 3 | 0 | 0 | 0 | 0 | 0.18 | 2.0 | 1.0 | 10 |
| Maximum | 30 | 27 | 4.0 | 25.0 | 28.0 | 130.00 | 74.0 | 5.0 | 100 |

K-MoCA: Korean version of montreal cognitive assessment; K-MMSE: Korean version of mini mental state examination; CDR: Clinical dementia rating; UPDRS: Untitled parkinson disease rating; H&Y staging: Hoehn and Yahr staging; K-IADL: Korean version of instrumental activities of daily living; Schwab and England ADL: Schwab and England avtivities of daily living scale.

**Table 4 Result of the neuropsychological profiles based on Parkinson's disease with dementia, mean ± SD**

| Variables | PD-MCI (*n* = 179) | PDD (*n* = 110) | *P* value |
|---|---|---|---|
| K-MMSE | 24.3 ± 3.4 | 18.8 ± 5.6 | < 0.001 |
| K-MoCA | 19.4 ± 4.9 | 11.9 ± 5.4 | < 0.001 |
| CDR (sum of boxes) | 1.6 ± 1.4 | 5.1 ± 4.9 | < 0.001 |
| K-IADL | 1.3 ± 2.9 | 3.0 ± 5.4 | 0.001 |
| UPDRS (Total UPDRS score) | 36.4 ± 17.9 | 56.1 ± 27.2 | < 0.001 |
| UPDRS (Motor UPDRS score) | 22.6 ± 10.1 | 29.4 ± 14.6 | < 0.001 |
| H&Y staging | 2.2 ± 0.6 | 2.7 ± 0.8 | 0.001 |
| Schwab and England ADL | 80.0 ± 14.4 | 65.6 ± 19.8 | < 0.001 |

K-MoCA: Korean version of montreal cognitive assessment; K-MMSE: Korean version of mini mental state examination; CDR: Clinical dementia rating; UPDRS: Untitled parkinson disease rating; H&Y staging: Hoehn and Yahr staging; K-IADL: Korean version of instrumental activities of daily living; Schwab and England ADL: Schwab and England avtivities of daily living scale.

well as other types of dementia while simultaneously considering the results of several neuropsychological tests related to cognitive impairment.

Nevertheless, in most of the previous studies, evaluating the predictive performance for PDD was conducted by comparing individual diagnostic performances in terms of accuracy and reliability[30,31,33,34]. The results of the present study suggest that among the various neuropsychological tests examined, the optimal classification scores by MMSE-K and Hoehn and Yahr Scale show that these two tests could be utilized for effective early discrimination of PDD from PD-MCI. Moreover, they could be used to clinically determine whether PD-MCI patients will develop PDD or whether existing PDD patients are getting worse. Conducting these tests when a PD-MCI patient visits the hospital (or Public Health Center) for the first time provides baseline information and carrying them out sequentially at regular visits can be used to recognize clinically meaningful changes.

Although it is very important to efficiently distinguish PDD from other diseases showing symptoms of PD as soon as possible, PD can only be accurately diagnosed through pathological examination with autopsy[6]. Dopamine transporter imaging has been reported as an effective test for diagnosing PDD at an early stage[35], but it is too expensive to be used as a screening test in the primary care setting. As a result, it is diagnosed through an interview on the symptoms of a patient and an examination of a specialist along with a cognitive screening test such as KOREAN version of MMSE in the clinical practice.

However, Rizzo *et al*[36] reported that the misdiagnosis rate of dyskinesis was at least 20% even for neurologists with extensive experience in dyskinesias. Therefore, to accurately diagnose PD-MCI, a specialist must have a broad perspective to comprehensively consider the symptoms of a patient (*e.g.*, resting tremor, bradypragia, postural changes, and gait abnormalities), living environment, presence of trauma, lifestyle, and occupation as well as the results of cognitive screening tests. Particularly, since cognitive issues and dyskinesias (*e.g.*, bradypragia, resting tremor, and ankylosis) are slowly

**Table 5 Results of regression with optimal scale**

| Test | b | SE by boost 1 | df | F | *P* value |
|---|---|---|---|---|---|
| K-MMSE | -0.522 | 0.168 | 2 | 9.684 | < 0.001 |
| KMoCA | -0.206 | 0.238 | 3 | 0.750 | 0.527 |
| CDR (Global CDR score) | 0.127 | 0.269 | 1 | 0.222 | 0.639 |
| CDR (sum of boxes) | -0.271 | 0.412 | 3 | 0.431 | 0.732 |
| K-IADL | 0.237 | 0.224 | 2 | 1.119 | 0.334 |
| UPDRS (Total UPDRS score) | 0.433 | 0.444 | 3 | 0.949 | 0.423 |
| UPDRS (Motor UPDRS score) | -0.338 | 0.330 | 3 | 1.045 | 0.380 |
| H&Y staging | 0.440 | 0.197 | 3 | 5.008 | 0.004 |
| Schwab and England ADL | 0.353 | 0.333 | 2 | 1.123 | 0.333 |

The regression model was adjusted for demographic factors, family disease history, health behaviors, disease history, Parkinson's disease-related motor signs and neuropsychological test. 1 SE by boost: Standard error by bootstrap (with $n$ = 1000); K-MoCA: Korean version of montreal cognitive assessment; K-MMSE: Korean version of mini mental state examination; CDR: Clinical dementia rating; UPDRS: Untitled parkinson disease rating; H&Y staging: Hoehn and Yahr staging; K-IADL: Korean version of instrumental activities of daily living; Schwab and England ADL: Schwab and England avtivities of daily living scale.

**Table 6 Quantification index of Korean version of mini mental state examination**

| Category (point) | Quantification index |
|---|---|
| 3-14 | -1.260 |
| 15-18 | -1.198 |
| 19-20 | -1.013 |
| 21-22 | -.706 |
| 23-24 | -.320 |
| 25 | 0.135 |
| 26 | 0.656 |
| 27 | 1.183 |
| 28 | 1.508 |
| 29-30 | 1.616 |

**Table 7 Quantification index of Hoehn and Yahr staging**

| Category (point) | Quantification index |
|---|---|
| 1.0 | -2.787 |
| 1.5 | -0.609 |
| 2.0 | -0.187 |
| 2.5 | -0.081 |
| 3.0 | 0.151 |
| 4.0 | 1.179 |
| 5.0 | 2.167 |

progressive cardinal symptoms, clinicians are more likely to rely on experience and the judgment of inexperienced clinicians may have low reliability.

It is believed that the analysis indices of this study can offer a range of information regarding the cognitive characteristics of the patient because they provide the optimal criteria for the screening test to distinguish PDD from PD-MCI. In particular, the optimal scale for early detection of PDD proposed in

**Table 8 Optimal classification scores: odds ratios and 95% confidence interval**

| Optimal classification scores | B | SE | Wald | *P* value | OR (95%CI) |
|---|---|---|---|---|---|
| K-MMSE 25+ (Ref) | | | 69.856 | < 0.01 | |
| 23-24 | 1.499 | 0.473 | 10.035 | 0.002 | 4.478 (1.77-11.32) |
| 21-22 | 2.731 | 0.494 | 30.522 | < 0.01 | 15.345 (5.82-40.43) |
| 19-20 | 2.587 | 0.549 | 22.195 | < 0.01 | 13.294 (4.53-39.00) |
| 15-18 | 3.111 | 0.505 | 37.937 | < 0.01 | 22.441 (8.33-60.39) |
| 3-14 | 4.008 | 0.799 | 25.185 | < 0.01 | 55.020 (11.50-263.19) |
| H&Y staging 1.0-2.5 (Ref) | | | | | |
| 3.0-5.0 | 1.110 | 0.350 | 10.079 | 0.001 | 3.035 (1.52-6.02) |

K-MMSE: Korean version of mini mental state examination; H&Y staging: Hoehn and Yahr staging.

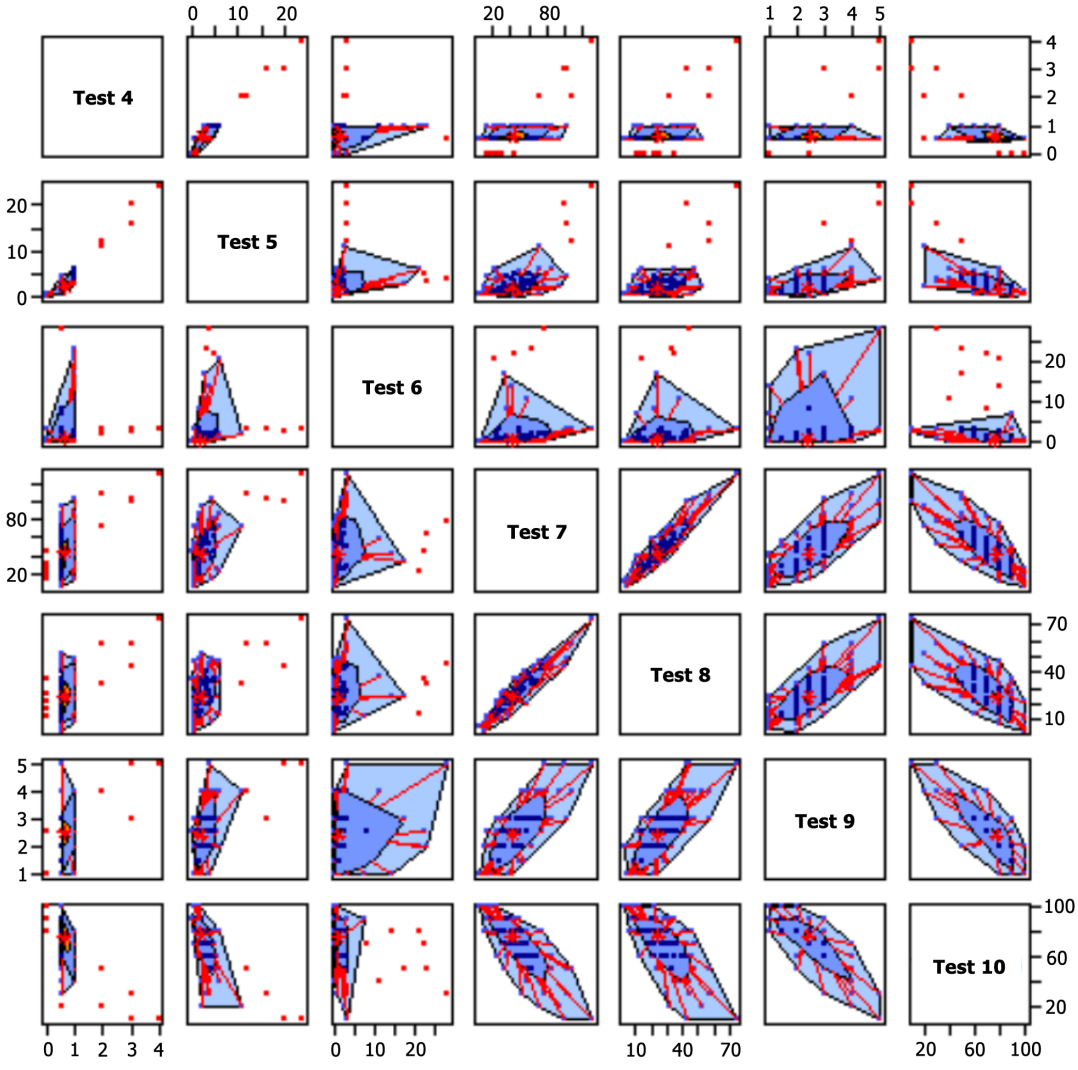


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**Figure 1 A bagplot that visualizes the location, spread, skewness, and outlier of the test results.** Test 4 = Global Clinical Dementia Rating score; Test 5 = Sum of boxes in Clinical Dementia Rating; Test 6 = Korean Instrumental Activities of Daily Living; Test 7 = Unified PD Rating Scale (Total UPDRS score); Test 8 = Unified PD Rating Scale (Motor UPDRS score); Test 9 = Hoehn and Yahr staging; Test 10 = Schwab and England Activities of Daily Living.

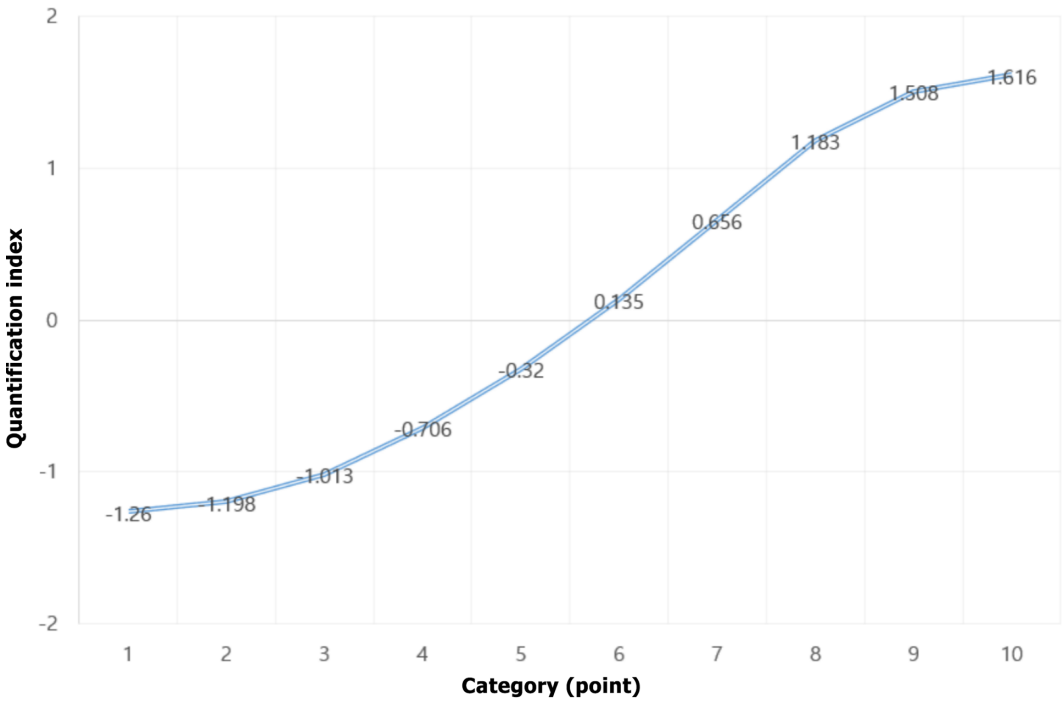


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**Figure 2 Quantification score graph among Korean Mini-Mental State Examination.** Category 1 = 3-14 point; Category 2 = 15-18 point; Category 3 = 19-20 point; Category 4 = 21-22 point; Category 5 = 23-24 point; Category 6 = 25 point; Category 7 = 26 point; Category 8 = 27 point; Category 9 = 28 point; Category 10 = 29-30 point.

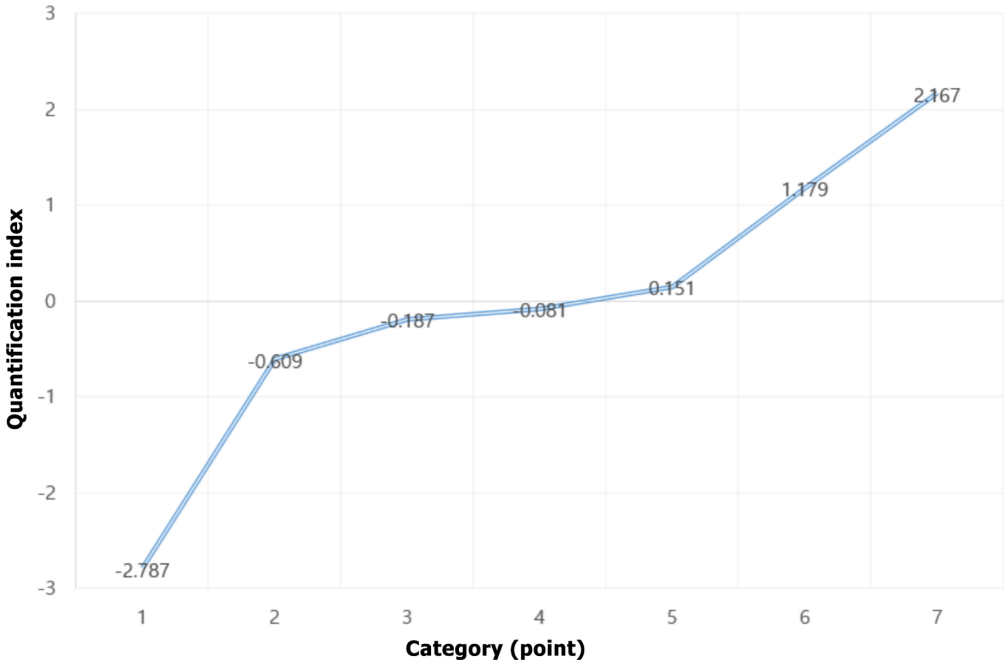


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**Figure 3 Quantification score graph among Hoehn and Yahr staging.** Category 1 = 1.0 point; Category 2 = 1.5 point; Category 3 = 2.0 point; Category 4 = 2.5 point; Category 5 = 3.0 point; Category 6 = 4.0 point; Category 7=5.0 point.

this study is inexpensive, unlike dopamine transporter imaging and other methods, which have been proposed as efficient tests for early diagnosis of PDD but have limitations as screening tests due to space and cost. Moreover, the proposed scale can be utilized as a screening test simply in the primary medical setting without spatial restrictions. Consequently, it is believed that clinical application will be easy. Additional longitudinal studies are required to prove the effectiveness of the optimal scale for distinguishing PDD from PD-MCI proposed in this study.

This study had several limitations. First, although we used secondary data from a national survey, it is difficult to generalize the results of the study because the number of subjects was small due to the difficulties in diagnosing PD-MCI, which is not yet being actively screened for in PD patients. Second, we included patients taking medications such as dopaminergic drugs to treat PD, which can cause behavioral symptoms such as visual hallucinations that could influence the neuropsychological examination. Future studies are required to develop a model that can predict PDD from PD-MCI quickly while considering the administration of dopaminergic medication for PD. Third, the results of this study cannot be interpreted as a causal relationship because it was conducted using secondary data and the PD with Dementia Epidemiologic Data, the source data of this study, was designed as a cross-sectional survey. Further longitudinal studies are needed to prove the causality of the results of this study. Fourth, the diagnosis of PSP-P was not distinguished in this study. Since the cognitive deficits in PD patients can be caused by PSP-P as well as PD-MIC, future studies are needed to exclude PSP-P in analysis.

## CONCLUSION

We developed a predictive model to discriminate PDD from PD-MCI based on the results of nine neuropsychological tests and found that only KOREAN version of MMSE and Hoehn and Yahr Scale could be successfully employed to this end. For most efficiently discriminating PDD from PD-MCI, the optimal scaling factors for KOREAN version of MMSE and Hoehn and Yahr Scale were 10 and 7, respectively. We believe that our optimal scaling approach can be used to detect PDD in the early stages. Further longitudinal studies are required to confirm the performance of neuropsychological tests such as KOREAN version of MMSE and MoCA in predicting the progression of PD-MCI to PDD.

## ARTICLE HIGHLIGHTS

### *Research background*

It has been reported that Parkinson's disease (PD) with dementia (PDD) occurs frequently in people with PD.

### *Research motivation*

The effective early detection of PD is an important topic in the field of geriatric medicine.

### *Research objectives*

The aims of the present study were to develop a model for early detection of PDD based on neuropsychological testing.

### *Research methods*

Data on 289 patients with PD [110 PDD and 179 Parkinson's Disease-Mild Cognitive Impairment (PD-MCI)] who were 60 years or older were used in the study. Regression with optimal scaling was used to identify independent relationships between the screening test results and PDD.

### *Research results*

The Korean version of mini mental state examination (MMSE) (KOREAN version of MMSE) (b = -0.52, SE = 0.16) and Hoehn and Yahr scale (b = 0.44, SE = 0.19) were significantly effective models for distinguishing PDD from PD-MCI ($P < 0.05$), even after adjusting for all of the test results.

### *Research conclusions*

The optimal number of categories (scaling factors) for KOREAN version of MMSE and Hoehn and Yahr Scale was 10 and 7, respectively.

### *Research perspectives*

We believe that our optimal scaling approach can be used to detect PDD in the early stages.

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## FOOTNOTES

**Author contributions:** Byeon H was designed the study, involved in data interpretation, preformed the statistical analysis, and assisted with writing the article.

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ORIGINAL ARTICLE

Observational Study

# Worldwide suicide mortality trends (2000-2019): A joinpoint regression analysis

Milena Ilic, Irena Ilic

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## Abstract

***BACKGROUND***

Studies exploring suicide mortality on a global scale are sparse, and most evaluations were limited to certain populations.

***AIM***

To assess global, regional and national trends of suicide mortality.

***METHODS***

Suicide mortality data for the period 2000-2019 were obtained from the mortality database of the World Health Organization and the Global Burden of Disease Study. Age-standardized rates (ASRs; expressed per 100000) were presented. To assess trends of suicide mortality, joinpoint regression analysis was used: The average annual percent change (AAPC) with the corresponding 95% confidence interval (95%CI) was calculated.

***RESULTS***

A total of 759028 (523883 male and 235145 female) suicide deaths were reported worldwide in 2019. The global ASR of mortality of suicide was 9.0/100000 population in both sexes (12.6 in males *vs* 5.4 in females). In both sexes, the highest rates were found in the region of Africa (ASR = 11.2), while the lowest rates were reported in Eastern Mediterranean (ASR = 6.4). Globally, from 2000 to 2019, ASRs of mortality of suicide had a decreasing tendency in both sexes together [AAPC = -2.4% per year; 95%CI: (-2.6)-(-2.3)]. The region of the Americas experienced a significant increase in suicide mortality over 2000-2019 unlike other regions that had a declining trend. Out of all 133 countries with a decline in suicide mortality, Barbados (AAPC = -10.0%), Grenada (AAPC = -8.5%), Serbia (AAPC = -7.6%), and Venezuela (AAPC = -6.2%) showed the most marked reduction in mortality rates. Out of all 26 countries with a rise in suicide mortality,

Lesotho (AAPC = +6.0%), Cyprus (AAPC = +5.1%), Paraguay (AAPC = +3.0%), Saudi Arabia (AAPC = +2.8%), Brunei (AAPC = +2.6%), Greece (AAPC = +2.6%), Georgia (AAPC = +2.1%), and Mexico (AAPC = +2.0%), are among those with the highest increase in mortality.

***CONCLUSION***

Decreasing trends in suicide mortality were observed in most countries across the world. Unfortunately, the mortality of suicide showed an increasing trend in a number of populations. Further research should explore the reasons for these unfavorable trends, in order to consider and recommend more efforts for suicide prevention in these countries.

**Key Words:** Suicide rates; Mortality; Trends; Average annual percent change; Joinpoint analysis

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**Core Tip:** Despite a decline in mortality during the last decades, suicides are one of the main health challenges worldwide. About 750000 suicide deaths were recorded in 2019 across the world. Globally, the rate of suicide mortality in 2019 was 9.0/100000 for both sexes together (12.6 in males *vs* 5.4 in females). Despite the decreasing trends recorded in both sexes in most countries in the world, the mortality of suicide showed an increasing trend in certain populations. Further research should clarify the reasons for these unfavorable trends, in order to provide more effective measures for suicide prevention.

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## INTRODUCTION

Suicides present a significant burden for societies around the world[1-3]. According to the 2019 estimates from the World Health Organization (WHO), suicides caused over 700000 deaths worldwide (representing about 1.3% of all deaths globally), making it the 17th leading cause of death in 2019[4]. In 2016, suicide was among the top 10 leading causes of death in Eastern Europe, Central Europe, Western Europe, Central Asia, Australasia, Southern Latin America, and in high-income areas of North America [3]. In the United States of America in 2019, and consistently over the past years, suicides were the 10th leading cause of death in both sexes[5] and 8th leading cause of death in males[6].

Globally, for both sexes, suicide was the 4th leading cause of death in young people aged 15-29 years in 2019[1]. In 2019, in several countries (such as Australia, Belarus, Canada, Finland, Germany, Japan, Kazakhstan, Mongolia, Montenegro, Netherlands, Norway, Republic of Korea, Russian Federation, Singapore, Sweden, Switzerland, and the United Kingdom), self-harm was the 1st leading cause of death in people aged 15-34 years for both sexes[6]. The estimates from the Global Burden of Disease (GBD) Study 2019 ranked self-harm as third among the top causes of disability-adjusted life years in adolescents aged 10-24 years[7].

The majority of suicide deaths (77%) occurred in low- and middle-income countries in 2019[4]. Age-standardized rate (ASR, per 100000) of suicide mortality was 27.5 in Eastern Europe, in high- income Asia Pacific 18.7, in Australasia 10.6, and in Central Europe 13.0 and high- income North America 12.7 in 2016[3]. For both sexes in 2016, the lowest suicide death rates were found in countries in North Africa and the Middle East (4.8/100000). In men in 2016, countries in Eastern Europe recorded the highest suicide mortality rate (50.0/100000), while in women the highest suicide mortality rate was observed in South Asia (12.5/100000)[3].

During the last decades of the 20th century, declining suicide mortality trends were observed in Eastern Europe, the European Union, the United States of America, and in Japan, while suicide mortality increased sharply in the Russian Federation[8]. Since the 2000s, mortality trends from suicide in 28 selected countries across Europe, the Americas, and Australasia showed downward trends in several areas, while in some countries suicide rates increased (in the United Kingdom, Brazil, Mexico, the United States of America, Republic of Korea, and Australia)[9].

WHO and the United Nations Sustainable Development Goals aim to reduce suicide mortality by one third by 2030[10]. Reducing the global suicide mortality rate by a third is both an indicator and a target (the only one for mental health) in the United Nations (UN)-mandated Sustainable Development Goals (SDGs). How the coronavirus disease 2019 pandemic is affecting the burden of suicide is not clear yet, considering the lockdown, increased mental stress, possible delays in mental and other illness

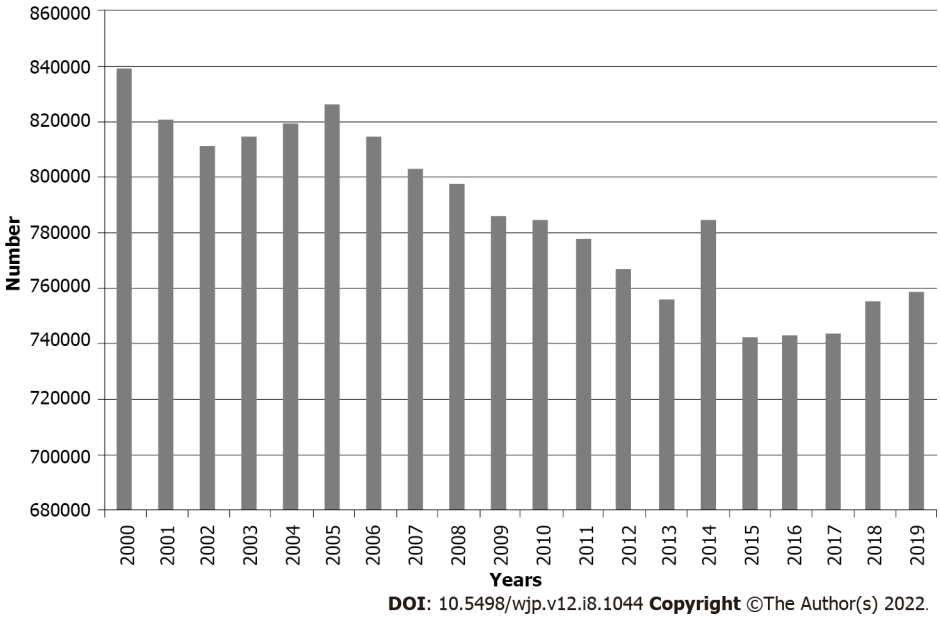

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**Figure 1 Global suicide deaths, 2000-2019.** Source: World Health Organization[6] and Global Burden of Disease estimates[7].

diagnoses, *etc*[11]. Nevertheless, there is a scarcity of studies that explored the mortality of suicide in different areas, as most evaluations are limited to certain populations[8,9]. The aim of this study was to estimate the recent global, regional and national trends of suicide mortality.

## MATERIALS AND METHODS

### Study design

For this descriptive epidemiological study, annual underlying cause of death data was used to describe trends in mortality from suicide for the period 2000-2019. We also cited high-quality articles in *Reference Citation Analysis* (https://www.referencecitationanalysis.com).

### Data sources

Figures of suicide mortality were extracted from the WHO database[4] and from the GBD Study[12]. Mortality estimates of suicide covered site codes X60–X84 and Y87.0, based on the 10th revision of the International Classification of Diseases and Related Health Problems to classify death, injury and cause of death[13]. The WHO and GBD databases provide a comprehensive and comparable assessment of mortality of suicide[4,12]. These databases provide high-quality death statistics by national vital registries worldwide, which were derived from death certificates. According to the WHO guidelines, the definition of the underlying cause of death includes a disease or injury that has started a series of diseases or an injury that has triggered a series of disease states that directly led to death. Mortality was recorded at a local civil registry with information on the cause of death. The information was collected by the health authority and reported to the WHO annually. Only mortality cases that were medically certified were reported. The WHO estimates only comprised national mortality data series that meet the minimal inclusion criteria according to the WHO-defined medium data quality level, based on the degree of population coverage, completeness and accuracy[14]. The WHO and GBD estimates have been documented following the Guidelines for Accurate and Transparent Health Estimates Reporting[15].

This manuscript presents data for 183 WHO Member States, *i.e.*, only members/countries with a population of 90000 or greater in 2019[16]. We extracted data for suicide in men and women for 183 countries worldwide, over the period 2000-2019. Also, suicide mortality was presented within six WHO regions: Africa, the Americas, South-East Asia, Europe, Eastern Mediterranean, and Western Pacific. For this purpose, ASRs (per 100000) calculated by direct method of standardization by age and sex, using the world standard population, were used[17]. Also, specific (age- and sex-specific) mortality rates (expressed per 100000 persons) were presented.

### Statistical analysis

The magnitude and direction of temporal trends for suicide mortality were assessed using the joinpoint regression analysis (Joinpoint regression software, Version 4.5.0.1 - June 2017, available through the Surveillance Research Program of the United States National Cancer Institute), proposed by Kim *et al*

[18]. The joinpoint regression analysis detected point(s), the so-called "joinpoints", where the statistically significant changes of suicide mortality rates occurred (increase or decrease), and determined the trends between joinpoints[18]. The analysis starts with a minimum of zero joinpoints (*i.e.*, a straight line) and tests whether a change in the trend was statistically significant by testing more joinpoints up to the maximum of four joinpoints (five segments). The annual percentage change (APC) for each of the identified trends of suicide rates using the calendar year as a regression variable was determined. For countries worldwide (including the global and regional level), the average APC (AAPC) over the entire considered period was calculated; for each AAPC estimate, the corresponding 95% confidence interval (CI) was determined[19]. In this manuscript, trend of suicide mortality of each country was presented with a straight line in the whole period, even if there were changes in trends in the observed period[18].

The terms "significant increase" or "significant decrease" were used in describing the direction of temporal trends, in order to signify that the slope of the trend was statistically significant ($P < 0.05$, on the basis of the statistical significance of the AAPC compared to zero). For non-statistically significant trends ($P > 0.05$, while AAPC with a 95%CI including zero), the terms "non-statistically significant increase" (for AAPC > 0.5%), and "non-statistically significant decrease" (for AAPC < -0.5%) were used, while the term "stable" was used for AAPC between -0.5% and 0.5%. Disparities in suicide mortality trends according to age and sex were tested by using a comparability test[20]. The objective of the comparability test was to determine whether the two regression mean functions were identical (test of coincidence) or parallel (test of parallelism). A *P*-value < 0.05 was considered statistically significant.

### *Ethics statement*

This study was approved by the Ethics Committee of the Faculty of Medical Sciences, University of Kragujevac (No. 01-14321).

## RESULTS

A total of 759028 (523883 male and 235145 female) suicide deaths were reported worldwide in 2019 (Figure 1). Per annum, the number of suicides ranged from 839548 in 2000 to 742962 in 2015. During the observed period, there were 15.7 million deaths from suicide in the world (10.6 million men and 5.1 million women). Figure 2 shows the global distribution of suicide deaths in 2019 by WHO regions and by sex. In both sexes, most suicide deaths (230453; 31% of the total) were recorded in the South-East Asia region, followed by the region of the Western Pacific (184918; 24%). Almost one fifth of suicide deaths (137266) occurred in the European region. Compared to the distribution for both sexes, the differences in suicide deaths by regions in males are less obvious. In contrast, in females the dominant participation of suicides is evident in the region of South-East Asia (93552; 40% of the total). The female participation in suicide deaths in the European region was twice as low (29008; 12%) compared to men (108268; 21%).

The global ASR of mortality from suicide was 9.0/100000 population in both sexes (Figure 3). The highest rates were found in the region of Africa (11.2/100000), followed by Europe (10.5), South-East Asia (10.2), the Americas (9.0) and Western Pacific (7.2), while the lowest rates were reported in the Eastern Mediterranean (6.4). The global ASR of suicide mortality in 2019 was more than a two-fold higher in males than in females (12.6 in men *vs* 5.4 in women). Suicide mortality in men was the highest in Africa (18.0) and Europe (17.1). The region of South-East Asia (with a rate of 8.1) tended to predominate in the suicide mortality of women across the world. In 2019, the lowest suicide mortality rates in both sexes in 2019 were noted in the Eastern Mediterranean region (9.2 and 3.5, respectively).

There were significant international variations in suicide mortality by sex in 2019 (Figure 4). In men, the suicide mortality rate was the highest in Lesotho (146.9/100000), followed by populations in Eswatini, Guyana, Kiribati (with rates of 78.7, 65.0 and 53.6, respectively), whereas the lowest mortality rates (1.0 or less per 100000 people) were registered in Barbados, Grenada, Antiqua and Barbuda (Figure 4A). Also, there was a great variation in suicide mortality in women across countries: The highest mortality rate was in Lesotho (34.6), followed by populations in Guyana (17.0), and then Zimbabwe, Republic of Korea, Federal States of Micronesia (equally about 13.0/100000 people), while the lowest mortality rate (0.2/100000 people) was observed in Barbados (Figure 4B).

Globally, from 2000 to 2019, ASRs of mortality of suicide had a decreasing tendency in both sexes together [AAPC = -2.4% per year; 95%CI: (-2.6)-(-2.3)] (Figure 5A). Overall suicide mortality rates peaked at 14.0/100000 in 2000, and declined thereafter to 9.0/100000 in 2019. Joinpoint analysis identified two joinpoints, in 2009 and 2016, with three consequent trends. The first and second period showed significantly decreasing trends, with APC of -2.2% [95%CI: (-2.5)-(-2.0)] and -3.0% [95%CI: (-3.4)-(-2.5)], respectively. The trend since 2016 was stable, with APC of -0.5% [95%CI: (-1.9)-0.9]. Suicide mortality rates in males decreased from 18.9/100000 in 2000 to 12.6/100000 in the last year observed; AAPC = -2.2%, 95%CI: (-2.3)-(-2.1) (Figure 5B). Joinpoint analyses of suicide mortality in males identified two joinpoints in the year 2005 and 2016, with three trends. The first and second period showed significantly decreasing trends, with APC of -1.4% [95%CI: (-2.0)-(-0.9)] and -2.5% [95%CI: (-2.7)-(-2.3)], respectively. The trend since 2016 was characterized by a non-significant decrease, with APC

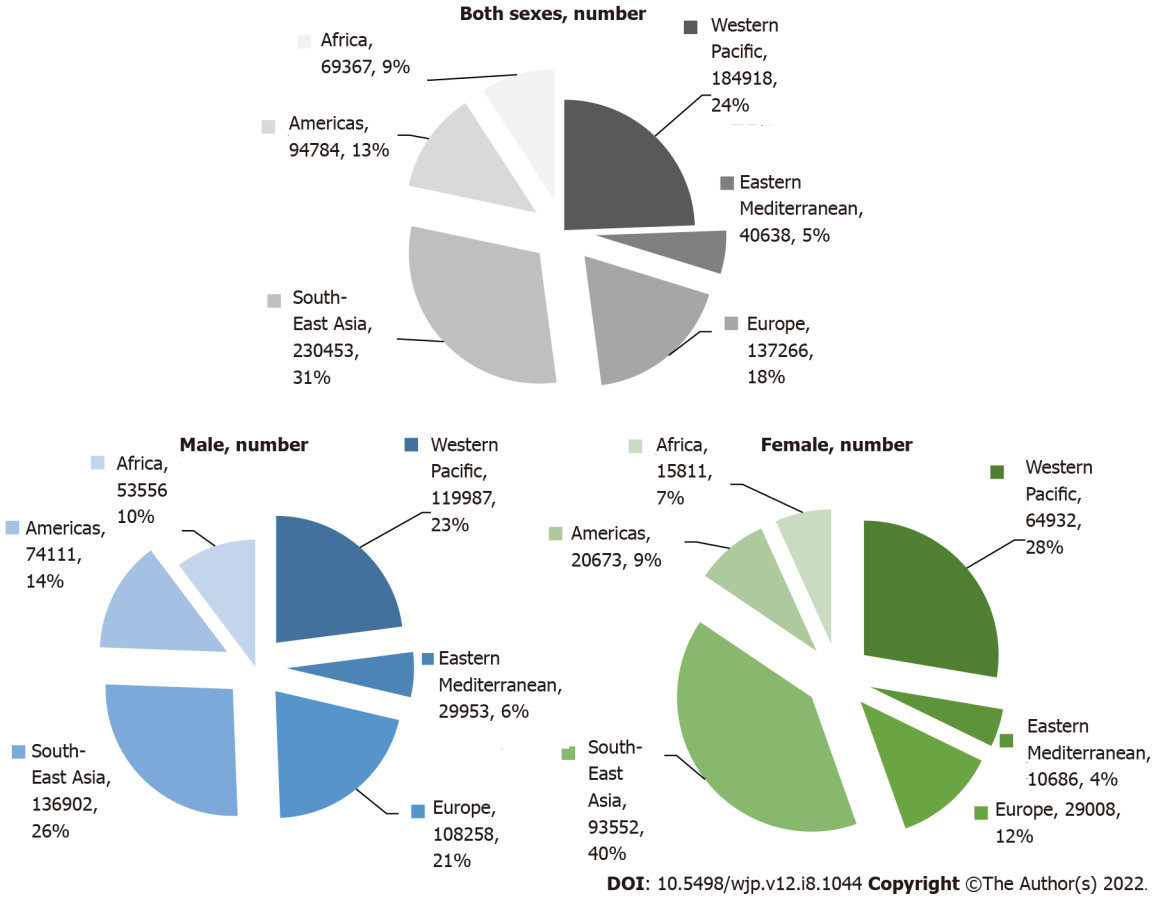


**Figure 2 Number of suicide (global and by World Health Organization regions), by sex, 2019.** Source: World Health Organization[6] and Global Burden of Disease estimates[7].

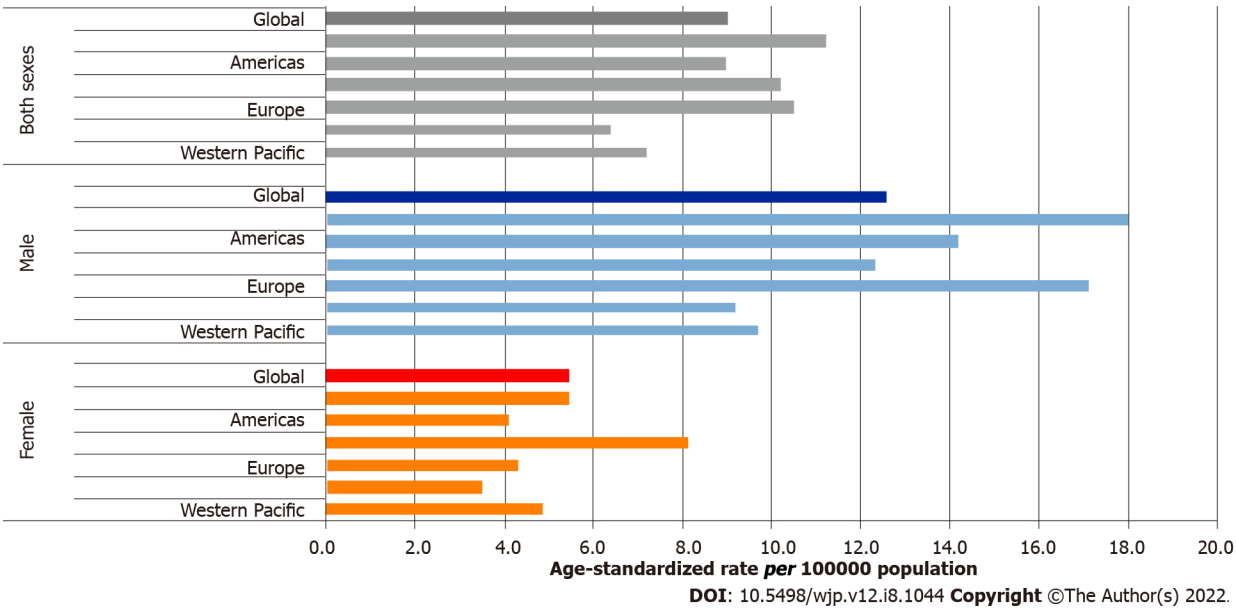


**Figure 3 Age-standardized suicide mortality rates (global and by World Health Organization regions), by sex, 2019.** Source: World Health Organization[6] and Global Burden of Disease estimates[7].

of -1.3% [95%CI: (-2.6)-0.0]. In females, suicide mortality rates decreased from 9.5/100000 in 2000 to 5.4/100000 in the last year observed; AAPC = -3.0%, 95%CI: (-3.2)-(-2.8). Also, joinpoint analyses of suicide mortality in females identified two joinpoints in the year 2011 and 2016, with three trends. The first and second period showed significantly decreasing trends, with APC of -3.0% [95%CI: (-3.3)-(-2.7)]

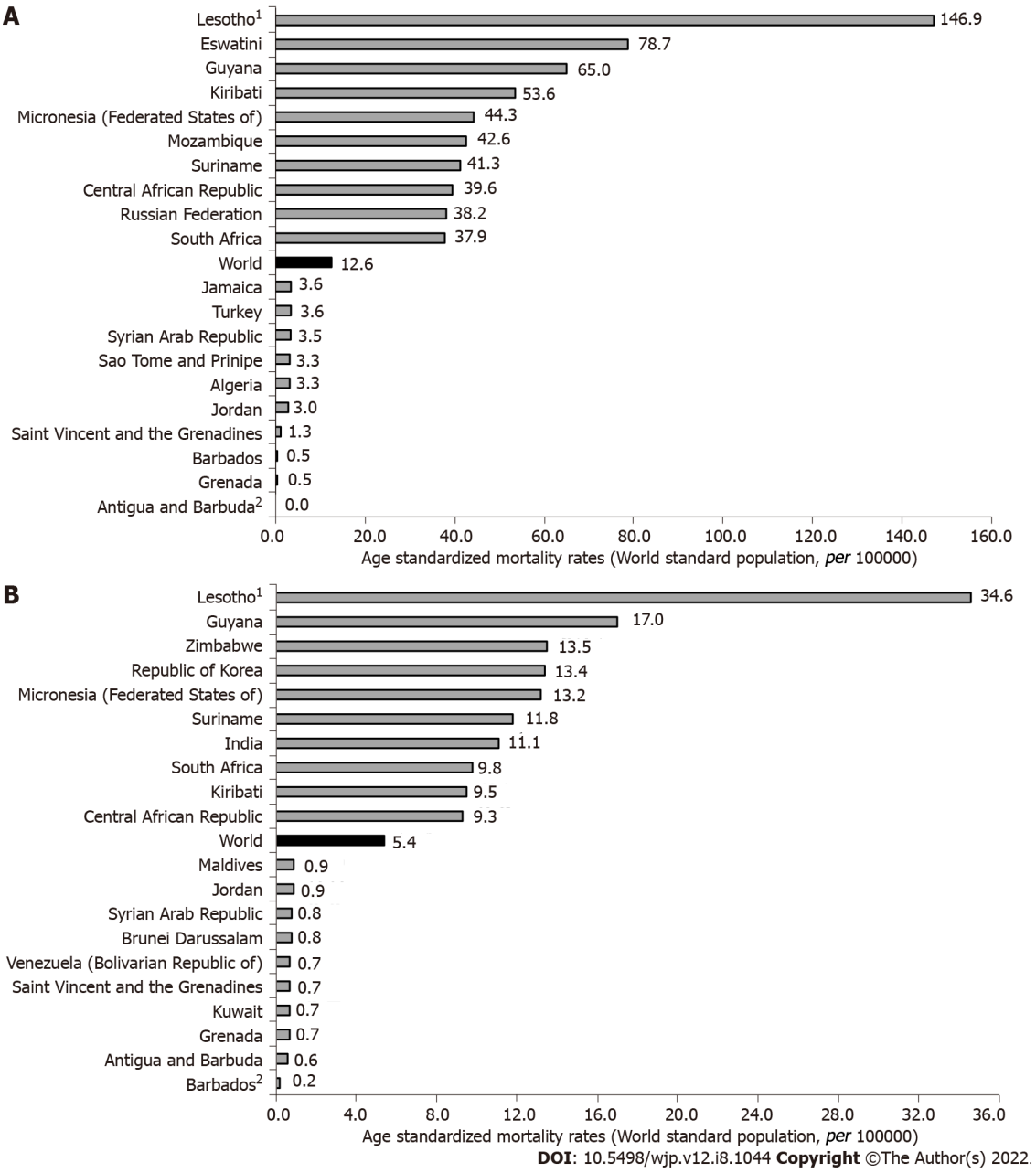

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**Figure 4 Suicide mortality, by countries, 2019.** [1]Country with the highest rates; [2]Country with the lowest rate. A: Men; B: Women. Source: World Health Organization[6] and Global Burden of Disease estimates[7].

and -3.8% [95%CI: (-5.2)-(-2.4)], respectively. The trend since 2016 was stable, with APC of -0.2% [95%CI: (-2.5)-2.2]. The trends in suicide mortality in men and women were not parallel and not coincident according to the comparability test ($P < 0.05$).

When the suicide mortality trend was analyzed by six WHO regions, in males (Figure 6A) significantly decreasing trends were observed in five regions: In Africa (AAPC = -1.5%), South-East Asia (-2.1%), Europe (-3.4%), Eastern Mediterranean (-0.6%), and Western Pacific (-2.9%); the only exception was the region of the Americas, with a significantly increasing suicide mortality trend (+0.6%). Also, significantly decreasing trends were noted in women in five regions: In Africa (-2.3%), South-East Asia (-2.4%), Europe (-2.3%), Eastern Mediterranean (-1.7%), and Western Pacific (-5.1%); the only exception was the region of the Americas, with an unfavorable suicide mortality trend (+1.2%) (Figure 6B).

In comparison to males, suicide mortality rates were lower in females in countries across the world in 2019: The only exception was for females in Grenada and Antigua and Barbuda in whom suicide mortality rates higher than in men were recorded (Table 1). In both sexes together, a total of 133 of 183 countries showed a significantly decreasing trend in suicide mortality. Among the 133 countries where a decline in mortality of suicide was observed, Barbados (AAPC = -10.0%), Grenada (AAPC = -8.5%), Serbia (AAPC = -7.6%), and Venezuela (AAPC = -6.2%) had the most marked reductions. In total, 26 countries had a significant increase in mortality of suicide and 24 countries reported stable trends. Out

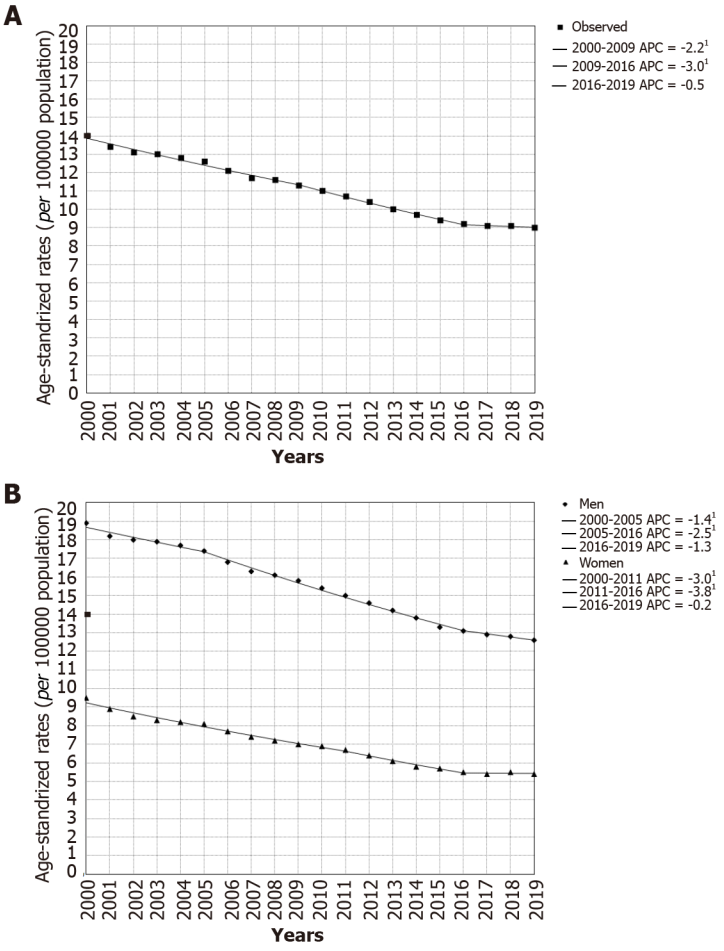


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**Figure 5 Joinpoint regression analysis of global suicide mortality.** [1]Indicates that the Annual Percent Change is significantly different from zero at the alpha = 0.05 level. Final selected model: 2 joinpoints. A: Both sexes, 2019: 2 joinpoints; B: By sex, 2019: Men: 2 joinpoints *vs* women: 2 joinpoints. APC: Annual percent change. Source: World Health Organization[6] and Global Burden of Disease estimates[7].

of all 26 countries with a rise in suicide mortality, Lesotho (AAPC = +6.0%), Cyprus (AAPC = +5.1%), Paraguay (AAPC = +3.0%), Saudi Arabia (AAPC = +2.8%), Brunei (AAPC = +2.6%), Greece (AAPC = +2.6%), Georgia (AAPC = +2.1%), and Mexico (AAPC = +2.0%), were among those with the highest increase in mortality. Other countries with an increasing trend were (in alphabetical order) Bahamas, Brazil, Dominican Republic, Guinea, Guyana, Jamaica, Micronesia, Mozambique, Netherlands, Niger, Papua New Guinea, Philippines, Syria, Tajikistan, United States of America, Uruguay, Viet Nam and Zimbabwe.

Trends in suicide mortality were increasing significantly in both sexes in several countries - Brazil, Dominican Republic, Greece, Guinea, Jamaica, Lesotho, Mexico, Micronesia, the Netherlands, Papua New Guinea, Paraguay, Philippines, Saudi Arabia, Solomon Islands, Tajikistan, and United States of America. Some countries have shown a significant increase in suicide mortality trends only in females - Australia, Canada, Equatorial Guinea, Nepal, Portugal, and Sierra Leone. On the other hand, several countries showed a significant increase in suicide mortality trends only among men - in Bahamas, Cyprus, Georgia, Haiti, Iraq, Lebanon, Mozambique, Niger, and Syria.

Suicide death rates increased with age both in males and females (Table 2). In both sexes, suicide mortality rates were almost three times higher in people aged 70 or older than in people under 70. Age-specific suicide mortality rates in males were two to three times higher than rates in females in all age groups, with only one exception for males and females in younger age groups of 10-19 years. Suicide mortality rates were decreasing significantly in all age groups in both men and women from 2000 to 2019. The trends in suicide mortality by age were not parallel and not coincident according to comparability test ($P < 0.05$) in either sex.

## DISCUSSION

This study presents global, regional and national trends in suicide mortality in 183 countries worldwide

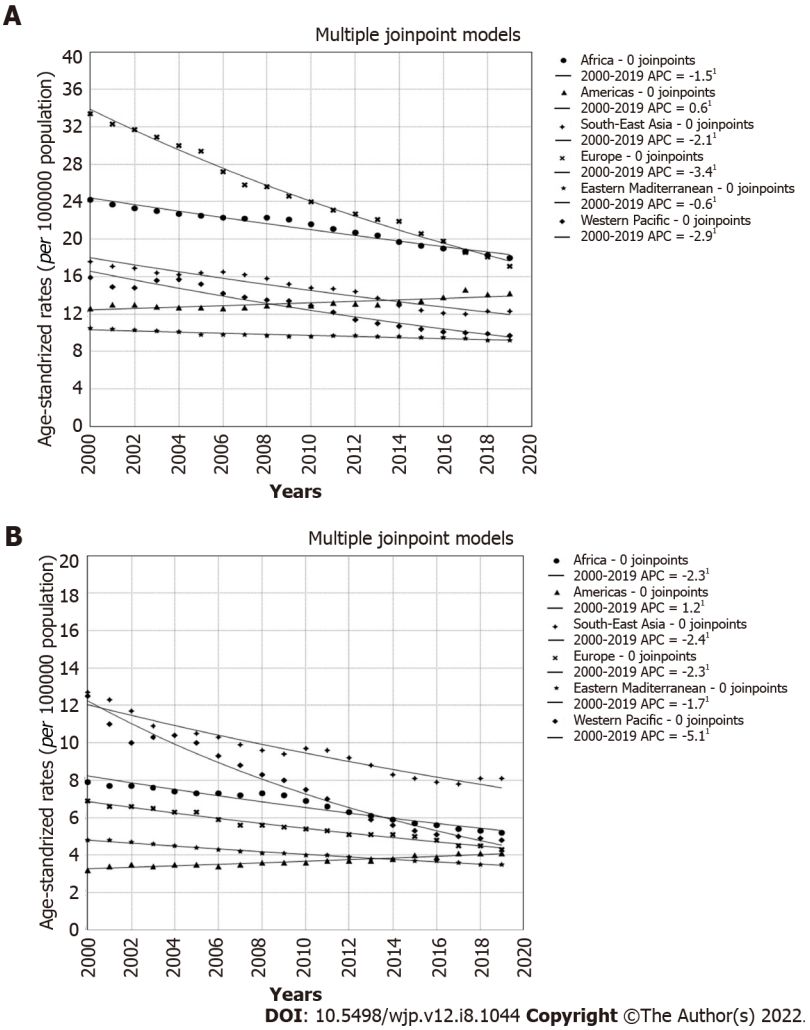

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**Figure 6 Suicide mortality trends (World Health Organization regions), 2000-2019; a joinpoint analysis.** [1]Statistically significant trend. A: In males; B: In females. APC: Annual percent change. Source: World Health Organization[6] and Global Burden of Disease estimates[7].

over the last two decades. Although a decrease in suicide mortality trends was seen in both sexes and in all age groups in most of the areas, increasing suicide mortality trends were reported in 26 countries. Worldwide, an estimated 759028 deaths from suicide occurred in 2019, with an ASR of 9.0/100000 people. Globally, compared to 2000, in 2019 there were approximately 80000 fewer deaths from suicides (less by about 18000 cases in males and about 62000 cases in females). In males, the decrease in number of total suicide deaths can be primarily attributed to the decrease in suicide deaths among men in the European region (from 153973 cases, *i.e.*, with a share of 28.4% in the total number of suicides among men in 2000 to 108258 deaths - 20.7% in 2019). In females, the decrease in number of total suicide deaths can be primarily attributed to the decrease in suicide deaths among women in the Western Pacific region (with 112377 cases, *i.e.*, with a share of 37.8% in the total number of suicides among women in 2000 to 64932 deaths by suicide - 27.6% in 2019).

Mortality rates from suicide were approximately 2.5 times higher in men than in women in 2019 (12.5/100000 men and 5.4/100000 women). In males in 2019, the regions of Africa (18.0/100000), Europe (17.1) and Americas (14.2) had suicide mortality rates which were higher than the global average. In females in 2019, only the South-East Asia region (8.1/100000) had suicide rates which were higher than the global average. For both men and women, the countries of the African region were ranked in the 3 leading places among the countries with the highest suicide rate in the world in 2019. These findings are consistent with previous research[3,8,9,21-25]: Men had higher rates of suicide at all time points, for all age groups. Divergence in male and female suicide rates could be due to the changes in availability and lethality of commonly used methods of suicide: Domestic gas poisoning was the most commonly used method of suicide in males, while in females drug overdose dominated as the method for suicide (an explanation of this trend could be replacement of barbiturates by the less toxic benzodiazepines which usually result in lower lethality, *etc*)[23,24]. In Canada[21] and in 16 countries participating in the European Alliance Against Depression[26], hanging was the most prevalent method of suicide in both males (followed by firearms and poisoning by drugs) and females (followed by poisoning by drugs and jumping from a high place). In the Republic of Korea, from 1991 to 2015, with a traditionally high rate of

**Table 1 Suicide mortality trends, by countries and sex, 2000-2019; a joinpoint analysis: Age-standardized rates (per 100000 population, world standard population)[6,7]**

| Countries[1] | Both sexes | | | Male | | | Female | | |
|---|---|---|---|---|---|---|---|---|---|
| | 2000 | 2019 | Trend[2] | 2000 | 2019 | Trend[2] | 2000 | 2019 | Trend[2] |
| Afghanistan | 7.7 | 6.0 | -1.8[a] | 7.6 | 6.2 | -1.7[a] | 7.8 | 5.7 | -2.1[a] |
| Albania | 5.2 | 3.7 | -2.0 | 7.6 | 5.3 | -2.0[a] | 2.9 | 2.2 | -2.0 |
| Algeria | 4.7 | 2.6 | -3.4[a] | 5.9 | 3.3 | -3.3[a] | 3.5 | 1.9 | -3.4[a] |
| Angola | 17.6 | 12.6 | -2.1[a] | 30.0 | 21.7 | -2.0[a] | 6.2 | 4.7 | -2.0[a] |
| Antigua | 2.0 | 0.3 | - | 4.5 | 0.0 | - | 0.0 | 0.6 | - |
| Argentina | 9.2 | 8.1 | -0.7[a] | 16.0 | 13.5 | -0.8[a] | 3.4 | 3.3 | -0.6 |
| Armenia | 3.3 | 2.7 | -0.3 | 5.5 | 4.9 | -0.2 | 1.7 | 1.0 | -0.3 |
| Australia | 11.8 | 11.3 | +0.6 | 18.8 | 17.0 | +0.2 | 5.0 | 5.6 | +1.6[a] |
| Austria | 15.8 | 10.4 | -1.8[a] | 24.9 | 16.6 | -1.9[a] | 7.9 | 4.6 | -2.1[a] |
| Azerbaijan | 3.4 | 4.0 | -0.1 | 5.8 | 6.6 | -0.1 | 1.3 | 1.5 | -0.5 |
| Bahamas | 2.5 | 3.4 | +1.5[a] | 4.2 | 5.8 | +1.6[a] | 1.1 | 1.2 | +0.1 |
| Bahrain | 7.0 | 7.2 | -1.9[a] | 10.2 | 9.9 | -2.1[a] | 2.5 | 2.3 | -2.4[a] |
| Bangladesh | 6.9 | 3.9 | -3.5[a] | 10.0 | 6.0 | -3.1[a] | 3.5 | 1.7 | -4.3[a] |
| Barbados | 2.6 | 0.3 | -10.0[a] | 4.9 | 0.5 | -8.7[a] | 0.5 | 0.2 | - |
| Belarus | 37.3 | 16.5 | -4.7[a] | 69.3 | 30.1 | -4.8[a] | 9.5 | 5.3 | -3.5[a] |
| Belgium | 18.3 | 13.9 | -1.3[a] | 27.0 | 19.6 | -1.6[a] | 10.1 | 8.4 | -0.6[a] |
| Belize | 10.0 | 7.7 | -0.9[a] | 17.2 | 13.6 | -0.7 | 2.9 | 1.8 | -2.6[a] |
| Benin | 14.7 | 12.7 | -0.8[a] | 23.6 | 20.3 | -0.8[a] | 7.5 | 6.1 | -1.1[a] |
| Bhutan | 6.9 | 5.1 | -1.6[a] | 8.6 | 6.8 | -1.2[a] | 5.0 | 3.1 | -2.6[a] |
| Bolivia | 8.4 | 6.8 | -0.7[a] | 11.8 | 9.6 | -0.8[a] | 5.2 | 4.2 | -0.7[a] |
| Bosnia and Herzegovina | 8.1 | 8.3 | -0.3 | 13.3 | 13.5 | -0.3 | 3.5 | 3.4 | -0.3[a] |
| Botswana | 46.3 | 20.2 | -4.4[a] | 76.2 | 35.5 | -4.0[a] | 20.6 | 7.8 | -5.3[a] |
| Brazil | 4.5 | 6.4 | +1.6[a] | 7.4 | 10.3 | +1.5[a] | 1.8 | 2.8 | +2.0[a] |
| Brunei | 1.7 | 2.5 | +2.6[a] | 3.0 | 4.2 | +1.9 | 0.4 | 0.8 | - |
| Bulgaria | 14.0 | 6.5 | -3.9[a] | 21.8 | 10.6 | -3.7[a] | 7.1 | 2.9 | -4.5[a] |
| Burkina Faso | 16.9 | 14.4 | -0.5[a] | 27.6 | 24.5 | -0.2[a] | 9.2 | 6.5 | -1.6[a] |
| Burundi | 23.4 | 12.1 | -3.3[a] | 35.5 | 18.9 | -3.0[a] | 13.6 | 6.4 | -4.1[a] |
| Cabo Verde | 18.2 | 15.2 | -0.8[a] | 33.3 | 27.4 | -1.1[a] | 6.8 | 5.1 | -1.3[a] |
| Cambodia | 6.8 | 5.5 | -1.2[a] | 9.2 | 8.4 | -0.5[a] | 5.0 | 3.1 | -2.7[a] |
| Cameroon | 19.1 | 15.9 | -1.2[a] | 29.8 | 25.2 | -1.1[a] | 9.7 | 7.6 | -1.5[a] |
| Canada | 10.7 | 10.3 | +0.1 | 16.6 | 15.3 | -0.1 | 5.0 | 5.4 | +0.8[a] |
| Central African Republic | 32.5 | 23.0 | -1.2[a] | 53.7 | 39.6 | -1.0[a] | 14.6 | 9.3 | -2.1[a] |
| Chad | 15.7 | 13.2 | -0.9[a] | 24.8 | 20.2 | -1.1[a] | 7.7 | 6.9 | -0.4[a] |
| Chile | 10.5 | 8.0 | -1.1[a] | 19.0 | 13.4 | -1.5[a] | 2.9 | 3.0 | +0.4 |
| China | 14.9 | 6.7 | -4.5[a] | 15.5 | 8.6 | -3.4[a] | 14.5 | 4.8 | -6.0[a] |
| Colombia | 5.3 | 3.7 | -1.5[a] | 8.4 | 6.0 | -1.3[a] | 2.6 | 1.7 | -2.4[a] |
| Comoros | 10.9 | 8.5 | -1.1[a] | 14.5 | 11.3 | -1.0[a] | 7.6 | 5.8 | -1.3[a] |
| Congo | 24.7 | 11.6 | -3.4[a] | 38.5 | 18.3 | -3.4[a] | 14.1 | 6.1 | -3.7[a] |
| Costa Rica | 6.9 | 7.6 | -0.4 | 12.3 | 13.3 | -0.6 | 1.6 | 1.9 | +0.4 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Côte d'Ivoire | 24.0 | 15.7 | -1.9[a] | 37.5 | 25.7 | -1.6[a] | 8.4 | 5.0 | -2.3[a] |
| Croatia | 16.3 | 11.0 | -2.0[a] | 27.1 | 17.7 | -2.1[a] | 6.9 | 5.1 | -1.7[a] |
| Cuba | 15.6 | 10.2 | -1.5[a] | 22.7 | 16.7 | -1.0[a] | 8.9 | 4.1 | -3.3[a] |
| Cyprus | 1.9 | 3.2 | +5.1[a] | 2.6 | 5.3 | +6.3[a] | 1.2 | 1.1 | +0.6 |
| Czechia | 13.4 | 9.5 | -1.2[a] | 22.6 | 15.4 | -1.5[a] | 5.1 | 3.8 | -0.8[a] |
| DPR Korea | 10.3 | 8.2 | -0.7[a] | 12.3 | 10.6 | -0.2 | 8.9 | 6.3 | -1.4[a] |
| DR Congo | 14.5 | 12.4 | -1.0[a] | 24.9 | 20.7 | -1.1[a] | 5.7 | 5.0 | -1.0[a] |
| Denmark | 12.5 | 7.6 | -2.3[a] | 18.9 | 11.1 | -2.3[a] | 6.4 | 4.2 | -2.3[a] |
| Djibouti | 12.1 | 11.9 | +0.1 | 17.1 | 16.3 | -0.2 | 7.5 | 7.6 | +0.2 |
| Dominican Republic | 4.9 | 5.1 | +1.1[a] | 8.3 | 8.5 | +1.1[a] | 1.6 | 1.9 | +1.3[a] |
| Ecuador | 6.8 | 7.7 | +0.2 | 9.6 | 11.9 | +0.8 | 4.2 | 3.6 | -1.3[a] |
| Egypt | 3.6 | 3.4 | -0.3 | 4.7 | 4.7 | +0.2 | 2.7 | 2.2 | -1.1[a] |
| El Salvador | 6.7 | 6.1 | -0.9 | 10.6 | 11.1 | -0.4 | 3.4 | 2.1 | -2.4[a] |
| Equatorial Guinea | 19.4 | 13.5 | -0.9[a] | 31.0 | 18.5 | -1.7[a] | 7.8 | 8.8 | +1.3[a] |
| Eritrea | 23.4 | 17.3 | -1.3[a] | 38.4 | 27.2 | -1.5[a] | 9.6 | 8.3 | -0.5[a] |
| Estonia | 25.0 | 12.0 | -3.8[a] | 43.1 | 20.2 | -4.0[a] | 9.6 | 4.5 | -3.2[a] |
| Eswatini | 40.6 | 40.5 | -0.8 | 65.5 | 78.7 | +0.4 | 20.9 | 6.4 | -7.5[a] |
| Ethiopia | 18.4 | 9.5 | -3.8[a] | 25.9 | 14.2 | -3.3[a] | 11.2 | 5.2 | -4.6[a] |
| Fiji | 11.7 | 9.5 | -0.6[a] | 15.3 | 13.1 | -0.2 | 8.2 | 6.0 | -1.4[a] |
| Finland | 21.7 | 13.4 | -2.5[a] | 33.3 | 20.1 | -2.7[a] | 10.4 | 6.8 | -2.1[a] |
| France | 15.8 | 9.7 | -2.6[a] | 24.2 | 15.2 | -2.3[a] | 8.3 | 4.5 | -3.3[a] |
| Gabon | 19.4 | 13.1 | -1.5[a] | 33.2 | 23.3 | -1.2[a] | 7.5 | 3.8 | -3.4[a] |
| Gambia | 11.1 | 9.6 | -0.9[a] | 15.3 | 13.3 | -1.0[a] | 7.1 | 6.2 | -0.8[a] |
| Georgia | 6.6 | 7.7 | +2.1[a] | 11.9 | 14.0 | +2.3[a] | 2.2 | 2.2 | +0.3 |
| Germany | 11.2 | 8.3 | -1.4[a] | 17.6 | 12.8 | -1.6[a] | 5.3 | 3.9 | -1.3[a] |
| Ghana | 9.8 | 10.5 | +0.3 | 17.2 | 20.0 | +0.7 | 2.9 | 1.8 | -3.0[a] |
| Greece | 2.9 | 3.6 | +2.6[a] | 4.6 | 5.9 | +2.5[a] | 1.2 | 1.5 | +3.4[a] |
| Grenada | 2.1 | 0.6 | -8.5a | 3.8 | 0.5 | - | 0.6 | 0.7 | - |
| Guatemala | 13.5 | 6.2 | -5.5[a] | 24.0 | 10.3 | -6.0[a] | 4.1 | 2.5 | -3.4[a] |
| Guinea | 9.7 | 12.3 | +1.6[a] | 13.7 | 18.4 | +1.9[a] | 6.7 | 8.0 | +1.3[a] |
| Guinea-Bissau | 17.5 | 12.4 | -1.6[a] | 28.7 | 19.8 | -1.8[a] | 8.8 | 6.7 | -1.3[a] |
| Guyana | 35.8 | 40.9 | +0.5[a] | 57.6 | 65.0 | +0.5 | 14.5 | 17 | +0.4 |
| Haiti | 12.7 | 11.2 | -0.4[a] | 14.7 | 14.9 | +0.5[a] | 11.1 | 8.0 | -1.5[a] |
| Honduras | 3.0 | 2.6 | +0.2 | 5.1 | 4.4 | +0.3 | 1.1 | 1.0 | -0.8[a] |
| Hungary | 26.6 | 11.8 | -3.7[a] | 44.7 | 19.1 | -3.9[a] | 11.0 | 5.5 | -3.1[a] |
| Iceland | 12.7 | 11.2 | -0.2 | 19.3 | 18.7 | +0.6 | 6.0 | 3.5 | -3.1[a] |
| India | 19.1 | 12.9 | -2.3[a] | 20.9 | 14.7 | -2.2[a] | 17.4 | 11.1 | -2.4[a] |
| Indonesia | 3.8 | 2.6 | -2.2[a] | 5.5 | 4.0 | -2.0[a] | 2.1 | 1.2 | -3.1[a] |
| Iran | 8.0 | 5.1 | -1.5[a] | 10.1 | 7.5 | -0.3 | 5.9 | 2.8 | -3.7[a] |
| Iraq | 5.3 | 4.7 | +0.0 | 7.2 | 7.3 | +0.6[a] | 3.4 | 2.4 | -1.3[a] |
| Ireland | 12.1 | 8.9 | -1.4[a] | 19.8 | 14.3 | -1.4[a] | 4.4 | 3.6 | -1.1[a] |
| Israel | 6.8 | 5.2 | -1.4[a] | 11.0 | 8.3 | -1.5[a] | 2.8 | 2.1 | -1.3[a] |
| Italy | 5.5 | 4.3 | -0.8[a] | 8.7 | 6.7 | -0.9[a] | 2.7 | 2.1 | -0.9[a] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Jamaica | 2.1 | 2.3 | +1.1[a] | 3.3 | 3.6 | +1.0[a] | 0.9 | 1.0 | +1.3[a] |
| Japan | 18.1 | 12.2 | -1.9[a] | 26.8 | 17.5 | -2.2[a] | 9.6 | 6.9 | -1.4[a] |
| Jordan | 3.5 | 2.0 | -3.4[a] | 4.5 | 3.0 | -2.5[a] | 2.4 | 0.9 | -6.0[a] |
| Kazakhstan | 39.4 | 18.1 | -4.2[a] | 71.7 | 30.9 | -4.5[a] | 11.4 | 6.9 | -2.9[a] |
| Kenya | 15.8 | 11.0 | -1.7[a] | 24.8 | 18.1 | -1.5[a] | 8.2 | 5.3 | -2.0[a] |
| Kiribati | 35.6 | 30.6 | -0.6[a] | 62.6 | 53.6 | -0.6[a] | 11.1 | 9.5 | -0.6[a] |
| Kuwait | 3.1 | 2.7 | -0.9[a] | 4.1 | 3.8 | -0.3 | 1.5 | 0.7 | -4.5[a] |
| Kyrgyzstan | 17.6 | 8.3 | -3.5[a] | 30.7 | 13.5 | -3.8[a] | 5.5 | 3.5 | -1.9[a] |
| Lao PDR | 8.7 | 6.0 | -2.0[a] | 11.0 | 8.6 | -1.3[a] | 6.5 | 3.5 | -3.5[a] |
| Latvia | 29.6 | 16.1 | -3.0[a] | 54.3 | 29.0 | -3.0[a] | 9.4 | 4.6 | -3.9[a] |
| Lebanon | 3.0 | 2.8 | -0.2 | 3.7 | 3.9 | +0.6[a] | 2.4 | 1.7 | -1.8[a] |
| Lesotho | 42.6 | 87.5 | +6.0[a] | 73.9 | 146.9 | +5.7[a] | 16.0 | 34.6 | +6.1[a] |
| Liberia | 8.8 | 7.4 | -0.7[a] | 11.0 | 9.4 | -0.6[a] | 6.7 | 5.5 | -0.7[a] |
| Libya | 5.3 | 4.5 | +0.1 | 7.1 | 6.1 | +0.2 | 3.3 | 2.9 | +0.3 |
| Lithuania | 45.8 | 20.2 | -3.4[a] | 80.7 | 36.1 | -3.4[a] | 15.3 | 6.2 | -3.4[a] |
| Luxembourg | 13.4 | 8.6 | -2.8[a] | 20.3 | 11.8 | -3.6[a] | 7.1 | 5.4 | -1.2 |
| Madagascar | 10.8 | 9.2 | -1.0[a] | 15.5 | 13.3 | -0.9[a] | 6.1 | 5.4 | -0.8[a] |
| Malawi | 19.2 | 10.6 | -2.4[a] | 31.8 | 20.0 | -1.8[a] | 8.4 | 3.3 | -4.1[a] |
| Malaysia | 6.1 | 5.8 | -0.5[a] | 9.1 | 9.0 | -0.3 | 3.1 | 2.4 | -1.3[a] |
| Maldives | 5.3 | 2.8 | -3.1[a] | 8.1 | 4.1 | -3.4[a] | 2.3 | 0.9 | -4.9[a] |
| Mali | 8.8 | 8.0 | -0.4[a] | 10.6 | 10.5 | +0.0 | 7.2 | 5.7 | -1.0[a] |
| Malta | 6.0 | 5.3 | +0.2 | 9.8 | 8.4 | +0.5 | 2.4 | 2.3 | -0.6 |
| Mauritania | 6.4 | 5.5 | -0.8[a] | 8.2 | 7.4 | -0.6[a] | 4.9 | 3.9 | -1.2[a] |
| Mauritius | 11.5 | 8.8 | -0.8 | 18.4 | 15.0 | -0.5 | 4.9 | 2.5 | -2.1[a] |
| Mexico | 3.9 | 5.3 | +2.0[a] | 6.9 | 8.7 | +1.7[a] | 1.1 | 2.2 | +3.6[a] |
| Micronesia | 28.0 | 29.0 | +0.3[a] | 43.4 | 44.3 | +0.2[a] | 13.0 | 13.2 | +0.3[a] |
| Mongolia | 23.6 | 18.0 | -1.5[a] | 37.6 | 31.1 | -1.1[a] | 10.2 | 5.6 | -2.8[a] |
| Montenegro | 18.9 | 16.2 | -0.8[a] | 28.9 | 25.4 | -0.7[a] | 9.8 | 7.9 | -1.1[a] |
| Morocco | 10.8 | 7.3 | -2.3[a] | 13.9 | 10.1 | -2.0[a] | 8.0 | 4.7 | -2.8[a] |
| Mozambique | 20.9 | 23.2 | +0.9[a] | 36.2 | 42.6 | +1.2[a] | 8.8 | 8.9 | +0.6 |
| Myanmar | 5.1 | 3.0 | -2.8[a] | 8.1 | 5.1 | -2.2[a] | 2.6 | 1.1 | -5.0[a] |
| Namibia | 27.5 | 13.5 | -4.1[a] | 47.5 | 24.9 | -3.9[a] | 11.4 | 4.4 | -4.8[a] |
| Nepal | 10.9 | 9.8 | -0.3 | 19.4 | 18.6 | +0.2 | 2.8 | 2.9 | +0.5[a] |
| Netherlands | 8.1 | 9.3 | +1.1[a] | 11.2 | 12.5 | +0.9[a] | 5.2 | 6.1 | +1.3[a] |
| New Zealand | 12.4 | 10.3 | -0.9[a] | 20.8 | 15.4 | -1.2[a] | 4.4 | 5.4 | +0.0 |
| Nicaragua | 6.3 | 4.7 | -1.7[a] | 9.3 | 7.8 | -1.5[a] | 3.6 | 1.9 | -2.4[a] |
| Niger | 9.5 | 10.1 | +0.3[a] | 12.6 | 14.1 | +0.6[a] | 6.7 | 6.4 | -0.2[a] |
| Nigeria | 9.2 | 6.9 | -1.7[a] | 13.7 | 10.1 | -1.7[a] | 5.1 | 3.8 | -2.0[a] |
| North Macedonia | 8.7 | 7.2 | -1.6[a] | 12.5 | 11.0 | -1.5[a] | 4.9 | 3.5 | -1.9[a] |
| Norway | 13.0 | 9.9 | -1.0[a] | 19.9 | 13.4 | -1.5[a] | 6.1 | 6.3 | +0.1 |
| Oman | 6.7 | 4.5 | -2.5[a] | 10.1 | 6.4 | -2.9[a] | 2.0 | 1.1 | -3.1[a] |
| Pakistan | 11.1 | 9.8 | -0.8[a] | 16.1 | 14.6 | -0.7[a] | 5.7 | 4.8 | -1.2[a] |
| Panama | 5.9 | 2.9 | -4.4[a] | 10.4 | 4.8 | -4.5[a] | 1.5 | 1.0 | -3.6[a] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Papua New Guinea | 2.8 | 3.6 | +1.1[a] | 4.4 | 5.2 | +0.9[a] | 1.4 | 1.9 | +1.4[a] |
| Paraguay | 3.6 | 6.2 | +3.0[a] | 4.8 | 9.0 | +3.5[a] | 2.5 | 3.3 | +1.5[a] |
| Peru | 3.4 | 2.7 | -0.8[a] | 4.6 | 4.1 | -0.2 | 2.4 | 1.4 | -2.3[a] |
| Philippines | 2.3 | 2.5 | +1.4[a] | 3.5 | 3.9 | +1.6[a] | 1.1 | 1.3 | +1.5[a] |
| Poland | 15.3 | 9.3 | -1.9[a] | 26.8 | 16.5 | -1.8[a] | 4.7 | 2.4 | -2.9[a] |
| Portugal | 5.5 | 7.2 | +0.4 | 9.5 | 11.6 | +0.1 | 2.1 | 3.5 | +1.3[a] |
| Qatar | 7.6 | 4.7 | -2.8[a] | 10.0 | 5.7 | -3.3[a] | 2.6 | 1.7 | -2.1[a] |
| Republic of Korea | 13.9 | 21.2 | +1.1 | 20.4 | 29.7 | +1.0 | 8.2 | 13.4 | +1.0 |
| Moldova | 16.3 | 12.2 | -1.9[a] | 30.7 | 22.1 | -2.0[a] | 4.2 | 3.3 | -2.0[a] |
| Romania | 11.3 | 7.3 | -2.1[a] | 19.4 | 12.6 | -2.1[a] | 3.7 | 2.4 | -2.4[a] |
| Russian Federation | 48.9 | 21.6 | -4.1[a] | 88.8 | 38.2 | -4.3[a] | 13.4 | 7.2 | -3.1[a] |
| Rwanda | 25.6 | 9.5 | -4.9[a] | 38.8 | 14.8 | -4.7[a] | 14.0 | 5.0 | -5.2[a] |
| Saint Lucia | 8.1 | 6.9 | -0.4 | 14.5 | 12.5 | -0.4 | 2.1 | 1.5 | -1.1[a] |
| Saint Vincent | 6.5 | 1.0 | - | 12.6 | 1.3 | - | 0.5 | 0.7 | - |
| Samoa | 16.3 | 14.6 | -0.5[a] | 24.1 | 20.9 | -0.7[a] | 7.8 | 7.8 | +0.2 |
| Sao Tome and Principe | 2.2 | 2.2 | -0.2 | 3.2 | 3.3 | -0.1 | 1.4 | 1.2 | -0.8[a] |
| Saudi Arabia | 3.8 | 5.4 | +2.8a | 5.7 | 7.8 | +2.6[a] | 1.4 | 1.9 | +3.2[a] |
| Senegal | 14.4 | 11.0 | -1.3[a] | 23.5 | 18.5 | -1.1[a] | 6.8 | 5.2 | -1.2[a] |
| Serbia | 18.9 | 7.9 | -7.6[a] | 29.0 | 12.2 | -8.1[a] | 10.1 | 3.9 | -6.9[a] |
| Seychelles | 9.8 | 7.7 | -1.2[a] | 18.4 | 14.0 | -1.5[a] | 1.7 | 1.3 | -1.4[a] |
| Sierra Leone | 10.1 | 11.3 | +0.2 | 14.4 | 14.8 | -0.2 | 6.5 | 8.2 | +0.9[a] |
| Singapore | 11.4 | 9.7 | -2.0[a] | 15.2 | 12.7 | -1.9[a] | 7.8 | 6.4 | -2.7[a] |
| Slovakia | 12.6 | 9.3 | -1.8[a] | 21.9 | 16.7 | -1.7[a] | 4.3 | 2.6 | -2.2[a] |
| Slovenia | 25.6 | 14.0 | -3.4[a] | 40.4 | 22.7 | -3.3[a] | 12.6 | 5.5 | -4.2[a] |
| Solomon Islands | 17.4 | 17.4 | +0.3 | 32.0 | 32.2 | +0.3[a] | 2.1 | 2.4 | +1.3[a] |
| Somalia | 16.8 | 14.7 | -0.8[a] | 26.0 | 22.8 | -0.8[a] | 7.9 | 7.1 | -0.5[a] |
| South Africa | 26.6 | 23.5 | -0.8[a] | 42.7 | 37.9 | -0.6[a] | 11.6 | 9.8 | -1.5[a] |
| South Sudan | 7.9 | 6.7 | -0.9[a] | 12.4 | 10.4 | -1.0[a] | 3.9 | 3.4 | -0.8[a] |
| Spain | 6.6 | 5.3 | -0.8[a] | 10.5 | 7.9 | -1.1[a] | 3.0 | 2.8 | +0.0 |
| Sri Lanka | 27.4 | 12.9 | -3.7[a] | 41.5 | 20.9 | -3.3[a] | 14 | 6.1 | -3.9[a] |
| Sudan | 5.6 | 4.8 | -0.8[a] | 7.2 | 6.3 | -0.7[a] | 4.0 | 3.3 | -0.9[a] |
| Suriname | 25.0 | 25.9 | -0.3[a] | 38.8 | 41.3 | -0.2 | 11.8 | 11.8 | -0.1 |
| Sweden | 12.2 | 12.4 | +0.1 | 17.1 | 16.9 | -0.1 | 7.5 | 7.7 | +0.4 |
| Switzerland | 15.9 | 9.8 | -2.8[a] | 23.7 | 14.2 | -2.7[a] | 8.6 | 5.7 | -3.0[a] |
| Syria | 2.0 | 2.1 | +0.5[a] | 3.2 | 3.5 | +0.7[a] | 0.9 | 0.8 | +0.1 |
| Tajikistan | 5.1 | 5.3 | +0.7[a] | 7.3 | 7.4 | +0.4[a] | 2.9 | 3.4 | +1.5[a] |
| Thailand | 11.6 | 8.0 | -2.1[a] | 16.4 | 13.9 | -1.2[a] | 7.1 | 2.3 | -5.4[a] |
| Timor-Leste | 4.9 | 4.5 | -0.2 | 6.5 | 6.7 | +0.4 | 3.3 | 2.4 | -1.7[a] |
| Togo | 17.3 | 14.8 | -1.0[a] | 27.0 | 24.0 | -0.8[a] | 8.6 | 6.5 | -1.7[a] |
| Tonga | 5.1 | 4.4 | -0.2 | 6.7 | 5.9 | -0.1 | 3.6 | 2.9 | -0.5[a] |
| Trinidad and Tobago | 16.2 | 8.3 | -3.2[a] | 26.4 | 13.1 | -3.5[a] | 6.3 | 3.7 | -1.8[a] |
| Tunisia | 3.9 | 3.2 | -1.6[a] | 5.2 | 4.6 | -1.1[a] | 2.6 | 1.8 | -2.3[a] |
| Turkey | 4.2 | 2.3 | -2.9[a] | 6.7 | 3.6 | -3.2[a] | 1.9 | 1.2 | -2.2[a] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Turkmenistan | 13.8 | 6.1 | -5.9[a] | 23.7 | 9.4 | -6.5[a] | 4.6 | 2.9 | -3.6[a] |
| Uganda | 21.7 | 10.4 | -4.5[a] | 38.6 | 19.4 | -4.2[a] | 8.6 | 3.7 | -5.4[a] |
| Ukraine | 33.5 | 17.7 | -3.7[a] | 62.7 | 32.7 | -3.8[a] | 8.5 | 4.7 | -3.2[a] |
| United Arab Emirates | 8.0 | 5.2 | -2.4[a] | 9.3 | 6.3 | -2.3[a] | 4.7 | 2.6 | -3.1[a] |
| United Kingdom | 7.7 | 6.9 | +0.0 | 12.0 | 10.4 | -0.1 | 3.6 | 3.4 | +0.2 |
| Tanzania | 15.6 | 8.2 | -3.1[a] | 24.5 | 13.5 | -2.8[a] | 8.1 | 3.7 | -3.7[a] |
| United States of America | 10.0 | 14.5 | +1.9[a] | 16.4 | 22.4 | +1.6[a] | 4.0 | 6.8 | +2.7[a] |
| Uruguay | 14.5 | 18.8 | +1.5[a] | 25.7 | 31.1 | +1.4[a] | 5.1 | 7.7 | +1.3[a] |
| Uzbekistan | 12.0 | 8.3 | -1.5[a] | 19.6 | 11.8 | -2.2[a] | 4.8 | 4.9 | +0.7[a] |
| Vanuatu | 23.2 | 21.0 | -0.4[a] | 36.0 | 33.1 | -0.3[a] | 10.1 | 9.0 | -0.6[a] |
| Venezuela | 6.4 | 2.1 | -6.2[a] | 11.3 | 3.7 | -6.2[a] | 1.7 | 0.7 | -5.6[a] |
| Viet Nam | 7.2 | 7.2 | +0.4[a] | 9.4 | 10.6 | +1.1[a] | 5.2 | 4.2 | -1.0[a] |
| Yemen | 8.5 | 7.1 | -1.1[a] | 10.5 | 9.0 | -1.0[a] | 6.5 | 5.3 | -1.3[a] |
| Zambia | 24.0 | 14.4 | -2.2[a] | 35.9 | 25.7 | -1.4[a] | 14.5 | 5.3 | -4.4[a] |
| Zimbabwe | 20.0 | 23.6 | +1.9[a] | 28.2 | 37.8 | +2.7[a] | 14.2 | 13.5 | +0.8 |

[a]Statistically significant trend ($P < 0.05$).
[1]Joinpoint results are not shown for mortality in some countries, because no case of suicide occurred in at least 1 year in the observed period.
[2]For full period presented average annual percent change.

pesticide suicide, female suicide victims were significantly more often of a lower educational level, unmarried/divorced/widowed and unemployed compared to males[27]. By contrast, studies in South Korea and Japan suggested that female suicide rates were less affected by the economic crisis than rates in males[28,29].

Globally, a substantial decrease in suicide mortality trends was observed both in males and females. But, the region of the Americas experienced a significant increase in suicide mortality in both sexes over 2000-2019, unlike other WHO regions that had a declining trend. Also, a total of 26 countries had an increase in suicide mortality: Although they were mostly less developed countries, there were also several more developed countries such as the United States, Mexico, Brazil, and the Netherlands. The reasons for substantial international differences in suicide mortality rates and trends since 2000 are not completely elucidated. Epidemiological studies suggested an association between suicide and socio-economic instability, particularly poverty, unemployment, limited educational achievement, homelessness, divorce rate, birth rate, female labor force participation, alcohol consumption and general practitioners *per* 100000 people[9,29,30], although these findings were inconsistent[29,31,32]. Also, according to the WHO mortality data, suicide methods between countries and world regions vary considerably: Pesticide poisoning was common in many countries in Asia and Latin America, firearm suicide dominated in the United States, poisoning by drugs was common in both Nordic countries and the United Kingdom, hanging was a common method of suicide in Eastern Europe and China, jumping from a high place in Hong Kong, and suicide by charcoal burning in some East/Southeast Asian countries[33]. Although the importance of suicide methods is not well understood yet, it is considered that suicide method is linked to occupation, mental illness, chronic physical illness accompanied by pain, lower educational level, gun laws, and type of medication prescription.

Significant geographic differences in suicide mortality could be explained by different prevalence of the main risk factors (such as mental and behavioral disorders, chronic pain, alcohol and drug abuse), variations in suicide prevention, medical and other resources and management in health expenditure [34,35]. Studies on suicide by recently discharged mental health patients have reported a high frequency of affective disorder (bipolar disorder and depression), personality disorder, schizophrenia and other delusional disorders, and other primary diagnosis (anxiety disorders, dementia, eating disorders)[34, 35]. Alcohol abuse is among the reasons explaining the very high suicide rates in Russia and the former Russian states; but the 2006 alcohol regulation decreased spirits consumption by 33% in the Russian Federation, and this was reflected in decline in suicides[36].

The implementation of national guidelines for suicide prevention only in some countries might, at least in part, explain the observed international differences in suicide mortality rates and trends[37]. Additionally, variations in suicide mortality within some countries described among certain indigenous groups (such as high death rates in the Aboriginal population in Australia and the Inuit in Canada) can help in better understanding of the epidemiology of suicides[38]. Besides, it is always a question whether the differences in suicide mortality are real or partially mirror differences in quality of data

**Table 2 Joinpoint regression analysis: global trends in age-specific suicide mortality rates (per 100000), by sex, 2000-2019**

| Age[1] | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Age-specific rates[2] (2000) | Age-specific rates[2] (2019) | AAPC (95%CI) | Age-specific rates[2] (2000) | Age-specific rates[2] (2019) | AAPC (95%CI) |
| 10-19 | 6.7 | 4.5 | -2.0[a] [(-2.2)-(-1.8)] | 6.7 | 3.8 | -3.0[a] [(-3.2)-(-2.7)] |
| 20-29 | 21.4 | 15.7 | -1.8[a] [(-1.9)-(-1.6)] | 14.9 | 7.9 | -3.3[a] [(-3.8)-(-2.8)] |
| 30-39 | 23.4 | 17.6 | -1.6[a] [(-1.7)-(-1.5)] | 12.6 | 6.3 | -3.6[a] [(-4.0)-(-3.2)] |
| 40-49 | 27.6 | 17.8 | -2.6[a] [(-2.8)-(-2.4)] | 11.0 | 6.4 | -2.7[a] [(-2.9)-(-2.5)] |
| 50-59 | 31.0 | 19.6 | -2.5[a] [(-2.6)-(-2.4)] | 11.6 | 7.8 | -2.3[a] [(-2.7)-(-2.0)] |
| 60-69 | 33.7 | 21.8 | -2.5[a] [(-2.6)-(-2.3)] | 13.7 | 9.2 | -2.3[a] [(-2.6)-(-2.0)] |
| 70-79 | 46.0 | 31.1 | -2.3[a] [(-2.5)-(-2.1)] | 21.4 | 13.6 | -2.8[a] [(-3.2)-(-2.4)] |
| 80 + | 71.5 | 52.3 | -1.7[a] [(-1.9)-(-1.6)] | 29.4 | 19.1 | -2.7[a] [(-3.1)-(-2.3)] |

[a]Statistically significant trend.
[1]Joinpoint results are not shown for the subgroups aged < 10 years for mortality, because fewer than 5 cases of suicide cases occurred in each of the decennium in any year.
[2]Average annual, per 100000 people. AAPC: Average annual percent change; CI: Confidence interval.

worldwide, in the registering causes of death process or under-reporting[14,16,17].

With the aging and growing population, the increasing prevalence of many risk factors (disorders considering mental health, alcohol abuse or non-communicable diseases), and with the fact that suicide prevention strategies have been implemented in only a few countries so far, it would be difficult to expect the UN-SDG's goal of reducing suicide mortality by one-third by 2030 to be achieved[1,4,6,37]. The differences between the regional and national rates and trends of suicide mortality indicate further opportunities to reduce mortality from suicide and also point to the necessity of improving the public health approach to suicide prevention worldwide. Therefore, the preventive strategies need to be tailored by different countries according to the burden of suicides, available medical and other resources, as legal, religious, and political circumstances.

### *Strengths and limitations*

This study reported comprehensive global, regional and national trends of suicide mortality in the last two decades. This study analyzed suicide mortality data for 183 WHO member countries. Therefore, the results of this study could be generalized to the entire world. The presented trends could be essential for monitoring and assessing the epidemiological characteristics of suicides around the world, as well as for assessing the effects of preventive measures. The international variations in rates and trends in mortality from suicides underline the necessity of improving the public health approach to suicide prevention around the world.

Still, this study had some limitations. First, a possibility of under-reporting of suicide, particularly in developing countries, could introduce bias in the assessment of suicide mortality. Also, the quality of mortality statistics (considering coverage, accuracy, and completeness of data) varies substantially across the countries, which may introduce bias in comparison of suicide mortality rates between countries. Further, the validity of death certification for suicide is a major issue in some countries, due to a share of suicides classified as undetermined intent or accident or violent deaths. Finally, the WHO and GBD estimates partly resulted from adjustments of mortality data for countries without high-quality vital statistics (for example, for under-reporting of deaths, unknown age and sex, and ill-defined cause of death) and were computed using standard methods in order to provide cross-country comparability (using other data, *e.g.*, household surveys, verbal autopsy, sample or sentinel registration systems, special studies, *etc*)[4,12]. Besides, our analysis did not cover countries with a population of less than 90000 in 2019, *i.e.*, it did not include 11 WHO members - Andorra, Cook Islands, Dominica, Marshall Islands, Monaco, Nauru, Niue, Palau, Saint Kitts and Nevis, San Marino, Tuvalu. Certainly, it is important to continue the efforts for improving the quality of mortality statistics of suicide across countries in the world.

## CONCLUSION

Globally, suicide mortality rates are declining, but this has not been observed in all countries. A total of 26 out of 183 countries reported a significant increase in suicide mortality, while in 24 countries suicide mortality trends were stable. However, further epidemiological studies are necessary in order to better elucidate the disparities of suicide mortality worldwide.

## ARTICLE HIGHLIGHTS

### *Research background*

Suicides are an important public health problem in the world.

### *Research motivation*

Studies exploring the mortality of suicide on a global scale are sparse, and most evaluations were limited to certain populations.

### *Research objectives*

The objective of this manuscript was to evaluate global, regional and national patterns and temporal trends of suicide mortality between 2000 and 2019.

### *Research methods*

Suicide mortality data were obtained from the World Health Organization and Global Burden of Disease mortality database. Age-standardized rates [(ASRs), expressed per 100000)] were presented. To assess trends of suicide mortality, joinpoint regression analysis was used: The average annual percent change (AAPC) with the corresponding 95% confidence interval (CI) was calculated.

### *Research results*

A total of 759028 (523883 male and 235145 female) suicide deaths were reported worldwide in 2019. The global ASR of suicide mortality was 9.0/100000 population in both sexes (12.6 in males *vs* 5.4 in females). Globally, from 2000 to 2019, age-standardized suicide mortality rates had a decreasing tendency in both sexes together [AAPC = -2.4% per year; 95%CI: (-2.6)-(-2.3)]. Out of all 133 countries with a suicide mortality decline, Barbados (AAPC = -10.0%), Grenada (AAPC = -8.5%), Serbia (AAPC = -7.6%), and Venezuela (AAPC = -6.2%) had the most marked reductions. Out of all 26 countries with a rise in mortality from suicide, Lesotho (AAPC = +6.0%), Cyprus (AAPC = +5.1%), Paraguay (AAPC = +3.0%), Saudi Arabia (AAPC = +2.8%), Brunei (AAPC = +2.6%), Greece (AAPC = +2.6%), Georgia (AAPC = +2.1%), and Mexico (AAPC = 2.0%), are among those with the highest increase in mortality.

### *Research conclusions*

Decreasing trends in suicide mortality were observed in most countries across the world. Unfortunately, the mortality of suicide showed an increasing trend in a number of populations.

### *Research perspectives*

Further research should explore the reasons for these unfavorable trends, in order to consider and recommend more efforts for suicide prevention.

## FOOTNOTES

**Author contributions:** All authors equally contributed to this paper with conception and design of the study, data acquisition and analysis, and drafting, critical revision, editing, and approval of the final version.

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**Informed consent statement:** The study was conducted using publicly available data. No patient approvals were sought nor required for this study. The data used for inputs and analysis were derived from public sources (such as websites) and published literature. Our research question for estimating the trends of suicide mortality was based on the number of suicide mortality figures in the world from 2000 to 2019. However, as our model-based analysis used data from published sources such as publications, websites and modelling methods, patients were not involved in

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ORIGINAL ARTICLE

Observational Study

# Peripartum depression and its predictors: A longitudinal observational hospital-based study

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## Abstract

### *BACKGROUND*

Depression is a common problem in women in childbearing years due to burdens of motherhood and building a family. Few studies estimate the prevalence of antepartum depression compared to those in the postpartum period.

### *AIM*

To estimate the prevalence and the severities of peripartum depression and major depressive disorder and their predictors.

### *METHODS*

This is a longitudinal observation study. It included 200 women scoring ≥ 13 with the Edinburgh Postpartum Depression Scale, indicating presence of symptoms of depression. They had a gestational age of ≥ 6 wk and did follow-ups until the 10$^{th}$ week to 12$^{th}$ weeks postpartum. Information of women's reactions to life circumstances and stressors during the current pregnancy were gathered from answers to questions of the designed unstructured clinical questionnaire. Severities of depression, anxiety, and parenting stress were determined by the Beck Depression Inventory, State-Trait Anxiety Inventory for Adults, and Parenting Stress Index-Short Form, respectively. Psychiatric interviewing was done to confirm the diagnosis of major depression. Measuring the levels of triiodothronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH) was done in both antepartum and postpartum periods.

### *RESULTS*

Out of 968 (mean age = 27.35 ± 6.42 years), 20.66% ($n$ = 200) of the patients had

clinically significant symptoms of depression and 7.44% had major depression. Previous premenstrual dysphoria, post-abortive depression, and depression unrelated to pregnancy and were reported in 43%, 8%, and 4.5% of the patients, respectively. Psychosocial stressors were reported in 15.5% of the patients. Antepartum anxiety and parenting stress were reported in 90.5% and 65% of the patients, respectively. Postpartum T3, T4, and TSH levels did not significantly differ from reference values. Regression analysis showed that anxiety trait was a predictor for antepartum (standardized regression coefficients = 0.514, $t$ = 8.507, $P$ = 0.001) and postpartum (standardized regression coefficients = 0.573, $t$ = 0.040, $P$ = 0.041) depression. Antepartum depression (standardized regression coefficients = -0.086, $t$ = -2.750, $P$ = 0.007), and parenting stress (standardized regression coefficients = 0.080, $t$ = 14.34, $P$ = 0.0001) were also predictors for postpartum depression.

***CONCLUSION***

Results showed that 20.66% of the patients had clinically significant symptoms of depression and 7.44% had major depression. Anxiety was a predictor for antepartum and postpartum depression. Antepartum depression and parenting stress were also predictors for postpartum depression.

**Key Words:** Peripartum depression; Antepartum depression; Postpartum depression; Anxiety; Edinburgh postpartum depression scale; Parenting stress

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**Core Tip:** The prevalence rates of depression and anxiety are higher in pregnant women compared to non-pregnant women because motherhood and family responsibilities represent additional burdens on pregnant woman. The prevalence rate of peripartum depression has been estimated to range from 5%-58% or even higher in different nations; however, meta-analyses studies from different countries and populations reported similar approximated prevalence rates for postpartum, as well as antepartum, depression, which is 10%-16.4%. A unified consensus has been made to use specific screening tools for determination of peripartum depression. The Edinburgh Postpartum Depression Scale is a commonly and widely used 10-item screening questionnaire with an estimated sensitivity of 75%-100% and a specificity of 76%-97%. Here, we estimated the prevalence of antepartum and postpartum depression for Egyptian women and determined their independent risk predictors.

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## INTRODUCTION

Depression is common among adults[1,2]. The estimated prevalence of depression among Americans aged 20 and over in a given 2-wk period during the years 2013 to 2016 was 8.1%, with twice folds higher rates in women than men[2] . During the childbearing years, women are also more susceptible to major stresses, depression, and other psychiatric conditions and disorders due to superimposed children and family burdens[1]. There is a wide range of prevalence rates of antepartum and postpartum depression ( *i.e.* peripartum depression) reported from different countries worldwide, with estimates ranging from 5% to 58% or even higher[3-7]. This is non-surprisingly attributed to different population characteristics, socioeconomic states, and time and methods for evaluation[8-12]. However, meta-analyses of large studies done in different areas of the world have shown that the approximate estimated prevalence is 10% to 15% for antepartum depression[13-17] and 10% to 16.4% for postpartum depression[18-20]. It has been indicated that the prevalence rates of postpartum depression seems closer or even similar to that of antepartum depression[21,22]. Studies have also shown the greater risk for being admitted to a psychiatric hospital is at the 1$^{st}$ month after delivery than at any time of life[3,8,13,18]. The American Psychiatric Association uses the term "peripartum depression" to define major depression in its diagnostic and statistical manual of mental disorders version 5 (DSM-5) to characterize depression which occurs in the antepartum (during pregnancy) and postpartum (within the first 4 wk after delivery) periods[23]. However, it has been recommended to expand the diagnostic criteria from 1 mo to 6 mo after delivery, as it has been observed that this entire period carries a high-risk for developing depression[24].

Despite the large amount of research over decades to determine the prevalence, risks, and causes of peripartum depression and find effective methods for its screening, prevention, and treatment, the risks and causes of peripartum depression are poorly understood. Several experimental and clinical research studies have suggested that the major risk for developing peripartum depression is the rapid fluctuation in reproductive hormones during pregnancy, delivery, and postpartum periods[25]. Others suggested "alternative biological processing" as the cause of peripartum depression which is based on the finding of different peripartum depression phenotypes that reflect complex mechanisms which include an interplay between: (1) Fluctuations in reproductive[25], thyroid[26], hypothalamic pituitary adrenal axis axis[27], and lactogenic hormones (prolactin and oxytocin)[28]; (2) Immunity[29]; (3) Genetics[30]; and (4) Social, obstetric, and psychological factors[3,8,13,18,31].

Peripartum depression is a major cause of maternal and neonatal morbidity if untreated[32]. Therefore, the World health Organization and United States Preventive Services Task Force recommend screening for peripartum depression. Interventions for mild/moderate symptoms include psychotherapy or treatment with antidepressants (*e.g.*, selective serotonin reuptake inhibitors) and combined psychotherapy and pharmacotherapy for moderate/severe symptoms[33,34].

Studies which estimated the prevalence of antepartum depression are few compared to those in the postpartum period. Here, we aimed to estimate the prevalence of depression in women in the antepartum and postpartum periods and their demographic, social, obstetric, psychological, and hormonal predictors.

## MATERIALS AND METHODS

### *Study design, period, region*

This is a longitudinal observational study completed over a period of 3 years (2017-2020). The initial sample size composed of 1100 women who were consequently recruited from the antenatal out-patient clinic of the department of Obstetrics and Gynecology, Mansoura University, Mansoura, Egypt. Inclusion criteria were: (1) Gestational age of more than or equal 6 wk (*i.e.* antepartum period); (2) Compliance to the study's follow-up schedule during pregnancy (*i.e.* antepartum period) and at least 10 to 12 wk after delivery (*i.e.* postpartum period)[24]; (3) Matched social, economic, and educational levels; and (4) Edinburgh Postpartum Depression Scale (EPDS) screening questionnaire scoring of at least 13, indicating presence of clinically significant symptoms of depression[35,36]. Exclusion criteria was: Past history of significant medical or psychiatric diseases. The ethics Committees of Faculties of Medicine of Mansoura and Assiut Universities, Mansoura and Assiut Governorates, Egypt, approved the study protocol. Women gave their informed consents for participation in the study, No. AUFM_NP/OG_422/2016.

### *Methods*

**The social, economic and educational level evaluations:** Evaluations for social, economic, and education levels were done using the Socio-Economic Scale[37], a structured questionnaire which collects information about level of parents' education, month's income, sanitation, and crowning index. Its total scoring is 30. The socioeconomic status is classified as high (scoring: more than 25 to at least 30), middle (scoring: more than 20 to at least 25), low (scoring: at least 15 to less than 20), or very low (scoring: less than 15).

**Psychometric evaluations and testing:** They were done by the specialist psychiatrist (ME).

### *In the Antepartum period (gestational age of more than or equal 6 wk)*

**EPDS:** This is a widely used screening questionnaire for perinatal depression. It has ten questions which ask about the recent reaction (a week prior to its administration) of the woman to life stressors and conditions. EPDS scoring more than 13 indicates presence of symptoms of depression[35,36].

**Clinical questionnaire:** We designated an unstructured clinical questionnaire to collect information about the woman's reactions to recent life circumstances, events, and stresses related to the recent pregnancy. The questions asked about: (1) Feeling of happiness; (2) Husband's feeling towards his wife's recent pregnancy; (3) Reaction of the husband towards baby's sex; (4) History of child loss (abortions or stillbirths); (5) Postpartum complications; (6) Psychosocial stressors (*e.g.*, divorce, loss of job, death of a husband, family arguments, and financial problems); (7) Husband's aggression against his wife (verbal, emotional, or physical); (8) Sexual abuse during childhood; (9) Previous psychiatric problems; and (10) Presence of family members with psychiatric problems.

**DSM-5:** Psychiatric interviewing was done for confirmation of the diagnosis of major depression according to the Structured Clinical Interview for DSM-5 (Structured clinical interview for DSM-5)[38].

### *Beck depression inventory II*

The severity of symptoms of depression was determined using Beck depression inventory II (BDI-II)[39,40]. They were classified as minimal (scoring: 0-13), mild (scoring: 14-19), moderate (scoring: 20-28), or severe (scoring: 29-63).

### *State-Trait Anxiety Inventory for adults*

The severity of manifestations of anxiety was determined using State-Trait Anxiety Inventory for adults (STAI-AD)[41,42]. STAI helps to differentiate between state from trait anxiety. State anxiety is a temporary condition while trait anxiety is long-lasting and more general condition. It also differentiates between subjective feelings of anxiety from depression. The severity of anxiety symptoms was classified as absent (scoring: less than or equal 20), mild (scoring: 21-30), less than moderate (scoring: 31-36), moderate (scoring: 47-42), more than moderate (scoring: 44-57), severe (scoring: 58-63), or very severe (scoring: more than or equal 64).

### *Antepartum laboratory testing*

Antepartum laboratory testing was done at the early week of the third trimester. After an overnight fast (for 12 h), blood samples were withdrawn at 8:00 a.m. to measure serum levels of triiodothronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH) using immunoenzymetric assay kits [IMMULITE reproductive hormone assays' kits (Diagnostic products corporation, Los Angeles, United States)]. The reference levels are: T3 = 81-178 ng/dL, T4 = 4.5-12.5 ng/dL, and TSH = 0.4-4 mIU/mL.

### *In the postpartum period (at least 10 to 12 wk after delivery):*

Participants were evaluated in the postpartum period using BDI-II[39,40].

**Parenting Stress Index-Short Form[43]:** The Parenting Stress Index-Short Form is 36-item questionnaire divided into three sets of questionnaires (or subscales of 12 items for each) to assess: (1) Parental Distress due to the parental role (*e.g.*, the new responsibility being a mother makes me as being locked down); (2) Parent-Child Dysfunctional Interaction (*e.g.*, this new child put on me a greater demand compared to my other kids); and (3) Difficult Child (*e.g.*, This child does not provide me with empathy as I expect from a child to a mother). Each subscale's set has score ranging from 12-60. Parenting stress index-short form (PSI-SF) score is the sum of three subscales' set scores (range: 36-180). The higher scoring indicates enhanced stress level. A raw score exceeding 90 indicates significant symptomatic stress.

**Postpartum laboratory testing:** Measurement of the levels of T3, T4, and TSH were done in the 10$^{th}$ week postpartum.

### *Statistical analyses*

Data were processed using SPSS for windows, version 20.0 (SPSS Inc., Chicago, IL, United States). Comparative statistics were carried out with *t*- and Chi-square tests or ANOVA (if variables are more than two). Correlation analyses between an antepartum score of BDI-II and the results of demographic, socio-economic status scoring, and psychometric testing's scores were carried out with Spearman's rho correlation coefficient. Multiple logistic regression analysis was carried out to check for demographic, clinical, and psychosocial factors, which independently predict or associate with antepartum and postpartum depression. Significance was considered with probability value less than 0.05.

## RESULTS

The number of women screened for depression was 968; of them 200 (20.66%) had EPDS scoring more than 13 (*i.e.* had clinically significant symptoms of depression) (Figure 1A). The patients' ages ranged from 17 years to 34 years (mean: 27.35 ± 6.42 years), with the majority having an age range between 23 years to 34 years ($n$ = 164, 82%). All were housewives, the majority were rural residents ($n$ = 155, 77.5%), cannot read ($n$ = 145, 72.5%), and were of middle socioeconomic status ($n$ = 132, 66%). Nearly half were multipara. A past history of fetal losses (abortions and still births) was found in 40%. The majority had normal vaginal deliveries in their past pregnancies, as well as the current pregnancy ($n$ = 168, 84%). Only one patient underwent *in vitro* fertilization in the current pregnancy. The majority ($n$ = 156, 78%) did their first visit to the antenatal care unit (parallel to our first psychiatric evaluation) in the 3$^{rd}$ trimester, with 13.5% ($n$ = 27) in the 2$^{nd}$ and 8.5% ($n$ = 17) in the 1$^{st}$ trimesters. Antenatal complications in the recent pregnancy which were indications for caesarian section were found in 16% ($n$ = 32). Only 4% ($n$ = 8) had postpartum problems (Table 1). Results of the unstructured clinical questionnaire showed that the majority of the patients (91%) were happy with their current pregnancy, and none had past history of postpartum depression; however, 43% had a history of premenstrual dysphoric disorder, 8% had history of post-abortive depression, and 4.5% had history of depression unrelated to pregnancies. Only one had history of sexual abuse during childhood. Psychosocial stressors were found in 15.5%

**Table 1 Demographic, social, and obstetric characteristics of screened women with symptoms of depression**

| Demographic and social characteristics | *n* = 200 |
|---|---|
| Age, yr | 17–34 (27.35 ± 6.42) |
| 17-22 yr, *n* (%) | 36 (18) |
| 23-34 yr, *n* (%) | 164 (82) |
| Residence | |
| Urban | 40 (20) |
| Rural | 160 (80) |
| Maternal education | |
| None (can't read) | 145 (72.5) |
| Can read (or can read and write) | 18 (9) |
| Primary | 6 (3) |
| Secondary | 12 (6) |
| High | 19 (9.5) |
| Socio-economic status | |
| Low | 36 (18) |
| Middle | 132 (66) |
| High | 32 (16) |
| Obstetric characteristics | |
| Parity | |
| Primipara | 97 (48.5) |
| Multipara | 103 (51.5) |
| History of fetal loss | |
| Abortions | 74 (37) |
| Still births | 6 (3) |
| Mode of previous deliveries | |
| Vaginal | 168 (84) |
| Cesarean | 30 (15) |
| Both vaginal and cesarean | 2 (1) |
| History of *in vitro* fertilization in the current pregnancy | 1 (0.5) |
| Gestational age of the first antenatal care visit | |
| First trimester | 17 (8.5) |
| Second trimester | 27 (13.5) |
| Third trimester | 156 (78) |
| Type of delivery in the current pregnancy | |
| Vaginal | 168 (84) |
| CS | 32 (16) |
| Indications of CS (*i.e.* antenatal complications) | 32 (16) |
| Placenta previa | 22 (11) |
| Accidental hemorrhage | 8 (4) |
| Obstructed labor | 2 (1) |
| Postpartum complications of current pregnancy | 8 (4) |

CS: Cesarean.

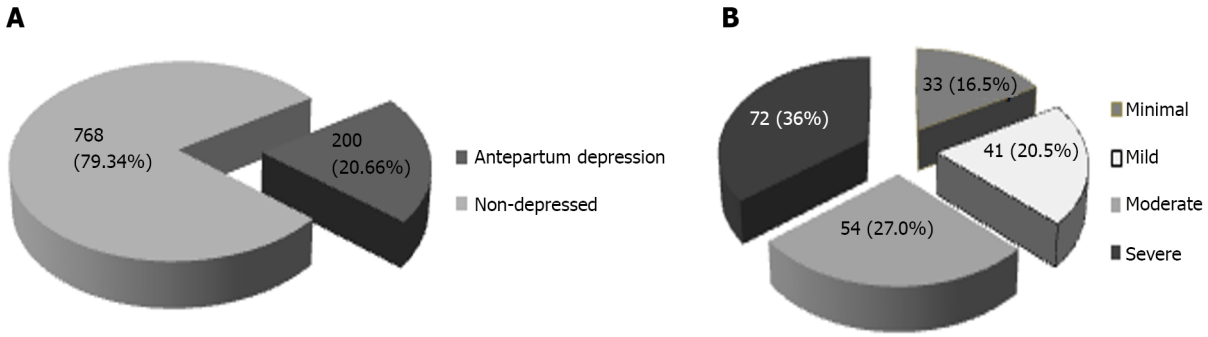


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**Figure 1 Antepartum depression.** A: Prevalence rate of antepartum depression. B: Severities of antepartum depression.

(Table 2).

During pregnancy, symptoms of severe depression were found in 36% (mean Beck Depression Inventory II or BDI-II scoring: 44.48 ± 6.55), while 27% (mean BDI-II scoring: 24.26 ± 3.32) and 20.5% (mean BDI-II scoring: 16.26 ± 2.86) had moderate and mild symptoms, respectively (Figure 1 and Table 3). Psychiatric interviewing also showed that 7.44% (72/968) had major depression (women with severe symptoms). When stratified according to demographic, social, and obstetric variables, we observed no difference in severities of symptoms of depression in relation to age ($P$ = 0.452), education levels ($P$ = 0.326), or socioeconomic status ($P$ = 0.482). When distributed according to the gestational age at presentation, the majority ($n$ = 156, 78%) had symptoms of depression during the 3rd trimester, 13.5% ($n$ = 27) during the 2nd, while only 8.5% ($n$ = 17) had depression during the 1st trimester ($P$ = 0.0001).

Compared to reference values, women in their 3rd trimester had higher levels of T3 and T4, but not TSH (Table 4). No difference in levels of T3, T4, and TSH in the postpartum period were detected compared to reference values.

The majority of women had symptoms of severe anxiety ($n$ = 181, 90.5%) compared to less severe symptoms ($P$ = 0.0001) [no anxiety = 1 (0.5%); mild = 6 (3%); less than moderate = 12 (6%); moderate = 8 (4%); more than moderate = 70 (35%); severe = 67 (33.5%); and very severe = 36 (18%)]. They had STAI-AD scoring ranged between 21 and 78 (mean: 53.31 ± 11.82) (Table 5).

Assessment of women in the postpartum period showed reduction in the severity of symptoms of depression ($P$ = 0.0001). Approximately, two thirds ($n$ = 130, 65%) had clinically significant parenting stress (Table 5).

Significant correlations were found between BDI-II scoring in the antepartum period and socioeconomic status scoring ($r$ = -0.224, $P$ = 0.001), STAI scoring ($r$ = 0.600, $P$ = 0.0001), and PSI-SF scoring ($r$ = 0.141, 0.047), but not with age ($r$ = -0.021; 0.763) and BDI-II scoring in the postpartum period ($r$ = -0.110, $P$ = 0.320). Significant correlation was found between BDI-II scoring in the postpartum period and PSI-SF scoring ($r$ = 0.158, 0.052). Multiple regression analysis showed that in the antepartum period, only anxiety was the strong predictor of depression (standardized regression coefficients = 0.514, $t$ = 8.507, $P$ = 0.001). In the postpartum period, antepartum depression (standardized regression coefficients: -0.086, $t$: -2.750, $P$ = 0.007), anxiety (standardized regression coefficients = 0.573, $t$ = 0.040, $P$ = 0.041), and parenting stress (standardized regression coefficients = 0.080, $t$ = 14.34, $P$ = 0.0001) were the predictors for postpartum depression (Table 6).

## DISCUSSION

Results of this study showed that 20.66% of pregnant women had clinically significant symptoms of depression. Severe symptoms were found in 36% (72/200) of women, and this group also fulfilled the criteria of major depression, meaning that 7.44% (72/968) of women developed major depression in the peripartum period. Women included in this study had a closer age for marriage and similar obstetric characteristics as the rest of the world. The majority were from rural areas, had lower levels of education, and moderate/low socioeconomic statuses. There also shared psychological stressors regardless of culture. However, ours had distinguished characters and predictors; for example, more than 90% were happy with their current pregnancy, 4.5% had history of depression unrelated to pregnancies, 15.5% had psychosocial stressors, 78% developed manifestations of depression in the 3rd trimester, and 90% had manifestations of anxiety (which varied from moderate to very severe), but none fulfilled the diagnostic criteria of isolated generalized anxiety disorder and none had T3 and T4 (but not

**Table 2 Results of the women's reactions to the recent life circumstances, events, and stresses related to recent pregnancy**

| Psychiatric characteristics | *n* = 200, *n* (%) |
|---|---|
| I was unhappy with the current pregnancy | 10 (5) |
| My husband was unhappy with the current pregnancy | 0 |
| Reaction to the current baby's sex | |
| Happy | 182 (91) |
| Indifference | 18 (9) |
| Past history of loss of a living child | 14 (7) |
| Past history of mental illness unrelated to pregnancy | 9 (4.5) |
| Depression and/or anxiety | |
| Treated | 2 (1) |
| Untreated | 7 (3.5) |
| Past history of postpartum depression | 0 |
| History of premenstrual dysphoric disorder | 86 (43) |
| Past history of post-abortive depression | 16 (8) |
| Past history of depression unrelated to pregnancies | 9 (4.5) |
| Family history of mental illness | 0 |
| Past history of being a victim of one of the followings | |
| Sexual abuse during childhood | 1 (0.5) |
| Physical abuse during childhood | 32 (16) |
| Physical abuse by a known person | 2 (1) |
| Physical abuse by an unknown person | 0 |
| Physical aggression during pregnancy | 2 (1) |
| Emotional/verbal abuse | 22 (11) |
| Current psychosocial stressors | 31 (15.5) |
| Divorce | 0 |
| Loss of a job | 0 |
| Death of spouse | 1 (0.5) |
| Family argument | 24 (12) |
| Financial problems | 6 (3) |

for TSH) levels out-ranged the reference values for non-pregnant women.

EPDS was the preferred screening tool for depression. In general, manifestations of peripartum depression are not specific. Therefore, a unified consensus has assigned 3 tools to screen women for peripartum depression[3-7], which are: (1) EPDS[35,36]: It is a 10-item questionnaire with an estimated sensitivity of 75% to 100% and a specificity of 76% to 97%; (2) Patient Health Questionnaire-9[44]: It has an estimated sensitivity of 75% and a specificity of 90%; and (3) The 35-question Postpartum Depression Screening Scale[45]: It has a sensitivity of 91% to 94% and a specificity of 72% to 98%. However, in practice, the family physicians usually use a familiar two-step screening questionnaire, Patient Health Questionnaire-2, as a first step, followed by comprehensive questionnaire if one from the two questions indicates presence of symptoms of depression.

Nationwide studies showed wide range prevalence rates for peripartum depression; however, a common prevalence estimate for antepartum depression nationwide is around 13%[20,21,46]. Our results showed a closer prevalence rate to those reported from different countries. In Egypt, few studies addressed the same topic (antepartum or postpartum depression) and its predictors[5,9,14]. Prevalence estimates from different countries are as follow: 14.8% in Spain[17], 16.8% in Turkey[47], 18% in Bangladesh[6], 24.3% in Oman[15], 27% in Canada[48], 32.9% in Cote d'Ivoire[7], 33.8% in Tanzania[49], and 44.2-57.5% in Saudi Arabia[16,50]. In Egypt, Abdelhai and Mosleh[9] did a cross sectional study on 376 randomly recruited pregnant women. The authors used a Hospital Anxiety and Depression Scale questionnaire and Hurt, Insulted, Threaten, and Scream Inventory (to screen for the presence of

**Table 3 Comparative statistical results of symptoms of depression during pregnancy according to social, demographic, and obstetric variable**

| Socio-demographic and obstetric variables | The severity of depression symptoms | | | | *P* value |
|---|---|---|---|---|---|
| | Minimal, *n* = 54, 27% | Mild, *n* = 41, 20.5% | Moderate, *n* = 33, 16.5% | Severe, *n* = 72, 36% | |
| Age, *n* (%) | | | | | 0.452 |
| 17-22 yr (*n* = 36) | 7 (19.4) | 8 (22.2) | 9 (25) | 12 (33.3) | |
| 23-34 yr (*n* = 164) | 47 (28.7) | 33 (20.1) | 24 (14.6) | 60 (36.6) | |
| Maternal education, *n* (%) | | | | | 0.326 |
| Low (*n* = 181) | 29 (16) | 40 (22.1) | 44 (24.3) | 68 (37.6) | |
| High (*n* =19) | 4 (10.5) | 1 (5.3) | 9 (47.4) | 5 (26.3) | |
| Socio-economic status, *n* (%) | | | | | 0.482 |
| Low (*n* = 36) | 9 (25) | 5 (13.9) | 3 (8.3) | 19 (52.8) | |
| Middle (*n* = 132) | 25 (18.9) | 33 (26.8) | 26 (19.7) | 48 (36.4) | |
| High (*n* = 32) | 20 (62.5) | 3 (9.4) | 4 (12.5) | 5 (15.6) | |
| Gestational age, *n* (%) | | | | | 0.0001 |
| 1st trimester (*n* = 17) | 2 (11.8) | 1 (5.9) | 5 (29.4) | 9 (52.9) | |
| 2nd trimester (*n* = 27) | 2 (7.4) | 5 (18.5) | 9 (33.3) | 11 (40.7) | |
| 3rd trimester (*n* = 156) | 50 (32.1) | 35 (22.4) | 19 (12.2) | 52 (33.3) | |

**Table 4 Hormonal results in the antepartum period**

| Laboratory investigations | Participants, *n* = 200 | | *P* value[1] | *P* value[2] |
|---|---|---|---|---|
| | Antepartum | Postpartum | | |
| T3 in ng/dL, range | 106–305 (184.22 ± 38.13) | 49.06–296 (164.70 ± 45.72) | 0.05 | 0.678 |
| High, *n* (%) | 98 (49) | 80 (40) | - | - |
| T4 in ng/dL, range | 5.2–28 (12.40 ± 2.38) | 4.5–19.1 (11.19 ± 2.67) | 0.05 | 0.845 |
| High, *n* (%) | 63 (31.5) | 82 (41) | - | - |
| TSH in mIU/mL, range | 0.02–8.50 (1.70 ± 0.11) | 0.01–8.44 (1.64 ± 0.32) | 0.435 | 0.760 |
| High, *n* (%) | 5 (2.5) | 22 (11) | - | - |
| Low, *n* (%) | 1 (0.5) | - | - | - |
| Borderline, *n* (%) | 15 (7.5) | - | - | - |

[1]Pregnant women *vs* reference.
[2]Antepartum *vs* postpartum.
Data are presented as mean ± SD. Reference values: T3: 106.32 ± 15.80 (81–178) ng/dL; T4: 9.32 ± 2.44 (4.5-12.5) ng/dL; TSH: 1.56 ± 0.32 (0.4–4) mIU/mL.
T3: Triiodothronine; T4: Thyroxine; TSH: Thyroid stimulating hormone.

domestic violence). The authors found both depression and anxiety in 63% of the subjects and only anxiety in 11.4% or depression in 10.4% of the subjects. Domestic violence was found in 30.6% of the subjects, with the majority (25.2%) experienced physical violence from the husband. The authors found significant independent association between the presence of anxiety and depression and exposure to domestic violence (OR = 3.27, 95%CI: 1.28-8.34; $P$ = 0.013), particularly among women who had husbands of low educational level compared to those with higher levels (*i.e.* a university-graduated) (OR = 0.22, 95%CI: 0.64-0.75, $P$ = 0.01).

Previous studies found that there are several factors which could either associate or potentiate antepartum depression[51]. In this study, although women encountered significant psychosocial stresses, regression analysis showed that none was an independent predictor for peripartum depression. Also, none of the demographic, education, socioeconomic, or obstetric factors independently predicted peripartum depression. It is not surprising to find absence of an association between younger age of

**Table 5 Comparative statistics between antepartum and postpartum manifestations of depression**

| Psychiatric manifestations | Participants, *n* = 200 | | *P* value |
|---|---|---|---|
| | Antepartum | Postpartum | |
| BDI-II score, range | 1–38 (26.13 ± 8.85) | 2–46 (22.27 ± 6.74) | 0.455 |
| Severity of depression, *n* (%) | | | 0.0001 |
| Minimal | 33 (16.5) | 104 (52) | |
| Mild | 41 (20.5) | 64 (32) | |
| Moderate | 54 (27) | 27 (13.5) | |
| Severe | 72 (36) | 5 (2.5) | |
| STAI score, range | 21–78 (53.31 ± 11.82) | - | - |
| PSI-SF score, range | - | 36–18 (136.57 ± 45.86) | - |
| Women with clinically significant stress, *n* (%) | - | 130 (65) | - |

Data are presented as mean ± SD. BDI: Beck Depression Inventory; PSI-SF: Parenting Stress Index-Short Form; STAI: State-Trait Anxiety Inventory.

marriage and low levels of education or socioeconomic status and antepartum depression, particularly in Arab and some low/middle income countries, because, a female is protected by her family or husband's family (*i.e.* each spouse's family will be responsible for the financial burden for pregnancy, delivery, and even earlier postnatal care). Oman Islam *et al*[52] found that neither the maternal age nor the gravidity was a risk for antepartum depression. In contrast, several studies found that the young age of marriage is a predictor for antepartum depression. They suggested that the financial hardship, unwanted pregnancies, and a lack of partner support are the main causes of depression among younger mothers[53,54]. Prost *et al*[55] found associations between stress and antepartum depression and older maternal age in Indian women. Some studies found correlations between peripartum depression and low levels of socioeconomic status and education[56,57]. In Brazilian women, Melo *et al*[57] found 2.38-fold increase in the odds of antepartum depression in association with low maternal educational level (OR = 2.38; 95%CI: 1.38-4.12). In Mexican women, Lara *et al*[56] found 5-fold increase in the odds of postpartum depression in association with low maternal education (OR = 5.61; 95%CI: 1.87-16.80).

In this study, when stratified according to gestational age, we observed that the majority (78%) developed depression in their 3rd trimester ($P$ = 0.0001); however, gestational age was not a predictor for depression. Also, none of the obstetric risk factors was a predictor for antepartum depression which is in contrast to several studies[31,58]. Bunevicius *et al*[31] found higher prevalence of depression in the 1st trimester and the lowest in mid-pregnancy. They even found differences in predictors of antepartum depression when stratified according to gestational age. They found that unwanted and unplanned pregnancy and high neuroticism were the independent predictors in the 1st, 2nd, and 3rd trimesters, while low education and previous episodes of depression were the independent predictors in the 3rd trimester. They also observed that psychosocial stressors in the end of pregnancy were trimester specific.

In this study, psychosocial stressors (including previous depression episodes, family history of depression, premenstrual dysphoria, domestic violence, and sexual abuse) were found in 15.5%. Prost *et al*[55] screened 5801 Indian mothers from rural Jharkhand and Orissa, eastern India, where over 40% of the population live below the poverty line, at 6 wk after delivery. The authors used the Kessler-10 item scale and found that 11.5% (95%CI: 10.7–12.3) had symptoms of distress (K10 score: more than 15). They found that the independent predictors for postpartum distress were high maternal age, severe poverty, health problems in the antepartum period, caesarean section, unwanted pregnancy from the mother's side, small infant size, and child loss (*e.g.*, stillbirths or neonatal death). They also found that the loss of an infant (OR = 7.06, 95%CI: 5.51–9.04) or an unwanted pregnancy (OR = 1.49, 95%CI: 1.12–1.97) significantly increased the risk of maternal distress.

In this study, 90.5% of women had symptoms of moderate/severe anxiety in the antepartum period. In Sao Paulo, Brazil, Faisal-Cury and Rossi Menezes[59] found symptoms of depression of different severities in 20% of pregnant women assessed by BDI and nearly 60% had anxiety assessed by STAI. Karmaliani *et al*[60] found manifestations of anxiety and depression in 18% Pakistani pregnant women.

In this study, although major depressive disorder was diagnosed in 7.44% of pregnant women, neither antepartum nor postpartum bipolar disorder or history of bipolar disorder in the non-pregnancy periods was observed in the 968 women screened for this study. This could be attributed to the fact that this is not a population-based study. It is also possible that the prevalence rate for peripartum bipolar disorder is lower than unipolar or bipolar depression[61-63]. There are many published studies on both unipolar and bipolar postpartum depression, whereas there are few on bipolar postpartum depression. A survey on general population of the United States estimated that a 12 mo prevalence rate for

**Table 6 Predictors for antepartum and postpartum depression in pregnant women**

| Predictor variables | B[1] | β[2] | *t* | *P* value |
|---|---|---|---|---|
| Age | -0.020 | -0.015 | -0.287 | 0.774 |
| | 0.046[3] | 0.058[3] | 1.193[3] | 0.234[3] |
| Socio-economic scale | -0.015 | -0.070 | -1.286 | 0 .200 |
| | -0.010[3] | -0.074[3] | -1.497[3] | 0.136[3] |
| Education | 0.011 | 0.067 | 1.187 | 0.2 |
| History of postpartum depression | -0.834 | -0.083 | -1.647 | 0.101 |
| | -0.857[3] | -0.091[3] | -2.647[3] | 0.121[3] |
| Antepartum anxiety trait | 0.469 | 0.514 | 8.507 | 0.001 |
| | 0.021[3] | 0.040[3] | 0.573[3] | 0.041[3] |
| Antepartum T3 level | -0.036 | -0.045 | -1.673 | 0.513 |
| | 0.033[3] | 0.065[3] | 2.867[3] | 0.578[3] |
| Antepartum T4 level | -0.046 | -0.056 | -1.893 | 0.654 |
| | 0.022[3] | 0.078[3] | 2.867[3] | 0.745[3] |
| Antepartum TSH level | -0.045 | -0.089 | -1.654 | 0.607 |
| | 0.049[3] | 0.037[3] | 2.867[3] | 0.425[3] |
| Antepartum depression | -0.086[3] | -0.148[3] | -2.750[3] | 0.007[3] |
| Parenting stress index | 0.080[3] | 0.697[3] | 14.34[3] | 0 .0001[3] |
| R = 0.843; R = 0.806[3] | | | | |
| R2 = 0.711; R2 = 0.649[3] | | | | |
| Adjusted R2 = 0.701; Adjusted R2 = 0.641[3] | | | | |
| Standard error = 6.094; Standard error = 7.254[3] | | | | |
| ANOVA < 0.001; ANOVA < 0.001[3] | | | | |

[1]Unstandardized regression coefficients.
[2]Standardized regression coefficients.
[3]Post-partum results.
ANOVA: Analysis of variance; T3: Triiodothronine; T4: Thyroxine; TSH: Thyroid stimulating hormone.

postpartum bipolar disorder was 2.9%[61]. Authors also found that many women with postpartum bipolar disorder had acute mood episodes and the risk of bipolar episodes were greater during the postpartum period than other periods of life[62]. Wisner *et al*[63] found that among the 14% of women with postpartum depression, 22.6% actually had bipolar disorder.

In this study, the only predictor for antepartum depression was antepartum anxiety trait ($P$ = 0.001). The predictors for postpartum depression were antepartum depression ($P$ = 0.007), anxiety trait ($P$ = 0.041), and parenting stress ($P$ = 0.0001). Despite the observed reduction in the severity of symptoms of depression in the postpartum period (2.5%) compared to the antepartum period (36%), antepartum depression was also a strong predictor for postpartum depression ($P$ = 0.007). Previous studies indicated that antepartum anxiety is an independent predictor for both antepartum and postpartum depression [64], and severe anxiety and even panic attacks are often associated with peripartum major depressive episode[65]. Faisal-Cury and Rossi Menezes[59] screened 432 women from Osasco, São Paulo, for depression and anxiety using STAI and BDI designed questionnaires. The authors found a prevalence of 59.5% for anxiety state (95%CI: 54.8-64.1), 45.3% for anxiety trait (95%CI: 40.6-50.0), and 19.6% for depression (95%CI: 15.9-23.4). The authors found that the mothers' low levels of education and the absence of formal marriage were significant independent predictors for anxiety trait (OR = 5.26; 95%CI: 2.17-12.5, $P$ = 0.001; OR = 3.43; 95%CI: 1.68-7.00, $P$ = 0.001), anxiety state (OR = 2.27; 95%CI: 1.08-4.76, $P$ = 0.02; OR = 2.22; 95%CI: 1.09-4.53, P = 0.02), and depression (OR = 2.43; 95%CI: 1.40-4.34, $P$ = 0.002; OR = 2.82; 95%CI: 1.35-5.97, $P$ = 0.005). They found that women with lower incomes (OR = 2.22; 95%CI: 0.98-5.26, $P$ = 0.05) and a race other than white (OR = 1.7; 95%CI: 1.00-2.91, $P$ = 0.04) were significant independent predictors for anxiety trait. They also found that couples with lower income (OR = 2.43; 95%CI: 1.40-4.34, $P$ = 0.001) and frequent previous abortions (OR = 2.21; 95%CI: 1.23-3.97, $P$ = 0.009)

were significant independent predictors for depression. In the two different community studies done by Karaçam and Ançel[65] on 1039 Turkish pregnant women, the authors found manifestations of severe depression in 27.9% which required antidepressants therapy. The authors found that the lack of social support, recent life stresses, or domestic violence just before or during the recent pregnancy, and negative self-perception were strong independent predictors for both depression and anxiety; and formal marriage and its dissatisfaction, unwanted pregnancy, and being a housewife were strong independent predictors for depression only.

In this study, we found that the only predictors for postpartum depression were antepartum depression, anxiety, and parenting stress. Studies from the developed and developing areas of the world indicated a strong association between postpartum and antepartum depression. Some even found that the only predictor for postpartum depression was antepartum depression[64-66] Several studies also found that antepartum anxiety is associated (10%-29%) and a strong predictor for postpartum depression[66]. In the recent study done by Abd Elaziz and Abdel Halim[19] on 120 Egyptian women, the authors found postpartum depression in 27.5% of the subjects. They found that the predictors for postpartum depression were the presence of domestic violence (OR = 6.4, 95%CI: 2.5-15.3), previous episodes of postpartum depression (OR = 5.5, 95%CI: 1.6-17.9), presence of stressful life events (OR = 3.6, 95%CI: 1.4-8.1), and difficult social interaction at the time of stress (OR = 4.1, 95%CI: 1.7-9.1). Previous studies reported an association between postpartum depression and parenting stress. Leigh and Milgrom[46] screened women from Angliss and Northern Victorian hospitals and found higher PSI scores in women with postpartum depression compared to non-depressed women ($P$ < 001). They found significant independent associations between postpartum depression and parenting stress ($P$ < 0.001) and previous history of depression ($P$ < 0.01). It has been suggested that in addition to parenthood, more burden is added on a working or career-oriented mother as being unable to carry out many work authorizations and home responsibilities.

In this study, we did not identify a significant correlation between thyroid hormonal changes in the peripartum period and depression. The role of hormonal fluctuations during perinatal period and its relationship to peripartum depression is not established. and many studies have controversial results [28,67-70]. For example, Amino *et al*[69] found low mean values of T4 levels during the 3rd trimester and early postpartum periods in women with postpartum depression. Abou-Saleh *et al*[70] found significant increase in levels of postpartum T4 in women with depression compared to unmarried/non-pregnant women; higher T4 was the only predictor for severe antepartum depression, and higher TSH was found in women with high scoring of EPDS, indicating presence of clinically significant symptoms of depression, and had previous history of depression compared to those without past history of depression. In the systematic review done by Szpunar and Parry[28] which included studies on women in the peripartum period who had major depression and did repeated measurements of TSH levels in the antepartum or postpartum periods, the authors found controversy between the studies and an absence of association between TSH and peripartum depression.

We suggest the followings as causes of differences between the results of this study and others: (1) Differences in methodologies (laboratory, screening questionnaires, and psychometric testing evaluation in different trimesters and postpartum periods) or study settings (*e.g.*, community or hospital-based or recruitment from primary health care center); (2) The causes and risks for peripartum depression could not be primarily or solely attributed to the biological changes during this stressful period of life; and (3) Differences in culture, beliefs, and genetic vulnerabilities: We suggest that that the observed high frequency of antepartum anxiety and its relationship to depression could be attributed to poverty, illiteracy, lack of social support, domestic violence, and psychological stressors.

## CONCLUSION

There is wide variation in prevalence rates of peripartum depression from different countries. Our results showed that 20.66% had clinically significant symptoms of depression and 7.44% had the diagnosis of major depression. Although the topic has already been addressed in other studies and the results of the study corroborate the data found in the literature with regards the prevalence, predictors, and severity of depressive symptoms, the results of this study may help improve knowledge, taking into account the prevalence of the disease which is not always recognized and valued. Antepartum anxiety was the only variable found as a predictor for antepartum depression and also for postpartum depression, together with antepartum depression and parenting stress. Therefore, screening for peripartum depression and its risks is important.

## ARTICLE HIGHLIGHTS

### *Research background*

Depression is a common public health problem. It is an important cause of morbidity for mothers in

their peripartum period, with an estimated prevalence of 7%-58% or even higher in some countries. A common prevalence of antepartum or postpartum depression reported in different studies is approximately 13%. The suggested mechanism(s) of peripartum depression include(s) complex interplay between biological factors (fluctuation in reproductive, thyroid, and hypothalamic pituitary adrenal axis hormones), immune system activity, genetics, and psychosocial stressors. Therefore, World health Organization and United States Preventive Services Task Force recommend screening for women in peripartum period looking for manifestations of depression and determine their risks.

### *Research motivation*

The research hotspots include determination of: (1) The prevalence of peripartum (antepartum and postpartum) depression. Because related studies are few for antepartum compared to postpartum depression; (2) The severities of depression in relation to different demographic, social, obstetric, hormonal, and psychological variables; and (3) The predictors which are independently associated with each of antepartum or postpartum depression.

### *Research objectives*

This study systematically assessed women in their peripartum period to estimate the prevalence and predictors of peripartum depression.

### *Research methods*

The Edinburgh Postpartum Depression Scale screening questionnaire; designed unstructured clinical questionnaire to gather information about the women's reactions to recent life circumstances, events, and stress in relation to the recent pregnancy; Beck Depression Inventory II, the State-Trait Anxiety Inventory for Adults, and Parenting Stress Index-Short Form for severity categorization of depression, anxiety, and parenting stress respectively; psychiatric interviewing to confirm the diagnosis of major depressive disorder (according to the Diagnostic and Statistical Manual of Mental Disorders, version 5); and measurements of triiodothronine, thyroxine, and thyroid stimulating hormone levels in the antepartum and postpartum periods.

### *Research results*

The prevalence of women with clinically significant symptoms of peripartum depression in our locality is 20.66%. Major depression was found in 7.44%. Symptoms of depression were less severe in postpartum period than antepartum. Antepartum anxiety was the only predictor for both antepartum and postpartum depression. Antepartum anxiety and depression and parenting stress were the predictors for postpartum depression.

### *Research conclusions*

Nearly one fifth of women developed clinically significant manifestations of depression in their peripartum period, mainly attributed to anxiety and parenting stress.

### *Research perspectives*

In our locality, the importance of antepartum depression as a risk for postpartum depression and subsequently parenting stress has been largely under-recognized. Health care providers and insurance policies need to focus attention to the magnitude of the problem of peripartum depression to encourage education for obstetricians, mothers, and families about its high prevalence and associated risks. A multidisciplinary team for screening and management of peripartum depression is required (*e.g.*, prevention and expertise guidance related to the recommended treatment options, such as psychotherapy and/or pharmacotherapy).

## FOOTNOTES

**Author contributions:** Hamed SA and Fawzy M carried out design of the study, statistical analyses, and manuscript drafting; Elwasify M and Abdelhafez M did the clinical evaluation of participants and participated in study design and drafting the manuscript; All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

# Cross-sectional survey following a longitudinal study on mental health and insomnia of people with sporadic COVID-19

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## Abstract

***BACKGROUND***

In the post-pandemic era, the emergence of sporadic cases of coronavirus disease

2019 (COVID-19) and the scale of the pandemic are unpredictable. Therefore, the impact of sporadic cases of COVID-19 and isolation measures on mental health and sleep in different groups of people need to be analyzed.

***AIM***

To clarify the severity of psychological problems and insomnia of staff and community residents around a hospital with sporadic cases of COVID-19, and their relationship with quarantine location and long-term changes.

***METHODS***

A cross-sectional survey was conducted on community residents and medical staff. Many of these medical staff had been subjected to different places of quarantine. Community residents did not experience quarantine. Hospital anxiety and depression scale (HADS), acute stress disorder scale (ASDS) and insomnia severity index (ISI) were used to evaluate anxiety and depression, acute stress disorder symptoms, and the severity of insomnia. Additionally, we conducted a 1-year follow-up study on medical staff, with related scales measurement immediately after and one year after the 2-wk quarantine period.

***RESULTS***

We included 406 medical staff and 226 community residents. The total scores of ISI and subscale in HADS of community residents were significantly higher than that of medical staff. Further analysis of medical staff who experienced quarantine showed that 134 were quarantined in hotels, 70 in hospitals and 48 at home. Among all subjects, the proportions of HADS, ASDS and ISI scores above normal cutoff value were 51.94%, 19.17% and 31.11%, respectively. Multivariable logistic regression analysis found that subjects with higher total ASDS scores had a greater risk to develop anxiety and depression. The total ISI score for medical staff in hotel quarantine was significantly higher than those in home quarantine. Total 199 doctors and nurses who completed the 1-year follow-up study. Compared with baseline, HADS and ASDS scores decreased significantly one year after the end of quarantine, while ISI scores did not change significantly.

***CONCLUSION***

Sporadic COVID-19 cases had a greater psychological impact on residents in surrounding communities, mainly manifested as insomnia and depressive symptoms. Hotel quarantine aggravated the severity of insomnia in medical staff, whose symptoms lasted ≥ 1 year.

**Key Words:** COVID-19; Depression; Anxiety; Insomnia; Quarantine

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**Core Tip:** This is the first study to research the severity of psychological problems and insomnia of medical staff and community residents around a hospital with sporadic coronavirus disease 2019 (COVID-19) cases, along with long-term changes in the post-pandemic era. We found that sporadic COVID-19 cases had a greater impact on mental health and sleep for community residents, and hotel quarantine had a higher risk for insomnia in doctors and nurses. The insomnia symptoms of doctors and nurses could last for ≥ 1 year. Therefore, our results indicate psychological and sleep problems after sporadic COVID-19 might need long-term mental and psychological intervention, especially for insomnia in doctors and nurses.

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## INTRODUCTION

Coronavirus disease 2019 (COVID-19)[1] is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[2] and was declared a public health emergency of international concern by the World Health Organization (WHO). According to the WHO report[3] by December 31, 2021, there were > 2.8

billion cases and > 5.4 million deaths worldwide. The number of new cases reported globally currently exceeds 135 million per day. It can be seen that the global outbreak of COVID-19 is still very serious.

The impact of the COVID-19 pandemic on mental health is expected to be immense and likely to be long-lasting worldwide[4,5]. The current COVID-19 pandemic may have psychological implications for many reasons[5]. Some of these reasons, including physical distance, fear of infection, inadequate information, stigma, quarantine measures, contribute to the pandemic and government responses[4,6,7]. China has adopted class A infectious disease prevention and control measures[8], which are also included in the management of quarantine for infectious diseases. That is, quarantine is needed not only for confirmed COVID-19 and suspected cases but also those who are in close contact. Quarantine measures urgently adopted to control the COVID-19 pandemic might have had negative psychological and social effects[6], such as senses of insecurity, shame, and hostility. Quarantine for COVID-19 often aggravates the above-mentioned mental and psychological reactions, and may cause anxiety, depression and suicide[9], and acute stress disorder (ASD) may appear[10,11], characterized by separation, avoidance, re-experience, and high alertness. The onset occurs within a few minutes or hours after the stress, and the symptoms usually do not exceed 1 mo. The results of a large-sample data study in China and worldwide suggest that the incidence of ASD among the public during the COVID-19 pandemic was 21.2% and 34.9%[12,13]. The long-term psychological impact of COVID-19 requires attention to the occurrence of post-traumatic stress disorder (PTSD)[14,15], which is characterized by repeated invasive traumatic experiences, avoidance behaviors, increased alertness symptoms, and even suicidal behaviors or psychoactive substances abuse.

With vaccination, various countries have adopted active prevention and control measures for COVID-19[16,17]. At present, the spread of COVID-19 in some countries and regions is mainly in the form of sudden and unpredictable disease and all types of people can be affected[4,5,16,17]. Although general hospitals do not admit patients with COVID-19 in China[8,18], compared with other locations, they are more likely to find cases of COVID-19. Therefore, in the post-pandemic era, the impact of sporadic cases of COVID-19 and isolation measures on mental health and sleep in different groups of people needs to be analyzed. This study focused on the psychological effects on hospital staff and surrounding community populations who reported patients with COVID-19, and the long-term impact on mental health and sleep for medical staff in the hospital.

## MATERIALS AND METHODS

### *Study population*

Subjects included in this study were divided into two groups: medical staff from the hospital where patients with COVID-19 were found, and residents from the community surrounding the hospital. Some of the medical staff had adopted different forms of quarantine according to the degree of close contact with COVID-19 patients. Those who were close contacts were isolated in a hotel (could not leave the room); those who were close contacts of close contacts (secondary close contacts) were isolated in the hospital in single quarters (could not leave the room); and those who were general contacts were quarantined at home (could not leave home). Different quarantine places have different restrictions on the range of activities of the individual, and they also have different risks of infection and may have different psychological effects on the individual. Community residents had not experienced isolation measures. Participants in the follow-up survey were doctors and nurses who completed the baseline survey and a 1-year after survey.

### *Survey instrument*

The hospital anxiety and depression scale (HADS)[19] is used to assess the anxiety and depression symptoms of medical staff in general hospitals. There are 14 items in total, divided into two parts: the anxiety subscale (HADS-A) and the depression subscale (HADS-D). A total score of 0–7 is classified as asymptomatic, 8–10 as marginal/suspicious, and 11–21 as abnormal.

The acute stress disorder scale (ASDS)[20,21] is a self-rating scale, compiled according to the diagnostic criteria of the fourth edition of the Manual of Diagnosis and Statistics of Mental Disorders, used to assess acute stress disorder (ASD) symptoms and predict PTSD. ASDS contains 19 items, including the characteristics of screening for ASD, and can identify individuals with acute trauma who need an in-depth assessment of the risk of PTSD. Generally, 56 points are selected as the cutoff value for predicting PTSD by ASDS: dissociative symptom score ≥ 9 points, and other symptom score ≥ 28 points, and the diagnostic sensitivity of ASD is 0.95, specificity is 0.83, positive predictive power is 0.80, negative predictive power is 0.96, and validity is 0.87.

The insomnia severity index (ISI)[22] is a simple tool for screening insomnia, including seven items to assess the severity of sleep symptoms, satisfaction with sleep patterns, impact of the degree of insomnia on daily functions, awareness of the impact of insomnia on the subjects, and level of depression caused by sleep disorders. Total score of 0–7 points = insomnia without clinical significance; 8–14 points = subclinical insomnia; 15–21 points = clinical insomnia (moderate); and 22–28 points = clinical insomnia (severe).

A general survey questionnaire was designed to collect demographic data (gender, age, occupation), quarantine information, and subjectively describe the psychological reactions.

### Study design and procedure

A cross-sectional survey was conducted on July 2, 2020, immediately after the quarantine was lifted, with participants who worked in a hospital with sporadic cases of COVID-19, and the surrounding community residents. HADS, ASDS and ISI were used to evaluate the anxiety and depression, ASD symptoms, and severity of insomnia. The general survey questionnaire was used to collect demographic information, quarantine information and psychological reactions.

A follow-up longitudinal survey was conducted in May 2021, one year after quarantine, to clarify any changes in the psychological and insomnia symptoms of medical doctors and nurses (D&N group) that had a higher infection risk. The flow chart of the study is shown in Figure 1.

The Department of Psychological and Behavioral Medicine carried out a missionary style psychological crisis intervention to the entire population in the hospital during quarantine from June 18 to July 1, 2021. The research team provided targeted and layered psychological interventions for the medical staff, such as providing psychological crisis team contact information and providing psychological rescue support 24 h a day. The research team daily released audio, video and text content for relaxation, meditation and mindfulness therapy through a WeChat (a social media software) group in the hospital; provided contact information actively to the medical staff who were seeking help to carry out in-depth psychiatric evaluations; and provided psychological crisis intervention and treatment through remote diagnosis, treatment, or combined antianxiety and antidepressant medications when necessary. At the same time, the hospital immediately released pandemic prevention and control information and data updates until the end of quarantine. There were no new cases of COVID-19 reported throughout the quarantine.

The protocol was registered at clinicaltrials.gov with identification number NCT04978220.

### Statistical analysis

We used independent $t$ test, $\chi^2$ test, nonparametric Mann–Whitney $U$ test, and Kruskal–Wallis test to compare the demographic characteristics at baseline, and scores of HADS, ASDS and ISI at baseline and at the end of 1-year follow up. The scores of the three scales were not all normally distributed and so are presented as medians with interquartile ranges. The ranked data, which were derived from the counts of each level for symptoms of depression, anxiety, stress and insomnia, were presented as numbers and percentages. To determine potential risk factors for symptoms of depression, anxiety, insomnia, and distress in participants, multivariable logistic regression analysis was performed to find the associations between risk factors and outcomes, and results presented as odds ratios (ORs) and 95%CIs.

## RESULTS

### Cross-sectional study

**Differences between medical staff and residents of surrounding community:** Medical staff ($n$ = 406), including doctors, nurses and other hospital staff, and residents of the surrounding community ($n$ = 226) were recruited through questionnaires distributed online on their own will. The demographic data and scale scores were compared between medical staff and residents of the surrounding community (Table 1).

The difference in total ISI scores between the two groups was significant ($Z$ = 2.050, $P$ = 0.040) and the severity of insomnia among medical staff was lower than that of residents in the surrounding community. Among the scores on the ISI scale (Mann–Whitney), the difference in daily function between the two groups was significant ($Z$ = 3.332, $P$ = 0.001).

There was no significant difference in the total HADS score between the two groups ($Z$ = 1.517, $P$ = 0.129). In HADS-D ($Z$ = 1.984, $P$ = 0.047), the score for the item of fidgeting ($Z$ = 2.809, $P$ = 0.005) was higher and the score for enjoyment of a good book/broadcast/program was lower ($Z$ = 2.787, $P$ = 0.005) in community residents than in medical staff. This meant that the depressive symptoms of community residents were significantly worse, and they showed more fidgeting and decreased ability to feel pleasure than the medical staff did. There was no significant difference in the HADS-A score between the two groups ($Z$ = 0.889, $P$ = 0.374).

There was no significant difference in the total ASDS score between the two groups ($Z$ = 0.439, $P$ = 0.660). However, the scores for each ASDS item in community residents showed a greater psychological impact on the subjective report ($Z$ = 2.478, $P$ = 0.013) and deeper fear of COVID-19 ($Z$ = 2.821, $P$ = 0.005) than the scores in medical staff.

**Impact of different quarantine places on medical staff:** To study the psychological and sleep effects of different quarantine places, we divided quarantined medical staff into the hospital group, hotel group, and home group according to the different quarantine measures. We did not find significant differences between each group for total HADS score ($\chi^2$ = 0.319, $P$ = 0.956), HADS-A score ($\chi^2$ = 0.920, $P$ = 0.821)

**Table 1 The demographic data and scale score comparison between medical staff (*n* = 406) and community residents (*n* = 226) on baseline**

| Variable | Medical staff (*n* = 406) | Community residents (*n* = 226) | $t/\chi^2/Z$ | *P* value |
|---|---|---|---|---|
| Age (yr), mean ± SD | 36.18 ± 8.83 | 41.54 ± 11.84 | 1.46 | 0.145 |
| Gender, *n* (%) | | | | |
| Male | 70 (17.24) | 80 (35.40) | | |
| Female | 336 (82.76) | 146 (64.60) | 632 | 0.000 |
| Scale scores, median (range) | | | | |
| HADS | 11 (4-35) | 12 (4-32) | -1.517 | 0.129 |
| HADS-A | 6 (2-18) | 7 (2-17) | -0.889 | 0.374 |
| HADS-D | 5 (1-20) | 5 (1-18) | -1.984 | 0.047 |
| ASDS | 28 (19-89) | 27 (19-76) | -0.439 | 0.66 |
| ISI | 4 (0-28) | 5 (0-28) | -2.05 | 0.040 |

The values are expressed as numbers (%), means ± SD or medians (range). HADS: Hospital anxiety and depression scale; HADS-A: Hospital anxiety and depression scale-anxiety subscale; HADS-D: Hospital anxiety and depression scale-depression subscale; ASDS: Acute stress disorder scale; ISI: Insomnia severity index.

and HADS-D score ($\chi^2$ = 1.049, $P$ = 0.789); total ASDS score ($\chi^2$ = 0.528, $P$ = 0.913); and total ISI score ($\chi^2$ = 0.290, $P$ = 0.407). Therefore, different quarantine places may have had no obvious influence on the anxiety and depression level, stress and insomnia in medical staff.

We further studied these quarantined doctors or nurses who had higher infection risk. There were 360 doctors or nurses. Among them, 252 experienced quarantine. These quarantined staff were divided into three subgroups according to the quarantine location: hospital single quarters ($n$ = 70), hotel ($n$ = 134) and home ($n$ = 48). There was no significant difference in the HADS and ASDS scores ($P$ > 0.05) among the three groups. There was a significant difference in total ISI scores between home and hotel quarantine ($t$ = 0.691, $P$ < 0.05), and the total ISI score for hotel quarantine was significantly higher than that of home quarantine (mean ± SE = 2.164 ± 0.960, 95%CI: 0.272–4.056, $P$ = 0.025). For ISI items, severity of recent insomnia (*e.g.*, in the past week) ($\chi^2$ = 7.654, $P$ = 0.022), difficulty in falling asleep ($\chi^2$ = 6.793, $P$ = 0.033), and difficulty staying asleep ($\chi^2$ = 9.290, $P$ = 0.010) were significantly higher in the hotel than home quarantine groups (Table 2).

**Subjective description of subjects:** The main symptoms of the subjects were decreased interest, fear, anticipatory anxiety, akathisia, and decreased pleasure. According to response to the item "subjectively describe the content of psychological reactions" collected by the general survey questionnaire, the above-mentioned psychological reactions and symptoms were mainly due to the following reasons: (1) Worry about being infected; (2) Restricted activities in isolation, especially when being isolated, and worry about family members; (3) Worry about work; (4) Sudden notification of isolation, with no psychological preparation; (5) Worry about economic problems; and (6) Depressed mood for unstated reasons.

**Risk factors for anxiety and depression in D&N group:** Among medical staff, 187 with anxiety and depression were screened based on HADS score ≥ 11. Logistic regression analysis found that differences in age and total ASDS scores between subjects with anxiety and depression were significant ($t$ = 2.858, $P$ < 0.01 and $t$ = 10.657, $P$ < 0.01, respectively). Subjects with higher total ASDS scores (OR = 1.227, 95%CI: 1.17–1.29) had a greater risk of developing anxiety and depression, and young age (OR = 0.995, 95%CI: 0.93–0.99) was a protective factor.

**Risk factors for insomnia in D&N group:** Among medical staff, 112 subjects with insomnia were screened based on ISI score ≥ 8. Logistic regression analysis was performed to analyze the risk factors for insomnia during quarantine. The differences in total ASDS scores ($t$ = 9.148, $P$ < 0.01) and quarantine between those with and without insomnia ($\chi^2$ = 7.895, $P$ < 0.05) were significant. Subjects who experienced quarantine (OR = 2.799, 95%CI: 1.099–7.129) and subjects with higher total ASDS scores (OR = 1.195, 95%CI: 1.145–1.246) had a greater risk of insomnia.

### *Follow-up research*

To clarify the changes in psychological and insomnia symptoms of doctors or nurses who had a higher infection risk, we followed up them for one year. At baseline, 360 subjects (D&N group) completed the

**Table 2 Comparison of the scores in each insomnia severity index items in different quarantine locations in doctors and nurses' group on baseline (*n* = 252)**

| Variable | Groups based on quarantine site's | | | $\chi^2$ | *P* value |
|---|---|---|---|---|---|
| | Hospital (*n* = 70) | Hotel (*n* = 134) | Home (*n* = 48) | | |
| ISI items | | | | | |
| Severity (1 + 2 + 3) | 1 (0, 9) | 2 (0, 12) | 1 (0, 9) | 7.654 | 0.022 |
| 1 Falling asleep | 0 (0, 3) | 0 (0, 4) | 0 (0, 4) | 6.793 | 0.033 |
| 2 Staying asleep | 0 (0, 3) | 0 (0, 4) | 0 (0, 3) | 9.29 | 0.010 |
| 3 Early awakening | 0 (0, 3) | 1 (0, 4) | 0 (0, 3) | 3.841 | 0.147 |
| 4 Satisfaction | 1 (0, 4) | 1 (0, 4) | 1 (0, 4) | 1.164 | 0.559 |
| 5 Interfere | 1 (0, 4) | 1 (0, 4) | 0.5 (0, 4) | 3.143 | 0.208 |
| 6 Noticeable | 1 (0, 4) | 1 (0, 4) | 0 (0, 3) | 4.293 | 0.117 |
| 7 Worried | 0 (0, 3) | 1 (0, 4) | 0 (0, 3) | 3.769 | 0.152 |

The values are expressed as medians (range). ISI: Insomnia severity index.

survey. The average age of the subjects was 35.79 ± 8.53 years, and 85.28% of them were women. One year later, 199 of 360 subjects, accounting for 55.28%, completed the whole study. There was no significant difference in age and gender for the subjects at the end point compared with baseline (Table 3).

The percentages of those whose HADS, ASDS and ISI scores were above the cut-off value were 51.9%, 19.17% and 31.11%, respectively. After 1-year follow-up, the percentages for HADS and ASDS scores decreased, and ISI increased to 43.72%, 18.09%, and 32.16%, respectively, but the differences were not significant ($\chi^2$ = 3.240, 0.097 and 0.065 respectively, $P > 0.05$).

Compared with baseline, the total HADS score was significantly lower ($Z = 3.923$, $P < 0.01$) after one year. The levels of anxiety and depression were both significantly lower than that at baseline (for HADS-A, $Z = 4.469$, $P < 0.01$; for HADS-D, $Z = 3.286$, $P < 0.01$). The total ASDS score also significantly decreased compared with that at baseline ($Z = 2.468$, $P < 0.05$), but the total ISI scores were not significantly different from those at baseline ($Z = 0.928$, $P > 0.05$) after one year (Table 3).

We further compared each item of the three scales between baseline and at the end of follow-up. The scores for items, such as "I enjoy the things I used to enjoy" ($Z = 2.336$, $P < 0.05$); "I get a sort of frightened feeling as if something awful is about to happen" ($Z = 4.277$, $P < 0.01$); "I can sit at ease and feel relaxed" ($Z = 12.771$, $P < 0.01$); and "I can enjoy a good book or radio or TV program" ($Z = 14.311$, $P < 0.01$), in HADS were significantly reduced after one year. The scores for items, such as "Feeling frightened" ($Z = 7.238$, $P < 0.01$); "Sense of re-experiencing" ($Z = 4.780$, $P < 0.01$); and "Feeling more alert to danger" ($Z = 2.173$, $P < 0.05$), in ASDS were significantly reduced after one year. The scores for each item in ISI did not have a significant difference between baseline and the end of follow-up.

## DISCUSSION

Our results showed that the psychological impact of COVID-19, such as depressive symptoms, on community residents was more obvious than that on medical staff. The main manifestations were restlessness and decreased ability to feel pleasure. The severity of insomnia in community residents was higher than that of medical staff. The main manifestations were impairment in daytime functions, such as daytime fatigue, ability to handle work and daily affairs, concentration, memory, and emotions. Because none of the community residents were quarantined, their depressive symptoms and the severity of insomnia were not directly related to quarantine. They might have been psychologically affected for the following reasons. They had been to the hospital for treatment, lived close to the hospital, or their family members were medical staff and they were worried that the medical staff may have been active in the community. Objectively speaking, the risk of COVID-19 infection among community residents who are not quarantined is less than that of medical staff. Therefore, although the difference in ASDS scores between the two groups was not significant, it could also explain the higher psychological reaction of community residents to acute stress.

The government has adopted various prevention and control measures to gradually return people's life to normal[23]. However, the impact of sporadic COVID-9 cases[24] and the spread of variants[25] on people's mental health and sleep in the post-pandemic era needs to be paid attention. In the post-pandemic era, government officials should also provide sufficient support, such as health education,

**Table 3 Demographic and scales of the participants at baseline (*n* = 360) and at the end of follow-up (*n* = 199) in doctors and nurses' group**

| Variable | Baseline (*n* = 360) | Follow-up (*n* = 199) | $t/\chi^2/Z$ | *P* value |
|---|---|---|---|---|
| Age (yr), mean ± SD | 35.79 ± 8.53 | 34.71 ± 7.80 | 1.46 | 0.145 |
| D&N group, *n* (%) | 360 (100) | 199 (100) | | |
| Gender, *n* (%) | | | | |
| Male | 53 (14.72) | 22 (11.06) | | |
| Female | 307 (85.28) | 177 (88.94) | 1.483 | 0.223 |
| Scale scores, median (range) | | | | |
| HADS | 11 (4-35) | 10 (0-33) | -3.923 | 0.000 |
| HADS-A | 6 (2-18) | 6 (0-19) | -4.469 | 0.000 |
| HADS-D | 4 (1-20) | 4 (0-16) | -3.286 | 0.001 |
| ASDS | 27.5 (19-89) | 26 (19-66) | -2.468 | 0.014 |
| ISI | 4 (0-28) | 5 (0-25) | -0.928 | 0.353 |

The values are expressed as numbers (%), means ± SD or medians (range). HADS: Hospital anxiety and depression scale; HADS-A: Hospital anxiety and depression scale-anxiety subscale; HADS-D: Hospital anxiety and depression scale-depression subscale; ASDS: Acute stress disorder scale; ISI: Insomnia severity index.

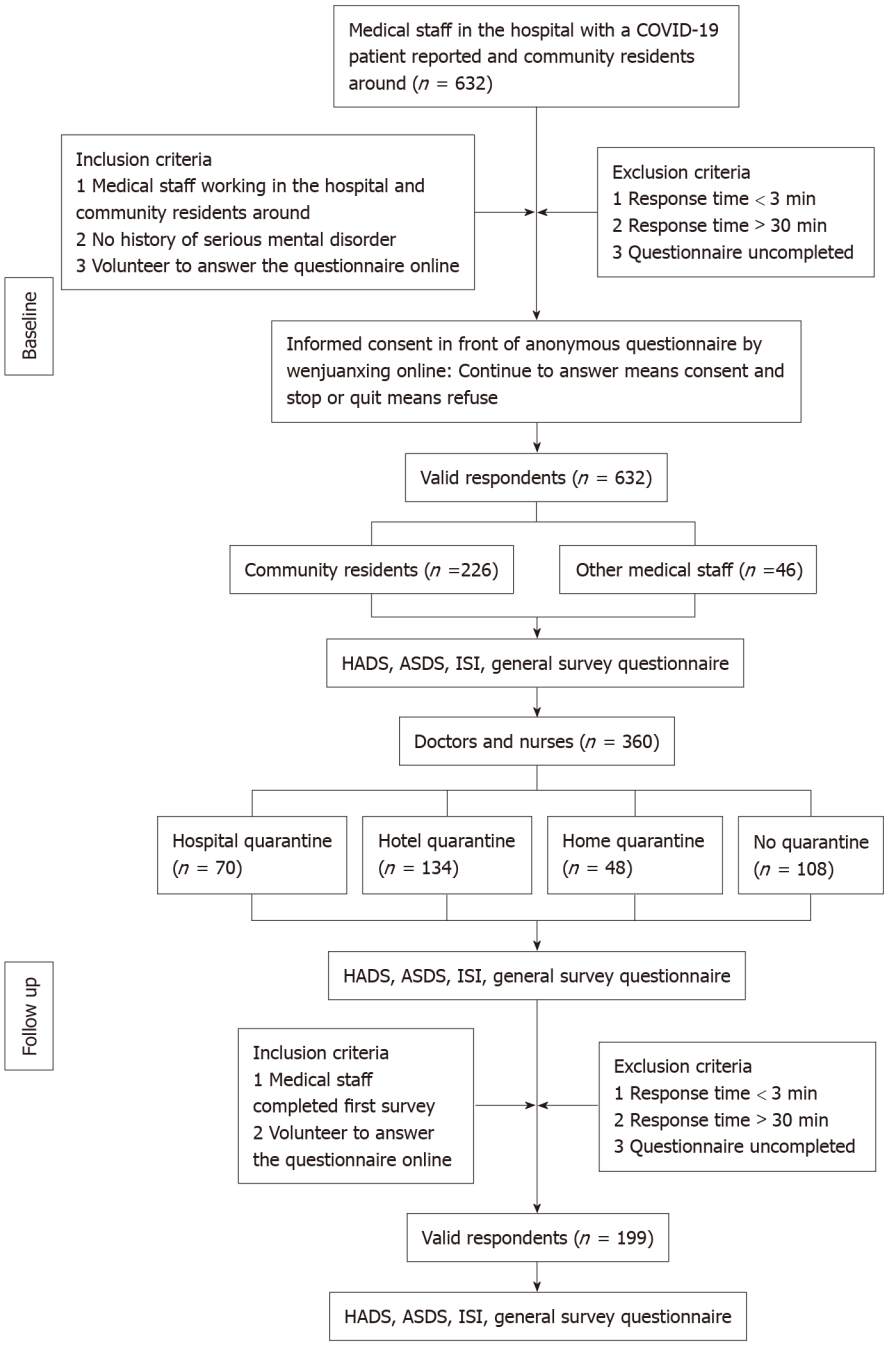
open a psychological hotline for consultation, psychological and sleep evaluation, and any necessary treatment.

Among all subjects, we found higher levels of anxiety and depression among the doctors and nurses in the hospital, according to the HADS screening results, regardless of quarantine. The proportion of doctors and nurses reaching abnormal levels of anxiety and depression was 51.94%. This result is similar to that of the front-line healthcare workers in Wuhan[26]. It is also comparable to the internationally reported upper levels of anxiety and depression of medical staff (anxiety, 6.33%–50.9%; depression, 6.33%–50.9%)[11]. Although the screening tools used[27,28] differed from ours, subjective description of the psychological reactions also reflects that sporadic COVID-19 cases still have a negative impact on medical staff. It suggests that the situation needs to be evaluated in a timely manner and active countermeasures need to be taken.

This study showed that the different quarantine locations did not result in anxiety and depression, or acute stress symptoms in doctors and nurses who are in quarantine. Many studies have reported the negative emotions of medical staff caused by quarantine measures[9,29,30]. This may be because the pandemic prevention and control was at a stable stage when this study was carried out. The domestic pandemic prevention task is to control mainly sporadic and imported cases, and the prevention and control pressure is greatly reduced. At the same time, the mental state of the doctors and nurses in the hospital may also be one of the reasons. The experiences learned from the outbreak of the pandemic and confidence in domestic pandemic prevention[31] may also reduce the severity of symptoms such as anxiety, depression and acute stress.

We also found that higher total ASDS score were risk factors for anxious and depressive symptoms and young age was a protective factor; total ASDS scores and quarantine were risk factors for insomnia; and the different quarantine locations had a significant impact on the sleep of doctors and nurses. The severity of insomnia among doctors and nurses in those who were in hotel quarantine was greater than those who were in home quarantine. The main manifestation of insomnia was difficulty in falling asleep and in maintaining sleep. The unfamiliar and simple environment of the hotel did not bring comfort to the doctors and nurses who were experiencing emergencies, while in home quarantine, they could enjoy regular daily life in familiar places. In addition, those who were in home quarantine could directly seek emotional help or obtain support from the family. This is consistent with a study on the current status of social support for doctors and nurses under the COVID-19 pandemic[32], in which good family support enabled individuals to quickly adapt to changes in the environment when faced with emergencies in order to obtain positive emotional responses and social support.

After one year, the proportion of respondents who used HADS to screen for anxiety and depression decreased to 43.72%, and the total HADS score was also lower than that at baseline. However, the proportion of respondents with anxiety and depression was still higher than at baseline, although the symptoms were significantly reduced and the number of affected individuals had also decreased. There may have been a benefit from the reduction of COVID-19 infection risk, release from quarantine, return to work and family, and timely and effective mental and psychological intervention and treatment. However, it is necessary to pay attention to the long-term psychological effects of COVID-19 infection




**DOI**: 10.5498/wjp.v12.i8.1076 **Copyright** ©The Author(s) 2022.

**Figure 1 Cross-sectional survey and follow-up study on psychological problems and insomnia in hospital staff and surrounding community residents of sporadic COVID-19 cases.** COVID-19: Coronavirus disease 2019; HADS: Hospital anxiety and depression scale; ASDS: Acute stress disorder scale; ISI: Insomnia severity index.

and the preventive measures on the hospital medical staff.

According to the results of ASDS assessment, we did not find any clear PTSD patients after 1-year follow-up. From the perspective of ASD, in the early stage of detection of COVID-19 infection cases, doctors and nurses showed typical symptoms: fear of COVID-19, anticipatory anxiety, and increased alertness[33]. Previous studies have reported that the general population[12] has similar stress symptoms and lower PTSD rate[14,34],which is in line with our findings. The time period from typical expression of acute stress symptoms after the discovery of sporadic COVID-19 to the improvement of related symptoms after 1-year follow-up showed a dynamic change in the psychological status of the medical staff in the hospital, and timely psychological crisis intervention was indispensable[35].

The insomnia symptoms of doctors and nurses had not improved along with improvement of their mental and psychological conditions after one year. This may be related to night shift work and the nature of work in the hospital. It suggests that concerns about the mental and psychological effects of the COVID-19 pandemic should be accompanied by concerns about insomnia symptoms among doctors

and nurses because sleep status is inseparable from mental health[36].

This was a single-center study, and the subjective assessments of people might cause bias in the results. In the future, the multiple center study could be done in different places for comparison, and objective testing, such as polysomnography, could be used to obtain more objective insomnia parameters.

## CONCLUSION

Sporadic cases of COVID-19 had a greater impact on residents in the surrounding community compared with hospital staff in the post-pandemic era, mainly manifested as insomnia and depression. The difference in quarantine location was an important factor affecting the severity of insomnia of doctors and nurses. Hotel quarantine aggravated the severity of insomnia of doctors and nurses. The early stage of sporadic COVID-19 cases appeared to have a significant impact on the mental health and sleep of doctors and nurses. Therefore, timely and effective psychological and behavioral intervention and treatment of insomnia symptoms, especially for those in hotel quarantine, is crucial. The long-term presence of insomnia symptoms in doctors and nurses should be paid high attention and be treated with positive intervention.

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## ARTICLE HIGHLIGHTS

### *Research background*

Coronavirus disease 2019 (COVID-19) is highly contagious and has a wide-ranging and serious impact on mental health. Although vaccination in some countries and regions has gradually restored people's lives, the emergence of virus mutations and sporadic cases might persist in the long term and affect mental health and sleep.

### *Research motivation*

There is a higher risk in general hospitals for COVID-19. The severity of psychological problems and insomnia of medical staff and community residents around a hospital with sporadic COVID-19 cases, and long-term changes in the post-pandemic period remain ambiguous. Additionally, the risk of COVID-19 and different quarantine locations among medical staff may affect doctors' and nurses' mental health and sleep. There have been few long-term follow-up studies about mental health and sleep in the post-pandemic era.

### *Research objectives*

This study aimed to clarify the severity of psychological problems and insomnia of staff and community residents around a hospital with sporadic cases of COVID-19, and their relationship with quarantine location and long-term changes in the post-pandemic era.

### *Research methods*

Medical staff from the hospital where patients with COVID-19 were found, and residents from the community surrounding the hospital were included in the study. Rating scales were provided by wenjuanxing on the internet. SPSS version 18.0 was used to perform statistical analysis. The significance level was set at $\alpha = 0.05$ and all tests were two-tailed.

### *Research results*

In the cross-sectional study, 632 subjects were recruited, including 406 medical staff in the hospital that reported sporadic COVID-19 cases and 226 community residents in the surrounding area. The total insomnia severity index (ISI) scores and hospital anxiety and depression scale (HADS) scores were significantly higher in the community residents than in the medical staff. Among medical staff, there were 360 doctors and nurses and 252 of them were quarantined in different locations according to contact level with the patient. The total ISI score for medical staff in hotel quarantine was significantly higher than that in home quarantine. One year later, 199 doctors and nurses completed the follow-up study. The total HADS and acute stress disorder scale scores of doctors and nurses were decreased, but

there was little change in ISI total score.

### *Research conclusions*

Our findings indicated that in the post-pandemic period, sporadic COVID-19 cases had a greater psychological impact on residents in the surrounding community than in hospital staff, and mainly manifested as insomnia and depressive symptoms. Doctors and nurses exposed to sporadic COVID-19 cases experienced anxiety and depression, stress, and insomnia in the early stage. Hotel quarantine means a higher risk of infection, and has a greater impact on doctors and nurses' insomnia than home quarantine. One year later, the anxiety and depression of doctors and nurses significantly improved. However, the long-term mental and psychological problems should not be ignored, especially their insomnia symptoms.

### *Research perspectives*

Sporadic COVID-19 has a greater psychological effect on surrounding community residents than on hospital staff. Government officials should give them relevant support, such as health education. A psychological and sleep rating hotline for people living in surrounding communities and those quarantined in hotels should help. We suggest that effective measures should also be implemented to treat the long-term insomnia in doctors and nurses.

## FOOTNOTES

**Author contributions:** All authors contributed to the study concept; Wang XQ, Li SX, Li XJ and Guo TZ designed the study; Li XJ, Guo TZ, Xie Y, Si JY, Xiong YT and Li H performed data acquisition and interpretation; Guo TZ, Bao YP, Wang XQ and Li SX performed the statistical analysis; Li XJ, Guo TZ, Li Z, Wang XQ and Li SX wrote the manuscript; Lu L revised the manuscript for important intellectual content. All the authors reviewed and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

# Fear of COVID-19 and emotional dysfunction problems: Intrusive, avoidance and hyperarousal stress as key mediators

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## Abstract

### *BACKGROUND*

There is mounting empirical evidence of the detrimental effects of the coronavirus disease 2019 (COVID-19) outbreak on mental health. Previous research has underscored the effects of similar destabilizing situations such as war, natural disasters or other pandemics on acute stress levels which have been shown to exacerbate current and future psychopathological symptoms.

### *AIM*

To explore the role of acute stress responses (intrusive, avoidance and hyperarousal) as mediators in the association between fear of COVID-19 and emotional dysfunction-related problems: Depression, agoraphobia, panic, obsessive-compulsive, generalized anxiety, social anxiety and health anxiety symptoms.

### *METHODS*

A sample of 439 participants from a university community in Spain (age: mean ± SD: 36.64 ± 13.37; 73.1% females) completed several measures assessing their fear of COVID-19, acute stress responses and emotional dysfunction syndromes through an online survey. Data collection was carried out from the start of home confinement in Spain until May 4, 2020, coinciding with initial de-escalation measures. Processing of the dataset included descriptive and frequency analyses, Mann-Whitney U Test of intergroup comparisons and path analysis for direct and indirect effects. This is an observational, descriptive-correlational and cross-sectional study.

### *RESULTS*

The prevalence of clinical symptoms in our sample, reported since the beginning of the pandemic, reached 31.44%. The female group presented higher scores although the effect size was small. Overall, the participants who exceeded the clinical cut-off points in emotional problems showed higher levels of fear of COVID-19 and of cognitive, motor and psychophysiological responses of acute stress, unlike the group with normative scores. In addition, the results show significant mediated effects of hyperarousal stress among fear of COVID-19 and emotional dysfunction psychopathology. However, the clinical syndromes most related to the consequences of the pandemic (*e.g.*, social contact avoidance or frequent hand washing), such as agoraphobia and obsessive-compulsive symptoms, were in fact predicted directly by fear of COVID-19 and/or the acute stress response associated with the pandemic and had a greater predictive power.

***CONCLUSION***

The present study illustrates a clearer picture of the role of acute stress on several forms of psychopathology during the COVID-19 crisis and home confinement.

**Key Words:** Fear of COVID-19; Acute stress; Emotional dysfunction; Psychophysiological activation; Mediated effects

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**Core Tip:** This study provides the prevalence of emotional dysfunction which reached 30% during the confinement stage in Spain. Our results point to higher levels of fear of coronavirus disease 2019 (COVID-19) and acute stress in participants with purely clinical symptoms compared with the normative group. We found clinically relevant associations between emotional dysfunction, fear of COVID-19 and acute stress. The mediated role of a psychophysiological activation response to explain indirect effects from fear of COVID-19 on various clinical syndromes is emphasized. These results support the need to include a therapeutic component of acute stress management in prevention and psychological intervention strategies in the face of exceptional events of a traumatic nature.

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## INTRODUCTION

### *Initial psychological impact of coronavirus disease 2019*

The coronavirus disease 2019 (COVID-19) pandemic has had an enormously consequential impact not just on financial and health systems worldwide, but also in day-to-day life. In many countries, a strict home confinement was implemented initially which resulted in a dramatic shift in a society's freedom of movement and general lifestyle affecting the population's mental health. Issues ranging from sleep quality to mood and anxiety disorders have been widely and closely scrutinized[1-3]. The incidence of depressive, anxiety-related, and acute stress moderate/severe symptoms in general population has been estimated around 16%, 28% and 8%, respectively[4-6], especially because of social isolation[7]. Prevalence of other psychopathological symptoms (*e.g.*, health anxiety) may have been dramatically increased and exacerbated by the outbreak of an infectious disease such as COVID-19[8]. In fact, preliminary evidence points toward the detrimental effects of COVID-19-related to quarantine on mental health as it has shown links to depression, stress, panic attacks, phobic symptoms, low mood and post-traumatic stress symptoms[9]. Considering that the symptoms of acute, as well as chronic stress [and in its most severe manifestation, posttraumatic stress disorder, (PTSD)[10]] have been associated with an array of destabilizing situations, such as war[11], financial crises[12] and natural disasters[13], and also with the psychopathology associated with trauma[14,15]. Exploring the effects of stress and its consequences during the COVID-19 outbreak seems important both theoretically and clinically.

### *Fear, stress reactions and psychopathology*

Prior research has highlighted the important role of psychological reactions such as infection-related fear, anxiety and uncertainty in the face of epidemics and pandemics, underscoring the high prevalence

of mental health symptoms in these circumstances[16]. In the current environment, studies have already been published on stress-related symptoms, the onset of which have been contingent with the coronavirus outbreak in patients[17] and in medical staff and the general population[18-20]. Acute stress could not only explain psychopathological manifestations, but its association with fear is also directly linked to anxious and mood disorders[10]. Fear has shown to be sensitized by acute traumatic stress [21], where stressful life events can lead to maladaptive, fear-related behaviors, facilitating the development of anxiety-related disorders[22,23]. Acute stress has been found to modulate the effects of fear on learning paradigms in humans, increasing the resistance to extinction in the case of cue-dependent fear[24]. The influence among fear and stress is reciprocal, such that stress responses are found to be more severe in the concurrent experience of fear[25]. In the context of the COVID-19 pandemic, this relation may yield greater psychopathological manifestations in at-risk patients as well as in the general population.

### *Mediated effects from stress*

Experiencing fear in critical conditions such as pandemics, natural disasters and financial crises has shown to lead to symptoms of acute stress which in some cases may persist and lead to forms of chronic stress[13] and other psychological problems like depression or anxiety[26]. Stress is a common symptom in several manifestations of psychopathology in the short and long-term[27] as well as an important antecedent toward the development of many different emotional dysfunction problems[28].

Several specific stress symptoms are described within the literature such as avoidance behaviors, hyperarousal or intrusive thoughts. Also, differentiated long-term effects from different types of symptoms are commonly found. For instance, intrusive recall is often described as a predictor of chronic stress[29]. Thus, it is normal to expect that these types of symptoms are related to several forms of stress (such as trauma and stress-related disorders). In contrast, the manifestation of hyperarousal would be a predictor of other stress responses such as avoidance and reexperiencing, thereby highlighting its distinctive nature in the expression of severe posttraumatic distress[30]. Moreover, it is also described as a strong predictor of psychological impact severity[31]. General acute stress, on its part, would be a determinant of future emotional recovery[32]. To our knowledge, there is very little evidence on the distinct effects of different stress responses on the psychopathology linked to COVID-19. As such, exploring early stress responses, especially hyperarousal, may be highly relevant toward prevention plans during stressful life events such as a health crisis derived from a pandemic.

### *Present study*

The main purpose of this study is to clarify the mediated role of acute stress reactions (*i.e.* intrusive reexperiencing, motor and cognitive avoidance strategies and psychophysiological activation) to explain the association between fear of COVID-19 and emotional dysfunction (*i.e.* depression, agoraphobia, panic, obsessive-compulsive, generalized anxiety, social anxiety and health anxiety symptoms). As secondary objectives, to examine the clinical prevalence and sex differences of emotional dysfunction and acute stress reported since the beginning of the pandemic and during confinement. Additionally, to compare levels of COVID-19 fear and acute stress among groups of participants with normative *vs* clinical scores on the different psychopathological syndromes and examine the associations between the study variables.

Based on the literature described above, we expected to find prevalence rates of emotional dysfunction and acute stress in the 10%-30% range, especially among the female group. We also expected to identify higher levels of fear of COVID-19 and acute stress in participants with scores above the cutoff point in the different clinical syndromes; and a positive, significant and clinically relevant raw association between all variables under study. Lastly, we expected that fear of COVID-19 and all seven assessed syndromes would be mainly indirectly linked *via* hyperarousal stress, such that higher fear of COVID-19 would be related to higher hyperarousal, which in turn would be associated with higher reports of psychological symptoms.

## MATERIALS AND METHODS

### *Participants and procedure*

The present study is part of the project PSICO-RECURSOS COVID-19, developed and implemented by the Centre of Applied Psychology from the Health Psychology Department at Miguel Hernández University in Elche (Alicante, Spain). This initiative arose with the goal of determining the psychological impact brought on by COVID-19 in the general population and underscores the influence of personal psychological resources such as resilience, coping strategies, socioemotional competencies and healthy habits. This is a descriptive-correlational, observational, cross-sectional study. Data collection was carried out employing self-reports which were completed through the application Detecta-Web, constructed with LimeSurvey software. Participation throughout the whole study process was completely voluntary. Anonymity and confidentiality of the data were also ensured by emphasizing its use exclusively for academic and/or research purposes. Approval for this study was granted by the

Ethics Committee of Miguel Hernández University (reference: DPS.JPR.01.20).

Thus, an initial sample of 660 participants from a university community were recruited until the 4th of May, the end of full confinement and beginning of de-escalation measures. Only participants who endorsed active acceptance to participate voluntarily and consented to use of the data and those that completed measures about fear of COVID-19, psychopathology and stress were included in the final analysis. Thereby, the final sample was composed of 439 participants (age: mean ± SD: 36.64 ± 13.37) where an overrepresentation of females was observed (73.1%; $n$ = 321). As for employment situation of the participants, 34.9% ($n$ = 153) were university students studying for state exams or civil servants; 52.2% ($n$ = 229) were active workers, including full-time and part-time workers, freelance workers and scholarship holders; and 12.8% ($n$ = 56) were unemployed, affected by temporary layoffs, currently on sick leave or retired, among others.

### Measures

For all measures, composite scores were created by averaging items. Higher scores indicated higher levels of the constructs.

**Fear of COVID-19 scale**[33]: This scale assesses fear of COVID-19 through 7 items answered on a 5-point, Likert-type scale, reflecting agreement with each statement (1: Totally agree; 5: Totally disagree). The total score ranges from 7 to 35, with higher values indicating a greater fear of COVID-19.

**Impact of event scale-revised**[34]: This instrument allows for assessment of the three core symptoms of acute stress contemplated by the Diagnostic and Statistical Manual of Mental Disorders (DSM)[10], regardless of its version: (1) Intrusive reexperiencing symptoms; (2) Motor and cognitive avoidance strategies; and (3) Level of psychophysiological activation. The impact of event scale-revised has 22 items and is answered on a 5-point Likert-type scale, reflecting the degree to which the symptoms are experienced (0: Absent or very mild; 4: Very severe). For this study, the content and verbal tenses of instructions and items were adapted to contextualize the stressful event to the COVID-19 health crisis and subsequent mandatory confinement measures.

**Anxiety and depression disorders symptoms scale, ESTAD**[35]: This instrument was designed to assess internalizing psychopathology according to the DSM-5[10]. Specifically, it allows for evaluation of agoraphobia, panic, generalized anxiety, social anxiety, obsessive-compulsive, health anxiety and depressive symptoms. The ESTAD consists of 36 items and is answered on a 5-point Likert-type scale (0: Never or almost never, 4: Always or almost always). The instructions were slightly modified to limit the questionnaire's scope to the beginning of the health crisis brought on by COVID-19 and mandatory home confinement measures.

### Statistical analyses

Prior to processing the dataset, the reliability of the psychological assessment measures was tested (Cronbach's alpha; criteria value $\alpha > 0.70$). Accordingly, descriptive (mean ± SD) and frequency (%) analyses were carried out to examine the clinical prevalence of emotional dysfunction problems, acute stress and fear of COVID-19 from the cutoff points reported in the respective validation studies. Then, a double intergroup comparison was made: (1) Sex differences for all study variables; and (2) Differences in fear of COVID-19 and acute stress associated to pandemic variables, according to the grouping of participants scoring above/below the cutoff point (normative *vs* clinical) for each psychological syndrome (alpha level: $P < 0.001$). For this purpose, the non-parametric Mann-Whitney U Test was used after ascertaining non-normality and heterogeneity of variances in all hypothesized comparisons (results of these previous analyses are available upon request). The effect size was calculated using Hedges' g (criteria values $g$: Approximately 0.20 small, approximately 0.50 medium, approximately 0.80 large). Then, the raw association between all the variables under study was analyzed using Pearson's correlation (magnitude criteria values $r$: Approximately 0.10 small, approximately 0.30 medium, approximately 0.50 large). This analysis block was performed using the IBM® SPSS® Statistics 27 software.

To explore the mediating role of acute stress between fear of COVID-19 and internalized psychopathology, a fully saturated path model was conducted using M*plus 8.4* software. Within the model, fear of COVID-19 was introduced as a predictor variable; acute stress in the form of avoidance, intrusive and hyperarousal reaction as a mediated variable; and psychopathological syndromes (agoraphobia, panic, generalized anxiety, social anxiety, obsessive-compulsive, health anxiety, and depressive symptoms) as output variables. Age and sex were entered as covariates in the model because of the differences observed among Spanish research[36] and even in this study. Missing data were handled using full information maximum likelihood[37]. Moreover, we examined the total, direct and indirect effects using bias-corrected bootstrapped estimates[38] based on 10000 bootstrapped samples which provides a powerful test of mediation[39] and is also robust to small departures from normality[40]. Statistical significance was determined by 99% bias-corrected bootstrapped confidence intervals not containing zero due to the sample size.

## RESULTS

### Descriptive data and sex differences

The prevalence of clinical symptoms reported since the beginning of the pandemic was 31.44% for agoraphobia, 13.44% for obsessive-compulsive, 11.62% for health anxiety, 11.39% for panic and social anxiety, 11.16% for depression and 8.43% for generalized anxiety in the whole sample. Likewise, the psychological impact of the health crisis in terms of acute stress was 21.18% severe, 6.83% moderate, 17.54% mild and 54.44% normative. The fear of COVID-19 scale does not have Spanish cutoff points to determinate its clinical prevalence among this sample. In addition, analysis of sex differences reported slightly higher scores in the female group although the effect size was small (Table 1).

### Comparisons between clinical vs normative groups

Table 2 presents comparisons in fear of COVID-19 and acute stress that were made according to the grouping of participants with normative *vs* clinical scores for each psychological syndrome. Fear of COVID-19 was clinically higher among participants who exceeded the cutoff point for health anxiety, panic, agoraphobia, and obsessive-compulsive syndromes ($P < 0.001$; $g$ from 0.84 to 1.17); while no differences were identified as reported in depression, generalized anxiety and social anxiety ($P > 0.001$). Motor and cognitive avoidance strategies were mostly found among clinical groups of generalized anxiety and social anxiety ($P < 0.001$; $g$ from 0.80 to 0.87). In this respect, no differences were identified in avoidance stress according to obsessive-compulsive and health anxiety indicators ($P > 0.001$). All clinical groups of emotional dysfunction problems presented high intrusive re-experiencing levels associated with the pandemic ($P < 0.001$), especially pronounced in panic, health anxiety and generalized anxiety syndromes ($g$ from 1.04 to 1.45). However, it was in the level of psychophysiological activation where the most statistically ($P < 0.001$) and clinically ($g > 0.80$) relevant intergroup differences were invariably found. In this regard, the differences between the normative and clinical groups of depression, panic and generalized anxiety presented a particularly large effect size ($g$ from 1.57 to 1.70). In the remaining intergroup comparisons analyzed, a moderate effect size was observed ($g$ approximately 0.50).

### Association between study variables

Bivariate correlations and general descriptive statistics for each measure are presented in Table 3. Fear of COVID-19 showed positive and significant associations ($P < 0.001$) with the three forms of acute stress manifestation, especially large with intrusive re-experiencing ($r = 0.55$). It also presented positive and significant correlations with the totality of psychopathological syndromes ($P < 0.001$). As expected, fear of COVID-19 was more strongly associated with health anxiety symptoms than others ($r = 0.56$). Also, a medium magnitude of association was observed between this construct and agoraphobia, obsessive-compulsive, panic, and generalized anxiety symptoms ($r$ from 0.36 to 0.41); while it was weakly linked to depression and social anxiety ($r = 0.18$ and 0.24, respectively). In turn, the correlation between acute stress and clinical syndromes associated to the pandemic was also positive and significant ($P < 0.001$). Avoidant strategies did not show strong relation magnitudes with emotional dysfunction problems, but moderate ones with panic, agoraphobia, depression, and generalized anxiety ($r$ from 0.30 to 0.45). Intrusive and hyperarousal stress showed large associations with generalized anxiety and panic ($r$ from 0.52 to 0.68). Depression and psychophysiological activation were also strongly associated ($r = 0.63$). The correlation of the sociodemographic data with the variables under study was very small ($r < 0.28$).

### Mediation model results

Total, direct and indirect effects are summarized in Figure 1 and Table 4. Significant direct effects (99%CI) from fear of COVID-19 to all three types of acute stress reactions (intrusive, hyperarousal and avoidance stress) were observed. Moreover, a significant direct effect from intrusive re-experiencing symptoms on social anxiety was found. Hyperarousal stress significantly predicted depression, panic, health anxiety, generalized anxiety and social anxiety symptoms. Among mediation effects, depression and generalized anxiety symptoms were significant and fully mediated *via* hyperarousal stress such that the higher fear of COVID-19 was related to higher levels of psychophysiological activation which in turn was related to higher levels of depression (β = 0.340, 99%CI: 0.236, 0.460) and generalized anxiety symptoms (β = 0.245, 99%CI: 0.162, 0.343). Similarly, significant partial mediated effects from fear of COVID-19 to panic and health anxiety symptoms were observed such that more fear of COVID-19 led to higher levels of hyperarousal which in turn led to more endorsement of panic (β = 0.258, 99%CI: 0.155, 0.382) and health anxiety symptoms (β = 0.120, 99%CI: 0.025, 0.229). It is important to note that significant positive direct effects between fear of COVID-19 and some types of emotional dysfunction ( *i.e.* agoraphobia, OCD, panic, and health anxiety) were still observed even when accounting for the effects of all variables.

**Table 1 Descriptive data and sex differences**

| Study variables | α | Total sample, *n* = 439 | | Females, *n* = 321 | | Males, *n* = 118 | | Mann-Whitney *U* test | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Mdn | Rng | Mdn | Rng | Mdn | Rng | *U* | *P* value | g |
| Fear of COVID-19 | 0.84 | 15 | 26 | 15 | 26 | 13 | 23 | 26026 | < 0.001 | 0.37 |
| Avoidance stress | 0.83 | 8 | 28 | 9 | 27 | 6 | 23 | 15317 | < 0.001 | 0.42 |
| Intrusive stress | 0.83 | 7 | 27 | 7 | 27 | 6 | 23 | 16208 | 0.001 | 0.38 |
| Hyperarousal stress | 0.84 | 6 | 27 | 7 | 25 | 5 | 27 | 16771 | 0.003 | 0.30 |
| Depression | 0.86 | 2 | 20 | 3 | 20 | 2 | 17 | 15536 | 0.004 | 0.27 |
| Agoraphobia | 0.83 | 3 | 19 | 3 | 19 | 2 | 15 | 16309 | 0.024 | 0.22 |
| Obsessive-Compulsive | 0.69 | 4 | 17 | 4 | 17 | 4 | 15 | 18604 | 0.775 | 0.01 |
| Panic | 0.88 | 1 | 19 | 1 | 19 | 0 | 16 | 16480 | 0.027 | 0.28 |
| Health anxiety | 0.87 | 3 | 20 | 3 | 18 | 3 | 20 | 17374 | 0.180 | 0.15 |
| Generalized anxiety | 0.91 | 5 | 20 | 6 | 20 | 3 | 20 | 13322 | < 0.001 | 0.50 |
| Social anxiety | 0.84 | 3 | 20 | 4 | 19 | 2 | 20 | 15102 | 0.001 | 0.33 |

COVID-19: Coronavirus disease 2019; Mdn: Median; Rng: Range; U: Mann-Whitney *U* test; Hedge's g effect size: Approximately 0.20 small, approximately 0.50 medium, approximately 0.80 large.

## DISCUSSION

The first objective of this study was to examine the clinical prevalence of emotional dysfunction problems and acute stress reported since the beginning of the pandemic and during the home confinement stage in Spain, in addition to analyzing sex differences. In line with our hypotheses, a prevalence ranging between 8.34% and 31.44% was found for clinical syndromes. In addition, 45.56% of the sample exceeded the cutoff score of acute stress, 21.18% at severe levels. The female group presented higher scores in all study variables although the effect size was small. In obsessive-compulsive and health anxiety symptoms, mostly associated with pandemic, sex differences were practically non-existent; however, the effect of this sociodemographic variable was controlled for in subsequent analyses. Previous studies in Spanish samples found similar prevalence in the assessment of anxious-depressive states and of specific fears during the same stage of the pandemic, also with a higher affectation in the female group[36], although obtaining lower scores for acute stress levels (*i.e.* approximately 15%)[7,41]; findings which are in the same vein as international studies[9]. In this regard, the selection of assessment instruments, diagnostic cut-off points, data collection methods, and idiosyncratic characteristics of samples, were highly heterogeneous among different studies focused on the psychological impact of COVID-19. This points to the need for standardized diagnostic assessment protocols that would allow for accurate and reliable comparisons between different groups and specific contexts (*e.g.*, cross-cultural studies).

The following objective was to compare levels of fear of COVID-19 and acute stress responses among normative *vs* clinical groups on the different psychopathological syndromes and analyze the association between all variables in the study. Then, we expected to identify higher levels of these constructs in participants with scores above the clinical cutoff point and a positive, significant and clinically relevant raw association between the variables. In comparison terms, clinical groups reported higher levels of fear of COVID-19 and acute stress reactions than the normative group. In addition, the raw association between variables was positive, significant and of a medium-to-large magnitude in almost all cases. In this regard, previous studies identified a significant exacerbation of symptoms in patients with specific psychopathological conditions, mostly associated with fear of COVID-19, worries and psychosocial stress generated by the pandemic[42], especially in health anxiety syndrome[8]. This finding highlights the need to provide special attention to psychologically vulnerable groups.

The last and main purpose of this study was to examine the (in)direct association between fear of COVID-19 and emotional dysfunction *via* intrusive, avoidance and hyperarousal acute stress reactions. In terms of predictive capability, and in line with the hypotheses, significant direct effects of fear of COVID-19 were found on motor and cognitive avoidance strategies, level of psychophysiological activation and especially intrusive re-experiencing symptoms. In this context, studies have already been published on stress-related symptoms, the onset of which have been contingent with the coronavirus outbreak in patients, medical staff and the general population[17-20]. To re-iterate a previous point, the influence among fear and stress is reciprocal, such that stress responses are found to be more severe in the concurrent experience of fear[25]. In addition, this construct presented direct effects on agoraphobia,

**Table 2 Mann-Whitney U Test according to the grouping of participants above/below the cutoff point in emotional dysfunction, *n* = 439**

| Emotional dysfunction | | *n* | Fear of COVID-19 | | | | | Acute stress associated to COVID-19 pandemic | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Avoidance stress | | | | | Intrusive stress | | | | | Hyperarousal stress | | | | |
| | | | Mdn | Rng | *U* | *P* value | g | Mdn | Rng | *U* | *P* value | g | Mdn | Rng | *U* | *P* value | g | Mdn | Rng | *U* | *P* value | g |
| Depression | ≤ 8 | 390 | 15 | 26 | 9080 | 0.515 | 0.15 | 7 | 28 | 6045 | < 0.001 | 0.69 | 6 | 26 | 5140 | < 0.001 | 0.91 | 5 | 22 | 2821 | < 0.001 | 1.60 |
| | ≥ 9 | 49 | 15 | 26 | | | | 11 | 27 | | | | 12 | 26 | | | | 14 | 27 | | | |
| Agoraphobia | ≤ 4 | 301 | 14 | 25 | 11712 | < 0.001 | 0.86 | 7 | 28 | 15261 | < 0.001 | 0.53 | 6 | 26 | 11894 | < 0.001 | 0.80 | 5 | 22 | 12931 | < 0.001 | 0.83 |
| | ≥ 5 | 138 | 17.5 | 26 | | | | 10 | 27 | | | | 10 | 27 | | | | 10 | 27 | | | |
| Obsessive-Compulsive | ≤ 8 | 380 | 14 | 26 | 6931 | < 0.001 | 0.84 | 8 | 28 | 9584 | 0.060 | 0.32 | 6 | 26 | 7616 | < 0.001 | 0.66 | 6 | 22 | 6707 | < 0.001 | 0.86 |
| | ≥ 9 | 59 | 19 | 26 | | | | 9 | 27 | | | | 12 | 27 | | | | 10 | 27 | | | |
| Panic | ≤ 5 | 389 | 14 | 25 | 5844 | < 0.001 | 0.90 | 7 | 28 | 5779 | < 0.001 | 0.79 | 6 | 26 | 4269 | < 0.001 | 1.16 | 5 | 22 | 3147 | < 0.001 | 1.57 |
| | ≥ 6 | 50 | 19.5 | 26 | | | | 11.5 | 26 | | | | 12 | 25 | | | | 14 | 25 | | | |
| Health anxiety | ≤ 8 | 388 | 14 | 22 | 4551 | < 0.001 | 1.17 | 8 | 28 | 8011 | 0.022 | 0.33 | 7 | 27 | 5591 | < 0.001 | 1.04 | 6 | 25 | 5013 | < 0.001 | 1.07 |
| | ≥ 9 | 51 | 21 | 26 | | | | 10 | 27 | | | | 13 | 24 | | | | 12 | 27 | | | |
| Generalized anxiety | ≤ 14 | 402 | 15 | 26 | 6009 | 0.046 | 0.49 | 8 | 28 | 3915 | < 0.001 | 0.87 | 6 | 26 | 2676 | < 0.001 | 1.45 | 6 | 22 | 2033 | < 0.001 | 1.70 |
| | ≥ 15 | 37 | 16 | 26 | | | | 13 | 23 | | | | 14 | 23 | | | | 16 | 23 | | | |
| Social anxiety | ≤ 9 | 388 | 15 | 26 | 7438 | 0.003 | 0.47 | 8 | 27 | 6277 | < 0.001 | 0.80 | 6 | 26 | 5276 | < 0.001 | 0.91 | 6 | 22 | 5242 | < 0.001 | 0.96 |
| | ≥ 10 | 51 | 16 | 26 | | | | 12 | 28 | | | | 12 | 26 | | | | 11 | 27 | | | |

COVID-19: Coronavirus disease 2019; ≤/≥: Normative/clinical cutoff points of ESTAD; Mdn: Median; Rng: Range; U: Mann-Whitney *U* test; Hedge's g effect size: Approximately 0.20 small, approximately 0.50 medium, approximately 0.80 large.

obsessive-compulsive, panic and health anxiety symptoms but not on depression, generalized anxiety and social anxiety. Acute stress associated to the pandemic showed, on the other hand, direct effects of intrusive re-experiencing on social anxiety while the level of psychophysiological activation had a strong influence on depression, panic and generalized anxiety and to a lesser extent on health anxiety and social anxiety. Avoidant acute stress did not present any direct effects. In this respect, different authors point to fear of illness, self-isolation/confinement and decreased quality of life having dramatically increased the level of stress-related disorders in the population. These symptoms and early warning signs may become episodic or chronic psychopathological problems[13,16,26-28,43].

The analysis of indirect effects of fear of COVID-19 on the different psychopathological syndromes showed a marked tendency of hyperactive stress to mediate this relation in line with previous longitudinal data[31]. Specifically, relevant indirect effects were found on health anxiety, generalized anxiety

**Table 3 Bivariate correlations and descriptive statistics among all study variables**

| No. | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Fear of COVID-19 | 1 | | | | | | | | | | |
| 2 | Avoidance stress | 0.39[c] | 1 | | | | | | | | | |
| 3 | Intrusive stress | 0.55[c] | 0.60[c] | 1 | | | | | | | | |
| 4 | Hyperarousal stress | 0.45[c] | 0.60[c] | 0.80[c] | 1 | | | | | | | |
| 5 | General anxiety | 0.36[c] | 0.45[c] | 0.59[c] | 0.68[c] | 1 | | | | | | |
| 6 | Depression | 0.18[c] | 0.36[c] | 0.45[c] | 0.63[c] | 0.71[c] | 1 | | | | | |
| 7 | Agoraphobia | 0.41[c] | 0.30[c] | 0.41[c] | 0.40[c] | 0.52[c] | 0.42[c] | 1 | | | | |
| 8 | Social Anxiety | 0.24[c] | 0.27[c] | 0.38[c] | 0.40[c] | 0.59[c] | 0.55[c] | 0.56[c] | 1 | | | |
| 9 | Panic | 0.39[c] | 0.37[c] | 0.52[c] | 0.61[c] | 0.69[c] | 0.63[c] | 0.60[c] | 0.54[c] | 1 | | |
| 10 | Obsessive-Compulsive | 0.40[c] | 0.20[c] | 0.32[c] | 0.33[c] | 0.43[c] | 0.31[c] | 0.56[c] | 0.43[c] | 0.46[c] | 1 | |
| 11 | Health anxiety | 0.56[c] | 0.27[c] | 0.44[c] | 0.45[c] | 0.54[c] | 0.36[c] | 0.49[c] | 0.42[c] | 0.52[c] | 0.56[c] | 1 |
| 12 | Sex | 0.15[b] | 0.18[c] | 0.17[c] | 0.14[b] | 0.22[c] | 0.12[a] | 0.10[a] | 0.15[b] | 0.12[a] | -0.00 | 0.07 |
| 13 | Age | 0.08 | -0.20[c] | -0.07 | -0.24[c] | -0.28[c] | -0.27[c] | -0.10[a] | -0.24[c] | -0.12[a] | -0.08 | -0.04 |

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
Sex was coded 0 = male, 1 = female. COVID-19: Coronavirus disease 2019.

and, especially, on depression and panic symptoms. This indicates that they were not predicted simply by the level of fear of COVID-19, but that a third variable was needed to observe a significant relationship like other studies where early stress response determined the subsequent psychological impact more than simple direct exposure[44]. This may point toward these symptoms being more reactive to the emergency posed by COVID-19 and, thereby, require special attention. Avoidant and intrusive acute stress, on the other hand, did not demonstrate a mediating role between fear of COVID-19 and psychopathological profiles assessed. In addition, none of the manifestations of acute stress had a direct or mediated influence on agoraphobia and obsessive-compulsive symptoms; in other words, these clinical syndromes, most related to the consequences of the pandemic (*e.g.*, social contact avoidance or frequent hand washing), were directly related to fear of COVID-19 with a greater predictive power. In this regard, Sandín's study identified intolerance to uncertainty and overexposure to the media as the main risk factors associated with fear of COVID-19[6]. On the one hand, the transdiagnostic nature of intolerance to uncertainty is purported to influence the etiopathogenesis of emotional disorders, especially anxiety disorders[45]. On the other hand, the informative overexposure

**Table 4 Summary of total, indirect, and direct effects of mediation models**

| Predictor variable: Fear of COVID-19 | Depression | Agoraphobia | Obsessive-Compulsive | Panic | Health anxiety | Generalized anxiety | Social anxiety |
|---|---|---|---|---|---|---|---|
| Total | 0.197 (0.074, 0.316) | 0.423 (0.296, 0.535) | 0.423 (0.295, 0.536) | 0.402 (0.252, 0.533) | 0.569 (0.463, 0.663) | 0.376 (0.261, 0.487) | 0.253 (0.115, -0.379) |
| Total indirect | 0.293 (0.190, 0.402) | 0.143 (0.006, 0.232) | 0.083 (0.006, 0.166) | 0.253 (0.166, 0.346) | 0.111 (0.035, 0.203) | 0.310 (0.211, 0.414) | 0.183 (0.100, 0.276) |
| Avoidance stress | -0.007 (-0.058, 0.041) | 0.006 (-0.067, 0.080) | -0.024 (-0.091, 0.042) | -0.012 (-0.068, 0.045) | -0.031 (-0.088, 0.020) | -0.002 (-0.050, 0.043) | -0.013 (-0.077, 0.053) |
| Intrusive stress | -0.041 (-0.145, 0.064) | 0.070 (-0.066, 0.208) | 0.034 (-0.080, 0.147) | 0.007 (-0.118, 0.134) | 0.023 (-0.092, 0.148) | 0.067 (-0.024, 0.167) | 0.114 (-0.013, 0.241) |
| Hyperarousal stress | 0.340 (0.236, 0.460) | 0.067 (-0.047, 0.197) | 0.073 (-0.028, 0.188) | 0.258 (0.155, 0.382) | 0.120 (0.025, 0.229) | 0.245 (0.162, 0.343) | 0.082 (-0.013, 0.189) |
| Direct | -0.096 (-0.224, 0.026) | 0.281 (0.135, 0.411) | 0.340 (0.196, 0.475) | 0.148 (0.009, 0.289) | 0.458 (0.340, 0.568) | 0.066 (-0.056, 0.193) | 0.069 (-0.076, 0.206) |

β (99%CI): Significant associations were determined by a 99% bias-corrected standardized bootstrapped confidence interval (based on 10000 bootstrapped samples) that does not contain zero. COVID-19: Coronavirus disease 2019.

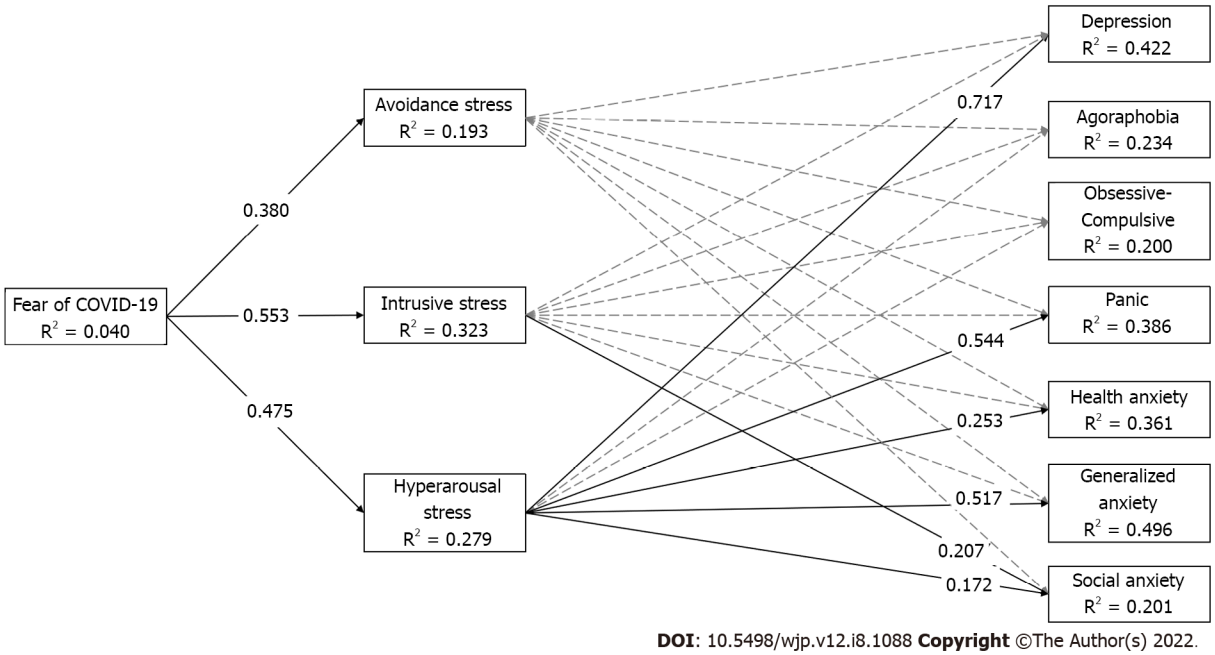


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**Figure 1 Estimated path mediation model.** Significant associations are indicated by the solid line for emphasis and were determined by a 99% bias-corrected standardized bootstrapped confidence interval (based on 10000 bootstrapped samples) that does not contain zero. Effects from covariates (age and sex) are omitted for parsimony but results are available upon request. COVID-19: Coronavirus disease 2019.

to the coronavirus through different media would have a direct negative effect on the levels of anxiety, worry and insomnia[46,47]. These findings should be considered as preventive measures.

In summation, the psychophysiological activation of stress would be a strong point to consider in developing specific protocols for screening, clinical assessment and early intervention of the psychological impact of the COVID-19 outbreak as a cost-effective way of dealing with trauma-consequences [30,31,48]. Also, interventions that may help to lower distress during the subsequent phases in overcoming COVID-19 may be of greater relevance given the evidenced association with other psychopathological syndromes[49-52] and/or other dimensional categories, such as specific fears and other distress syndromes such as PTSD[53]. Thus, a transdiagnostic approach intervention based on reducing the manifestation and dysfunctionality of initial psychological impact produced by fear of COVID-19 and acute stress reactions could be decisive in preventing future comorbidities and/or serious mental health problems. These results may be of interest and serve as a basis for future research related to other exceptional situations of a traumatic nature such as the current war in Ukraine.

### *Limitations and future lines of research*

Whereas we believe that this study contributes to the evidence of psychopathological symptoms being linked to COVID-19, some limitations should be considered. Due to the cross-sectional study design, it is not possible to infer causal relations between the variables. In this sense, it is considered relevant to longitudinally test whether the persistence of high levels of acute stress, especially in its hyperarousal manifestation, predicts a worse prognosis of the reported psychopathology. It would also be appropriate to consider the use of different representative samples, in terms of age (*e.g.*, adolescents) and other groupings (*e.g.*, clinical populations), individual-vulnerability factors related to disasters[26] and other idiosyncratic characteristics (*e.g.*, personality traits, especially neuroticism[54]). Also, it is important to note that this study was conducted during the COVID-19 pandemic, thereby specific factors of the confinement situation (*e.g.*, remote work, uncertainty and lack of control associated with the alarm state, among others) could be affecting our findings. It is also important to underscore that given the adaptation of measures to the COVID-19 situation, our findings revolve around reactive and specific symptoms to the current environment. Therefore, we cannot extrapolate the results to other, more general settings. In any case, these findings are much in line with previous studies.

## CONCLUSION

Fear of COVID-19 is indirectly related to several psychopathological syndromes (generalized anxiety, depression, health anxiety and panic) *via* specific hyperarousal acute stress. Thereby, higher levels of psychophysiological activation led to explain the indirect effect of fear of COVID-19 during the global "crisis" on the emotional dysfunction observed. The present study extends the literature on the relevant role of acute stress in better understanding the origin, development and exacerbation of different symptoms of psychopathology in a similar social-health context. It also responds to the call made to provide and expand the evidence on the early psychological impact of these events and their related factors contributing to the construction of an empirical basis for the design of preventive and intervention strategies during the "de-escalation" process and other future stages of this global crisis.

## ARTICLE HIGHLIGHTS

### *Research background*

The coronavirus disease 2019 (COVID-19) pandemic and initial home confinement stage have had an indisputable psychological impact on society. Previous studies show that similar destabilizing events of a traumatic nature have resulted in the origin and exacerbation of current and future psychopathological symptoms in which fear plays a key role. In this sense, scientific literature underlines the importance of early reduction of the initial acute stress response to that fear since its continuity over time could be the prelude to more severe clinical conditions (*e.g.*, post-traumatic stress disorder).

### *Research motivation*

This study sought to elucidate a threefold question: (1) Does fear of COVID-19 produce emotional dysfunction problems? (2) Does the level of acute stress play a mediating role between fear of COVID-19 and psychopathological symptoms? and (3) If affirmative, do the 3 core symptoms of acute stress (*i.e.* intrusive re-experiencing, motor and cognitive avoidance strategies and psychophysiological activation) equally modulate this relation? Knowing the answer to these questions would allow us to identify the pandemic risk factors that contribute to the manifestation and chronicity of associated psychopathology.

### *Research objectives*

The main purpose of this study is to explore the role of acute stress responses (intrusive, avoidance and hyperarousal) as mediators in the association between fear of COVID-19 and emotional dysfunction problems: Depression, agoraphobia, panic, obsessive-compulsive, generalized anxiety, social anxiety and health anxiety symptoms. As secondary objectives: (1) To examine the clinical prevalence and sex differences; (2) To compare levels of COVID-19 fear and acute stress among groups of participants with normative *vs* clinical scores on the psychopathological syndromes; and (3) To examine the associations between the study variables.

### *Research methods*

This is an observational, descriptive-correlational and cross-sectional study. Data collection was conducted through an online survey since the beginning of the pandemic and during the home confinement stage in Spain. It was disseminated among the members of the university community ($n$ = 439; age: mean ± SD = 36.64 ± 13.37; 73.1% females). Processing of the dataset included descriptive and frequency analyses, Mann-Whitney U Test of intergroup comparisons and path analysis using the

double software: IBM® SPSS® Statistics 27 and *Mplus 8.4*.

### *Research results*

The main findings indicate that the hyperarousal stress assume mediator role among fear of COVID-19 and emotional dysfunction. However, the clinical syndromes most related to the consequences of the pandemic (*i.e.* agoraphobia and obsessive-compulsive symptoms) were predicted directly by fear of COVID-19 and/or the acute stress response associated with the pandemic. In addition, the prevalence of clinical symptoms reached 31.44%. The female group presented higher scores although the effect size was small. Overall, the participants who exceeded the clinical cut-off points in emotional problems showed higher levels of fear of COVID-19 and acute stress.

### *Research conclusions*

Our findings highlight the mediator role of hyperarousal response to explain indirect effects from the fear of COVID-19 on the origin, development and exacerbation of psychopathological syndromes. These results provide an empirical basis for reducing the psychological impact of the pandemic through selection of more targeted intervention techniques and application in future similar social and health conditions.

### *Research perspectives*

We consider it relevant to longitudinally test whether the persistence of high levels of acute stress, especially in its hyperarousal manifestation, predicts a worse prognosis of the reported psychopathology. It would also be appropriate to consider the use of different representative samples and even analyze whether this psychological component of fear and acute stress influences the manifestation, course and prognosis of COVID-19 disease as previous studies in the field of Health Psychology have shown (for instance, in cancer patients).

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## FOOTNOTES

**Author contributions:** Falcó R and Vidal-Arenas V wrote the original draft and performed the formal analyses and interpretation; Vidal-Arenas V conceptualized the study; Ortet-Walker J helped on the theoretical framework and English editing; Marzo JC and Piqueras JA led the project and collaborated on reviewing and editing the manuscript; PSICO-RECURSOS COVID-19 Study Group designed the project and collected the data; All authors approved the final version of the article.

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LETTER TO THE EDITOR

# Difference between treatment-resistant schizophrenia and clozapine-resistant schizophrenia

Ping-Tao Tseng, Mu-Hong Chen, Chih-Sung Liang

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Grade E (Poor): 0

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## Abstract

We read the impressive review article "Clozapine resistant schizophrenia: Newer avenues of management" with great enthusiasm and appreciation. The author believes that preventing clozapine resistance from developing may be the most effective treatment strategy for patients with clozapine-resistant schizophrenia (CRS), and optimizing clozapine treatment is a key component. Disentangling the differences between treatment-resistant schizophrenia and CRS is important for studies addressing treatment strategies for these difficult-to-treat populations.

**Key Words:** Treatment-resistant schizophrenia; Clozapine; Clozapine-resistant schizophrenia; Ultra-resistant schizophrenia; Ultra-treatment-resistant schizophrenia; Super-refractory schizophrenia

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**Core Tip:** A diagnosis of clozapine-resistant schizophrenia (CRS) is made after administering an adequate trial of clozapine and excluding "pseudo-resistance" in patients who have been diagnosed with treatment-resistant schizophrenia (TRS). Disentangling the differences between TRS and CRS is important point for studies addressing treatment strategies for patients with CRS.

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## TO THE EDITOR

We read the impressive review article by Chakrabarti[1] with great enthusiasm and appreciation. The author suggests that clinicians need newer treatment approaches that go beyond the evidence for patients with clozapine-resistant schizophrenia (CRS). The author believes that preventing clozapine resistance from developing may be the most effective treatment strategy for patients with CRS, and optimizing clozapine treatment is a key component. Although this suggestion is new and insightful, we would like to discuss the differences between treatment-resistant schizophrenia (TRS) and CRS.

Treatment Response and Resistance in Psychosis (TRRIP) Working Group has suggested that CRS is a subspecifier of TRS[2]. A valid diagnosis of CRS needs to be based on: (1) Administering an adequate trial of clozapine; (2) Excluding the possibility of nonadherence to clozapine (*i.e.*, pseudo-resistance); and (3) Blood levels of clozapine ≥ 350 ng/mL. The TRRIP Work Group also recommend a minimum dose of 500 mg/d for patients who cannot undergo the blood test for clozapine concentration[2]. In the review article[1], the recommended adequate dose of clozapine is 200 to 500 mg/d, which may be low for patients with CRS.

Besides, when pooling available evidence for the management of CRS, we need to include studies that specifically addressing patients with a valid diagnosis of CRS. For example, Chakrabarti[1] cited a study by Masoudzadeh and Khalillian[3] who compared three interventions for patients with TRS, namely, clozapine, electroconvulsive therapy (ECT), and combined clozapine and ECT. In this study, a 40% reduction in the Positive and Negative Syndrome Scale scores was observed in patients who were treated with only clozapine[3]. It is clear that the study by Masoudzadeh and Khalillian[3] had included patients with TRS not CRS. Therefore, this study could not be considered as a CRS study.

## FOOTNOTES

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LETTER TO THE EDITOR

# Genetics of adult attachment and the endogenous opioid system

Alfonso Troisi

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## Abstract

Since the pioneering work by Panksepp *et al*, the neurobiological bases of attachment behavior have been closely linked with opioid neurotransmission. Candidate gene studies of adult individuals have shown that variation in the mu-opioid receptor gene (*OPRM1*) influences attachment behavior. Early maternal care and the A/A genotype of the A118G polymorphism interact in modulating levels of fearful attachment. Compared to their counterparts carrying the A/A genotype, individuals expressing the minor 118G allele show lower levels of avoidant attachment and experience more pleasure in social situations. Brain imaging research has strengthened the biological plausibility of candidate gene studies. The avoidance dimension of attachment correlates negatively with mu-opioid receptor availability in the thalamus and anterior cingulate cortex, as well as the frontal cortex, amygdala, and insula. Overall, findings from human studies combined with those from animal models suggest that research on the genetic bases of attachment should include the endogenous opioid system among the investigated variables.

**Key Words:** Genetics; Avoidant attachment; Fearful attachment; Endogenous opioids; *OPRM1*; A118G polymorphism

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**Core Tip:** Genetic studies of attachment should target the endogenous opioid system. Candidate gene studies of adult individuals have shown that variation in the mu-opioid receptor gene (*OPRM1*) influences attachment behavior. Early maternal care and the A/A genotype interact in modulating levels of fearful attachment. Compared to their counterparts carrying the A/A genotype, individuals expressing the minor 118G allele show lower levels of avoidant attachment. Brain imaging research has strengthened the biological plausibility of candidate gene studies. The avoidance dimension of attachment correlates negatively with mu-opioid receptor availability in the thalamus and anterior cingulate cortex, as well as the frontal cortex, amygdala, and insula.

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## TO THE EDITOR

I read with interest the narrative review by Erkoreka *et al*[1] who analyzed the existing literature regarding the implication of candidate genes related to oxytocin, dopaminergic pathways, serotonergic pathways, and brain-derived neurotrophic factor in adult attachment. Yet, the authors failed to discuss the studies that focused on the opioid pathways, which is surprising considering that, since the pioneering work by Panksepp *et al*[2], the neurobiological bases of attachment behavior have been closely linked with opioid neurotransmission. In this letter, I summarize the findings of the studies that Erkoreka *et al*[1] failed to report and show why genetic research on attachment should target the endogenous opioid system.

There is evidence that variation in the mu-opioid receptor gene (*OPRM1*) influences attachment behavior in both healthy volunteers and patients with psychiatric disorders. Troisi *et al*[3] aimed at ascertaining if the A118G polymorphism of the *OPRM1* moderates the impact of early maternal care on fearful attachment in 112 psychiatric patients. Early maternal care and fearful attachment were measured using the Parental Bonding Inventory and the Relationship Questionnaire (RQ), respectively. The pattern emerging from the RQ data was a crossover interaction between genotype and maternal caregiving. Participants expressing the minor 118G allele had similar and relatively high scores on fearful attachment regardless of the quality of maternal care. By contrast, early experience made a major difference for participants carrying the A/A genotype. Those who recalled higher levels of maternal care reported the lowest levels of fearful attachment whereas those who recalled lower levels of maternal care scored highest on fearful attachment. These data fit well with the differential susceptibility model which stipulates that plasticity genes would make some individuals more responsive than others to the negative consequences of adversity and to the benefits of environmental support and enrichment. In a mixed sample ($n$ = 214) of adult healthy volunteers and psychiatric patients, Troisi *et al*[4] analyzed the association between the A118G polymorphism of the *OPRM1* and avoidant attachment as measured by the Attachment Style Questionnaire. The findings showed that, compared to their counterparts carrying the A/A genotype, both healthy volunteers and psychiatric patients expressing the minor 118G allele showed lower levels of avoidant attachment and experienced more pleasure in social situations.

The biological plausibility of the candidate gene studies reported above is strengthened by findings from brain imaging research. Nummenmaa *et al*[5] scanned 49 healthy subjects using a mu-opioid receptor-specific ligand and measured their attachment avoidance and anxiety with the Experiences in Close Relationships-Revised scale. The avoidance dimension of attachment correlated negatively with mu-opioid receptor availability in the thalamus and anterior cingulate cortex, as well as the frontal cortex, amygdala, and insula. These results confirm that the endogenous opioid system may underlie inter-individual differences in avoidant attachment style in human adults, and that differences in mu-opioid receptor availability are associated with the individuals' social relationships and psychosocial well-being.

Overall, findings from human studies combined with those from animal models[6] suggest that research on the genetic bases of attachment should include the endogenous opioid system among the investigated variables.

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LETTER TO THE EDITOR

# Cardiotoxicity of current antipsychotics: Newer antipsychotics or adjunct therapy?

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## Abstract

Use of newer antipsychotics for substitution of current antipsychotics might be one way awaiting to be clinically verified to address antipsychotic cardiotoxic effects. Alternatively, the combination of existing antipsychotics with cardioprotective agents is also beneficial for patients with mental disorders for avoiding cardiotoxicity to the maximum.

**Key Words:** Antipsychotics; Cardiotoxicity; Combined medication; Adjunct therapy

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**Core Tip:** The newer antipsychotics have been reported to have fewer side effects and better performance in efficacy in short-term studies. Still, a dilemma lies between the benefit of ameliorating psychotic symptoms and severe side effects especially life-threatening cardiotoxicity in antipsychotic medications in clinical practice. The combination of antipsychotics with other therapeutic agents providing cardioprotection, such as β-blockers, cannabinoid 1 receptor antagonists, cannabinoid 2 receptor agonists, spliceosome inhibitors, angiotensin-converting enzyme inhibitors, and $\omega$-3 polyunsaturated fatty acids, may represent a promising strategy and sweet pledge.

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## TO THE EDITOR

We read with interest a recent paper entitled "Newer antipsychotics: Brexpiprazole, cariprazine, and lumateperone: A pledge or another unkept promise" by Barman *et al*[1] published in this journal[1]. The paper appraised the scientific data on psychopharmacology, safety profile, and efficacy of the newer antipsychotics, namely, brexpiprazole, cariprazine, and lumateperone. The authors compared the characteristics and indications of the three newer antipsychotic agents to indicate their promising future in treating schizophrenia in the short term, particularly due to their properties of less metabolic toxicity and potential control of negative symptoms.

In previous studies, several toxic effects were revealed in the use of first-generation antipsychotics and second-generation antipsychotics (SGAs), especially the life-threatening cardiotoxicity. The manifestations of cardiotoxicity range from heart rate change (*e.g.*, bradycardia or tachycardia) and blood pressure alternation (*e.g.*, hypotension or hypertension) to fatal issues such as QT prolongation and congestive heart failure. The three newer antipsychotics mentioned in the article are typical third-generation antipsychotics (TGAs), which display well-documented lower metabolic liability and better performance in targeting negative symptomatology and improving cognitive domains[2]. In addition, some TGAs such as roliperidone are associated with a lower incidence of cardiovascular side effects in short term. However, long-term clinical studies are limited, leading to a deficiency in clinical evidence of TGA cardiotoxicity. Further clinical trials are needed to determine whether TGAs perform better than their precursors in both safety and efficacy.

Given that the clinical application of TGAs is still under debate, the combination of existing antipsychotics with other therapeutic agents in the treatment of mental disorders, especially the cardioprotective agents, may also represent a promising strategy. Several therapeutic agents which are promising in combined medications are listed in Table 1. β-adrenal receptor blockers, as classical antiarrhythmic agents, have been verified to offer symptomatic relief in patients who suffer from tachycardia [3]. Some researchers have reached a consensus that optimal doses of β-blockers like propranolol can be well tolerated and are effective in alleviating clozapine-induced tachycardia and myocarditis[4]. In our serial works, we elaborated that both cannabinoid 1 receptor (CB1R) and cannabinoid 2 receptor (CB2R) were critically involved in SGAs-induced cardiac side effects and played opposite roles in the process of toxicity[5,6]. Administration of SGAs (clozapine or quetiapine) in 2-3 wk caused a decrease in CB1R but an increase in CB2R expression in a dose- and time-dependent manner. The functional rivalry between CB1R and CB2R suggests that specific antagonists of CB1R or agonists of CB2R could relieve antipsychotic cardiotoxicity, such as inflammation suppression and myocardial fibrosis remission. Of note, the opposite effects of cannabinoid receptors suggest that adjunct therapy should be based on single cannabinoid receptor agonism or antagonism since dual agonism/antagonism would unfortunately yield neutralizing effects[7]. In addition, CB1R antagonists have been marketed for weight loss, and CB2R agonists have also been shown to maintain metabolic process[8]. The use of CB1R antagonists or CB2R agonists in combination with antipsychotics might thus exert dual clinical benefits: One to inhibit drug cardiac toxicity and the other to attenuate antipsychotic-induced glycolipid metabolic disorders. Since cardiovascular and metabolic adverse effects compose the major concerns associated with SGAs use, the potential dual benefits derived from CB1R antagonists or CB2R agonists seem to be particularly important in the clinic[9]. However, since individual antagonists of CB1R like rimonabant may cause additional psychiatric disorders due to brain penetrance, development of beneficial CB1R antagonists or CB2R agonists that are peripherally restricted could assuage the clinical concerns.

In addition to those G protein-coupled receptor-based adjunct strategies, our recent animal study also suggested that pharmacological inhibition of intracellular spliceosome signaling at a relatively low concentration might also confer cardioprotection against SGAs cardiotoxicity[10]. Since clozapine cardiotoxicity is mainly manifested as cardiac inflammation (myocarditis), inhibition of oxidative stress and proinflammatory cytokines (*e.g.*, tumor necrosis factor-α) were also shown to be protective against clozapine-induced cardiotoxicity[11-13]. Current studies further showed that omega-3 polyunsaturated fatty acids (ω-3 PUFAs) were beneficial for schizophrenia patients in view of its protections against cardiovascular morbidity and mortality[14]. Of note, the dose-related cardioprotective and antiarrhythmic effects of ω-3 PUFAs have been observed in large clinical trials and consequently, this outcome may have provided strong evidence for ω-3 PUFAs becoming a potential candidate in the combined medication[15].

In summary, we are in agreement with the conclusion in the main body of the paper that all three newer antipsychotic agents are promising in the treatment of psychiatric disorders based on short-term studies. However, long-term studies are still limited to provide further evidence for systematic comparison between newer antipsychotics and their precursors. Thus, we put forward that the combination of existing antipsychotics with other cardioprotective agents, such as β-blockers, CB1R antagonists, CB2R agonists, spliceosome inhibitors, angiotensin-converting enzyme inhibitors, and ω-3 PUFAs, may reach the expectation that the combined medication can avoid the severe adverse effects of antipsychotics to the maximum in the treatment of mental disorders. The peripherally-restricted CB1R antagonists or CB2R agonists might merit further large clinical trials since they might provide beneficial control of SGAs-induced both metabolic and cardiac side effects.

**Table 1 Therapeutic agents for potential adjunct therapy in combination with existing antipsychotics**

| Therapeutic agents | Beneficial effect | Ref. |
|---|---|---|
| β-adrenal receptor blockers | Alleviating tachycardia and myocarditis | [3,4] |
| CB1R antagonists | Suppressing inflammation, ameliorating myocardial fibrosis | [5,6] |
| CB2R agonists | Suppressing inflammation, ameliorating myocardial fibrosis | [5,6] |
| Spliceosome inhibitors (*e.g.*, pladienolide B) | Inhibition of SGAs-induced alternative splicing events and consequent amelioration of inflammation and myocardial cell death | [10] |
| ACEIs (*e.g.*, captopril) | Oxidative stress and proinflammatory cytokine inhibitors | [11-13] |
| ω-3 PUFAs | Anti-arrhythmia | [15] |

ACEI: Angiotensin-converting enzyme inhibitor; PUFAs: Polyunsaturated fatty acids; SGA: Second-generation antipsychotics; CB1R: Cannabinoid 1 receptor; CB2R: Cannabinoid 2 receptor.

## FOOTNOTES

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LETTER TO THE EDITOR

# Underlying disease may increase mortality risk in users of atypical antipsychotics

Zhi-Peng Li, Yu-Shun You, Jun-Dong Wang, Lian-Ping He

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## Abstract

Schizophrenia is a group of the most common types of mental illness. Commonly used antischizophrenia drugs all increase mortality to some extent. The increased risk of death in older individuals and patients with dementia using atypical antips -ychotics may be due to myocardial damage, increased mobility and increased risk of stroke.

**Key Words:** Aripiprazole; Atypical antipsychotics; Dementia; Mortality rate; Psychiatry

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**Core Tip:** Schizophrenia is a group of the most common types of mental illness. Type I schizophrenia involves mainly positive symptoms and type II schizophrenia involves mainly negative symptoms. The patients are indifferent and lack initiative. Clinically, atypical antipsychotics are often used as first-line drugs for first-episode schizophrenia. Although antipsychotics may increase mortality to some extent, observational studies suggest that atypical antipsychotics are associated with a lower risk of all-cause mortality when compared with conventional antipsychotics.

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## TO THE EDITOR

We were interested to read the article by Phiri *et al*[1], which was published in the

*World Journal of Psychiatry*. The authors used mega data, python software, *etc.* to summarize and analyze nearly 2000 clinical reports. They point to the commonly used atypical antipsychotics such as olanzapine and risperidone increasing the risk of death in people with dementia; however, the data analysis of this study showed that the association between quetiapine and the increased risk of death in patients with dementia was insignificant. Their study promoted the research and development of drugs for mental disorders in patients with dementia, and encouraged a normative role in the medication prescribed by clinicians in primary and secondary medical institutions, which has considerable reference significance. Although the research work of the author and his team has been sufficient, and the conclusions drawn are also supported by big data, we believe that some points of this article are worthy of further exploration. We would like to contribute to the debate and look forward to hearing from the authors.

Schizophrenia is a group of the most common types of mental illness, characterized by incoordination between thinking, emotion and behavior, and separation of mental activities from reality[2,3]. Schizophrenia includes two subtypes. Type I is mainly characterized by positive symptoms, and patients report hallucinations and delusions. Type II is mainly characterized by negative symptoms, and patients report apathy and lack of initiative[4]. At present, the commonly used classical antipsychotics drugs include chlorpromazine, Chlorprothixene, also called tardan, is a representative of the thiaxanthene class of anti-schizophrenia drugs, *etc.* However, long-term use of classical antipsychotics usually causes extrapyramidal reactions, that is, the patient's ability to regulate fine motion is weakened. The later developed atypical antipsychotics have obvious advantages over classical antipsychotics. First, atypical antipsychotics are well tolerated, show good compliance, and rarely cause extrapyramidal reactions. Second, atypical antipsychotics are better than classic antipsychotics in treating the negative symptoms of psychosis. Clinically, atypical antipsychotics are often used as first-line drugs for first-episode schizophrenia. Although antipsychotics may increase mortality to some extent[5,6], observational studies suggest that atypical antipsychotics are associated with a lower risk of all-cause mortality when compared with conventional antipsychotics[7].

Farlow and Shamliyan[8] have reported modest improvements in neuropsychiatric symptoms with aripiprazole, risperidone and olanzapine compared with placebo. Aripiprazole, risperidone, quetiapine and olanzapine are associated with increased odds of acute myocardial invasion, and risperidone and olanzapine with increased odds of hip fracture. Observational studies have shown no difference in all-cause mortality with atypical antipsychotics, and atypical antipsychotics are associated with a lower risk of all-cause mortality and extrapyramidal symptoms compared with conventional antipsychotics, but a higher risk of stroke. Therefore, there is reason to believe that the increased risk of death in older and dementia patients given atypical antipsychotics may be due to myocardial damage, increased mobility, and increased risk of stroke.

The authors refer to the use of atypical antipsychotics such as aripiprazole in patients with dementia and highlight the risk of death with aripiprazole. Use of aripiprazole has been reported in patients with dementia, but it is associated with a higher risk of cardiac arrest, fractures, constipation, extrapyramidal disorders, somnolence and apathy[8,9]. Therefore, for use of aripiprazole for treatment of schizophrenia in older people, special attention should be paid to the adverse effects of aripiprazole, in addition to the decline in drug metabolism caused by age. The authors did not explain why aripiprazole increases the risk of death in dementia patients, so we suggest that the authors add relevant content.

### *Conclusion*

The increased risk of death among dementia patients using atypical antipsychotics may be due to underlying diseases or to a different baseline risk of death.

## FOOTNOTES

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EDITORIAL

# Suicidal behavior-advances in clinical and neurobiological research and improvement of prevention strategies

Thomas Sobanski, Gregor Peikert, Ulrich W Kastner, Gerd Wagner

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## Abstract

Suicide is the 14th leading cause of death worldwide. It is responsible for 1%-5% of all mortality. This article highlights the latest developments in universal, selective, and indicated prevention strategies. Concerning universal suicide prevention, current research has shown that strategies such as restricting access to lethal means (*e.g.*, control of analgesics and hot-spots for suicide by jumping) and school-based awareness programs are most efficacious. Regarding selective prevention, substantial progress can be expected in psychological screening methods for suicidal behavior. The measurement of implicit cognition proved to be more valid in predicting future suicide attempts than classic clinical assessment. Latest developments are smartphone-based interventions and real-time monitoring of suicidal behavior. Great effort has been made to establish valid neurobiological screening methods (*e.g.*, genetic and epigenetic risk factors for suicide, hypothalamic-pituitary-adrenal axis) without yielding a major breakthrough. Potentially, multiple biomarkers rather than a single one are necessary to identify individuals at risk. With regard to indicated prevention in form of psychopharmacological treatment, recent pharmacoepidemiological studies and meta-analyses have supported a protective role of antidepressants, lithium, and clozapine. However, the data concerning a specific anti-suicidal effect of these drugs are currently not consistent. Promising results exist for ketamine in reducing suicidal ideation, independently of its antidepressant effect. Concerning psychotherapy, recent findings suggest that psychotherapeutic interventions

specifically designed to prevent suicide re-attempts are most efficacious. Specifically, cognitive behavioral therapy and psychodynamic therapy approaches proved to decrease the number of suicide re-attempts significantly.

**Key Words:** Antidepressants; Biomarkers; Cognitive behavioral therapy; Ketamine; Prevention; Suicide

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**Core Tip:** This Editorial highlights recent developments concerning suicide prevention. According to current research, measures such as restricting access to lethal means and school-based awareness programs are the most efficacious universal prevention strategies. Novel psychological screening methods for suicidal behavior (implicit cognition, smartphone-based interventions, and real-time monitoring) have improved suicide risk assessment. Pharmacoepidemiological studies and meta-analyses support a protective role of antidepressants, lithium, and clozapine. Promising results exist for ketamine in reducing suicidal ideation. However, its suicide-preventive effect is under debate. Specific psychotherapeutic approaches for suicide attempters that focus on suicidal episodes proved to be efficacious for reducing suicide re-attempts.

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## INTRODUCTION

Suicide and suicidal behavior are major public health concerns. Around 700000 people commit suicide each year. Suicide was the fourth leading cause of death among 15 to 29 year-old individuals globally in 2019[1]. According to the United Nations, more people die by suicide every year than by both homicide and war[2]. In developed countries, more than 90 percent of all suicide victims suffered from mental illnesses, most frequently from mood disorders[3]. In the developing countries, on the other hand, the reasons for suicidal behavior are likely to be similar but the number of suicides is significantly higher there potentially due to a lack of access to medical and especially psychiatric care[4-7]. Mood disorders are regarded as a proximal factor for developing of an increased suicide risk[8]. The risk of suicide is 17 times higher in people with mood disorders than in the general population[9]. Follow-up studies documented that ten to fifteen percent of the patients with major depressive disorder (MDD) die by suicide during the course of the disease[10]. Despite this remarkably high association, however, it remains unclear why most people with mood disorders do not attempt suicide. This suggests that there may be a predisposition to suicidal behavior that is, to some extent, independent of the psychiatric disorder itself[8,11,12]. Although suicidal behavior often occurs in association with affective disorders, there is evidence from genetic, familial and neurobiological studies that it might represent a separate diagnostic entity[13]. In the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5)[14], "suicidal behavior disorder" is therefore included as a "condition for further study". It is characterized by "attempted suicide within the past two years" and does not include suicidal ideation or non-suicidal self-injurious behavior. A key feature of this definition is the intent to die, which distinguishes suicidal behavior from suicidal ideation and non-suicidal self-injury (NSSI).

There is still too little knowledge about the risk factors that facilitate the transition from suicidal ideation to suicidal action. The majority of people considering suicide do not go as far as attempting suicide. Therefore, the central concern is to understand the differences between suicide ideators and suicide attempters and to identify which ideators are at the greatest risk of suicidal behavior[15]. This information could significantly improve risk assessment and theoretical models of suicide. In the subsequent sections we will highlight some recent developments in clinical and neurobiological research that have the potential to significantly improve future suicide prevention strategies. It is likely that these advances will primarily concern selective and indicated prevention measures (*i.e.*, screening methods and therapy).

At this point, we would like to briefly address the existing controversy regarding the classification of preventive measures for mental disorders. First of all, Caplan (1964) introduced his concept of primary, secondary, and tertiary prevention which had a strong influence on the development of early prevention models[16,17]. In 1983, Gordon[18] developed another three-tiered model, in which a division into universal, selective, and indicated preventive interventions was made, depending on the targeted population group. With the 1994 Institute of Medicine (IOM) Framework [IOM, *i.e.*, Institute of

Medicine; the IOM changed its name to National Academy of Medicine (NAM) in 2015], the Caplan model was abandoned in favor of an adapted Gordon approach. At the same time, prevention measures were strictly separated from therapy and maintenance interventions. The term "prevention" was now reserved for interventions designed to reduce the occurrence of new cases (NAM, 2007)[19]. However, only a few years later the National Advisory Mental Health Council (NAMHC) Workgroup on Mental Disorders Prevention Research stated that the IOM definition was too narrow because it excluded all individuals with full-blown disorders[20]. Other authors have also claimed that benefits could be gained from closer integration of prevention and treatment research without separating both from each other, thus sharing methodological advances in the corresponding field[21].

In the present work, we refer to the classification according to the 1994 IOM Framework. On the other hand, we use a unified approach with the inclusion of therapeutic measures, as it was also applied in the most relevant systematic reviews[22,23].

It has already been implicitly mentioned that we are referring here to suicidal behavior and not to NSSI, which has a different etiological background and requires other prevention strategies.

## UNIVERSAL PREVENTION STRATEGIES

Universal prevention refers to strategies designed for an entire population regardless of the presence of individual risk factors. Since the 1960s, several developed countries have implemented national suicide prevention plans. According to the WHO[24], universal prevention programs include, inter alia: (1) Limitation of access to lethal means, (2) school-based awareness programs, (3) initiatives with regard to public education and awareness, (4) responsible media reporting, (5) access to health care, and (6) policies to reduce harmful use of alcohol or other substances (Table 1). As one of the first, Mann *et al*[22] performed an exhaustive review on the effectiveness of suicide prevention strategies. Experts from 15 countries evaluated all eligible studies published between 1966 and 2005. Only articles were included that used completed suicide, suicide attempts or suicidal ideations as outcome criteria. The main results were that restricting access to lethal means and the education of physicians (selective prevention; please see the following section) have the potential to prevent suicide. Other measures like public education and media education needed more evaluation. More recently, Zalsman *et al*[23] performed a systematic review using a similar methodology to assess the progress in suicide prevention research between 2005 and 2014. The authors assessed several universal prevention measures: public education, media strategies, and restricting access to suicide means. Moreover, they included studies on selective prevention measures like screening procedures, crisis helplines, and education of physicians, as well as on indicated prevention approaches like treatment methods and community support. Eighteen suicide prevention experts from 13 European countries reviewed all relevant articles and rated the strength of evidence. According to the authors, restricted access to lethal means has been further shown to be an effective suicide preventive measure, especially relating to control of analgesics (overall decrease by 43 percent) and to securing hot-spots for suicide by jumping (reduction by 86 percent). School-based awareness programs have proved to have a protective effect on suicide attempts and suicidal ideation. Other approaches that still needed further investigation included gatekeeper training and education of physicians. These results substantiate that several components of prevention programs as many countries realize them prove to be effective. In the quest for effective suicide prevention programs, no single strategy clearly stands above the others. The lacking efficacy proof of some measures might be due to a paucity of randomized controlled trials (RCTs) which is a major limitation in the evaluation of preventive interventions.

Furthermore, despite implementing various prevention approaches, an increasing trend in the number of suicides over the last two decades is detectable in the United States (Centers for Disease Control and Prevention, CDC), Web-Based Injury Statistics Query and Reporting System (WISQARS) Fatal Injury Reports[25]. Thus, further improvement in specific suicide prevention programs will be necessary to enhance our understanding of these complex and heterogeneous behaviors at the individual level in order to develop more personalized preventive strategies.

## SELECTIVE PREVENTION STRATEGIES

Selective prevention refers to strategies designed for one or more subgroups of a population being at risk for suicidal behavior, like patients suffering from an affective disorder. Typical selective prevention strategies are the education of physicians, gatekeeper training, as well as psychological and neurobiological screening methods (Table 1).

### *Long-established risk factors for suicidal behavior*

In suicidology, an important individual-level approach is characterized by searching for valid screening methods or markers of suicidal behavior. Broadly accepted clinical risk factors are, for instance, prior

**Table 1 Allocation of single preventive measures to the overarching strategies of universal, selective, and indicated prevention**

| Type of prevention strategy | Prevention measures |
|---|---|
| Universal prevention strategies | Limitation of access to lethal means (*e.g.*, control of analgesics and hot-spots for suicide by jumping) |
| | School-based awareness programs |
| | Initiatives with regard to public education and awareness |
| | Media education |
| | Access to health care |
| | Policies to reduce harmful use of alcohol or other substances |
| Selective prevention strategies | Education of physicians |
| | Gatekeeper training |
| | Psychological screening methods (*e.g.*, measurement of implicit cognition by the IAT, smartphone-based interventions, real-time monitoring of suicidal thoughts and behaviors) |
| | ZS model |
| | Neurobiological screening methods; crisis helplines |
| Indicated prevention strategies | Assessment and management of suicidal behavior |
| | Psychopharmacologic treatment approaches (antidepressants [caveat], ketamine, lithium, clozapine) |
| | Psychotherapeutic treatment approaches (recent methods, specifically focusing on suicidal behavior) |
| | Assessment and management of substance abuse and other mental disorders |
| | Community support |

IAT: Implicit Association Test; ZS: Zero Suicide.

suicide attempts[26], mental disorders (particularly depression and other mood disorders)[9], abuse of alcohol[27] and other drugs[28], access to lethal means[22], social isolation, gender, and age[13]. However, a careful examination of the suicide literature reveals a considerable gap in knowledge. In particular, commonly known risk factors for suicidal behaviors are, in fact, more likely risk factors for suicidal ideas, and not for the transition from ideas to attempts[15].

For example, hopelessness has long been deemed to be a central risk factor for suicidal behavior[29]. However, several studies have indicated that, while elevated among suicide ideators relative to non-suicidal controls, hopelessness fails to discriminate between suicide ideators and attempters[15]. For example, a study investigating 102 psychiatric patients with bipolar disorder demonstrated that the level of hopelessness was higher among both suicide ideators and attempters compared to healthy controls, but comparable between ideators and attempters[30]. A similar finding that hopelessness is not different between attempters and ideators has been observed in psychiatric patients with Major Depression[31] and adolescents undergoing psychiatric treatment[32]. The same pattern can be seen even when comparing hopelessness between "severe attempters" and suicide ideators[33].

Interestingly, the same also applies for the role of impulsivity, which has been considered as a significant risk factor for suicidal behavior. Furthermore, it has been postulated that this is a key factor in the transition from suicidal ideas to suicide attempts[15]. For example, individuals with high impulsivity scores have been described as being "more likely to act on suicidal feelings"[34]. Similarly, impulsivity has been suggested as "a more significant indicator of suicide attempt than the presence of a specific suicide plan"[15]. An implication of these theoretical perspectives is that impulsivity should be higher in suicide attempters than in ideators. Remarkably, empirical findings do not support the theory that impulsivity is higher in attempters than in ideators. In a large military sample, impulsivity was higher among attempters and ideators compared with non-suicidal individuals, but equivalent between attempters and ideators[15].

The differences between ideators and attempters obviously need further evaluation. Regardless of this, it is important to note that suicide attempters themselves seem to represent a heterogeneous group regarding demographic features, histories of suicide attempts, and the assumed clinical factors, *e.g.*, hopelessness or impulsivity. The authors recently conducted a study on this issue and compared single and multiple suicide attempters for this purpose[35]. A sample of patients with a recent suicide attempt ($n$ = 252) was recruited. Statistical analyses revealed that the re-attempters had more severe psychopathology with significantly higher levels of suicidal ideation and hopelessness. Furthermore, re-attempters had more often first-degree relatives with suicidal behavior and emotional abuse during

childhood. They also exhibited a higher degree of specific personality traits, *i.e.*, higher excitability and higher self-aggressiveness[35]. Multivariate discriminant analysis discriminated the re-attempters from single attempters by higher levels of self-aggressiveness[35]. Although suicidal behavior is a complex and multifaceted phenomenon, in the future individual factors such as self-aggressiveness could be suitable as an indicator in order to identify patients who are particularly at risk and to provide them with suitable therapeutic measures.

### *Psychological screening methods for suicidal behavior*

Another major challenge to scientific and clinical research in this area is that most assessment methods rely on the patients' self-report about suicidal thoughts and intent. This makes the evaluation of suicidal behavior especially difficult because patients often are motivated to deny suicidal thoughts for fear of undesired measures (*e.g.*, involuntary hospitalization)[36]. Moreover, suicidal thoughts are transient in nature and may not be present upon assessment but can return shortly thereafter and some people may lack conscious awareness of their current level of risk[37]. Indeed, nearly 80% of people who die by suicide in hospital wards explicitly deny suicidal thoughts or intent in their last communication before dying[38]. Recently, Woodford *et al*[26] explicitly investigated in a meta-analysis the accuracy of unassisted clinician predictions of future suicidal behavior. Based on 22.499 predictions, this meta-analysis revealed a pooled sensitivity of 0.31 (95%CI: 0.18-0.50), indicating that nearly 70% of patients with repeated suicidal behavior were considered being at low risk. The reported pooled negative predictive value (NPV) of 0.89 (0.86-0.92) shows that nearly 10% of patients classified as low-risk cases will show future suicidal behavior.

Thus, there is an enormous need for standardized methods of assessing suicide risk that do not rely on explicit self-report and unassisted clinicians' decisions. In the last decades, psychological methods were developed to assess people's implicit cognition (*i.e.*, unconscious mental processes that can influence behavior) which could have a significant influence on suicide prediction. For instance, the Suicide Implicit Association Test (IAT) is a brief psychological test that measures reaction times of patients when viewing suicide-related and other stimuli. Previous studies demonstrated that it significantly predicted future suicidal behavior better than other factors like the presence of a mental disorder or a clinicians' prediction of a future suicide attempt[36]. Glenn *et al*[39] replicated these results in a large sample of participants ($n$=7.015) demonstrating that implicit associations related to suicidal behavior were stronger among individuals with a history of suicide attempt. The results also showed that these implicit associations were robust and sensitive to recency and severity of a given history of suicidal behavior. Associations turned out to be stronger for more recent and more lethal prior suicide attempts[39].

Recent studies have shown that even brief, smartphone-based interventions that aimed to increase aversion to self-harm, can significantly reduce such behavior[40]. Another promising approach is the real-time monitoring of suicidal thoughts and behaviors. Real-time monitoring has provided important information about several essential characteristics of suicidal thinking. Some of these studies have revealed that the severity of suicidal ideation varies significantly over a short period of time[41]. Two studies have shown that the occurrence of suicidal ideas varies from hour to hour almost as much as from person to person[42,43]. Moreover, episodes of suicidal ideation have a quick onset with nearly one third of all observations in one study differing by a standard deviation or more from the prior rating just a few hours earlier[42]. In the same sense, episodes of suicidal ideation tend to be brief, with participants reporting that most episodes are shorter than an hour[37]. Furthermore, suicidal ideation can be differentiated from thoughts of NSSI using real-time assessment. Thus, it turned out that thoughts of suicide co-occur less than half the time with thoughts of NSSI[37].

Prior suicide prevention studies have failed to provide sufficient evidence for the benefits of screening individuals in primary care and of establishing internet and helpline support[24]. Hopefully, this is going to change due to the development of improved screening methods as well as the use of multiple screening and assessment tools.

In this regard, the Zero Suicide (ZS) model also represents a remarkable advance. In this prevention approach all persons receiving care for a mental disorder are screened for suicidal thoughts and behaviors at intake. Whenever a patient screens positive for suicide risk, a full risk formulation is completed for the client[44]. The core features of this prevention strategy are the targeted detection and support of people at risk by trained specialist staff, but also by gatekeepers and family members, as well as the development and implementation of specific interventions[44]. Layman *et al*[45] were able to demonstrate in a current study that less suicidal behavior occurred in clinics that had introduced and used ZS organizational best practices.

### *Neurobiological screening methods for suicidal behavior*

Previous biological studies on suicidal behavior have consistently revealed that biological factors underpin this condition in terms of a predisposing diathesis[46]. This diathesis rests on the known genetic risk factors for suicide[47], but also on epigenetic mechanisms, which represent changes in gene expression and activity due to environmental factors[48]. One such factor discussed for suicidal behavior and producing pronounced effect on the epigenome, is early life adversity (ELA), *e.g.*, physical or sexual abuse during childhood[46,49]. A significant number of subjects with suicidal behavior have a

history of early life adversities, which is therefore considered as a risk factor for future suicide attempts [50]. In our recent work (see above) we were able to show that especially patients with multiple suicide attempts had higher levels of early life adversities compared to single attempters[35].

Animal studies[51] have shown that epigenetic alterations following early life adversities may affect the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, a key system for cortisol release and stress response. A dysregulated HPA axis has also been often reported in subjects with suicidal behavior. For example, a lack of decrease in cortisol levels in the dexamethasone suppression test (DST) was associated with an increased risk of a future suicide death[52]. Postmortem studies in suicide victims indicated that early life adversities may lead to increased methylation of the promoter region of the glucocorticoid receptor and decreased expression of its mRNA in the hippocampus[53]. Recently, Jokinen *et al*[54] showed reduced methylation of several HPA-related genes in individuals at high-risk of suicide. Thus, dysregulation of this major stress system is an important component of diathesis to suicide.

Moreover, markers of neuroinflammation influencing the stress response by modulation of the HPA axis, have been recently investigated in suicide. Altered levels of cytokines, such as IL-1, IL-6, and tumor necrosis factor alpha (TNF-α) have been detected in the frontopolar cortex of suicide victims[55]. Additionally, microgliosis was observed in prefrontal, anterior cingulate, and thalamic regions in suicide victims[56]. Due to the putative role of cytokines in neuroplasticity and neurotoxicity, the authors related the detected microglial activation to pre-suicidal stress.

Recently, growing attention was paid to the polyamine system, also important for stress-response, and its relation to suicide risk[57]. Studies investigating postmortem suicide brains show that expression levels of gene products associated with the polyamine stress response system are dysregulated[46,58]. Expression of the enzyme spermine N1-acetyltransferase (SAT1) was found to be altered in the brain of suicide victims, which has been therefore recognized as a potential biomarker for suicide[59].

Thus, all these studies suggest a complex stress-diathesis interaction between genetic, epigenetic factors, and early traumatic experiences, which alter the response of stress systems to proximal stressors and accompanied response of the immune system, thus increasing the risk for suicidal acts.

Furthermore, the serotonergic system was extensively studied in subjects with suicidal behavior. Low levels of the main metabolite of serotonin (5-hydroxyindoleacetic acid, 5-HIAA) were detected in suicide attempters[60] and predicted future suicide deaths[52]. Postmortem studies additionally showed alterations in serotonin (5-HT) markers[61]. Blunted prolactin response to fenfluramine challenge was found in high *vs* low lethality suicide attempters. High lethality suicide attempters had significantly lower prolactin response than low lethality suicide attempters[62]. Recently, PET studies showed greater raphe 5-HT1A receptor binding potential in high compared to low lethality suicide attempters [63]. Variants in several 5-HT genes have also been associated with the risk of suicide[64,65]. While persisting 5-HT deficits are robustly associated with suicide, the causal mechanisms remain to be clarified.

Finally, based on recent clinical studies suggesting an "anti-suicidal effect" of ketamine[66], the role of the glutamatergic system in suicidal behavior received growing attention. However, previous findings on glutamatergic alterations in suicidal behavior are inconsistent and need further examinations. For example, N-methyl-D-aspartate (NMDA) binding in the prefrontal cortex in suicide has been shown to be decreased[67] or unaffected[68].

To sum up, a number of biological alterations in different systems have been detected in subjects with suicidal behavior. However, currently, there are no biomarkers with a positive predictive value for suicide. A deeper understanding of the biological foundation of suicidal behavior and thus identification of stable and clinically useful biomarkers for suicide would equip clinicians with additional valuable information to properly address suicidal behavior in those most at risk. In light of the number of biological findings in suicidal behavior, Oquendo *et al*[69] state in their review on biomarkers for suicide that potentially multiple biomarkers, rather than a single one, are necessary to identify individuals at risk.

## INDICATED PREVENTION STRATEGIES

Indicated prevention strategies target individuals showing suicidal ideations and/or having past suicidal behavior. Psychopharmacological and psychotherapeutic treatment approaches are used for this (Table 1).

### *Psychopharmacological treatment approaches*

Regarding psychopharmacological treatment approaches, the role of antidepressants has been discussed controversially. Indeed, meta-analyses indicate a slightly increased risk for suicidal behavior in pediatric patients and young adults[70,71]. In contrast, there seems to be a protective effect in older adults[71]. Pharmacoepidemiological studies, however, show a protective effect across the whole life span[72]. In the same sense, Simon *et al*[73] reported in a population-based study that the rate of suicide attempts subsequently to the initiation of an antidepressant was much lower than the rate before the initiation.

From a methodological point of view, the question arises as to why the results of RCTs and pharmacoepidemiological studies differ so remarkably. From our point of view, three decisive factors are involved in this discrepancy: (1) Suicidal patients are not usually included in RCTs and the design of RCTs is therefore poorly suited for assessing the influence of antidepressants on suicidal behavior; (2) the duration of the majority of RCTs is too short to detect the possible beneficial long-term effects of antidepressants on suicidal behavior; on the contrary, during the earlier stages of treatment antidepressants may act as an additional stress factor for the patients, due to adverse drug reactions, unfulfilled expectations or dissociated states during partial remission (*e.g.*, willpower improved, mood still depressed); and (3) additionally, the sample size of pharmacoepidemiological studies is much larger, and the time frame much longer compared with RCTs. Thus, although pharmacoepidemiological studies still have some challenges regarding standards in conducting and reporting, they have the strengths to have sufficient statistical power to measure differences in the actual frequency of rare events like suicides (instead of "suicidal events" as is usual in RCTs)[72].

The important role of effective pharmacological treatment of depression for suicide prevention was also emphasized in an influential systematic review by Zalsman *et al*[23] In addition, the authors were in favor of suicide-protective effects of lithium and clozapine. Several RCTs have supported the assumption that lithium reduces the risk of suicide in patients with mood disorders[74-77]. A specific anti-suicidal effect of lithium was suggested in a controlled treatment study on suicide attempters, although the number of suicides was very small (three suicides in the control group *vs* no suicides on lithium)[77]. Clozapine is the only drug that has been approved by the United States Food and Drug Administration (FDA) for reduction of the suicide risk in psychosis. A meta-analysis of the effects of clozapine in comparison with other dopamine and serotonin-receptor antagonists (*e.g.*, olanzapine and risperidone) supports its anti-suicidal effects in schizophrenia[78]. Nevertheless, a recent review has called into question, whether certain drugs that improve the underlying disease also have an independent anti-suicidal effect[79].

Other promising drugs for the treatment of suicidal behavior are ketamine and esketamine. Ketamine (a racemic mixture of S- and R-ketamine) is a drug with dissociative properties. It was approved by the FDA in 1970 for anesthetic use[66]. The mechanism of action of ketamine has not yet been fully elucidated, but it is known that ketamine antagonizes glutamatergic NMDA receptors in the central nervous system[80]. Moreover, several studies have implied a role for opioid neurotransmission, as ketamine also appears to activate the mu, kappa, and delta-opioid receptors[81-84]. In recent years, it became a target of research for its antidepressant effects, which occur within hours at subanesthetic doses[80]. Grunebaum *et al*[66] reported the acute effect of intravenous ketamine on suicidal ideation in patients with MDD. Ketamine therapy resulted in a clinically significant reduction of suicidal ideation in depressed patients within 24 h. Adverse drug reactions (ADRs) were transitory, and clinical improvement was maintained for several weeks. Abbar *et al*[85] investigated the anti-suicidal efficacy of intravenous infusions of ketamine in a placebo-controlled RCT. The primary outcome was that at day 3 of the study more participants in the ketamine group reached full remission of suicidal ideas than in the placebo arm (63.0% *vs* 31.6%)[85]. This effect persisted at follow-up after 6 wk[85].

To avoid the distress of intravenous ketamine therapy, alternative formulations and routes of application were sought[86]. Esketamine has four times higher affinity for the NMDA receptor than ketamine and thus allows for a lower dosage with a corresponding decrease in dissociative symptoms [87]. Moreover, esketamine is available through an intranasal delivery system[88]. Ultimately, esketamine was approved by FDA in 2019 as a nasal spray for treatment-resistant depression in adults and in conjunction with an oral antidepressant for treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior. Because of the potential risks associated with this drug, including sedation, dissociation, and abuse or misuse, its label contains boxed warnings, and esketamine is subject to strict safety controls on administration under a safety program called Risk Evaluation and Mitigation Strategy (REMS)[89]. In 2019, esketamine was also approved by the European Medicines Agency (EMA) for the same indication. Because of the risk of abuse, the approval applies only to inpatient treatment[90].

Unfortunately, recent studies on ketamine and esketamine have been less conclusive with regard to their anti-suicidal effects[91-93]. In their current review, Witt *et al*[92] came to the conclusion that the reduction of suicidal ideations might be stronger after intravenous ketamine than after esketamine administration. However, there was still no evidence of a long-lasting effect beyond 3 d[92]. Siegel *et al* [93] performed a review of trials on patients with high level of baseline suicidal ideations. In this work, esketamine was not superior to placebo regarding the effect on suicidal ideations. Intravenous ketamine appeared to immediately and significantly ameliorate suicidal ideation, but was not superior to placebo regarding long-lasting effects[93]. Finally, it should be noted that esketamine seems to be inferior to intravenous ketamine in the treatment of depression as Bahji *et al*[91] reported in their meta-analysis.

In previous sections we pointed out that suicidal ideation represents only a comparatively unspecific parameter that only provides limited information about imminent suicide attempts. Therefore, the validity of studies that only refer to suicidal ideation as an outcome criterion is limited. To date there are no prospective RCTs, which investigated the effect of ketamine/esketamine treatment on future suicidal behavior and suicides as outcome parameter. Thus, the evidence for the efficacy of ketamine/esketamine therapy as a suicide preventive treatment measure has yet to be determined.

### *Psychotherapeutic treatment approaches*

Regarding psychotherapeutic treatment, it has to be noted that results differ considerably and even the adequate targets of suicide interventions are still a matter of debate. For instance, Franklin *et al*[94] point out that the majority of applied intervention targets are derived from untested theoretical assertions, moderate correlates, or weak risk factors of suicidal thoughts and behaviors. None of these forms of evidence would allow somebody to draw conclusions regarding causal inferences. For cutting this Gordian knot, we first of all recommend to make a strict distinction between suicidal ideation and suicidal behavior[95]. Suicidal ideation refers to any thoughts, imaginations, beliefs, or other cognitions associated with ending one's life. Previous studies demonstrated a consistent reduction in suicidal ideations during psychotherapeutic or antidepressant treatment of affective disorders, very likely resulting from the general effect on depression[96,97]. Furthermore, the predictive value of suicidal ideation for suicidal behavior has been shown to be low[29]. There is also some evidence for the notion that the genetic transmission of suicidal ideation may follow a different pathway than suicidal behavior [95]. Suicidal behavior, on the other hand, is a strong predictor for suicide re-attempts[98]. This fact underscores the need for development of specific psychotherapeutic approaches for individuals with suicidal behavior to reduce the risk of suicide re-attempts. In a most recent meta-analysis on psychotherapeutic interventions only RCTs were included that referred directly to suicide attempts and used the number of re-attempts as an outcome variable[99]. By this procedure, 18 studies were identified. Statistical comparison of all studies showed that psychotherapeutic interventions in general reduced the risk of future suicidal behavior nearly by a third[99]. Separate analyses revealed that cognitive behavioral therapy (CBT) as well as two different psychodynamic therapy approaches were significantly more efficacious than control conditions. Dialectical behavior therapy (DBT) and elementary problem solving therapy (PST) were not superior to control conditions in reducing the number of suicide re-attempts[99]. Based on the results of this meta-analysis, it appears as a key recommendation for future psychotherapeutic approaches to focus the intervention directly on the episodes of suicidal behavior.

## CONCLUSION

In this work we have pointed out significant advances in the field of scientific suicidology. We would like to add that, from our point of view, it already represents a progress that suicidal behavior disorder was included in the DSM-5 as a disorder for further consideration. This decision has sharpened the focus on suicidal behavior and both, screening methods and therapeutic approaches can be developed in a more targeted manner. As an example, we would like to point out the advances in screening methods, *e.g.*, using implicit cognition, smartphone-based interventions, and real-time monitoring. These methods should be further developed and much more involved in the patient care. The same applies to the development of a valid biomarker set. On the other hand, existing psychotherapy approaches should be further developed. In our view, the greatest opportunities arise for procedures that are aimed directly at suicidal behavior. Concerning pharmacotherapy, a specific anti-suicidal effect of antidepressants, lithium, and clozapine is likely but not yet proven. Ketamine is a promising new drug with promising results for reducing suicidal ideation. However, more evidence is needed to demonstrate sustained and specific anti-suicidal efficacy. The advances such as highlighted in this editorial make us optimistic. Since each of the methods shown has its strengths and weaknesses, we believe that far-reaching future progress can only be achieved with a multifaceted approach using appropriate universal, selective and indicated prevention strategies.

## FOOTNOTES

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OPINION REVIEW

# Emerging role of psychosis in Parkinson's disease: From clinical relevance to molecular mechanisms

Shuo Zhang, Yan Ma

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## Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease. Psychosis is one of the common psychiatric presentations in the natural course of PD. PD psychosis is an important non-motor symptom, which is strongly correlated with a poor prognosis. Increasing attention is being given to PD psychosis. In this opinion review, we summarized and analyzed the identification, screening, epidemiology, mechanisms, risk factors, and therapeutic approaches of PD psychosis based on the current clinical evidence. PD psychosis tends to have a negative effect on patients' quality of life and increases the burden of family caregiving. Screening and identification in the early stage of disease is crucial for establishing tailored therapeutic strategies and predicting the long-term outcome. Development of PD psychosis is believed to involve a combination of exogenous and endogenous mechanisms including imbalance of neurotransmitters, structural and network changes, genetic profiles, cognitive impairment, and antiparkinsonian medications. The therapeutic strategy for PD psychosis includes reducing or ceasing the use of dopaminergic drug, antipsychotics, cholinesterase inhibitors, and non-pharmacological interventions. Ongoing clinical trials are expected to provide new insights for tailoring therapy for PD psychosis. Future research based on novel biomarkers and genetic factors may help inform individualized therapeutic strategies.

**Key Words:** Psychosis; Parkinson's disease; Hallucinations; Delusions; Antipsychotics

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**Core Tip:** Parkinson's disease (PD) psychosis encompasses a variety of misperception symptoms including illusions, passage hallucinations, presence hallucinations, and delusions as well as formed visual hallucinations. PD psychosis is an independent predictor of mortality. A variety of risk factors for development of PD psychosis have been identified. Side effects of anti-Parkinsonism medications and patient-specific characteristics are both involved in the onset and progression of PD psychosis. Targeting the 5-hydroxytryptamine subtype 2A receptor is a promising pharmacological intervention.

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## INTRODUCTION

With progressive aging of the population, Parkinson's disease (PD) has become the second most common neurodegenerative disease after Alzheimer's disease. Studies have shown a global increase in the prevalence and incidence of PD with increasing age, with no predilection for a particular sex[1]. The neuropathological hallmarks of PD are gradual degeneration and loss of dopaminergic neurons in the pars compacta of the substantia nigra, along with the formation of Lewy bodies. Since these dopaminergic neurons project to the striatum, it causes reduction in dopamine levels in striatum, impairing neurotransmitter homeostasis in the central nervous system. PD is traditionally recognized as a movement disorder with prominent motor symptoms including tremor, bradykinesia, rigidity, gait disturbance, and unstable posture[2], which is the main cause of disability in these patients. However, PD is also believed to be associated with a variable spectrum of complex non-motor symptoms, such as cognitive and affective impairment, hyposmia, sleep disturbance, neuropsychiatric complications (depression, psychosis, apathy, dementia), and autonomic disorders. Hyposmia may precede the onset of typical motor symptoms of PD by up to 20 years[3]. These findings highlight that PD not only involves the dysfunction of the dopaminergic system, but also other neurotransmitter systems, such as cholinergic, noradrenergic, and serotonergic systems related to the above clinical entities[4].

Psychosis is one of the common psychiatric presentations in the natural course of PD. Studies have indicated a diverse range of psychotic symptoms in patients with PD; however, there is no standardized classification of these symptoms. The spectrum of PD psychosis encompasses a variety of misperception symptoms including illusions, passage hallucinations, presence hallucinations, delusions, well-structured visual hallucinations, and other perceptual disturbances. In general, visual illusions, passage and presence hallucinations are termed minor hallucinations, which are the most common psychotic phenomena of psychosis in PD[5]. Minor hallucinations are accompanied by other non-motor symptoms (typically rapid eye movement sleep behavior disorder and cognitive impairment) in PD psychosis[6,7].

The onset of some psychotic manifestations may occur even earlier than motor symptoms of PD[6]. The presence of severe psychotic symptoms is an independent risk factor of impaired health-related quality of life in PD[8].

PD psychosis has a negative influence on patients' quality of life and increases the burden of caregiver and family. A study including 80 patients with PD who were followed up for approximately four and a half years, found that visual hallucinations and visual illusions in PD patients heralded a higher risk in development of dementia[9]. A large-scale longitudinal study with approximately 10-year follow-up including 12077 PD patients revealed an increased risk of falls and fractures in PD patients with psychosis[10]. A small case-control study involving 21 PD patients with mild cognitive impairment suggested that patients with visual hallucinations may have a higher rate of dementia progression (50% *vs* 25% in patients without visual hallucinations)[11]. A long-term follow-up study showed that PD psychosis is an independent factor for predicting mortality[12] and likewise, increased occurrence of hallucinations contributed markedly to mortality in PD patients[13].

Furthermore, it is currently considered that minor hallucinations are important events during the natural history of PD; this is because patients with PD psychosis not only require increasing levels of assistance and care from their caregivers but also have increased likelihood of moving to a nursing home and being at potential risk of mortality[14,15].

## EPIDEMIOLOGY

Almost all PD patients develop at least one of the neuropsychiatric manifestations in the late stage of the disease[16]. Nevertheless, the reported frequency of PD psychosis is slightly discrepant among studies due to the different assessment and screening methods used in epidemiological studies. In a

community-based cross-sectional study of 250 PD patients, the prevalence of any psychotic symptom was 26%; 47.7% of PD patients with psychosis had mild phenomena and 52.3% had hallucinations and/or delusions[17]. Similarly, Kulick *et al*[18] reported a 29% prevalence of any psychotic symptom in a cohort of 199 PD outpatients[18]. Longitudinal studies have suggested that the prevalence of psychosis in PD patients tends to increase over time. The incidence of PD psychosis gradually increases with the progression of PD[19]. Data from Parkinson's Progression Markers Initiative showed that the incidence of PD psychosis at baseline, 1st year, and 2nd year was 3%, 5.3%, and 10%, respectively, increasing with duration of PD[20]. Yoritaka *et al*[21] conducted a retrospective study of 1,453 PD outpatients, and found that 53.9% of patients with late-onset PD and 22.1% of patients with early-onset PD finally developed psychosis by the 12th year[21]. In a recent cross-sectional study, 38% of PD patients were found to suffer minor hallucinations based on questionnaire analysis[22]. Moreover, it is noted that minor phenomena such as presence, passage hallucinations presented as a pre-motor symptom in approximately one-third of drug-naive PD patients; moreover, the minor phenomena preceded the onset of the first representative motor symptoms of PD by 7 mo to 8 years[6]. The variable rates of psychotic symptoms in PD patients may be attributable to different diagnostic criteria and study settings. However, more than 50% PD patients are expected to develop at least one psychotic symptom during the course of the disease[19].

## IDENTIFICATION AND SCREENING

### *Diagnostic criteria*

According to the consensus from working groups of National Institute of Neurology and Stroke (NINDS), and the National Institute of Mental Health (NIMH), the diagnostic criteria for psychosis spectrum related to PD is mainly defined as follows: (1) Hallucinations (passage and presence hallucinations, visual formed hallucinations), illusions, delusions, and a false perception of things or people that do not actually exist around them with preservation of insight. The psychotic and misperception symptoms appear periodically or continuously for more than 1 mo in the setting of a clear sensorium; (2) Diagnosis of PD is based on United Kingdom brain bank criteria and onset of characteristic phenomena follows the diagnosis of PD; and (3) Exclusion of other disorders characterized by similar psychotic symptoms such as dementia with Lewy bodies (DLB) (with accompanying visual hallucinations), primary psychiatric disorders, delirium, and extrapyramidal symptoms induced by drugs[23].

Notably, given the shared symptoms and overlapping crucial neuropathological characteristics, some clinicians considered that DLB and PD dementia are the two extremes or the different stages in the spectrum of a clinical entity[24,25]. Both PD and DLB are categorized as alpha synucleinopathies spectrum which commonly present with hallucination and delusions distress[26]. The relationship between DLB and PD dementia is still under debate; nevertheless, according to some experts, the treatment principles and the pathogenetic mechanisms of psychosis in DLB and PD share a certain commonality[27].

However, the diagnostic criteria formulated by NINDS-NIMH work group for PD psychosis was not completely concordant with the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-V) criteria for "psychosis due to a medical condition," proposed by the American Psychiatric Association, which is generally acknowledged as the diagnostic reference standard for psychosis and psychotic disorders. It was highlighted that patients with PD psychosis who fulfilled the NINDS-NIMH criteria but not the formal DSM-V criteria for psychosis due to PD manifested only mild psychotic symptoms, suggesting that NINDS-NIMH diagnostic criteria would be useful for the surveillance and identification of early symptoms of emerging psychosis[28]. Gordon *et al*[29] proposed a modified score assessment for NINDS-NIMH criteria and showed that the scoring approach can improve the diagnostic performance for PD psychosis[29]. The NINDS-NIMH diagnostic criteria work group, DSM-V criteria, and modified NINDS criteria proposed by Gordon *et al*[29] are summarized in Table 1.

Patients who develop hallucinations can still retain their awareness about misperception in the early stage, a phenomenon previously referred to as "benign hallucinations." However, with advancing disease, patients tend to lose insight into discerning hallucinations, a phenomenon referred to as "malignant hallucinations." Malignant hallucinations are disabling, and are interspersed with paranoid thoughts of suspiciousness, accusations, and being slovenly[5]. In patients with PD psychosis, any form of hallucinations tend to persist intermittently once they occur. Minor hallucinations, such as illusions, are relatively easier to handle than visual hallucinations[30,31].

### *Screening tools*

Explicitly screening for minor hallucinations in the early stage of disease might be crucial for establishing tailored therapeutic strategies and predicting the long-term outcome[30]. The high incidence and prevalence of PD psychosis in different stages and the associated mortality risk underlies the importance of routine screening for psychosis in all patients with PD. Optimal screening and identification of PD psychosis is vital for following treatment and management. Though some neuropsychiatric scales such as the Positive and Negative Syndrome Scale (SAPS), Brief Psychiatry Rating Scale,

**Table 1 Diagnostic criteria for Parkinson's disease psychosis according to the National Institute of Neurology and Stroke-National Institute of Mental Health and Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition and Modified National Institute of Neurology and Stroke score**

| NINDS-NIMH diagnostic criteria | | DSM-V criteria | Modified NINDS criteria score proposed by Gordon *et al*[29] |
|---|---|---|---|
| PD diagnosis | (1) United Kingdom Brain Banks criteria; and (2) The onset of PD must be preceded the psychotic symptoms | Prominent hallucinations or delusions | Assigning scores to each psychotic symptoms of NINDS-NIMH diagnostic criteria: (1) Delusions score with 2; (2) Other psychotic symptoms score with 1; and (3) Cut-off sum for PD psychosis equal to or higher than 2 |
| Psychotic symptoms: At least one of the following | (1) Hallucinations; (2) False perceptions; (3) Illusions; and (4) Delusions | There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of PD | |
| The duration of psychotic symptoms | (1) Periodically or continuously; and (2) Last more than 1 mo | The disturbance is not better explained by another mental disorder | |
| Exclusion of other probable disorders and conditions | (1) Dementia with Lewy bodies; (2) Primary psychiatric disorders; (3) Extrapyramidal symptoms induced by drugs; and (4) Delirium | (1) The disturbance does not occur exclusively during the course of a delirium; and (2) The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning | |

DSM-V: Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition; PD: Parkinson's disease; NINDS-NIMH: National Institute of Neurology and Stroke and the National Institute of Mental Health.

Neuropsychiatric Inventory, Clinical Global Impression Scale, Schedule for Assessment of Positive Symptoms are recommended for assessment of psychotic symptoms, none of these scales has been tailor-made for PD psychosis[32]. In clinical practice, some tools need to be combined with other PD assessment scales such as Movement Disorder Society United PD Rating Scale (MDS-UPDRS) and Parkinson's Psychosis Questionnaire. Currently, some abridged and clinically-designed versions such as perception/hallucinations domains of Non-Motor Symptom Assessment Scale for PD[33,34], SAPS for PD (SAPS-PD)[35], and modified version of SAPS-PD[18] with high reliability and sensitivity have been widely applied in clinical trials.

In summary, the NINDS-NIMH diagnostic criteria should be the basis for identifying PD psychosis in suspected patients. Since minor hallucinations may be missed in clinical practice, we recommend the use of scales such as SAPS-PD specifically for screening and assessment of abnormal perceptions in all patients with a diagnosis of PD.

## MECHANISMS AND RISK FACTORS

Although insights obtained from studies investigating the mechanisms of PD psychosis have opened new avenues for individualized treatment strategies for PD, the pathophysiology of PD psychosis is not fully elucidated owing to its complexity and multifactorial nature. Current evidence suggests the involvement of a combination of exogenous and endogenous mechanisms[36]. Studies of the endogenous pathophysiological features of PD psychosis will facilitate the development of novel treatment strategies.

### *Neurotransmitters imbalance*

Some neurobiochemical studies have revealed the involvement of impaired homeostasis of some neurotransmitters (especially serotonin, dopamine, acetylcholine, and glutamate) in the endogenous development of PD psychosis. The imbalance between serotonergic and dopaminergic neurotransmission is one of the pivotal factors mediating the occurrence of PD psychosis[37]. Serotonin activators can elicit delirium and psychosis by inducing the release of dopamine from glutaminergic neurons in the ventral tegmental area and nucleus accumbens, while reducing the activity of serotonin can alleviate psychiatric symptoms[38,39]. Additionally, PD patients have been considered to have cholinergic deficiency in the nucleus basalis of Meynert; this phenomenon is more likely to occur in patients with PD who have cognitive impairment and psychotic symptoms[40].

Abnormal activation of the special serotonin (5-hydroxyltryptamine) receptor subtype, 5-hydroxytryptamine subtype 2A (5-HT2A) results in psychotic symptoms[41]. Ballanger *et al*[42] first performed a serotonergic imaging study using the 5-HT2A receptor ligand setoperone-F18 positron emission tomography. They found remarkable enhancement of 5-HT2A receptor binding in PD patients with visual hallucinations. The regions with excessive binding were located in the cortex and were involved

in ventral visual pathway, medial orbitofrontal cortex, and bilateral dorsolateral prefrontal cortex[42]. Additionally, Huot *et al*[43] performed an autoradiographic study using [(3)H]-ketanserin and spiperone binding 5-HT2A receptor, and revealed increased 5-HT2A receptor binding in inferolateral temporal cortex, which is also involved in visual processing[43]. By contrast, another study using a similar imaging technique found no relationship between 5-HT1A receptor-binding and psychosis, though high expression of 5-HT1A binding was universally observed in all patients with PD, regardless of visual hallucination status[44].

### Clinical biomarkers

A variety of risk factors related to the underlying mechanisms of the development of PD psychosis have been identified[45]. Studies have focused on clinical presentations and laboratory indices as clinical markers of PD psychosis. In a case-control study including 111 PD patients, elevated level of plasma C-reactive protein was found to be an independent predictor of the occurrence of hallucinations or illusions[46]. A cross-sectional study conducted in Japan showed a significant correlation of minor hallucinations with cognitive impairment and rapid eye movement (REM) sleep behavior disorders[22]. In a study of 423 subjects (mean follow-up: More than 4 years), patients with PD early-onset psychosis had lower cerebrospinal fluid amyloid Aß1-42, decreased olfactory scores, increased depression scores, and increased symptoms of REM sleep behavior disorders compared with those without early-onset psychosis. A pathological study revealed a close association of visual hallucination with amyloid deposition, the density of neurofibrillary tangles, and α-synuclein in the brain of PD patients[47].

### Structural and network changes

Recent studies have revealed that PD psychosis may also be triggered by altered brain structural connectivity that disturbs the normal attention and perception, resulting in high-amplitude activity of the default mode network.

In a study by Ffytche *et al*[48], patients with early-onset formed hallucinations showed low-level visual function, thinning of right cortex (frontal, occipital, parieto-temporal, and insular lobes), and reduced volumes of bilateral basal ganglia and bilateral hippocampus at baseline[48]. Firbank *et al*[49] studied 36 patients with PD by magnetic resonance spectroscopy, and found that the ratio of γ-aminobutyric acid/creatine in occipital lobe of PD patients with visual hallucinations was lower than that in PD patients without any psychotic symptom; in addition, there were signs of gray matter loss in V4 region of anterior temporal lobe and visual cortex[49]. Patients with PD with minor hallucinations showed reduced gray matter atrophy in visuoperceptive regions[50,51]. Zarkali *et al*[52] used fixel-based analysis to assess neural network and structure; they found that left inferior fronto-occipital white matter tracts connected with posterior thalamic projections were degenerated and decreased in PD patients with hallucinations[52], suggesting that splenium and posterior thalamus may play a major role in maintaining the network balance and regulating the default mode network.

### Genetic profiles

Genetic susceptibility to PD psychosis is a subject of ongoing research. Studies have largely focused on the polymorphism of related genes such as apolipoprotein (Apo) E genes, cholecystokinin system-related genes, dopamine system-related genes, serotonergic system-related genes, and tau protein-related genes. However, with the exception of polymorphisms of cholecystokinin system-related genes, the conclusions pertaining to most of the other studies were inconsistent with respect to predicting the development of any psychotic profile in PD[53]. This suggests that Mendelian genetic inheritance may not play a predominant role in the development of PD psychosis. Additionally, a longitudinal cohort study of 215 PD patients and 126 controls with up to 12 years of follow-up identified mutations in the glucocerebrosidase gene as a susceptibility factor for early-onset PD psychosis[54]. This highlights that standardized long-term follow-up studies may help unravel the predisposing genes of PD psychosis.

### Motor and cognitive impairment

Motor symptoms of PD are also inextricably linked with psychosis. In a cross-sectional study of 500 subjects, PD psychosis was related to freezing of gait (as evaluated by UPDRS Part II score), age, and disease duration, rather than genetic polymorphisms of ApoE, α-synuclein promoter, and microtubule-associated protein tau[55]. In a retrospective cohort study of PD patients ($n$ = 331) conducted by Sawada *et al*[56] (duration of follow-up: 2 years), longer duration and high severity of PD (modified Hoehn-Yahr stage ≥ 4) was identified as a risk factor for PD psychosis[56]. Cognitive impairment (Mini-Mental State Examination scores ≤ 24) increases the risk of PD psychosis[56]. In addition, PD clinical subtypes are also believed to be closely related to PD psychosis. A prospective study categorized 206 PD patients into four subgroups based on motor symptoms. Compared with the tremor subtype, patients with rigid-kinetic subtype showed a tendency for development of visual hallucinations[57]. Moreover, the prevalence of visual hallucinations in patients with late-onset PD was found to be higher than that in patients with early-onset PD[58].

However, research on the pathophysiology of PD psychosis is still in the exploratory stage, and there is no robust evidence of the pathophysiology and risk factors for PD psychosis. Neither biomarkers nor

genetic mutations play a dominant role as endogenous factors in the pathophysiology of PD psychosis. Multivariate analysis of data from large-scale clinical trials with long-term follow-up may help characterize the pathogenesis of PD psychosis.

### *Antiparkinsonian medications*

Both environmental susceptibility factors and patient-specific characteristics are involved in the initiation and progression of PD psychosis. The side effects of some antiparkinsonian medications are well recognized as exogenous factors triggering PD psychosis. Currently, the treatment strategy for motor symptoms of PD involves targeting several molecular targets. Based on these targets, there are eight categories of antiparkinsonian drugs in clinical use: Dopamine (DA) precursor (levodopa), dopamine receptor (DR) agonists (ropinirole, pramipexole, rotigotine), DA decarboxylase inhibitors (carbidopa, benserazide), catechol-O-methyltransferase (COMT) inhibitors (entacapone, tolcapone), monoamine oxidase (MAO)-B inhibitors (rasagiline, selegiline, safinamide), N-methyl-D-aspartate receptor antagonists (amantadine), anticholinergics (trihexyphenidyl, benztropine), and adenosine A2A antagonist (istradefylline)[59]. Long-term use of almost all types of antiparkinsonian medications may lead to psychotic symptoms in patients with PD.

A decade earlier, treating with higher levodopa equivalent daily dose at baseline was found to be a predictor of developing PD psychosis in a large-scale prospective study during 12 years of follow-up[60] and in a small retrospective study[22].

Compared with levodopa, the risk of psychosis may be higher with DR agonists. DR agonists are widely prescribed to patients with early-onset PD and PD patients in whom levodopa does not effectively control the motor symptoms. In a prospective multicenter study, patients with early-onset PD receiving DR agonist treatment at baseline were more likely to develop PD psychosis during the 2 years of follow-up[61]. In the PROPARK study, both DR agonists and DA precursors were identified as independent risk factors for hallucinations in patients with PD[62]. Barrett *et al*[63] showed a significant relationship between the occurrence of psychosis and the use of dopamine agonists in PD patients without dementia[63]. Similarly, in a cross-sectional study involving 805 PD patients, use of DR agonists was associated with impulse control disorders (mainly pathological gambling and hypersexuality)[64]. A comprehensive retrospective analysis of serious adverse drug events reported by the United States Food and Drug Administration (FDA) over a 10-year period also revealed an association of DR agonists with impulse control disorders; of these, pramipexole and ropinirole showed the strongest correlation due to their strong affinity for dopamine D3 receptors[65]. Moreover, a cross-sectional study of 805 PD patients also found an association between DR agonists and delusional jealousy[66].

PD psychosis also occurred during long-term treatment with amantadine, especially in elderly patients. A report showed that excessive reduction or sudden withdrawal of amantadine can cause delirium, which may be due to the rapid shortage of functional dopamine in the cerebral cortex and limbic system[67]. In addition, other anti-PD drugs, such as anticholinergics[56] and COMT inhibitors [68] may also increase the risk of PD psychosis.

The underlying mechanism of the relationship between antiparkinsonian medications and PD psychosis has not been fully elucidated, and relevant clinical studies have yielded contradictory results [69]. PD psychosis induced by dopaminergic drugs may be associated with abnormal upregulation of serotonin receptors in the cerebral cortex and the ventral striatum that presumably are the results of shift from dorsal to ventral in midbrain dopaminergic projections and increased thalamic/raphe serotonergic function[70]. Slow and sustained stimulation of DA receptors by dopaminergic drugs in the nigra-striatal pathway can also enhance the sensitivity of dopamine receptor and dysfunction of cerebral limbic system. PD psychosis is also believed to be due to dyshomeostasis of serotonin-dopamine balance [37].

It is worth noting that not all PD patients receiving dopamine replacement therapy present psychotic symptoms. A high prevalence of minor symptoms was shown in drug-naïve PD patients[6], and in some prospective studies, L-dopa dose equivalence was not found to increase the risk of psychosis[71]. We believe that psychosis and other neuropsychiatric complications are potential side effects of DA replacement therapy. That is, in the pathophysiology of PD psychosis, antiparkinsonian medications may act as an external factor that triggers the development of psychosis in genetically-predisposed individuals.

## TREATMENT AND MANAGEMENT

Development of psychosis in PD patients should prompt careful evaluation of the potential causes by neurologists and psychiatrists. If psychotic symptoms are regarded to be related to antiparkinsonian medications, PD medications should be gradually withdrawn, and discontinued in the following sequence: Firstly, reduce the dosage or discontinue anticholinergic drugs, followed by MAO-B inhibitors, amantadine, DR agonists, COMT inhibitors, and finally DA precursors[72]. If psychotic symptoms persist after withdrawal of antiparkinsonian medications, antipsychotic drugs should be initiated early. Although reducing or even stopping the use of DA precursor and DA agonists may

minimize psychological distress, it may lead to worsening of motor symptoms of PD. Otherwise, if PD psychosis is less relevant with deterioration of motor symptoms, use of antipsychotics should be considered.

### *Serotonin 5-HT2A receptors antagonists*

Antipsychotics can be divided into two categories. First-generation antipsychotics are not recommended for the treatment of PD psychosis due to extrapyramidal side effects (EPS). EPS caused by the use of antipsychotics can cause deterioration of motor function, including acute dystonia, akathisia, parkinsonism, and tardive dyskinesia[73]. Second-generation antipsychotics, also known as atypical antipsychotics (including clozapine, quetiapine, olanzapine, risperidone, and amisulpride) mainly mitigate or antagonize the activity of DA on receptors of DA2 and 5-HT2A. Two network meta-analyses and systematic reviews revealed that most antipsychotic medications may potentially cause EPS in schizophrenia[74] and worsening of motor function in PD psychosis[75]. EPS occurs less frequently during treatment with second-generation antipsychotics compared to the first-generation antipsychotics, which were widely used as the standard treatment for PD psychosis. The development of EPS is believed to be related to the non-specific blocking of DA2 receptors signaling in the nigrostriatal dopaminergic system by antipsychotics. Targeting only the 5-HT2A receptor is an ideal pharmacological intervention which can relieve PD psychosis without worsening PD motor function [38].

Prior to the approval of pimavanserin for the treatment of PD psychosis by the United States FDA, most guidelines for pharmacological treatment relied mainly on clinical evidence pertaining to second-generation antipsychotics. Among the antipsychotics, clozapine and quetiapine were the most commonly prescribed for PD psychosis[76].

Clozapine is a benzodiazepine antipsychotic that can regulate DA receptors (binding affinity DR1 > DR4 > DR2). It also targets multiple types of receptors, and is a potent antagonist at the 5-HT2A receptor. The therapeutic efficacy of clozapine is believed to be mediated through antagonism of the dopamine type 2 and 5-HT2A receptors. In addition, it acts as an antagonist at alpha-adrenergic, histamine H1, cholinergic, and other dopaminergic and serotonergic receptors. Clozapine was the first atypical antipsychotic drug to be proven effective in the treatment of PD psychosis with relatively low impact on PD motor symptoms[75]. Two randomized, controlled, double-blind trials conducted more than 10 years ago demonstrated the effectiveness of low-dose clozapine for the treatment of PD psychosis without significantly worsening the motor symptoms[77,78]; however, poor patient tolerance of the adverse effects of clozapine (granulocytopenia, excessive sedation, orthostatic hypotension, salivation, and metabolic syndrome) limits its clinical utility. A recent network meta-analysis suggested a notable therapeutic performance of clozapine without marked exacerbation of motor symptoms in patients with PD psychosis[79].

Quetiapine, an atypical antipsychotic medication with a similar molecular structure to clozapine, is a selective antagonist of 5-TH2 and DA2 in the limbic system of the midbrain, and it also has a high affinity for histamine and adrenergic α1 receptors in the brain. In a double-blind, placebo-controlled study of quetiapine for treatment of PD psychosis, none of the PD patients withdrew from the clinical trial due to adverse reactions, indicating favorable safety profile of quetiapine in PD patients[80]. In comparative studies for PD psychosis, the efficacy of quetiapine was similar to that of clozapine, but the results were not consistent between quetiapine and placebo[80-83]. A meta-analysis of data from six studies indicated that the efficacy of quetiapine for alleviating psychotic symptoms in PD is not higher than that of clozapine[84]. A recent systematic review of seven controlled trials revealed that the efficacy of quetiapine for treatment of psychosis in patients with PD, PD dementia, and DLB is not superior to that of placebo or clozapine; however, quetiapine showed less adverse reactions, EPS, and greater safety than clozapine[85]. Although the therapeutic benefit of quetiapine does not fully meet the need in the treatment of PD psychosis, quetiapine was one of the predominant first-line antipsychotic drugs due to its high tolerability and safety.

### *Pimavanserin*

Pimavanserin has a unique mechanism of action in the treatment of PD psychosis. It is a highly-selective inverse agonist of the serotonin 5-HT2A receptors (Ki value: 0.087 nmol/L) rather than a DR antagonist. Different with other atypical antipsychotics with 5-HT2A receptor antagonism, pimavanserin is an inverse agonist which not only predominantly mediates 5-HT2A receptor antagonism but also mitigates the intrinsic activity of the receptors. It also has a certain affinity for 5-HT2C (Ki value: 0.44 nmol/L) [86]. In the neocortex of PD patients, with the increase in 5-HT2A receptor affinity in the visual regions, PD patients are more likely to experience visual hallucinations. Pimavanserin regulates 5-HT2A activity by targeting and controlling the excitatory impulses in the central nervous system, reducing the risk of hallucinations and delusions. In addition, pimavanserin has minimal effect on 5-HT2B, dopaminergic, adrenergic, histaminergic and muscarinic receptors, and calcium channels. Therefore, theoretically, unlike other antipsychotics, it is not expected to have adverse effects, such as worsening of motor symptoms, excessive sedation, or orthostatic hypotension[87].

The efficacy and safety of pimavanserin were evaluated in a randomized, double-blind, placebo-controlled multicenter phase III clinical trial. The trial was conducted at 52 medical centers in the United States and Canada and included 199 patients with PD psychosis recruited from August 2010 and August 2012. Compared to placebo, patients receiving pimavanserin showed 37% improvement in SAPS-PD scores without any noteworthy safety concerns or deterioration of PD motor function as assessed by the UPDRS. The results of this trial indicated a clinically significant therapeutic effect of pimavanserin for psychotic symptoms related to PD[88]. In another 6-wk, randomized, double-blind, placebo-controlled phase III clinical trial enrolling 298 PD patients with psychotic symptoms, pimavanserin arm showed a significant improvement in nighttime sleep score without affecting daytime sleepiness[89]. Ballard *et al*[90] reported the largest clinical trial to date evaluating the long-term tolerability and safety of pimavanserin in the treatment of PD psychosis with a median follow-up of approximately 15 mo (mean follow-up: Approximately 2 years; maximum: Approximately 9 years). The phase III open-label extension study was performed in 14 countries spanning three continents and included 459 PD patients with psychotic symptoms who had completed previous randomized, placebo-controlled studies. The results indicated a favorable benefit/risk profile of long-term treatment with 34 mg daily of pimavanserin without increasing caregiver burden or mortality risk related to long-term use of pimavanserin. Pimavanserin had some moderate and mild adverse reactions, the most common of which were falls, urinary tract infection, mental, and psychological abnormalities[90].

Overall, there is conclusive evidence of the favorable therapeutic effect, safety, and tolerability of pimavanserin for PD psychosis[91]. Ten-week treatment with pimavanserin showed persistent efficacy in improving psychotic symptoms, as evaluated by SAPS-PD, and improved the quality of life of caregivers[92]. A meta-analysis of four randomized controlled trials ($n$ = 680) in patients with PD psychosis showed that pimavanserin significantly recovered psychotic symptoms, as assessed by SAPS score[93].

A recent systematic review and Bayesian network meta-analysis of four antipsychotics showed that both pimavanserin and clozapine are effective antipsychotics that may improve the symptoms of PD psychosis compared to a placebo; however, the adverse effects of clozapine were a cause for concern[79,94].

Compared with quetiapine, pimavanserin exhibited lower discontinuation rate with in early duration and higher discontinuation rate with in late duration for treating DLB and PD psychosis[95] Moreno *et al*[96] retrospectively analyzed medical records of 676 PD patients treated with atypical psychotics, and found that patients receiving pimavanserin monotherapy showed a lower risk of mortality than patients receiving quetiapine or a combination of pimavanserin and quetiapine[96]. Coincidentally, in a multicenter, open-label extension safety study assessing the long-term impact of antipsychotics compared with pimavanserin, subjects treated with pimavanserin with an add-on antipsychotic drug showed higher mortality rate in comparison with pimavanserin monotherapy group[97].

The therapeutic responsiveness of pimavanserin may be enhanced or facilitated by other PD-related drugs or interventions, such as cholinesterase inhibitors and deep brain stimulation[98]. Currently, there is limited understanding of the discrepancy between pimavanserin and other antipsychotics with respect to efficacy, safety, and tolerability and further large-scale multicenter studies are required to confirm the clinical utility of pimavanserin in other clinical settings[84].

### *Cholinesterase inhibitors*

An increasing body of evidence from experimental and clinical research has indicated a pivotal role of dysfunction of cholinergic system in addition to dysfunction of serotonergic and dopaminergic systems in the causation of PD psychosis. These findings indicate that the cholinergic system is a viable therapeutic target in the context of PD psychosis[99,100]. In a randomized controlled study, pimavanserin significantly improved PD psychotic symptoms (assessed by SAPS-PD score) either with or without accompanying cognitive dysfunction; the study also demonstrated that cholinesterase inhibitors as cognitive-enhancing medications may augment the efficacy of pimavanserin[101]. Long-term use of anticholinergic drugs (benzhexol) was strongly associated with high risk of developing PD psychosis, while cholinesterase inhibitors (donepezil) reduced the risk[56]. The cholinesterase inhibitor rivastigmine has been recommended as first-line drug for the treatment of PD dementia by the collaborators of the Parkinson's Disease Update on Non-Motor Symptoms Study Group[102]. Cholinesterase inhibitors may also ameliorate the gait disturbance and risk of falls in PD patients[103]. Furthermore, compared with PD dementia without psychosis, PD patients with concomitant dementia and psychosis were more likely to benefit from rivastigmine[104,105]. In a randomized, double-blind, placebo-controlled phase II single-center trial, donepezil showed a significant protective effect against the development of psychotic symptoms in PD patients with apolipoprotein E ε4 non-carriers, suggesting that ApoE ε4 allele status may contribute to the resistance of cholinesterase inhibitors[106].

Most Parkinson's hallucinations are accompanied by a decline in cognitive function, ranging from mild cognitive impairment to severe dementia. In addition to improving cognitive performance, cholinesterase inhibitors may significantly alleviate hallucinations in patients with PD. Because the reported incidence of adverse effects of cholinesterase inhibitors is much lower than that of atypical antipsychotics, cholinesterase inhibitors may be an alternative treatment for improving "benign or minor" hallucinations, especially in PD dementia with psychosis[104].

### *Other antipsychotics and N-methyl-D-aspartate receptors agonists*

Ondansetron is a selective 5-HT3 receptor antagonist which can theoretically attenuate PD psychosis. Compared with other 5-HT receptors, the 5-HT3 receptor is the only ligand-gated 5-HT receptor which has a particular mechanism to mediate the release of neurotransmitters. Although a series of clinical studies on ondansetron in the treatment of PD psychosis were carried out in the 1990s, there are three open-label trials on the efficacy of ondansetron with contradictory results, to our knowledge. In two open-label trials enrolling 40 patients, ondansetron moderately improved the symptoms of hallucination and paranoid delusion with favorable tolerability, and without severe adverse effects; furthermore, ondansetron did not deteriorate motor functions of PD or attenuate the efficacy of levodopa. However, in another study of 5 patients with PD psychosis, a similar dose of ondansetron failed to show long-term benefit. Due to the high cost of ondansetron, no further clinical trials have been reported in the subsequent two decades[107]. Investigations of other antipsychotic drugs including rispehdone, ziprasidone, aripiprazole, however, have been confined to small open-label trials.

Dysfunction of N-methyl-D-aspartate receptors (NMDAR)-mediated neurotransmission is believed to contribute to neuropsychiatric symptoms of PD. Enhancing glutamatergic transmission through blocking of glycine re-uptake was found to ameliorate the psychosis-like behaviors in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced PD marmoset model[108]. NMDAR stimulation, accomplished through allosteric modulation *via* the glycine modulatory site, may be a potential therapeutic target for PD psychosis. As a glycine re-uptake inhibitor, sarcosine was found to increase synaptic glycine concentration to activate NMDAR glycine site, thereby enhancing NMDAR function. A small-scale randomized controlled study suggested that sarcosine may relieve the neuropsychiatric symptoms of PD with dementia[109].

Further high-quality randomized controlled trials examining the efficacy and tolerability of other antipsychotics and NMDAR agonists are required to confirm these findings.

### *Non-pharmacological interventions*

A recent cross-sectional study showed that caregivers and partners of PD patients were more inclined to use non-pharmacological treatment strategies to cope with the occurrence of psychosis compared to the use of medications[110]. Nevertheless, there is inadequate clinical evidence supporting the use of non-pharmacological interventions for PD psychosis. The role of psychological therapies such as cognitive behavioral therapy, reasoning and rehabilitation is less certain than pharmacological interventions in the therapeutic strategy for PD psychosis. Physical activity can not only improve motor symptoms, but may also play a role in relieving non-motor symptoms of PD.

## CONCLUSION

The current review suggests that PD psychosis is an important non-motor symptom that predicts poor outcome. Development of PD psychosis may involve dyshomeostasis of neurotransmitters, structural and network changes, genetic profiles, and cognitive impairment. The side effects of anti-Parkinsonism medications and patient-specific characteristics are both involved in the onset and progression of psychosis during the course of PD. Unfortunately, most of the studies included in this review were observational studies which did not distinguish between treated and non-treated PD patients, since treatment with antiparkinsonian medications (*e.g.*, DA agonists) is considered as a potential cause of PD psychosis. A follow-up prospective study investigating whether antiparkinsonian medications have a significant impact on the development and progression of PD psychosis in a cohort of patients receiving different kinds and doses of antiparkinsonian medications should be conducted in future. The therapeutic approaches for PD psychosis include reducing or ceasing the use of dopaminergic drugs, and use of antipsychotics, cholinesterase inhibitors, NMDAR agonist, and non-pharmacological interventions. Pharmacological interventions for PD psychosis remain an outstanding need in clinical practice. Emerging research on future targeted therapies based on new biomarkers and genetic factors may help inform tailored therapeutic strategies.

## FOOTNOTES

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*REVIEW*

# Underlying mechanisms of mindfulness meditation: Genomics, circuits, and networks

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## Abstract

Understanding neuropsychological mechanisms of mindfulness meditation (MM) has been a hot topic in recent years. This review was conducted with the goal of synthesizing empirical relationships *via* the genomics, circuits and networks between MM and mental disorders. We describe progress made in assessing the effects of MM on gene expression in immune cells, with particular focus on stress-related inflammatory markers and associated biological pathways. We then focus on key brain circuits associated with mindfulness practices and effects on symptoms of mental disorders, and expand our discussion to identify three key brain networks associated with mindfulness practices including default mode network, central executive network, and salience network. More research efforts need to be devoted into identifying underlying neuropsychological mechanisms of MM on how it alleviates the symptoms of mental disorders.

**Key Words:** Mindfulness meditation; Gene expression; Neural circuits; Neural networks

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**Core Tip:** Recently, understanding neuropsychological mechanisms of mindfulness meditation (MM) has been a hot topic. We describe progress made in assessing the effects of MM on gene expression in inflammatory processes, with particular focus on stress-related inflammatory markers and associated biological pathways. We then discuss primary brain circuits related to MM and effects on symptoms of mental disorders, and three brain networks associated with MM including default mode network, central executive network, and salience network. More research examining MM effects and outcomes at the potential molecular mechanisms, critical genes and the network level is necessary.

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## INTRODUCTION

Mindfulness meditation (MM) refers to a conscious, non-judgmental way of concentrating on the present[1-3], which has originated from a systematically Buddhist notion 2550 years ago[4]. It is an instant and tranquil mental state with observing all mental contents (including virtually sensations, perceptions, cognitions and feelings) at any given moment[5,6]. MM was first introduced into the mainstream medical practices by Dr. Kabat-Zinn[7] of the Massachusetts Medical School in 1982. MM developing strategies include sustained attention training, somatic and non-judgmental awareness, emotion control, detaching from a self-centered view and acceptance of the "here-and-now"[8-10]. The great majority of MM research is about clinical practices[11], especially in mental disorders such as anxiety disorder, major depressive disorder, attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, eating disorder and substance abuse[12-16].

In recent years, there has been a burgeoning interest in underlying mechanisms of MM, mainly due to increasing evidence of its positive effects on mental disorders and physical well-being. In parallel to research evaluating the effectiveness of these MM approaches, a second line of investigation focuses on unraveling the neurophysiological and psychological processes involved[17]. Recent functional and structural neuroimaging studies are beginning to provide evidence that diverse brain areas have been congruously found in both beginners undergoing temporary practice and experienced meditators[18,19]. These areas have been determined to specialize in some of these critical functions[20]. However, many of these neural areas or correlates are much more complicated and the so-called "networks or neural circuits" are likely to perform higher-level processes and multiple mental functions[21].

Understanding neuropsychological mechanisms of MM has been a hot topic in recent years. This review was conducted with the goal of synthesizing empirical relationships *via* the genomics, circuits and networks between MM and mental disorders. We describe progress made in assessing the effects of MM on gene expression in immune cells, with particular focus on stress-related inflammatory markers and associated biological pathways. We then discuss key brain circuits related to MM and effects on symptoms of mental disorders, and three brain networks associated with MM including default mode network (DMN), central executive network (CEN), and salience network. More research examining MM effects and outcomes at the potential molecular mechanisms, critical genes and the network level is necessary.

## GENETIC STUDIES OF MM

Genetic studies of MM showed that differential transcription occurs in genes involved in DNA damage response, oxidative stress, and inflammatory metabolism processes, in both short and long-term practitioners[22-24]. In most studies, these results were correlated with reduced stress and fatigue, improved immune response, and clinical symptoms. A few studies examined neurotrophins[25,26]. Transcriptomic analyses were performed in both healthy and clinical populations combining diverse MM activities in several longitudinal and mixed design studies and obtained similar results[24,27-29].

Creswell and colleagues reported NF-κB-related gene expression in older adults responding to the Mindfulness-Based Stress Reduction (MBSR) intervention compared to a wait-list control group, who in contrast, showed the gene to be up-regulated[30,31]. Bakker *et al*[32] showed that genetic variation in muscarinic acetylcholine receptor M2 (CHRM2) and the μ1 opioid receptor (OPRM1) moderate the positive impact on the level of positive affect following mindfulness-based cognitive therapy (MBCT) with depressive symptoms, and proposed that variation in genetic factors in response to MBCT may be contingent on the association with the regulation of positive affect[32].

In the study by Dada *et al*[33], intraocular pressure in primary open angle glaucoma appeared significantly decreased after MM. Significant upregulation of the anti-inflammatory genes and downregulation of the proinflammatory genes were found in glaucoma patients who underwent a 3-wk MM course. These results indicate that MM has a direct impact on trabecular meshwork gene expression in ocular tissues. Similarly, the practice of MM was shown to improve immune function by normalizing stress-related serum biomarkers, and positively modifying gene expression[25]. Moreover, increased blood levels of brain-derived neurotrophic factor indicated a positive impact on retinal ganglion cells rescue from death in patients with primary open angle glaucoma[26].

## GENOME-WIDE ASSOCIATION STUDIES

Genome-wide approaches to gene activity have started to elucidate the effects of MM on gene modulation[34]. For example, utilizing microarray analysis of global mRNAs to study the methylome of peripheral blood mononuclear cells of 17 experienced meditators of one-day intensive MM practice, found 61 differentially methylated regions[35]. Similarly, studying the transcriptomic effects in six individuals after twice-daily transcendental MM practice revealed 200 genes differentially expressed [24]. Studies focusing on the impact of MM for treating hypertension, irritable bowel syndrome and inflammatory bowel disease showed that several genes related to fundamental pathways were differentially expressed[27,28].

Nevertheless, most previous studies were cross-sectional studies with small sample sizes[22,26,36, 37]. The large-scale genomic study, by Chandran *et al*[38], analyzed the meditation-specific core network of advanced MM practice, rather than changes in the expression of a few individual genes. They observed that the up-regulated RNA coexpression networks are directly related to the immune response, including 68 genes differentially expressed after MM. Interestingly, these authors reported that the top 10 hub genes in the up-regulated module included many previously identified genes known to regulate the immune system and related to the type I interferon signaling pathway. They identified nine coexpression and protein–protein interaction networks associated with MM using a multistage approach. This suggests that MM, as a behavioral intervention, may be an effective component in treating diseases characterized by increased inflammatory responsiveness with a weakened immune system.

## NEURAL CIRCUITS RELATED TO MM

### *Feelings of fear circuit related to MM*

The connections between the amygdala and key areas of the prefrontal cortex, specifically the anterior cingulate cortex (ACC) and orbitofrontal cortex can regulate the feelings of fear (Figure 1A). Specifically, the overactivation of these circuits may lead to feelings of fear. King *et al*[39] examined the neurobiological effects of 16-week mindfulness-based exposure therapy (MBET) compared with present-centered group therapy in task-evoked functional connectivity of combat veterans with posttraumatic stress disorder (PTSD). The MBET group showed higher neural activation in the rostral ACC, dorsal medial prefrontal cortex (mPFC), and left amygdala that were significantly associated with improvement in PTSD symptoms. The interactive results of group and time showed that MBET increased responses of the left medial PFC related to fearful faces, and greater post-therapy effects on the fusiform/lingual gyrus and amygdala to angry faces, suggesting that MM practices may be related to greater involvement in threat cues of patients with PTSD. It also found that MBET was associated with increased activation of the lingual/fusiform gyrus and amygdala to angry faces. It was proved that mindfulness-based art therapy is associated with significant changes in cerebral blood flow, including the insula, amygdala, hippocampus, and caudate nucleus, which is associated with a period of reduced anxiety within 8 wk[40]. These brain structures are involved in MM tasks and emotional processing related to anxiety[41-43].

### *The physiology of fear circuit related to MM*

Hoge and colleagues provide some support that MM could mitigate the elevated response to acute stress observed in generalized anxiety disorder on the hypothalamic pituitary adrenal (HPA) axis, by measuring blood levels of cortisol and adrenocorticotropic hormone (ACTH) with treatment. Over the course of the treatment, participants in the MM group exhibited a reduction in their ACTH Area-Under-the-Curve concentrations[44]. Similarly, Pace *et al*[45] demonstrated that healthy participants who practiced more MM had a faster drop in cortisol after the Trier Social Stress Test than healthy participants who practiced MM less frequently[45]. The physiological reaction to a fearful stimulus involves activation of multiple systems, including the autonomic nervous system, respiratory system, and endocrine system[46,47]. Part of the characteristic of the fear response may be endocrine influence [48]. The HPA axis is responsible for endocrine output during the stress/fear response, and is regulated

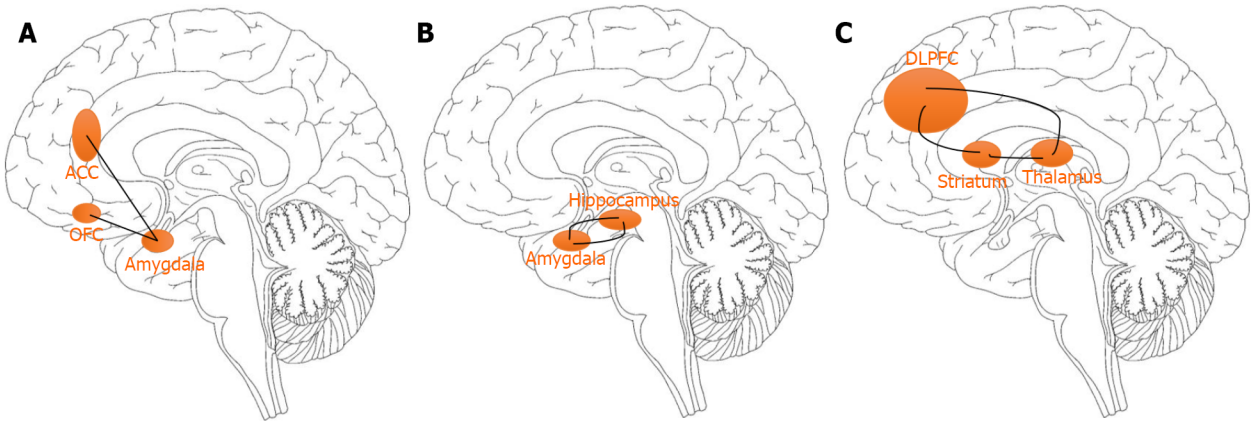


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**Figure 1 Circuits associated with mindfulness meditation.** A: Feelings of fear circuit related to mindfulness meditation; B: Re-experiencing circuit related to mindfulness meditation; C: Worry/obsessions circuit related to mindfulness meditation. DLPFC: Dorsolateral prefrontal cortex; ACC: Anterior cingulate cortex; OFC: Orbitofrontal cortex.

by the amygdala *via* reciprocal connections with the hypothalamus[49-51].

Activation of the autonomic system is regulated by connections between the amygdala, the locus coeruleus, and parabrachial nucleus and leads to an increase in heart rate, respiration rate and blood pressure that is necessary for a fight/flight reaction[52,53]. Several studies have consistently found an association between cardio-respiratory parameters and MM related to slow paced breathing[54]. Park and Park[55], and Stark *et al*[56] found an increase in the high frequency power paralleled during paced breathing of MM at 10 b/min as compared to spontaneous breathing. Generally, slow breathing techniques (such as MM exercises) enhance interactions between autonomic nerves, cerebral, and mental flexibility, linking parasympathetic and central nervous system activities with emotional control and well-being. Slow breathing techniques seem to promote a predominance of the parasympathetic autonomic system with respect to the sympathetic one, mediated by the vagal activity[57,58].

### *Re-experiencing circuit related to MM*

Sevinc *et al*[59] investigated potential neural correlates of MM intervention and in extinction learning (the context-dependent recall of extinction) using MBSR training. Group-by-time interactions found that MBET was associated with greater increases in the hippocampus and the supramarginal gyrus during extinction recall. Also during the early phase, the MBSR training group showed increased hippocampal connectivity to the supramarginal gyrus. Increased connectivity between the hippocampus and primary somatosensory cortex during retrieval of extinguished stimuli following MBSR training was also observed[60]. Furthermore, Sevinc *et al*[61] demonstrated an association between functional changes in the hippocampal connectivity and changes in anxiety following MM training. These findings provide a better understanding of the mechanisms through which MM training relieves anxiety. Anxiety can be triggered not only by an external stimulus but also internally through traumatic memories stored in the hippocampus (Figure 1B), which can activate the amygdala, causing the amygdala, in turn, to activate other brain regions and generate a fear response[46,62]. This is known as re-experiencing and is a central feature of PTSD[63].

### *Worry/obsessions circuit related to MM*

King *et al*[64] studied the potential neural relevance of MBET among combat veterans who suffered from PTSD following deployment to Afghanistan and/or Iraq. MBET showed increased connectivity with the dorsolateral prefrontal cortex (DLPFC) and dorsal ACC following therapy by a group × time interaction; and posterior cingulate cortex (PCC)-DLPFC connectivity was related to improvement of avoidant and hyperarousal symptoms in PTSD. Worry refers to anxious misery, apprehensive expectation, catastrophic thinking, and obsessions (Figure 1C). It is hypothetically related to a cortico-striatal-thalamic-cortical loop originating in the DLPFC and projecting the striatal complex, than the thalamus, and ending in the DLPFC[65,66]. Overactivation of the DLPFC can result in symptoms such as worry or obsessions[67-69].

## MM AND BRAIN NETWORKS

In identifying the neural mechanism of MM, most inferences have focused on the role of isolated brain areas in supporting the observed cognitive processes and concurrently enhancing behavioral outcomes;

however, consisting of key areas that are temporally correlated with one another (a large-scale brain network) must be considered[70]. There are three key functional networks related to attention, cognitive control and interoceptive awareness: DMN, CEN, and salience network according to the former neuroimaging literature on MM[71].

The DMN is associated with task-irrelevant and mind-wandering thoughts[72,73]. Greater activations in core nodes of the PCC, mPFC, and bilateral parietal cortices, lead to introspective thought, including activities such as daydreaming or retrieving memories[74-77]. The CEN, with core nodes located in the bilateral parietal cortices and DLPFCs, is typically associated with increased activation during distractibility and goal-directed behavior[78-80]. The CEN is linked to decision making by converging external information with internal representations[75,81-83]. The salience network is responsible for changing and monitoring the states of the CEN and the DMN, and presumably accepts the distribution of attentional resources to support cognitive control[84].

Based on structural and functional neuroimaging studies, MM is related to the activities and connections in the three networks, each of which is responsible for different stages of MM in experienced practitioners[85-87]. The activity and connectivity of the DMN have been suggested as potential biomarkers for monitoring the effect of MM[88]. It describes that MM may improve DMN, CEN and salience network functions to target symptoms of anxiety disorders[9]. King *et al*[64] investigated potential neural correlates of MBET in patients with PTSD compared with an active control therapy. After MM training, the connection between the DMN and CEN increase, which may improve the ability to shifting of voluntary attention. There is increased connection between the DMN and the DLPFC areas in CEN before and after MBET.

## FUTURE DIRECTIONS

Currently, few scientific studies have investigated the neural connections of MM at the level of critical genes and brain networks[89-93]. Notably, there has been a shift from isolated areas to large-scale networks, circuits or large-scale genetic changes[38,94,95]. Further research examining MM effects and outcomes at the potential molecular mechanisms, critical genes and the network level is necessary[96,97]. As the knowledge of brain function increases, we can better understand what the neural connections that affect clinical symptoms are. In turn, this will better characterize the specific deficiencies of any particular patient. We can predict that the development of neuroscience research on MM will help strengthen neuronal circuits that are damaged by mental disorders, and help develop personalized interventions for individuals' unique defects and strengths.

## CONCLUSION

Recently, understanding neuropsychological mechanisms of MM has been a hot topic[98-100]. We describe progress made in assessing the effects of MM on gene expression in inflammatory processes, with particular focus on stress-related inflammatory markers and associated biological pathways. We then discuss primary brain circuits related to MM and effects on symptoms of mental disorders, and expand our discussion to identify three brain networks associated with MM including the DMN, CEN, and salience network. More research examining MM effects and outcomes at the potential molecular mechanisms, critical genes and the network level is necessary.

## FOOTNOTES

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*REVIEW*

# Depressive disorder and antidepressants from an epigenetic point of view

Iris Šalamon Arčan, Katarina Kouter, Alja Videtič Paska

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## Abstract

Depressive disorder is a complex, heterogeneous disease that affects approximately 280 million people worldwide. Environmental, genetic, and neurobiological factors contribute to the depressive state. Since the nervous system is susceptible to shifts in activity of epigenetic modifiers, these allow for significant plasticity and response to rapid changes in the environment. Among the most studied epigenetic modifications in depressive disorder is DNA methylation, with findings centered on the brain-derived neurotrophic factor gene, the glucocorticoid receptor gene, and the serotonin transporter gene. In order to identify biomarkers that would be useful in clinical settings, for diagnosis and for treatment response, further research on antidepressants and alterations they cause in the epigenetic landscape throughout the genome is needed. Studies on cornerstone antidepressants, such as selective serotonin reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors, norepinephrine, and dopamine reuptake inhibitors and their effects on depressive disorder are available, but systematic conclusions on their effects are still hard to draw due to the highly heterogeneous nature of the studies. In addition, two novel drugs, ketamine and esketamine, are being investigated particularly in association with treatment of resistant depression, which is one of the hot topics of contemporary research and the field of precision psychiatry.

**Key Words:** Epigenetics; Depression; DNA methylation; Histone tail modification; microRNA; Antidepressants

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**Core Tip:** Deeper knowledge on the biological background of depressive disorder could be achieved through understanding of epigenetic mechanisms that alter the response of cells to environmental stimuli. Antidepressants are of particular interest since it has been shown that they affect DNA methylation, histone modifications, and microRNA expression. As not all patients respond to prescribed antidepressants, it is of interest to discover specific biomarkers that could be used in a clinical setting.

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## INTRODUCTION

### *Depressive disorder*

Depressive disorder is a complex heterogeneous disease that affects more than 280 million people[1]. The principal form of depressive disorder is major depressive disorder (MDD). Symptoms of depressive disorder are persistent depressive mood, diminished ability to feel pleasure and rejoice, weight changing, disturbed sleep, loss of energy, lowered self-esteem, trouble with concentration, elevated emotional psychomotor activity in children and teenagers, psychomotor agitation or motor retardation, and self-injuring or suicidal ideation[2]. The suicidality phenotype includes ideation, suicide attempt, and death by suicide. MDD is, along with bipolar disorder, schizophrenia, and substance use disorder, one of the most common mental disorders in people who die by suicide[3]. Depression contributes to suicidality, and it increases mortality risk by 60%-80%[4]. According to the Diagnostic and Statistical Manual of Mental Disorder Diagnosis, MDD must exhibit five (or more) out of ten symptoms[2].

The prevalence of depression is higher for women (4.1%) than for men (2.7%)[5]. Sex differences are exhibited in multiple cells of the central nervous system (CNS), neurons, astrocytes, and microglia[6]. Emerging data is showing that besides hormones, epigenetic differences have considerable sexual dimorphism[7]. However, steroid hormone levels influence levels of DNA methyltransferases (DNMTs). For example, female rats had higher levels of DNMT3a and methyl CpG binding protein 2 (MeCP2) in the amygdala (an important center for modulating juvenile social play, aggression, and anxiety)[6] and the preoptic area[7]. As a result of a difference in DNMT3a, there is also a difference in the DNA methylation level[6].

Moreover, people aged 50 years and more have a 1.5 times higher risk for developing depression than younger people[5]. Modern lifestyle promotes independence of the environmental light/dark cycle, which leads to shifting in sleep-wake patterns. Circadian rhythm disruption is affected by the increase in nocturnal activity, decrease of sleep, and extended exposure to artificial light during the nighttime [8]. Limbic brain regions, monoamine neurotransmitters, and the hypothalamic-pituitary-adrenal (HPA) axis are under circadian regulation. It is thought that the perturbation of circadian rhythms contributes to the prevalence of depression and other mood disorders[9].

Depressive disorder is a result of the interplay of many different factors: Environmental, genetic, neurobiological, and cultural[10]. Known environmental risk factors for developing depressive disorder are poverty, negative experiences in the family (bad relationship, violence, divorce, child maltreatment), or other stressful life events. In the time after a stressful life event, the risk for depressive disorder is elevated but the effects of adversity can persist over time[4]. In depressive symptoms that persist over time, stable molecular adaptations in the brain, especially at the level of epigenetics, might be involved [11].

Genetic heritability for depressive disorder, estimated from twin studies, is around 35%–40%[10,12]. Genome-wide association studies have discovered multiple loci with small effects that contribute to MDD[13]. Pandya *et al*[14] collected results from neuroimaging, neuropsychiatric, and brain stimulation studies and showed similar results. In recent years, more and more studies are oriented towards epigenetics to understand new mechanisms and the way epigenetics is linked to a depressive state.

The nervous system is susceptible to shifts in the activity of epigenetic modifiers, which allow for significant plasticity and response to rapid changes in the environment[15]. Epigenetic mechanisms are dynamic. They are very important for early development of the organism as well as later in life, as a response to external factors[16].

From a biological perspective, there are four theories of depressive disorder: Monoamine theory, stress induced theory, neurotrophic theory, and cytokine theory (Figure 1).

### *Theories of depressive disorder*

**The monoamine theory of depressive disorder:** Monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) are chemical messengers involved in the regulation of emotion, arousal, and

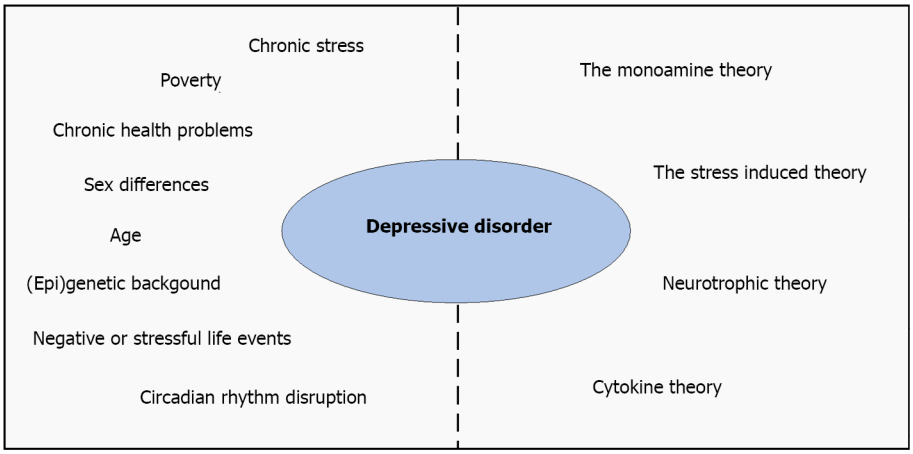


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**Figure 1 Depressive disorder risk factors.** Depressive disorders are influenced by various and often overlapping risk factors that form theories of depressive disorders.

certain types of memory. The monoamine hypothesis of depressive disorder proposes development of depressive disorder by signal dysfunction between neurons: A decreased level of neurotransmitters leads to the depressive state[2,17].

**The stress induced theory of depressive disorder:** Prenatal stress, early-life adversities, chronic stress, and stressful life events are all strong predictors of the onset of depressive disorder. The HPA axis, a neuroendocrine system, is responsible for adaptation to changing environments. Response to stress begins in the hypothalamus, with the secretion of corticotropin-releasing hormone, which affects the pituitary gland to release adrenocorticotropic hormone. Adrenocorticotropic hormone circulates in the blood and stimulates the release of glucocorticoid hormones (cortisol) in the adrenal cortex. Cortisol binds to glucocorticoid receptors in the brain, which are key regulators of the stress response. Cortisol with a negative loop inhibits the HPA axis. Dysregulation of the negative loop is associated with depressive disorder[2,17].

**Neurotrophic theory of depressive disorder:** Neurotrophic factors are peptides or small proteins that support the growth, survival, and differentiation of developing and mature neurons. Decreased neurotrophic support affects the development of depressive symptoms. Brain-derived neurotrophic factor (BDNF) is a very well examined neurotrophic factor. Many studies made on brain and blood showed decreased expression of *BDNF* in patients with depressive disorder. Also, decreased *BDNF* expression has been associated with epigenetic modifications of the *BDNF* gene[17].

**Cytokine theory of depressive disorder:** Cytokines are small secreting proteins important in cell signaling. Cytokines include chemokines, interferons, interleukins (IL), lymphokines, and tumor necrosis factors (TNF)[18]. The cytokine (or inflammation) theory of depressive disorder suggests that inflammation has a significant role in its pathophysiology. Patients with depressive disorder have increased inflammatory markers, IL-1β, IL-6, TNF-α, and C-reactive protein[19]. Depressive disorder is not a typical autoimmune disease, so the elevation of cytokines in patients with depressive disorder is lower than in autoimmune or infectious diseases[2].

There are several proposed theories by which the immune system (cytokines and immune cells) could affect depressive-like behavior[20]. For example, inflammation in peripheral tissue can signal the brain *via* the vagus nerve, cytokine transport systems, and a leaky blood-brain barrier caused by rising TNF-α, which leads to brain accessibility for other peripheral signals[19].

Cytokines in the brain elevate during chronic stress and depressive disorder, but besides peripheral cytokines they can also arise from the CNS. Cytokines IL-6 and TNF-α activate indoleamine-2,3-dioxygenase, which decreases tryptophan (a serotonin precursor) and consequently reduces serotonin. Moreover, indoleamine-2,3-dioxygenase is included in the kynurenine pathway. Metabolites from this pathway activate monoamine oxidase (MAO), which degrades serotonin, dopamine, and norepinephrine. Cytokines might also act directly on neurons, changing excitability, synaptic strength, and synaptic scaling. Furthermore, cytokine IL-1β can contribute to heightened activation of the HPA axis and lowering inflammatory response to stress. During chronic stress microglia (neural immune cells) enhance phagocytic activity and synaptic remodeling[20].

Microglia represent 10% of all brain cells[21]. During the development of the organism, microglia are extremely active. They significantly contribute to shaping and refining developing neural circuits by regulating neurogenesis, synaptogenesis, synaptic pruning, and behavior. Early life stress, which is strongly associated with depressive disorder and other mental disorders, can trigger microglia perturb-

ations and affect development through changed morphological and functional changes of microglia. For example, microglial phagocytic activity and neuronal-microglial signaling can disrupt neural circuits and alter the formation of behavior. Furthermore, aberrant functionality of maturing microglial cells can alter their developmental programs and have long-lasting consequences for their reactivity[22]. It is thought that innate immune memory is mediated through epigenetic reprogramming and can last *in vivo* for several months[23].

### Epigenetics

In the 1940s, Waddington named the environmental influence of the genome epigenetics. Epigenetic modifications alter gene expression without changing the DNA sequence. The three key types of epigenetic change that occur in cells are DNA methylation, histone posttranslational modifications, and non-coding RNAs. The first two regulate gene transcription through altered chromatin structure and DNA accessibility, while the latter one regulates already transcribed messenger RNA (mRNA)[10]. Studies of epigenetics have escalated in the last 20 years and are gaining importance in the field of psychiatry. Through epigenetic studies, further understanding of depressive disorder is being achieved, but there are still many questions left to answer (Figure 2).

**DNA methylation:** DNA methylation is a process in which a single methyl group is added on the 5C of the cytosine DNA base. Methyl groups are transferred from S-adenosyl-L-methionine to cytosine by DNMTs[17]. In mammals, there are three groups of DNMTs; DNMT1, DNMT2, and DNMT3. DNMT1 maintains DNA methylation, DNMT3a and DNMT3b carry out *de novo* DNA methylation, and DNMT3L modulates DNMT3a and DNMT3b. DNMT2 has no DNA methylation activity. Instead it catalyzes RNA methylation, specifically on transfer RNAs[24]. DNA methylation mainly occurs at cytosine-phosphate-guanine (CpG) dinucleotides. When those dinucleotides are repeated many times in DNA sequence, they are called CpG islands. CpG islands have an average length of 1000 bp, and they contain more than 50% guanines and cytosines. Approximately 40% of genes contain CpG islands in promoter regions. Methylation of a promoter results in the inability of transcription factors to bind properly to regulatory elements and repression of gene transcription[17]. However, in mammals DNA methylation also occurs at CpA, CpT, and CpC. Those non-CpG methylation sites are common in brain tissue and several other tissue types[25] but at a three times lower rate than CpG methylation[26]. Besides methylation in promoter regions, it can also occur in the gene body and in intergenic regions and affect gene transcription[27]. DNA methylation is a stable cell state, but it can be reversed. Demethylation occurs when 5-methylcytosines are oxidized back to cytosines *via* three cytosine derivate forms: 5-hydoxymethylcytosine, 5-formylcytosine, and 5-carboxylcytosine[28].

**Histone tail modification:** The basic unit of chromatin is the nucleosome, which consists of negatively charged DNA and positively charged histone proteins. The nucleosome is an octamer, containing two copies of H2A, H2B, H3, and H4 proteins. Typically, a 147 bp long segment of DNA is wrapped around each nucleosome. H1 protein serves as a linker protein between the other histones that helps to condense nucleosomes even more[29]. Histone proteins have a long amino acid tail on their N-terminal end. In contrast with the core part of the histone protein, this extended part is very dynamic and is prone to chemical modifications[30]. To describe histone modifications we follow a standard nomenclature. First we write the name of the histone protein (H2A, H2B, H3, H4, or H1), then the modified amino acid residue (the name of amino acid and its site; for example, K4–lysine at site 4), and finally the type of modification (for example trimethylation–me3). An example of a final structure is H3K4me3. Specific proteins chemically modify histones and change chromatin conformation. Changes in conformation lead to the opening or closing of the chromatin, which allows or prevents transcription.

There are many different types of histone posttranslational modification, such as acetylation, methylation, phosphorylation, ubiquitination, *etc*, that can be modified differently and by different proteins called "writers" and "erasers." Furthermore, "readers" are proteins important for cross-talk between different epigenetic modifications. For example, DNA methylation and histone modifications mutually influence each other. There are many different reader domains that recognize histone modifications[31]. The most studied histone modifications are acetylation and methylation[29].

Histone acetyltransferases are proteins that transfer acetyl groups to lysine residues on the amino acid tail of histone proteins, while histone deacetylases (HDACs) are proteins that remove acetyl groups from the histone tails. Addition of a negative acetyl group loosens the tight bond between the negatively charged DNA and positively charged histones. This enables access of transcriptional machinery to the regulatory parts of DNA and consequently gene transcription[10].

Histone methylation is the adding of methyl groups to lysine and arginine residues on the histone tail. Histone methyltransferases add methyl groups to the histone tail, and histone demethylases remove methyl groups. Methylation of the histone tail can work in two ways. It can open chromatin or condense it. This depends on the position of the lysine/arginine residue in the histone tail and the number of methyl groups added to the amino acid[10].

**MicroRNAs:** Non-coding RNAs include many different RNAs: PIWI-interacting RNAs, small nucleolar RNAs, long non-coding RNAs and the most studied, microRNAs (miRNAs). MiRNAs are noncoding, 19–24 nt long RNAs that bind to mRNAs. A mature miRNA goes through biogenesis before it achieves

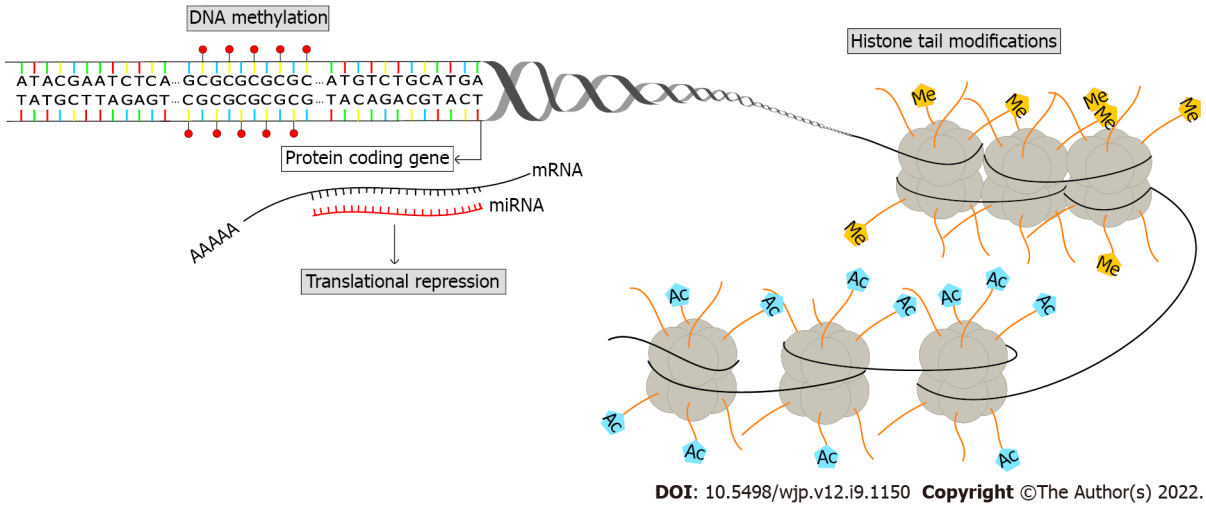


**Figure 2 Epigenetic mechanisms.** Epigenetic mechanisms include DNA methylation, noncoding RNA activity (such as microRNA), and posttranslational histone tail modifications. Ac: Histone acetylation; Me: Histone methylation; mRNA: Messenger RNA.

its final form. Briefly, it is transcribed as a 1 kb long primary RNA with a stem and loop structure. Primary miRNA is cleaved by Drosha ribonuclease III into a 60–100 bp long precursor miRNA. Precursor miRNA is then translocated from the nucleus into the cytoplasm where the endonuclease Dicer converts it into an unstable, double stranded small RNA. One strand of the duplex is degraded and the other, the mature miRNA, incorporates into the RNA-induced silencing complex along with Argonaut protein. Mature miRNA is complementary to one or more mRNAs. It binds to the 3′ untranslated region of the target mRNA and silences targeted mRNA or sends mRNA to degradation when binding is highly complementary[32].

## EPIGENETICS AND DEPRESSIVE DISORDER

Biomarkers that could be associated with MDD are BDNF, the cortisol response, cytokines, and neuroimaging. However, due to the complex nature of depressive disorder a single biomarker is not sufficient for use in diagnosis or monitoring of the disorder. Therefore, it has been proposed to examine multiple biomarkers and use them for patient examination[33]. In genetic studies several polymorphisms associated with a depressive state were found in genes of the monoaminergic system (the gene that encodes for serotonin transporter, receptor genes for dopamine and serotonin, genes involved in signaling of noradrenaline and dopamine…), and genes involved in the functioning and regulation of the HPA axis[2] but did not reveal the role of the DNA sequence itself in the etiology of depressive disorder. Future epigenetics may present new findings, which could be included as possible biomarkers for MDD[33].

Epigenetic modifications were studied in the saliva and blood of the depressed patients, postmortem brain tissue of depressed patients who died by suicide, and rodent animal models (rats and mice). There are several ways to induce stress and a depressed state in animal models[34]. Chronic stress is induced with "bullying" by a bigger more aggressive mouse or witnessing another mouse being physically aggressed for several days[10]. Early life stress from humans can be evoked on animal models by maternal separation of offspring during early postnatal periods. Such induced stress in animals results in mimicking certain behavioral features of human depressive disorder. It has been shown that these methods evoke epigenetic changes, similar to those seen in humans[34].

Tables 1–4 show selected studies of epigenetic changes detected in samples of depressed patients and animal models. The most studied epigenetic modification is DNA methylation, and it has been rather extensively investigated in the *BDNF* gene, specifically exon I. In studies of depressive disorder induced by stress in the prenatal and early stages of life, methylation of glucocorticoid receptor gene (*NR3C1*) was the most analyzed. Lately, more studies are also considering histone 3 modifications among which are methylation of lysines 27, 9, and 4 and acetylation of lysine 14. Studies of miRNAs are diverse and are showing that a more standardized approach is needed.

DNA methylation studies (Table 1 and Table 4) were performed on blood, buccal swabs, or brain tissue of humans and brain tissue of animal models. As we can see from Table 1, there are a lot of studies investigating DNA methylation in the *BDNF* gene (different parts of the *BDNF* gene were tested; exon I, IV, IX, promoter region, whole gene). Most studies showed elevated DNA methylation in the *BDNF* gene in depressed patients. However, a few studies showed that DNA methylation is decreased.

**Table 1 DNA methylation studies on depressed subjects, also associated with suicidality and life adversities**

| Gene (region) | Alteration | Subjects and collected tissue | Ref. |
|---|---|---|---|
| *NR3C1* 1-F and *FKBP5* intron 7 promoter | ↑ DNA methylation at *NR3C1* 1-F, without significant differences at any of the measured individual CpG site in depressed patients. Association in salivary cortisol level and DNA methylation. ↑ DNA methylation in *NR3C1* 1-F at CpG 38 site in depressed patients, with early life adversity. No differences in *FKBP5* intron 7 promoter | 33 depressed patients (24 females, 9 males), 34 controls (21 females, 13 males). Whole blood and saliva | Farrell *et al*[67], 2018 |
| *MAOA* and *NR3C1* exon 1-F | ↓ DNA methylation at *MAOA*'s first exon/intron junction; significantly ↓ at CpG 8 site from the intron region. ↑ DNA methylation at *NR3C1* 1-F's promoter and exon in individuals experienced early parental death; significant ↑ at CpG 35 and 10.11 (sites close to NGFI-A binding site) | 82 (for *MAOA* gene) and 93 (for *NR3C1* 1-F gene) depressed females, victims of early-life adversity and 92 or 83 controls. Saliva | Melas *et al*[35], 2013 |
| *BDNF*, *NR3C1*, and *FKBP5* | Significant alteration in DNA methylation at 9 sites in *BDNF* gene body, at 6 sites in *NR3C1* promoter region, and at 4 sites in *FKBP5* gene body, 3'UTR and promoter | 94 maltreated and 96 non-traumatized children. Saliva | Weder *et al*[68], 2014 |
| *BDNF* exon I | ↓ DNA methylation; differences at loci 87, 88 and 92–94, located within the CpG island region on the promoter of the exon I | 360 depressed patients (32 females, 328 males). Saliva | Song *et al*[69], 2014 |
| *BDNF* promoter between –694 and –577 relative to the transcriptional start site (12 CpG sites). *SLC6A4* promoter adjacent to exon 1a between –479 and –350 relative to the transcriptional start site (10 CpG sites) | Depressed mood in 2$^{nd}$ trimester associated with ↓ DNA methylation at maternal *SLC6A4* promoter methylation status. ↓ DNA methylation at *SLC6A4* promoter in infants, from mothers with higher depressed mood during 2$^{nd}$ trimester. No difference in *BDNF* gene | 82 female and male infants exposed to prenatal maternal stress–33 mothers treated with SRI and 49 mothers not treated with SRI. Blood | Devlin *et al*[70], 2010 |
| *NR3C1* exon 1-F and *BDNF* promoter IV | ↑ DNA methylation within *NR3C1* 1-F gene (male infants). ↓ DNA methylation within *BDNF* promoter IV region (female and male infants) | 20 female and male infants exposed to prenatal maternal stress and 37 controls. Buccal tissue | Braithwaite *et al*[71], 2015 |
| *NR3C1* exon 1-F | Depressed mood in 2$^{nd}$ trimester associated with ↑ DNA methylation of CpG 2 site (relative to translational start site) at *NR3C1* exon 1-F in infants. Depressed mood in 3$^{d}$ trimester associated with ↑ DNA methylation of CpG 2 and CpG 3 site (relative to translational start site) at *NR3C1* exon 1-F in infants | 46 depressed females (33 treated with SRI and 13 not medicated), 36 controls, and their infants. Blood | Oberlander *et al*[72], 2008 |
| *BDNF*, *NR3C1*, *CRHBP*, *CRHR1*, *FKBP5* promoter | Hypermethylated *BDNF*, *NR3C1*, *CRHBP* and *FKBP5* promoter. mRNA down regulation of *BDNF, NR3C1, FKBP5* and *CRHBP* in MDD-suicidal ideation group | 15 females and 9 males with MDD (14 with and 10 without suicidal ideation) and 20 controls (14 females and 6 males). PBMC | Roy *et al*[73], 2017 |
| *BDNF* exon I promoter | ↑ percentage of methylated reference values | 207 female and male MDD patients and 278 controls. PBMC | Carlberg *et al*[58], 2014 |
| *BDNF* exon I promoter | ↑ at CpG 1, CpG 3 and CpG 5 site, ↓ BDNF serum level | 49 female and male MDD patients and 57 controls. Blood | Schröter *et al*[74], 2020 |
| *BDNF* exon I and IV promoter | ↑ methylation at CpG site 3 of promoter IV | 251 female and male MDD patients aged 65 > and 773 controls. Buccal tissue | Januar *et al*[75], 2015 |
| *BDNF* exon IX | Changes in DNA methylation; ↑ at CpG site 217, ↓ at CpG site 327, and 362. ↓ BDNF level and mRNA levels | 51 MDD patients (35 females and 16 males) and 62 controls (39 females and 23 males). Venous blood | Hsieh *et al*[60], 2019 |
| *BDNF* upstream of exon I and IV | Changes in DNA methylation within CpG exon I promoter | 20 MDD patients (12 females and 8 males) and 18 controls (8 females and 10 males). Blood | Fuchikami *et al*[76], 2011 |
| *MYO16* and *IDE* | ↑ 5hmc in one CpG position of *MYO16* and two CpG positions of *IDE* in the PFC. ↑ gene expression of *MYO16*. ↓ gene expression of *IDE* | 19 depressed male suicide victims and 19 controls. Brain tissue (PFC; inferior frontal gyrus) | Gross *et al*[77], 2017 |
| $GABA_A$ receptor α1 subunit promoter | ↑ DNA methylation of the CpG 2 and CpG 4 site (500 bp from transcriptional start site). ↑ DNMT-3B expression in FPC. ↓ expression of *DNMT1* mRNA and ↑ expression of *DNMT3b* mRNA in FPC. ↓ expression of *DNMT3b* and *DNMT1* mRNA in AMG | 10 male suicide victims and 10 controls. Brain tissue (FPC, AMG) | Poulter *et al*[78], 2008 |

| | | | |
|---|---|---|---|
| *SLC6A4* promoter | ↑ mean methylation level | 28 MDD patients (20 females and 8 males) and 29 controls (21 females and 8 males). Blood | Iga *et al*[79], 2016 |
| *NR3C1* exon 1 promoter | ↑ methylation at CpG 30 and 32 site. ↓ expression of total *NR3C1* mRNA and *NR3C1*-1F mRNA in suicide victims without childhood abuse and control group | 12 suicide victims with traumatic childhood experience, 12 suicide victims without traumatic childhood experience, and 12 controls. Brain tissue (HPC) | McGowan *et al* [80], 2009 |

↓: Decreased expression; ↑: Increased expression; AMG: Amygdala; *BDNF*: Brain derived neurotrophic factor; bp: Base pair; CpG: Cytosine-phosphate-guanine; *CRHBP*: Corticotropin releasing hormone binding protein; *CRHR1*: Corticotropin releasing hormone receptor 1; *DNMT3B*: DNA methyltransferase 3; *FKBP5*: FK506 binding protein 5; FPC: Frontopolar cortex; $GABA_A$: γ-aminobutyric acid; H3K14ac: Acetylation of lysine 14 on histone 3; *HDAC2*: Histone deacetylase 2; HPC: Hippocampus; *IDE*: Insulin-degrading enzyme; MDD: Major depressive disorder; *MAOA*: Monoamine oxidase A; mRNA: Messenger RNA; *MYO16*: Myoxin XVI; NGFI-A: Nerve growth factor-induced protein A; *NR3C1*: Nuclear receptor subfamily 3 group C member 1; PFC: Prefrontal cortex; PBMC: Peripheral blood mononuclear cells; *SLC6A4*: Solute carrier family 6 member 4; SRI: Serotonin reuptake inhibitor antidepressant; UTR: Untranslated region; 5hmc: 5-hydroxymethylcytosine.

**Table 2 Histone tail modifications studies on depressed suicide victims**

| Gene (region)/histone tail modification | Alteration | Subjects and collected tissue | Ref. |
|---|---|---|---|
| *BDNF*, H3K9/14ac, H3K27me2 | ↓ H3K9/14ac, ↑ HDAC2, ↑ HDAC3, ↑ H3K27me2, ↓ BDNF in HPC and NAc. ↑ Sin3a in HPC | 14 suicide victims (5 females and 9 males) without psychiatric diagnosis and 8 controls (3 females and 5 males). Brain tissue (HPC, NAc, and FCx; BA10) | Misztak *et al*[53], 2020 |
| H3K4me3 | ↑ In H3K4me3 at promoter of *SYN2*. ↑ expression *SYN2b*; no changes in *SYN2a* expression | 7 females and 11 males with MDD suicide victims and 14 controls (3 females and 12 males). Brain tissue (PFC; BA10) | Cruceanu *et al*[81], 2013 |
| H3K14ac | ↑ H3K14ac. ↓ *HDAC2* mRNA expression | 8 depressed females and males. Brain tissue (NAc) | Covington *et al*[11], 2009 |

↓: Decreased expression; ↑: Increased expression; BA10: Brodmann area 10; *BDNF*: Brain derived neurotrophic factor; FCx: Frontal cortex; H3K14ac: Acetylation of lysine 14 on histone 3; H3K9/14ac: Acetylation of lysine 9/14 on histone 3; H3K27me2: Dimethylation of lysine 27 on histone 3; H3K4me3: Trimethylation of lysine 4 on histone 3; HDAC2: Histone deacetylase 2; HDAC3: Histone deacetylase 3; HPC: Hippocampus; MDD: Major depressive disorder; mRNA: Messenger RNA; NAc: Nucleus accumbens; Sin3a: SIN3 transcription regulator family member A; PFC: Prefrontal cortex; *SYN2*: Synapsin II; *SYN2b*: Synapsin IIb; *SYN2a*: Synapsin IIa.

The main conclusion is that alteration in *BDNF* methylation is associated with a depressive state.

The gene *NR3C1* is included in many studies of early life adversities (childhood abuse, parental loss, exposure to maternal depression during pregnancy and after birth). Results show an association between increased methylation of the exon 1-F of the *NR3C1* gene, decreased total *NR3C1* mRNA, and early life adversities[35]. *NR3C1* encodes for the glucocorticoid receptor and is responsible for the effects of cortisol on peripheral tissues. It is self-regulated by a negative feedback loop within the HPA axis [36]. The glucocorticoid receptor can work as a transcription factor that binds to glucocorticoid receptor elements in the promoters of glucocorticoid responsive genes or as a regulator of other transcription factors[37].

In terms of the histone modification data presented in Table 2 and Table 4, H3K27me and H3K14ac are the most studied. The majority of the studies are carried out on animal models and a few on postmortem brain tissue. Studies include information of whole tissue histone modifications and not of single genes. From studies on animal models (Table 4), we can see that the histone tail modifications change over time and are different regarding tissue type.

Many studies in the last 15 years took into consideration miRNAs as important contributors either to the depressive state or as a biomarker of the depressive state. Studies examining humans (Table 3) are in correlation with studies performed on rodents (Table 4). For example, miR-218 and miR-511 are both downregulated in the prefrontal cortex of depressed subjects who died by suicide and in rodent models (mice or rat). On the other hand, miR-16 and miR-376b were oppositely regulated in humans *vs* animal models. This might be due to different tissues tested. There are several more miRNAs regulated in the same direction in human *vs* animal (rodent) models[38]. Upregulation of miR-139-5p is seen in blood-derived exosomes from MDD patients and in brain tissue from chronically depressed mice. Upregulation of miR-323-3p is seen in lateral habenula and Brodmann area 24 in depressed subjects. Consistently, there is also upregulation of miR-323-3p in the brains of rats exposed to prenatal stress. MiR-155 is downregulated in peripheral blood mononuclear cells of depressed subjects and serum of mice exposed to restraint stress. Furthermore, blood-derived exosomes with increased levels of miR-

**Table 3 MicroRNA expression studies on depressed suicide victims**

| miRNAs | Alteration | Subjects and collected tissue | Ref. |
|---|---|---|---|
| miR-218 | ↓ miR-218 and ↑ *DCC* in PFC | 11 male suicide victims with MDD and 12 male controls. Brain tissue (PFC; BA44) | Torres-Berrío *et al*[82], 2017 |
| ↓ miR-142-5p, miR-137, miR-489, miR-148b, miR-101, miR-324-5p, miR-301a, miR-146a, miR-335, miR-494, miR-20b, miR-376a*, miR-190, miR-155, miR-660, miR-130a, miR-27a, miR-497, miR-10a, miR-20a, miR-142-3p. ↓ by 30% or more: miR-211, miR-511, miR-424, miR-369-3p, miR-597, miR-496, miR-517c, miR-184, miR-34a, miR-34b-5p, miR-24-1*, miR-594, miR-34c-5p, miR-17*, miR-545, miR-565 | Globally ↓ miRNAs expression by 17% on average in depressed subjects. miR-148b targets *DNMT3B*, protein level was upregulated in depressed subjects. miR-34a targets *BCL2*, protein level was downregulated in depressed subjects | 18 suicide victims (2 females and 16 males) with depression and 17 male control subjects. Brain tissue (PFC; BA9) | Smalheiser *et al*[83], 2012 |
| miR-1202 | ↓ miR-1202, and ↑ *GRM4* mRNA expression in BA44 | 25 suicide victims (2 females and 23 males) with MDD and 29 control subjects (4 females and 25 males). Brain tissue (PFC; BA44). 32 subjects with MDD (24 females and 10 males) and 18 control subjects (8 females and 10 males). Blood | Lopez *et al* [84], 2014 |
| miR-30e | ↑ miR-30e, ↓ ZDHHC21 protein | 16 suicide victims (7 females and 9 males) with MDD and 16 controls (6 females and 10 males). Brain tissue (PFC; BA9) | Gorinski *et al*[85], 2019 |
| miR-19a-3p | ↑ miR-19a-3p (might be involved in the modulation of TNF-α signaling) | 12 depressed patients with severe suicidal ideation, 12 control subjects. PBMC | Wang *et al* [86], 2018 |
| More than 10 miRNAs | ↑ miR-17-5p, miR-20b-5p, miR-106a-5p, miR-330-3p, miR-541-3p, miR-582-5p, miR-890, miR-99b-3p, miR-550-5p, miR-1179. ↓ miR-409-5p, let-7g-3p, miR-1197 | 9 depressed suicide victims (3 females and 6 males) and 11 control subjects (2 females and 9 males). Brain tissue (*locus coeruleus*) | Roy *et al* [37], 2017 |
| miR-326 | ↓ miR-326, ↑ UCN1 | 5 male suicide victims with MDD and 8 male controls. Edinger-Westphal nucleus | Aschrafi *et al*[87], 2016 |
| 10 miRNAs tested | ↑ miR-34c-5p, miR-139-5p, miR-195, miR-320c. ↓ *SAT1* and *SMOX* mRNA | 15 male suicide victims with MDD and 16 male control subjects. Brain tissue (BA44) | Lopez *et al* [88], 2014 |
| miR-204-5p, miR-320b, miR-323a-3p, miR-331-3p | ↑ miR-204-5p, miR-320b, miR-323a-3p, miR-331-3p in ACC and lateral habenula. miR-323a-3p influences the expression of *ERBB4*. Decreased expression in ACC and lateral habenula | 39 suicide victims with MDD (13 females and 26 males) and 41 control subjects (10 females and 31 males) for ACC region. 24 suicide victims with MDD (10 females and 14 males), 13 control subjects (5 females and 8 males) for lateral habenula. Brain tissue (ACC and lateral habenula) | Fiori *et al* [89], 2021 |
| 171 miRNA differently expressed | ↑ 117 miRNAs. ↓ 54 miRNAs | 22 (10 females and 12 males) MDD subjects (10 died by suicide, 12 died from cause other than suicide) and 25 control subjects (10 females and 15 males). Brain tissue (ACC) | Yoshino *et al* [90], 2020 |
| miR-128-3p | ↑ miR-128-3p. ↓ WNT5B, DVL1 and LEF1 | 20 MDD (10 females and 10 males) subjects and 22 control subjects (9 females and 13 males). Brain tissue (AMG) | Roy *et al* [91], 2020 |
| miR-16 | ↓ miR-16 | 36 MDD (21 females and 15 males) subjects and 30 controls (17 females and 13 males). CSF | Song *et al* [92], 2015 |

↓: Decreased expression; ↑: Increased expression; ACC: Dorsal anterior cingulate cortex; AMG: Amygdala; BA44: Brodmann area 44; BA9: Brodmann area 9; *BCL2*: B-cell lymphoma 2; CSF: Cerebrospinal fluid; *DCC*: Developmental netrin-1 guidance cue receptor; *DNMT3B*: Gene coding for DNA methyltransferase 3; DVL1: Dishevelled segment polarity 1; *GRM4*: Gene coding for metabotropic glutamate receptor 4; LEF1: Lymphoid enhancer binding factor 1; MDD: Major depressive disorder; miR: MicroRNA; mRNA: Messenger RNA; PBMC: Peripheral blood mononuclear cells; PFC: Prefrontal cortex; *SAT1*: Gene coding for spermidine/spermine N1 -acetyltransferase 1; *SMOX*: Gene coding for spermine oxidase; TNFα: Tumor necrosis factor; UCN1: Urocortin; WNT5B: Wingless-related integration site, member 5B.

139-5p collected from depressed subjects, evoked depressive-like behavior when administered intravenously in mice[38].

However, from all the data currently available, it is hard to pinpoint particular miRNAs that could be used as biomarkers for depressive disorder. Studies presented in Table 4 show lack of overlap between

**Table 4 Epigenetic (DNA methylation, histone tail modifications, and microRNAs) studies on animal models of depressive disorder**

| Epigenetic modification | Gene (region)/histone tail modification/miRNA | Alteration | Organism and collected tissue | Ref. |
|---|---|---|---|---|
| DNA methylation | *Crf* promoter of exon 1 and intronic region between exon 1 and exon 2 (relative to exon 1 start site) | Overall ↑ DNA methylation, and specific ↑ in CpG –147 and CpG –101 site of the *Crf* gene in stressed female rats in the PVN. No changes in male rats. ↓ DNA methylation in CpG –15 (male and female rats), ↓ DNA methylation in CpG –226, CpG –55 and ↑ in CpG +485 and CpG +494 (male rats) and ↓ DNA methylation in CpG –95 site (female rats) in BNST. ↑ DNA methylation in CpG –232 and CpG –226 (male rats), ↓ CpG –226 and CpG +535 (female) in the CeA | Male and female Wistar-R Amsterdam rats; sacrificed 2 h after stress. Brain tissue (PVN, BNST, CeA) | Sterrenburg *et al* [93], 2011 |
| DNA methylation | *Crf* promoter (relative to exon 1 start site) | Chronic social stress induced ↑ DNA methylation in *Crf* promoter region at CpG site –226 and ↓ DNA methylation level in intronic region of the gene *Crf* in the PVN. Long term effect of social defeat in mice susceptible to social defeat: ↑ in *Crf* mRNA levels in PVN and ↓ DNA methylation level at CpG –226, –101, –95, and –79 | Chronically stressed adult mice C57BL/6. Brain tissue (PVN) | Elliott *et al*[94], 2010 |
| DNA methylation and histone tail modification | *Gdnf* | ↑ DNA methylation at CpG site 2. ↓ H3ac in NAc of BALB mice and C57BL/6 mice. C57BL/6 mice had higher H3ac and higher *Gdnf* expression | BALB/c mice with maladaptive response to stressful stimuli and stress resilient strain C57BL/6. Brain tissue (NAc) | Uchida *et al*[95], 2011 |
| Histone tail modification | H3K14ac | ↓ H3K14ac 1 h after final stress. ↑ H3K14ac 24 h and 10 d after final stress. ↓ *Hdac2* mRNA expression 24 h and 15 d after final stress in NAc | Chronically social defeated adult male mice C57BL/6J. Brain tissue (NAc). | Covington *et al* [11], 2009 |
| Histone tail modification | H3K14ac | H3K14ac ↑ after 24 h and ↓ at longer time in HPC. H3K14ac ↑ after 1 h and 24 h, no changes 10 d and longer in AMG | Chronically social defeated adult male mice C57/BL6J. Brain tissue (HPC and AMG) | Covington *et al* [96], 2011 |
| Histone tail modification | *Bdnf* exon IV, H3ac, H4ac | ↓ exon IV *Bdnf* mRNA. ↓ H3ac and H4ac. ↑ MeCP2 levels. ↑ *Hdac* mRNA | Rats (early life adversity induced by maternal separation). Brain tissue (HPC) | Seo *et al*[97], 2016 |
| Histone tail modification | *Bdnf* III and IV promoter, H3K27me2 | ↑ H3K27me2 at promoter *Bdnf* III and IV. ↓ total *Bdnf* mRNA. No change at H3K9me2 | Chronic social defeat stress mice. Brain tissue (HPC) | Tsankova *et al* [62], 2006 |
| Histone tail modification | H3K9me2 | ↑ H3K9me2 in HPC and mPFC. ↓ *Bdnf* expression in HPC and mPFC | Wistar rats exposed to maternal separation and chronic unpredicted mild stress. Brain tissue (HPC and mPFC) | Jiang *et al*[98], 2021 |
| Histone tail modification | H3K4me3, H3K9me3, H3K27me3 | Acute restrain stress: ↑ in H3K9me3 in CA1 and DG; no changes in CA3; ↓ in H3K27me3 in DG and CA1; not significantly altered in CA3. No significant changes for H3K4me3. Subchronic 7-d restraint stress: The basal level of H3K9me3 on day 7 increased in DG, CA1 and CA3. ↓ in H3K9me3 in CA1, CA3 and DG. ↓ in H3K27me3 in DG | Adult male Sprague–Dawley rats (acute stress/7 d restraint stress). Brain tissue (HPC parts: DG, CA1, CA3) | Hunter *et al*[99], 2009 |
| miRNA | miR Let-7a-1, miR-9, miR-25a/b | ↑ miR Let-7a-1, miR-9, miR-25a/b after acute stress in FCx. No changes in HPC | Male CD1 mice with induced acute or repeated stress. Brain tissue (FCx and HPC) | Rinaldi *et al* [100], 2010 |
| miRNA | miR-218 | ↓ miR-218 and ↑ *DCC* in PFC | Chronically social defeated adult male mice C57BL/6. Brain tissue (mPFC) | Torres-Berrío *et al*[82], 2017 |
| miRNA | miR-16 | ↑ miR-16. ↓ *Bdnf* mRNA | Sprague-Dawley rats exposed to maternal deprivation. Brain tissue (HPC) | Bai *et al*[101], 2012 |
| miRNA | 342 miRNAs differently expressed (response to gestational stress) and 336 miRNAs differently | ↑ 147 miRNAs and ↓ 195 miRNAs in FCx of female rats. ↑ 205 miRNAs and ↓ 131 miRNAs in offspring | Stress induced through pregnant female Long-Evans rats. Offspring | Zucchi *et al*[102], 2013 |

| | | | | |
|---|---|---|---|---|
| | expressed in offspring (response to prenatal stress) | | (decapitated 1 to 5 h after parturition). Brain tissue (FCx) | |
| miRNA | AMG: 10 miRNAs under acute stress and 28 after chronic stress; HPC CA1: 16 after acute stress and 22 after chronic stress | The overlap: ↑ miR Let-7a-1 in AMG affected by acute and chronic stress. ↑ miR-376b and miR-208, ↓ miR-9 in HPC by acute and chronic stress. Other changes are unique to acute/chronic stress or brain region analyzed | Adult male rats with induced acute or chronic stress. Brain tissue (AMG, HPC CA1 region) | Meerson *et al* [103], 2010 |
| miRNA | miR-124a, miR-18a, miR-511 | ↑ miR-124a, miR-18a in PFC and HPC persistently. ↓ miR-511 in PFC (in adult rats experienced CUMS) | Adolescent male Wistar rats were stressed with CUMS. Brain tissue (PFC and HPC) | Xu *et al*[104], 2019 |

↓: Decreased expression; ↑: Increased expression; AMG: Amygdala; *Bdnf*, brain derived neurotrophic factor; BNST: Bed nucleus of the stria terminalis; CeA: Central amygdala; CpG: Cytosine-phosphate-guanine; *Crf*: Corticotropin releasing factor; CUMS: Chronic unpredictable mild stress; *DCC*: Gene coding developmental netrin-1 guidance cue receptor; DG: Dentate gyrus; FCx: Frontal cortex; *Gdnf*: Glial cell-derived neurotrophic factor; HDAC: Histone deacetylase; H3ac: Acetylation of histone 3; H4ac: Acetylation of histone 4; H3K14ac: Acetylation of lysine 14 on histone 3; H3K9me2: Dimethylation of lysine 9 on histone 3; H3K9me3: Trimethylation of lysine 9 on histone 3; H3K27me2: Dimethylation of lysine 27 on histone 3; H3K27me3: Trimethylation of lysine 27 on histone 3; H3K4me3: Trimethylation of lysine 4 on histone 3; *Hdac2*: Histone deacetylase 2; HPC: Hippocampus; HPC CA1: Hippocampal CA1 region; HPC CA3: Hippocampal CA3 region; MeCP2: Methyl CpG binding protein 2; mPFC: Medial prefrontal cortex; miR: Micro RNA; miRNA: Micro RNA; mRNA: Messenger RNA; NAc: Nucleus accumbens; PFC: Prefrontal cortex; PVN: Hypothalamic paraventricular nucleus.

studies; there are several different tissues used, and the number of miRNAs interrogated vary from whole RNome studies to single miRNA studies. Although many limitations exist in the miRNA research, current results are promising enough to persist with the search for miRNAs or even miRNA networks that could serve as biomarkers.

Due to variation in study design, comparisons between the obtained results are limited. In particular, criteria for subject inclusion are very diverse (inclusion of one/two sexes, age, ethnic background, and so on), and studies are frequently underpowered. In addition, the background of the depressive state is not the same for all depressed patients. Some studies analyze the consequences of early life adversity, others include patients with depressive disorder at older age or depressed patients without a known cause. When working with animal models the study design is more standardized and controlled, while the trigger of depressed state is selected based on the interest of the study.

## POSSIBLE TREATMENTS OF DEPRESSIVE DISORDER

There are pharmacological and nonpharmacological (psychotherapy, lifestyle interventions, and neuromodulatory treatment) ways of treating depressive disorder. For pharmacological treatment, there are many different antidepressants available, and they are a cornerstone for treating depressive disorder [39]. The main drug classes of antidepressants are selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors, noradrenergic and specific serotonergic agents, tricyclic antidepressants, MAO inhibitors, and melatonin modulators (agomelatine)[40]. However, there is no universally effective treatment for all depressed patients[39].

People suffering from depressive disorder can recover in a year or not recover in more than 20 years. Furthermore, depressive episodes recur in almost half of recovered patients[5]. Even though there are many different antidepressants available and many different treatment options, 34%–46% of MDD patients still do not respond effectively to one or more antidepressant treatments (*i.e.* fail to achieve remission). That is why there is still a great need for new antidepressants for curing treatment-resistant depression[41]. Among novel drugs, ketamine and eskatemine are being extensively used. Also, the HDAC inhibitors (HDACis) are being tested on animal models as one possibility of treatment.

### *Selective serotonin inhibitors*

SSRIs are the most commonly prescribed antidepressants and are used as the first treatment step for depressive disorder. Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter that modulates mood, reward, learning, and memory. Deficiency in serotonin release is not associated with serotonin biosynthesis. The serotonin deficit is more likely due to less serotonin neuron firing and less serotonin release. However, SSRIs block the reabsorption of serotonin into presynaptic neuron cell and with that improve message transmission between cells[40].

Fluoxetine was the first SSRI to be developed and is the most used antidepressant for children and adolescents. Many different SSRIs have now been developed that vary in binding affinity; some are more specific to serotonin than others. It became clear that using the available antidepressants targeting specific monoamines also have side effects. Those side effects come from neurotransmitters binding to different receptors. For example, when serotonin binds to the 5HT1A receptor, there is an antide-

pressant and anxiolytic effect; when it binds to 5HT2A/C receptor, there is an effect on sexual dysfunction. Multimodal antidepressants directly target specific serotonin receptors and inhibit reuptake of serotonin. Vilazodone is an example of a multimodal antidepressant, which targets a specific receptor (5HT1A). Still, vilazodone is not as superior as it was expected to be compared to other antidepressants[40,42]. Vortioxetine is more promising since it shows superior efficacy compared to the other antidepressants in trials. Vortioxetine is an agonist of 5HT1A, (partial) antagonist of other receptors, and a potent serotonin reuptake inhibitor. Besides the antidepressant effect, it also improves cognitive function[40,42].

### Ketamine

Novel treatments that target outside of the monoaminergic system are ketamine [targeting the glutamate system through N-methyl-aspartate (NMDA) receptor antagonism] and agomelatin (a melatonin receptor agonist)[40]. Agomelatin is a melatonin agonist and a selective serotonin antagonist. For antidepressant effect, both actions are necessary. Agomelatin showed good antidepressant effect for people with seasonal affective disorder[43].

Ketamine is used in many clinical studies for treatment-resistant patients who fail to respond to SSRIs. Ketamine showed good results, with a response rate between 40% and 90%[43]. Intravenous infusion of ketamine produces a rapid and prolonged effect within a few hours of administration. It is accompanied by psychotomimetic effects, which subside within 2 h. The effect of a single intravenous insertion lasts 2–14 d, and it has an anti-suicide effect[41]. Ketamine is restricted for routine clinical use due to its side effects: Dissociative effects, changes in sensory perception, intravenous administration, and risk of abuse[44].

Ketamine is a mixture of two enantiomers, S-ketamine and R-ketamine. In the past few years, esketamine (S-ketamine) has been studied as a better option than ketamine because of its easier administration. Esketamine can be inserted intranasally and is therefore easier for at home administration. Recently, researchers investigated R-ketamine. Preclinical and clinical studies on intravenously infused R-ketamine elicit a fast and sustained antidepressant state, without psychotic symptoms[45].

**Ketamine's action:** Ketamine affects the glutamate system. Glutamate is an excitatory neurotransmitter and is involved in neurodevelopment, neurocognitive (memory learning) function, and neuroplasticity (neurogenesis, neuronal growth and remodeling, maintenance, and synaptic plasticity). Dysregulation of neuroplasticity can contribute to MDD and other neuropsychiatric conditions. The majority of neurons use glutamate as a neurotransmitter. Two types of glutamate receptors (ionotropic or metabotropic glutamate receptors) are categorized into four major classes: α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid receptors, NMDA receptors (NMDAR), kainate receptors, and metabotropic glutamate receptors[46]. NMDARs are located at the postsynaptic and presynaptic side of glutamatergic synapses in the CNS[47]. In postmortem brains of MDD patients, many studies have revealed alteration in NMDAR. Several changes were discovered, such as NMDAR dysfunction (reduced glutamate recognition and allosteric regulation) and altered expression of NMDAR subunits. The latter might be manifested by altered glutamatergic input and abnormal glutamate neurotransmission[46].

There are several mechanisms of ketamine action, which may act complementarily. Ketamine can bind to NMDAR on presynaptic or postsynaptic glutamatergic neuron and on GABAergic interneurons. Binding leads to blockade and inhibition of NMDAR. For the antidepressant effects of ketamine, cascades of actions happen: γ-aminobutyric acid decrease, glutamate release, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors activation, BDNF release, tropomyosin receptor kinase B activation, and mammalian target of rapamycin complex 1 activation. The result is an acute change in synaptic plasticity and sustained strengthening of excitatory synapses[44]. The process of synaptogenesis is activated and further probably affects cognition, mood, and thought patterns[48].

### HDACis

Decreased acetylation is associated with a depressive state and because of that, HDACs (as erasers of acetylation) might become a novel treatment target[10]. HDACs, "erasers" of histone acetylation, are classified into two categories: The zinc-dependent and nicotinamide-adenine-dinucleotide–dependent sirtuins (Table 5)[49].

HDACs I, II, and IV are expressed in the brain, primarily in neurons. Class I and II regulate histone deacetylation at most genes, and class III deacetylates nuclear and cytoplasmic substrates beside histones[50]. The balance between histone acetyltransferases and HDAC activity determines the (de)condensation status of the chromatin and gene transcription[10].

HDACis are potent to specific classes of HDACs. The United States Food and Drug Administration has approved a few HDACis [vorinostat (SAHA), belinostat, panobinostat, and romidepsin] for treatment of some types of cancers. Many preclinical studies on mice showed an antidepressant effect of HDACis by reversing the acetylated state. Moreover, HDACis also promote neuronal rewiring and recovery of motor functions after traumatic brain injury. Use in clinical practice is limited due to severe side effects including thrombocytopenia and neutropenia[51].

**Table 5 Histone deacetylase classification and localization**

| HDAC category | HDAC class | HDAC type | Localization |
|---|---|---|---|
| Zinc-dependent HDACs | Class I | HDACs 1, 2, 3, 8 | Localized in nucleus |
| | Class II | HDACs 4, 5, 7, 9, 10 | Pass between nucleus and cytoplasm |
| | | HDAC6 | Localized in the cytoplasm |
| | Class IV | HDAC11 | |
| NAD-dependent SIRTs | Class III | SIRTs 1, 2, 6 and 7 | Localized in the nucleus |
| | | SIRTs 3, 4 and 5 | Localized in the mitochondria |

HDACs: Histone deacetylases; NAD-dependent sirtuins: Nicotinamide-adenine-dinucleotide–dependent sirtuins; SIRTs: Sirtuins.

## DEPRESSIVE DISORDER ASSOCIATED GENES AND CLASSICAL ANTIDEPRESSANT DRUGS

How different antidepressants affect depressive symptoms can be measured by a subject's phenotype (behavior for animals and psychiatric evaluation for humans). Epigenetic alterations might become one of the tools to check how well specific subjects respond to the antidepressant[52].

### *BDNF and depressive disorder*

One of the most studied genes of depressive disorder is *BDNF*. BDNF is one of the most important neurotrophins. The human *BDNF* gene contains nine exons (I–IX), each regulated by its own promoter. All the different transcripts are translated into an identical BDNF protein[53]. It is highly expressed in the CNS[54] and plays an important role in proper brain development and functioning, including neuronal proliferation, migration, differentiation, and survival[53]. BDNF binds to p75 neurotrophin receptor (p75NTR) and tropomyosin receptor kinase B[54]. In many studies, exon I and IV showed alteration in expression levels in depressed subjects. Splice variant tropomyosin receptor kinase B.T1 is an astrocytic variant and has gained a lot of interest in the study of the depressive state[10]. Two single nucleotide polymorphisms, Val66Met and *BE5.2*, of *BDNF* reduce BDNF release. In addition, studies show significant effects of epigenetic changes on the depressive state[53]. Treatment with SSRIs and HDACi antidepressants increases levels of BDNF in peripheral tissues. If BDNF does not increase early after administration, this predicts non-response to antidepressants[55].

**BDNF and antidepressants:** Human studies: The studies on DNA methylation and antidepressant effect in general include a rather low number of subjects but several different antidepressants.

Two studies analyzed H3K27me3 modification, and both reported decreased H3K27me3 in patients with MDD. Chen *et al*[56] performed a study on Caucasians (French Canadian origin, 9 control subjects, 11 MDD subjects without a history of antidepressant use, and 7 MDD subjects who used antidepressants). All MDD subjects died due to suicide. Several different antidepressants were administered: Fluoxetine ($n$ = 1), venlafaxine ($n$ = 2), clomipramine ($n$ = 1), amitriptyline ($n$ = 1), citalopram ($n$ = 1), and doxepin ($n$ = 1). Analysis of the epigenetic modification H3K27me3 in brain tissue from Brodmann area 10 between the control group and the non-medicated MDD group showed no differences. Subjects with a history of antidepressant use showed an increase in *BDNF* IV expression but not *BDNF* I, II, and III expression and a decreased level of H3K27me3 at the *BDNF* IV promoter[56].

Lopez *et al*[57] investigated 25 MDD patients (13 females and 12 males) whose blood levels of total BDNF and H3K27me3 were measured before antidepressant treatment and after 8 wk of citalopram administration. After treatment, there was an elevation of peripheral *BDNF* mRNA in patients responsive to antidepressant treatment and a decrease in H3K27me3 level at promoter IV of the *BDNF* gene[57].

An increase of *BDNF* DNA methylation level after antidepressant administration was shown in three studies. Carlberg *et al*[58] (2014) studied *BDNF* methylation on peripheral blood mononuclear cells of 207 MDD patients and 278 control subjects from Vienna, Austria. From 207 MDD patients, 140 subjects were treated with antidepressant medication and 25 subjects were not. There was an alteration in DNA methylation at the *BDNF* exon I promoter. After antidepressant administration, there was an increase in methylation in MDD patients compared with patients without antidepressant medication and healthy controls[58].

D'Addario *et al*[59] reported that there was an increase in DNA methylation at the *BDNF* promoter in 41 MDD patients with stable pharmacological treatment in comparison to 44 healthy control subjects. In addition, there was a significant reduction in expressed *BDNF* from peripheral blood mononuclear cells in MDD patients than in the control group. Patients who took only SSRIs or selective serotonin and norepinephrine reuptake inhibitors had a higher methylation level of the *BDNF* promoter than patients

who received antidepressants and mood stabilizers[59].

In a study by Wang *et al*[16], 85 Chinese Han patients with MDD (females and males) were treated with escitalopram. Blood samples were tested for DNA methylation in the *BDNF* region. DNA methylation before treatment was significantly lower than after 8 wk of treatment. A difference was seen between remitted and non-remitted patients. Patients with remission had higher DNA methylation than non-remitters[16].

Two studies included analysis of patients who responded and those who did not. In both, higher methylation level was an important contributor to treatment response. Hsieh *et al*[60] included 39 patients with MDD (females and males) and 62 healthy controls (females and males). Higher methylation levels were detected at CpG site 217 and lower methylation level at CpG sites 327 and 362 in the *BDNF* exon IX promoter in MDD patients compared to controls. After drug administration (SSRIs; fluoxetine, paroxetine, and escitalopram), 25 patients who responded to SSRIs had a higher methylation level at CpG sites 24 and 324 than patients who did not respond ($n$ = 11). Methylation analysis results also showed consistent results of BDNF protein level and mRNA level in peripheral blood[60].

A study by Tadić *et al*[52] (2014) included 46 MDD patients (females and males) with different monoaminergic antidepressants prescribed: Escitalopram ($n$ = 5), fluoxetine ($n$ = 2), sertraline ($n$ = 6), venlafaxine ($n$ = 19), duloxetine ($n$ = 2), mirtazapine ($n$ = 6), amitriptyline ($n$ = 1), clomipramine ($n$ = 3), trimipramine ($n$ = 1), or tranylcypromine ($n$ = 1). Although different antidepressants were used, the main observation of the study was the response or non-response to the antidepressant treatment. From 13 CpG sites checked for methylation status on blood samples within the *BDNF* IV promoter, one stood out; antidepressant non-responders had lower methylation at CpG position –87 (relative to the first nucleotide of exon IV). There were no other DNA methylation changes after treatment[52].

Animal studies: In animal models, it has been shown that histone tail modifications significantly affect gene expression and that they are changed after antidepressant administration.

In the study by Park *et al*[34], male Sprague-Dawley rat pups were separated from mothers during early life. Maternal separation evoked a decrease of exon I mRNA *Bdnf*, H3 acetylation (ac) levels and an increase in *Dnmt1* and *Dnmt3a* mRNA level in the hippocampus. After 3 wk of escitalopram administration in adult rats subjected to maternal separation, the result was an increase in BDNF protein, exon I mRNA, levels of H3ac, and a decrease in *Mecp2*, *Dnmt1*, and *Dnmt3a* mRNA levels[34].

Xu *et al*[61] showed that mice stressed in the adolescent period show epigenetic changes also in adult life. Stress in tested male C57BL/6J mice were induced by confrontation of aggressor mice CD1. The expression level of total *Bdnf* and *Bdnf* IV mRNA were decreased in the medial prefrontal cortex (the same results were observed in the hippocampus). *Bdnf* I and VI mRNA levels changed over time in the medial prefrontal cortex. Adult mice had upregulated H3K9me2 in a region downstream of the promoter of the gene *Bdnf* IV, but there were no differences in H3K4me3, H3K9ac, and H3K4ac. Tranylcypromine administration reversed this change and increased levels of H3K4me3. Tranylcypromine is a non-selective MAO inhibitors[61].

Tsankova *et al*[62] showed decreased expression of *Bdnf* III and IV, which manifested in the total level of *Bdnf* mRNA in the hippocampus in chronically defeated BL6/C57 mice. Changes in *Bdnf* III and IV expression persisted a month after cessation of the chronic defeat stress. On the promoter of *Bdnf* III and *Bdnf* IV there was an increase of H3K27me2 but not H3K9me2. Chronic imipramine (a tricyclic antidepressants) administration reversed changes of *Bdnf* expression but did not reverse H3K27me2 to the base level. After chronic social defeat stress and imipramine administration, H3 was hyperacetylated (H3K9/14ac) at the promoter *Bdnf* III and IV, which affected mRNA expression. Furthermore, H3K4me2 was similarly enriched in the *Bdnf* III promoter and correlated with transcriptional activation. There were no changes in H4ac. There was a decrease in *Hdac5* mRNA level but only on chronically stressed mice treated with chronic imipramine. Acute imipramine did not influence *Hdac* level[62].

### *Solute carrier family 6 member 4 and depressive disorder*

Solute carrier family 6 member 4 (*SLC6A4*) is a gene that codes for serotonin transporter. The protein's name comes from the name of the monoamine neurotransmitter serotonin (5-HT) that binds to it. The gene *SLC6A4* was associated with the protein later. Serotonin transporter is an integral membrane protein that transports serotonin from synapse to presynaptic neurons. Besides involvement in regulation of the serotonergic system, *SLC6A4* also acts as an important element of stress susceptibility. Serotonin transporter linked promoter region polymorphism at gene *SLC6A4* has 2 variants, a short allele and a long allele. The short allele results in lower gene transcription and is therefore associated with a depressive state[63]. In addition, there are also several epigenetic studies explaining its dysfunction. Some studies have shown how treatment with classical antidepressants affects epigenetic changes of the *SLC6A4* gene. Therefore, *SLC6A4* is a key target for antidepressant treatment research.

***SLC6A4* and antidepressants:** Human studies: There is a difference in the response to antidepressants seen when analyzing DNA methylation in *SLC6A4* gene. Two studies reported higher methylation status after antidepressant administration and one lower methylation status.

Booij *et al*[64] included in their study 33 MDD patients (females and males). MDD patients who were taking SSRIs had higher methylation levels at CpG 11 and 12 within the regulatory region upstream of the promoter of the *SLC6A4* than patients who did not use antidepressants ($n$ = 36). Research was done

on whole blood samples. There was no association between mRNA expression and DNA methylation [64]. In the study of Okada *et al*[65], peripheral blood was taken from 50 Japanese MDD patients (females and males) before and after antidepressant treatment. Different antidepressants (paroxetine, fluvoxamine, milnacipran) were used in this study. There were no differences in DNA methylation of *SLC6A4* exon I promoter between the healthy control group ($n$ = 50) and patients without antidepressant administration. There was a significant increase in methylation at the CpG 3 site after 6 wk of antidepressant treatment[65].

Domschke *et al*[66] included 61 Caucasian MDD patients who were tested for changes in DNA methylation from blood cells. Administration of escitalopram was evaluated 6 wk after treatment. There was lower average methylation in the transcriptional control region upstream of exon 1A of *SLC6A4* gene. The CpG 2 site specifically stood out from these results[66].

## CONCLUSION

Depressive disorder is affected by dysregulation of many different genes, each contributing a small effect. All hypotheses of depressive disorder involve a variety of changes that can occur in a depressive state. These are a consequence of gene variations or epigenetic changes that affect DNA transcription and/or mRNA translation resulting in imbalanced protein levels regulating the processes in the CNS. With the development of technologies and new knowledge, epigenetic research has become accessible for investigation in the field of psychiatry. Among candidate genes particular interest was placed on *BDNF, NR3C1,* and *SLC6A4*, as their roles in CNS regulation have been identified in association with response to external stress stimuli and mood regulation. Although the research has been fairly extensive, we still cannot identify a reliable biomarker or a set of them, either proteomic or (epi)genetic, to be used in a clinical setting.

However, in many studies scientists discuss the importance of epigenetic factors (DNA methylation and histone modifications) as playing a key role in predicting antidepressant response. The aggregation of subthreshold levels of the epigenetic changes in several different genes might show alterations caused by a depressive state. It appears that to date we have uncovered a few pieces of the jigsaw puzzle but that more studies are needed for understanding this complex disorder. For example, it has been determined that classical antidepressants change the epigenome, and it has been proposed that this effect might be an important contributor to treatment. These results have triggered further investigation of drugs targeting epigenetic modifiers (HDACs, histone methyltransferases). HDACis seem to be promising drugs, but there are no HDACis used for depression treatment.

Further research in clinical settings will be important to determine which epigenetic markers are informative for treatment response prediction and which markers actually change as a response to treatment. Although the field of pharmacoepigenetics is only starting to develop, we can already identify some potential genes that we can expect to become biomarkers with clinical value. With rapid technological advancement, enabling determination of markers from multi-omic data with the use of artificial intelligence and carefully designed studies in the growing field of psychiatry, we could expect to obtain relevant biomarkers that could be used by clinicians as meaningful guidance in addition to clinical interviews in the future. With the development of the field of pharmacoepigenetics, it will be possible to move towards personalized treatments, where combinations of genetic and environmental factors will need to be incorporated in treatment selection.

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ORIGINAL ARTICLE

Case Control Study

# Delayed improvements in visual memory task performance among chronic schizophrenia patients after high-frequency repetitive transcranial magnetic stimulation

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## Abstract

### *BACKGROUND*

Cognitive impairments are core characteristics of schizophrenia, but are largely resistant to current treatments. Several recent studies have shown that high-frequency repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (DLPFC) can reduce negative symptoms and improve certain cognitive deficits in schizophrenia patients. However, results are inconsistent across studies.

### *AIM*

To examine if high-frequency rTMS of the DLPFC can improve visual memory deficits in patients with schizophrenia.

### *METHODS*

Forty-seven chronic schizophrenia patients with severe negative symptoms on

stable treatment regimens were randomly assigned to receive active rTMS to the DLPFC ($n$ = 25) or sham stimulation ($n$ = 22) on weekdays for four consecutive weeks. Patients performed the pattern recognition memory (PRM) task from the Cambridge Neuropsychological Test Automated Battery at baseline, at the end of rTMS treatment (week 4), and 4 wk after rTMS treatment (week 8). Clinical symptoms were also measured at these same time points using the Scale for the Assessment of Negative Symptoms (SANS) and the Positive and Negative Syndrome Scale (PANSS).

***RESULTS***

There were no significant differences in PRM performance metrics, SANS total score, SANS subscores, PANSS total score, and PANSS subscores between active and sham rTMS groups at the end of the 4-wk treatment period, but PRM performance metrics (percent correct and number correct) and changes in these metrics from baseline were significantly greater in the active rTMS group at week 8 compared to the sham group (all $P < 0.05$). Active rTMS treatment also significantly reduced SANS score at week 8 compared to sham treatment. Moreover, the improvement in visual memory was correlated with the reduction in negative symptoms at week 8. In contrast, there were no between-group differences in PANSS total score and subscale scores at either week 4 or week 8 (all $P > 0.05$).

***CONCLUSION***

High-frequency transcranial magnetic stimulation improves visual memory and reduces negative symptoms in schizophrenia, but these effects are delayed, potentially due to the requirement for extensive neuroplastic changes within DLPFC networks.

**Key Words:** Cognition; High-frequency repetitive transcranial magnetic stimulation; Non-invasive brain stimulation; Randomized controlled study; Schizophrenia; Visual memory deficits

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**Core Tip:** The main objective of this study was to evaluate the efficacy of high-frequency repetitive transcranial magnetic stimulation (rTMS) in the treatment of visual memory disorders in schizophrenia. Forty-seven patients with chronic schizophrenia who had significant negative symptoms during stabilization therapy were randomly assigned to two groups: Active rTMS over dorsolateral prefrontal cortex ($n$ = 25) or false stimulation ($n$ = 22) for 4 wk, followed by 4 wk of follow-up. Our results suggest that high-frequency transcranial magnetic stimulation improves visual memory function and relieves negative symptoms in patients with schizophrenia, but with a delay.

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## INTRODUCTION

Schizophrenia is a chronic psychiatric disorder characterized by distorted thinking and perception[1]. A comprehensive epidemiological survey reported a median prevalence of 15.2/100000 persons, but individual prevalence estimates in various regions have varied from 7.7–43.0/100000[2], potentially due to genetic factors, diagnostic standards, and the heterogeneity of symptom presentation. The clinical symptoms of schizophrenia are divided into three groups or domains: Positive symptoms such as hallucinations, negative symptoms such as flat affect and anhedonia, and cognitive symptoms, and the predominance of different symptom clusters in individual patients determines the treatment strategy and influences long-term outcome[1,3]. At present, the main treatments for schizophrenia are antipsychotics, but these agents are effective only against positive symptoms[3], while it remains more difficult to improve the negative and cognitive symptoms of chronic schizophrenia even during long-term hospitalization.

Cognitive impairments in schizophrenia include deficits in attention, executive functions such as response inhibition and working memory, verbal learning and memory, and social memory[4] that vary

markedly in severity among individual patients. These symptoms may be detectable prior to clinical disease onset and remain relatively stable over time despite improvements in other symptoms[4,5]. Further, these cognitive deficits contribute to functional disability and predict poor life outcome[4,6,7]. Visual memory is a critical faculty for various forms of learning and for daily activities such as employment. Although prior research has indicated that visual memory impairments are minor in comparison to other cognitive impairments[8], a recent study found that patients with a family history of schizophrenia have considerably worse visual memory scores[9]. Furthermore, several earlier studies reported that patients with schizophrenia have poor visual memory[10,11] and that improvement is associated with better job retention and successful recovery[8]. Thus, any improvement in visual memory that occurs during treatment could be broadly beneficial, especially to patients with a family history of schizophrenia[9].

The prefrontal cortex (PFC) is critical for executive functions such as working memory, cognitive flexibility, and behavioral inhibition; some or all of which may be disrupted in psychiatric disorders including depression, anxiety and schizophrenia. A recent study of patients with bilateral lesions in the ventromedial (vm)PFC[12,13] revealed deficits in the acquisition of Pavlovian threat conditioning (*i.e.*, emotional learning). A recent theoretical review[14,15] on the neurobiology of emotional conditioning concluded that the vmPFC is fundamental for the representation and evaluation of safety- and threat-related information and thus for the relative influence of this information on sustained physiological responses. Imaging studies of patients with depression exhibiting executive dysfunction also revealed damage to dorsolateral prefrontal circuits[16,17]. Therefore, the PFC is a promising target for therapeutic interventions aimed at treating the cognitive and emotional symptoms of schizophrenia. In addition, some scholars proposed that the anatomical–functional interplay between the PFC and heart-related dynamics in human emotional conditioning (learning) and proposes a theoretical model to conceptualize these psychophysiological processes, the neurovisceral integration model of fear, that can be impaired in the context of psychiatric disorders (as schizophrenia)[18-20].

While antipsychotic drugs clearly benefit positive symptoms, they may also disrupt attention and memory in unimpaired subjects. In this regard, atypical antipsychotics are less deleterious than conventional antipsychotics. Nonetheless, cognitive dysfunction is still a major predictor of poor clinical and life outcome among patients with schizophrenia, necessitating the continued development of interventions for improving cognitive function[21]. Among potential treatments, nonpharmaceutical and noninvasive treatments may be particularly effective as patient noncompliance to drug treatment is a major obstacle to effective long-term patient management. Repetitive transcranial magnetic stimulation (rTMS) is one such alternative as it is noninvasive, well-tolerated, and has demonstrated efficacy for the treatment of various psychiatric and neurological diseases, in particular in treatment-resistant depression (TRD), for which it has received United States Food and Drug Administration approval[22,23]. However, studies of clinical efficacy for schizophrenia treatment have thus far reported inconsistent results, possibly to heterogeneity in illness factors (such as duration of illness and baseline psychopathology), assessment methods (such as the assessment tool used and evaluation of bias), and stimulation parameters (such as stimulus location, frequency, intensity and duration)[24,25]. Due to these discrepancies, several meta-analyses have been conducted to investigate the impact of rTMS on the clinical symptoms of schizophrenia[5,26], and a recent report concluded that rTMS of the dorsolateral PFC (DLPFC) is an effective method for the treatment of negative symptoms[24]. A more recent meta-analysis concluded that 1-Hz rTMS had a significant therapeutic effect on auditory hallucinations[27]. In contrast, the same study found no significant effect of 10-Hz rTMS on negative symptoms compared to sham treatment. However, there has been no examination on the efficacy of rTMS targeting the DLPFC on cognitive symptoms such as visual memory. Here, we examined this question and presented possible reasons for the differential efficacy of previous protocols[8-11].

Given the major influence of cognitive dysfunction on long-term outcome, cognitive improvement should be a primary treatment goal[27,28]. Second-generation antipsychotic drugs have been shown to improve positive symptoms, but have little effect on negative symptoms and cognitive deficits[7,28,29]. Alternatively, nonpharmacological interventions such as cognitive remedial training and aerobic exercise have shown promising results for the treatment of cognitive impairment[30]. As well, a previous open label study reported that 1-Hz rTMS of the left temporal parietal cortex and 10-Hz rTMS of the DLPFC improved short-term auditory verbal memory[31]. Wölwer *et al*[21] also reported improved facial affect recognition, a critical component of social cognition, in schizophrenia patients following 10 Hz rTMS to the left DLPFC[21]. A double-blind sham-controlled randomized treatment trial found that 20-Hz rTMS of the bilateral DLPFC improved working memory as measured by the three-back task[32]. However, Mittrach *et al*[33] did not find any beneficial effect of 10-Hz rTMS of the DLPFC on long-term verbal memory, attention, or frontal executive functioning. Similarly, a recent randomized sham-controlled trial including schizophrenia patients with prominent negative symptoms found that active 10-Hz rTMS of the left DLPFC was no more effective than sham treatment for improving cognitive performance[34]. In contrast, we found that rTMS of the left DLPFC can improve the negative symptoms of schizophrenia[35].

Therefore, the primary objective of the current randomized, double-blind sham-controlled study was to examine if a similar rTMS protocol improved visual memory performance. Accordingly, chronic schizophrenia patients with marked negative symptoms among the Chinese Han population were

randomized to receive five sessions *per* week of high-frequency rTMS to the left DLPFC or sham stimulation and were examined periodically for visual memory performance. We hypothesized that visual memory performance would be improved to a greater degree by real rTMS than sham treatment. The secondary objective was to analyze the association between improvement in visual memory and negative symptoms during and following rTMS treatment. This study highlighted the therapeutic potential of rTMS targeting the DLPFC for schizophrenia patients with predominant negative and cognitive symptoms. More broadly, rTMS may be an effective component of more precise and individualized treatment regimens for neurologic and psychiatric disorders.

## MATERIALS AND METHODS

### Subjects

The subjects of this study also participated in our previous clinical trial published in 2016[35]. Forty-seven schizophrenia inpatients were recruited from Suzhou Guangji Hospital, a city-owned psychiatric hospital in Suzhou City, from June 2013 to May 2015. The inclusion criteria were: (1) Meeting ICD-10 diagnostic criteria for schizophrenia according to two senior psychiatrists; (2) Eight-handed; (3) Aged 20–60 years and Han Chinese ancestry; (4) ≥ 5-years' duration of illness; (5) Antipsychotic medication fixed for at least 12 mo before enrollment; and (6) Marked negative symptoms as evidenced by a score ≥ 20 on the Scale for the Assessment of Negative Symptoms (SANS). Baseline demographic and clinical characteristics of the study population are summarized in Table 1.

All subjects received a complete medical history review and detailed physical examinations. We excluded candidates with physical diseases such as aneurysm, seizure, stroke, and cardiovascular disorders as well as patients with illegal drug or alcohol abuse/dependence.

This study was approved by the Institutional Review Board of Suzhou Guangji Psychiatric Hospital and each subject provided written informed consent prior to participation following a full explanation of project goals, methods, and risks by a research staff member. All study procedures were performed in accordance with the Declaration of Helsinki. This clinical trial was registered with https://www.clinicaltrials.gov/ on September 5, 2017 as NCT03273439 (5/9/2017).

### Design

This was a single-center, randomized, sham-controlled, double-blinded study conducted as described in our previous report[35]. Briefly, participants received active or sham rTMS on all weekdays for 4 wk (20 sessions in total). Antipsychotic medications and all other medications remained unchanged during treatment. Clinical assessments and cognitive tests were performed at baseline, after the 4-wk treatment (week 4) and 4 wk post-treatment (week 8).

### Active and sham rTMS

Repetitive TMS was delivered through a figure-of-eight coil connected to a MAGPRO-R30 magnetic stimulator (Medtronic DantecNeuroMuscular, Skovlunde, Denmark). Prior to each TMS or sham administration, motor threshold (MT) at the left primary motor cortex (M1) was determined as the lowest possible energy required to produce at least five potentials ≥ 0.05 mV in 10 trials from the X. During each active rTMS session, thirty 5-s trains of 10 Hz stimulation were delivered in 30-s intervals at 110% of MT over the left DLPFC (defined as the F3 position of the 10–20 electroencephalogram system). These trains were administered once each weekday for four consecutive weeks (for a total of 30000 individual stimuli). The left DLPFC was chosen as the rTMS target because the majority of previous studies performed rTMS on DLPFC[5,24]. For sham rTMS, all procedures were identical except that the figure-of-eight coil was rotated 180° during stimulator activation. Since rTMS machine was used in a blinded fashion in this study, the coil was thick enough and had a magnetic shielding function (Figure 1).

### Psychopathological measures

General psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS). Negative symptoms were also assessed with the SANS, which consists of 19 items assessing five symptoms of the negative dimension: Affect flattening, alogia, avolition-apathy, anhedonia-asociality, and poor attention. Two clinical psychiatrists blinded to treatment condition (real *vs* sham rTMS) assessed PANSS and SANS scores at baseline, at weeks 4 and 8. Inter-rater reliability was satisfactory for both tests (κa = 0.88 for PANSS and κa = 0.86 for SANS).

### Cognitive performance

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a widely used computerized assessment tool for cognition in schizophrenia. Since the patients in this study had relatively long disease histories (> 20 years) and most had not received any higher education (Table 1), only the pattern recognition memory (PRM) component of the CANTAB, a relatively straightforward two-choice forced

**Table 1 Demographic and baseline clinical characteristics of active and sham repetitive transcranial magnetic stimulation groups**

| | Active rTMS (*n* = 25) | Sham rTMS (*n* = 22) | $\chi^2$ or F | *P* value |
|---|---|---|---|---|
| **Sex (male/female)** | 12/13 | 11/11 | 0.02 | 0.89 |
| **Age (yr)** | 45.9 ± 10.0 | 45.1 ± 10.4 | 0.05 | 0.83 |
| **Education (yr)** | 13.0 ± 4.7 | 12.5 ± 5.7 | 0.11 | 0.74 |
| **Age of onset (yr)** | 22.3 ± 6.3 | 25.2 ± 7.5 | 2.48 | 0.13 |
| **Antipsychotics** | | | 0.42 | 0.94 |
| Clozapine | 14 | 12 | | |
| Quetiapine | 3 | 4 | | |
| Aripiprazole | 3 | 2 | | |
| Risperidone | 3 | 1 | | |
| Olanzapine | 1 | 2 | | |
| Chlorpromazine | 1 | 1 | | |
| **Daily antipsychotic dose (mg) (chlorpromazine equivalent)** | 323.5 ± 193.1 | 341.7 ± 168.7 | 0.08 | 0.78 |
| **PANSS total score** | 72.1 ± 15.3 | 69.3 ± 11.5 | 0.45 | 0.51 |
| P-subscore | 12.6 ± 4.0 | 10.0 ± 3.3 | 3.52 | 0.07 |
| N-subscore | 26.7 ± 7.5 | 25.9 ± 6.9 | 0.25 | 0.62 |
| G-subscore | 33.8 ± 6.0 | 33.4 ± 5.4 | 0.01 | 0.91 |
| **SANS total score** | 88.1 ± 17.9 | 88.1 ± 15.2 | 0.18 | 0.68 |
| Affect flattening | 23.5 ± 5.8 | 24.1 ± 5.8 | 0.09 | 0.76 |
| Alogia | 16.0 ± 4.6 | 16.3 ± 3.4 | 0.12 | 0.73 |
| Avolition-apathy | 14.0 ± 3.1 | 14.6 ± 3.1 | 0.05 | 0.83 |
| Anhedonia-Asociality | 21.4 ± 3.3 | 21.7 ± 3.2 | 0.27 | 0.61 |
| **Attention** | 11.6 ± 2.3 | 11.4 ± 3.0 | 0.2 | 0.66 |
| **PRM-number correct** | 14.7 ± 4.0 | 15.5 ± 3.7 | 0.47 | 0.5 |
| **PRM-percent correct (%)** | 61.3 ± 16.9 | 64.6 ± 15.6 | 0.47 | 0.5 |

rTMS: Repetitive transcranial magnetic stimulation; P: Positive symptom; N: Negative symptom; G: General psychopathology; SANS: Scale for the Assessment of Negative Symptoms; PRM: Pattern recognition memory; PANSS: Positive and Negative Symptom Scale.

discrimination task, was administered. Subjects were presented with a series of 12 visual geometric patterns, one at a time, at the center of the screen (first presentation phase) and then were required to choose between an already seen pattern and a novel pattern (first recall phase). In the recall phase, previously viewed patterns were presented in reverse order from original presentation. Then, a new series of patterns was presented, followed by a second recognition test given either immediately or after a delay (20 min) to test delayed recognition memory. Performance on the PRM is measured as the number and proportion (%) of correct responses, with a maximum score of 100 (best pattern recognition memory).

### *Statistical analysis*

Continuous variables were first tested for normality using the Kolmogorov–Smirnov one-sample test ($P < 0.05$). All continuous datasets met this criteria, so they were presented as mean ± SD. Continuous baseline variables were compared between active and sham rTMS groups by independent samples *t*-test. Categorical variables were presented as frequency and compared by $\chi^2$ test. Data were analyzed using the intention-to-treat principle so missing data points were replaced with the last observation.

The primary objective of this study was to evaluate the effect of rTMS on visual recognition memory in patients with schizophrenia. Since all variables were normally distributed according to the Kolmogorov–Smirnov one-sample test, the principal outcome (visual memory performance as measured by % correct) was analyzed by repeated-measures analyses of variance with measurement time (baseline and weeks 4 and 8) as the within-group factor and active *versus* sham rTMS as the

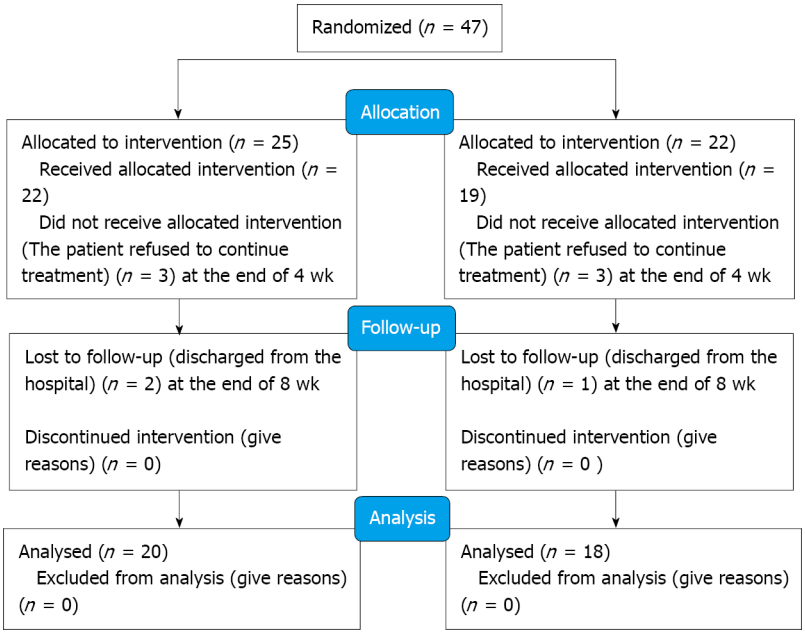


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**Figure 1 Flow diagram.**

between-group factor. If the time × group interaction was significant, analysis of covariance (ANCOVA) was used to test for differences between groups at the end of weeks 4 and 8, with baseline score as the covariate. If the interaction was not significant, no further statistical tests were performed. The same method was used to analyze changes in PANSS and SANS scores.

The second objective was to determine whether negative symptoms (SANS scores) were correlated with PRM performance (number and proportion correct) in the active and sham rTMS groups before and after treatment. Correlations between changes in SANS scores and visual memory performance were examined by Pearson correlation coefficients, and when significant, the Bonferroni correction was used. Finally, multiple linear regression was used to investigate potential response predictors associated with changes in visual memory scores.

All statistical analyses were conducted using SPSS version 18.0. $P \leq 0.05$ (two-tailed) was considered significant for all tests. In cases with multiple comparisons, $P$ values were adjusted by Bonferroni correction.

## RESULTS

### *Demographic and basic descriptive data*

The full details of this clinical trial examining the effects of DLPFC-targeted rTMS on schizophrenia symptoms were reported previously[35]. In total, 47 patients were randomly divided into an active rTMS group ($n$ = 25) and sham rTMS group ($n$ = 22). However, six subjects withdrew their consent before starting treatment (three in the active and three in the sham rTMS groups). Therefore, 41 participants completed the full set of clinical trial, including 22 in the active rTMS group and 19 in the sham rTMS group.

At baseline, there were no significant differences in demographic variables, PANSS total and subscale scores, SANS total and subscale scores, PRM-number correct, and PRM-percent correct between active and sham rTMS treatment groups (Table 1). Consistent with a potential association between negative symptoms and poor visual memory, PRM performance metrics (number correct and percent correct) at baseline were negatively correlated with SANS total score and all subscale scores ($P$ < 0.05–0.001) except for the affect flattening subscale ($P$ > 0.05).

### *Efficacy of rTMS treatment for improving cognitive performance*

Three participants were lost to follow-up due to premature discharge before week 8 (2 in the active group and 1 in the sham rTMS group), so treatment efficacy analysis included 20 patients in the active group and 18 in the sham group. Repeated measures ANCOVA revealed a significant test time (baseline *vs* week 4 *vs* week 8) × group interaction (F = 22.1, df = 274, $P$ < 0.001) and a significant main effect of test time (F = 13.2, df = 274, $P$ < 0.001) on PRM performance, but no significant effect of group (F =1.37, df = 137, $P$ = 0.25). However, the PRM-number correct was significantly higher in the active rTMS group

than the sham group at week 8 (F = 16.8, df = 137, $P < 0.001$; effect size = 1.35) but not immediately after the 4-week treatment period (F = 0.49, df = 136, $P = 0.48$). The difference at week 8 was still significant after controlling for the effects of sex, age, disease duration, and drug dose (chlorpromazine equivalent) (F = 19.2, df = 133, $P < 0.001$), while the difference at week 4 did not reach significance (F = 0.63, $P = 0.43$).

In the active rTMS group, the mean number of correct answers on the PRM test increased by 4.54 ± 2.98 from baseline to week 8, while the correct number in the sham group decreased slightly (-0.92 ± 2.72) and the difference between these changes was highly significant (mean 5.46 ± 0.92, 95%CI: 3.43–7.14, F = 33.3, df = 137, $P < 0.0001$, effect size = 0.474) (Table 2). However, from baseline to week 4, there was no significant difference in the correct response change between groups (0.41 ± 4.1 *vs* −0.62 ± 2.8, F = 0.75, $P = 0.39$). rTMS treatment also significantly shortened select time (Figure 2A) and interval time (Figure 2B) in PRM from baseline to week 8 compared to the sham group. We can see that the treatment group decreased with the selection time and interval time in PRM compared with the control group at week 8.

### *rTMS treatment for psychopathological symptoms*

Changes in PANSS and SANS total scores as well as subscale scores (secondary outcomes) are also summarized in Table 2. These SANS results are included from our previous study[35] for comparison and to assess the relationship between effects on negative symptoms and visual recognition memory following rTMS. By the end of 4 wk of treatment, there were no significant differences in SANS total score, all five SANS subscale scores, PANSS total score, and PANSS subscale scores between active and sham rTMS groups (all $P > 0.05$). At 8 wk, however, SANS total score as well as avolition/apathy, anhedonia/asociality, and attention subscores were significantly lower (improved) in the active rTMS group compared to the sham group (all $P < 0.05$) (Table 2). Alternatively, there were no between-group differences in PANSS total and subscale scores at week 4 and week 8 compared to baseline (all $P > 0.05$).

### *Relationship between improvement in cognitive ability and changes in psychopathological symptoms*

The increase in PRM-number correct from baseline to week 8 was significantly correlated with the changes in SANS total score ($r = 0.34$, df = 38, $P = 0.034$; Figure 3), SANS alogia subscale score ($r = 0.37$, df = 38, $P = 0.024$), and SANS avolition/apathy subscale score ($r = 0.34$, df = 38, $P = 0.037$). However, none of these univariable correlations were significant after Bonferroni correction (all $P > 0.05$). Multiple regression analysis revealed a significant association between the increase in PRM-number correct and the change in SANS total score from baseline to week 8 (= 0.42, $t = 2.53$, $P = 0.017$).

## DISCUSSION

The key results of this study were as follows. (1) DLPFC-targeted 10-Hz rTMS (20 single weekday sessions over 4 wk) had a significant therapeutic effect on the visual recognition memory deficit exhibited by schizophrenia patients with strong negative symptoms, but this response was delayed until several weeks after the end of treatment; and (2) This improvement in visual recognition memory was associated with a reduction in negative symptoms. The delay between treatment and response may help explain previous inconsistencies among studies on the therapeutic efficacy of rTMS.

There is growing acceptance of noninvasive brain stimulation (NIBS) techniques for the treatment of cognitive deficits[7], but only a few studies have examined the efficacy of rTMS for cognitive impairments in schizophrenia. Here, we showed that this specific NIBS regimen can mitigate multiple core symptoms of schizophrenia. Furthermore, this regimen may be a promising therapeutic option for other disorders presenting with emotional dysregulation and cognitive dysfunction. Recent studies have reported that NIBS stably mitigates psychiatric symptoms by noninvasively modulating the abnormal activity of neural circuits (*i.e.*, amygdala–PFC–hippocampus pathways) involved in the regulation of mood and cognition[36]. For instance, a recent review suggested that NIBS can improve mood by modulating emotional memories, while others[37,38] have reported that NIBS can suppress abnormally persistent fear memories in anxiety disorder patients that do not respond to psychotherapy and/or anxiolytic drugs. Multiple studies have also demonstrated the value of NIBS as a research tool for examining the neurological mechanisms underlying depression and anxiety in schizophrenia and other psychiatric disorders[39,40]. For instance, NIBS to the DLPFC after memory reactivation was reported to reduce the subsequent response to learned fear, suggesting that stimulation alters the synaptoplastic processes re-engaged during memory retrieval (term reconsolidation)[41-43]. In accordance with the current study, Barr and colleagues reported that daily 20-Hz rTMS of the DLPFC for 4 wk significantly improved working memory compared to sham stimulation in schizophrenia patients as measured by a three-back task[32]. More impressively, three-back accuracy was similar to that of healthy subjects after treatment[32]. Taken together, these findings suggest that high-frequency rTMS may be an effective treatment for visual and working memory deficits in patients with schizophrenia. In contrast, however, Prikryl and colleagues reported that 15-Hz rTMS over the left DLPFC for 4 wk had no significant effect

**Table 2 Cognitive performance measures and clinical symptoms at baseline, week 4, and week 8 in active repetitive transcranial magnetic stimulation and sham multichannel transcranial magnetic stimulation groups**

| | Baseline (*n* = 47) | Week 4 (*n* = 41) | Week 8 (*n* = 38) | Group F (*P* value) | Time F (*P* value) | Group × Time F (*P* value) |
|---|---|---|---|---|---|---|
| **PRM-number correct** | | | | 1.37 (0.25) | 13.2 (< 0.001) | 22.1 (< 0.001) |
| rTMS (*n* = 25) | 14.7 ± 4.0 | 15.1 ± 3.8 | 19.2 ± 2.7[c] | | | |
| Sham (*n* = 22) | 15.5 ± 3.7 | 14.9 ± 4.4 | 14.6 ± 4.1 | | | |
| **SANS total score** | | | | 0.89 (0.35) | 38.11 (< 0.001) | 11.36 (0.002) |
| rTMS | 88.1 ± 17.9 | 79.0 ± 21.5 | 72.5 ± 16.8[a] | | | |
| Sham | 88.1 ± 15.2 | 83.6 ± 19.2 | 83.5 ± 20.5 | | | |
| **Affect flattening** | | | | 0.39 (0.54) | 43.56 (< 0.001) | 6.83 (0.013) |
| rTMS | 23.5 ± 5.8 | 20.1 ± 6.7 | 18.8 ± 4.8 | | | |
| Sham | 24.1 ± 5.8 | 22.5 ± 5.9 | 21.9 ± 6.7 | | | |
| **Alogia** | | | | 0.23 (0.64) | 8.27 (0.007) | 5.30 (0.027) |
| rTMS | 16.0 ± 4.6 | 15.0 ± 4.7 | 13.6 ± 3.6 | | | |
| Sham | 16.3 ± 3.4 | 15.9 ± 4.1 | 16.1 ± 5.1 | | | |
| **Avolition-apathy** | | | | 1.56 (0.22) | 29.56 (< 0.001) | 10.00 (0.003) |
| rTMS | 14.0 ± 3.1 | 12.4 ± 3.5 | 11.4 ± 2.6[a] | | | |
| Sham | 14.6 ± 3.1 | 14.1 ± 3.9 | 14.0 ± 3.9 | | | |
| **Anhedonia-Asociality** | | | | 1.48 (0.23) | 1.48 (0.23) | 3.84 (0.058) |
| rTMS | 21.4 ± 3.3 | 20.0 ± 3.9 | 29.9 ± 6.5[a] | | | |
| Sham | 21.7 ± 3.2 | 20.8 ± 3.8 | 31.9 ± 6.0 | | | |
| **Attention** | | | | 0.70 (0.41) | 37.00 (< 0.001) | 11.61 (0.002) |
| rTMS | 11.6 ± 2.3 | 9.9 ± 2.9 | 8.7 ± 2.2[a] | | | |
| Sham | 11.4 ± 3.0 | 10.4 ± 3.7 | 10.6 ± 3.5 | | | |
| **PANSS total score** | | | | 0.03 (0.86) | 60.02 (< 0.001) | 8.42 (0.006) |
| rTMS | 72.1 ± 15.3 | 65.3 ± 15.9 | 64.6 ± 16.8 | | | |
| Sham | 69.3 ± 11.5 | 61.9 ± 16.6 | 63.1 ± 14.3 | | | |
| **P-subscore** | | | | 2.99 (0.09) | 1.05 (0.313) | 0.50 (0.49) |
| rTMS | 12.6 ± 4.0 | 12.4 ± 4.0 | 12.5 ± 4.0 | | | |
| Sham | 10.0 ± 3.3 | 10.5 ± 3.9 | 10.3 ± 3.6 | | | |
| **N-subscore** | | | | 0.01 (0.93) | 77.76 (< 0.001) | 10.12 (0.003) |
| rTMS | 26.7 ± 7.5 | 22.8 ± 8.8 | 21.0 ± 7.1 | | | |
| Sham | 25.9 ± 6.9 | 22.6 ± 7.5 | 23.1 ± 7.6 | | | |
| **G-subscore** | | | | 0.31 (0.58) | 37.90 (< 0.001) | 5.38 (0.026) |
| rTMS | 33.8 ± 6.0 | 30.3 ± 6.6 | 29.9 ± 6.5 | | | |
| Sham | 33.4 ± 5.4 | 31.7 ± 6.2 | 31.9 ± 6.0 | | | |

[a]*P* < 0.05.
[c]*P* < 0.001.
rTMS: Repetitive transcranial magnetic stimulation; PANSS: Positive and Negative Symptom Scale; P: Positive symptom; N: Negative symptom; G: General psychopathology; SANS: Scale for the Assessment of Negative Symptoms; PRM: Pattern recognition memory.

on working memory performance in schizophrenia patients[44]. Thus, the efficacy of different rTMS regimens for the cognitive deficits of schizophrenia requires further investigation in larger clinically heterogenous populations.

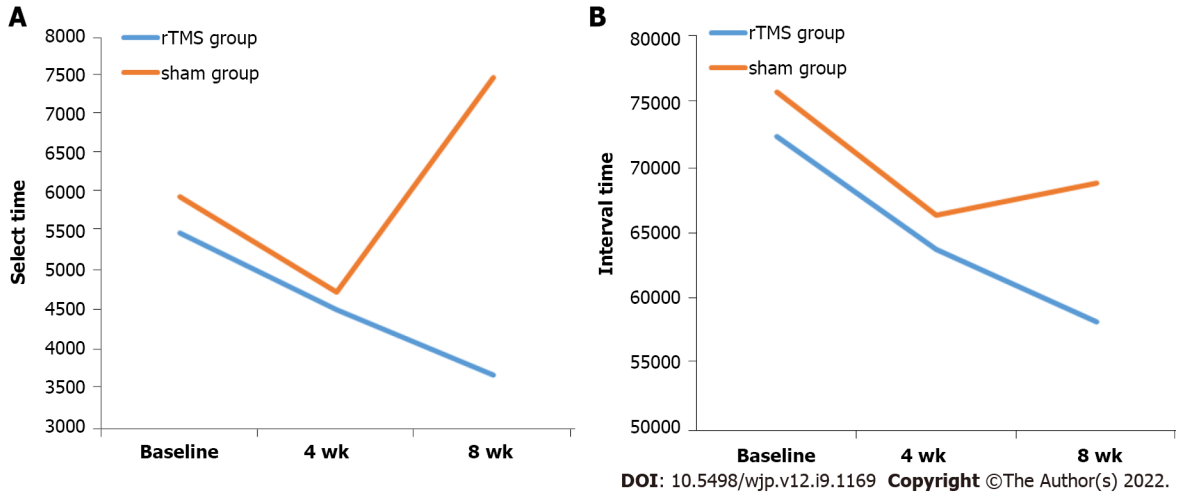

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**Figure 2 Repetitive transcranial magnetic stimulation treatment also significantly shortened select and interval time in pattern recognition memory from baseline to week 8 compared to the sham group.** A: Select time; B: Interval time. rTMS: Repetitive transcranial magnetic stimulation.

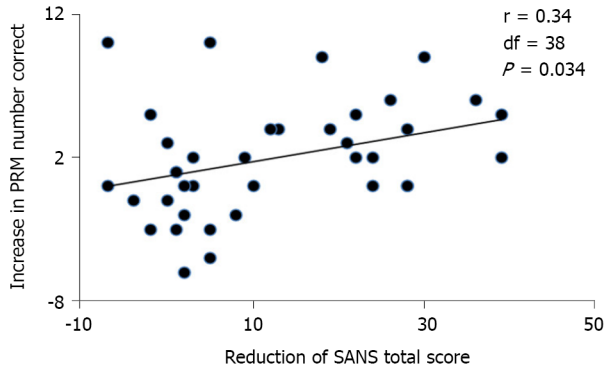

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**Figure 3 The increase in pattern recognition memory-number correct from baseline to week 8 was significantly correlated with the reduction in Scale for the Assessment of Negative Symptoms total score ($P < 0.05$).** This association was confirmed by multiple regression analysis (beta = 0.42, $t = 2.53$, $P = 0.017$). PRM: Pattern recognition memory; SANS: Scale for the Assessment of Negative Symptoms.

In our recently published study[35], we reported that high-frequency rTMS over the left DLPFC for four consecutive weeks reduced the negative symptoms of schizophrenia compared to sham rTMS[42-45], consistent with numerous studies using rTMS to treat the negative symptoms of schizophrenia[42,43,46-50] but in contrast to many others[34,42,43,51,52]. Further, multiple meta-analyses have also found mixed results[26,53-55]. Our previous and current findings provide a potential explanation for these discrepancies as the effects of multichannel TMS (mTMS) on both SANS scores and PRM task performance were not statistically significant until several weeks post-treatment. The exact reasons for these delayed effects are unclear but are not unusual following NIBS. For example, a recent randomized, sham-controlled two-arm study reported that active intermittent theta burst transcranial stimulation (iTBS) of the left DLPFC significantly reduced negative symptom severity in treatment-resistant schizophrenia patients compared to sham iTBS at 6 mo after the end of treatment[56]. Similarly, a randomized, double-blind, sham-controlled crossover study of accelerated iTBS for 2 wk in patients with TRD found a greater response rate (defined as a 50% reduction in Hamilton Depression Rating Scale score) after two additional weeks compared to immediately after treatment[57]. We speculate that this delay is due to the slow nature of the changes underlying reversal of negative symptoms, such as circuit-level plasticity and improvements facilitated by interpersonal relationships and social activities occurring over an extended period after treatment. In addition, plasticity may also take longer in older patients such as those examined in the current study. Further studies are warranted to test these and other potential mechanisms.

The improvement in visual recognition memory performance (increased number of correct responses) correlated significantly with a decrease in SANS total score at week 8 but not week 4. Moreover, PRM-number correct was correlated with SANS total score and all subscale scores except the affect flattening

subscale at baseline, suggesting shared neurological mechanisms. It is known that both cognitive deficits and negative symptoms of schizophrenia are associated with generalized dopamine (DA) signaling deficits in cortical and extrastriatal regions[58], and recent studies have shown that prefrontal hypodopaminergia can cause striatal DA disorders that in turn can lead to cognitive impairments[59,60]. Conversely, increasing DA release by administering low or moderate doses of psychostimulants improved negative symptoms and cognitive deficits in schizophrenia[60]. High-frequency rTMS applied over the left PFC also increased the release of DA in mesostriatal brain pathways[46] possibly accounting for improved negative symptoms and cognitive deficits. However, a host of other therapeutic mechanism may contribute, warranting further clinical and preclinical investigations.

This study had several limitations. First, the sample size was small, limiting statistical power and precluding exploratory subgroup analyses. Second, due to the homogeneity of the study population, these findings may not be applicable to other ethnic groups, patients in earlier phases of the disease including untreated first-episode patients, and those with distinct symptom clusters. Third, 180° rotation of the figure-of-eight coil did not completely prevent brain stimulation, so a real sham coil should be used in subsequent studies. Fourth, carrying forward the last observation is less suitable for small samples, although this was necessary in only a small portion of individual datasets. Fifth, the 4-wk follow-up period may not be sufficient to measure the full extent (or stability) or symptom improvement. Indeed, previous studies have monitored patients for 3 to 12 mo following treatment. Sixth, it is possible that visual recognition memory is particularly responsive to rTMS, so more comprehensive evaluations are required to establish clinical efficacy, including effects on executive functions, which are markedly impaired in many patients with schizophrenia. Seventh, it is uncertain if some patients recognized the specific treatment (active or shame) as we did not compensate for possible somatosensory effects. Eighth, we chose the left DLPFC based on past studies but other sites may be more effective. In addition, we did not use neuronavigation to determine the location of the DLPFC, which may introduce response heterogeneity. Finally, although antipsychotic drugs were included as covariates in statistical analysis, the different antipsychotic regimens may have distinct effects on the efficacy of rTMS.

## CONCLUSION

High-frequency rTMS targeting the DLPFC can improve visual recognition memory in patients with schizophrenia. This high-frequency rTMS protocol may be of substantial clinical value because cognitive deficits are a major barrier to recovery and predict adverse clinical outcomes in patients with schizophrenia and other psychiatric disorders. Although the results of our study are encouraging, larger-scale studies with longer follow-up are needed to confirm the effectiveness of DLPFC-targeted rTMS for the treatment of cognitive deficits in first-episode schizophrenia patients and patients of different ethnicities. Moreover, therapeutic effects on other cognitive domains and the underlying mechanisms warrant further investigation.

## ARTICLE HIGHLIGHTS

### *Research background*

At present, antipsychotic drug therapy has little effect on the improvement of some psychiatric symptoms in schizophrenia patients, and drug therapy is not acceptable due to the unbearable adverse drug reactions. There is growing evidence that repetitive transcranial magnetic stimulation (rTMS) is effective for both positive and negative symptoms of schizophrenia.

### *Research motivation*

Schizophrenia has brought great burden to the whole society with high morbidity and disability rate. The United Kingdom and the United States spend around 2% of GDP each year on the treatment, care and rehabilitation of people with schizophrenia. In particular, long-term hospitalization of patients wastes a large number of medical resources, and the existence of negative symptoms is one of the important reasons for long-term hospitalization of patients. Therefore, the use of rTMS adjuvant therapy to explore the possibility of improving the negative symptoms of patients, to promote the remission of patients, improve the social function and quality of life of patients, has good social and economic benefits.

### *Research objectives*

In this study, we assessed the therapeutic effects and safety of left dorsolateral prefrontal cortex (DLPFC) high-frequency rTMS on negative symptoms of schizophrenia. We evaluated the efficacy of rTMS on recognition in patients with chronic schizophrenia.

### Research methods

This was a randomized, sham-controlled, double-blinded trial. Patients diagnosed with schizophrenia on stable antipsychotic treatment were randomly assigned to active rTMS treatment group ($n$ = 25) or a sham rTMS treatment group ($n$ = 22). 25 patients in the active rTMS group received 10-Hz 110% motor threshold rTMS, while 22 patients were subjected to sham rTMS, both being given 4-wk treatment (5 d/wk). Efficacy of negative symptom was assessed with the Scale for the Assessment of Negative Symptoms (SANS), the Positive and Negative symptom scale (PANSS) at baseline, the end of 4 and 8 wk. The cognitive function was assessed with Cambridge Neuropsychological Test Automated Battery at baseline, the end of 4 and 8 wk. The side effects were assessed with TESS at baseline and the end of 4 wk.

### Research results

There were no significant differences in pattern recognition memory (PRM) performance metrics, SANS total score, SANS subscores, PANSS total score, and PANSS subscores between active and sham rTMS groups at the end of the 4-wk treatment period, but PRM performance metrics (percent correct and number correct) and changes in these metrics from baseline were significantly greater in the active rTMS group at week 8 compared to the sham group (all $P < 0.05$). Active rTMS treatment also significantly reduced SANS score at week 8 compared to sham treatment. Moreover, the improvement in visual memory was correlated with the reduction in negative symptoms at week 8. In contrast, there were no between-group differences in PANSS total score and subscale scores at either week 4 or 8 (all $P > 0.05$).

### Research conclusions

High-frequency TMS can improve visual memory and reduce negative symptoms in patients with schizophrenia, but these effects are delayed, potentially due to the requirement for extensive neuroplastic changes within DLPFC networks.

### Research perspectives

In the future, it is necessary to further explore more scientific treatment parameters and more sensitive assessment tools (such as SANS and neuropsychological assessment kits) for rTMS in the treatment of negative symptoms of schizophrenia, and carry out multicenter, large-sample studies.

## FOOTNOTES

**Author contributions:** Du XD contributed to the project administration, funding acquisition, supervision, wrote the review and editing; Li Z contributed to clinical data collection, wrote review and editing; Yuan N contributed to the data curation, investigation; Yin M, Zhao XL, Lv XL, Zou SY, Zhang J, Li CW, Pan H, Yang L, Wu SQ, Yue Y and Wu YX contributed to the conceptualization, data curation and investigation; Zhang XY contributed to the formal analysis, wrote the original draft; Du XD, Li Z and Yuan N have congtributed equally to this work.

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**Informed consent statement:** Each subject provided written informed consent to participate in the study after a researcher staff explained the whole study to each of them.

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**Data sharing statement:** The data will be available on request from the readers.

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ORIGINAL ARTICLE

Case Control Study

# Galectin-3 mediated risk of inflammation in stable schizophrenia, with only possible secondary consequences for cognition

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## Abstract

### *BACKGROUND*

Evidence suggests that cytokines cause immune disturbances, shape immunological sequelae later in life, and modulate the risk of schizophrenia (SC). Galectin-3 (Gal-3), a multifaceted molecule of the glycan family, is involved in the formation of the immunological synapse and modulates the signalling pathway and effector functions of T lymphocytes, which are major producers of cytokines. We have previously reported elevated serum Gal-3 levels in stable SC patients. However, Gal-3 as a link between cognitive functioning and inflammation has not yet been investigated in SC.

### *AIM*

To investigate the relationship between serum Gal-3 levels and cognitive performance, serum cytokines, and white blood cell count in three-month stably treated SC patients.

### *METHODS*

Twenty-seven patients with SC in remission and 18 healthy volunteers participated in this case-control and correlational study. Clinical assessment was performed using the Positive and Negative Syndrome Scale and the Montreal-Cognitive Assessment. The results of previously measured serum levels of Gal-3, interleukin (IL)-33, soluble suppression of tumorigenicity 2 (sST2), tumor necrosis factor-alpha (TNF-α), IL-6 and IL-17 were used for further statistical analyses, and IL-4, IL-23, IL-1β and transforming growth factor-beta (TGF-β) were now additionally measured with a sensitive enzyme-linked immunosorbent assay. The number of leukocytes in the blood and the percentage of neutrophils, lymphocytes, and monocytes were determined with a standardized routine measurement procedure (Sysmex Technology). Statistical analyses were performed using SPSS 20.0 software.

***RESULTS***

We found no correlation between serum Gal-3 levels and cognitive functioning in SC patients. A positive correlation was found between the levels of Gal-3 and TNF-α ($r$ = 0.476; $P$ = 0.012), Gal-3 and IL-23 ($r$ = 0.417; $P$ = 0.031), and Gal-3 and sST2 ($r$ = 0.402; $P$ = 0.038). The binary logistic model, which included all nine cytokines measured in this patient sample, indicated the particular role of Gal-3 and TGF-β in the duration of SC. In the stabilization phase of SC, we observed a moderate and negative correlation between serum Gal-3 levels and leukocytes ($r$ = -0.449; $P$ < 0.019). Additional linear regression analysis showed a positive correlation between Gal-3 expression and risperidone dose (F: 4.467; $P$ < 0.045; $r^2$ = 0.396).

***CONCLUSION***

The combined activity of Gal-3 and proinflammatory cytokines, TGF-β downregulation and lower counts of leukocytes influence the SC duration. Gal-3 likely manifests indirect immunometabolic regulation of cognition in SC.

**Key Words:** Schizophrenia; Galectin-3; Cytokines; Leukocytes; Antipsychotics

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**Core Tip:** In clinical sampling, there is an urge to place the results of biological measurements in a much broader context. Elevated serum galectin-3 (Gal-3) levels in schizophrenia (SC) have not been studied in relation to other peripheral biomarkers and subsequent neuroinflammation. We found that Gal-3 contributes to ongoing peripheral systemic inflammation and disease duration in patients with SC. All of this may be an underlying indirect immunometabolic mechanism for cognitive performance in patients with SC.

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## INTRODUCTION

Immune dysregulations during prenatal and postnatal life are increasingly associated with neurodevelopmental disorders and have also recently been shown to be an important etiological construct of schizophrenia (SC)[1,2]. Multiple post-mortem brain and neuroimaging studies have also provided evidence for neuroinflammation in SC[3,4]. One of the best-known hypotheses, proposed by Bechter, links SC to mild and localized encephalitis[5]. There is strong evidence that cytokines cause these immune disturbances, shape immunological sequelae later in life, and modulate SC risk. In particular, T lymphocytes are one of the major producers of cytokines, and it has been reported that blood levels of cytokines derived from various lineages of T lymphocytes such as T helper 1 (Th1), Th2, Th17 and regulatory T cells (Treg) are altered in SC[6-8]. Studies have shown that patients with SC have increased serum concentrations of proinflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α)[9,10].

Studies have also shown that Gal-3, a multifaceted molecule in the glycan family, is directly involved in the formation of the immunological synapse and appears to play a pivotal role in modulating the signalling pathway and effector functions of T lymphocytes[11]. It is noteworthy that Gal-3 has both

immune and non-immune functions in the brain. Gal-3 appears to play a neuroprotective role in neuronal tissue and is involved in the reparative processes of brain lesions and ischemia. In contrast, Gal-3 may promote microglia-mediated neuroinflammation and contribute to neuroprogression[12]. Gal-3 increases the secretion of proinflammatory cytokines from microglia and astrocytes[13] and is also required for leukocyte recruitment during an acute inflammatory response[14].

Biomarkers that can be conveniently measured in blood may also reflect changes in the central nervous system and dysfunction of the blood-brain barrier (BBB). There is evidence of BBB dysfunction in brain disorders, including SC. Brain microvascular endothelial cells (BMECs) are a key element of the microvasculature that forms the BBB and shields the brain from toxins and reactive immune cells. However, it is not known whether BMECs themselves are functionally compromised and lead to BBB dysfunction in brain disorders[15]. An increased ratio of cerebrospinal fluid to serum albumin in patients with SC suggests increased permeability of the BBB[16]. Given the important role of galectins in cell adhesion, migration, polarity, and chemotaxis, it is likely that modulation of galectin levels in BMECs that form the BBB could compromise BBB integrity and consequently contribute to neuroinflammation[17]. Plasma levels of Gal-3 have been shown to be increased after aneurysmal subarachnoid hemorrhage (SAH), and a Gal-3 inhibitor could potentially prevent post-SAH BBB disruption by inhibiting Gal-3[18].

We have previously reported elevated serum Gal-3 levels in patients with SC who received stable 3-mo antipsychotic therapy[19]. We wanted to go further in exploring Gal-3 interactions and not only measure serum levels during stabilisation of SC. Recently, such an association between Gal-3 and cognition was found in Alzheimer's disease[20]. In this additional analysis, we tested the hypothesis that serum Gal-3 levels in patients with stable SC might be related to cognitive functioning and different white blood cell counts and types of cytokines in stable SC patients. In this way, we aimed to investigate the possible involvement of this glycan in peripheral systemic inflammation and disease duration, but also its position as a link between cognitive functioning and inflammation, which has not yet been investigated in SC.

## MATERIALS AND METHODS

### Participants

Patients with SC in remission (SC in remission) were recruited in 2016 in the Psychiatric Day Hospital of the Kragujevac Clinical Centre. Participants were between 18 and 65 years old. Diagnoses were made using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) criteria[21] for SC (F20). The major inclusion criterion was stable mental functioning and adherence to three months of stable antipsychotic depot therapy with risperidone or paliperidone. Add-on therapy for patients included anxiolytics or hypnotics only. A complete medical history was obtained from each patient.

Exclusion criteria were current infections during the three-month remission period, allergies or autoimmune disorders, current anti-inflammatory or antiviral medications, or dual diagnoses of other mental illnesses. Healthy controls (HCs) were recruited during blood donation at the Blood and Blood Products Service of the Kragujevac Clinical Centre, and controls with a family history of psychosis were excluded. All laboratory measurements and immunoassays were performed at the Centre for Molecular Medicine and Stem Cell Research, Faculty of Medical Sciences, University of Kragujevac. The study was conducted after the Ethics Committee of the Kragujevac Clinical Centre gave its approval. Participants were able to give informed consent, and each patient signed the informed consent form before participating in the study.

The study sample was estimated considering the first type error (α) of 0.05 and the power of the study of 0.8 for the two-tailed t-test for two independent samples using the statistical softer G* Power 3.1.9.2. Considering previous studies and similar methods for measuring serum cytokine levels[22], the minimum number of participants required in each group was estimated to be 14.

### Clinical assessment

Psychological assessment was performed by trained raters. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS)[23]. Cognition was assessed using the cognitive factor of the PANSS (consisting of items P2-N5-G11)[24], which primarily refers to sustained attention, and executive functioning such as mental flexibility and problem-solving as components of executive functioning[25]. In addition, cognitive impairment was assessed using the Montreal-Cognitive Assessment (MoCA)[26], a cognitive screening tool for older population with mild cognitive impairment and dementia that has also been shown to be useful in patients with psychosis[27]. The MoCA test assesses multiple cognitive domains including attention, concentration, executive functions, memory, language, visual-constructive skills, conceptualization, and orientation, with a maximum total score of 30 and a lower limit for normal cognition of 26.

### Blood collection and cytokine measurements

Blood samples were taken in the morning (approximately 8 am) after overnight fasting. The blood clot was cut and then centrifuged. After separation, serum samples were stored at -20° until analysis. The results of previously measured serum levels of Gal-3, IL-33, soluble suppression of tumorigenicity 2 (sST2), TNF-α, IL-6 and IL-17[19,28] were used for further statistical analyses, and IL-4, IL-23, IL-1β and transforming growth factor-beta (TGF-β) were now additionally measured using sensitive Enzyme-Linked Immuno-Sorbent Assay kits specific for the human cytokines according to the manufacturer's instructions (R&D System, Minneapolis, MB). The procedure has been described in detail previously [19]. Briefly, 96-well plates coated with capture antibody and incubated overnight were washed with wash buffer and incubated with blocking buffer for 1 h at room temperature. Serum samples or standard recombinant IL-4/IL-23/IL-1β/TGF-β were added to the plates for 2 h before a biotinylated detection antibody and streptavidin peroxidase were applied for 1 h each at room temperature. The plates were developed with substrate reagent for 20 min, and the reaction was stopped by addition of 4 mol/L sulfuric acid. The absorbance was read at 495 nm using a microplate reader. The exact concentration of the above biomarkers was measured by interpolating a standard curve with a series of known concentrations according to the manufacturer's instructions. The values of the measured cytokines are expressed in pg/mL. Blood cell populations were determined using a standardized routine laboratory procedure (Sysmex Technology).

### Statistical analysis

Demographic and clinical data were presented descriptively. Various covariates were included in linear and multiple linear regression models to examine the effects of these variables on the results. Pearson's or Spearman's correlation analysis was used to examine the significance of the correlation between serum Gal-3 levels and blood cell counts, serum cytokine levels, and clinical scores and subscores of PANSS and MoCA. To determine the best prediction of serum cytokine levels for the presence of illness, binary logistic regression analysis was performed. A $P$-value of ≤ 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0. Armonk, NY: IBM Corp.

## RESULTS

### Demographic and clinical characteristics

There were no statistically significant differences in age ($P$ = 0.886) and sex ($P$ = 0.851) between patients ($n$ = 27) and HC subjects ($n$ = 18). The demographic and clinical characteristics of the patients were the same as those presented previously[19,28] and are listed in Table 1. Among patients with SC, the duration of illness was 9.95 ± 7.71 years, with 2.18 ± 1.92 years as multiple previous hospitalizations. Most patients were individuals with high school education ($n$ = 22). The mean PANSS total score and subscores, MoCA total score and subscores, and medications taken in the SC group are shown in Table 1.

### Differentiation of serum cytokine levels between groups

In this study, lower TGF-β levels (272.09 ± 101.59 *vs* 360.41 ± 45.13, $P$ = 0.003) were observed in patients with SC (Figure 1A), with no difference in serum IL-4, IL-23 and IL-1β levels (data not shown). The binary logistic model, which included the presence of illness as a dependent variable and all measured cytokine serum levels as covariates in a stepwise Backward-Wald method, highlighted the particular role of Gal-3 and TGF-β in SC, both of which have an impact on disease presentation with an odds ratio for Gal-3: 1.002 (95%CI: 1.000-1.004; $P$ = 0.022) and TGF-β: 0.982 (95%CI: 0.9968-0.997; $P$ = 0.015) (Figure 1B), suggesting that higher Gal-3 levels are associated with stabilization in later phases of SC.

### Serum Gal-3 levels correlate significantly with proinflammatory mediators and risperidone dosing

The correlation between Gal-3 serum levels and cognitive functioning considering MoCA total score, subscores, and PANSS Cog was not significant (data not shown). In addition, we now examined the relationship between systemic Gal-3 levels and cytokines with divergent immune properties. A positive and moderate correlation was observed between Gal-3 and TNF-α ($r$ = 0.476; $P$ = 0.012), Gal-3 and IL-23 ($r$ = 0.417; $P$ = 0.031), and Gal-3 and sST2 ($r$ = 0.402; $P$ = 0.038) levels (Figure 2).

Moreover, linear regression analysis revealed a positive correlation between Gal-3 and risperidone dose (F: 4.467; $P$ < 0.045; $r^2$ = 0.396).

### Serum levels of Gal-3 inversely correlate with leukocyte count

We also examined the correlation between Gal-3 and the number of leukocytes (neutrophils, lymphocytes, and monocytes) involved in the immune response. A negative correlation was found between Gal-3 and total leukocyte count ($r$ = -0.449, $P$ < 0.019), with no other significant correlations with the percentages of specific populations.

**Table 1 Demographic and clinical characteristics of subjects**

| Characteristics | SC in remission (*n* = 27) | Healthy control (*n* = 18) | *P* value |
|---|---|---|---|
| Age (yr), mean ± SD | 36.18 ± 9.27 | 37.67 ± 9.96 | 0.862 |
| Sex (male/female) | 16/11 | 12/6 | 0.851 |
| Duration of illness (yr), mean ± SD | 9.95 ± 7.71 | - | - |
| Number of previous hospitalizations | 2.18 ± 1.92 | - | - |
| **PANSS** | | | |
| PANSS total score | 99.22 ± 18.2 | - | - |
| Positive syndrome scale | 22.26 ± 5.97 | - | - |
| Negative syndrome scale | 27.52 ± 6.09 | - | - |
| General psychopathology scale | 49.44 ± 7.83 | - | - |
| **MoCA** | | | |
| MoCA total score | 22.74 ± 4.76 | - | - |
| Visuospatial/Executive | 4.11 ± 1.25 | - | - |
| Naming | 2.78 ± 0.69 | - | - |
| Attention | 5.07 ± 1.21 | - | - |
| Language | 1.89 ± 0.69 | - | - |
| Abstraction | 1.41 ± 0.84 | - | - |
| Delayed recall | 1.81 ± 1.62 | - | - |
| Orientation | 5.74 ± 0.81 | - | - |
| **Medications** | | | |
| Long-acting risperidone/paliperidone | 22/5 | - | - |
| Long-acting risperidone dosage 25/37.5/50 mg | 3/9/13 | - | - |
| **Cell counts** | | | |
| Leukocytes (× $10^9$/L) | 6.67 ± 2.06 | - | - |
| Neutrophils (%) | 0.61 ± 0.07 | - | - |
| Lymphocytes (%) | 0.31 ± 0.07 | - | - |
| Monocytes (%) | 0.08 ± 0.02 | - | - |

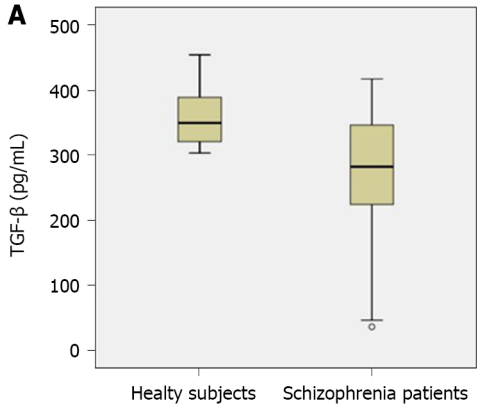
PANSS: Positive and Negative Syndrome Scale of Schizophrenia; MoCA: Montreal-Cognitive Assessment; SC: Schizophrenia.

## DISCUSSION

The current study contains several new and interesting findings. One of the salient findings was a significant correlation between serum Gal-3 levels and levels of proinflammatory cytokines in a stable phase of SC. Serum Gal-3 correlated positively with TNF-α, IL-23, and soluble ST2 in SC in remission (Figure 2) and was associated with downregulation of the counterregulatory cytokine TGF-β and appears to play a role in disrupting leukocyte migration. In addition, the increase in Gal-3 might be influenced by risperidone dosing.

This study was the first to investigate a possible relationship between Gal-3 and cognitive functioning in SC patients. No correlation was found between serum Gal-3 levels and cognitive performance, suggesting a more indirect immunometabolic regulation of cognition in SC, as we have recently discussed[12]. It has been demonstrated that proinflammatory cytokines and mediators of oxidative stress could influence serum Gal-3 levels, and a reciprocal role of Gal-3 in these cascades could not be excluded[29]. Recently, Dal Lin *et al*[30] (2020) pointed out the close relationship and regulatory effect of cognitive functioning on some molecular processes in the human body, including acute attenuation of oxidative stress and inflammation, which inversely affect Gal-3 levels. Based on these findings, Gal-3 may prove to be a potential therapeutic target in SC.

Currently, there are no studies on the correlation between Gal-3 and proinflammatory cytokine levels in SC patients. In our previous study on the same cohort, we found higher systemic Gal-3 levels[19] and




B

| Cytokine impact on illness[1] | B | SE | Wald | df | Sig. | Exp(B) | 95%CI | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| TGF-β | -0.018 | 0.007 | 5.902 | 1 | 0.015 | 0.982 | 0.968 | 0.997 |
| Gal-3 | 0.002 | 0.001 | 5.279 | 1 | 0.022 | 1.022 | 1.000 | 1.004 |

[1]Binary logistic regression, 9 steps analysis included cytokines representing different types of immune responses [galectin-3, interleukin (IL)-33, soluble suppression of tumorigenesis, tumor necrosis factor-alpha, IL-4, IL-6, IL-23, IL-1β and transforming growth factor-beta]

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**Figure 1 Transforming growth factor-beta and galectin-3 levels impact the illness.** A: Lower transforming growth factor-beta (TGF-β) levels (272.09 ± 101.59 *vs* 360.41 ± 45.13 pg/mL, *P* = 0.003) were measured in patients; B: These parameters of serum concentrations of galectin-3 and TGF-β both had an impact on disease presentation. TGF-β: Transforming growth factor-beta; IL: Interleukin; Gal-3: Galectin-3.

TNF-α[24]. In addition to our study, Kajitani *et al*[31] (2017) also reported elevated serum Gal-3 levels in a stable phase of SC. In one study, Gal-3 was tested for its capacity to induce proinflammatory cytokines such as TNF-α and IL-6 from plasmacytoid dendritic and form myeloid dendritic cells isolated from blood. This lectin was found to activate both, TNF-α and IL-6[32]. In addition, a pre-clinical model of intracerebral haemorrhage (ICH) also demonstrated increased expression of Gal-3 in perihematomal brain regions after ICH and Gal-3-induced release of IL-6, suggesting a role for Gal-3 in inflammatory responses after ICH[33]. These findings suggest the hypothesis that neuronal damage could be followed by inflammation involving Gal-3. The elevated serum Gal-3 levels observed in SC patients in the current study could lead to BBB disruption and contribute to the persistence of mild chronic neuroinflammation suspected in SC.

In particular, somatic comorbidities common in SC, such as obesity, hyperlipidaemia, dyslipidaemia and type 2 diabetes, could be monitored by measuring Gal-3[34]. Gal-3 correlates positively with obesity and inflammation, as measured by the inflammatory markers IL-6 and C-reactive protein (CRP)[35]. Contrary to this finding, the IL-6 axis was not active in this phase and in the specific subpopulation of patients, but rather overweighted type-1 immune response with representative TNF-α. Taken together, these findings suggest potential systemic inflammatory properties of Gal-3 through its interactions with proinflammatory markers in SC that contribute to immunometabolic processes in SC.

The association of Gal-3 and sST2 and their changes at follow-up with the development of heart failure in patients with ST-segment elevation myocardial infarction showed that the levels of Gal-3 and sST2 were significantly increased at one-year follow-up[36]. Interestingly, the increased serum Gal-3 concentration correlated with the production of IL-17 and exhibited a significant correlation with neutrophil/lymphocyte ratio, white blood cell count, and CRP, but inversely correlated with the production of IL-10 and IL-12 in patients with untreated colorectal cancer[37]. Some findings suggest that Gal-3 is required to efficiently recruit leukocytes during an acute inflammatory response[14]. These findings may indicate the diverse role of Gal-3 in this SC chronic inflammation, as we have previously discussed that Gal-3 plays a predominant role in the resolution of inflammation[12]. In chronic SC, our studies have shown that serum Gal-3 levels are elevated and that Gal-3 is negatively correlated with leukocyte count. This lower leukocyte count may be related to the decline in immunity of patients with SC in later stable phases and their greater susceptibility to infection.

Although the Gal-3 signalling pathway is not well understood, Gal-3 can be secreted into the extracellular space, where it can interact with different structures such as cell surface and extracellular matrix glycoproteins[38]. In autoimmune neuroinflammation, endogenous Gal-3 may potentiate its severity by decreasing the frequency of Treg cells, controlling IL-10 production, and modulating Notch activation[39]. The Notch and TGF-β signalling crosstalk, which plays an important role in regulating endothelial and neural development[40], could also be influenced by Gal-3. Our findings might shed important light on the Notch-TGF-β axis in SC (Figure 1B). As for TGF-β, our previous data indicate that serum levels of TGF-β are significantly increased in patients with SC in relapse and first-episode psychosis compared to healthy subjects[41,42]. However, in the current study, significantly lower TGF-β levels were observed in SC patients in remission compared to a group of HC subjects (Figure 1A), suggesting that TGF-β levels vary during the course of SC.

Regarding the possible influence of antipsychotics, a recent *in vitro* study reported that the atypical antipsychotic risperidone reduced the production of proinflammatory cytokines by lipopolysaccharide-stimulated glial cells but had no effect on IL-10[43]. However, paliperidone increased TGF-β and IL-10 during acute stress and during prolonged chronic stress[44]. Our recent hypotheses about the

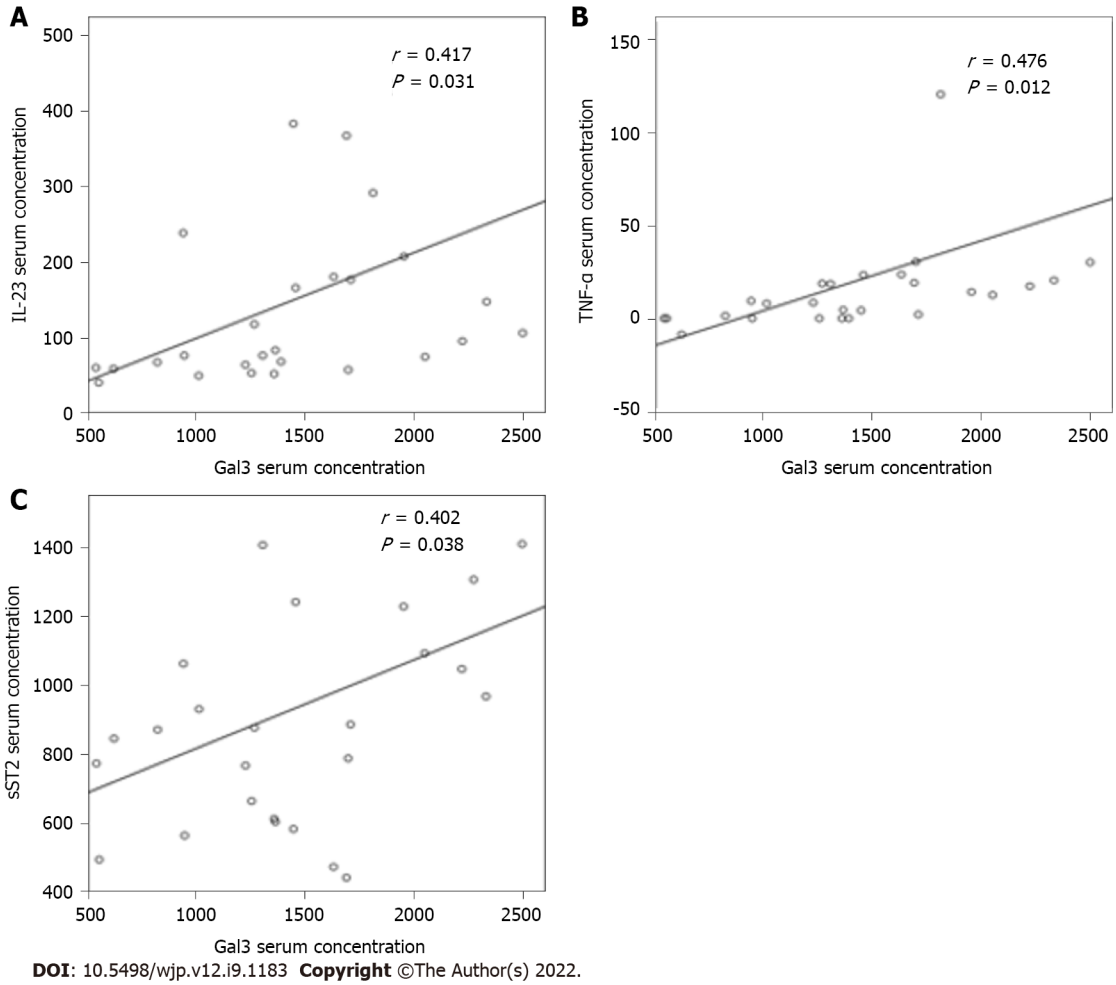


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**Figure 2 Correlations of serum concentrations of galectin-3 with proinflammatory mediators.** A positive and moderate correlation was observed between serum concentrations of galectin-3 (Gal-3) and interleukin-23 (IL-23), Gal-3 and tumor necrosis factor-alpha (TNF-α), and Gal-3 and soluble suppression of tumorigenicity 2 (sST2). A: IL-23 serum concentration; B: TNF-α serum concentration; C: sST2 serum concentration. IL: Interleukin; TNF-α: Tumor necrosis factor-alpha; sST2: Soluble suppression of tumorigenicity 2.

involvement of antipsychotics in the processes of glycosylation can be explained by the effects of their higher doses on serum Gal-3 levels. The findings of the current study suggest that higher doses of prescribed risperidone may lead to an increase in Gal-3 levels. Whole-serum proteins show increased glycosylation after antipsychotic use, indicating the usefulness of these processes for understanding the pathogenesis and monitoring the treatment of patients with SC[34,45].

A higher percentage of Gal-3-expressing innate and adaptive immune cells in the lamina propria was observed in patients with comorbid ulcerative colitis and metabolic syndrome[46]; this encouraged us to explore other immune biomarkers in patients with SC. N-acetylcysteine (NAC) has been proposed for the adjunctive treatment of SC and ulcerative colitis[47]. Oral intake of NAC was shown to lower inflammatory biomarkers, CRP and Gal-3 in patients with acute myocardial infarction receiving fibrinolytic therapy[48]. Preliminary results indicated the usefulness of NAC in improving all domains of SC functioning[49].

As a limitation of our study in terms of cognitive assessment, we must consider that only specific domains of cognitive functioning were assessed, using available validated and brief instruments to detect cognitive impairment in SC in our population. Although we tried to exclude all somatic states, we should be aware that comorbidity and psychotropic medication could influence the results of both cognitive functioning and serum measurements. We believe that it is necessary to investigate these issues further in a larger sample with a much more thorough analysis of confounding factors, which has not been done within the scope of this manuscript, but these results are valuable to guide us in the future.

## CONCLUSION

In clinical sampling, there is an urge to place the results of biological measurements into a much wider concept. Higher serum levels of Gal-3 in SC have not been explored in interaction with other peripheral biomarkers reflecting possible inflammatory changes. We observed that Gal-3 contributes to ongoing peripheral systemic inflammation and disease duration in patients with SC. Moreover, its influence on BBB permeability and consequent neuroinflammation should be explored. Our data revealed some new complex roles of Gal-3, such as its possible involvement in neuroinflammation and cognitive processing, contributing to a better understanding of the specific immune profile in patients with SC. Inflammation also appears to be the potential pathway by which Gal-3 may affect cognitive functioning in SC. The efficacy of antipsychotics could be improved and their adverse effects corrected if the role of Gal-3 in glycosylation processes were considered. These findings provide a rationale for further strategies targeting Gal-3 for therapeutic intervention in SC.

## ARTICLE HIGHLIGHTS

### *Research background*

Galectin-3 (Gal-3), a multifaceted molecule of the glycan family, modulates T lymphocytes' signalling pathway and effector functions. We have previously reported elevated serum Gal-3 levels in stable schizophrenia (SC) patients, but Gal-3 as a link between cognitive functioning and inflammation has not yet been investigated in SC.

### *Research motivation*

Elevated serum Gal-3 levels in SC have not been studied in relation to other peripheral biomarkers and subsequent neuroinflammation. All of this may be an underlying indirect immunometabolic mechanism for cognitive performance in patients with SC.

### *Research objectives*

Investigating the relationship between serum Gal-3 levels and cognitive performance, serum cytokines, and white blood cell count in three-month stably treated SC patients could contribute to a better understanding of the specific immune profile in patients with SC.

### *Research methods*

Twenty-seven patients with SC in remission and 18 healthy volunteers participated in this case-control and correlational study. Clinical assessment was performed using the Positive and Negative Syndrome Scale and the Montreal-Cognitive Assessment. The results of previously measured serum levels of Gal-3, interleukin (IL)-33, soluble suppression of tumorigenicity 2 (sST2), tumor necrosis factor-alpha (TNF-α ), IL-6 and IL-17 were used for further statistical analyses, and IL-4, IL-23, IL-1β and transforming growth factor-beta (TGF-β) were now additionally measured with a sensitive enzyme-linked immunosorbent assay. The number of leukocytes in the blood and the percentage of neutrophils, lymphocytes, and monocytes were determined with a standardized routine measurement procedure. Statistical analyses were performed using SPSS 20.0 software.

### *Research results*

Serum Gal-3 correlated positively with TNF-α, IL-23, and soluble sST2 in SC in remission and was associated with downregulation of the counterregulatory cytokine TGF-β and appears to play a role in disrupting leukocyte migration. The increase in Gal-3 might be influenced by risperidone dosing.

### *Research conclusions*

The combined activity of Gal-3 and proinflammatory cytokines, TGF-β downregulation and lower counts of leukocytes influence the SC duration. Gal-3 likely manifests indirect immunometabolic regulation of cognition in SC.

### *Research perspectives*

We observed that Gal-3 contributes to ongoing peripheral systemic inflammation and disease duration in patients with SC. Moreover, its influence on blood-brain barrier permeability and consequent neuroinflammation should be explored. Inflammation also appears to be the potential pathway by which Gal-3 may affect cognitive functioning in SC.

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## FOOTNOTES

**Author contributions:** Minic Janicijevic S and Borovcanin MM presented the design of this project, recruited the participants, performed the psychological and somatic assessment, collected the samples for laboratory measurements, structured the manuscript and incorporated all parts of the manuscript; Jovanovic IP, Gajovic NM and Arsenijevic NN performed the cytokine measurements; Jurisevic MM and Borovcanin MM did the statistical analysis and prepared tables and figures; All authors, especially Debnath M, additionally searched the literature and provided new insights into specific areas of their expertise, made a final revision of the manuscript, and corrected the figures; All authors read, discussed, and approved the final version of the manuscript.

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**Informed consent statement:** All study participants provided informed written consent prior to study enrollment.

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ORIGINAL ARTICLE

Observational Study

# Associations between social support and anxiety during the COVID-19 lockdown in young and middle-aged Israelis: A cross-sectional study

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## Abstract

***BACKGROUND***

This study examined the associations between social support and anxiety during the coronavirus disease 2019 (COVID-19) in an Israeli sample.

***AIM***

To examine the associations between social support and anxiety during the COVID-19 in an Israeli sample.

***METHODS***

Data for this cross-sectional study were retrieved from an online survey. Linear regression, logistic regression and restricted cubic spline models were conducted to test for associations between social support and anxiety.

***RESULTS***

A total of 655 individuals took part in the present study. In the univariate linear regression model, there is a negative correlation between the Generalized Anxiety Disorder-7 score (GAD-7) and the Multidimensional Perceived Social Support Scale (MSPSS) score. For MSPSS score, the multivariable adjusted regression coefficient and 95% confidence interval (CI) of GAD-7 score were -0.779 (-1.063 to -0.496). In the univariate logistic regression model, there was a negative correlation between anxiety (GAD-7 ≥ 9) and MSPSS score, and there was still a negative correlation in multivariate logical regression analysis. The odds ratios and 95%CI were 0.709 (0.563-0.894).

*CONCLUSION*
Social support was inversely correlated with anxiety during COVID-19 in an Israeli sample.

**Key Words:** Cross-sectional study; Social support; Anxiety; COVID-19; Lockdown; Correlation

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**Core Tip:** Coronavirus disease 2019 (COVID-19) is a worldwide pandemic caused by the severe acute respiratory syndrome coronavirus 2. Due to the massive spread and high infectivity of the virus, most countries have adopted various lockdown measures to control the epidemic. Anxiety disorder is one of the most common mental disorders. To examine the associations between social support and anxiety during the COVID-19 in an Israeli sample. A total of 655 individuals took part in the present study. Our results show that in the Israeli sample social support is negatively correlated with anxiety during COVID-19. This underscores the importance of social support for anxiety prevention during COVID-19 locking.

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## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a worldwide pandemic caused by the severe acute respiratory syndrome coronavirus 2. COVID-19 was first reported in Wuhan, China, causing pneumonia and other respiratory complications. Due to the massive spread and high infectivity of the virus, most countries have adopted various lockdown measures to control the epidemic. Changes in social distance and daily life activities during the blockade can affect personal well-being, mental health, and increase the risk of mental illness[1]. Anxiety disorder is one of the most common mental disorders.

Anxiety disorder is a common mental disorder with a global incidence of 7.3%[2]. Patients with anxiety disorders often feel excessive fear, anxiety or aim to avoid threats in the environment and within themselves, which can lead to disability and places a heavy burden on individuals and society[3]. Adequate social support is always significantly important for an individual's mental health. There are no significant side effects associated with social support, as compared to typical drug therapy. In addition, social support is one of the social resources to deal with stressful life events[4]. Social support is defined as allowing individuals to take advantage of the positive effects of social interactions to directly protect their mental health and directly resist stressful situations. Social support, as a function of interpersonal emotion regulation, can reduce the risk of mental illness[5]. In a trial of 947 colorectal cancer patients in Spain, patients with more social support were more likely to have better results in anxiety and depression one year after surgery[6]. In patients with multiple sclerosis, higher social support was associated with lower depression and anxiety[7]. In a cross-sectional study of young pregnant women, pregnant adolescents with anxiety disorders were found to have less social support in all areas[8]. Similarly, adolescents' exposure to negative life events was shown to be associated with social anxiety disorder, whereas changing social support can reduce anxiety symptoms in at-risk adolescents[4]. It is, thus, assumed that this inverse association exsits between the absence of social support and anxiety in different negative events and various populations.

It is not clear whether social support is equally protective of anxiety disorders in the context of the unique features of the first wave of COVID-19 pandemic in Israel in particular during lockdown. This study used data from an interim study on the lockdown enforced during the first wave of the COVID-19 pandemic in Israel to clarify the potential associations between social support and anxiety disorders.

## MATERIALS AND METHODS

### *Data collection*

The Qualtrics$^{XM}$ platform (https://www.qualtrics.com/) digital questionnaire for data collection method was implemented in this study. It included a sociodemographic and personal questionnaire, the Generalized Anxiety Disorder-7 (GAD-7), the Multidimensional Perceived Social Support (MSPSS) and other measures and was administered using a snowball sampling method to recruit participants across

Israel *via* email and mobile phone applications. All responses were anonymous. The responses to the questionnaire were collected from April 19 to May 2, 2020, when Israel was experiencing the peak of the first wave of the COVID-19 epidemic. During that time, the government imposed three weeks of strict lockdown measures, banning social gatherings. The experimental procedure was approved by the Ethics Committee of the Academic College of Tel-Aviv Yafo, Israel (Approval No. 2020085), and all participants an signed electronic informed consent, allowing access to the full set of questionnaires[9].

### Sample

A total of 655 participants took part. 200 participants did not complete the questionnaire. Of these, 45% did not complete sociodemographic and personal questionnaire. Of the remaining 55% of participants, only 1.3% completed the GAD-7 questionnaire. Participants who failed to complete all the questionnaires were excluded. The inclusion criteria were over 18 years of age and fluent in Hebrew.

### Demographic information

The demographic information included the participants' age, gender, and socioeconomic status (based on question assessment of educational level, subjective perception of socioeconomic status, and financial resources for the next three months).

### Assessment of anxiety

The GAD-7 is a self-reported anxiety questionnaire that can measure the anxiety level of the general population with sufficient validity and accuracy[10]. The Hebrew version was used, which contains 7 items, with scores ranging from 0 to 21. These scores represent 0-4 (minimal anxiety), 5-9 (mild anxiety), 10-14 (moderate anxiety), and 15-21 (severe anxiety). In this study, anxiety was defined as an overall score ≥ 9[11]. The internal consistency of the current sample was $\alpha = 0.892$.

### Assessment of social support

Social support was evaluated on the Hebrew version of the MSPSS, which assesses participants' subjective feelings about their degree of social support[12]. The scale consists of three sub-scales related to family, friends, and significant others, with a total of 12 items. The higher the participants' scores, the more social support they felt.

### Covariates

Covariates includes demographic variables (age, gender) and other background factors, including number of children, education, socioeconomic status, occupation, exercise and use of antidepressants.

### Statistical analysis

SPSS 20.0 and R 3.5.1 were used for analysis. Linear regression was performed to analyze the association between social support and anxiety symptoms. Logistic regression was performed to examine the association between social support and anxiety disorders (GAD-7 score ≥ 9). To further investigate the relationship between social support and anxiety, a restricted cubic spline analysis was performed in the fully adjusted model. *P* values of less than 0.05 (two-tailed) were considered statistically significant.

## RESULTS

### Sample characteristics according to GAD score

Table 1 shows the characteristics of the 655 participants in terms of GAD-7 scores. The sample was composed of 246 men and 409 women, with a median age of 30. There were significant differences in age, gender, number of children, education, socioeconomic status, occupation, history of depression, and use of antidepressants between those with and without anxiety disorders (GAD-7 score ≥ 9). Those classified as exhibiting anxiety were younger than those who were classified as not exhibiting anxiety. Anxiety was also more common among women. Of the participants classified as anxious, 80% had no children, 50% had a bachelor's degree, 41.1% had an average economic status and 54.2% had a full-time or part-time job.

### Association of MSPSS with the GAD-7 score

Table 2 uses linear regression to analyze the association between social support and anxiety symptoms. In the univariate linear regression model, GAD-7 score was negatively correlated with MSPSS score, and the regression coefficient and 95% confidence interval (CI) were -0.692 (-0.990 to -0.394). Further multivariate linear regression analysis showed that there was still a negative correlation between GAD-7 score and MSPSS score, and the regression coefficient and 95%CI was -0.779 (-1.063 to -0.496). This negative correlation was independent of age, sex, socio-economic status and the use of antidepressants.

**Table 1 Characteristics of participants according to Generalized Anxiety Disorder-7 score, represented by medians and interquartile range**

| Variable | Total (*n* = 655) | GAD-7 score < 9 (*n* = 585) | GAD-7 score ≥ 9 (*n* = 70) | *P* value |
|---|---|---|---|---|
| Age (yr) | 30 (26-47) | 31 (26-49) | 27 (23-33) | < 0.001 |
| Gender | | | | 0.007 |
| Male | 246 (37.6%) | 230 (39.3%) | 16 (22.9%) | |
| Female | 409 (62.4%) | 355 (60.7%) | 54 (77.1%) | |
| Number of children | | | | 0.008 |
| Zero | 392 (59.8%) | 336 (57.4%) | 56 (80.0%) | |
| One | 37 (5.6%) | 34 (5.8%) | 3 (4.3%) | |
| Two | 95 (14.5%) | 91 (15.6%) | 4 (5.7%) | |
| Three | 100 (15.3%) | 94 (16.1%) | 6 (8.6%) | |
| Four | 31 (4.7%) | 30 (5.1%) | 1 (1.4%) | |
| Education | | | | 0.003 |
| Without diploma | 23 (3.5%) | 21 (3.6%) | 2 (2.9%) | |
| 12 years or less | 125 (19.1%) | 102 (17.4%) | 23 (32.9%) | |
| Bachelor | 295 (45.0%) | 260 (44.4%) | 35 (50.0%) | |
| Master (or higher) | 187 (28.5%) | 178 (30.4%) | 9 (12.9%) | |
| Other | 25 (3.8%) | 24 (4.1%) | 1 (1.4%) | |
| Socio-economic status | | | | < 0.001 |
| Low | 21 (3.2%) | 16 (2.7%) | 5 (7.1%) | |
| Low-average | 79 (2.1%) | 60 (10.3%) | 19 (27.1%) | |
| Average | 281 (42.9%) | 252 (43.1%) | 29 (41.1%) | |
| Average-high | 224 (34.2%) | 209 (35.7%) | 15 (21.4%) | |
| High | 50 (7.6%) | 48 (8.2%) | 2 (2.9%) | |
| Occupation | | | | 0.029 |
| Full-time job | 280 (42.7%) | 261 (44.6%) | 19 (27.1%) | |
| Partially employed | 109 (16.6%) | 90 (15.4%) | 19 (27.1%) | |
| Unpaid vacation | 4 (0.6%) | 4 (0.7%) | 0 (0.0%) | |
| Lost job | 33 (5.0%) | 31 (5.3%) | 2 (2.9%) | |
| Unemployed | 55 (8.4%) | 47 (8.0%) | 8 (11.4%) | |
| Retired | 174 (26.6%) | 152 (26.0%) | 22 (31.4%) | |
| Exercise | | | | 0.112 |
| Yes | 190 (29.0%) | 164 (28.0%) | 26 (37.1%) | |
| No | 465 (71.0%) | 421 (72.0%) | 44 (62.9%) | |
| History of depression | | | | < 0.001 |
| Yes | 538 (82.1%) | 494 (84.4%) | 44 (62.9%) | |
| No | 117 (17.9%) | 91 (15.6%) | 26 (37.1%) | |
| Use of antidepressants | | | | 0.001 |
| Yes | 563 (86.0%) | 512 (87.5%) | 51 (72.9%) | |
| No | 92 (14.0%) | 73 (12.5%) | 19 (27.1%) | |
| MSPSS score | 6.08 (5.25-6.67) | 6.08 (5.33-6.75) | 5.75 (4.67-6.50) | 0.009 |
| GAD-7 score | 3 (1-6) | 3 (1-5) | 13 (11-15) | < 0.001 |

MSPSS: Multidimensional Perceived Social Support Scale; GAD-7: Generalized Anxiety Disorder-7.

**Table 2 Associations of Generalized Anxiety Disorder-7 score with Multidimensional Perceived Social Support Scale score (regression coefficient and 95% confidence intervals)**

| Variable | Univariate linear regression | | Multivariate linear regression | |
|---|---|---|---|---|
| | β (95%CI) | *P* value | β (95%CI) | *P* value |
| MSPSS | -0.692 (-0.990, -0.394) | < 0.001 | -0.779 (-1.063, -0.496) | < 0.001 |
| Age | -0.056 (-0.077, -0.035) | < 0.001 | -0.048 (-0.068, -0.028) | < 0.001 |
| Sex | 1.888 (1.246, 2.529) | 0.316 | 1.641 (1.021, 2.261) | < 0.001 |
| Number of children | -0.524 (-0.760, -0.289) | < 0.001 | - | - |
| Education | -0.399 (-0.763, -0.034) | 0.032 | - | - |
| Occupation | 0.142 (-0.006, 0.289) | 0.059 | - | - |
| Socio-economic status | -0.952 (-1.300, -0.603) | < 0.001 | -0.514 (-0.854, -0.174) | 0.003 |
| Exercise | -0.460 (-1.162, 0.241) | 0.198 | - | - |
| Use of antidepressants | 2.589 (1.781, 3.397) | < 0.001 | 2.046 (1.279, 2.813) | < 0.001 |

MSPSS: Multidimensional Perceived Social Support Scale; CI: Confidence interval.

### *Association of MSPSS with anxiety*

Table 3 shows the odds ratios (OR) and the 95%CI for social support and anxiety disorders (GAD-7 score ≥ 9). In the univariate logistic regression model, the occurrence of anxiety was negatively correlated with MSPSS score. Multivariate logical regression analysis with backward method showed that the occurrence of anxiety was still negatively correlated with MSPSS score, and the OR and 95%CI were 0.709 (0.563-0.894). This negative correlation is independent of gender, age, education level, socio-economic status and the use of antidepressants.

### *Restricted cubic spline analyses*

To further clarify the relationship, a restricted cubic spline analysis was used to analyze the association between social support and anxiety (Figure 1). The results showed that social support was inversely correlated with anxiety symptoms (GAD-7 score ≥ 9). Anxiety symptoms decreased with increasing social support scores.

## DISCUSSION

In this study, a cross-sectional analysis was conducted using data from an interim study conducted while Israel was in lockdown during the first wave of the COVID-19 pandemic to assess the relationship between social support and anxiety symptoms. The data included 655 participants. The results showed that participants' social support scores were inversely correlated with GAD-7 scores. Social support was inversely associated with anxiety (GAD-7 score ≥ 9) in logistic regression model, and this negative correlation is independent of gender, age, education level, socio-economic status and the use of antidepressants.

During the COVID-19 pandemic, people in most countries were placed under tight lockdown measures due to the dangers of the rapid spread of the disease and the severe shortage of medical resources. In instances of insufficient supply and personnel, medical workers tend to give priority to serious physical diseases and ignore patients' mental symptoms[13]. At the same time, for quarantined individuals, the panic caused by the COVID-19 outbreak, as well as the economic losses caused by the lockdown, the lack of protective gear and other complications all exacerbated the psychological difficulties. In an epidemiological survey conducted in Hong Kong, 25.4% of the population's mental health was reported to have deteriorated since the outbreak of COVID-19, and 14% of the population suffers from anxiety[14]. Anxiety is an emotion characterized by physical changes such as tension, anxious thoughts and elevated blood pressure, with a lifetime prevalence rate of more than 20%[15]. When severe acute respiratory syndrome broke out in Hong Kong in 2013, 13% of the population developed anxiety disorders after discharge from hospital[16]. Anxiety disorders often occur at the same time as post-traumatic stress disorder (PTSD). Pre-existing anxiety has been proved to be a risk factor

**Table 3 Odds ratios (95% confidence intervals) of anxiety (Generalized Anxiety Disorder-7 score ≥ 9) across Multidimensional Perceived Social Support Scale score**

| Variable | Univariate logistic regression | | Multivariate logistic regression | |
|---|---|---|---|---|
| | OR (95%CI) | *P* value | OR (95%CI) | *P* value |
| MSPSS | 0.747 (0.605, 0.921) | 0.006 | 0.709 (0.563, 0.894) | 0.004 |
| Age | 0.965 (0.944, 0.986) | 0.001 | 0.976 (0.953, 0.999) | 0.041 |
| Sex | 2.187 (1.222, 3.913) | 0.008 | 2.151 (1.142, 4.053) | 0.018 |
| Number of children | 0.658 (0.514, 0.842) | 0.001 | - | - |
| Education | 0.617 (0.464, 0.822) | 0.001 | 0.615 (0.445, 0.851) | 0.003 |
| Occupation | 1.096 (0.980, 1.227) | 0.109 | - | - |
| Socio-economic status | 0.539 (0.409, 0.710) | < 0.001 | 0.628 (0.465, 0.849) | 0.003 |
| Exercise | 0.659 (0.393, 1.106) | 0.114 | - | - |
| Use of antidepressants | 2.613 (1.461, 4.672) | 0.001 | 2.588 (1.384, 4.841) | 0.004 |

MSPSS: Multidimensional Perceived Social Support Scale; CI: Confidence interval; OR: Odds ratio.

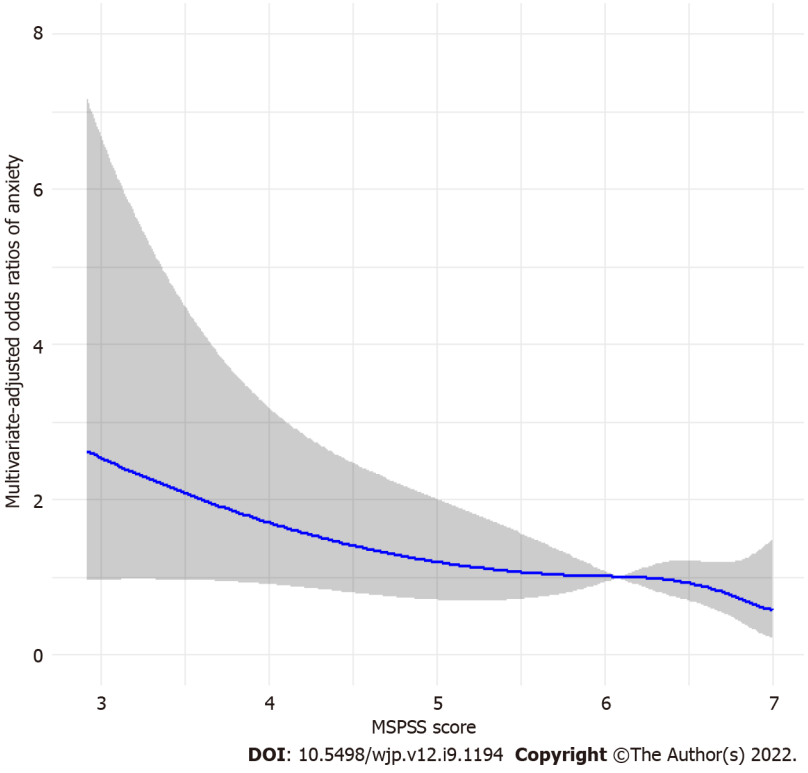


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**Figure 1 A restricted cubic spline model of the odds ratio between anxiety (Generalized Anxiety Disorder-7 score ≥ 9) and Multidimensional Perceived Social Support Scale score.** The grey area represents a 95% confidence interval. Adjusted for age, gender, number of children, education, socioeconomic status, occupation, exercise, history of depression, and use of antidepressants. MSPSS: Multidimensional Perceived Social Support Scale.

for the development of urban population into PTSD[17]. Studies have shown that participants with higher symptoms of depression and anxiety are more likely to develop more severe PTSD symptoms, and higher social support may be associated with lower PTSD[18].

Social support, as a way to foster a sense of belonging and love, is crucial for the mental health of the population. Social support can promote mental health in several ways. First social support can enable people receive more information and care from others. Certain specific groups, such as pregnant and postpartum mothers and parents of young children with special medical needs can obtain social support from social media to relieve negative emotions such as psychological anxiety and glean useful suggestions[19,20]. During the lockdown period, people mainly used social media to get social support from a range of sources to ease anxiety and fight the epidemic collectively. Second, social support can

alleviate people's pain, and can encourage physical activity, including those who are physically limited by pain, and thus have a positive impact on people's health behaviors[21]. Finally, social support can improve individuals' physical condition and promote mental health by directly influencing the body's pathophysiological mechanisms. Studies have found that people with higher social support and integration have lower mortality rates, and a comprehensive meta-analysis has shown that social support is inversely correlated with inflammation levels *in vivo*[22]. In addition, social support can significantly reduce the cardiovascular response of the population and lower cardiovascular recovery to its pre-stress level[23]. All these studies thus suggest that social support not only provides information and care from the outside world, but also modulates the mental health of the population by reducing physical pain and improving inflammation levels.

In a cross-sectional study of women who had undergone a therapeutic abortion, more than half reported symptoms of anxiety, and social support from these women's family and friends significantly reduced anxiety levels. Furthermore, social support from partners can also reduce women's anxiety symptoms[24]. Another longitudinal cohort study of caregivers of patients diagnosed with cancer showed that accurate information and social support from other members of the community, as well as physical activity reduced anxiety in partners in the first months after a cancer diagnosis[25]. These epidemiological studies underscore the positive effects of social support on anxiety disorders. Similarly, during the special period of COVID-19's outbreak, in a cross-sectional survey of 3500 Spanish adults, it was found that for those without pre-pandemic mental disorders, higher levels of social support decreased the odds of GAD-7[26]. During the COVID-19 pandemic in Turkey, it was also found that anxiety levels decreased significantly when perceived social support increased[4]. This study conducted a survey during Israel's first blockade in 2020, taking into account the effects of age, sex, number of children, education level, socio-economic status, occupation, exercise and antidepressant use, the results here show that social support is negatively correlated with post-blockade anxiety.

This study makes several contributions beyond its limitations. Using data collected during the first wave of COVID-19 lockdown in Israel, this study reports on relationship between social support and anxiety during COVID-19 lockdown. In addition, we considered the impact of confounding factors such as age, gender, education, socioeconomic status and other potential influences. Note, however, that the cross-sectional design of this study is a major limitation because it is difficult to make causal inferences. Second, the results were adjusted for a variety of major potential confounding factors; however, the existence of unmeasured factors and some unknown factors cannot be ruled out. Third, randomly distributed questionnaires may lead to age selection bias of the study population, which may make the results not generalized. Fourth, this study does not include the limitations on generalization to younger and older ages. Fifth, this study does not include people who have been infected with COVID-19, whether infected with COVID-19 may have an impact on the correlation coefficient between social support and anxiety.

Prolonged home confinement may be the main reason that affects people's mental health during the blockade of the COVID-19 pandemic, and it is very important to give proper physical and mental care and social support. In addition, the long epidemic period of COVID-19 and the continuous mutation of virus strains undoubtedly bring new challenges to people's mental health. How to make rational use of multimedia or the internet to improve the psychological state of the population during the COVID-19 blockade is a research direction worthy of attention for future researchers.

## CONCLUSION

Overall our findings suggest that social support was inversely associated with anxiety symptoms during COVID-19 pandemic lockdown. Thus providing social support may reduce the prevalence of anxiety in the population.

## ARTICLE HIGHLIGHTS

### *Research background*

Due to the massive spread and high infectivity of coronavirus disease 2019 (COVID-19), most countries have adopted various lockdown measures to control the epidemic. Changes in social distance and daily life activities during the blockade can affect personal well-being, mental health, and increase the risk of mental illness. Anxiety disorder is one of the most common mental disorders.

### *Research motivation*

It is not clear whether social support is equally protective of anxiety disorders in the context of the unique features of the first wave of COVID-19 pandemic in Israel in particular during lockdown. This study used data from an interim study on the lockdown enforced during the first wave of the COVID-19 pandemic in Israel to clarify the potential associations between social support and anxiety disorders.

### *Research objectives*
The purpose of this study was to study the relationship between social support and anxiety in Israelis during the first COVID-19 epidemic.

### *Research methods*
Data for this cross-sectional study were retrieved from an online survey. Linear regression, logistic regression and restricted cubic spline models were conducted to test for associations between social support and anxiety.

### *Research results*
A total of 655 individuals took part in the present study. In the univariate linear regression model, there is a negative correlation between the Generalized Anxiety Disorder-7 score (GAD-7) and the Multidimensional Perceived Social Support Scale (MSPSS) score. For MSPSS score, the multivariable adjusted regression coefficient and 95% confidence interval (CI) of GAD-7 score were -0.779 (-1.063 to -0.496). In the univariate logistic regression model, there was a negative correlation between anxiety (GAD-7 ≥ 9) and MSPSS score, and there was still a negative correlation in multivariate logical regression analysis. The odds ratios and 95%CI were 0.709 (0.563-0.894).

### *Research conclusions*
Social support was inversely correlated with anxiety during COVID-19 in an Israeli sample.

### *Research perspectives*
Our findings suggest that social support was inversely associated with anxiety symptoms during COVID-19 pandemic lockdown. Thus providing social support may reduce the prevalence of anxiety in the population.


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## FOOTNOTES

**Author contributions:** Xi Y, Elkana O and Jiao WE contributed to the work equally. Y Xi, Li D, and Jiao WE contributed to the data analysis and interpretation; Elkana O and Jiao WE involved in data acquisition; Tao ZZ contributed to the study conception and design final approval of the manuscript for submission.

**Institutional review board statement:** The experimental procedure was approved by the Ethics Committee of The Academic College of Tel-Aviv Yafo, Israel (Approval No. 2020085).

**Informed consent statement:** All participants a signed electronic informed consent, allowing access to the full set of questionnaires.

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SYSTEMATIC REVIEWS

# Psychotic symptoms in bipolar disorder and their impact on the illness: A systematic review

Subho Chakrabarti, Navdeep Singh

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## Abstract

*BACKGROUND*

Lifetime psychotic symptoms are present in over half of the patients with bipolar disorder (BD) and can have an adverse effect on its course, outcome, and treatment. However, despite a considerable amount of research, the impact of psychotic symptoms on BD remains unclear, and there are very few systematic reviews on the subject.

*AIM*

To examine the extent of psychotic symptoms in BD and their impact on several aspects of the illness.

*METHODS*

The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were followed. An electronic literature search of six English-language databases and a manual search was undertaken to identify published articles on psychotic symptoms in BD from January 1940 to December 2021. Combinations of the relevant Medical Subject Headings terms were used to search for these studies. Articles were selected after a screening phase, followed by a review of the full texts of the articles. Assessment of the methodological quality of the studies and the risk of bias was conducted using standard tools.

*RESULTS*

This systematic review included 339 studies of patients with BD. Lifetime psychosis was found in more than a half to two-thirds of the patients, while current psychosis was found in a little less than half of them. Delusions were more common than hallucinations in all phases of BD. About a third of the patients reported first-rank symptoms or mood-incongruent psychotic symptoms, particularly during manic episodes. Psychotic symptoms were more frequent in bipolar type I compared to bipolar type II disorder and in mania or mixed episodes compared to bipolar depression. Although psychotic symptoms were not more severe in BD, the severity of the illness in psychotic BD was consistently greater.

Psychosis was usually associated with poor insight and a higher frequency of agitation, anxiety, and hostility but not with psychiatric comorbidity. Psychosis was consistently linked with increased rates and the duration of hospitalizations, switching among patients with depression, and poorer outcomes with mood-incongruent symptoms. In contrast, psychosis was less likely to be accompanied by a rapid-cycling course, longer illness duration, and heightened suicidal risk. There was no significant impact of psychosis on the other parameters of course and outcome.

*CONCLUSION*

Though psychotic symptoms are very common in BD, they are not always associated with an adverse impact on BD and its course and outcome.

**Key Words:** Psychotic symptoms; Bipolar disorder; Extent; Impact

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**Core Tip:** This systematic review examined the extent and impact of psychosis in 339 studies of bipolar disorder (BD). The results endorsed the high rates of all types of psychotic symptoms in BD. However, psychosis was associated with an adverse impact only in a few domains of the illness including the severity of BD, the rate/duration of hospitalizations, switches to BD, and poorer outcomes with mood-incongruent symptoms. No consistent associations were found in other areas, suggesting that psychosis is not always associated with a negative impact on BD. This finding conformed to the current consensus in the literature on psychotic BD.

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## INTRODUCTION

Psychosis in bipolar disorder (BD) is characterized by the presence of either delusions or hallucinations or both[1]. It is well known that over half of the patients with BD develop psychotic symptoms during their lifetimes[2,3]. Psychotic symptoms are more frequent in bipolar than in unipolar depression[3-5]. Rates of psychotic symptoms in BD may be comparable to schizophrenia, and there appears to be no qualitative distinction in psychotic symptoms found in BD or schizophrenia[6-8]. Psychotic symptoms are much more frequent during manic than depressive episodes[3,5,8]. Their rates are so high in mania that it is often indistinguishable from primary psychotic disorders[9]. All kinds of psychotic symptoms may occur among patients with BD, though grandiose, persecutory, and referential delusions, auditory verbal hallucinations or hearing voices, and visual hallucinations are particularly common[2,8,10]. Both mood-congruent and mood-incongruent psychotic symptoms as well as Schneiderian first-rank symptoms (FRS) also occur in BD[2,3,6,8].

Given their ubiquity, psychotic symptoms in BD have the potential to adversely affect its course, outcome, and response to treatment. Somewhat surprisingly, the impact of psychosis on the course and outcome of BD remains unclear despite extensive research on the subject. While some reviews regarding the impact of psychosis on BD have indicated that psychotic BD represents a more severe form of the illness with an adverse course and outcome[9,11,12], the majority of the others have not been able to find an association between psychotic symptoms and outcome in BD[2,3,5,8,13]. Nevertheless, the presence of psychotic symptoms in BD may be of some significance in determining its current nosology [12-14]. Moreover, the similarity of psychotic BD with schizophrenia on genetic, neurobiological, and cognitive aspects indicates common etiological underpinnings of these disorders[14-16]. In both aspects, BD seems to lie in an intermediate position between psychotic and non-psychotic disorders, leading to the hypothesis of a continuum of psychosis stretching from major depressive disorders with psychosis to psychotic BD and schizophrenia[15-18]. Finally, from the clinical perspective, psychotic symptoms have a considerable influence on the way BD is diagnosed and treated. The high prevalence of psychotic symptoms in BD often results in a mistaken diagnosis of schizophrenia. This can lead to inappropriate treatment and can have negative social and economic consequences for those with BD[2,6,8,19]. Moreover, the best way to manage psychotic BD is not clear. Though guidelines emphasize the role of antipsychotics or electroconvulsive therapy, research on adjunctive psychosocial interventions for psychotic symptoms is limited[8,14].

Over the years there have been many reviews of psychotic symptoms in BD including the seminal ones by Goodwin and Jamison[3,5] and by other authors[2,6,9,14,20]. However, there have been very few systematic reviews on the subject. Only three such systematic reviews could be identified. Two of them were primarily focused on hallucinations in BD, unipolar depression, or other disorders[10,21]. Only one systematic review had examined the phenomenology of auditory verbal hallucinations and delusions along with their clinical and cognitive correlates in 32 studies of BD[8].

### Aims and objectives of the current systematic review

The current systematic review was specifically intended to address the gaps in the literature regarding psychotic symptoms and their impact on BD. It attempted to comprehensively examine the extent of psychotic symptoms in BD with a particular emphasis on the associations of psychotic symptoms with the course and outcome of BD. For this purpose, it focused on four groups of studies including those of BD [type I (BP I) and type II (BP II) disorders], studies of mania, bipolar depression, and mixed episodes. Four types of psychotic symptoms were examined including delusions, hallucinations, mood-congruent and mood-incongruent symptoms, and FRS. Mood-congruent and incongruent symptoms and FRS were examined separately because these symptoms usually indicate a more severe form of BD and may have a greater impact on its outcome. The impact of psychotic symptoms was determined by exploring the demographic correlates of psychotic symptoms, their clinical correlates, and the influence of psychotic symptoms on different parameters of the course and outcome of BD.

## MATERIALS AND METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[22]. Supplementary Table 1 includes the PRISMA 2009 Checklist.

### Search strategy

The search for the studies was carried out in 2021. A comprehensive literature search was undertaken using six English-language databases, MEDLINE, PubMed, PsycINFO, EMBASE, Cochrane, and Google, to identify published articles on psychotic symptoms in BD from January 1940 to December 2021. The *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) was also used to search these databases. The year 1940 was chosen as the inception point because the initial search revealed that very few studies of psychotic symptoms in BD had been conducted before that year. Only two studies from 1931 identified by the manual search were included in the final list of studies.

The following Medical Subject Headings search terms or combinations of these terms were used to search for the relevant studies: BD, mania, depression, psychosis, psychotic, delusions, hallucinations, FRS, mood-congruent symptoms, mood-incongruent symptoms, prevalence, course, and outcome. Supplementary Table 1 includes a list of the search strings used and the results retrieved from the PubMed search.

### Selection of studies

During the screening phase, all relevant original research articles were identified based on their titles and abstracts. At this stage, articles with no relevant information on the subject, those not in English, reviews, case reports/series, conference abstracts, editorials, and viewpoints were excluded. Full texts of the articles derived from the screening phase were reviewed to determine whether they met the selection criteria. These full texts were also searched manually to identify additional studies.

Inclusion criteria: Studies were included if they: (1) Had examined psychotic symptoms in BD; psychosis was defined as the presence of delusions and/or hallucinations; (2) Had a patient sample that included adult subjects (> 18 years of age); and (3) Had provided information on the relevant aspects of psychotic symptoms in BD including the rates and types of psychotic symptoms, clinical and demographic correlates, or the association with different parameters of outcome.

Exclusion criteria: The following were excluded: (1) Studies providing only qualitative data; (2) Studies where data on psychotic symptoms were not provided separately for BD; (3) Studies of child and adolescent subjects with BD; (4) Studies conducted exclusively among subjects with schizophrenia, schizoaffective disorder, and unipolar depression; and (5) Studies exclusively reporting neurocognitive outcomes of psychosis in BD (these studies were excluded because there are already several systematic reviews and meta-analyses on the subject).

### Data extraction

The following data were extracted for each study included in the final list: Authors, year of study, sample size, assessment procedures, results related to the areas of interest, and any indices that estimated the strength of associations, *e.g.*, odds or hazard ratios. The mean, median, and range were estimated for the rates of psychosis and different types of psychotic symptoms. The relationship of psychotic symptoms with the clinical and demographic correlates and outcome parameters was

determined based on studies reporting either positive or negative associations. Other aspects, such as the difference between BP I and BP II disorders or between mania, mixed episodes, and depression were also examined.

### Assessment of the quality of studies and risk of bias from the review

The STROBE Checklist for cohort, case-control, and cross-sectional studies (combined) was used to rate the quality of studies included in this review[23]. Additional considerations included a sample size of 200 patients (determined by power calculations based on the included studies), the use of standardized interviews to ascertain the diagnosis, the use of validated operational criteria, and the use of validated scales to measure outcomes. Based on these criteria, the studies included in the review were judged to be of good, moderate, or poor quality. The Risk of Bias in Systematic Reviews tool was used to ascertain the risk of bias arising from the quality of included studies, or the methods of this review[24].

To reduce the selection bias arising from included studies as well as the bias in rating the quality of studies, these procedures were initially carried out independently by the two authors. Any discrepancies were resolved by joint consensus following the independent evaluations.

## RESULTS

### Studies included for the review

The final list of this review included 339 studies. (These have been cited from reference number 25 to 363[25-363]). Figure 1 shows how these studies were eventually selected. Supplementary Table 2 includes the complete list of these studies with their methodological details. The largest number of studies provided data on patients with current episodes of mania ($n$ = 121), followed by the studies on lifetime psychosis among patients with BD ($n$ = 113), current psychosis in patients with BD ($n$ = 66), bipolar depression ($n$ = 57), and mixed episodes ($n$ = 43). Comparatively fewer studies had provided lifetime data among patients with mania ($n$ = 29), bipolar depression ($n$ = 21), and mixed episodes ($n$ = 8).

### Ratings of study quality and risk of bias

Supplementary Table 2 also includes the quality ratings for individual studies. According to these ratings, 97 studies were of good quality, 168 were of moderate quality, and 74 were poor quality studies. Since the majority of studies were of moderate quality, the risk of bias from studies included in this review was moderate to high.

### Prevalence of psychosis in BD

The lifetime and current rates of psychosis for BD, and manic, depressive, and mixed episodes are shown in Table 1. Supplementary Table 3 includes the complete details of these studies.

More than half of the patients with BD and about two-thirds of those with BP I disorder had psychotic symptoms during their lifetimes. The lifetime rates of psychosis were about 40%-60% in mania and mixed episodes but only about 20% in the episodes of bipolar depression. The current rates of psychosis were somewhat lower but still in the range of 40%-60% for BD, BP I disorder, mania, and mixed episodes. The current rates of psychosis were less than 20% for bipolar depression. Both the lifetime and current rates of psychosis were about two to three times higher in BP I compared to BP II disorder; this difference was more marked for mixed episodes where the current rates of psychosis in BP I disorder were about five times that of BP II disorder. Lifetime rates of psychosis were about twice as common in mania than in bipolar depression, while the current rates of psychosis were about three times higher in mania compared to bipolar depression. On the other hand, both the lifetime and current rates of psychosis were similar in mania and mixed episodes. Finally, about 60 studies had compared the rates of psychosis in bipolar and unipolar depression. In all but 12 of them, the rates of psychosis were higher in BD than in unipolar disorder. In contrast, 18 of the 20 studies that had compared BD with schizophrenia found much higher rates among patients with schizophrenia. An obvious problem in obtaining an accurate picture of the rates of psychosis was that the average rates tended to get skewed as the number of available studies declined. Though relying on median rates and excluding outliers resolved the problem to an extent, this did not completely correct the imbalance. Thus, the only reliable rates were those for BD, BP I disorder, and the current rates of psychosis in mania.

### Rates of different psychotic symptoms in BD

The lifetime and current rates of the different psychotic symptoms for BD, mania, bipolar depression, and mixed episodes are shown in Table 2. Supplementary Table 4 includes the complete details of these studies.

Predictably, there was greater variability in the rates of the four types of psychotic symptoms. The number of studies from which these rates were derived was also smaller, ranging from 1 to 25. However, certain consistent trends could still be made out.

**Table 1 Prevalence of psychosis in bipolar disorder**

| Study groups | Lifetime rates | Current rates |
|---|---|---|
| BD | *n* = 40, mean 57%; Median 56%; Range: 17%-93% | *n* = 32, mean 46%; Median 44%; Range: 11%-99% |
| BD I | *n* = 32, mean 61%; Median 64%; Range: 30%-90% | *n* = 10, mean 43%; Median 40%; Range: 12%-75% |
| BD II | *n* = 12, mean 22%; Median 20%; Range: 1%-49% | *n* = 6, mean 19%; Median 18%; Range: 9%-29% |
| Mania | BD-*n* = 5, mean 43%; Median 48%; Range: 19%-63% | BD-*n* = 20[1], mean 60%; Median 58%; Range: 25%-90% |
| | BP I-*n* = 4, mean 60%; Median 56%; Range: 44%-86% | BP I-*n* = 51, mean 56%; Median 56%; Range: 8%-91% |
| Bipolar depression | BD-*n* = 10, mean 21%; Median 19%; Range: 8%-42% | BD-*n* = 24[2], mean 24%; Median 19%; Range: 10%-80% |
| | BP I-*n* = 11, mean 27%; Median 27%; Range: 6%-55% | BP I-*n* = 12, mean 18%; Median 19%; Range: 3%-28% |
| | BP II-*n* = 6, mean 15%; Median 10%; Range: 7%-30% | BP II-*n* = 11, mean 11%; Median 8%; Range: 5%-28% |
| Mixed episodes | BD-*n* = 2, mean 50%; Median 50%; Range: 34%-66% | BD-*n* = 14, mean 47%; Median 40%; Range: 8%-97% |
| | BP I-*n* = 3, mean 43%; Median 33%; Range: 10%-86% | BP I-*n* = 14[3], mean 52%; Median 50%; Range: 15%-89% |
| | | BP II-*n* = 2, mean 11%; Median 11%; Range: 7%-15% |

[1]After excluding outliers, mean and median = 51%.
[2]After excluding outliers, mean = 19% and median = 18%.
[3]After excluding outliers, mean = 41% and median = 40%.
Complete details in Supplementary Table 3. BD: Bipolar disorder; BP I: Bipolar disorder type I; BP II: Bipolar disorder type II.

The average rates of delusions ranged from 44%-87% (median: 43%-87%) with the highest rates being obtained for a lifetime and current psychosis in BD, BP I disorder, mania, and mixed episodes. The average rates of delusions in bipolar depression were much less, ranging from 12%-20% in a lifetime and current episodes. In contrast, hallucinations were reported only in about a third of the patients, except for those with lifetime episodes of mania and mixed states where rates ranged from 55%-100%. However, the high rates in these two groups were probably because of the small number of studies involved. The number of studies was also small for bipolar depression, and the average rates were about 22% (median: 19%), with greater variability across individual studies. The lifetime rates of delusions and hallucinations in patients with BP I disorder far exceeded the rates among those with BP II disorder.

The rates of FRS were high, particularly for the studies of lifetime mania (mean and median: 45%, range up to 59%), current mania (mean: 28%, median: 32%, range up to 48%), and current mixed episodes (mean and median: 32%, range up to 49%). About a fifth of the patients with BD and BP I disorder also reported FRS during psychotic episodes, whereas the average rates in bipolar depression were somewhat lower. None of the studies of patients with BP II disorder reported FRS. However, apart from the current mania group, the number of studies was too small in the other groups to obtain an accurate estimate of the rates.

Mood-congruent psychotic symptoms were far more frequent and were present in about a third to half of the patients. Though some groups such as patients with current BP I disorder, lifetime depression, and lifetime mixed episodes reported very high rates of mood congruence, the number of studies was too small for these rates to be reliable. Mood-incongruent psychotic symptoms were usually reported by about a third of the patients (mean: 33%; median: 37%) apart from two exceptions. Rates were very high (72%-74%) for the lifetime mania and mixed groups, but these were based only on one or two studies. On the other hand, the rates in six studies of current bipolar depression were less than 10%. No studies of BP II disorder reported mood-congruent or incongruent symptoms. Finally, the difficulties of ascertaining mood congruence were reflected by the fact that nine studies had found that about 14% of the patients (range 2%-55%) had both types of symptoms simultaneously.

### *Types of delusions, hallucinations, and FRS in BD*

The different types of delusions, hallucinations, and FRS found in BD are shown in Tables 3-5. Supplementary Tables 5-7 include the complete details of these studies.

The number of studies from which these rates were derived was generally small, apart from certain exceptions such as those reporting grandiose and persecutory delusions and auditory and visual hallucinations. Very few studies had examined the different types of FRS.

Nevertheless, it appeared that both grandiose and referential delusions were equally common in BD, particularly among patients with mania. Persecutory delusions were present in about a third of the patients with BD and were almost equally common in the groups with mania, depression, or mixed episodes. Other common delusions included religious and erotomanic delusions; both were more common in mania and mixed episodes. Somatic delusions, delusional jealousy, and depressive

**Table 2 Rates of different psychotic symptoms in bipolar disorder**

| Study groups | Delusions | Hallucinations | First-rank symptoms | Mood congruent symptoms | Mood incongruent symptoms |
|---|---|---|---|---|---|
| Lifetime BD (*n* = 6-16) | Mean = 69%; Median = 71%; Range: 29%-100% | Mean = 37%; Median = 32%; Range: 13%-100% | Mean = 17%; Median = 11%; Range: 4%-44% | Mean = 49%; Median = 47%; Range: 18%-90% | Mean = 37%; Median = 40%; Range: 3%-76% |
| Lifetime BP I (*n* = 4-8) | Mean = 55%; Median = 71%; Range: 25%-82% | Mean = 32%; Median = 32%; Range: 23%-43% | Mean = 22%; Median = 25%; Range: 1%-38% | Mean = 37%; Median = 34%; Range: 11%-70% | Mean = 36%; Median = 30%; Range: 19%-66% |
| Lifetime BP II (*n* = 0-1) | Mean = 4%; Median = 4%; Range: 4% | Mean = 1%; Median = 1%; Range: 1% | - | - | - |
| Current BD (*n* = 2-13) | Mean = 54%; Median = 49%; Range: 16%-99% | Mean = 26%; Median = 19%; Range: 10%-58% | Mean = 26%; Median = 24%; Range: 5%-49% | Mean = 39%; Median = 39% Range: 24%-35% | Mean = 42%; Median = 46%; Range: 8%-75% |
| Current BP I (*n* = 1) | - | - | - | Mean = 68%; Median = 68%; Range: 68% | Mean = 32%; Median = 32%; Range: 32% |
| Current BP II | - | - | - | - | - |
| Lifetime mania (*n* = 1-5) | BD and BP I Mean = 77%; Median = 77%; Range: 33%-98% | BD and BP I Mean = 83%; Median = 83%; Range: 55%-100% | Only BP I Mean = 45%; Median = 45%; Range: 34%-59% | Only BD Mean = 87%; Median = 87%; Range: 87% | Only BP I Mean = 74%; Median = 74% Range: 74% |
| Current mania (*n* = 8-25) | BD and BP I Mean = 57%; Median = 62%; Range: 11%-87% | BD and BP I Mean = 35%; Median = 41%; Range: 10%-55% | BD and BP I Mean = 28%; Median = 32%; Range: 6%-48% | BD and BP I Mean = 41%; Median = 36%; Range: 20%-87% | BD and BP I Mean = 34%; Median = 36%; Range: 9%-64% |
| Lifetime bipolar depression (*n* = 1-3) | BD and BP I Mean = 16%; Median = 16%; Range: 10%-20% | BD and BP I Mean = 25%; Median = 25%; Range: 4%-73% | Only BP I Mean = 18%; Median = 18%; Range: 18% | Only BD Mean = 100%; Median = 100%; Range: 100% | - |
| Current bipolar depression (*n* = 2-13)[1] | BD and BP I Mean = 28%; Median = 22%; Range: 6%-97% | BD and BP I Mean = 14%; Median = 9%; Range: 7%-73% | Only BD Mean = 14%; Median = 14%; Range: 8%-20% | BD and BP I Mean = 54%; Median = 54%; Range: 7%-100% | BD and BP I Mean = 7%; Median = 6%; Range: 0-32% |
| Lifetime mixed episodes (*n* = 0-3) | Only BD Mean = 66%; Median = 66%; Range: 33%-100% | Only BD Mean = 55%; Median = 55%; Range: 10%-100% | - | BD and BP I Mean = 64%; Median = 64%; Range: 28%-100% | Only BP I Mean = 72%; Median = 72%; Range: 72% |
| Current mixed episodes (*n* = 2- 8) | BD and BP I Mean = 55%; Median = 53%; Range: 19%-90% | BD and BP I Mean = 38%; Median = 38%; Range: 23%-67% | Only BP I Mean = 32%; Median = 32%; Range: 16%-49% | BD and BP I Mean = 27%; Median = 28%; Range: 14%-37% | BD and BP I Mean = 41%; Median = 39%; Range: 22%-63% |

[1]Lifetime rates of hallucinations in bipolar disorder type II: Mean = 17%, median = 17%, range: 13%-21%. Complete details in Supplementary Table 4. BD: Bipolar disorder; BP I: Bipolar disorder type I; BP II: Bipolar disorder type II.

delusions, particularly delusions of guilt were found in all phases. Auditory hallucinations, especially auditory verbal hallucinations, were the most frequent types of hallucinations reported in BD and were equally common across all the groups. Visual hallucinations were much less common and found more frequently in mania. Other types of hallucinations were rare including somatic, tactile, olfactory, and gustatory hallucinations. Among the FRS, passivity delusions were the most common, followed by delusional perception, "running commentary" type of hallucinations, "voices conversing," thought echo, thought broadcast, thought insertion, somatic passivity, and thought withdrawal. As expected, the rates of all FRS were more common in mania, BD, and BP I disorders.

### *Demographic correlates of psychosis in BD*

Demographic correlates of psychosis in BD are included in Table 6. Supplementary Table 8 includes the complete details of these studies. The results showed that there were very few consistent associations of psychotic symptoms with sociodemographic variables in BD. Many studies (*n* = 27) had not found significant relationships between psychotic BD and any of the demographic characteristics. Moreover, when significant associations were found with demographic parameters in some of the studies, an equal number of studies usually reported contrary results. Finally, the number of studies that had failed to find significant associations of psychosis with individual demographic parameters far outweighed the studies that had found positive associations.

### *Clinical correlates of psychosis in BD*

Clinical correlates of psychosis in BD are also shown in Table 6. Supplementary Table 9 includes the complete details of these studies.

(1) The severity of psychosis and severity of illness in psychotic BD. Whether psychotic BD represents a more severe form of the illness has been examined by three groups of studies. The first group examined the severity of psychosis in BD relative to schizophrenia and unipolar depression. The

**Table 3 Types of delusions in bipolar disorder**

| Delusions | Grandiose | Referential | Persecutory | Erotomanic | Jealousy | Somatic | Depressive | Religious |
|---|---|---|---|---|---|---|---|---|
| Lifetime BD and BP I (*n* = 11) | Mean (*n* = 7) 52%; Median 61%; Range: 24%-69% | Mean (*n* = 3) 59%; Median 61%; Range: 54%-62% | Mean (*n* = 9) 40%; Median 40%; Range: 16%-56% | - | Mean (*n* = 2) 8%; Median 8%; Range: 3%-13% | - | Mean (*n* = 2) 13%; Median 13%; Range: 12%-15% | Mean (*n* = 1) 35%; Median 35%; Range: 35% |
| Current BD ( *n* = 9) | Mean (*n* = 9) 36%; Median 39%; Range: 4%-75% | Mean (*n* = 3) 42%; Median 5%; Range: 5%-75% | Mean (*n* = 8) 35%; Median 30%; Range: 7%-71% | Mean (*n* = 2) 4%; Median 4%; Range: 4% | - | Mean (*n* = 3) 16%; Median 11%; Range: 7%-31% | Mean (*n* = 7) 9%; Median 6%; Range: 3%-36% | Mean (*n* = 2) 5%; Median 5%; Range: 5% |
| Lifetime mania (N = 3) | Mean (*n* = 3) 66%; Median 69%; Range: 41%-88% | - | Mean (*n* = 3) 21%; Median 21%; Range: 12%-30% | - | Mean (*n* = 1) 2%; Median 2%; Range: 2% | Mean (*n* = 2) 16%; Median 16%; Range: 16% | Mean (*n* = 2) 10%; Median 7%; Range: 7%-13% | Mean (*n* =1) 3%; Median 3%; Range: 3% |
| Current mania (*n* = 23) | Mean (*n* = 17) 57%; Median 59%; Range: 20%-80% | Mean (*n* = 7) 43%; Median 41%; Range: 14%-69% | Mean (*n* = 20) 46%; Median 47%; Range: 8%-90% | Mean (*n* = 4) 29%; Median 24%; Range: 9%-61% | Mean (*n* = 1) 3%; Median 3%; Range: 3% | Mean (*n* = 5) 15%; Median 13%; Range: 1%-35% | Mean (*n* = 3) 10%; Median 10%; Range: 6%-14% | Mean (*n* = 7) 27%; Median 27%; Range: 22%-31% |
| Lifetime depression ( *n* = 2) | - | - | Mean (*n* = 2) 17%; Median 17%; Range: 15%-20 | - | - | - | - | - |
| Current depression ( *n* = 5) | - | Mean (*n* = 2) 32%; Median 32%; Range: 32%-33% | Mean (*n* = 4) 37%; Median 39%; Range: 1%-7% | - | Mean (*n* = 1) 20%; Median 20%; Range: 20% | Mean (*n* = 1) 17%; Median 17%; Range: 17% | Mean (*n* = 3) 12%; Median 7%; Range: 3%-30% | - |
| Lifetime mixed (*n* = 1) | - | - | Mean (*n* = 1) 33%; Median 33%; Range: 33% | - | Mean (*n* = 1) 33%; Median 33%; Range: 33% | - | - | - |
| Current mixed (*n* = 4) | Mean (*n* = 3) 42%; Median 41%; Range: 19%-66% | Mean (*n* = 2) 71%; Median 71%; Range: 56%-86% | Mean (*n* = 4) 46%; Median 31%; Range: 16%-90% | - | - | Mean (*n* = 3) 7%; Median 10%; Range: 7%-13% | Mean (*n* = 2) 19%; Median 19%; Range: 6%-33% | - |
| Overall rates | Mean (*n* = 39) 51%; Median 54%; Range: 4%-88% | Mean (*n* = 17) 49%; Median 42%; Range: 5%-86% | Mean (*n* = 52) 34%; Median 32%; Range: 1%-90% | Mean (*n* = 6) 16%; Median 14%; Range: 4%-61% | Mean (*n* = 6) 13%; Median 13%; Range: 3%-33% | Mean (*n* = 14) 14%; Median 13%; Range: 1%-35% | Mean (*n* = 19) 12%; Median 10%; Range: 3%-36% | Mean (*n* = 11)18%; Median 17%; Range: 3%-42% |

Complete details in Supplementary Table 5. BD: Bipolar disorder; BP I: Bipolar disorder type I; BP II: Bipolar disorder type II.

number of studies showing that psychotic symptoms were either less or more severe in BD was exactly equal suggesting that the severity of psychotic symptoms in BD was no different from the other patient groups with psychosis. The second group of studies focused on the association between psychotic symptoms and the overall severity of BD or the severity of manic and depressive symptoms. Here, the number of studies showing that the severity of illness or mood symptoms was greater in psychotic BD outnumbered those that did not find a difference. This indicated that the overall severity of the illness and severity of acute episodes was greater in psychotic BD. However, about a third of these studies had found this to be true only for the severity of manic symptoms. Therefore, the association between severe mood symptoms and psychotic BD was largely applicable to patients with current manic episodes. The third group of studies had examined the severity of BD with psychosis in terms of its impact on the course and outcome of the disorder. These are discussed later.

(2) Other indicators of severity. There was some evidence that psychotic BD was associated with poorer insight and a higher frequency of symptoms of agitation, aggression, and anxiety. Then again, this finding was also derived from the studies of mania, where agitation, violence, lack of insight, and psychosis often co-occurred. On the other hand, the rates of psychiatric comorbidity did not appear to be greater in those with psychotic BD.

### *Impact of psychotic symptoms on the course and outcome of BD*

The impact of psychosis on the different aspects of the course and outcome of BD is summarized in Table 7. Supplementary Table 10 includes the complete details of these studies.

The overall conclusion from these studies was that psychotic BD was not inevitably associated with a more adverse course and poorer outcome of BD. While several studies had found psychosis was associated with a poorer overall outcome, the number of those that had failed to find such an association

**Table 4 Types of hallucinations in bipolar disorder**

| Hallucinations | Auditory/AVH | Visual | Tactile | Olfactory | Gustatory | Somatic | Others |
|---|---|---|---|---|---|---|---|
| Lifetime BD and BP I ($n$ = 13) | Mean ($n$ = 13) 26%; Median 24%; Range: 3%-52% | Mean ($n$ = 10) 23%; Median 23%; Range: 9%-47% | Mean ($n$ = 1) 16%; Median 16%; Range: 16% | - | - | - | Mean ($n$ = 3) Median 12%; 9%; Range: 3%-13% |
| Current BD ($n$ = 3) | Mean ($n$ = 3) 17%; Median 17%; Range: 8%-17% | Mean ($n$ = 2) 6%; Median 6%; Range: 3%-9% | Mean ($n$ = 1) 0.3%; Median 0.3%; Range: 0.3% | Mean ($n$ = 2) 1%; Median 1%; Range: 1% | Mean ($n$ = 2) 1%; Median 1%; Range: 1% | Mean ($n$ = 2) 2%; Median 2%; Range: 0.4%-3% | - |
| Lifetime mania ($n$ = 3) | Mean ($n$ = 3) 40%; Median 39%; Range: 22%-52% | Mean ($n$ = 1) 25%; Median 25%; Range: 25% | - | - | - | Mean ($n$ = 1) 11%; Median 11%; Range: 11% | - |
| Current mania ($n$ = 18) | Mean ($n$ = 17) 33%; Median 41%; Range: 12%-57% | Mean ($n$ = 8) 20%; Median 17%; Range: 2%-61% | Mean ($n$ =2) 4%; Median 4%; Range: 3%-5% | Mean ($n$ = 2) 8%; Median 8%; Range: 6%-13% | - | Mean ($n$ = 2) 11%; Median 11%; Range: 1%-21% | Mean ($n$ = 5) 27%; Median 28%; Range: 7%-46% |
| Lifetime depression ($n$ = 2) | Mean ($n$ = 2) 40%; Median 40%; Range: 13%-67% | Mean ($n$ = 1) 7%; Median 7%; Range: 7% | - | - | - | - | Mean ($n$ = 2) 18%; Median 18%; Range: 4%-33% |
| Current depression ($n$ = 6) | Mean ($n$ = 6) 16%; Median 9%; Range: 4%-50% | Mean ($n$ = 3) 5%; Median 3%; Range: 1%-11% | - | Mean ($n$ = 1) 0.5%; Median 0.5%; Range: 0.5% | Mean ($n$ = 1) 0.5%; Median 0.5%; Range: 0.5% | - | Mean ($n$ = 1) 2%; Median 2%; Range: 2% |
| Lifetime mixed ($n$ = 1) | Mean ($n$ = 1) 33%; Median 33%; Range: 33% | - | - | - | - | - | - |
| Current mixed ($n$ = 3) | Mean ($n$ = 3) 37%; Median 41%; Range: 4%-67% | Mean ($n$ = 3) 13%; Median 18%; Range: 2%-20% | Mean ($n$ = 1) 5%; Median 5%; Range: 5% | - | Mean ($n$ = 1) 0.5%; Median 0.5%; Range: 0.5% | Mean ($n$ = 1) 2%; Median 2%; Range: 2% | Mean ($n$ = 1) 6%; Median 6%; Range: 6% |
| Overall rates | Mean ($n$ = 48) 30%; Median 30%; Range: 3%-67% | Mean ($n$ = 28) 14%; Median 13%; Range: 3%-47% | Mean ($n$ = 1) 6%; Median 6%; Range: 0.3%- 16% | Mean ($n$ = 5) 3%; Median 3%; Range: 1%- 16% | Mean ($n$ = 4) 1%; Median 1%; Range: 0.5%-1% | Mean ($n$ = 5) 8%; Median 8%; Range: 0.4%-47% | Mean ($n$ = 10) 12%; Median 1%; Range: 1%-46% |

Complete details in Supplementary Table 6. AVH: Auditory verbal hallucinations or hearing voices; BD: Bipolar disorder; BP I: Bipolar disorder type I; BP II: Bipolar disorder type II.

was almost the same or even more. This trend also appeared to be true for several individual measures of outcome including earlier age of onset, a persistent or chronic course of the illness, lack of remission or recovery, more frequent relapses or recurrences, a greater number of lifetime mood episodes, poor functioning, poor quality of life, and poor functional outcome. Since a large number of studies with reasonable methodological quality had examined these outcome parameters, this lent further support to the notion that psychosis was not always associated with poor outcomes in BD. Moreover, studies that had estimated odds or hazard ratios also showed that psychotic symptoms were not associated with earlier age of onset, poorer functional, or poorer overall outcomes[51,159,256,313,355]. Though some of the studies based on similar estimations of risk had found adverse outcomes in psychotic BD[103,104,137,157], the positive association of psychosis with poor outcomes in these studies was usually found only in a few outcome measures and not in others[64,250,288,342].

Additionally, negative associations between psychosis and outcome were reported in other domains such as the manic polarity of BD, a seasonal pattern of the illness, the response to lithium treatment, and a poorer outcome with FRS. However, these findings were uncertain because of the small number of studies involved.

Finally, psychosis appeared to be linked to better outcomes in three other areas including a lower proportion of rapid cycling, a shorter duration of illness, and a lowered suicidal risk. The negative association with suicidal behavior appeared to be particularly strong based on the number of studies and estimations of risk[40,57,105,306].

Nevertheless, psychosis appeared to be more consistently linked with adverse outcomes in some of the other areas. The rate and the duration of hospitalizations were consistently higher among patients with psychotic BD. Some studies had found the risk of hospitalization to be about one and a half times in psychotic BD[209]. Patients with depression were more likely to switch to BD if they had psychotic

**Table 5 Types of first rank symptoms in bipolar disorder**

| Study groups | Passivity/control | Delusional perception | Somatic passivity | Thought broadcast | Thought insertion | Thought withdrawal | Running commentary | Two or more voices conversing | Thought echo |
|---|---|---|---|---|---|---|---|---|---|
| Lifetime BD and BP I (*n* = 9) | Mean (*n* = 4) 10%; Median 11%; Range: 4%-16% | Mean (*n* = 1) 20%; Median 20%; Range: 20% | - | Mean (*n* = 3) 11%; Median 14%; Range: 3%-17% | Mean (*n* = 1) 20%; Median 20%; Range: 20% | Mean (*n* = 1) 4%; Median 4%; Range: 4% | Mean (*n* = 4) 17%; Median 17%; Range: 10%-27% | Mean (*n* = 4) 16%; Median 17%; Range: 5%-27% | Mean (*n* = 1) 13%; Median 13%; Range: 13% |
| Current BD (*n* = 4) | Mean (*n* = 2) 36%; Median 36%; Range: 18%-49% | Mean (*n* = 2) 6%; Median 6%; Range: 2%-10% | Mean (*n* = 1) 7%; Median 7%; Range: 7% | Mean (*n* = 3) 14%; Median 5%; Range: 5%-18% | Mean (*n* = 1) 5%; Median 5%; Range: 5% | Mean (*n* = 1) 2%; Median 2%; Range: 2% | Mean (*n* = 2) 20%; Median 20%; Range: 4%-37% | Mean (*n* = 2)12%; Median 12%; Range: 4%-20% | Mean (*n* = 1) 4%; Median 4%; Range: 4% |
| Lifetime mania (*n* = 2) | Mean (*n* = 2) 27%; Median 27%; Range: 3%-52% | - | - | Mean (*n* = 1) 6%; Median 6%; Range: 6% | Mean (*n* = 1) 4%; Median 4%; Range: 4% | Mean (*n* = 1) 3%; Median 3%; Range: 3% | Mean (*n* = 1) 1%; Median 1%; Range: 1% | Mean (*n* = 1) 1%; Median 1%; Range: 1% | Mean (*n* = 2) 14%; Median 14%; Range: 14%-15% |
| Current mania (*n* = 8) | Mean (*n* = 8) 23%; Median 20%; Range: 5%-48% | - | - | Mean (*n* = 5) 12%; Median 14%; Range: 2%-21% | Mean (*n* = 3) 9%; Median 7%; Range: 1%-18% | Mean (*n* = 3) 9%; Median 3%; Range: 3%-13% | Mean (*n* = 3) 9%; Median 3%; Range: 2%-14% | Mean (*n* = 3) 5%; Median 3%; Range: 2%-6% | Mean (*n* = 3) 5%; Median 2%; Range: 1%-12% |
| Lifetime depression (*n* = 1) | Mean (*n* = 1) 1%; Median 1%; Range: 1% | - | - | Mean (*n* = 1) 1%; Median 1%; Range: 1% | Mean (*n* = 1) 1%; Median 1%; Range: 1% | Mean (*n* = 1) 4%; Median 4%; Range: 4% | - | - | Mean (*n* = 1) 10%; Median 10%; Range: 10% |
| Current depression (*n* = 1) | - | - | - | - | - | - | - | Mean (*n* = 1) 17%; Median 17% | - |
| Current mixed (*n* = 1) | Mean (*n* = 1) 49%; Median 49%; Range: 49% | - | | - | - | - | - | - | - |
| Overall rates | Mean (*n* = 18) 24%; Median 24%; Range: 1%-49% | Mean (*n* = 3) 13%; Median 13%; Range: 2%-20% | Mean (*n* = 1) 7%; Median 7%; Range: 7% | Mean (*n* = 17) 9%; Median 8%; Range: 1%-18% | Mean (*n* = 7) 8%; Median 7%; Range: 1%-20% | Mean (*n* = 7) 4%; Median 3%; Range: 2%-13% | Mean (*n* = 10) 12%; Median 10%; Range: 1%-20% | Mean (*n* = 11) 10%; Median 10%; Range: 1%-27% | Mean (*n* = 8) 9%; Median 9%; Range: 4%-15% |

Complete details in Supplementary Table 7. BD: Bipolar disorder; BP I: Bipolar disorder type I; BP II: Bipolar disorder type II.

symptoms. Though this finding was based on only ten studies, some of them had estimated the risk to be between one and a half to two times based on odds ratios[186,216,222]. Lastly, the number of studies that found mood-incongruent psychotic symptoms to be associated with a poorer outcome was considerably more than those that had not found such an association.

## DISCUSSION

The current systematic review examined the extent of psychotic symptoms in BD and their impact on the course and outcome of BD based on the 339 studies that were selected. Before focusing on its findings, it is imperative to understand the strengths and weaknesses of the studies included in this review.

### *Methodological considerations*

This review showed that there is no dearth of studies on the subject of psychotic symptoms in BD. Moreover, almost every aspect such as the prevalence of psychotic symptoms, their correlates, and the impact of psychosis on the course and outcome of BD have been systematically assessed by a number of these studies. However, the existing literature has several methodological shortcomings that often make it difficult to reach firm conclusions.

**Table 6 Demographic and clinical correlates of psychosis in bipolar disorder**

| Correlates | Studies showing positive association with psychosis | Studies showing inverse association or no association with psychosis[1] |
|---|---|---|
| Younger age | *n* = 14 | *n* = 48 |
| Female sex | *n* = 16 | *n* = 51 |
| Single status | *n* = 11 | *n* = 14 |
| Lower educational levels | *n* = 9 | *n* = 26 |
| Low income or unemployment | *n* = 6 | *n* = 14 |
| Ethnic minority status | *n* = 4 | *n* = 10 |
| **Severity of psychotic symptoms in bipolar disorder** | | |
| Studies showing that psychotic symptoms are less severe in bipolar disorder | Studies showing that psychotic symptoms are more severe in bipolar disorder | |
| *n* = 20 | *n* = 20 | |
| **Severity of illness/mood symptoms in psychotic bipolar disorder** | | |
| Studies showing that the illness/mood symptoms are not more severe in psychotic bipolar disorder | Studies showing that severity of illness/mood symptoms is greater in psychotic bipolar disorder | |
| *n* = 16 | *n* = 34 | |
| **Insight and psychotic symptoms in bipolar disorder** | | |
| Studies showing that psychosis is associated with lack of insight in bipolar disorder | Studies showing that psychosis is not associated with lack of insight in bipolar disorder | |
| *n* = 15 | *n* = 9 | |
| **Agitation, aggression and anxiety in psychotic bipolar disorder** | | |
| Studies showing that agitation, aggression and anxiety are associated with psychosis in bipolar disorder | Studies showing that agitation, aggression and anxiety are not associated with psychosis in bipolar disorder | |
| *n* = 13 | *n* = 2 | |
| **Comorbidity and psychotic symptoms in bipolar disorder** | | |
| Studies showing that psychosis associated with greater comorbidity in bipolar disorder | Studies showing that psychosis is not associated with greater comorbidity in bipolar disorder | |
| *n* = 21 | *n* = 27 | |

[1]Twenty-seven studies found no significant relationships between psychotic bipolar disorder and any of the demographic characteristics. Complete details in Supplementary Tables 8 and 9.

The studies covered a period from 1940 to 2021, during which the definition of BD has undergone many changes. Thus, there may be some difficulty in equating labels such as manic-depressive psychoses and BD. However, there were only minor differences between the definitions in older studies and the current definitions of the disorder. Moreover, leaving out studies conducted before the 1980s would have resulted in a significant loss of data. Psychosis has usually been defined as the presence of delusions and/or hallucinations by most studies. Though this definition fits the current standards and is easily established by using structured interviews[364], a few studies have included formal thought disorder as a part of the definition[142]. This complicates matters since thought disorder is relatively non-specific and more difficult to ascertain. Nevertheless, the broader definition seems to be commonly used[365], while the narrower one has its critics[366]. The method of assessment also had a bearing on the results of the studies. Although the majority of the studies had used structured interviews and validated scales to assess psychotic symptoms, some especially the older ones had not. However, rather than the assessment method, the inadequate sample size of most of the studies compromised their methodological adequacy. Moreover, almost all studies included hospital-based patients. The lack of community studies hinders the generalization of these findings to patients with BD in real-world settings. These lacunae in the quality of most of the studies included in the review raise the possibility of a moderate to high risk of bias in the findings of this review. The variability in results could also result from the lack of control for potential confounders such as age[159,321], sex[357,367], mood state[8], comorbidity[162], and chronicity of the illness[46]. Although multivariate statistics have been used in many studies to control for these factors, risk estimates are only offered by a few of them, and the estimation of the strength of associations by calculating effect sizes is rare. Finally, there was a lack of

**Table 7 Impact of psychotic symptoms on the course and outcome of bipolar disorder**

| Outcome measure | Studies with positive association with psychosis in bipolar disorder | Studies with negative or no association with psychosis in bipolar disorder |
|---|---|---|
| Poor overall outcome | *n* = 38 | *n* = 39 |
| Earlier age of onset | *n* = 30 | *n* = 36 |
| Persistent or chronic course of illness | *n* = 23 | *n* = 18 |
| Lack of remission or lack of recovery | *n* = 12 | *n* = 15 |
| More frequent relapses or recurrences | *n* =5 | *n* = 5 |
| Greater number of mood episodes | *n* = 13 | *n* = 19 |
| Lower proportion with rapid cycling | *n* = 6 | *n* = 6 |
| Longer duration of illness | *n* = 5 | *n* = 23 |
| Manic polarity of illness | *n* = 9 | *n* = 6 |
| Seasonal pattern of illness | *n* = 2 | *n* = 2 |
| More frequent hospitalizations or longer hospital stays | *n* =26 | *n* = 15 |
| Poor functioning, poor quality of life, or poor functional outcome | *n* = 45 | *n* = 46 |
| More frequent suicidal attempts or heightened suicidal behavior | *n* = 14 | *n* = 35 |
| Good response to lithium treatment | *n* = 5 | *n* = 10 |
| Switch to diagnosis of bipolar disorder | *n* = 10 | - |
| Poorer outcome with mood-incongruent psychotic symptoms | *n* = 21 | *n* = 13 |
| Poorer outcome with first-rank symptoms | *n* = 3 | *n* = 9 |

Complete details in Supplementary Table 10.

studies examining the descriptive and subjective aspects of psychotic symptoms in BD[8].

### *Principal findings of this review*

As a consequence of the methodological variability across the studies, some of the findings of this review were more reliable than the others.

One of the more reliable findings was the very high rates of psychotic symptoms in BD. In keeping with the earlier reviews, more than half of the patients with BD, mania, or mixed episodes developed such symptoms during their lifetimes[2,3,5,14,89]. Current rates of psychosis were also high and found in a little less than half of these patients. In contrast, earlier reviews have reported that about a third of the patients have psychotic symptoms during their current episodes[6,368].

Like the earlier reports, psychosis was much more common in mania and mixed episodes than in bipolar depression[3,5,8]. Psychosis was about twice as common in BP I compared to BP II disorder. Despite the smaller number of studies of patients with BP II disorder, this has been a consistent finding in the existing literature[3]. This could be because psychosis can be present only during depressive episodes in BP II disorder according to the current definitions or because of the lower severity of illness in this subtype[44,62]. In agreement with the earlier reviews[3-5], a large number of studies found the rates of psychosis to be much higher in bipolar compared to unipolar depression. However, the rates of psychosis were usually lower than those found in schizophrenia[6-8].

The rates of different types of psychotic symptoms were somewhat less reliable, principally because of the smaller number of studies involved. Nevertheless, the trends were similar to the existing reports. Thus, delusions were far more frequent than hallucinations in all phases of BD[2,3,5,8,10]. The higher rates in mania compared to bipolar depression and BP I compared to BP II disorder were also in keeping with the previous reviews[3,8-10,368]. Though based on the smallest number of studies, about a third of the patients reported experiencing FRS, particularly during acute manic episodes. This was almost equal to the rates of FRS reported in the existing literature[2,3,8,10]. Similar to the earlier reports, mood-congruent psychotic symptoms were more common among patients with BD[2,3,6,8,10]. As found in these reviews, mood-incongruent symptoms were reported in about a third of the patients with BD, and the rates were highest for those with mania. However, because of the small number of studies and the

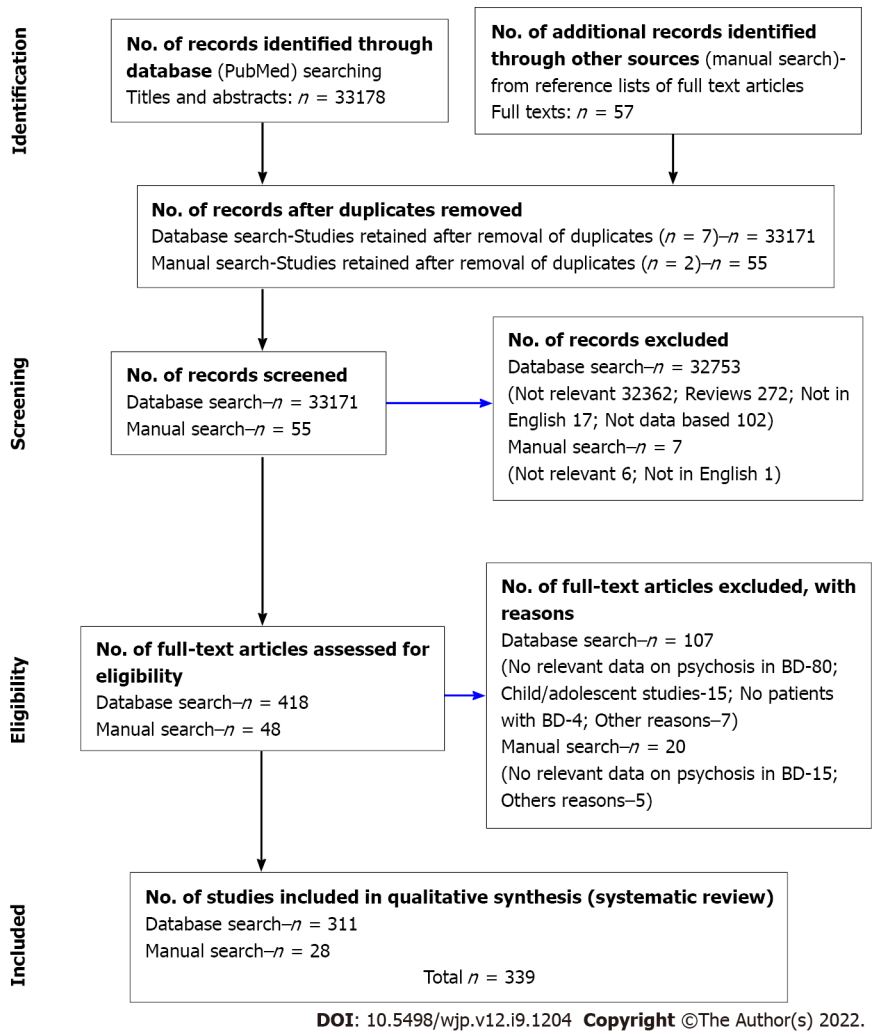


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**Figure 1 PRISMA flow diagram of the PubMed and manual searches for the selection of articles included in the current review.** BD: Bipolar disorder.

difficulties in ascertaining mood congruence, the validity of these findings is questionable. Similarly, the findings regarding the different types of delusions, hallucinations, and FRS were also based on very few studies but conformed to what has been reported earlier[3,5,8,10,89].

One of the principal objectives of this review was to examine the impact of psychosis on the course, outcome, clinical correlates, and demographic profile of BD. The findings of this aspect of the current review proved to be the most reliable since they were based on the largest number of studies, which were of moderate to good quality. Moreover, taken together these studies had carried out a comprehensive examination of different facets of BD that could be impacted by the presence of psychosis. The overall conclusion of this section of the review was that psychotic BD is not always associated with a negative impact on the illness. This reflected the continuing debate about the prognostic implications of psychosis in BD, with some reviews concluding that psychosis is associated with a poorer prognosis[9,11,12,89], whereas the majority have found an uncertain impact of psychosis on BD[2,3,5,8,46].

In line with the other reviews[3,8,10], the current one found few consistent associations of psychotic symptoms in BD with sociodemographic variables. Thus, the case for psychosis being associated with an adverse demographic profile[89] was not proven. The findings concerning the clinical correlates were more equivocal. As reported earlier[3,10,13], psychotic symptoms were not more severe in BD, particularly when compared to schizophrenia. On the other hand and in keeping with the existing evidence[2,3,12,89], the severity of the illness in psychotic BD appeared to be consistently greater. However, this finding was largely based on manic symptom severity, which tends to be inevitably higher than the other phases of BD[2]. Moreover, the genesis of psychotic symptoms is likely to be only partly mediated by clinical severity and partly by other factors such as early-onset, shorter duration of illness, comorbid conditions, and sex[8]. Psychosis was associated with a lack of insight, particularly during severe manic episodes. Then again, because most patients regain insight once mania resolves, the extent of impaired insight was less among patients with psychotic mania compared to those with schizophrenia[61,161]. Psychosis was also associated with a more frequent occurrence of agitation, anxiety, and hostility, but this association could be a consequence rather than the cause of psychosis in BD[8]. Finally, comorbid

disorders were less common in psychotic BD, which was in agreement with the other reviews[3].

There was greater uncertainty about the impact of psychosis on the other parameters of course and outcome. The number of studies reporting poorer overall outcomes in psychotic BD was no different from those that failed to find such a relationship. Moreover, there was no consistent association between psychotic symptoms and earlier age of onset, lack of remission and recovery, more frequent relapses and recurrences, the persistence of psychosis, poorer functional outcomes, and lithium response. Lastly, psychosis was less likely to be associated with a rapid-cycling course, longer duration of illness, and heightened suicidal behavior. This emulated the uncertainty in the existing literature regarding the associations of psychosis in BD with an earlier age of onset[2,89,369-371], a poorer long-term course[2,3,8,46,89], impaired functioning[88,367,372,373], more frequent suicide attempts[3,374,375], more frequent rapid-cycling course[46], predominant manic polarity[376], and lithium response[2,6,89,377]. The lack of impact on functioning was surprising but not unexpected. The existing literature suggests that though a significant proportion of the patients with BD have impaired functional and social outcomes, this does not appear to be mediated by the presence of psychotic symptoms[83,141].

Nevertheless, psychosis was associated with poor outcomes in three domains. Psychosis was associated with a higher risk of switching to BD, which is known to occur in about a fifth of the patients with depression[8]. Psychotic symptoms were also associated with more frequent hospitalizations and longer hospital stays, which has been noted by other reviews[9]. Finally, mood-incongruent symptoms appeared to be associated with poorer overall outcomes. Most of the earlier reviews have reported both positive and negative associations of mood-congruent symptoms with outcome[2,3,6,46,250]. However, the most comprehensive review on the subject found that though mood-incongruent symptoms were associated with poor outcomes, the differences between psychotic and non-psychotic BD were small and rarely significant[378]. Moreover, in line with the existing evidence, the current review also found that psychotic BD had a better outcome than schizophrenia[7,11].

## CONCLUSION

The current systematic review has shown that there is no paucity of evidence on the subject of psychotic symptoms in BD. However, because of methodological shortcomings of the evidence, there are few consistent and reliable findings. One of them was the high prevalence of psychotic symptoms and the other was the lack of an adverse impact of psychosis on several domains of BD, including its course and outcome. These findings together with the genetic, neurobiological, and neurocognitive evidence suggest that psychotic BD lies on a continuum between non-psychotic forms of the disorder and schizophrenia[379-382]. Mood-incongruent psychotic BD, which is a severe form of BD overlaps with schizophrenia, whereas non-psychotic BD is similar to unipolar disorders[17,18,79,383]. The evidence from this review thus supports the current classification of BD as lying in an intermediate position between unipolar depression and schizophrenia[1]. Finally, from the clinicians' perspective, this review suggests that greater awareness and understanding of this subject is needed so that psychotic BD can be properly diagnosed and adequately treated in routine practice.

## ARTICLE HIGHLIGHTS

### *Research background*

Psychotic symptoms are very common in bipolar disorder (BD) and have the potential to adversely affect its course, outcome, and treatment. However, despite the considerable amount of research and several reviews on the subject, the impact of psychotic symptoms on the course and outcome of BD remains unclear. Moreover, there are very few systematic reviews on the impact of psychosis in BD.

### *Research motivation*

The lack of information about the impact of psychotic symptoms in BD in existing literature prompted the current systematic review. Moreover, it was prompted by the possibility that the presence of such symptoms in BD and their impact on the illness may have significant etiological, nosological, and clinical implications.

### *Research objectives*

The current systematic review was specifically intended to address the gaps in the literature regarding psychotic symptoms in BD. Therefore, it aimed to examine psychotic symptoms in BD and their impact on several domains of BD. This review focused on four groups of studies and four types of psychotic symptoms. The impact of psychotic symptoms was determined by exploring demographic correlates of psychotic symptoms, their clinical correlates, and the influence of psychotic symptoms on different parameters of course and outcome of BD.

### *Research methods*

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. It undertook an electronic search supplemented by a manual one. Articles were selected in two phases: Screening of abstracts and review of full texts. The methodological quality of the studies and the risk of bias were ascertained by standard tools.

### *Research results*

This systematic review included 339 studies of BD. The results endorsed the high rates of all types of psychotic symptoms found in BD. More than a half to two-thirds of the patients experienced psychosis during their lifetimes. Current psychosis was found in a little less than half of these patients. Delusions were more common than hallucinations. About a third of the patients had first-rank symptoms or mood-incongruent psychotic symptoms. Psychotic symptoms were more frequent in bipolar type I disorder, and in mania or mixed episodes. However, psychosis was associated with an adverse impact only in a few domains of the illness including the severity of BD, lack of insight, more frequent occurrence of agitation, anxiety, and hostility, the rate of and the duration of hospitalizations, switch to BD among patients with depression, and poorer outcomes with mood-incongruent symptoms. No consistent associations were found in other areas, suggesting that psychosis is not always associated with a negative impact on BD. This finding conformed to the current consensus in the literature on psychotic BD.

### *Research conclusions*

Though psychotic symptoms are very common in BD, they are not always associated with an adverse impact on BD and its course and outcome.

### *Research perspectives*

The ongoing debate about the impact of psychosis in BD is yet to be resolved. Studies with more improved methodology are needed to ascertain the true impact of psychotic symptoms in several domains of BD.


## FOOTNOTES


**Author contributions:** Both the authors have contributed equally to the planning of this review, carrying out the literature search, analyzing and preparing the results, and writing the manuscript.

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SYSTEMATIC REVIEWS

# Mental health impact on Black, Asian and Minority Ethnic populations with preterm birth: A systematic review and meta-analysis

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## Abstract

***BACKGROUND***

Preterm birth (PTB) is one of the main causes of neonatal deaths globally, with approximately 15 million infants are born preterm. Women from the Black, Asian, and Minority Ethnic (BAME) populations maybe at higher risk of PTB, therefore, the mental health impact on mothers experiencing a PTB is particularly important, within the BAME populations.

***AIM***

To determine the prevalence of mental health conditions among BAME women with PTB as well as the methods of mental health assessments used to characterise the mental health outcomes.

***METHODS***

A systematic methodology was developed and published as a protocol in PROSPERO (CRD420-20210863). Multiple databases were used to extract relevant data. $I^2$ and Egger's tests were used to detect the heterogeneity and publication bias. A trim and fill method was used to demonstrate the influence of publication bias and the credibility of conclusions.

***RESULTS***

Thirty-nine studies met the eligibility criteria from a possible 3526. The prevalence rates of depression among PTB-BAME mothers were significantly higher than full-term mothers with a standardized mean difference of 1.5 and a 95% confidence interval (CI) 29%-74%. The subgroup analysis indicated depressive symptoms to be time sensitive. Women within the very PTB category demonstrated a significantly higher prevalence of depression than those categorised as non-very PTB. The prevalence rates of anxiety and stress among PTB-BAME mothers were significantly higher than in full-term mothers (odds ratio of 88% and 60% with a CI of 42%-149% and 24%-106%, respectively).

***CONCLUSION***

BAME women with PTB suffer with mental health conditions. Many studies did not report on specific mental health outcomes for BAME populations. Therefore, the impact of PTB is not accurately represented in this population, and thus could negatively influence the quality of maternity services they receive.


**Key Words:** Preterm labor; Preterm birth; Black, Asian, and Minority Ethnic; Mental health; Women's health; Wellbeing

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**Core Tip:** Preterm birth is a multi-etiological condition and a leading cause of perinatal mortality and morbidity. This study demonstrates the mental health impact due to preterm birth among the Black, Asian and Ethnic minority women. There is minimal research available at present around this subject matter, and this important disease sequelae.

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## INTRODUCTION

Preterm birth (PTB) is a multi-etiological condition and a leading cause of perinatal mortality and morbidity[1]. PTB can be categorized as per the World Health Organization classification methods as extreme preterm (gestational age < 28 wk), very preterm (gestational age of 28-32 wk) and moderately preterm (32-37 wk). Most preterm infants are at risk of developing respiratory and gastrointestinal complications[2]. The PTB rates are higher in most developed regions of the world, despite advances in medicine. PTB are at the highest level in the US for between 12%-15% and 5%-9% in Europe. In comparison, PTB rates in China range between 4.7%-18.9% (1987-2006) and Taiwan 8.2%-9.1%[3]. The prevalence of PTB increased from 9.8% in 2000 to 10.6% by 2014 and has become a global public health

issue[1]. However, the mental health impact associated with PTB is not extensively examined, despite it potentially may exacerbate the patient's experience of a distressing birth. Furthermore, clearly pronounced risk of PTB among Black women have been reported in studies from United States or United Kingdom[4,5], with limited data on the risk among other ethnic groups. While health disparities, social deprivation are recognised risk factors for PTB that are also frequently associated with Black, Asian, and Minority Ethnic (BAME) populations, the available data on ethnic disparities associated with PTB remains limited.

In the United Kingdom, health disparities within Caribbean and West African populations demonstrate a significant risk of very PTB in comparison to Caucasians. Similar risks within the South Asian community appear to be less consistent in comparison to Caucasian PTB women[11]. In the United Kingdom, National Health Service (NHS) England reports improvements to maternity services are a priority as part of the NHS 10-year plan[12]. As per the 2018 Public Health England report on maternity services, 1 in 4 of all births within Wales and England were to mothers born outside the United Kingdom[12]. Additionally, 13% of all infants born between 2013-2017 are from the BAME population[12]. Importantly, Black women were 5 times more at risk of death during parturition and Asian babies are 73% more likely to result in neonatal death compared to Caucasian women[12], therefore, the mental health impact experienced by PTB mothers is vital to evaluate particularly in the BAME population. A number of socio-economic, genetic and obstetric causes have been proposed to explain mental health disorders among PTB women, but these theories do not fully explain the aetiology. Furthermore, they also exclude the bidirectional relationship between PTB, and mental health conditions demonstrated by some studies[13,18,19].

This available evidence demonstrates a need to explore the mental health impact on BAME women with PTB. We believe that gathering this evidence would inform the forthcoming evidence-based women's health strategy in the United Kingdom to explore both the physical and mental health components, and to be inclusive using cultural adaptations where appropriate.

## MATERIALS AND METHODS

An evidence synthesis methodology was developed using a systematic protocol that was developed and published on PROSPERO (CRD42020210863). The aims of the study were to determine the prevalence of mental health conditions among BAME women with PTB as well as the mental health assessments used to characterise the mental health outcomes.

### *Data searches*

Multiple databases were used, including PubMed, EMBASE, Science direct, and The Cochrane Central Register of Controlled trials for the data extraction process. Searches were carried out using multiple keywords and MeSH terms such as "Depression", "Anxiety", "Mood disorders", "PTSD", "Psychological distress", "Psychological stress", "Psychosis", "Bipolar", "Mental Health", "Unipolar", "self-harm", "BAME", "Preterm birth", "Maternal wellbeing" and "Psychiatry disorders". These terms were then expanded using the 'snow-ball' method and the fully developed methods are in the supplementary section (Supplementary material).

### *Eligibility criteria and study selection*

All eligible randomised controlled trials (RCTs) and non-RCTs published in English were included. The final dataset was reviewed independently. Multiple mental health variables were used alongside of the 2 primary variables of PTB and BAME.

### *Data extraction and analysis*

The extraction and eligibility has been demonstrated using a PRISMA diagram. The data was collected using Endnote and Microsoft excel. Stata 16.1 was used as a way to complete the final statistical analysis. Standardized mean difference (SMD) and 95% confidence interval (CI) were extracted for analysis. Heterogeneity was assessed by way of funnel plots, $\chi^2$-test ($P$ value) and $I^2$. A sub-group analysis was conducted to determine the mental health symptomatologies identified and the geographical location.

Due to the unified use of mental health assessments, in order to standardize the mean differences reported within each study, the following mathematical method was used[25-27]:

$$\widehat{g_k} = (1 - \frac{3}{4n_k - 9}) \frac{\widehat{u_{ek}} - \widehat{u_{ck}}}{\sqrt{((n_{ek} - 1)s_{ek}^2 + (n_{ck} - 1)s_{ck}^2)/(n_k - 2)}}$$

$$\widehat{Var}(\widehat{g_k}) = \frac{n_k}{n_{ek} \cdot n_{ck}} + \frac{\widehat{g_k}^2}{2(n_k - 3.94)}$$

where, $n_k = n_{ek} + n_{ck}$, $n_{ek}$, $\widehat{u_{ek}}$, $s_{ek}$ are the number, mean and standard variation of exposed group and $n_{ck}$, $\widehat{u_{ck}}$, $s_{ck}$ are the number, mean and standard variation of control group. Then we can obtain the 95%

confidence interval by $\widehat{g_k} \pm 1.96 * S.E.(\widehat{g_k})$ where $S.E.(\widehat{g_k}) = \sqrt{\widehat{Var}(\widehat{g_k})}$.

### Meta-regression and sub-group analysis

To eliminate heterogeneity, a meta-regression and sub-group analyses were conducted by mental health assessment timepoints and country.

### Sensitivity analysis

To further analyse the heterogeneity of studies reporting depression and anxiety, a sensitivity analysis was conducted.

### Risk of bias quality assessment

Studies included within this study were critically appraised individually using mental health variables. All studies appraised for methodological quality and risk of bias based on the Newcastle-Ottawa Scale (NOS), which is commonly used for cross-sectional and/or cohort studies as demonstrated by Wells *et al* [73]. These could be further modified using the adapted NOS version as reported by Modesti *et al*[74]. The NOS scale includes 8 items within 3 specific quality parameters of selection, outcome and comparability. The quality of these studies was reported as good, fair or poor based on the details below: Good quality score of 3 or 4 stars were awarded in selection, 1 or 2 in comparability and 2 or 3 stars in outcomes; Fair quality score of 2 stars were awarded in selection, 1 or 2 stars in comparability and 2 or 3 stars in outcomes; Poor quality score was allocated 0 or 1 star in selection, 0 stars in comparability and 0 or 1 star in outcomes.

### Outcomes

The following outcomes were included within the meta-analysis: Prevalence of anxiety and depressive symptoms, and parenting stress; Clinical significance of the data identified; Critical interpretive synthesis of common mental health reported outcomes.

Outcomes such as post-partum depression could not be synthesised for the meta-analysis. Therefore, these aspects have been included in the narrative analysis only.

### Publication bias

Publication bias is a concern to the validity of conclusion of a meta-analysis. As a result, several methods could be used to assess this aspect. An egger's test was used to report on publication bias. Additionally, a trim and fill (TAF) method was used to analyze the influence of publication bias. TAF estimates any missing studies due to publication bias within the funnel plot to adjust the overall effect estimate.

### Patient and public involvement

A representative from a patient-public focus group associated with a multi-morbid project investigating women's physical and mental health sequelae was invited to review the protocol and the resulting paper. This is a vital facet of developing and delivering an authentic evidence synthesis to reduce the gap between evidence production, development of solutions to address the identified gaps and the implementation of the solutions into practice as well as their acceptability by patients.

## RESULTS

Of the 3526 studies, 39 met the eligibility criteria. All 39 studies reported the mental health status of BAME women with PTB although it remained unclear if they reported mental health symptoms or clinical diagnoses. Figure 1 shows the PRISMA diagram. The mental health assessments and frequency of the data gathering varied across studies. The 39 studies primarily reported stress, anxiety and depression as indicated in Table 1 along with other characteristics. The quality assessment using the Newcastle Ottawa scale (NOS) and Risk of Bias identified within the pooled studies are shown in Tables 2 and 3 and Supplementary Table 1. Brief description of various scales used to assess depression, anxiety, and stress across studies is presented in the supplementary file on Mental Health Questionnaires.

### Depression

Of the 39 studies, 36 primarily reported an association between the prevalence of depression and PTB. Fifteen studies only examined the differences of non-depressive symptoms as well other factors such as race, ethnicity, plurality across multiple assessment timepoints although, they were not compared to full-term birth mothers of BAME decent. The overall SMD was 0.4 and 95%CI of a range of 0.25-0.56, indicating the prevalence of depression in PTB mothers to be significantly higher than mothers who delivered at term. $I^2$ = 82.69% indicated high heterogeneity among the depression group.

**Table 1 Key features of the studies included in the systematic review**

| ID | Ref. | Study type | Country | Symptoms | | | Outcome assessment[1] |
|---|---|---|---|---|---|---|---|
| 1 | Ballantyne *et al* [37] | Cross-sectional study | Canada | Depression | | Stress | (1) CES-D; and (2) PSS: NICU |
| 2 | Baptista *et al*[48] | Cross-sectional study | Portugal | Psychological problem | | Stress | (1) BSI; and (2) Daily hassles questionnaire |
| 3 | Barroso *et al*[38] | Cross sectional study | United States | Depression | | | EPD-S |
| 4 | Bener[60] | Hospital-based study (cross sectional study) | Qatar | Depression | Anxiety | Stress | (1) DASS-21; (2) DASS-21; and (3) DASS-21 |
| 5 | Bouras *et al*[34] | Cross-sectional study | Greece | Depression | Anxiety | | (1) BDI; and (2) STAI |
| 6 | Brandon *et al*[39] | Descriptive study | United States | Depression | Anxiety | Stress | (1) EPDS; (2) STAI-S; (3) PPQ; and (4) CHWS |
| 7 | Carson *et al*[49] | Cohort study | United Kingdom | Psychological problem | | | Modified RMI |
| 8 | Cheng *et al*[13] | Cohort study | United States | Depression | | | CES-D |
| 9 | Davis *et al*[57] | Cross-sectional study | Australia | Depression | | Stress | (1) EPDS; and (2) DASS |
| 10 | Drewett *et al*[50] | Cross-sectional study | United Kingdom | Depression | | | EPDS |
| 11 | Edwards *et al*[58] | Cohort study | Australia | Depression | | Parenting stress | (1) EPDS; and (2) PSI |
| 12 | Fabiyi *et al*[40] | Cross-sectional study | United States | | (1) State anxiety; and (2) Trait anxiety | | STAI |
| 13 | Gambina *et al*[33] | Case-control study | Italy | Depression | (1) State anxiety; and (2) Trait anxiety | Stress | (1) EPDS; (2) STAI-State and STAI-Trait; and (3) PSM |
| 14 | Gueron-Sela *et al* [30] | Cross-sectional study | Israel | Depression | | Stress | (1) CES-D; and (2) PSS: NICU |
| 15 | Gulamani *et al* [24] | Cohort study | Pakistan | Depression | | | EPDS |
| 16 | Gungor *et al*[35] | Case-control study | Turkey | Depression | (1) State anxiety; (2) Trait anxiety | | (1) BDI; and (2) STAI |
| 17 | Hagan *et al*[59] | Prospective, randomised, controlled study | Australia | Depression | Anxiety | | (1) EPDS; and (2) BDI |
| 18 | Henderson *et al* [51] | Cross-sectional study | United Kingdom | Depression | | | EPDS |
| 19 | Holditch-Davis *et al*[44] | Cross-sectional study | United States | Depression | Anxiety | Stress | (1) CES-D; (2) STAI; and (3) PSS: NICU |
| 20 | Ionio *et al*[52] | Longitudinal study | Italy | Depression | | | Profile of mood states |
| 21 | Logsdon *et al*[41] | Descriptive study | United States | Depression | | | CES-D |
| 22 | Misund *et al*[53] | Longitudinal study | Norway | Psychological distress | Anxiety | Trauma-related stress | (1) GHQ likert sum and case sum; (2) STAI-X1; and (3) Impact of event scale (IES) |
| 23 | Misund *et al*[53] | Cohort study | Norway | Psychological distress | Anxiety | Trauma-related stress | (1) GHQ likert sum and case sum; (2) STAI-X1; and (3) IES |
| 24 | Pace *et al*[32] | Longitudinal, prospective, follow-up cohort study | Australia | Depression | Anxiety | | (1) CES-D; and (2) Hospital anxiety and depression scale |
| 25 | Rogers *et al*[42] | Cohort study | United States | Depression | Anxiety | | (1) EPDS; and (2) STAI |
| 26 | Sharan *et al*[61] | Cross-sectional study | Israel | Depression | | | EPDS |
| 27 | Shaw *et al*[43] | Cross-sectional study | United States | Depression | Anxiety | Stress | (1) BDI-II; (2) BAI; and (3) SASRQ |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 28 | Trumello *et al*[54] | Longitudinal study | Italy | Depression | (1) State anxiety; and (2) Trait anxiety | | (1) EPDS; and (2) STAI-State Y1 and Y2 |
| 29 | Holditch-Davis *et al*[44] | Longitudinal study | United States | Depression | State anxiety | Stress | (1) CESD; (2) STAI; (3) PSS: NICU; and (4) PSS:PBC |
| 30 | Mautner *et al*[55] | Prospective, longitudinal study | Austria | Depression | | | EPDS |
| 31 | Gray *et al*[28] | Cross-sectional study | Australia | Depression | | Parenting stress | (1) EPDS; and (2) PSI-SF |
| 32 | Gray *et al*[29] | Cross-sectional study | Australia | Depression | | Parenting stress | (1) EPDS; and (2) PSI-SF |
| 33 | Howe *et al*[62] | Cross-sectional study | Taiwan | | | Parenting stress | PSI-Chinese version |
| 34 | Miles *et al*[45] | Longitudinal, descriptive study | United States | Depression | | | CES-D |
| 35 | Mew *et al*[46] | Correlational analysis | United States | Depression | | | CES-D |
| 36 | Madu and Roos [31] | Cross-sectional study | South Africa | Depression | | | EPDS |
| 37 | Suttora *et al*[36] | Descriptive study | Italy | | | (1) PTSD; and (2) Parenting stress | (1) PPQ-Modified version; and (2) PSI-SF |
| 38 | Korja *et al*[56] | Cross-sectional study | Finland | Depression | | | EPDS |
| 39 | Younger *et al*[47] | Descriptive correlational study | United States | Depression | | Stress | (1) CES-D; and (2) MSI |

[1]Outcome assessment scales: Edinburgh Postnatal Depression Scale; State-Trait Anxiety Inventory; Hospital Anxiety and Depression Scale; Centre for Epidemiological Studies Depression; Beck's Depression Inventory; Profile of Mood States; Parent Stress Index; Professional Personality Questionnaire; Perceived Stress Measure. EPDS: Edinburgh Postnatal Depression Scale; STAI: State-Trait Anxiety Inventory; HADS-A: Hospital Anxiety and Depression Scale; CES-D: Centre for Epidemiological Studies Depression; BDI: Beck's Depression Inventory; POMS: Profile of Mood States; PSI: Parent Stress Index; PPQ: Professional Personality Questionnaire; PSM: Perceived Stress Measure.

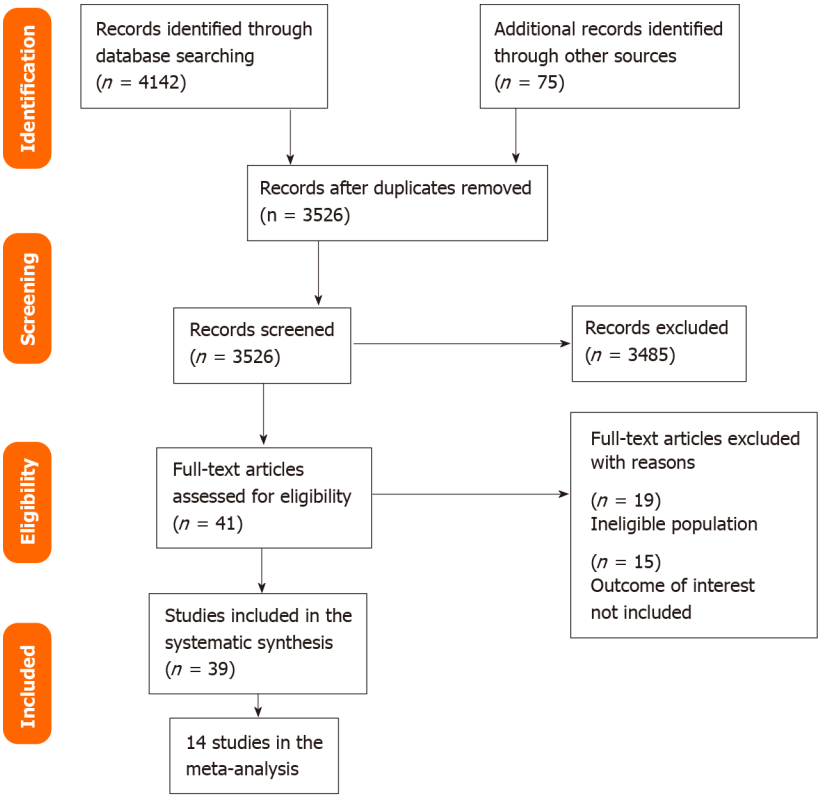


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**Figure 1 PRISMA diagram.**

**Table 2 The quality assessment outcomes using the Newcastle-Ottawa Scale**

| ID | Ref. | Study type | Country | Symptoms | | | Outcome assessment | NOS score |
|---|---|---|---|---|---|---|---|---|
| 1 | Ballantyne *et al* [37] | Cross-sectional study | Canada | Depression | | Stress | (1) CES-D; and (2) PSS: NICU | ****** (6) |
| 2 | Baptista *et al* [48] | Cross-sectional study | Portugal | Psychological problem | | Stress | (1) BSI; and (2) Daily hassles questionnaire | ***** (5) |
| 3 | Barroso *et al* [38] | Cross sectional study | United States | Depression | | | EPD-S | ****** (6) |
| 4 | Bener[60] | Hospital-based study (Cross sectional study) | Qatar | Depression | Anxiety | Stress | (1) DASS-21; (2) DASS-21; and (3) DASS-21 | ***** (5) |
| 5 | Bouras *et al*[34] | Cross-sectional study | Greece | Depression | Anxiety | | (1) BDI; and (2) STAI | ****** (6) |
| 6 | Brandon *et al* [39] | descriptive study | United States | Depression | Anxiety | Stress | (1) EPDS; (2) STAI-S; (3) PPQ; and (4) CHWS | ******* (7) |
| 7 | Carson *et al* [49] | Cohort study | United Kingdom | Psychological problem | | | Modified RMI | ***** (5) |
| 8 | Cheng *et al*[13] | Cohort study | United States | Depression | | | CES-D | ***** (5) |
| 9 | Davis *et al*[57] | Cross-sectional study | Australia | Depression | | Stress | (1) EPDS; and (2) DASS | ***** (5) |
| 10 | Drewett *et al* [50] | Cross-sectional study | United Kingdom | Depression | | | EPDS | ***** (5) |
| 11 | Edwards *et al* [58] | Cohort study | Australia | Depression | | Parenting stress | (1) EPDS; and (2) PSI | ***** (5) |
| 12 | Fabiyi *et al*[40] | Cross-sectional study | United States | | (1) State anxiety; and (2) Trait anxiety | | STAI | ****** (6) |
| 13 | Gambina *et al* [33] | Case-control study | Italy | Depression | (1) State anxiety; and (2) Trait anxiety | Stress | (1) EPDS; (2) STAI-State and STAI-Trait; and (3) PSM | ****** (6) |
| 14 | Gueron-Sela *et al*[30] | Cross-sectional study | Israel | Depression | | Stress | (1) CES-D; and (2) PSS: NICU | ******* (7) |
| 15 | Gulamani *et al* [24] | Cohort study | Pakistan | Depression | | | EPDS | **** (4) |
| 16 | Gungor *et al* [35] | Case-control study | Turkey | Depression | (1) State anxiety; (2) Trait anxiety | | (1) BDI; and (2) STAI | ****** (6) |
| 17 | Hagan *et al*[59] | Prospective,randomised, controlled study | Australia | Depression | Anxiety | | (1) EPDS; and (2) BDI | ****** (6) |
| 18 | Henderson *et al*[51] | Cross-sectional study | United Kingdom | Depression | | | EPDS | ******* (7) |
| 19 | Holditch-Davis *et al*[44] | Cross-sectional study | United States | Depression | Anxiety | Stress | (1) CES-D; (2) STAI; and (3) PSS: NICU | ****** (6) |
| 20 | Ionio *et al*[52] | Longitudinal study | Italy | Depression | | | Profile of mood states | ***** (5) |
| 21 | Logsdon *et al* [41] | Descriptive study | United States | Depression | | | CES-D | ****** (6) |
| 22 | Misund *et al* [53] | Longitudinal study | Norway | Psychological distress | Anxiety | Trauma-related stress | (1) GHQ likert sum and case sum; (2) STAI-X1; and (3) Impact of Event Scale (IES) | ****** (6) |
| 23 | Misund *et al* | Cohort study | Norway | Psychological | Anxiety | Trauma- | (1) GHQ likert sum | ***** (5) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | [53] | | | distress | | related stress | and case sum; (2) STAI-X1; and (3) IES | |
| 24 | Pace *et al*[32] | Longitudinal, prospective, follow-up cohort study | Australia | Depression | Anxiety | | (1) CES-D; and (2) Hospital anxiety and depression scale | ****** (6) |
| 25 | Rogers *et al*[42] | Cohort study | US | Depression | Anxiety | | (1) EPDS; and (2) STAI | ***** (5) |
| 26 | Sharan *et al* [61] | Cross-sectional study | Israel | Depression | | | EPDS | ****** (6) |
| 27 | Shaw *et al*[43] | Cross-sectional study | US | Depression | Anxiety | Stress | (1) BDI-II; (2) BAI; and (3) SASRQ | ****** (6) |
| 28 | Trumello *et al* [54] | Longitudinal study | Italy | Depression | 1) State anxiety2) Trait anxiety | | (1) EPDS; and (2) STAI-State Y1 and Y2 | ******* (7) |
| 29 | Holditch-Davis *et al*[44] | Longitudinal study | US | Depression | 1) State anxiety | Stress | (1) CESD; (2) STAI; (3) PSS: NICU; and (4) PSS:PBC | ****** (6) |
| 30 | Mautner *et al* [55] | Prospective, longitudinal study | Austria | Depression | | | EPDS | ****** (6) |
| 31 | Gray *et al*[28] | Cross-sectional study | Australia | Depression | | Parenting stress | (1) EPDS; and (2) PSI-SF | ****** (6) |
| 32 | Gray *et al*[29] | Cross-sectional study | Australia | Depression | | Parenting stress | (1) EPDS; and (2) PSI-SF | ****** (6) |
| 33 | Howe *et al*[62] | Cross-sectional study | Taiwan | | | Parenting stress | PSI-Chinese version | ****** (6) |
| 34 | Miles *et al*[45] | Longitudial, descriptive study | United States | Depression | | | CES-D | ***** (5) |
| 35 | Mew *et al*[46] | Correlational analysis | United States | Depression | | | CES-D | ***** (5) |
| 36 | Madu and Roos[31] | Cross-sectional study | South Africa | Depression | | | EPDS | ****** (6) |
| 37 | Suttora *et al* [36] | Decriptive study | Italy | | | (1) PTSD; and (2) Parenting stress | (1) PPQ-Modified version; and (2) PSI-SF | ***** (5) |
| 38 | Korja *et al*[56] | Cross-sectional study | Finland | Depression | | | EPDS | ****** (6) |
| 39 | Younger *et al* [47] | Decriptive correlational study | United States | Depression | | Stress | (1) CES-D; and (2) MSI | ****** (6) |

*: Quality of the included cross-sectional studies was measured using the modified Newcastle-Ottawa Measurement Scale specific for Cross-sectional studies. We rated the quality of the studies (good, fair and poor) by allocating each domain with stars in this manner: A good quality score was awarded 3 or 4 stars in selection, 1 or 2 in comparability, and 2 or 3 stars in outcomes; A fair quality score was awarded 2 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes; A poor quality score was allocated 0 or 1 star(s) in selection, 0 stars in comparability, and 0 or 1 star(s) in outcomes domain in line with the Newcastle-Ottawa Scale guidelines. NOS: Newcastle-Ottawa Scale; EPDS: Edinburgh Postnatal Depression Scale; STAI: State-Trait Anxiety Inventory; HADS-A: Hospital Anxiety and Depression Scale; CES-D: Centre for Epidemiological Studies Depression; BDI: Beck's Depression Inventory; POMS: Profile of Mood States; PSI: Parent Stress Index; PPQ: Professional Personality Questionnaire; PSM: Perceived Stress Measure.

Shaw *et al*[43] focused on the association between depression symptoms and the efficiency of Edinburgh Postnatal Depression Scale (EPDS), although the specificity of EPDS to the BAME population was not demonstrated. Since most of the studies reported mean and SD, we pooled mean differences and its 95%CI. Seven of the studies lacked information about mean score and SD, thus, were excluded from the meta-analysis. Gray *et al*[28,29] used the same dataset in two papers, therefore one of these was included into the meta-analysis. Therefore, a total of 12 studies were included in the meta-analysis as indicated by Table 4. Additionally, Gueron-Sela *et al*[30] studied two ethnicities, therefore it was used twice as reported in Table 4. Therefore, 13 items were reported in the meta-analysis for depression. The meta-analyses for anxiety and stress had 5 studies each, as demonstrated in Tables 5 and 6.

### Anxiety

The 12 studies reporting anxiety utilised EDPS, the State-Trait Anxiety Inventory (STAI), Hospital

**Table 3 Risk of Bias using the Newcastle-Ottawa Scale**

| | Selection (S) | | | | Comparability (C) | | Exposure/outcome E/O | | | Sub total assessment | | | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 1a | 1b | 1 | 2 | 3 | S[1] | C[2] | E/O[2] | |
| Ballantyne *et al*[37] | * | * | No | * | * | * | No | * | * | Good | Good | Good | Good |
| Baptista *et al*[48] | * | * | No | * | * | * | * | * | * | Good | Good | Good | Good |
| Barroso *et al*[38] | * | * | * | * | * | * | * | No | * | Good | Good | Good | Good |
| Bener[60] | * | No | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Bouras *et al*[34] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Brandon *et al*[39] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Carson *et al*[49] | * | No | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Cheng *et al*[13] | * | * | No | * | No | * | * | * | * | Good | Good | Good | Good |
| Davis *et al*[57] | * | * | No | No | * | * | * | * | * | Fair | Good | Good | Good |
| Drewett *et al*[50] | * | * | * | * | No | * | * | * | * | Good | Good | Good | Good |
| Edwards *et al*[58] | * | No | No | * | No | * | * | * | * | Fair | Good | Good | Fair |
| Fabiyi *et al*[40] | * | No | * | No | No | * | * | * | * | Fair | Fair | Good | Fair |
| Gambina *et al*[33] | * | No | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Gueron-Sela *et al*[30] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Gulamani *et al*[24] | * | No | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Gungor *et al*[35] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Hagan *et al*[59] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Henderson *et al*[51] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Holditch-Davis *et al*[44] | * | * | No | * | No | * | * | * | * | Good | Good | Good | Good |
| Ionio *et al*[52] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Logsdon *et al*[41] | * | No | No | * | No | * | * | * | * | Fair | Fair | Good | Fair |
| Misund *et al*[53] | No | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Misund *et al*[53] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Pace *et al*[32] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Rogers *et al*[42] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sharan *et al*[61] | No | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Shaw *et al*[43] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Trumello *et al*[54] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Holditch-Davis *et al*[44] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Mautner *et al*[55] | * | No | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Gray *et al*[28] | * | * | No | * | No | * | * | * | * | Good | Good | Good | Good |
| Gray *et al*[29] | * | * | No | * | No | * | * | * | * | Good | Good | Good | Good |
| Howe *et al*[62] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Miles *et al*[45] | * | No | No | * | No | * | * | * | * | Fair | Good | Good | Fair |
| Mew *et al*[46] | * | No | No | * | No | * | * | No | * | Fair | Fair | Good | Fair |
| Madu and Roos[31] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Suttora *et al*[36] | * | * | * | * | * | * | * | * | * | Good | Good | Good | Good |
| Korja *et al*[56] | * | * | No | * | No | * | * | * | * | Good | Good | Good | Good |
| Younger *et al*[47] | * | No | No | * | No | * | * | * | * | Fair | Good | Good | Good |

[1]Domain scored: 0-1 (Poor); 2 (Fair); 3+ (Good).
[2]Domain scored: 0 (Poor); 1 (Fair); 2+ (Good).
*: Domain acceptable.

Anxiety and Depression Scale (HADS-A), Centre for Epidemiological Studies Depression, Beck's Depression Inventory and Profile of Mood States as their assessment tool. The total scores of these scales are different, and the mean difference of the studies are not compatible. Four studies reported on anxiety using STAI and HADS-A as their mental health assessment of choice. The overall SMD of Anxiety was 0.63 with 95%CI of 0.35-0.91. $I^2$ = 86.83% also indicated high heterogeneity among anxiety group.

### Stress and parent stress index

Studies reporting stress used the Parent Stress Index assessment on three separate timepoints along with the Professional Personality Questionnaire and the Perceived Stress Measure. The total scores of these scales in each meta-analysis are different, and the mean difference of the studies are not compatible. The overall SMD of Stress was 0.47 with 95%CI 0.22-0.72. $I^2$ =77.55% indicated high heterogeneity among stress group.

### Posttraumatic stress disorder

Suttora *et al* [36] was the only study reporting on posttraumatic stress disorder (PTSD). The reported

**Table 4 Characteristics of the 12 studies included within the meta-analysis for depression**

| ID | Ref. | Study type | Country | Sample size | Outcome assessment |
|---|---|---|---|---|---|
| 1 | Brandon *et al*[39] | Descriptive study | United States | 60 | EPDS |
| 2 | Bouras *et al*[34] | Cross-sectional study | Greece | 200 | BDI |
| 3 | Cheng *et al*[13] | Cohort study | United States | 5350 | CES-D |
| 4 | Drewett *et al*[50] | Cross-sectional study | United Kingdom | 10838 | EPDS |
| 5 | Gambina *et al*[33] | Case-control study | Italy | 84 | EPDS |
| 6 | Gray *et al*[28,29] | Cross-sectional study | Australia | 217 | EPDS |
| 7 | Gueron-Sela *et al*[30] | Cross-sectional study | Israel | 103 (Bedouin); 230 (Jewish) | CES-D |
| 8 | Gungor *et al*[35] | Case-control study | Turkey | 299 | BDI |
| 9 | Ionio *et al*[52] | Longitudinal study | Italy | 50 | Profile of mood states |
| 10 | Madu and Roos[31] | Cross-sectional study | South Africa | 100 | EPDS |
| 11 | Mautner *et al*[55] | Prospective, longitudinal study | Australia | 61 | EPDS |
| 12 | Pace *et al*[32] | Longitudinal, prospective cohort study | Australia | 230 | CES-D |

EPDS: Edinburgh Postnatal Depression Scale; BDI: Beck's Depression Inventory; CES-D: Centre for Epidemiological Studies Depression.

**Table 5 Characteristics of the 5 studies included within the meta-analysis for anxiety**

| ID | Ref. | Study type | Country | Sample size | Outcome assessment |
|---|---|---|---|---|---|
| 1 | Brandon *et al*[39] | Descriptive study | United States | 60 | STAI-S |
| 2 | Bouras *et al*[34] | Cross-sectional study | Greece | 200 | STAI-T; STAI-S |
| 3 | Gambina *et al*[33] | Case-control study | Italy | 84 | STAI-T; STAI-S |
| 4 | Gungor *et al*[35] | Case-control study | Turkey | 299 | STAI-T; STAI-S |
| 5 | Pace *et al*[32] | Longitudinal, prospective cohort study | Australia | 230 | HADS-A |

STAI: State-Trait Anxiety Inventory.

**Table 6 Characteristics of the 5 studies included within the meta-analysis for stress**

| ID | Ref. | Study type | Country | Sample size | Outcome assessment |
|---|---|---|---|---|---|
| 1 | Brandon *et al*[39] | Descriptive study | United States | 60 | PPQ |
| 2 | Gambina *et al*[33] | Case-control study | Italy | 84 | PSM |
| 3 | Gray *et al*[28,29] | Cross-sectional study | Australia | 217 | PSI-SF |
| 4 | Howe *et al*[62] | Cross-sectional study | Taiwan | 420 | PSI-Chinese version |
| 5 | Suttora *et al*[36] | Descriptive study | Italy | 243 | PSI-SF |

PPQ: Professional Personality Questionnaire; PSM: Perceived Stress Measure; PSI: Parent Stress Index.

mean and SD of the symptoms of PTSD were transformed to SMD. The SMD was 1.12 with a 95%CI of 0.84-1.40 indicated significantly high PTSD symptoms among BAME PTB women than the term mothers.

Assessment of mental health at differing time-points for depression, anxiety and stress were evaluated between full term and PTB mothers. Different mean scores and SD values were reported across the included studies. The dataset was unified with converting the mean difference to the SMD and demonstrated in the forest plots (Figures 2-4).

This meta-analysis identified depression to be a primary mental health outcome among PTB mothers and significantly higher prevalence rates of depression was reported in PTB mothers compared with full-term mothers.

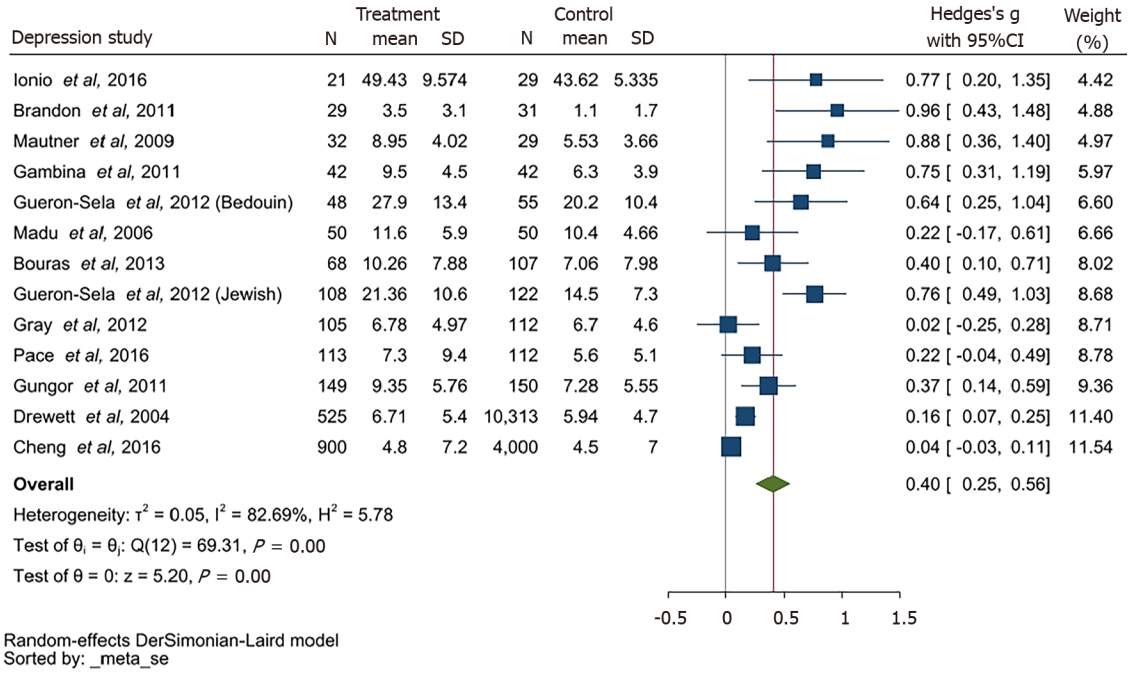


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**Figure 2 Forest plot for depression (full term *vs* preterm birth).** CI: Confidence interval.

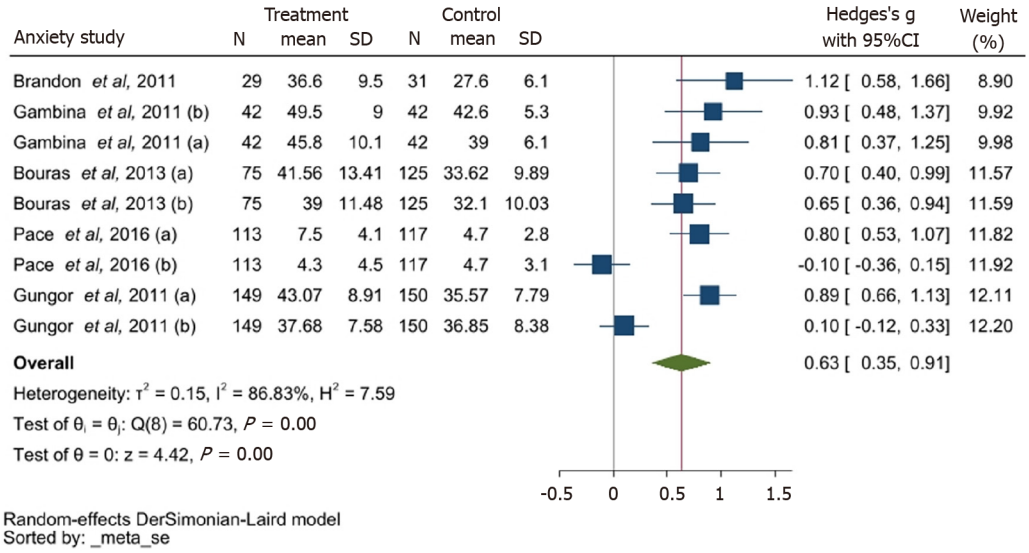


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**Figure 3 Forest plot for anxiety (full term *vs* preterm birth).** CI: Confidence interval.

### *Meta-regression analysis*

Of the 16 studies included within the meta-regression analysis for depression, 5 reported mean scores and SD of the mental health questionnaires used at parturition. Four studies recorded the mean and SD at 1-mo post-delivery, while another four studies reported the same at 1 mo to 8 mo post-delivery. To eliminate the heterogeneity, these studies were adjusted by timepoints (Figure 5).

The estimated intercept for depression is 0.629 with a 95%CI of 0.455-0.804. This indicates the mental health assessment scores within the PTB group were significantly higher than full-term group at the birth. The coefficient of the covariate time was -0.061 with a 95%CI of -0.094, -0.028 indicating that the coefficients of time were significantly lower than 0. This is indicative of a reduction depression symptoms post-delivery. Heterogeneity decreased from 82.69% to 79.82%, and the differences of assessment time points could explain the 31.75% of the heterogeneity identified.

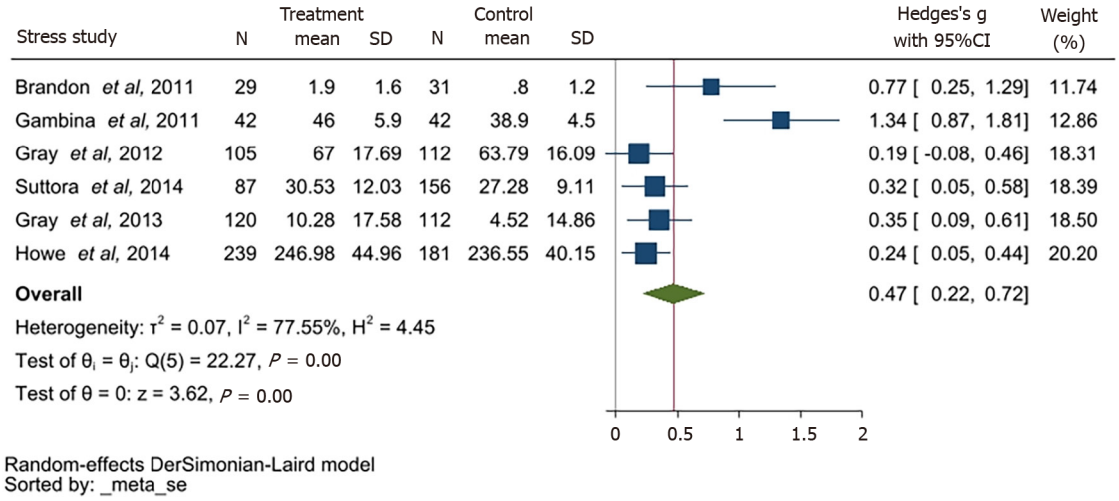


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**Figure 4 Forest plot for stress (full term *vs* preterm birth).** CI: Confidence interval.

```
Random-effects meta-regression                  Number of obs   =        16
Method: DerSimonian-Laird                       Residual heterogeneity:
                                                          tau2 =  0.04072
                                                       I2 (%)  =    79.82
                                                          H2   =     4.96
                                                R-squared (%)  =    31.75
                                                Wald chi2(1)   =    13.41
                                                Prob > chi2    =   0.0002
------------------------------------------------------------------------------
     _meta_es |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       tvalue |  -0.0609896   0.0166533    -3.66   0.000    -0.0936296   -0.0283497
        _cons |   0.6294887   0.0889261     7.08   0.000     0.4551968    0.8037807
------------------------------------------------------------------------------
Test of residual homogeneity: Q_res = chi2(14) = 69.38   Prob > Q_res = 0.0000
```

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**Figure 5 Meta regression conducted by time for depression.**

Nine studies that reported anxiety were included in the meta-regression (Figure 6). The estimated intercept was 0.772 with a 95%CI of 0.500-1.045 which indicates the mental health assessment scores of the PTB group are significantly higher than the scores of full-term group. The coefficient of the covariate time is -0.136 with 95%CI of -0.262, -0.010 indicating that the symptoms of anxiety gradually disappeared among PTB group following birth. Heterogeneity reduced from 86.83% to 80.29%. The differing time points in administering the mental health assessment could explain 34.91% of the heterogeneity (Figure 6).

Following the reduction of heterogeneity by way of the meta-regression method, the statistical conclusions demonstrate a statistical significance where the prevalence of depression among BAME women with PTB was higher in comparison to BAME women who delivered at full-term. The $I^2$ was almost 80% which indicates a high heterogeneity.

The pooled SMD within the studies using PTB mothers from United States was 0.46 with a 95%CI of -0.43 – 1.35. The pooled SMD within Australia was 0.44 with a 95%CI of 0.07-0.81. $I^2$ of these two subgroups indicated a high heterogeneity: 91.14% and 87.79% respectively. The assessment timepoints of these two groups have a significant difference, which could be the source of the high heterogeneity. As there were only 2 studies, a meta-regression of the timepoints could not be completed.

### *Subgroup analysis*

A subgroup analysis of depression and anxiety was completed using geographical location as demonstrated in Supplementary Figures 1-3. For depression, the pooled SMD within Greece, Italy, Israel and Turkey was 0.57 with a 95%CI of 0.4-0.74. The pooled SMD within United Kingdom was 0.12 with a 95%CI of 0.03-0.21. $I^2$ was denoted to be indicating a lack of heterogeneity as demonstrated in Supplementary Figure 1.

```
Random-effects meta-regression                  Number of obs  =         9
Method: DerSimonian-Laird                       Residual heterogeneity:
                                                          tau2 =    0.1002
                                                       I2 (%)  =     80.29
                                                          H2   =      5.07
                                                  R-squared (%) =    34.91
                                                Wald chi2(1)    =      4.50
                                                Prob > chi2     =    0.0338
------------------------------------------------------------------------------
     _meta_es |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       tvalue |  -0.1359486   0.0640626    -2.12   0.034    -0.261509  -0.0103882
        _cons |   0.7723931   0.1391725     5.55   0.000     0.4996201    1.045166
------------------------------------------------------------------------------
Test of residual homogeneity: Q_res = chi2(7) = 35.51    Prob > Q_res = 0.0000
```

**DOI**: 10.5498/wjp.v12.i9.1233 **Copyright** ©The Author(s) 2022.

**Figure 6 Meta regression conducted by time for anxiety.**

Although a meta-regression was not conducted for the pooled SMD within the studies with PTB mothers from United States, a subgroup analysis demonstrated that the high heterogeneity could be attributed to the differences of time points of the mental health assessments.

Of the 39 studies included in the systematic review, thirteen studies were from North America[1,3,6,8,12,19,21,25,27,29,34,35,39], thirteen from Europe[2,5,7,10,13,18,20,22,23,28,30,37,38], six studies from Australia[9,11,17,24,31,32], three from Asia[15,16,33], three from the Middle East[4,14,26] and one from South Africa[36]. These have been demonstrated in Table 1. Depression was the most frequently reported theme across all the studies, followed by anxiety and stress (Table 7). A variety of diagnostic tools were used across the studies, which reflects the diverse clinical practices across different countries.

Based on the identified data, PTB women from the Mediterranean region (Greece, Italy, Turkey and Israel) may be more prone to depressive symptoms in comparison to BAME women with PTB in Australia and the United States. The pooled odds ratio (OR) and its respective 95%CIs appear credible for PTB BAME women experiencing a significantly higher prevalence of depression post-parturition, although the mental health symptoms appear to reduce over time.

The pooled SMD of anxiety within United States was 1.12 with 95%CI of 0.58-1.66 whilst the pooled SMD of the Mediterranean region (Greece, Italy, Turkey) was 0.66 with a 95%CI of 0.37-0.95. The pooled SMD of Australia was 0.35 with a 95%CI of -0.54 -1.23 (Supplementary Figure 2). BAME women with PTB from Australia appear to have less symptoms of anxiety and the main source of the high heterogeneity in subgroup was still from the time points.

In relation to assessing stress, Gray *et al*[28,29] conducted mental health assessments at months 4 and 12, post-parturition. Whilst this appears to be useful follow-up data to evaluate, the outcome measures were analysing 2 different mental health variables of parenting stress and general stress. As shown in Supplementary Figure 4 four studies reported on parenting stress and 2 of them reported on the overall state of stress. The subgroup analysis conducted indicated a lack of heterogeneity between these studies. Mild heterogeneity was identified within the studies included in the stress group alone. The pooled SMD within the parenting group was 0.27 with a 95%CI of 0.15-0.39. In the stress group, the pooled SMD was 1.07 with a 95%CI of 0.51-1.62. Additionally, the symptoms of parenting stress were less severe within the PTB group (Table 7 and Supplementary Figures 4 and 5).

### *Sensitivity analysis*

Studies reporting depression[32] demonstrated women with severe PTB indicated a high SMD at parturition indicating elevated levels of depressive symptoms (Supplementary Figure 6). A combination of worries about very premature babies and the trauma following parturition may further attribute to elevated depressive symptoms. Only Pace *et al*'s study conducted the assessment of questionnaires among the very PTB women group at the birth[32]. Women with a more severe PTB may indicate higher scores of depression, therefore this study was excluded from the sensitivity analysis. After removing Pace *et al*'s study, the heterogeneity in Australia reduced from an $I^2$ of 87.79% to 52.99%[32]. Therefore, conclusions were adjusted from a pooled SMD of 0.42 (with 95%CI: 0.28-0.56) to 0.34 (with 95%CI: 0.22-0.46). Despite this numerical change, an elevated level of depression among BAME PTB women were visible in comparison to those with a full-term pregnancy (Supplementary Figure 6).

Based on the anxiety studies, Gungor *et al*[35] in particular, reported extremely small OR and a sensitivity analysis was conducted excluding one possible outlier study, as indicated by Supplementary Figure 7. The heterogeneity identified without Gungor *et al*[35] was 0%. Therefore, this study in particular appears to have design and methodological issues limiting generalisability of the findings. As a result, conclusions were amended from an SMD of 0.63 (with 95%CI: 0.35-0.91) to 0.7 (with 95%CI: 0.42-0.98). Therefore, despite the amendment[35], a significantly high prevalence among BAME PTB

**Table 7 The thematic synthesis**

| Themes | Population group |
|---|---|
| | Women who had a preterm birth |
| Depression | ++++++++++++++++++++++++++++++++ |
| Stress | ++++++++++ |
| Anxiety | ++++++++++ |
| Parenting stress | +++++ |
| State anxiety | +++++ |
| Trait anxiety | ++++ |
| Psychological distress | ++ |
| Trauma-related stress | ++ |
| Psychological problem | ++ |
| Post-traumatic stress disorder | + |

women is observed (Supplementary Figure 7).

### *Publication bias*

For studies with a small sample size, the pooled OR is significantly higher based on the funnel plots, therefore, these would be prone to publication bias. To assess this further, Egger's tests were conducted for all studies included within the meta-analysis.

Funnel plots developed within this sample intuitively revealed publication bias (Supplementary Figures 8-10. Egger's test of meta-analysis studies for depression (*P* value = 0.001), indicated the small sample sizes are a source of publication bias (Supplementary Figure 11). The pooled SMD 0.4 and associated CI (0.25-0.56) may have been overrated. Therefore, the TAF method was used to further improve the statistical conclusions (as indicated in Supplementary Figures 11 and 12). The asymmetry of the funnel plot demonstrates the studies could minimally impact publication bias.

Based on the findings demonstrated in Supplementary Figures 11, 3 further studies were imputed to correct the effect size of small studies. The small study effect was eliminated with using the imputation method, and publication bias was corrected (demonstrated in Supplementary Figure 12). The Hedge's g (Supplementary Figure 12) was significantly higher than 0 among the meta-analysis based and imputed studies. After imputing the 3 new studies and removing the publication bias, the statistical conclusion was adjusted from a SMD of 0.4 with 95%CI of 0.25-0.56 to 0.32 (95%CI of 0.18-0.47). Despite the adjustments of publication bias, there was significant evidence that the prevalence of depression among BAME PTB women were higher than those who gave birth at full-term (Supplementary Figures 12 and 13).

Egger's test *P* value for anxiety was 0.198, indicating no publication bias exists (demonstrated in Supplementary Figure 14). Egger's test *P* value for stress was 0.036, indicating a slight publication bias among the studies (demonstrated in Supplementary Figure 15).

Ascertainment bias was considered within the context of the meta-analysis. Due to the lack of required details such as the proportion of different ethnic groups and mental health assessments, it was not possible to assess this numerically. However, within the context of all the studies included in the systematic review portion of the study, it is evident, there could be ascertainment bias as the sampling methods used in the studies comprise of patients who may or may not have a higher or lower probability of reporting mental health symptomatologies. These studies may be subjected to selection bias due to the lack of consistency around frequency of administering the relevant mental health instruments. In essence, studies should have had samples with all ethnicities and races (including Caucasians) to better evaluate the true mental health impact due to PTB. Furthermore, the sample population should have received a standardised set of mental health assessments to determine anxiety, depression, PTSD and other mental illnesses at specific time points during the pre and post-natal period since it is common to have undiagnosed mental health conditions. In addition to this, some studies have had attempted to evaluate the mental health impact after birth at 8 mo although this lacks scientific justification and thereby, epidemiologically insignificant. Furthermore, due to the lack of consistency in assessing and reporting mental health outcomes post-natally, attrition bias may be present. However, a definitive conclusion could not be attained numerically due to limitations in the sample sizes reported.

## DISCUSSION

In this meta-analysis, the prevalence rate of depression among PTB BAME mothers was identified to be significantly higher than in full-term mothers with an OR of 1.50 and 95%CI of 29%-74%. Depressive symptoms in mothers and fathers of premature infants were frequently reported in the post-natal period[13]. There may be many causes for this including the social support. Cheng *et al*[13] reported that mothers with non-resident fathers experienced higher rates of depressive symptoms, as did the non-resident fathers included in this study. Lack of social support is likely to be further exacerbated by prolonged hospitalisation of preterm infants and the unique challenges faced by infants the premature following hospital discharge. Additionally, mothers may be admitted to hospital prior to delivery, in some cases for weeks, due to conditions like severe preeclampsia or PROM associated with PTB and hence they may be more isolated than mothers of term infants.

This study defined three sub-groups; assessment timepoint < 1 mo, 1-8 mo and > 8 mo, and indicated that shorter the time after giving birth, the more significant was the depression. Therefore, the provision of mental health support following the immediate post-partum period would benefit patients. Within the first month after delivery, depressive symptoms were significant among PTB mothers; however, by 8 mo and after 8 mo, the increased prevalence of depression was only slightly significant among PTB mothers (OR of 1.17 with 95%CI of 8%-27%; OR of 1.06 with a CI of 1%-12%).

Separation of the infant and the mother is an important and frequent occurrence in PTB, which may explain why mothers of preterm infants are at increased risk of depression. Furthermore, maternal co-morbidities including preeclampsia or recovery from an obstetrics intervention such as a caesarean section may also impact on a mother's ability to bond with her new-born, who maybe in a neonatal intensive care unit (NICU) or special care unit. One study from South Africa[31] demonstrated a high prevalence of depression in mothers of both full term and preterm infants from lower socioeconomic groups. Women from lower socioeconomic groups are likely exposed to greater stressors relevant to the scarcity of resources[31], affecting their mental health.

Adjusting to parenthood is important for all parents. In the case of PTB mothers may not have sufficient time to prepare, which may lead to maternal stress[47]. Familiarity with the situation, possibly by having had a previous preterm infant, and predictability of birth outcome have been found to reduce stress and anxiety[47]. Medically indicated preterm delivery may have been planned, for example, in multiple pregnancies or mothers with diabetes and thus, predictable. Therefore, it is possible that those mothers experience less stress than those who give birth following an acute spontaneous onset preterm labor. In addition to mental preparation, the former group of parents of preterm infants may have had time to visit the NICU and speak with neonatologists to gain further information and this may reduce anxiety following birth.

Parenting stress is found to be higher in mothers of preterm infants at one year[29]. This relationship may by predicted by maternal depression as well as impaired parent and infant interactions[29]. Interestingly, parenting stress is not significantly different in mothers of preterm or full-term infants in early infancy[28], suggesting all mothers require support in the immediate post-partum period to reduce parental mental health but prolonged provision of such support is important in managing PTB mothers.

Increased and unexpected medical interventions associated with PTB, including painful corticosteroid injections or the use of magnesium sulphate. Mothers may have additional intimate examinations and the need for emergency procedures such as caesarean sections, which may negatively impact a mother's physical and mental health. These may exacerbate the underlying stress faced by a PTB mother and her partner; their feelings of anxiety and stress are compounded in some circumstances by the lack of preparedness and loss of control. Together, these experiences may explain why mothers and fathers of preterm infants have greater levels of stress[29] and depression[13].

Cheng *et al*[13] conducted the comparison between fathers and mothers suffering as a result of PTB among Hispanic, Non-Hispanic White, Non-Hispanic Black and Non-Hispanic as well as other races. Gueron-Sela *et al*[30] on the other hand focused on depression and stress symptomatologies among Bedouin and Jewish women. Based on Gueron-Sela *et al*'s findings, Bedouin women experienced the highest level of depression[30]. In comparison to these, Rogers *et al*[42] compared the Caucasian and African American PTB patients that indicated a lack of significant differences between the two groups. Ballantyne *et al*[37] conducted their study on Canadian PTB women which included immigrant women. However, immigrant's status had no contribution to the differences in mental health disorders or symptomatologies.

The mental health impact on those with PTB could be exacerbated due to understandable feelings of helplessness and hopelessness, and low mood is commonly reported by these women. On the contrary, Jotzo and Poets[14] demonstrated PTB could lead to traumatising effects on parents with 49% of mothers reporting traumatic reactions even after a year. Muller-Nix *et al*[15] demonstrated this correlation of traumatic stress and psychological distress between mother and child. Pierrehumbert *et al*[16] indicated post-traumatic stress symptoms after PTB was a predictor of a child's eating and sleeping problems. Similarly, Solhaug *et al*[17] found that parents, who had hospital stays following a PTB requiring NICU, demonstrated high levels of psychological reactions that required treatment.

Perinatal mental health around suicidality or suicidal ideation should be considered as a priority to be addressed among BAME women, which is vital in particular within the United Kingdom. BAME women are at a higher risk of suffering from mental health disorder in comparison to Caucasian women in the United Kingdom and they are less likely to access healthcare support. This is particularly true for women of Pakistani and Indian background. Additionally, Anderson *et al*[63] reported prevalence and risk of mental health disorders among migrant women. These factors should be considered by those treating clinical groups. In addition to the timepoint, we also considered the impact of population. It remains unclear whether the prevalence rate of depression varies after PTB in different ethnic groups. Gulamani *et al*[64] have found the depressive symptoms of women with PTB may be associated with race and culture, but further evidence is lacking. Due to the higher risk of mental health symptoms around the time of PTB, this data may help the health service providers to focus on delivering timely support to the BAME mothers with PTB.

Interestingly, alcohol consumption and substance abuse that are linked to worsening of mental health and poor pregnancy outcomes were not identified within the literature pertinent to BAME population in the scope of this study[65-70].

Similarly, substance abuse among pregnant women increases the risk of PTB and the association of mental illness among the BAME population[71,72]. Holden *et al*[72] demonstrated self-reported depressive symptoms associated with a group of 602 BAME and Caucasian pregnant women that had substance abuse and were subjected to intimate partner violence. This study used the EPDMS which demonstrated elevated levels of depressive illness that required clinical diagnoses and treatments at a mental health care facility. Additionally, women abuse screening tool was used to evaluate relationship issues and those needing appropriate support was referred to social services[71,72]. There is limited information available around substance abuse and partner violence associated with mental health among BAME women. Research conducted within this area appears to lack consistency and this makes systematic evaluation of cultural paradigms relevant to BAME women and the direct association with PTB and mental health difficult, given the complexity of these issues.

### *Limitations*

Heterogeneity of studies gathered within this review challenged the evidence synthesis. Studies identified reported on mental health outcomes without a clear distinction mostly between mental health symptomatologies and psychiatric comorbidities. Timelines for administering mental health instruments and other tools such as talking therapies were not unified across all studies. Collectively, these are design and methodological flaws influencing heterogeneity. Studies were excluded if they discussed quality of life as this does not demonstrate the identification or reporting of mental health outcomes such as pre or postnatal depression, anxiety, psychosis and other mood disorders.

## CONCLUSION

PTB has a significant association with depression, anxiety and stress symptoms in new mothers during the immediate postpartum period. The mental health symptoms are more significant in very preterm mothers than non-very preterm mothers. However, the effect of PTB on the incidence of depression and other mental health outcomes is unclear among different ethnic groups and therefore more studies are needed to explore this.

This study identified a methodological gap to evaluate disease sequelae between PTB and mental health among BAME populations. This important facet should be considered in future research studies, which requires the involvement of multidisciplinary teams. Most included studies did not indicate a publicly available protocol, and availability of such would have assisted in reducing potential biases during study selection in this systematic review to improve sampling techniques and the subsequent data analysis. Future PTB research will be benefited by Population Intervention (s) Comparator and Outcome (s) based reporting to address true mental health impact within BAME populations. The evidence gap that exists from multi-stakeholder needs to be filled to improving patient care. The development of a classification framework for healthcare systems to better assess BAME women at risk with PTB and mental health outcomes would be beneficial. Including cultural adaptation methods as well as training of healthcare professionals will help to manage patients' expectations with the required sensitivities. Similarly, cost-effectiveness and long-term sustainability should be considered when developing a suitable framework.

It is also vital to acknowledge health inequalities and avoidable disparities should be addressed as a matter of urgency. Maternal care should have integrated methods of working with mental health care professionals and a culturally adapted and sensitive specialist service to support BAME women after a PTB may improve the patient outcomes. It is important to improve quality of care received by vulnerable BAME women such as those who are refugees or migrants and do not speak English. Equally, mental health services should work more cohesively within the women's health in the community setting and training should be offered to all healthcare professionals to provide a personalised care.

## ARTICLE HIGHLIGHTS

### *Research background*

Preterm birth (PTB) is a complex clinical condition contributing to significant maternal morbidity and a leading cause of neonatal morbidity and mortality. Therefore, potential mental health impact of PTB on women is an important clinical and social sequel that requires further understanding.

### *Research motivation*

Existing research primarily reports the mental health impact of women with PTB within the Caucasian population. There remains a paucity of research on the ethnic minority populations. Thus, we aimed to assess the current research gap relevant to ethnic minorities to inform future research that could aid with improving patient and clinical reported outcomes.

### *Research objectives*

(1) We aimed to describe the prevalence of mental health conditions and/or symptoms reported by women with PTB experiences within the ethnic minorities; and (2) We also extended our study to report the commonly used methods of mental health assessments to charactertise the identified mental health conditions and/or symptoms with the pooled sample.

### *Research methods*

A systematic methods protocol was developed, peer reviewed and published in PROSPERO (CRD42040210863). Multiple databases were used to extract relevant data for a meta-analysis. A trim and fill method was used to report publication bias in addition to an Egger's test. $I^2$ was used to report heterogeneity.

### *Research results*

From a total of 3516 studies identified, we included 39 studies that met the inclusion criteria. Depression was the most commonly reported mental illness among PTB mothers in comparison to those who had a full-term pregnancy. The subgroup analysis demonstrated depression to be time-sensitive relative to the PTB. Stress and anxiety were also prevalent among PTB mothers as opposed to full-term mothers.

### *Research conclusions*

There appears to be a mental health impact among PTB mothers from ethnic minorities. This is an important aspect to consider for maternity care services to improve the quality care provided to PTB women.

### *Research perspectives*

Future researchers should consider inclusion of all ethnicities and races to ensure generalizability of any findings to all mothers that could truly improve maternity care services.

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## FOOTNOTES

**Author contributions:** Delanerolle G and Hapangama DK developed the systematic review protocol and embedded this within the ELEMI project's evidence synthesis phase; Delanerolle G, Zeng Y, Phan T, Shi JQ and Hapangama DK wrote the first draft of the manuscript; Delanerolle G, Phan T, Zeng Y, Hapangama DK, Shi JQ and Phiri P shared database searches, study selection and extraction for analysis; Zeng Y, Shi JQ and Delanerolle G conducted the analysis; all authors critically appraised and commented on previous versions of the manuscript; all authors read and approved the final manuscript.

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LETTER TO THE EDITOR

# Sodium selenite may be not the optimal speciation as an effective therapy for arsenic-induced anxiety-/depression-like behavior

Xiao-Hua Ren, Xiao-Xuan Wang, Lian-Ping He

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## Abstract

Major depressive disorder is a serious and prevalent neuropsychiatric disorder, affecting more than 350 million people worldwide. Here, sodium selenite (SS) was selected as the selenite supplement to improve the behavior in a mouse model of depression induced by As. SS may be not the optimal speciation for selenite supplementation and the source of the SS used in the study was not disclosed. There are many mouse models of depression and anxiety; however, in the current study, a classical mouse model of depression was not used. Thus, several questions still need to be further discussed. Taken together, the results indicate that SS may be not the optimal speciation as an effective therapy for As-induced anxiety-/depression-like behavior.

**Key Words:** Depression; Arsenic; Major depressive disorder; Sodium selenite; Optimal speciation

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**Core Tip:** Sodium selenite (SS) may be not the optimal speciation for selenite supplementation and the source of the SS used in the study was not disclosed. There are many mouse models of depression and anxiety; however, in the current study, a classical mouse model of depression was not used.

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## TO THE EDITOR

Major depressive disorder is a highly disabling psychiatric syndrome associated with deficits of specific subpopulations of cortical GABA-ergic interneurons[1,2]. We were pleased to read the article by Samad *et al*[3]. Their work highlights that Se, as a dietary source and/or supplement, is an effective therapy for As poisoning and its associated disorders. Furthermore, this study provides important findings regarding the prevention and treatment of anxiety disorders and depression. However, we believe there are several issues with the research design that need to be addressed. First, the use of sodium selenite (SS) as the Se supplement to improve the behavior of depression-like behavior in mice induced by As. Second, the use of the mouse model of depression. There are many mouse models of depression and anxiety; however, the authors chose not to use a classical mouse model of depression. As a result, questions remain regarding the validity of the study.

The main weakness of the study is SS as a means of Se supplementation. In particular, Se biological activity is dependent on its metabolic disposition; for example, absorption and excretion. It was observed that selenomethionine (SeMet) in organic form is more rapidly and completely (98%) absorbed than SS (84%) in inorganic form, and that liver uptake occurs faster after intake of organically bound Se than that of inorganic Se (SS)[4,5]. Moreover, various excretion indices confirm that SeMet has lower excretion (4%) than SS (18%)[4]. SS was also reported to induce DNA damage, particularly DNA strand breaks and base damage[6]. Se nanoparticles can also be used as a means to supplement Se. A recent study found Se nanoparticles to be a Se species with novel biological activities, bioavailability, and low toxicity[7]. Therefore, SS may not be the optimal speciation for selenite supplementation and as the source of the SS used in the study was not disclosed, questions remain.

The failure to select a suitable mouse model for depression was another issue with the study. A chronic unpredictable mild stress (CUMS) mouse model of depression is widely used[8]. As-induced depressive-like behavior cannot be used as a model of depression. Whether dietary Se can alleviate symptoms of the CUMS mouse model of depression needs to be further determined. In addition, dietary Se supplementation for depression in large-scale clinical trials is also necessary. As-induced depression-like behavior in mice may be associated with a large number of inflammatory factors and neurotransmitter changes that were not explored in this study.

### *Conclusion*

Overall, SS may be not the optimal speciation for selenite supplementation and the source of the SS used in the study was not disclosed. The failure to select a suitable mouse model for depression was another issue, which the authors need to address.

## FOOTNOTES

**Author contributions:** Ren XH and He LP contributed to the conception of research; Ren XH and Wang XX wrote the letter; Wang XX and He LP contributed to the revision of the letter; all authors approved the final manuscript for submission.

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LETTER TO THE EDITOR

# Beneficial for mental health, exercise more or less?

Wen-Jie Yan, Fan Zhang, Hui Ouyang, Chen-Qi Xing, Wei-Zhi Liu

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## Abstract

Regular physical activity may improve mental health during the pandemic by reducing inflammatory responses. However, overtraining or prolonged exercise training may adversely affect mental health.

**Key Words:** Physical activity; Exercise; Mental health; Runner's high

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**Core Tip:** Several empirical studies have provided evidence regarding coronavirus disease 2019 (COVID-19)'s deleterious effects on people's physical and mental well-being. Those who exercised frequently before the COVID-19 pandemic, such as professional athletes, may suffer from significant imbalance, which can be as uncomfortable as withdrawal symptoms. Further research should focus on groups with high physical activity levels.

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## TO THE EDITOR

We recently reviewed the article "Physical activity and mental well-being during the coronavirus disease 2019 (COVID-19) pandemic," issued in Volume 11 No. 12 of *World J of Psychiatry*. The authors assert that the COVID-19 pandemic may have deleterious effects on physical and mental well-being, including a growing level of angiotensin-converting enzyme 2 (ACE-2), associated with highly inflammatory effects[1].

Furthermore, they highlighted the significance of regular physical activities that maintain individuals' mental health during the pandemic. The conclusion should be adequately considered. Additionally, several empirical studies have provided evidence supporting this opinion, along with our comments in this correspondence.

Previous studies have shown that quarantine during an epidemic can be detrimental to mental health. In particular, it may lead to an increased probability of depression, anxiety, or post-traumatic stress disorder symptoms[2,3]. Moreover, the pandemic presents an explicit threat of suicide risk for some individuals[4]. During the pandemic, Brazilian undergraduate students had a higher rate of suicide risk than they had in the past[5]. Notably, one of the most visible negative changes the pandemic forced upon the public owing to the isolation policy, is increased sedentary behavior and reduced physical activity[6]. According to a multi-country cross-sectional analysis involving 8424 adults[7], negative changes in exercise behavior were associated with worse mental health and low happiness during the early COVID-19 restrictions compared to pre-pandemic restrictions. Research has proved that even home-based physical activities, such as cleaning the floor, bathing pets, or singing with children, can meet the WHO's recommendations when it is necessary to stay at home[8].

Abdelbasset *et al*[1] concluded in the article that regular physical activities might improve mental health during the pandemic by reducing inflammatory responses. However, they also noted that overtraining or prolonged exercise may adversely induce mental disorders. The endorphin hypothesis is a part of the physiological mechanism that explains the effect of exercise on mental health. Athletes who endured prolonged stress and overtraining may experience a feeling of well-being under the impact of endorphin; this phenomenon was acknowledged as "runner's high"[9]. Recently, Pearce *et al*[10] conducted a meta-analysis to explore the dose-response association between physical activity and incident depression in adults. They noted an inverse curvilinear association, in which the benefits were maximized when the frequency of activity changed from none to some. Additionally, the differences in the risk of depression were most significant with low doses of physical activity. Those who exercised frequently before COVID-19, such as professional athletes, may suffer from more imbalance, which is as uncomfortable as withdrawal symptoms. We call for further research focusing on these groups, enriching the data available about populations with higher physical activity levels.

## FOOTNOTES

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LETTER TO THE EDITOR

# Magnesium may be an effective therapy for Alzheimer's disease

Dao-Yun Lei, Jie Sun

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## Abstract

Magnesium deficiency in serum or the brain of Alzheimer's disease (AD) patients has been shown to be associated with AD. Current research suggests that supplementing or restoring magnesium may be a novel approach to AD treatment. However, the physiological properties of magnesium make such treatment difficult. It is undeniable that magnesium may be an effective therapy for AD.

**Key Words:** Alzheimer's disease; Magnesium; Therapy; Deficiency

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**Core Tip:** Magnesium deficiency in serum or the brain of Alzheimer's disease (AD) patients has been shown to be associated with AD. However, the physiological properties of magnesium make such treatment difficult. Undeniably, magnesium may be an effective therapy for AD.

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## TO THE EDITOR

Alzheimer's disease (AD) is the most common dementia characterized by the decline of cognitive function in the elderly. The accumulation of β-amyloid plaques and the existence of neurofibrillary tangles are the pathological bases for the dysfunction of various signaling pathways in the nervous system[1]. Since the pathogenic mechanism of AD is still not clear, its treatment approaches are unlikely to be meaningfully effective. Several approved drugs ameliorate some of the symptoms of AD, but no

current interventions can modify the underlying disease mechanisms[2,3]. We read the interesting article by Xiong *et al*[4], which was published in *World Journal of Psychiatry*. Their study found that magnesium L-threonate alleviated neuronal apoptosis by inhibiting oxidative stress, especially in the hippocampus. Although the research work revealed a potential scheme for the treatment of AD, we still believe that some views deserve further consideration and look forward to receiving the reply from the authors.

Admittedly, magnesium is one of the most abundant cations in the intracellular environment after potassium. $Mg^{2+}$ is tightly regulated and kept at basal levels by normal $Mg^{2+}$ intake, absorption, and metabolism under physiological conditions. Total magnesium levels in the hippocampus of AD patients decreased by 18% compared with that of normal subjects[5]. Although the presence of magnesium deficiency in patients with AD is notable, its severity may be underestimated. The concentration of serum $Mg^{2+}$ in healthy people ranges from 0.70 mM to 1.05 mM[6]. $Mg^{2+}$ deficiency is generally determined by measuring the total serum $Mg^{2+}$ concentration, but it cannot accurately reflect the concentration of magnesium in the human body. Most $Mg^{2+}$ is stored in bone, muscle, and soft tissue, and the proportion of serum $Mg^{2+}$ is very low. Even if the human body is in a serious state of $Mg^{2+}$ depletion, serum magnesium may also be in the normal range. Although the magnesium concentration in AD patients is reduced, the degree of deficiency cannot be accurately evaluated. It is not only difficult to evaluate magnesium deficiency, but also a reasonable supplement of magnesium. Slutsky *et al* found that following long-term magnesium supplementation, $Mg^{2+}$ concentration in cerebrospinal fluid only increases by 15%[7]. On one hand, systemic magnesium is closely regulated by renal function. On the other hand, the blood-brain barrier separates the brain from the daily fluctuations of blood magnesium. Hippocampal synapses are very sensitive to small changes in extracellular $Mg^{2+}$ concentration (increasing the concentration of magnesium by 15% can increase the synaptic density by 50%)[8]. Encouragingly, compared with other $Mg^{2+}$ compounds (such as magnesium chloride, magnesium citrate, and magnesium gluconate), dietary intake of magnesium L-threonate could significantly increase $Mg^{2+}$ levels in the brain[4]. Therefore, restoring brain magnesium may be a potential way to treat cognitive impairment in patients with AD.

### Conclusion

In summary, magnesium may be a novel therapeutic strategy for AD-induced cognitive impairment. However, numerous clinical studies are still needed to confirm the clinical application of magnesium.

## FOOTNOTES

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LETTER TO THE EDITOR

# Why do we not reverse the path? Stress can cause depression, reduction of brain-derived neurotrophic factor and increased inflammation

Angelo Emilio Claro, Clelia Palanza, Marianna Mazza, Alessandro Rizzi, Linda Tartaglione, Giuseppe Marano, Giovanna Muti-Schuenemann, Marta Rigoni, Paola Muti, Alfredo Pontecorvi, Luigi Janiri, Gabriele Sani, Dario Pitocco

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## Abstract

The aim of this paper is to describe the direction of the link between stress, depression, increased inflammation and brain-derived neurotrophic factor (BDNF) reduction. We hypothesize that severe stress or prolonged stress can be the driving factor that promote the onset of depression. Both stress and depression, if not resolved over time, activate the production of transcription factors that will switch on pro-inflammatory genes and translate them into cytokines. This cascade fosters systemic chronic inflammation and reduced

plasma BDNF levels. Since people with depression have a 60% increased risk of developing type 2 diabetes (T2D) and show high levels of inflammation and low levels of BDNF, we hypothesize possible reasons that might explain why T2D, depression and dementia are often associated in the same patient.

**Key Words:** Depression; Inflammation; Brain-derived neurotrophic factor; Type 2 diabetes mellitus; Dementia; Psychological stress

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**Core Tip:** This paper proposes a distinct interpretation of the link that exists between increased inflammation and reduction of brain-derived neurotrophic factor (BDNF). We describe why most of the people with altered inflammatory status and low BDNF do not automatically have depression, and why some people become depressed without diverging from average serum levels of these markers. We also suggest a reason why the use of tumor necrosis factor-α inhibition has no effect as a therapy in patients with resistant depression and high inflammatory levels.

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## TO THE EDITOR

We read with great interest the work of Porter and O'Connor[1] describing how brain-derived neurotrophic factor (BDNF) and inflammation are considered key players in the pathogenesis of depression.

We found the ideas of our colleagues very interesting and sharable. In this letter, we would like to suggest a different way to evaluate the link between BDNF, inflammation and depression. Following the "*social signal transduction theory of depression*"[2] we consider stress as the main cause of development of depressive symptoms; depression, in turn, is able to induce increased inflammation and reduced BDNF production.

It has been demonstrated that when a person lives in an environment characterized by numerous stressful situations (physical and social threat, or internal perceived stressors, like internal thoughts) that are severe or prolonged over time and he is not able to eliminate or psychically rework them, he displays a greater risk of developing depression[2,3].

Stress and depression, if not resolved over time, can activate brain regions connected with pain. These areas will project into lower regions that regulate inflammation *via* the hypothalamus–pituitary–adrenal axis and the sympathetic nervous system (SNS)[3]. The SNS, in the first stage of modulation, will set up the production of epinephrine and norepinephrine. These neurotransmitters will activate the production of transcription factors that will switch on pro-inflammatory genes and translate them into cytokines that will foster major inflammation or Systemic Chronic Inflammation (SCI)[2]. If this state is sustained for years, there is a high risk of developing inflammation-related disorders, quickened biological aging, infections, and premature mortality[4].

Moreover, stress and chronic inflammation are capable of inducing reduction of BDNF and indeed plasma BDNF levels are significantly lower in depressed patients compared with matched controls[5].

These considerations might explain why most of the people with altered inflammatory status and low BDNF do not automatically develop depression, and why some people become depressed without presenting the serum levels of either of the two markers far from the average[1]. It is neither the reduced BDNF nor the increased inflammation that induces depression, but rather it is stress itself that is able to promote the onset of depression. Moreover, if stress and depression last over time they can lead to increased inflammation and decreased BDNF[1]. Following this reasoning, it appears clearer why pharmacological intervention with tumor necrosis factor-α antagonist as an anti-depressant treatment in patients with resistant depression and high inflammation does not give positive results, while the same type of intervention is quite effective in treatment resistant patients with high inflammation and without depression[6,7]. That is because in patients with inflammatory diseases inflammation recognizes physical causes as an origin while in patients with depression it recognizes stress as the underlying

cause of inflammation. If patients are not able to eliminate the source of stress, this will continue to generate depression, inflammation and reduced BDNF.

The article by Porter and O'Connor[1] allowed us to move even further and to hypothesize a possible link between stress, depression, inflammation, development of type 2 diabetes (T2D), BDNF reduction, and dementia.

Patients suffering from depression have high levels of stress which lead them to overeating, in particular food rich in carbohydrates or snacks, because this high-calorie food acts as a self-medication and is able to increase serotonin levels[8,9]. These patients are accordingly more prone to develop overweight and obesity, the strongest risk factors for the onset of T2D[10-12]. It has been showed that people with depression have a 60% increased risk of developing T2D[13] and 25% of patients with T2D have depression[14]. Nevertheless, depression in T2D patients is frequently unrecognized and therefore not treated[15-17].

Thus depression, untreated for years, contributes to maintain T2D and both depression and T2D can lead to increased SCI and decreased BDNF. In this way, the reduction of neurogenesis and synaptogenesis, a reduction of the vascular bed and vascular support and neuroinflammation are determined, finally leading to an increasing risk of dementia onset. Low BDNF levels are present in dementia patients[18,19] and patients with T2D are approximately two to four times more likely to develop dementia than individuals without T2D. These associations might explain why T2D, depression and dementia are often associated in the same patient[20-23]. We are aware that these are hypotheses, but we can consider them as useful reflections inspired by the article by Porter and O'Connor[1] to be validated in future studies.

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*REVIEW*

# Substance use and substance use disorders in Africa: An epidemiological approach to the review of existing literature

Olakunle James Onaolapo, Anthony Tope Olofinnade, Foluso Olamide Ojo, Olufunto Adeleye, Joshua Falade, Adejoke Yetunde Onaolapo

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## Abstract

The relationship between man and substances that have abuse potentials, and whose use has been associated with the development or progression of substance use disorders has continued to evolve in terms of geography, economic implications, and time. History shows that local plants with psychoactive constituents can get exported worldwide through global travel, commerce, or even conquest. Time and globalization also change people's relationship with substances of abuse; hence, an area that was initially alien to certain substances might evolve to becoming a trafficking hub, and then a destination. A case in point is Africa where a rapidly increasing prevalence of substance use/abuse and substance use disorder among adolescents and young adults is putting enormous strain on the economy, healthcare system, and society at large. However, there appears to be a paucity of scientific literature and data on the epidemiology, risk assessment, and contributing factors to substance use and the development of substance use disorders across Africa. In this narrative review, we examine extant literature (PubMed, Google scholar, Medline) for information on the prevalence, trends, and

influencers of substance use and the development of substance use disorders. This is with a view of understanding the determinants of substance use and factors that influence the development of substance use disorders in the region, and how this information can be channeled towards developing a comprehensive intervention and treatment program.

**Key Words:** Addiction; Cannabis; Catha edulis; Datura metal; Drug dependence; Novel psychoactive substances

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**Core Tip:** Substance use for medicinal and recreational purposes dates back centuries; however, in recent times, substance use is increasingly becoming a global public health crisis. In Africa, there is a consensus that substance use is emerging as a public health crise, but there appears to be a paucity of data on the epidemiology, risk assessment, and contributing factors to substance use and the development of substance use disorders across Africa. Here, we examined the extant literature for information on the prevalence, trends, and influencers of substance use and substance use disorders as it relates to Africa.

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## INTRODUCTION

Substance use and substance use disorders are increasingly becoming a global public health crisis, largely due to their increasing prevalence, worsening disability-adjusted life years, and high socioeconomic burden[1]. According to the World Drug Report, 2021[2], approximately 275 million people used drugs worldwide in the preceding year, with another 36 million persons diagnosed with substance use disorders globally[2]. In 2019 alone, substance use disorders were linked to about 18 million years of healthy life lost. Also, about 180000 deaths were directly linked to substance use disorders, while another half million deaths were attributed to illicit drug use[3].

Substance use is generally defined as a patterned use of any substance (including alcohol and/or psychoactive drugs) in quantities (or through methods) that are harmful to the user or others[4]. Substance use is often associated with varying degrees of intoxication, which is associated with alteration of judgment, attention, and perception. The use of alcohol, illicit drugs, and illegal use of prescription medications has been associated with negative impact on the individual's health and productivity, as well as a high socioeconomic burden on the family and society[5,6]. Globally, there is a rapidly rising prevalence of substance use and substance use disorders, with an associated increase in the morbidity and mortality. Also, in Africa, the use of illicit substances such as cannabis (the most widely used substance in Africa, with a prevalence of between 5.2% and 13.5% in West and Central Africa), amphetamine-type stimulants, and benzodiazepines is increasing rapidly[7]. Again, in the last decade, Africa has begun to be recognized as a consumer and a destination for illicit drugs, compared to being previously regarded as mainly a transit zone for these drugs (serving as a link between Latin America and Europe)[8,9]. This reversal of the illicit drug trend is believed to be a contributing factor to the rapid development of substance use epidemic, particularly in the urban centers of Africa.

There is a consensus that substance use (particularly among adolescents and young adults) in Africa is emerging as a public health crises; however, there appears to be a paucity of scientific literature and data on the epidemiology, risk assessment, and contributing factors to substance use and the development of substance use disorders across Africa. Here, we reviewed the extant literature for information on the prevalence, trends, and influencers of substance use and the development of substance use disorders. This is with a view of understanding the determinants of substance use and the factors that influence the development of substance use disorders in the region, and how this information can be channeled towards developing a comprehensive interventions and treatment program.

### *History of substance use and substance use disorders*

Substance use for medicinal, religious, and recreational purposes dates back centuries. The earliest mentions of the use of alcoholic or fermented beverages in Chinese writing dates far back as the 7$^{th}$

millennia B.C.E[10], although there is also evidence from Sumerian writing (2100 B.C.E) of the use of opium from the poppy plant[11]. While the earliest use had been linked mainly to medicinal and religious purposes[10-12], there are also documentations of their use for recreational purposes[12]. However, since ancient times, humans have recognized the health problems that may be associated with excess alcohol consumption[12-14].

In 2019, the United Nations Office on Drugs and Crime reported an estimated 35 million people having a substance use disorder necessitating treatment[15]. Surveys and results of prospective studies examining patterns of drug use among the general population has revealed substance use peaks between 18 years and 25 years of age[15,16] with drug use among young people exceeding that of older people[15,17].

### *History of substance use in Africa: From transit nations to major illicit drug destinations*

The African continent has a long history of drug cultivation, production, trade and consumption; and there are also indigenous plants and herbs with psychoactive effects such as cannabis resin (known as hashish in North Africa), Catha edulis (known as Kath in East Africa), and cannabis (known as dagga in Southern Africa) that have also been used traditionally for centuries[18-21]. In the last few years, rapidly growing large-scale trade and recreational use of opiates, synthetic psychoactive stimulants, and prescription drugs are emerging threats in the African continent[21].

The relationship between North Africa and cannabis has existed for centuries, predating the arrival of the Spanish and French in the 19$^{th}$ century. Also, during the colonial era, cannabis was cultivated in small quantities across the northern Rif mountains in Morocco, and throughout the northern parts of Tunisia and Algeria[22]. While production was mainly to meet local demands (with some smuggling and exportation to Europe), the era following independence of the different countries in the region saw regulations and laws being enacted and enforced to control the production, sale, and use of cannabis. However, across the four countries (Morocco, Algeria, Tunisia and Libya) that make up the Maghreb (an area also known as northwest Africa), the drug trade has not only continued to grow, it is also evolving. In the last few decades, a region known mainly for the production of cannabis destined for other markets (particularly the European market) has increasingly become an important route for the trafficking of cocaine and different psychotropic pills. Since the beginning of the 21$^{st}$ century, trafficking routes for cocaine, cannabis resin, and psychotropic pills that existed between South America, Africa, and Europe shifted to transect the Maghreb region[22]. This change has been partly attributed to an increase in the demand for drugs in the region, and the perturbations of other transit zones such as the Sahel region, which has become unstable. Most important is the geographic location of the region, being a link between Africa, Middle East and Europe. While drug transit routes through North Africa is increasing, of more importance is the increasing rate of consumption of these drugs in the region. The use of psychotropic drugs, which are very addictive, is nearing epidemic proportions in the region; also, other substances being consumed include cannabis, cocaine and opioids[22].

Before West Africa began to be considered a transit zone for drugs, it was also a producer of cannabis products (although not on the scale of the North African countries), which were shipped to Europe and the United States. Although, at the same time, marijuana was being imported into Nigeria from South Africa and a region now known as the Democratic Republic of Congo[23]. The smuggling of heroin through West Africa was first documented in 1952[23]; however, West Africa's rise as a major drug smuggling hub began sometime in the 1960s, coinciding with a period of increased demand for illegal drugs, including marijuana which was grown and exported from Nigeria in large quantities to Europe. Despite attempts by governments in these countries to stem the tide of the marijuana export, marijuana trade continued illegally for several years until the demand for newer psychoactive substances such as cocaine and heroin overtook the demand for marijuana[24]. By the 990$^{th}$ year of the 2$^{nd}$ millennium and the 90$^{th}$ year of the 20$^{th}$ century, West Africa had become a major transit and repackaging center for substances such as cocaine and heroin through a transnational trade route that originated from South America and Asia, to Europe. While drug trafficking through Africa was not new, an intense clamp-down on the South-North American trade routes by the United States anti-narcotics strategies and the increase in demand for drugs across Europe saw to the rapid expansion of the West African trade routes in the early 21$^{st}$ century[25,26]. The geography of the West African states (made up of large areas of uninhabited islands and archipelagoes found in countries like Guinea Bissau) eased transit and made detection difficult[27]. Also, the vulnerable political environment with the presence of civil wars/insurgencies created fertile grounds for the development of criminal networks in the West African sub region [27].

Previously, when compared to West Africa, the drug trafficking routes through the Eastern belt of Africa were less robust; however, in the last few decades of this century, the trend is an increase in the trafficking of and the variety of trafficked drugs through the East African states of Kenya, Uganda, and Tanzania. Specifically, the trafficking of heroin and cocaine through these countries has grown considerably. Trafficking routes begin in Afghanistan where heroin is produced, through Pakistan and then East Africa enroute over Europe. The cocaine transnational trafficking routes began to go through East Africa in a bid to bypass the West African routes that were increasingly being watched by anti-drug trafficking authorities[28]. Also observed was that the increased consumption of these substances coincided with an increase in trafficking and affordability of the drugs.

In South Africa, a country in the southern region of Africa, the trafficking of drugs has increased. There are reports that since the period prior to and following the transition to democracy, there has been an escalation of drug trafficking. Trafficking in these parts has increased as a result of the easing of the strict control of land, air and sea borders, and an increase in international trade that occurred following the reintegration of South Africa into the committee of nations following the end of apartheid. Also, the effective policing of traditional smuggling routes prompting the search for other shipping routes also accounts for the increased trafficking of drugs through South Africa[29]. The increased trafficking is also worsening the substance use problems as a proportion of the drugs trafficked end up on the local market. There have also been reports that drugs such as methaqualone are also produced in clandestine laboratories in the region[30]. Overall, the level of affluence in the region makes it an attractive 'emerging market' for illicit drugs[30-32]. South Africa also has a history of drug use that dates as far back as the 15$^{th}$century. Cannabis, which is known as dagga in South Africa, has been consumed traditionally for centuries. The cannabis plant was brought to southern Africa by Saheli merchants from eastern Africa and some members of the bantu tribe of central and southern Africa where it has been cultivated since the 15$^{th}$ century. Around the 16$^{th}$ and 18$^{th}$ century, the consumption of cannabis increased significantly[33]. Although initially popular only among the African population, over time, its use extended to the white population of South Africa[30].

Overall, while the current substance use epidemic in the African continent could be linked to the global trend in substance use, the transformation of African nations from mainly transit points in the international drug network to consumer countries would seem inevitable[34]. Also, the rapid socioeconomic changes that have occurred across the different countries that make up the African continent could have facilitated this shift in what can be assumed to be the "normal trend".

## EPIDEMIOLOGY OF SUBSTANCE USE ACROSS THE AFRICAN CONTINENT

Across Africa, reports spanning the last two decades show that substance use especially among adolescents and young adults is increasing at alarming rates[19,35-41]. The World Health Organization and the United Nations Office on Drugs and Crime reported, an exponential increase in the per capita consumption of alcohol as well as the cultivation, trade, and consumption of cannabis in most of the countries in Africa, with suggestions that this could inevitably have adverse socioeconomic and public health implications[42-44]. At the time, about 10 countries in Africa were listed among the 22 countries with the highest increases in the use of alcohol and other psychoactive substances including cannabis, tobacco, cocaine, and heroin[45]. In 2013, the United Nations Office on Drugs and Crime World Drug Report estimated that across the African continent, more than 28 million people had a current history of substance use. Cannabis was also reported to be the most commonly used drug on the continent, with the prevalence estimated to be 7.5%, which was almost twice the global average. The use of opioids was also reportedly on the rise[46].

While it has been recognized that Africa is beginning to battle a drug use epidemic, with an estimated 37000 people in Africa dying annually from substance use-associated complications[47-49]; available data for Africa are still either weak or nonexistent. To date, in many African countries, there is still a paucity of national data regarding the epidemiology and patterns of substance use across populations, with available data largely limited to small prospective population studies and retrospective hospital-based studies.

In West Africa, the paucity of data regarding the prevalence of drug use undermines our ability to adequately understand the full extent of the substance use problem, and how it is creating a public health problem that further threatens the already fragile health system that currently exists. It also creates a false sense of safety, because it fosters the erroneous belief that substance use is under control. However, in the last few years, this trend is becoming more difficult to ignore, because there is now increasing evidence from the increase in crime/criminal behaviors and an increasing need for medical attention that arises from the development of substance use disorders or complications of risky behaviors that are consequences of drug use. In the last decade, in West African countries like Ghana, incident reports from health professionals, lawyers, and law enforcement officers are beginning to show dramatic increases in the domestic consumption of illicit drugs. However, these reports do not adequately portray the scale of substance use problem; because there is a dearth of national figures that can accurately quantify the prevalence of drug use in Ghana or most other West African countries. All of these result in a huge dependence on small-scale cross-sectional studies (Table 1). A 2008 population-based study conducted among school-going adolescents, reported that the prevalence of any substance use in the preceding 1 mo was 3.6%[50]. The results of an earlier study that interviewed a sample of 894 high school students with a mean age of 17.4 years, reported that the lifetime alcohol use in these cohort was 25.1%; with cigarette use and lifetime marijuana use being 7.5% and 2.6%, respectively. Also, current alcohol use was reported to be 46.2%; current cigarette and marijuana use was 44.6% and 58.3%, respectively[51]. The result of a 2014 cross-sectional survey of a sample of 227 street children and youths revealed that the current prevalence of alcohol and marijuana use was 12% and 16.2%, respectively. Sex differences in substance use was also reported with more females using alcohol, marijuana, and

**Table 1 Epidemiology of substance use across the African continent**

| Region | Study type | Study group | Result | Ref. |
|---|---|---|---|---|
| Ghana | Population-based study | School-going adolescents | 3.6% prevalence of substance use in the preceding 1 mo | [50] |
| Ghana | Cross-sectional study | 894 high school students with a mean age of 17.4 yr | Lifetime alcohol use was 25.1%; with cigarette use and lifetime marijuana use being 7.5% and 2.6% respectively. Current alcohol use was 46.2%; current cigarette and marijuana use was 44.6%; and 58.3%, respectively | [51] |
| Ghana | Cross-sectional survey | 227 street children and youths | Current prevalence of alcohol and marijuana use was 12% and 16.2%, respectively | [52] |
| Nigeria | Cross-sectional study Northwestern Nigeria | 280 secondary school students | 56% of them had a history of substance use (kolanut, cigarettes, and marijuana) | [53] |
| Nigeria | Cross-sectional study Southwestern Nigeria | 249 secondary school students | Prevalence of alcohol and substance use was 21.7% and 26.3%, respectively, tramadol being the substance of choice | [54] |
| Nigeria | National drug survey | Population-based | Approximately 14.3 million people (accounting for 14.4% of the population aged between 15-64 yr) had a history of current and continuing substance drug use, with close to 3 million having at least a form of drug use disorder | [55] |
| Ethiopia | Demographic and health survey | Population-based | 4% of youths and 6.3% of individuals in age groups of 25-29 yr smoked cigarettes, while 53% of men and 45% of women consumed alcohol | [59] |
| Ethiopia | Analysis of data extracted from the 2016 Ethiopia Demographic and Health Survey | 12688 male cohorts | 62.5% (7931 males) had a current history of substance use (alcohol, Kath, or tobacco). Inhabitants of the Amhara, Tigray and Oromia regions had a current substance use prevalence of 18.5%, 14.2% and 12.8%, respectively | [60] |
| Ethiopia | Cross-sectional study Northeastern Ethiopia | 730 university students in | Lifetime prevalence of alcohol consumption, Kath chewing, and cigarette smoking was 33.1%, 13% and 7.9%, respectively, and current prevalence was 27.9%, 10.4% and 6.4% | [61] |
| Ethiopia | Cross-sectional study | 794 university students | 73.7% had a history of substance use with the lifetime prevalence of illicit drugs being 23.3% | [63] |
| Egypt | Hospital-based study (single-center experience) | First episode drug-induced psychosis patients | Substance abuse rates are as high as 10%-20% the global average with cannabis and tramadol being the most abused substance | [65] |
| Tunisia | Cross-sectional study | 298 persons with a history of drug use | Cannabis was the most widely consumed illicit drug, followed by benzodiazepines, buprenorphine, cocaine, and ecstasy | [68] |
| Tunisia | Mediterranean school survey project | Secondary school students | Tobacco, alcohol, and cannabis were the substances most frequently used | [66, 67] |
| Tunisia | Epidemiologic/toxicological investigation Northern Tunisia | 11170 suspected drug users | A preponderance of males (97.4%), with a median age of 29 ± 7.91 yr. 91.3 % were single | [69] |
| South Africa | School-based survey | Secondary school students | 13% of the students (aged 19 yr and below) had an history of cannabis use, although current use was 9%. 12% had a current use of heroin, 11% used inhalants and 6% consumed mandrax | [73] |
| South Africa | National household survey | Population-based | Past 3 mo prevalence for cannabis among 15-19-years-old was 3% | [74] |

smoking cigarettes compared to males[52]. In Nigeria, reports from small-scale studies have demonstrated a high prevalence of substance use among adolescents and young adults. A 2009 study that examined the prevalence of substance use among 280 students at a senior secondary school in a town in Northwest Nigeria, revealed that about 56% of them had a history of substance use, with the most common being kolanut, cigarettes, and marijuana[53]. Idowu *et al*[54] also examined the prevalence of substance use among 249 students (mean age = 16.3 ± 2 standard deviations) of secondary schools in a metropolis in south western Nigeria and reported that the prevalence of alcohol and substance use was 21.7% and 26.3%, respectively, with tramadol being the substance of choice[54]. The magnitude of the effect was best conveyed by the results of the 2018 National Drug Use Survey which revealed that approximately 14.3 million people (accounting for 14.4% of the population aged between 15 years and 64 years) had a history of current and continuing substance drug use, with close to 3 million having at least a form of drug use disorder[48,55]. A difference was also observed in the prevalence of drug use between the Northern and Southern geopolitical zones, with a higher prevalence in the regions in the south (13.8%-22.4% of the population) compared to those in the northern geopolitical zone (10%-14.9% of the population). In Nigeria, cannabis was the most commonly used drug, which was followed by opioids (non-prescription or in cough syrup)[48,56]. The survey also highlighted

a rise in the current use of psychoactive substances (including cannabis), the non-medical use of prescription drugs such tramadol, codeine, morphine or cough syrups that contain codeine or dextromethorphan[55]. Also observed was an overall high incidence of drug use (excluding alcohol) among males compared to females (10.8 million males *vs* 3.4 million females), although the sex difference in the non-medical use of prescription opioids, cough syrups, and sedatives was not as significant (6% among men compared to 3.3 among women). The survey also reported a higher incidence of drug use among young adults (24-39) compared to those aged 24 and below[55].

In East Africa, there is also a dearth of national statistical data on the prevalence of substance use in a number of the countries, with researchers and policy makers needing to rely on information from studies involving subsets of the populations. In Ethiopia, alcohol, Kath and tobacco are the most popular substances that are consumed[57,58]. A 2012 Ethiopian demographic and health survey reported that 4% of youths and 6.3% of individuals in age groups of 25-29 years smoked cigarettes, whereas 53% of men and 45% of women consumed alcohol[59]. Also, the results of a study by Girma *et al*[60] that analyzed data extracted from the 2016 Ethiopia Demographic and Health Survey revealed that of the 12688 male cohorts of the Ethiopian Demographic and Health Survey, at least 62.5% (7931 males) had a current history of substance use (alcohol, Kath, or tobacco) as at the time of the survey. Inhabitants of the Amhara, Tigray, and Oromia regions have a current substance use prevalence of 18.5%, 14.2%, and 12.8%, respectively. Alcohol (53.1%) is reportedly the most commonly consumed substance, followed closely by Kath, which has a prevalence of 25.9%[60]. Reports of small cross-sectional studies have also corroborated the high prevalence of alcohol, Kath, and cigarette smoking among Ethiopian youths[61]. Adere *et al*[61] examined a cohort of 730 university students in Northeastern Ethiopia and reported that the lifetime prevalence of alcohol consumption, Kath chewing, and cigarette smoking was 33.1%, 13%, and 7.9%, respectively, whereas the current prevalence of these substances is 27.9%, 10.4%, and 6.4%, respectively[61]. The prevalence observed in this study was similar to that observed in an earlier study carried out among the students at a University in a town in North Ethiopia[62]. While earlier studies among university students did not report evidence to suggest the use of illicit drugs, the results of a 2021 cross-sectional study among 794 students of Addis Ababa University, showed that 73.7% of the study participants had a history of substance use with the use of illicit drugs having a lifetime prevalence of 23.3%[63]. However, similar to other studies, alcohol, Kath, and cigarettes were still the most commonly abused substances[63].

In North Africa, data and information on substance use, production, trafficking, and consumption are also limited. This has been attributed to a lack of capacity for data collection and analysis[64]. In Egypt, there are reports that substance abuse rates are as high as 10%-20% the global average, with cannabis and tramadol being the most abused substances[65]. In Tunisia, an increase in the trafficking and consumption of psychoactive substances have been observed since the political uprising that occurred in 2011[66]. There have also been reports of increased availability of drugs of abuse, particularly to school students[66]. These increases have been confirmed by a few epidemiological studies[66-68]. Moslah *et al*[68] carried out a study to examine the pattern of substance use among 298 persons with a history of drug use between 2010 and 2015. The results showed that among these cohort of young adults, cannabis was the most widely consumed illicit drug, followed by benzodiazepines, buprenorphine, cocaine, and ecstasy[68]. Reports from the Mediterranean School Survey Project on Alcohol and Other Drugs (II) carried out in Tunisia in 2017 revealed that tobacco, alcohol, and cannabis were the substances most frequently used by secondary school students[67], whereas psychotropic drugs such as ecstasy, cocaine, and buprenorphine were less frequently consumed. More importantly, it was observed that the frequency of use of these substances has increased significantly since the first survey published in 2014[66]. Chaouali *et al*[69] carried out an epidemiologic/toxicological investigation to evaluate patterns of drug abuse in 11170 suspected drug users. Urine samples collected between January 2016 and December 2018 were also analyzed. Results revealed a preponderance of males (97.4%) compared to females, with a median age of 29 ± 7.91 years. Also observed was that a large percentage of these drug users were single (91.3%). Examination of the urine samples revealed that about 48.4% tested positive for illicit drugs, with cannabis being the most widely consumed drug (95%), others were benzodiazepines, buprenorphine, cocaine, and opiates (0.13%). There was also a history of poly drug use[69].

In Southern Africa (although there are limited national data in most countries in the region), a rise in substance use has been reported[70]. In some of these countries including Zimbabwe, there is anecdotal evidence suggesting an increase in substance use among adolescents and young adults, with prevalence of substance use reportedly ranging from 6.1% to 13.8%[70]. Alcohol, cannabis, heroin, glue, and cough mixtures are among the most commonly consumed products in Zimbabwe. Cannabis, which is commonly known as mbanje, is grown locally (also smuggled into Zimbabwe from Malawi and Mozambique), and remains the most popular illicit drug among young Zimbabweans. Drugs are also trafficked through Zimbabwe to other countries in the region, including South Africa. In South Africa, an increase in substance use has been reported, which has been linked to the increased availability of illicit drugs including cannabis, cocaine, heroin, amphetamines, and ecstasy; either from diversion during trafficking or increased cultivation and local production[29,30,71,72]. Other factors that have contributed to the increase in substance use include an increase in migration and easing of border controls following the commencement of democracy, which have facilitated the development of youths'

movements that indirectly or directly promote substance use[30]. Results from surveys have revealed a gradual increase in cannabis consumption among adolescents and young adults in South Africa.

A 2002 school-based survey reported that 13% of the students (aged 19 years and below) had an history of cannabis use, although current use was 9%. About 12% had a current use of heroin, 11% used inhalants, and 6% consumed Mandrax[73]. The results of another study (a 2005 National household survey) showed that the prevalence in the past 3 mo for cannabis among 15-19-years-old was 3%[74]. In another study examining the prevalence and patterns of use of illicit substances among persons presenting at drug treatment centers in South Africa, it was revealed that cannabis (16.9%), methamphetamine (12.8%), cocaine (9.6%), and prescription drugs (2.6%) were the substances commonly used among patients. Also, there was evidence of poly drug use, with cannabis and mandrax having a prevalence of 3.4%, whereas heroin and opiates had a prevalence of 9.2%[75].

Prior to 1994 and the first democratic elections, alcohol, cannabis, and methaqualone were the primary substances of misuse in South Africa. With South Africa's transition to democracy and subsequent reopening of borders, there has been an influx of and a growing burden of harm associated with illicit drug use. Alcohol, however, remains the most commonly misused substance, with 14% of the population having a lifetime diagnosis of alcohol abuse and/or dependence (Herman *et al*[76], 2009). Although the overall levels of alcohol consumption do not exceed those in the developed world, the pattern of consumption differs markedly, with hazardous and binge drinking being common.

### *New and emerging psychoactive substances in Africa*

Use of novel psychoactive substances is an emerging trend in substance use that is fast becoming a public health challenge globally[77,78]. Novel or new psychoactive substances have been defined by the United Nations Office on Drugs and Crime[79] as substances of abuse (existing either in its pure form or as a preparation) that are not controlled by either the 1961 or 1971 conventions on narcotic drugs and psychotropic substances, respectively, but pose significant threats to public health globally due to spikes in intoxications and fatalities associated with their use[79,80]. The term 'novel' or 'new' that is used in relation to these substances depicts their recent emergence in the global market. Substances that currently fall within the novel psychoactive substance category include (but are not limited to) synthetic cathinone and cannabinoids, synthetic opioids, image and performance-enhancing substances, tryptamine derivatives, piperazines, phencyclidine-like dissociatives, gamma amino-butyric acid (A)/beta receptor agonists, novel hallucinogens, benzodiazepines and psychotropic plants/herbs[77,81,82].

In the last few years or more, there has been a growing demand and supply chain for these new psychoactive substances[77,78,81]. In the last 10-12 years, the number of novel psychoactive substances has increased considerably. In 2009, only about 166 of them had been detected; however, by 2019, the number had risen to about 950, with more than 70% of these substances available in Europe[80,83]. While in the developed economies, a lot is being done to ensure continued documentation of novel psychoactive substances as they emerge, it would seem that Africa is only beginning to awaken to the emerging public health threat that these substances pose to her teeming population of adolescents and young adults[82]. While the lifetime prevalence of novel psychoactive substance use in countries such as the United States have been examined[80], there is a paucity of data on the prevalence of novel psychoactive substance use in Africa. Although across the continent, there is increasing awareness of the dangers of novel psychoactive substance use.

In 2017, attention was called to an increase in the use of designer drugs in Nigeria. Some of these substances which have street names such as "black mamba", Colorado", "Lamba", "happy boy", and" Scooby snax" are believed to contain synthetic cannabinoids. Their use is associated with a rise in the incidence of hallucinations, convulsions, psychiatric disorders, kidney failure and fatalities[84]. News outlets, including the British Broadcasting Corporation News and Premium Times, also reported that the use of and addiction to non-conventional psychoactive substances such as tramadol and codeine cough syrups among Nigerian youths was reaching epidemic proportions[85,86]. In Nigeria, available novel psychoactive substances also include mixtures with street names such as "gutter water", a cocktail of cannabis, tramadol, codeine and ethanol), and "monkey tail", a cocktail of locally made gin and cannabis (seeds, leaves, stems, and roots). Some people have also been in a state of euphoria from drinking the mixture of specific carbonated drinks and menthol flavored candies[82]. The sniffing of dry human fecal matter, dry cassava leaves and seeds, Datura metal seeds, Moringa leaf, burnt tires, sewer gas, and nail polish have also been reported[82,87]. Different parts of some lizards, including the whitish part of their dung, are also smoked in a bid to achieve a "high"[82,87]. The inhalation of urine, sewage, petrol, and glue are also common practice among drug users in Africa. It is believed that the hallucinogens present in hydrocarbons from petrol, and gases produced from fermentation of sewage have the ability to cause a "euphoric high" similar to (but longer lasting) when compared to that derived from the ingestion of cocaine[88].

In southern Africa, particularly South Africa, there have been reports of the use of "Nyaope" also known as "Whoonga", which is a cocktail of low-grade heroin (black tar heroin), marijuana, antiretroviral drugs (Efavirenz), and other undisclosed substances[88]. In East African countries such as Uganda and Kenya, the habit of using novel psychoactive substances such as the sniffing of aviation gas/jet fuel, toluene and glue is reaching epidemic proportions among persons aged between 16-25

years[89-91]. Other substances that are abused in this region include "kuber" and" shisha", also known as hookahs ,which are variants of smokeless tobacco. There have been reports that compared to cigarettes, the smoking of the shisha or hookah pipe exposes the user to higher volumes of smoke containing high levels of benzene, tar, and other carcinogens and increased risk of lung cancer[92-95].

In Northern Africa, the smoking of hashish and the chewing of Kath has become very rampant. Although there is little data from the region regarding the prevalence and patterns of use of novel psychoactive substances; reports from studies carried out in Egypt have suggested that the estimated prevalence of novel psychoactive substance use among adolescents in the country are largely underestimated[96]. However, tabloid reports have called attention to an increasing demand and use of novel psychoactive substances including "voodoo" and "strox" among adolescents and young adult in Egypt [97,98]. "Voodoo" is gaining popularity rapidly, and it is usually packaged and sold as an herbal incense. "Voodoo" is a heterogeneous mixture of several psychoactive substances, including synthetic cannabinoids, tramadol, amphetamine, methadone, benzodiazepines, penitrem A (a neurotoxin) and morphine derivatives. The concentrations of the chemical constituents and adulterants of voodoo also vary substantially among the different clandestine laboratories that produce it[96,99]. Another novel psychoactive substance that is gaining popularity in Egypt is "Strox"[100]. "Strox" or "Egyptian Spice" has been reported to account for approximately 4.3% of the over 10400 patients requiring medical support for drug-related complications[101]. Also, addiction to "strox" was responsible for 22% of calls to the addiction center hotline[101]. "Strox" is a potent synthetic narcotic that is mixed with tobacco and smoked; it is compounded in clandestine laboratories by adding veterinary grade chemicals to aromatic herbs such as marjoram. There have also been reports of the addition of pesticides to increase the potency, although this increases the toxicity[97].

The search for novel psychoactive substances is fueled by the need to create drugs that are able to evade the chemical processes used for detection and the legal processes that criminalizes the use and possession of conventional drugs of abuse. Also, the need for compounds that deliver fast and sustained psychoactive effects when compared to the conventional drugs also drive the search for novel psychoactive compounds[102]. However, the variability of the chemical constituents and/or adulterants of the different compounds present a conundrum for the health professional who has to decipher and manage the divergent symptoms and signs that complicate the use of these substances. Hence. there is an increasing need for continuous surveillance so that new or emerging psychoactive substances can be discovered before they wreak havoc on our communities.

### *African plants and herbs with psychostimulant potential: Are they being abused?*

Several plants and parts of plants have been shown to have central nervous system effects[103-109]. Also, current literature reveals that novel psychoactive substances can be derived from either synthetic compounds or from bioactive principles of natural compounds. These bioactive principles which are mainly alkaloids are present in a wide variety of plants including Ayahuasca, Catha edulis and nicotiana tabacum; and have been reported to possess hallucinogenic and/or stimulant effects[110]. Plants with psychoactive properties are found all over the globe and have been used for centuries by humans, for religious, therapeutic and recreational purpose[111,112]. Studies have shown that the bioactive principles of these plants enable the profound alteration of the human perception allowing for divination, ancestral contact, and spiritual enlightenment[111-113].

Africa has a high floral diversity and a rich tradition of indigenous medicinal plant and herb use [111]. Africa is also rich in flora of medicinal plants that possess central nervous system effects[107]. Although there is a paucity of ethnobotanical surveys on African plants with psychoactive effects, evidence from African traditional healers and diviners who use plants such as the 'Ubulawu', a preparation containing *Sileneundulata* and *Synaptolepis* are pointers that there are plants indigenous to Africa that contain compound which have mood altering effects[113]. A few plant species that are indigenous to Africa, such as the Cola species (Cola nitida, and Cola acuminata), Catha edulis (Kath), Datura species (Datura stramonium), Pausinystalia yohimbe (Burantashi Pausinytalia yohimbe) and Tabernanthe iboga have reported psychoactive properties[111,114], and have been used recreationally (Table 2) for centuries in the countries in which they are cultivated. However, in recent times, the use of and dependence on some of these plants by adolescents and young adults (either alone or combined with established illicit drugs) is reaching epidemic proportions. In this section, we reviewed the abuse potential of some psychoactive plants that are indigenous to the African continent.

Kath (Catha edulis Forsk) is a flowering plant native to countries in East Africa and the Horn of Africa. Fresh young leaves and twigs from Kath are chewed daily by large populations of people for its psycho-stimulatory properties. The chewing of Kath dates back centuries, being a practice that is rooted in tradition, social custom and the culture of the indigenous populations[115]. It has been reported that more than 20 million people worldwide chew Khat[116,117]. Although traditionally a custom associated with older middle Eastern and Eastern African men, Khat's use is now expanding to include women and younger persons. In the Eastern region of Ethiopia, approximately 30% of adolescent girls and 70% of adolescent boys chew Khat. The active principle contained in Khat is cathinone (an alkaloid), which is a stimulant that causes excitement, appetite loss and euphoria[117]. In countries such as Somalia, Ethiopia, Djibouti, and Kenya, the dependence on Kath is warranting its consideration as a substance of abuse. In Somalia a law prohibiting the use, cultivation, importation and trade of Kath was enacted and

**Table 2 African plants and herbs with psychostimulant potential**

| Region | Herbal preparation | Plant | Bioactive compound | Central nervous system activity | Toxicity | Ref. |
|---|---|---|---|---|---|---|
| East Africa | Khat chewing, drink made from dried leaves or smoking dried leaves | Catha Edulis | Phenylalkylamines and the cathedulins (Cathinone) | Improves performance, stay alert and to increase work capacity, excitement, appetite loss and euphoria | Memory impairment, sleeping disorders, liver toxicity, cardiovascular disease, psychosis and poor academic performance | [115, 117, 124-126] |
| West Africa | Different parts of the plant are smoked or used to make concoctions | Datura specie including stramonium and Datura metal | Atropine, scopolamine, and hyoscamine | Anticholinergic and hallucinogenic activity | Hyperthermia, tachycardia, delirium, pronounced amnesia, severe mydriasis, bizarre behaviors and painful photophobia | [135, 136, 141, 145-148] |
| West Africa | Root bark concoctions | Tabernanthe iboga | Ibogaine | Stimulatory, hallucinogenic, and sedative effects | Development of ataxia, tremor, cardiac toxicity, and death | [149-151] |
| South Africa | Ubulawu drink | Silene undulata and Synaptolepis | Triterpenoid saponins | Mood altering effects including stimulating vivid or lucid dreams | Confusion | [113] |
| South Africa | Chewed, smoked, snorted or swallowed | Sceletium tortuosum | Mesembrenone, mesembrenol, mesembrine and tortuosamine | Increased libido, decreased stress, euphoria and appetite suppression | Anxiety, headache, hypertension, irritability, insomnia and nausea | [154, 155] |

enforced by comprehensive national program[118]. At about the same period (approximately two decades ago), Kath was also considered by the World Health Organization and classified as a drug of abuse, although its abuse potential was not thought to constitute a serious problem compared with that of alcohol or tobacco[119]. Across a region extending across Africa and the Middle East, predominantly among the Ethiopians, Somalians and Yemenis, approximately 5 to 20 million people use Kath[116,120], with the consumers engaged in the practice for the best part of a day resulting in a loss of manpower and national income[121,122]. In 2005, a survey by the World Health Organization revealed a prevalence of 20% Kath abuse in Kenya, exceeding the prevalence observed in most of the other countries in the region[123]. However, more recent studies are demonstrating that in spite of attempts by the respective countries to criminalize the use of Kath, Kath chewing is fast becoming a common practice among young adults in countries like Kenya, Ethiopia, Somalia, Djibouti[124-126]. In Ethiopia, a study carried out among academic staff of a university revealed that the lifetime prevalence of Kath chewing was 41%[126], while another study carried out among college students reported a prevalence of 42%[124]. In Kenya, a recent household survey revealed that the prevalence of current Kath chewing in the region was 36.8%[125], which would suggest a significant rise from the 20% prevalence reported by the World Health Organization[123]. While Kath chewing was not previously known outside the regions within which it was cultivated, the effects of migration and trade have propelled it to a widely used psychostimulant globally[115,127]. Kath chewing has been associated with adverse health effects that is creating public health challenges in countries across Asia, Europe, Australia, and the United States of America[128-130]. When chewed concurrently with tobacco, there have been reports of cardiovascular stress response[129]. It has also been associated with the alteration of physical, mental, social and cognitive aspects of human functioning[131]. Chewing Kath chronically has been reported to cause memory impairment, sleeping disorders, liver toxicity, cardiovascular disease, psychosis and poor academic performance[126,132]. While attempts are being made by countries to criminalize the importation and trade of Kath, smugglers continue to find new avenues and trade routes. For example, in 2016, the National Drug Law Enforcement Agency of Nigeria reported seizures of Kath load, which was possibly destined for the Nigerian market or enroute countries[133]. However, in 2020, the United States customs reported seizure of Kath load from Nigeria destined for the United States suggesting that Nigeria is fast becoming a Kath transit hub[134].

In Nigeria, complicating the substance abuse epidemic is the emerging trend of experimenting with plant extracts or brews from a group of flowering plants belonging to the Datura specie, of the nightshade family Solanaceae[135,136]. Although members of the Datura specie which are broadly known as thorn apple, devil's apple, devil's trumpet or angel's trumpet have their origin in central Americas and in the south-west region of the United States if America[137,138], they have become naturalized all over the world, being widespread in Asia, Europe, and Africa[139]. The datura specie is made up of herbs and shrubs with erect or branched stems, with alternate simple basal leaves and opposite leaves on terminal branches[139]. The fruit has a spiny capsule and reniform seeds[139,140]. All parts of the Datura stramonium and Datura metal plant has been shown to contain tropane alkaloids such as atropine, scopolamine, and hyoscyamine which have significant anticholinergic and hallucinogenic activity[141]. The high tropane alkaloid content of these plants increases their medicinal value and also opens them up to potential abuse. In Nigeria, Datura stramonium (thorn apple, devil's

snare, devil's trumpet or jimsonweed) and Datura metal (Indian thorn apple) are naturalized. Similar to a number of countries across the world (United States of America and Canada) where there has been reports of datura-induced poisoning among adolescents who abuse the plant for its hallucinogenic effects[142-144], adolescents and young adults in Nigeria are also experimenting with the plant and getting poisoned[136]. Datura metal grows wildly (although at times it is cultivated) across the different regions of Nigeria where it is called 'Myaramuo' by the Igbos of south eastern Nigeria, 'Zakami' by Hausas of northern Nigeria and 'Apikan' by the Yorubas of southwestern Nigeria[145,146]. Datura stramonium also grows as a weed and is also cultivated across the different states of Nigeria. It is known as 'Gegemu' by the Yorubas and 'Zakami' by the Hausas[136]. Both plants have been reported to have hallucinogenic and euphoric effects when the different parts of the plant are either smoked or used to make concoctions[147]. Datura stramonium poisoning is associated with hyperthermia, tachycardia, delirium, pronounced amnesia, severe mydriasis, bizarre behaviors and painful photophobia[136,148]. These features can appear as early as 30 min to 1 h following consumption of the extract or smoking of the weed and have been reported to last several hours to days or at times even as long as 2 wk[148].

Another plant with psychoactive properties is the Western African shrub Tabernanthe iboga from whose root bark ibogaine, a hallucinogenic alkaloid is extracted. Traditionally, the concoctions from the roots have been used for their stimulatory, hallucinogenic, and sedative effects[149]. Ibogaine has been reported to exhibit stimulant effects at low doses and result in the development of hallucinations at high doses. Its use has also been associated with the development of ataxia, tremor, cardiac toxicity, and death[149-151]. There have also been reports that ibogaine has anti-addictive properties, although its use is limited by its deleterious effects[152,153].

In southern Africa, the use of extracts, dried-powdered herb, tincture, tea bags and seeds of the plant sceletium tortuosum also known as Kanna is also gaining traction. These different compositions of the plant can be chewed, smoked, snorted or swallowed resulting in increased libido, decreased stress, euphoria and appetite suppression. There are reports attributing the antidepressant and mood-elevating effects of the plant to the serotoninergic activity of its alkaloids including mesembrenone, mesembrenol, mesembrine, and tortuosamine. Indiscriminate use has been associated with the development of anxiety, headache, hypertension, irritability, insomnia and nausea[154,155]. A serotonin syndrome has also been observed especially when consumed alongside selective serotonin reuptake inhibitors or monoamine oxidase inhibitors. Although the use of a number of these plants and herbs may not be illegal in the countries in which they are consumed, increasing reports of poisoning arising from the use or these psychoactive plants solely or in combination with other compounds is drawing attention to the need to enact public health laws that can criminalize their use.

### *Synthetic cannabinoid in herbal products*

Synthetic cannabinoids are compounds which are structurally similar to natural cannabinoids [tetrahydrocannabinol and cannabidiol ( CBD)] allowing them to exert their effect through binding to cannabinoid receptors (CBD1 and CBD2)[156,157]. Synthetic cannabinoids can be agonists at the $CB_1$ receptors or antagonists at other cannabinoid receptors. Although many of the synthetic cannabinoids are used in pharmacology in structure - activity relationships and receptor binding studies, others have medicinal uses including in the treatment of anorexia, as antiemetics in cancer chemotherapy and in pain management. In the last two decades, commercial preparations containing synthetic cannabinoids have become popular for their use as designer drugs marketed as herbal incense or herbal blends under the names 'Spice', 'synthetic marijuana', and 'K2'[158-160]. The cannabinoid compound is sprayed onto inert plant material and smoked or ingested in liquid form[160,161]. Although often considered legal and safe alternatives to cannabis, there is evidence indicating that synthetic cannabinoids use is associated with significant health risks when compared to marijuana; there have also been reports that their distinct pharmacological effects and metabolic activity could also be a contributing factor to the increased toxicity observed following their use[157,162,163].

To date, the abuse of herbal preparations that have been spiked with synthetic cannabinoids continues to increase. This is evidenced by an increasing list of commercial preparations marketed in the United States and Europe under the names fairly legal, Pandora's box, Angry birds, exodus, bonzai, annihilation, weekend blend, fire, strong spice, green Buddha, smoke, and Scooby snacks[102,164]. In the last few years, Africa is also beginning to experience a surge in demand for and use of synthetic cannabinoids. In Mauritius, since the year 2015, there has been a reported increase the number of arrests involving synthetic cannabinoids[165]. In different countries in the continent they are marketed under various street names including, Wiz in South Africa[166]. In Nigeria it is marketed as Black Mamba, Colorado, Lamba, Happy Boy or Scooby Snax[167].

Across Africa, available evidence points to a growing use of novel psychoactive compounds which mainly contain synthetic cannabinoids. Synthetic cannabinoids have effects that are similar to that experienced with natural cannabis, although they are more potent and have been associated with more severe physical and psychological adverse effects necessitating hospitalizations[168,169].

## PREVALENCE OF SUBSTANCE USE DISORDERS AND AVAILABILITY OF EVIDENCE-BASED TREATMENT CENTRES IN AFRICA

Substance use disorders are defined as the persistent use of alcohol or other psychoactive substances despite significant harm and untoward health consequences[170]. They are characterized by an array of social, emotional and behavioral problems. Across Africa, there is also a dearth of scientific data on the prevalence of substance use disorders or drug dependence[48,55,56,171]. In Nigeria, reports from the 2018 National Drug Survey revealed that one in every five persons who used drug in the past year also had a drug-related disorder[48,55,56]. In South Africa, results obtained from a nationally representative sample of 4351 persons aged 18 years and above revealed a lifetime prevalence of substance use disorders of 13%, with alcohol use disorder being the most prevalent type of substance use disorders[72,171-173]. In Egypt, reports obtained from the National Addiction Research Study revealed the prevalence of drug dependence in the different regions ranged from 3.2%-9.3%[174].

Left untreated, substance use disorders contribute significantly to the global burden of disease, including increasing morbidity and mortality and societal cost implications such as increased healthcare costs, lost productivity and costs related to social welfare and criminal justice[4,5]. Access to evidence-based treatment has been linked with a reduction in the risk for ill health[171]. Accordingly, towards reducing the burden of substance use globally, availability and access to evidence-based treatment facility were included in the United Nations' Sustainable Development Goals for 2030[175]. However, despite reports of increasing prevalence of drug dependence and substance use disorders, reports from surveys carried out in a number of countries in Africa suggest that the availability of treatment centers are limited[171,176]. Factors contributing to this treatment gap include treatment infrastructure constraints, poor funding, and the high cost of private-for-profit treatment centers[171,176].

### *How can Africa's burgeoning substance use and substance use disorder problem be addressed*

It has become evident that there is a burgeoning illicit drug use problem across the African continent[47-49,177]. There had been predictions that by the year 2050, increased life expectancy and a rapidly growing population would result in approximately 130% increase in the burden of mental and substance use disorders to about 45 million years lived with disability in Africa[178]. While different factors, including increased access to illicit drugs and high level of youth unemployment have been adduced to explain the emerging drug use pandemic; its significant contribution to economic instability, crime, criminality and insecurity across Africa and worldwide means that governments and policy makers need to prioritize the need to develop ways to mitigate these problems. The dearth of comprehensive data and the uniqueness of the manifestation of illicit drug use to individual countries within the African region are factors that impede progress towards addressing this looming pandemic.

Understanding the different determinants of drug use within the different populations of Africans and how these impact the prevention and treatment of substance abuse disorders in the individual countries would be an important step towards addressing this emerging pandemic. Currently available data suggests that influencers of drug use (particularly in adolescents) which include family, social networks and peer pressure are common to most of the countries[179-184]. Other determinants of drug use also include childhood trauma and adverse life experiences such as sexual, emotional or physical abuse. Across age groups, demographic factors such as being male, lower level of education and attendance of private schools have also been reported by researchers from the different regions of Africa [185-187].

In addition to understanding the influencers and determinants of drug use, there is also a need for up-to-date national and regional data that can adequately determine the prevalence and incidence of drug use across all demographics. The availability of a detailed and comprehensive national data would provide a background against which policy successes or failures can be measured, it would also alert governments and international partners on the need for increased funding or more treatment facilities.

The deleterious health effects of drug use disorders means that the provision of effective prevention, treatment and care facilities for substance use disorders is a necessary investment in the health of the society as a whole. Research has shown that the availability of evidence based prevention programs and policies have the ability to significantly reduce substance use and related harmful effects[188]. Behavioral and medication-assisted treatment using a chronic-illness-management approach has also been shown to aid recovery and prevent relapse. There have been suggestions that easy access to support services assist previous substance users to achieve and maintain wellness long-term[188].

Addressing the ease of access to drugs and other illicit substances within communities and regions need to be taken more seriously. There is a need to gather information on the different types of novel psychoactive substances that are available within communities and also create awareness as to the adverse health effects associated with consuming these compounds.

### *Limitations and recommendations*

One of the major limitations encountered in this review was the dearth of recent, community based and age specific scientific data on the prevalence and extent of the substance abuse problems in most of the countries in Africa. There was also a deficit of data on the details and impact of the country-specific

intervention protocols. This led to reliance mainly on third party data from international; partners and a few independent researchers. The battle to win this emerging substance–use pandemic in Africa can only be successful if there is increased emphasis in documenting the extent of the problem and country specific interventions; particularly at the community levels with emphasis on how different age groups are impacted by substance abuse.

## CONCLUSION

In Africa, substance use and substance use disorders drain struggling economies and health care systems. While the continent might have some general idea of what it is up against, understanding the details of the problem and availability of the willpower/wherewithal to subdue it remains a challenge. It is becoming obvious that there is no substitute for well-designed, accurate and comprehensive population-focused efforts at obtaining data that relates to substance use and substance use disorders, since such data will form the foundations for designing effective intervention strategies. Also, in Africa, interventional strategies should place emphasis on prevention, through identification of and mitigation of risk factors, as this approach is likely to consume less resources in the long run.

## FOOTNOTES

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*MINIREVIEWS*

# Artificial intelligence-assisted psychosis risk screening in adolescents: Practices and challenges

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## Abstract

Artificial intelligence-based technologies are gradually being applied to psychiatric research and practice. This paper reviews the primary literature concerning artificial intelligence-assisted psychosis risk screening in adolescents. In terms of the practice of psychosis risk screening, the application of two artificial intelligence-assisted screening methods, chatbot and large-scale social media data analysis, is summarized in detail. Regarding the challenges of psychiatric risk screening, ethical issues constitute the first challenge of psychiatric risk screening through artificial intelligence, which must comply with the four biomedical ethical principles of respect for autonomy, nonmaleficence, beneficence and impartiality such that the development of artificial intelligence can meet the moral and ethical requirements of human beings. By reviewing the pertinent literature concerning current artificial intelligence-assisted adolescent psychosis risk screens, we propose that assuming they meet ethical requirements, there are three directions worth considering in the future development of artificial intelligence-assisted psychosis risk screening in adolescents as follows: nonperceptual real-time artificial intelligence-assisted screening, further reducing the cost of artificial intelligence-assisted screening, and improving the ease of use of artificial intelligence-assisted screening techniques and tools.

**Key Words:** Psychosis risk; Adolescents; Artificial intelligence; Big data; Social media; Medical ethics; Chatbot; Machine learning

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**Core Tip:** Artificial intelligence-assisted psychosis risk screening must be emphasized and applied in adolescents. This review summarizes the application of two artificial intelligence-assisted screening methods (chatbot and large-scale social media data analysis), and proposes that the first challenge in applying artificial intelligence to psychosis risk screening concerns ethical issues. The methods must follow four biomedical ethics principles, *i.e.*, respect for autonomy, nonmaleficence, beneficence, and justice. Three directions should be considered in the future: nonperceptual real-time artificial intelligence-assisted screening, further reducing the cost of artificial intelligence-assisted screening, and improving the ease of use of artificial intelligence-assisted screening techniques and tools.

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## INTRODUCTION

In recent years, the prevalence of psychosis among adolescents has been increasing. According to the data released by the World Health Organization, approximately one in five children and adolescents worldwide suffers from a mental disorder, and half of these individuals show symptoms before the age of 14[1]. The risk of psychosis shows not only a trend of a younger age but also many disease categories and high heterogeneity[2-5], and its potentially high prevalence warrants attention. Two studies in Europe and North America revealed that adolescents with prodromal symptoms of psychosis who actively sought help still experienced a risk of eventual psychosis at rates of 19% and 35%, respectively [6,7]. In fact, due to the lack of independence, fear of being discriminated against by people around them, and a dearth of adequate attention from parents and schools, some adolescents even do not actively seek medical treatment and thus often miss their best treatment window. Since 2020, the rapid spread and persistence of the coronavirus disease 2019 pandemic worldwide has caused further major and hidden risks to population health, including psychosis. A study revealed that the deadly hazard of coronavirus disease 2019 and the resulting national lockdown policies in Italy caused intense psychosocial stress in individuals, which can be a trigger for first-episode psychosis[8]. In particular, children and adolescents are the most vulnerable groups[9]. Compared with other groups, children and adolescents are more vulnerable to the negative effects of the pandemic[10,11], *e.g.*, anxiety, depression, and posttraumatic symptoms, which increase the psychosis risk and may cause long-term negative consequences[12,13]. Additionally, adolescents are at a greater risk of first-episode psychosis than adult-onset psychosis, which is often associated with more severe symptoms and worse outcomes[14,15]. People who suffer from severe mental disorders die 10 years to 20 years earlier than the average person [1] and are more vulnerable to long-term disadvantages in terms of career advancement in the labor market, social status, mental health, and life beliefs[2,16]. Undoubtedly, this reality is not conducive to the stable economic and social development of any country worldwide.

### *Influencing factors*

The prior literature has concluded that psychosis risk is the result of an interaction between various internal and external factors[12,17], which can be divided into three main categories. First, national and social factors, such as those associated with schizophrenia, are unequally distributed across cultures and countries[18], and a cultural atmosphere that stigmatizes psychosis can create barriers to the timely detection of the illness[19]. The second category comprises family factors, including the two aspects of congenital inheritance and acquired growth environment. Adolescents who grow up in families with psychotic parents, domestic violence, or abuse are at a greater risk of psychosis[20]; adolescents suffering from psychosis have higher rates of broken homes, substance abuse, chronic disease[21], and lack of social capital[22]. Third, individual factors include demographic characteristics and addictive behaviors; for example, males account for a larger proportion of children and adolescents with first-episode psychosis[21], while marijuana use is also a risk factor for psychosis[23,24]. Indeed, a combination of risk factors, including genetics, birth season, birth complications, infection and immune system factors, autoimmune diseases, ethnicity, marijuana use, and urban residence, increase an individual's risk of developing schizophrenia[18].

### *Main benefits of artificial intelligence-assisted adolescent psychosis risk screening*

Despite this severe reality, shortages of medical resources and professional psychiatrists and uneven medical care are still common. Many nonpsychiatric specialists in hospitals and psychological service personnel on campus or in the community are unable to accurately and efficiently identify psychotic patients, and even if they diagnose the condition, they still cannot perform effective follow-up and

treatment[25-28]. A consensus holds that one of the best strategies to promote early intervention against psychosis is to improve the early identification of individuals at risk for psychosis through screening[29-31]. However, screening for psychosis mainly relies on scales, complicating the accurate identification of adolescents with a psychosis risk in a timely manner.

Over the past few years, artificial intelligence has shown explosive development inseparable from the emergence of new algorithms and the speed of high-performance parallel computing, coupled with the development of large-capacity storage space and video, text, sound, and other technologies to promote its rapid growth. Recent advancements in artificial intelligence have promoted improvement in the methods and technological innovations used in the treatment of human mental diseases, and artificial intelligence-based technologies are gradually being applied to psychiatric research and practice[19,32-35]. The main benefits of artificial intelligence-assisted adolescent psychosis risk screening are as follows: (1) Compared with traditional screening, the introduction of artificial intelligence can improve the speed and timeliness of identifying those who are already sick or who have a potential risk of a disease[36], which helps with early intervention and treatment[37,38] and timely correction of patients' risky behaviors, all of which can prevent the occurrence and further aggravation of symptoms; (2) Using advanced technology and objective data, artificial intelligence further enhances the accuracy and objectivity of screening methods. Appropriate screening tools that have been developed for all conditions in adolescent psychosis risk are relatively inadequate[39,40], while the clinical significance of adolescent self-assessment results is limited[41]; and (3) Artificial intelligence mitigates the scarcity of medical resources[42] and increases the coverage of screenings. Additionally, artificial intelligence can process massive amounts of data and use these data to improve generalization[43,44] while playing a pivotal role in identifying and detecting heterogeneity in schizophrenia and other mental illnesses[5] and can help doctors make the right decisions for subsequent diagnostic treatment[45].

### *Existing challenges*

Ethical issues constitute one of the greatest challenges encountered in the application of AI to psychosis risk screening in adolescents in terms of both technical development and concrete practice[46,37] in the following four aspects: (1) Whether the autonomy of adolescents to participate in screening is duly respected and protected[47]; if the screening is conducted without their full approval, they should be responsible for the possible negative consequences; (2) The personal information and privacy of adolescents are leaked and exposed to unauthorized surveillance and security risks; the use and management of data collected based on artificial intelligence technology deserves attention[48,49]; (3) There is no unified understanding of the ethical assessment and acceptance of technology among different stakeholders[37]; and (4) The benefits of AI technology development do not reach all adolescents fairly and equitably.

### *Contribution*

Clearly, there is a strong necessity and feasibility to focus on and apply artificial intelligence-assisted psychiatric risk screening in adolescents. However, there is a paucity of research concerning artificial intelligence-assisted psychiatric screening and a dearth of narrative literature reviews focusing on this important population characteristic of adolescents. Therefore, this paper reviews the main literature concerning artificial intelligence-assisted adolescent psychiatric risk screening to clarify the current state of development and recent explorations of this important topic in terms of practice and challenges with the aim to contribute to a more effective use of artificial intelligence methods for adolescent psychiatric risk screening in the future on a global scale.

## PRACTICES

Traditional psychosis risk screening methods are mostly based on various self-assessment questionnaires with obvious limitations as follows: (1) Performance is not comparable among different screening tools; (2) The measurement criteria (such as content, number of items, and thresholds) widely vary; and (3) Dynamic and longitudinal tracking data are lacking[40]. In addition, scale-based self-assessment relies on individual self-perceptions, recollections, and subjective evaluations, and in some situations, individuals may exaggerate or mask some of their symptoms, weakening the accuracy of the results. For example, a general recall bias is evident among patients with depression, and symptoms can fluctuate over time or even throughout the day, which complicates capturing dynamic changes in symptoms with high accuracy[50].

The emergence of artificial intelligence can address and largely overcome the above limitations. The main machine learning algorithms currently used for psychosis screening are traditional ones, *e.g.*, decision tree, naive Bayes, random forest, support vector machine, K-nearest neighbor, and shallow neural networks. Of these, relevant studies have shown that the support vector machine method is the most commonly used[51,52]. With the advancement of deep learning algorithms, algorithms, such as convolutional neural networks, autoencoders, and deep belief networks, have begun to be used in psychosis risk screening research and are viewed as an important development trend of the future[3,53,

54]. By summarizing the pertinent literature, the artificial intelligence tools most often applied to psychosis risk screening are chatbot and large-scale social media data analysis.

### *Chatbot*

Chatbot is a computer program that allows human–computer interactions in the form of textual dialog based on the technology of natural language processing[55]. The world's first chatbot, ELIZA, was developed in the 1960s[56] and responds according to special rules by recognizing keywords in user-entered texts[57]. Due to substantial advancements in artificial intelligence, chatbots have developed from being driven by static databases and learning new responses and contexts based on real-time interactions with humans to the fusion of real-time learning and evolutionary algorithms. Currently, chatbots have powerful capabilities of simulating the structures of natural language communication and creating a realistic environment in which users can achieve human–computer interaction. Chatbots in the healthcare field include Tess, HealthBuddy, Florence, Buoy Health, and Your.Md. In addition to natural language processing, the machine learning methods adopted by chatbots also include natural language understanding, artificial neural networks, and recurrent neural networks[58].

The prior literature has shown that psychosis is usually strongly correlated with human manifestations, such as facial expressions, voice, textual tone, and gestures. According to these human manifestations, chatbots with cognitive ability can ascertain the needs of users in real time to provide emotional responses and predictions and assessments of their mental health conditions[46,59]. Based on existing experience, one study improved upon the feature extraction of previous studies by using deep learning and fusion regression methods to construct an artificial intelligence system that automatically predicted depression levels based on vocal and visual expressions, which showed better predictive performance than other existing methods using the same dataset. Artificial intelligence is currently used in some chatbots. This study used deep learning methods to extract key visual features from facial expression frames, spectral low-level descriptors and mel-frequency cepstral coefficient features from short audio segments, and time movements in feature space through feature dynamic history histograms (FDHHs). Finally, regression techniques were used to fuse these FDHHs and audio features to predict the Baker Depression Scale II scores. The artificial intelligence developed in that study was a general framework that can be used to automatically predict depression scale scores from facial and vocal representations. It has FDHH dynamic functionality, leveraging the ideas of motion history histograms on deep learning images and handcrafted feature spaces, and enables feature fusion of different descriptors of face images[34].

The chatbot Woebot is used as an example. Woebot can be used on mobile communication devices in the form of short daily conversations and mood tracking to help users acquire anxiety reduction skills by identifying cognitive distortions to monitor anxiety and depression episodes while using fully automated conversational agents to address poor adherence to some extent. In a previous randomized controlled trial using Woebot, 70 college students who reported symptoms of depression and anxiety were randomly assigned to an intervention group that chatted with Woebot in an instant messaging application and a control group that received the National Institute of Mental Health e-book on depression in college students. The results revealed that the anxiety levels decreased in both groups, and the students who interacted with Woebot had significantly lower levels of depression compared to those reading the e-book. Future validation of the findings is needed with more participants, longer doses, and longer-term follow-up data[60].

In summary, the advantage of chatbots is that they can bring hope to psychosis risk screening for those who were previously inaccessible to screenings or who are economically constrained[61], build trusting relationships with potential patients, increase self-disclosure, and reduce the shame that patients or their families often feel when talking to doctors about mental illness. Nevertheless, these chatbots still have some shortcomings as follows: (1) They can be promoted by financial sponsors, causing conflicts of commercial interests; (2) In contrast to humans, they do not truly have subtle emotional awareness or empathic responses; and (3) They have issues with privacy, ethical risks, and other negative problems.

### *Large-scale social media data analysis*

Currently, large numbers of users express their emotions and communicate daily through social media, such as Facebook and Twitter. Based on informative data such as textual information, emojis, user log information, and pictures, psychosis can be identified and predicted by combining natural language processing, sentiment analysis, and machine learning[49,62,63].

As the use of social media platforms becomes increasingly common in people's lives, screening for psychosis risk based on collected social media data will become easier. For instance, one study systematically analyzed artificial intelligence depression detectors and concluded that artificial intelligence systems that identify users at a high risk for depression from their social media data have made remarkable progress[37]. Given that depression is common in the adolescent population[26,64] and is underdiagnosed and undertreated, which underscores the need to expand the current screening methods, some investigators used the text of posts of consenting individuals on Facebook to predict depression as documented in electronic medical records and demonstrated correlative accuracy in identifying people with depression[65,66]. Therefore, the use of machine learning technology to screen

depression patients by acquiring the social media data for consenting individuals may become an effective and scalable supplement to existing screening methods[67]. Based on the language behaviors of Facebook user posts, Islam *et al*[68] achieved a classification accuracy of 99.0% with a depression prediction model using the decision tree method. Another study applied a logistic regression and highly randomized trees as modeling algorithms to approximately 20 million words of social media posts by 999 consenting volunteers and found that applying the method to Facebook posts significantly improved the predictive accuracy of demographic variables (age, sex, and ethnicity) in 18 of 21 disease categories, and it was particularly effective at predicting mental health conditions (anxiety, psychosis, and depression)[69]. In one study, big data were collected from China's Sina Weibo to understand differences in language style, emoji use, and the number of followers between depressive patients and nondepressed patients by using a deep neural network for feature extraction and dimensionality reduction. By constructing input data suitable for the classifier and applying the deep integrated support vector machine algorithm to classify the input data, the study achieved a more stable and accurate identification of depression in college students[70]. The development of Internet-of-Things technology has realized the exchange of information between hardware such that various wearable devices can carry a large amount of health information. Applying the Internet of Things to the field of psychosis through machine learning, the objective behavioral characteristics collected through mobile phones and wearable devices can effectively predict depressive symptoms[71,72]. Data related to daily activity, sleep, social communication, *etc.* have been collected through smartphone sensors to predict individuals' depression situations[73,74]. Advanced artificial intelligence methods, including natural language analysis and chatbots, were used by the Horyzons website to analyze the sentiment and language of newsfeed posts and other relevant factors (*e.g.*, user preferences and history), which enabled personalized treatment recommendations to be made for adolescents with early symptoms of psychosis [75]. Orabi *et al*[76] extracted unstructured text data posted on Twitter by 327 depression patients, 246 posttraumatic stress disorder patients, and 572 healthy individuals, and based on these data, users with depression tendencies were detected using the convolutional neural network method. Convolutional neural networks represent the most popular deep learning method in the field of natural language processing, boasting an accuracy as high as 87.9%, and have achieved remarkable progress in the field of image recognition[76]. In the future, more technologies, such as multimodal perception, understanding, and natural dialog and interaction (a multimodal auxiliary screening mechanism established through artificial intelligence perception technology), are needed to achieve more comprehensive and accurate screening of psychosis risk among adolescents.

## CHALLENGES

The technology of artificial intelligence-assisted psychosis risk screening in adolescents will become more mature and a major development trend in the future. However, it can only do so by overcoming the existing challenges in the application of artificial intelligence-assisted psychosis screening in the adolescent population, which have rarely been addressed to date. Especially when applying artificial intelligence to psychosis risk screening, the primary challenge is ethical issues. The four principles of biomedical ethics, *i.e.*, respect for autonomy, nonmaleficence, beneficence, and justice[77], must always be firmly followed. On this basis, a new principle aiming to realize other principles through understandability and accountability[78] such that the development of artificial intelligence can truly meet the moral and ethical requirements of mankind has been proposed. Table 1 presents the four widely accepted ethical principles, their connotations, and the corresponding issues that adolescents may face.

### *Respect for autonomy*

Respect for autonomy requires respect for the patient's personal dignity and autonomy, such as ensuring informed consent and informed choice, ensuring that humans have complete and effective autonomy, and requiring that the operation of any artificial intelligence be supervised by humans. Adolescents are still minors, and this age group is in the typical age when psychosis develops. Discussions have addressed whether adolescents have autonomy and how they should be "empowered". For example, in the United Kingdom, adolescents under the age of 16 can be competent to give consent if they demonstrate sufficient maturity and intelligence (as judged through Gillick competence). For minors deemed incompetent (and adults who are incompetent due to mental illness), questions arise regarding whether guardian advocates or those with parental responsibility should be empowered to provide proxy consent for psychosis risk screening[80]. Therefore, assuming that a given artificial intelligence-assisted psychosis risk screening method is safe and trustworthy, improving the awareness and attitudes of teenagers and their parents toward the psychosis risk and the importance of early screening is vital as their willingness to use artificial intelligence for screening can be increased only with their full approval[79]. Moreover, how to improve adolescents' autonomous participation in psychosis risk screening by ensuring effective informed consent and meaningful disclosure of results still requires further discussion.

**Table 1 Connotations of ethical principles and issues faced by adolescents**

| Ethical principles | Connotations | Issues faced by adolescents |
|---|---|---|
| Respect for autonomy | Ensuring informed consent and informed choice, ensuring that humans have complete and effective autonomy, and requiring that the operation of any artificial intelligence be supervised by humans | Safety and trustworthiness of screening methods; full approval from adolescents and parents; willingness to use artificial intelligence for screening[79] |
| Nonmaleficence | Privacy, security and "capability warnings"[78]; artificial intelligence technology must be able to strongly resist malicious use, including avoiding harm to the natural environment and all living things | Privacy leakage and data abuse; difficulties in oversight and accountability; adverse effects and stigma with irreversible damage |
| Beneficence | Must be beneficial for not only the patients but also the medical cause, medical sciences and even the well-being of the entire human race | Screening scales need to be refined; no consensus (such as ethical evaluation acceptance of the technology) among different stakeholders[37] |
| Justice | Everyone in society has equal rights to reasonably enjoy health resources and participate in the distribution; prosperity is promoted; and unity is maintained | Development of artificial intelligence cannot benefit all groups of young people[12,14,21,22,80]; intergenerational transmission maintains inequality[46,78] |

### *Nonmaleficence*

Nonmaleficence requires privacy, security, and "capability warning"[78]. To protect the integrity of the human body, mind, and dignity, artificial intelligence technology must be able to strongly resist malicious use, including avoiding harm to the natural environment and all living things. Smart data collection technologies are becoming increasingly powerful, posing a greater threat to user privacy and security. The protection of adolescents' personal information and privacy is very important, but some privacy leakage and data abuse problems remain, which have been extremely harmful. With the rapid development of artificial intelligence, the existing ethical and regulatory norms have fallen behind. Their failure to keep pace with the latest environmental and artificial intelligence technologies creates difficulties in oversight and accountability. Especially in the presence of potential commercial interests or vested interests, *e.g.*, some social platforms may be abused by enterprises/people with criminal minds or illegal attempts, the usage of artificial intelligence in biomedical fields must be monitored and regulated from an ethical and moral standpoint. Furthermore, an artificial intelligence-assisted screening result may have adverse effects on some adolescents with a psychosis risk and introduce stigma when they are labeled with psychosis, which may, in turn, cause irreversible damage to their mental health, interpersonal relationships, and even long-term personal development. Thus, in addition to psychosis, many social factors related to its diagnosis cause extra damage to adolescents.

### *Beneficence*

Beneficence requires that something be beneficial for not only the patients but also the medical cause, medical sciences and even the well-being of the entire human race. Although many studies have confirmed the positive role of artificial intelligence in psychosis risk screening, people still use scales for screening in practice. On the one hand, time is required to ensure that any technology is foolproof, and on the other hand, different stakeholders (adolescents and their parents, doctors, research and development personnel, *etc.*) have not yet reached a consensus, and the ethical evaluation and acceptance of the technology are still open questions[37], *e.g.*, whether medical professionals are willing to replace traditional screening with artificial intelligence-driven products and technologies. Therefore, whether this technology is truly beneficial for the health and well-being of society as a whole and humanity is worth discussing.

### *Justice*

Justice requires everyone in society to have equal rights to reasonably enjoy health resources, resources to be fairly distributed, everyone to have the right to participate in the distribution and use of these resources and the benefits of artificial intelligence to be distributed fairly and equitably while avoiding any discrimination or stigma, promoting prosperity, and maintaining unity. The development of artificial intelligence cannot benefit all groups of young people. Previous studies revealed that adolescents born in the lower classes of society and those from disadvantaged families are more likely to suffer from psychosis[21,22]. In fact, vulnerable groups have a greater need to exploit the advantages of artificial intelligence technology for psychosis risk screening[12,14,80]. In reality, a "digital divide" and a "knowledge gap" still exist between urban and rural youths, the accessibility of digital technologies and services is unevenly distributed, and some youths still do not have the opportunity to access advanced technologies[81,82]. Furthermore, this unevenness is exacerbated by intergenerationally maintained inequality[46,78].

In addition to ethical issues, artificial intelligence-assisted psychosis risk screening in adolescents faces several other issues, including: (1) Small sample sizes: the use of machine learning to establish prediction models with high accuracy and strong generalization ability requires large samples[83], but

many studies have mentioned the problem of too few samples, resulting in overfitting, which may lead to model errors and low accuracy[21,84,85]; (2) The prediction model must be optimized: for the same problem and the same sample set, the prediction accuracies of prediction models based on different algorithms vary, and the applicable scope and characteristics of each algorithm are different[86,87]; (3) Compliance: the level of the technical knowledge of patients is a key factor affecting their compliance [88], which also directly affects the accuracy of conclusions; and (4) Research bias: most research samples are active users of social media or patients who are informed in advance, while broader groups of real-world patients are not included; thus, the representativeness of the samples and generalizability of the findings may be limited.

## LIMITATIONS

This study has two limitations. First, this paper is a narrative review and provides an outlook. This paper discusses the current status and challenges of using artificial intelligence-assisted methods for screening adolescents for psychiatric disorders, but we do not use an explicit approach, such as a systematic review. Therefore, the study is primarily intended to evoke research interest in the field but cannot be directly applied to clinical care. Second, this paper only summarizes the relevant literature in English and does not consider the literature published in languages other than English.

## CONCLUSION

While focusing on the psychosis risk faced by adolescents worldwide, this paper reviews the influencing factors of adolescent psychosis risk, which can be divided into the following three main categories: national and social factors, family factors, and individual factors. This paper summarizes the benefits of artificial intelligence-assisted psychosis risk screening in adolescents, which are mainly manifested in improving the speed and timeliness of screening for those who are already sick and those with a potential risk of disease, promptly correcting the risky behavior of patients to prevent the occurrence and further aggravation of symptoms, and improving the accuracy and objectivity of screenings and the screening coverage. The application of chatbots and large-scale social media data analysis in psychosis risk screening is discussed in detail. The advantage of chatbots in psychosis risk screening is that they can provide services to those with psychosis who have limited resources or accessibility problems, although privacy concerns and other ethical issues may exist. The accuracy of large-scale social media data analysis is gradually improving, and more technologies based on multimodal perception, understanding, and natural dialog and interactions are still needed to help comprehensively and accurately screen for psychosis risk in adolescents.

After surveying the current literature concerning artificial intelligence-assisted adolescent psychosis risk screening, we found that although artificial intelligence has been gradually applied to early psychosis risk screening, it has rarely been applied in studies that directly use adolescents as subjects. In view of the prevalence and harm of psychosis among adolescents worldwide, the timely screening of adolescent psychosis risks with artificial intelligence technology has considerable prospects for development. Furthermore, scientific progress must follow relevant ethical principles, not ignore vulnerable groups of adolescents, and ensure that artificial intelligence-assisted psychosis risk screening is conducted in an ethically acceptable manner, thereby minimizing potential adverse effects.

Based on the current status of psychiatric artificial intelligence research and practice, we propose that ethical issues constitute the main challenge of artificial intelligence-assisted psychosis risk screening in adolescents. The four biomedical ethics principles (respect for autonomy, nonmaleficence, beneficence, and justice) should be strictly obeyed. In addition to ethical issues, artificial intelligence-assisted psychosis risk screening in adolescents faces problems, such as small sample sizes, unoptimized prediction models, compliance, and research bias.

We propose that assuming compliance with ethical requirements, three main directions can be considered for artificial intelligence-assisted psychosis risk screening in adolescents in the future. First, we should develop nonperceptual real-time artificial intelligence screening with the help of technological advancements, such as 5G technology and the Internet of Things, to allow both the collection of individual emotional and health data and the prediction of individuals' mental health status in real time. Second, we should further reduce the cost of artificial intelligence-assisted screening. Psychosis is an important part of human health, and both poor and rich people should enjoy the benefits of technological progress. The long-term goal of artificial intelligence-assisted psychosis risk screening is that users should not pay high prices for the screening. Third, we should improve the ease of use of artificial intelligence-assisted screening techniques and tools such that regardless of an individual's level of knowledge, he or she can easily use artificial intelligence tools to screen for a psychosis risk.

## FOOTNOTES

**Author contributions:** Liu XQ designed the study; Cao XJ and Liu XQ wrote the manuscript and managed the literature analyses; all authors approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

# Overlap of orthorexia, eating attitude and psychological distress in some Italian and Spanish university students

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## Abstract

***BACKGROUND***

Orthorexia nervosa (ON) is the persistent concern of maintaining the self-imposed diet to improve one's health. Many factors have been associated to ON in university students.

***AIM***

To assess the prevalence of ON in Italian and Spanish university students in relation to eating attitude and psychological distress, and the possible overlaps between ON (evaluated with different scored questionnaires from the originally proposed ORTO-15), distress and risk of eating disorders.

***METHODS***

This study was carried out on 160 students recruited at La Sapienza University of Rome and at the Catholic University of Murcia. Questionnaires were administered to evaluate ON (ORTO-15 and sub-scores), body concerns (Multidimensional Body-Self Relations Questionnaire, MBSRQ, and Body Uneasiness test, BUT), psychological distress (Kessler Psychological Distress Scale, K10), physical activity (International Physical Activity Questionnaire, IPAQ), eating attitude (Eating Attitudes Test, EAT-26) and malnutrition (Starvation Symptom Inventory, SSI). Sex differences, within the same country, and differences between Italian and Spanish students, within the same sex, were evaluated.

***RESULTS***

The ORTO-15 positive subjects, assessed with the originally proposed cut-off, were above 70% in both Italian and Spanish students, with a higher prevalence in

the Spanish sample (Italian females 76.3%, Italian males 70.7%; Spanish females 97.0%, Spanish males 96.3%). According to ORTO-7, about 30% of Italian and 48% of Spanish students were positive to ON with no significant sex differences. When excluding students underweight (UW), overweight (OW) or obese (OB), as well as those potentially at risk of eating disorders or presenting mild, moderate and severe distress, in the resultant normal weight (NW)-K10$^{neg}$-EAT-26$^{neg}$ subgroup, we did not find many correlations observed in the whole sample, including those between ORTO scores and BUT, SSI, Total MBSRQ and some of its components. Moreover, ORTO-7 resulted in the only ON score unrelated with Body Mass Index, MBSRQ components and IPAQ-assessed intense activity, in the NW-K10$^{neg}$-EAT-26$^{neg}$ subgroup. After this sort of "exclusion diagnosis", the prevalence of ON of these students on the overall sample resulted in 16.9%, 12.2%, 15.2% and 25.9% for Italian females, Italian males, Spanish females and Spanish males, respectively.

*CONCLUSION*

In some university students ON could be a symptom of other conditions related to body image concerns and distress, as well as to high physical activity and appearance, fitness, health or illness orientation (from MBSRQ). However, ORTO-7 became independent from these confounding variables, after the exclusion of UW, OW, OB and students positive to EAT-26 and K10, suggesting the possibility of identifying orthorexic subjects with this specific questionnaire.

**Key Words:** Diet; Exercise; Food avoidance; Other Specified Feeding and Eating Disorder; Lifestyle

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**Core Tip:** This study explores the overlap of orthorexia nervosa with eating attitude and psychological distress in Italian and Spanish university students. After excluding, among normal weight students, those with high score on the Kessler Distress Scale and Eating Attitudes Test, we did not find correlations among orthorexia and Starvation Symptoms Inventory, Body Uneasiness Test, and Multidimensional Body Self-Relations Questionnaire (MBSRQ), observed in the whole sample. After this kind of "exclusion diagnosis", sub-scores of MBSRQ indicating body concerns correlated with ORTO-12 and ORTO-9, whereas ORTO-7 resulted the only score unrelated with all outcomes, including fitness and health orientations (MBSRQ), and intense physical activity.

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## INTRODUCTION

The term orthorexia nervosa (ON) is referred to the psychological obsession with a healthy, organic and pure diet, and it is often based on stereotyped or erroneous nutritional beliefs, which can lead to dietary restrictions with resulting nutritional deficiencies[1-4]. Although ON shares several aspects in common with Anorexia Nervosa (AN)[5] and other eating disorders (EDs)[6], and around 70% of health professionals[7,8] believe that ON should be a distinct, clinically recognized ED, it is not included in the ICD-11 (International Statistical Classification of Diseases and Related Health Problems)[9,10]. In the Diagnostic and Statistical Manual of Mental Disorders, the terminology "eating disorders" has been changed to "Feeding and Eating Disorders", including eight categories: AN, bulimia nervosa, binge ED, pica, rumination, Avoidant or Restrictive Food Intake Disorder (ARFID), Other Specified Feeding and Eating Disorder (OSFED), and unspecified feeding and EDs[11]. Among these, ON has yet to be recognized as a separate ED, but has been included in OSFED, whereas ARFID refers to a persistent avoidance of food for various reasons (depressed temperament, phobias, sensory repulsion of the appearance, smell, texture of food), not necessarily associated with the search for a healthy diet that characterizes the subject with ON.

Although individuals with ON have an obsessive focus on healthy eating and may eliminate entire food groups, fearing they are unhealthy, they can later develop a typical ED[7,11]. Despite the awareness of clinicians on this condition[7,8,12], it is assumed that the estimate of subjects affected by ON is very complex, given the lack of explicit diagnostic criteria[13-16]. In particular, it has been

recently pointed out that the conflicting data on the prevalence of ON depend on differences in the tools used and in the cut-off points[17]. Moreover, authors concluded that the use of the ORTO-15 questionnaire to diagnose ON is questionable due to a high percentage of false-positive results[17], and different cut-offs or sub-scores have been proposed[18-24]. Abdullah *et al*[18] have suggested that a cut-off point of 35 is preferable than a cut-off at 40, and have reported that ON tendency is affected by sex and body mass index (BMI), and not affected by educational level. No differences were found in the prevalence of ON among students attending health-scientific, economic-humanistic, sport sciences and dietetics and nutrition university courses[25,26]. However, the reported prevalence of ON in university students was variable and affected by EDs, dieting and a high level of physical activity (PA)[25-30].

Among the criticisms relative to ORTO-15, Roncero *et al*[31] highlighted the risk of including those who are on-diet among the individuals with ON, and the redundancy between the ORTO-15 and the Eating Attitudes Test (EAT-26). Accordingly, an overlap between ORTO-15 and EAT-26 has been reported in university students[32,33], but individuals with ON had lower psychological distress than those with ED risk[33]. Furthermore, it has been reported that overweight (OW) preoccupation and appearance orientation (AO), assessed with the Multidimensional Body-Self Relations Questionnaire-Appearance Scale (MBSRQ-AS), were significant predictors of ON[34].

The aim of this observational study was to evaluate the prevalence of ON in Italian and Spanish university students in relation to eating attitude and psychological distress, and the possible overlaps between ON (evaluated with different scored questionnaires), distress and risk of EDs. Moreover, a decision tree for the exclusion diagnosis of ON in healthy university students has been proposed.

## MATERIALS AND METHODS

### *Study design, recruitment, and data collection*

This study was carried out on a sub-group of participants from a previous study[35]. Undergraduate and doctoral students aged between 18 years and 35 years were recruited at La Sapienza University of Rome and at the Catholic University of Murcia. All the volunteers included in the study signed the informed consent, accompanied by an informative note, and the recruiter assigned them an alphanumeric code to guarantee privacy during the data management (all details about recruitment and protocol are available online at https://www.clinicaltrials.gov/ct2/show/NCT04099420). Body mass and stature were measured with the OMRON BF511 electronic scale and the SECA 217 portable stadiometer, respectively. BMI was calculated with the following formula: BMI = weight (kg)/height squared ($m^2$). Moreover, several standardized questionnaires were administered.

### *ON*

The ORTO-15 test is a questionnaire made up of 15 multiple-choice items based on a Likert scale (always, often, sometimes, never)[36]. The items concern three areas: the cognitive-rational area (items 1, 5, 6, 11, 12, 14), the clinical area (items 3, 7-9, 15), mainly related to anxiety-inducing and obsessive psychiatric disorders, and the emotional area (items 2, 4, 10, 13)[36]. A score of 1 was given to responses that were more indicative of ON, whereas a score of 4 was attributed to those that indicated a normal eating behavior. Therefore, lower scores correspond to a more pathological behavior, and total score ranges from 15 to 60, with the cut-off point equal to 40[36]. This value has been questioned as it was considered too high; consequently, a lower cut-off (35) was also chosen[18,19].

Additional versions of the ORTO test have been developed based on the selection of ORTO-15 items that more specifically could be indicative of the presence of symptoms of ON. ORTO-12 is a shorter version of 12 items, obtained by excluding items 5, 6 and 8 from the original ORTO-15, since they contribute less to the definition of ON, but a specific cut-off point was not determined[20]. ORTO-11 excludes items 5, 8, 14 and 15 of the ORTO-15. Final score ranges from 11 to 44, and a cut-off point < 25 has been considered the most appropriate to suggest a tendency to ON[21]. The ORTO-9 is a version of ORTO test which excludes items 1, 2 and 8, with a cut-off < 26.7. This test was found to be ineffective in predicting ON[22]. The ORTO-7 is based on items (1, 3, 4, 7, 9, 11 and 13) that mostly highlight the presence of ON with a cut-off ≤ 19[23,24].

### *Body image concerns*

Two questionnaires were used to evaluate body image concerns, the MBSRQ[37,38] and the Body Uneasiness Test (BUT).

We evaluated the total MBSRQ and the MBSRQ Factor Subscales (FSs): AO, fitness orientation (FO), health orientation (HOr) and illness orientation (IO). In addition to these FSs, we evaluated the MBSRQ subscales: body areas satisfaction scale (BASS) and OW preoccupation (OP). Each of the MBSRQ scales has its corresponding items that can be answered by a primary number from 1 (strongly disagree) to 5 (strongly agree). The score of contraindicative items (6, 15-17, 23, 25, 28, 32-34, 36-38, 40, 42, 43, 45, 47-49) is reversed (*i.e.*, 1 = 5, 2 = 4, 4 = 2, 5 = 1). MBSRQ subscale scores are the means of the constituent items. The MBSRQ-AS is the shorter (34-item version) form of MBSRQ that assesses only the appearance-related components of the body image construct[37].

On the other hand, BUT includes two parts, BUT A (34 statements) and BUT B (37 body parts). Items are rated on a 6 points Likert-type scale (range 0-5, from "never" to "always") and high rates indicate greater body uneasiness[39]. In addition to the total score, we evaluated BUT A weight phobia (WP, fear of being or becoming fat) and body image concerns (BIC, worries related to physical appearance) components.

### Eating attitudes and malnutrition

Eating Attitudes Test (EAT-26) and Starvation Symptom Inventory (SSI) were administered to participants. The former is a standardized measure of symptoms and concerns characteristic of EDs, whereas the latter can reveal the presence of malnutrition.

EAT-26 is made up of 26 items and represent a screening tool to assess "ED risk"[40]. Although it does not provide a diagnosis of ED, the EAT-26 items include the subscales: "dieting" scale (items 1, 6, 7, 10, 11, 12, 14, 16, 17, 22, 23, 24, 26) and "bulimia and food preoccupation" scale (items 3, 4, 9, 18, 21, 25). Four behavioral questions are included to determine the presence of extreme weight-control behaviors. These items assess self-reported binge eating, self-induced vomiting, use of laxatives and treatment for ED over the preceding 6 mo. Participants were required to judge whether the item applied "always", "very often", "often", "sometimes", "rarely" or "never". Each extreme response in the "anorexic" direction is scored as a worth of 3 points, while the adjacent alternatives are weighted as 2 points and 1 point, respectively. A score ≥ 20 on the EAT-26 does not necessarily mean that respondent has an ED. However, it indicates a high level of concern about dieting, body weight or problematic eating behaviors.

SSI is a 16-item questionnaire and participants were asked to estimate the number of days out of the preceding 28, in which they had experienced symptoms of starvation (hunger, poor concentration, heightened satiety, dizziness, reduction in rate of weight loss) on a 7-point Likert scale: never (0), 1-5 d (1), 6-12 d (2), 13-15 (3), 16-22 (4), 23-27 (5), and always (6)[41]. The highest score indicates increased frequency of starvation symptoms over the last 28 d.

### Psychological distress and PA

The Kessler Psychological Distress Scale (K10)[42] and the International Physical Activity Questionnaire (IPAQ)[43] were used to evaluate distress and PA level, respectively.

K10 is a 10-item questionnaire about emotional states, each with a five-level response scale. The measure can be used as a brief screen to identify levels of distress[42]. Each item is scored from 1 (none of the time) to 5 (all of the time). Scores from the 10 items were then summed, yielding a minimum score of 10 and a maximum score of 50. According to the total score, the likelihood of having a mental disorder (psychological distress) is established[42]; in particular, 10-19 likely to be well, 20-24 likely to have a mild disorder, 25-29 likely to have a moderate disorder, and 30-50 likely to have a severe disorder.

The IPAQ (short form)[43] includes items assessing the frequency and duration of PA in three ranges of intensity: intense PA (8.0 metabolic equivalent of tasks: METs), moderate PA (4.0 METs), and walking fast (3.3 METs), moderate (3.0 METs) and slow (2.5 METs) pace[43]. Based on collected data about the frequency and duration of PA, energy expenditure (expressed as MET-min/wk) has been estimated. One MET is the rate of energy expenditure at rest, and it is approximately equal to 3.5 mL O2 kg-1 min-1 in adults. According to the Italian Society of Endocrinology, IPAQ allows to classify population in three PA levels: Low (the lowest level of PA, less than 700 METs-min/wk), Moderate (Total PA between 700 and 2519 METs-min/wk) and High (Total PA of at least 2520 METs- min/wk).

### Statistical analysis

Categorical variables were expressed as percentages and significance assessed by the $\chi^2$ test. Continuous variables showing a normal pattern (normality test Shapiro-Wilk passed) were expressed as means with SD, otherwise data were expressed as median (25%-75% range). Results were analyzed by analysis of variance (ANOVA, Shapiro-Wilk test passed), or by Kruskal-Wallis one-way analysis of variance on ranks (Shapiro-Wilk test failed). The significance of the differences between females and males within the same country, and those between the different countries within the same sex, were evaluated using the Student-Newman-Keuls method (Shapiro-Wilk test passed) or the Dunn's method (Shapiro-Wilk Test failed). Spearman correlation was performed between variables. The level of significance was set below 5% ($P < 0.05$).

## RESULTS

### Country and sex differences

Characteristics of students and differences between Italy and Spain (evaluated within the same sex), and sex differences (evaluated within the same country) are reported in Table 1. Only in Italy, females (IT-F) had a significant lower BMI than males (IT-M), whereas the different prevalence of underweight (UW),

**Table 1 Students' characteristics**

| | IT-F, *n* = 59 | IT-M, *n* = 41 | SP-F, *n* = 33 | SP-M, *n* = 27 |
|---|---|---|---|---|
| Age (yr) | 24 (23-28) | 25 (23-28) | 23 (21-28) | 24 (24-26) |
| Height (m) | 1.64 ± 0.06[a] | 1.78 ± 0.08[a] | 1.63 ± 0.06[a] | 1.78 ± 0.07[a] |
| Weight (kg) | 55.9 (53.0-61.0)[a] | 77.0 (70.9-87.5)[a] | 58.7 (52.4-66.5)[a] | 76.3 (67.1-82.0)[a] |
| BMI (kg/m$^2$) | 20.7 (19.4-22.4)[a] | 24.5 (22.1-27.1)[a] | 23.3 (20.2-24.5) | 24.1 (21.8-25.5) |
| Underweight (%) | 11.9 | 0.0 | 9.1 | 3.7 |
| Overweight (%) | 6.8 | 31.7 | 15.1 | 25.9 |
| Obese (%) | 5.1 | 9.7 | 3.0 | 3.7 |
| IPAQ (MET-min/wk) | 2232 (1080-4986) | 4380 (2305-6277) | 2100 (1202-4395)[a] | 4970 (2575-6780)[a] |
| IPAQ walking | 630 (315-1260) | 700 (488-1323) | 525 (244-1230) | 600 (240-1470) |
| IPAQ moderate | 720 (160-1680) | 600 (240-1440) | 600 (240-1440) | 720 (120-1440) |
| IPAQ intense | 480 (0-1920)[a] | 2160 (400-3840)[a] | 800 (0-1680)[a] | 2400 (960-4320)[a] |
| PA low (%) | 16.9 | 7.3 | 18.2 | 7.4 |
| PA moderate (%) | 40.7 | 19.5 | 36.4 | 14.8 |
| PA high (%) | 42.4 | 73.2 | 45.5 | 77.8 |
| Smokers (%) | | | | |
| Habitual | 15.3 | 19.5 | 9.1 | 7.7 |
| Occasional | 16.9 | 19.5 | 15.2 | 15.4 |
| Ex-smokers | 8.5 | 9.8 | 9.1 | 3.8 |
| K10 | 15.0 (13.0-19.0) | 14.0 (12.0-17.0) | 19.0 (15.0-27.5) | 17.0 (14.0-20.0) |
| Mild (%) | 11.9 | 0.0[b] | 15.2 | 25.9[b] |
| Moderate (%) | 6.9 | 9.8 | 18.2 | 3.7 |
| Severe (%) | 5.1 | 4.9 | 15.2 | 3.7 |

[a]$P < 0.05$ between females and males within country.
[b]$P < 0.05$ between Italians and Spaniards within sex.
Categorical variables are expressed as percentages. Continuous variables are expressed as means with standard deviation (Shapiro-Wilk Test passed), or as median (25%-75% range, Shapiro-Wilk Test failed). BMI: Body mass index; IPAQ: International Physical Activity Questionnaire; IT-F: Italian females; IT-M: Italian males; K10: Kessler Psychological Distress Scale; SP-F: Spanish females; SP-M: Spanish males; PA: Physical activity.

OW and obese (OB) students, as well as of volunteers who practice Low, Moderate or High PA, did not reach significance in both countries (Table 1). However, Spanish males (SP-M) on average practiced more PA than females (SP-F), and sex differences were found in IPAQ intense (MET-min/wk from intense activities) in both countries (Table 1). No differences were found in smoking habits, whereas a high percentage of SP-M reported mild psychological distress (assessed by K10) than IT-M (Table 1). SP-M were also those with higher total MBSRQ, MBSRQ-AO, -FO, -HOr, -AS and -BASS, whereas no differences were found in MBSRQ-IO and -OP (Table 2). On the contrary, IT-F had higher BUT-A - BIC and - WP than IT-M, but lower compared to SP-F (Table 2). Differences in total BUT and in its components (BUT-A and BUT-B) did not reach statistical significance (Table 2).

Concerning ORTO-15, lower values (indicating high ON) were observed in Spanish students compared to Italians, when using the first proposed cut-off point of 40[36], and with ORTO-12, -11 and -9 (Table 3). By using the lower cut-off point of 35 for ORTO-15 or the ORTO-11, -9, and -7, IT-F resulted with less tracts of ON than SP-F (Table 3). Both SP-F and SP-M had higher EAT-26 total score than Italian counterparts, despite dieting and bulimia components did not reach statistical significance (Table 3). Similar results came from SSI, suggesting more starvation symptoms in Spaniards compared to Italians (Table 3).

### *Overlaps and correlations among outcomes*

Figure 1A illustrates the prevalence of ON in the whole sample ($n$ = 160), by using different cut-off points and scores for ORTO questionnaire, among students who presented ED risk (EAT-26) or mild, moderate, and severe psychological distress (K10). In addition to the overlaps among these conditions

**Table 2 Body image concerns**

| | IT-F, *n* = 59 | IT-M, *n* = 41 | SP-F, *n* = 33 | SP-M, *n* = 27 |
|---|---|---|---|---|
| MBSRQ | 227.0 ± 21.7 | 231.6 ± 27.6[b] | 227.9 ± 24.3[a] | 249.3 ± 27.5[a,b] |
| MBSRQ-AO | 3.3 ± 0.9 | 3.2 ± 0.5[b] | 3.5 ± 0.5 | 3.5 ± 0.5[b] |
| MBSRQ-FO | 3.4 (3.0-3.9) | 3.5 (3.2-4.2) | 3.5 (3.0-4.0)[a] | 4.2 (3.6-4.4)[a] |
| MBSRQ-HOr | 3.4 ± 0.5 | 3.4 ± 0.6 | 3.2 ± 0.6[a] | 3.6 ± 0.6[a] |
| MBSRQ-IO | 3.3 ± 0.6 | 3.3 ± 0.5 | 3.4 ± 0.5 | 3.6 ± 0.6 |
| MBSRQ-AS | 3.1 ± 0.3 | 3.1 ± 0.4[b] | 3.1 ± 0.4[a] | 3.4 ± 0.4[a,b] |
| MBSRQ-BASS | 3.2 ± 0.7 | 3.4 ± 0.6 | 3.1 ± 0.8[a] | 3.5 ± 0.7[a] |
| MBSRQ-OP | 2.0 (1.8-2.8) | 2.5 (1.8-3.0) | 2.5 (2.1-3.0) | 2.5 (2.0-3.3) |
| BUT | 33.0 (19.0-61.0) | 16.0 (6.0-39.0) | 60.0 (30.5-82.0) | 35.0 (21.0-74.0) |
| BUT-A | 16.0 (9.0-36.0) | 10.0 (2.0-20.0) | 33.0 (12.5-51.0) | 18.0 (13.0-42.0) |
| BUT-A - WP | 0.9 (0.4-1.6)[b] | 0.5 (0.1-1.0) | 1.8 (0.8-2.6)[b] | 1.1 (0.6-1.8) |
| BUT-A - BIC | 0.7 (0.2-1.3)[a] | 0.2 (0.0-0.9)[a] | 0.9 (0.5-1.6) | 0.6 (0.2-1.6) |
| BUT-B | 15.0 (7.0-31.0) | 11.0 (3.5-21.0) | 25.5 (14.0-42.5) | 21.0 (8.0-36.0) |

[a]$P < 0.05$ between females and males within country.
[b]$P < 0.05$ between Italians and Spaniards within sex.
Categorical variables are expressed as percentages. Continuous variables are expressed as means with standard deviation (Shapiro-Wilk Test passed), or as median (25%-75% range, Shapiro-Wilk Test failed). AO: Appearance orientation; AS: Appearance scales; BASS: Body areas satisfaction scale; BIC: Body image concerns; BUT: Body Uneasiness Test; FO: Fitness orientation; HOr: Health orientation; IO: Illness orientation; IT-F: Italian females; IT-M: Italian males; MBSRQ: Multidimensional Body-Self Relations Questionnaire; OP: Overweight preoccupation; SP-F: Spanish females; SP-M: Spanish males; WP: Weight phobia.

and ON, psychological distress was observed both in students presenting ED risk or in those resulting negative to the EAT-26 test, without sex differences (Figure 1B). On the other hand, in Figure 2 is presented the prevalence of ON among different BMI classes and lifestyle factors, such as PA level and smoking habits.

From the aforementioned results, and in order to reduce the potential confounder as being on caloric restriction[31], Spearman correlations were evaluated in both the total sample ($n$ = 160, 92 F and 68 M) and a subgroup of students ($n$ = 66, 38 F and 28 M) with normal weight (NW), excluding those who suffered from mild, moderate and severe distress, or potentially at ED risk (NW-K10$^{neg}$-EAT-26$^{neg}$).

As regards the NW-K10$^{neg}$-EAT-26$^{neg}$ group, all subjects resulted with ON when ORTO-15 (40 cut-off point) was applied, whereas a prevalence of 37.9% was observed applying ORTO-15 (35 cut-off point), 18.2% considering ORTO-11, 22.7% with ORTO-9, and 40.0% with ORTO-7. Concerning lifestyle, the percentage of non-smokers (60.6%) was higher ($P < 0.05$) compared to those of ex-smokers (7.6%) and smokers (13.6%) among students with ON, assessed with ORTO-15 (40 cut-off). Similar results were reported when ORTO-15 (35 cut-off point) was used, with a prevalence of ON in non-smokers and smokers corresponding to 60.0% and 16.0%, respectively, as well as for results of ORTO-11 (prevalence of ON: non-smokers 66.7% and smokers 16.7%), ORTO-9 (prevalence of ON: non-smokers 66.7% and smokers 13.3%) and ORTO-7 (prevalence of ON: non-smokers 74.1% and smokers 7.4%). Among the students with ON, the percentage of those practicing high PA was higher ($P < 0.05$) compared to low PA for ORTO-15 (cut-off 40: high PA 54.4% and low PA 15.2%; cut-off 35: high PA 68.0% and low PA 8.0%), ORTO-11 (high PA 75.0% and low PA 0%), ORTO-9 (high PA 80.0% and low PA 0.0%) and ORTO-7 (high PA 59.3% and low PA 11.1%).

Considering the whole sample, among the different ORTO scores a relationship between ORTO-9 and BMI was found, and Table 4 depicts the Spearman correlations between ORTO scores and those from the other questionnaires. All ORTO scores were inversely correlated to SSI (Table 4), which indicates that high ON corresponds to more starvation symptoms since ORTO has reverse scores. Similarly, all ORTO scores were correlated to EAT-26 and its components (Table 4). On the contrary, the relationships between each ORTO score and BUT components were different (Table 4). Weight phobia (BUT A-WP) was correlated with ORTO-12, ORTO-9 and ORTO-7. The latter resulted the only one not related to MBRSQ-AS, MBSRQ and its health component (MBSRQ-HOr), as well as to the MBSRQ-OP (Table 4). Moreover, the correlation coefficients between ORTO scores and MBSRQ-AO and -FO were lower for ORTO-7 compared to the other scores (Table 4). On the other hand, ORTO-7 resulted in the only one that was related to the MBSRQ-BASS, and ORTO-9 was the only score related to IPAQ and to its intense activities and walking components (Table 4).

**Table 3 Orthorexia, eating attitude and malnutrition**

| | IT-F, *n* = 59 | IT-M, *n* = 41 | SP-F, *n* = 33 | SP-M, *n* = 27 |
|---|---|---|---|---|
| ORTO-15 | 36.8 ± 3.4[a] | 36.4 ± 34.2[a] | 34.2 ± 3.6[a] | 33.8 ± 3.4[a] |
| Cut-off 40 (%) | 76.3[a] | 70.7[a] | 97.0[a] | 96.3[a] |
| Cut-off 35 (%) | 23.7[a] | 36.5 | 48.5[a] | 55.5 |
| ORTO-12 | 30.7 ± 3.0[a] | 30.4 ± 3.4[a] | 27.5 ± 2.9[a] | 27.2 ± 2.7[a] |
| ORTO-11 | 27.8 ± 2.8[a] | 27.6 ± 3.4[a] | 25.2 ± 2.9[a] | 25.4 ± 3.0[a] |
| Cut-off 25 (%) | 11.9[a] | 19.5[a] | 36.4[a] | 25.9[a] |
| ORTO-9 | 30.4 ± 3.4[a] | 30.0 ± 3.7[a] | 27.8 ± 3.2[a] | 27.1 ± 3.2[a] |
| Cut-off 26.7 (%) | 13.6[a] | 19.5[a] | 30.3[a] | 40.7[a] |
| ORTO-7 | 20.0 (18.0-22.0)[a] | 19.0 (18.0-21.0) | 19.0 (15.5-19.5)[a] | 19.0 (16.0-19.0) |
| Cut-off 19 (%) | 32.2 | 29.3 | 48.5 | 48.1 |
| EAT-26 | 6.0 (3.0-10.0)[a] | 5.0 (3.0-8.5)[a] | 11.0 (5.0-17.5)[a] | 13.0 (7.0-17.0)[a] |
| Cut-off 20 (%) | 8.5 | 4.9 | 21.2 | 11.1 |
| Dieting | 2.0 (0.0-5.0) | 2.0 (0.04.5) | 4.0 (0.5-9.5) | 6.0 (3.0-9.0) |
| Bulimia | 3.0 (3.0-3.0) | 3.0 (3.0-3.0) | 3.0 (3.0-5.5) | 3.0 (3.0-5.0) |
| SSI | 14.0 (8.0-22.0)[a] | 10.0 (4.5-16.0)[a] | 24.0 (20.0-43.0)[a] | 18.0 (12.0-30.0)[a] |

[a]$P < 0.05$ between Italians and Spaniards within sex. Not significant between females and males within country.
Categorical variables are expressed as percentages. Continuous variables are expressed as means with standard deviation (Shapiro-Wilk Test passed), or as median (25%-75% range, Shapiro-Wilk Test failed). EAT-26: Eating Attitudes Test; IT-F: Italian females; IT-M: Italian males; ORTO: Scores for orthorexia nervosa (ON, reverse scores, lower values indicate high ON); SP-F: Spanish females; SP-M: Spanish males; SSI: Starvation Symptom Inventory.

In the NW-K10$^{neg}$-EAT-26$^{neg}$ subgroup, we did not find many correlations as observed in the whole sample, including those between ORTO scores and BUT, SSI, total MBSRQ and some of its components (Table 4). Although no relationship was found among ORTO score and SSI in the NW-K10$^{neg}$-EAT-26$^{neg}$ subgroup, SSI was correlated with MBSRQ-OP (0.291, $P < 0.05$). The latter, as well as MBSRQ-AO and -AS, was correlated with ORTO-12 and ORTO-9 (Table 4), but also with BMI (0.260, $P < 0.05$).

On the other hand, in the NW-K10$^{neg}$-EAT-26$^{neg}$ subgroup, MET-min/wk from intense activities correlated with ORTO-15, -12, -11 and -9 (Table 4), as well as with BMI (0.442, $P < 0.001$), MBSRQ-FO (0.629, $P < 0.001$), -HOr (0.387, $P < 0.01$), that were highly related (coefficient of correlation MBSRQ-FO *vs* MBSRQ-HOr: 0.629, $P < 0.001$) and, to a lesser extent, IPAQ-intense activity was related to MBSRQ-OP (0.253, $P < 0.05$). MBSRQ-IO correlated with both MBSRQ-HOr (0.447, $P < 0.001$) and -AO (0.256, $P < 0.05$), that was related to MBSRQ-FO (0.329, $P < 0.01$). Interestingly, ORTO-7 resulted in the only score unrelated neither with BMI nor with the other evaluated outcomes in the NW-K10$^{neg}$-EAT-26$^{neg}$ subgroup (Table 4). The prevalence of ON from ORTO-7 in students included in the NW-K10$^{neg}$-EAT-26$^{neg}$ subgroup on the overall sample resulted to be 16.9%, 12.2%, 15.2% and 25.9% for IT-F, IT-M, SP-F and SP-M, respectively.

## DISCUSSION

In light of the reported overlaps of ON with other conditions and of the criticism highlighted from literature about ORTO-15[17-34], we have evaluated the prevalence of ON among 160 Italian and Spanish university students, from the 194 recruited in a previous study[35], who agreed to fill the standardized questionnaires: EAT-26, K10, BUT, MBSRQ, and IPAQ. The sample had, on average, a medium adherence to the Mediterranean diet and a low risk of excessive alcohol consumption[35]. Concerning country differences, the prevalence of mild distress was higher in SP-M compared to IT-M (Table 1), whereas IT-F had lower BUT-A -WP than SP-F (Table 2). SP-M had higher total MBSRQ, MBSRQ-AO, -FO, -HOr, -BASS and -AS, whereas no differences were found in MBSRQ-IO and -OP (Table 2).

Higher SSI, EAT-26 and ON, by using ORTO-15 (40 cut-off), -12, -11 and -9, were observed in Spanish students compared to Italians, regardless of sex (Table 3). Accordingly, no significant difference between female and male students in ORTO-15 has been reported in university students[25,44,45].

**Table 4 Spearman correlations**

| | ORTO-15 | ORTO-12 | ORTO-11 | ORTO-9 | ORTO-7 |
|---|---|---|---|---|---|
| BMI ($n$ = 160) | NS | NS | NS | -0.184[a] | NS |
| BMI NW-K10$^{neg}$-EAT-26$^{neg}$ ($n$ = 66) | -0.315[a] | -0.304[a] | -0.284[a] | -0.432[c] | NS |
| SSI ($n$ = 160) | -0.169[a] | -0.264[c] | -0.223[b] | -0.244[b] | -0.228[b] |
| EAT-26 ($n$ = 160) | -0.363[c] | -0.414[c] | -0.349[c] | -0.432[c] | -0.357[c] |
| Dieting ($n$ = 160) | -0.429[c] | -0.444[c] | -0.387[c] | -0.516[c] | -0.307[c] |
| Bulimia ($n$ = 160) | -0.188[a] | -0.263[c] | -0.180[a] | -0.304[c] | -0.223[b] |
| BUT ($n$ = 160) | NS | NS | NS | NS | -0.160[a] |
| BUT A – WP ($n$ = 160) | NS | -0.187[a] | NS | -0.181[a] | -0.166[a] |
| BUT B ($n$ = 160) | NS | NS | NS | NS | -0.165[a] |
| MBSRQ ($n$ = 160) | -0.354[c] | -0.279[c] | -0.341[c] | -0.414[c] | NS |
| MBSRQ-AO ($n$ = 160) | -0.333[c] | -0.296[c] | -0.326[c] | -0.359[c] | -0.177[a] |
| MBSRQ-AO NW-K10$^{neg}$-EAT-26$^{neg}$ ($n$ = 66) | NS | -0.285[a] | NS | -0.289[a] | NS |
| MBSRQ-FO ($n$ = 160) | -0.361[c] | -0.310[c] | -0.358[c] | -0.414[c] | -0.180[a] |
| MBSRQ-FO NW-K10$^{neg}$-EAT-26$^{neg}$ ($n$ = 66) | -0.304[a] | -0.371[a] | -0.373[a] | -0.450[c] | NS |
| MBSRQ-HOr ($n$ = 160) | -0.341[c] | -0.248[b] | -0.333[c] | -0.402[c] | NS |
| MBSRQ-HOr NW-K10$^{neg}$-EAT-26 $^{neg}$ ($n$ = 66) | -0.358[b] | -0.408[c] | -0.433[c] | -0.491[c] | NS |
| MBSRQ-IO ($n$ = 160) | -0.162[a] | NS | -0.181[a] | NS | NS |
| MBSRQ-BASS ($n$ = 160) | NS | NS | NS | NS | -0.169[a] |
| MBSRQ-OP ($n$ = 160) | -0.177[a] | -0.216[b] | -0.165[a] | -0.302[c] | NS |
| MBSRQ-OP NW-K10$^{neg}$-EAT-26$^{neg}$ ($n$ = 66) | NS | -0.366[b] | NS | -0.357[b] | NS |
| MBRSQ-AS ($n$ = 160) | -0.195[a] | -0.155[a] | -0.161[a] | -0.265[c] | NS |
| MBSRQ-AS NW-K10$^{neg}$-EAT-26$^{neg}$ ($n$ = 66) | NS | -0.244[a] | NS | -0.306[a] | NS |
| IPAQ ($n$ = 160) | NS | NS | NS | -0.183[a] | NS |
| Walking ($n$ = 160) | NS | NS | NS | -0.162[a] | NS |
| Intense activity ($n$ = 160) | NS | NS | NS | -0.178[a] | NS |
| Intense activity NW-K10$^{neg}$-EAT-26$^{neg}$ ($n$ = 66) | -0.404[c] | -0.330[b] | -0.273[a] | -0.461[c] | NS |

[a]$P$ < 0.05.
[b]$P$ < 0.01.
[c]$P$ < 0.001.
AO: Appearance orientation; AS: Appearance scales; BASS: Body areas satisfaction scale; BMI: Body mass index; BUT: Body Uneasiness Test; EAT-26: Eating Attitudes Test; FO: Fitness orientation; HOr: Health orientation; IO: Illness orientation; IPAQ: International Physical Activity Questionnaire; MBSRQ: Multidimensional Body-Self Relations Questionnaire; NS: Not significant; NW- K10$^{neg}$-EAT-26$^{neg}$: Normal weight students excluded those with K10 or EAT-26 positive test; OP: Overweight preoccupation; ORTO: Scores for orthorexia nervosa; SSI: Starvation Symptom Inventory; WP: Weight phobia.

Among NW Polish university students, ORTO-15 correlated with MBSRQ-OP, -AO, -FO, -HOr and -BASS in females, whereas in male students, body image concerns were not associated with ON[38]. The Spearman correlations (Table 4) confirmed the previously reported relationship between ON, depending on ORTO score applied to the whole sample, and MBSRQ-OP, -AO[34], and EAT-26[32,33], and we have observed overlaps between ORTO scores, EAT-26 and K10 (Figure 1). Although the prevalence of UW, OW and OB students did not reach significance in the whole sample, IT-F had a lower BMI (Table 1) and higher BUT-A – BIC (Table 2) than IT-M.

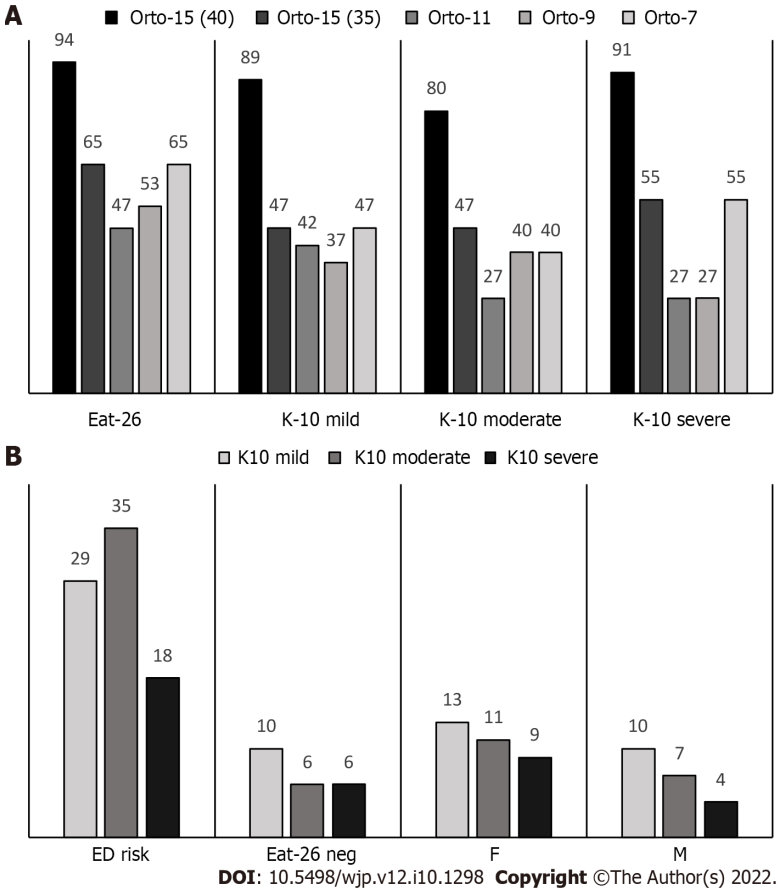

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**Figure 1 Prevalence of orthorexia nervosa.** A and B: Prevalence of orthorexia nervosa among students who presented an eating disorder (ED) risk [Eating Attitudes Test (EAT)-26] or psychological distress [Kessler Psychological Distress Scale (K10)] (A) and overlap of EAT-26 and K10 (B), in the whole sample. ORTO: Scores for orthorexia nervosa; K10: Kessler Psychological Distress Scale; EAT-26: Eating Attitudes Test; F: Italian and Spanish females; M: Italian and Spanish males; ED: Eating disorder.

In order to reduce the potential confounder as being on a diet[31], we have evaluated a subgroup of NW students, excluding volunteers who presented distress or ED risk (NW-K10$^{neg}$-EAT-26$^{neg}$). All students in the NW-K10$^{neg}$-EAT-26$^{neg}$ group had ON, when ORTO-15 with the 40 cut-off was applied, whereas the percentage of ON varied with ORTO-15 (35 cut-off), -11, -9 and -7. Concerning lifestyle, the percentage of non-smokers was higher compared to those of smokers among students with ON in the NW-K10$^{neg}$-EAT-26$^{neg}$ group. In this context, it has been proposed to distinguish between ON and healthy orthorexia (HO), a non-pathological tendency to follow a healthy diet[46]. HO can be the successful result of dissemination campaigns aimed to increase nutrition knowledge from WHO and National recommendations, but the proposed etiology of ON includes high level of education, pseudoscientific nutritional news on social media and psychological factors[12]. From a study carried out in nutrition and dietetics, university students emerged that Instagram use might be considered as an ON-risk factor[47]. Besides, K10 median of the scores of students enrolled in health-related study courses was higher than those of non-health-related degree courses[48]. Furthermore, it has been suggested that obsessive healthy eating fixations may increase the risk for ED in athletes and that more education and awareness are warranted to minimize the risk for ON and ED in student-athletes[30]. High level of PA in association with ON, assessed with ORTO-15 using cut-off scores of 35, was more often seen in men from sports science and less often in women from business course[27]. With a cut-off of 40, ORTO-15 resulted lower among students who performed more than ten h/wk of exercise, regardless of the engagement in university sport teams, including athletes competing in aesthetic and weight dependent sports[28]. In our sample, sex differences were found in MET-min/wk from intense activities in both countries (Table 1). In the NW-K10$^{neg}$-EAT-26$^{neg}$ group, among the students with ON, the percentage of those practicing high PA was higher compared to those having low PA, whereas we did not find correlations observed in the whole sample, including those between ORTO scores and BUT, SSI, and total MBSRQ.

The present study has both strengths and limitations, taking into account the suggestion of a pilot study[49] that reported high levels of disparity among psychometric scores, including ORTO-15, EAT-26 and MBSRQ, recommending the use of multiple psychometric instruments for ON diagnosis. Furthermore, the evaluation of dietary intakes of 10 individuals (assessed using 24-h recall) failed to meet the guidelines for several nutrients[49]. As a point of strength, we have used different stan-

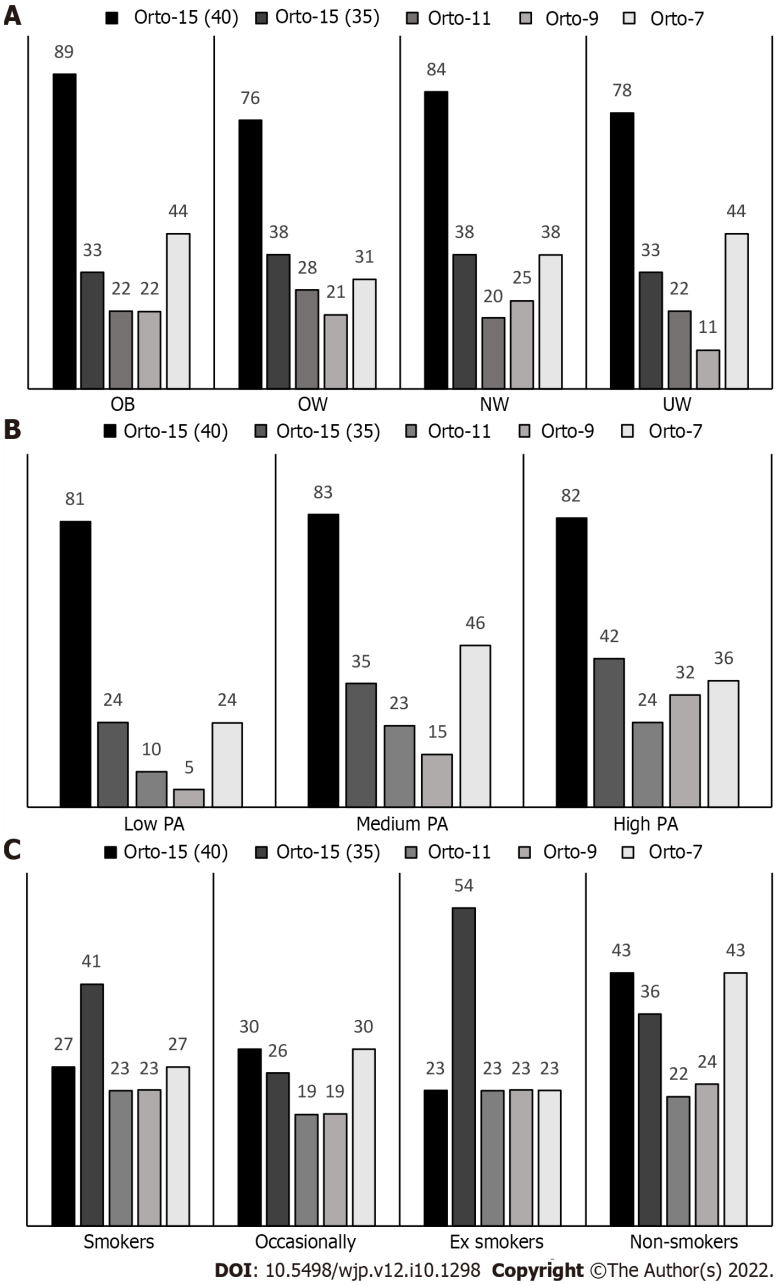


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**Figure 2 Prevalence of orthorexia nervosa among different body mass index classes and lifestyle factors.** A: Body mass index; B: Physical activity; C: Lifestyle factors. ORTO: Scores for orthorexia nervosa; OB: Obese; OW: Overweight; NW: Normal weight; UW: Underweight; PA: Physical activity.

dardized questionnaires in order to exclude students presenting overlaps. As a limitation, we did not evaluate the nutritional status. However, the relationships between SSI and all ORTO scores observed in the whole sample, but not in the NW-K10$^{neg}$-EAT-26$^{neg}$ subgroup, suggest that students with more starvation symptoms were excluded from the applied exclusion criteria. In fact, the greatest strength is that ORTO-7 resulted in the only score unrelated neither with BMI nor with the other evaluated outcomes in the NW-K10$^{neg}$-EAT-26$^{neg}$ subgroup (Table 4). The prevalence of ON from ORTO-7 after the "exclusion diagnosis" in the NW-K10$^{neg}$-EAT-26$^{neg}$ subgroup on the overall sample ranged between 12.2% and 25.9%, values lower than those reported in the whole sample. However, it was higher than some observed with other sub-scores of ORTO test (Table 4). This finding suggests that, among the limitations, we did not include the OCD in the "exclusion diagnosis"[50]. However, Łucka *et al*[29] using ORTO-15 (score of 35 was considered as cut-off point), EAT-26 and Maudsley Obsessive Compulsive Inventory (MOCI), found that individuals with suspected ON (ORTO-15, score of 35) had higher BMI and EAT-26 score, whereas MOCI did not differ from ORTO-15 negative group. From that, authors suggested that ON meets the criteria of ED and not of OCD[29]. On the other hand, considering the relationship among other ORTO scores and body concerns, and high PA component of IPAQ, also questionnaires evaluating exercise addiction[51,52] and muscle dysmorphia[26] should be included in the "exclusion diagnosis".

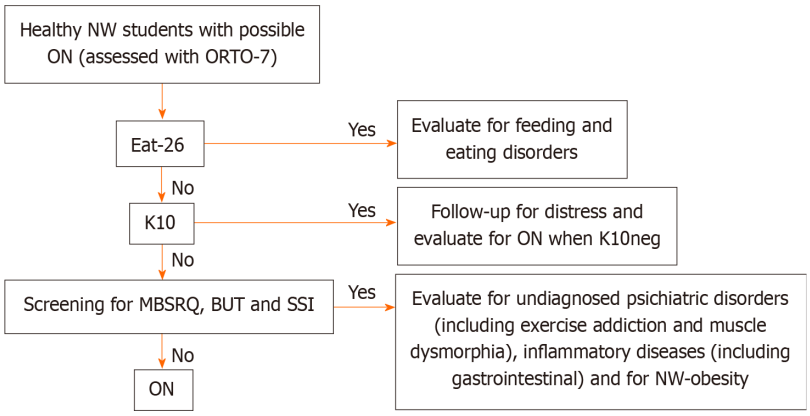


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**Figure 3 Decision tree for the exclusion diagnosis of orthorexia nervosa (ON) in healthy normal weight university students.** ORTO-7: Score for orthorexia nervosa; K10: Kessler Psychological Distress Scale; EAT-26: Eating Attitudes Test; MBSRQ: Multidimensional Body-Self Relations Questionnaire; BUT: Body Uneasiness Test; SSI: Starvation Symptom Inventory; NW: Normal weight.

Among exclusion diagnosis (gastrointestinal disorders) there are functional dyspepsia[53], non-celiac gluten sensitivity (NCGS)[54,55] and irritable bowel syndrome (IBS)[55]. Both NCGS and IBS are more prevalent in young women compared to men[55], and up to 90% of patients with IBS exclude certain foods to improve their gastrointestinal symptoms[56]. Besides, negative effects of prescribing restrictive diets can be observed due to the association between ED and gastrointestinal symptoms[56]. In this context, the differential diagnosis and assessment of AN already began with the exclusion of diseases, including inflammatory bowel disease (Crohn's disease or ulcerative colitis), malignancies, thyrotoxicosis, diabetes, cerebral tumor, major depressive or schizophrenic illnesses[10].

Although the scientific community is divided into those who consider ON as a separate ED and those who do not[7], agreement exists on the needs of prevention (primary and secondary) and some diagnostic criteria, as reviewed by Atzeni *et al*[16], including: obsessive concern for healthy eating, fear anxiety and avoidance of certain foods components (additives, preservatives, fats or other elements considered unhealthy). Furthermore, there is broad consensus on the induction of malnutrition by ON and impacts on social and professional functioning. Other suggested criteria (not endorsed by all experts) included differences between ON and OCD or from schizophrenia, excessive time spent or rituals in preparing meals, excessive spending money for buying healthy foods; anxieties and fears concerning transgressions, and the exclusion of individuals who observe a religious practice or have medical problems[16]. Our work suggests including EDs and psychological distress among the medical problems for the exclusion diagnosis of ON in healthy NW individuals. Otherwise, we suggest considering ON as a symptom of other diseases or a disease-induced comorbidity.

## CONCLUSION

Although a generalization to the whole population should not be made, considering the recent suggestions on the need for further investigation of the comorbidity between ON and OCD across different cultural groups[50], it emerged that ON could be an indicator/symptom of other problems related to body image perception, as well as high PA, psychological distress, appearance, fitness, health, or IO, in some university students. Accordingly, recent studies have found relationships between ON, vigorous-intensity PA and dieting[47,57]. In our study, the ORTO-7 was found to be independent from these confounders, after the exclusion of UW, OW, OB, and EAT-26 and K10 positive students, suggesting the possibility of defining subjects with ON. Therefore, considering the overlap conditions, we suggest a decision tree for differential/exclusion diagnosis of ON (Figure 3). In order to identify the real orthorexic subjects among healthy students with NW, firstly the presence of EDs should be assessed, followed by the evaluation of the distress level, and lastly the presence of body image concerns and malnutrition (Figure 3). Moreover, a high percentage of students (25.5% males and 40.1% females) with NW obesity (NWO) have been reported, and stress management behavior decreased the risk of NWO in females[58]. In this context, Villa *et al*[47] observed that ON was associated not only with heavy exercise but also with sedentary behavior. In students with NWO, low PA could be associated with dieting, inducing ON. In conclusion, due to the several confounders and overlap conditions, flowcharts, diagnostic algorithms and a decision tree for differential diagnosis and management of ON should be included, as well as guidelines and consensus statements of experts in the future.

## ARTICLE HIGHLIGHTS

### *Research background*

Many factors have been associated to orthorexia nervosa in university students.

### *Research motivation*

To assess the prevalence of orthorexia nervosa in Italian and Spanish university students.

### *Research objectives*

To assess the prevalence of orthorexia nervosa in relation to eating attitude and psychological distress.

### *Research methods*

Questionnaires were administered to evaluate orthorexia nervosa, body concerns, psychological distress, physical activity, eating attitude and starvation symptoms.

### *Research results*

When excluding students underweight (UW), overweight (OW) or obese (OB), as well as those potentially at risk of eating disorders or presenting distress, in the resultant normal weight (NW)-K10$^{neg}$-EAT-26$^{neg}$ subgroup, we did not find many correlations observed in the whole sample, including those between ORTO scores and Body Uneasiness Test, Starvation Symptom Inventory, Total Multidimensional Body-Self Relations Questionnaire (MBSRQ) and some of its components. Moreover, ORTO-7 resulted the only ON score unrelated with Body Mass Index, MBSRQ components and IPAQ-assessed intense activity, in the NW-K10$^{neg}$-EAT-26$^{neg}$ subgroup. After this sort of "exclusion diagnosis", ORTO-7 became independent from these confounding, after the exclusion of UW, OW, OB and students positive to EAT-26 and K10, suggesting the possibility of identifying orthorexic subjects with this specific questionnaire.

### *Research conclusions*

In some university students ON could be a symptom of other conditions related to body image concerns and distress, as well as to high physical activity and appearance, fitness, health or illness orientation. ORTO-7 became independent from these confounding factors, after the exclusion of UW, OW, OB and students positive to EAT-26 and K10, suggesting the possibility of identifying orthorexic subjects with this specific questionnaire.

### *Research perspectives*

Considering the overlap conditions, we suggest a decision tree for differential/exclusion diagnosis of ON.

## FOOTNOTES

**Author contributions:** Peluso I and Villaño D contributed to the conceptualization; Aiello P, Toti E and Raguzzini A contributed to the investigation; Aiello P and Peluso I contributed to the original draft preparation; Toti E, Raguzzini A and Villaño D contributed to the review and editing; Peluso I contributed to the supervision.

**Institutional review board statement:** The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee for Human Experimentation of the La Sapienza University of Rome (protocol code 1382/2019, approved on 16 July 2019) and by the Ethics Committee of the Catholic University of Murcia (UCAM) (protocol code CE071906, approved on 3 July 2019).

**Informed consent statement:** Informed consent was obtained from all subjects involved in the study. Volunteers did not sign consent to share single individual data, but only cumulative results.

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**Data sharing statement:** No additional data are available.

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## ORIGINAL ARTICLE

### Observational Study

1323 Investigating adolescent mental health of Chinese students during the COVID-19 pandemic: Multicenter cross-sectional comparative investigation

*Huang BW, Guo PH, Liu JZ, Leng SX, Wang L*

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*MINIREVIEWS*

# Impacts of COVID-19 on children and adolescents: A systematic review analyzing its psychiatric effects

Italo Wanderson de Moura Gabriel, Danielly Gonçalves Sombra Lima, Jeully Pereira Pires, Nélio Barreto Vieira, Aloisio Antonio Gomes de Matos Brasil, Yara Talita Gomes Pereira, Erika Galvao de Oliveira, Hildson Leandro de Menezes, Nadia Nara Rolim Lima, Alberto Olavo Advíncula Reis, Ruan Neto Pereira Alves, Uanderson Pereira da Silva, Jucier Gonçalves Junior, Modesto Leite Rolim-Neto

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## Abstract

***OBJECTIVE***

To summarize the most relevant data from a systematic review on the impact of COVID-19 on children and adolescents, particularly analyzing its psychiatric effects.

***METHODS***

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and included experimental studies (randomized-individually or pooled-and non-randomized controlled trials), observational studies with a group for internal comparison (cohort studies-prospective and retrospective-and case-control) and qualitative studies in the period from 2021 to 2022.

***RESULTS***

The search identified 325 articles; we removed 125 duplicates. We selected 200 manuscripts, chosen by title and selected abstracts. We excluded 50 records after screening titles and abstracts, as they did not meet the inclusion criteria. We retrieved 150 records selected for a full reading. We excluded 90 text articles and we selected 25 records for the (n) final. Limitations: Due to the short period of data collection, from 2021 to 2022, there is a possibility of lack of relevant studies related to the mental health care of children and adolescents. In addition, there is the possibility of publication bias, such as only significant findings being published.

***CONCLUSION***

The impact of COVID-19 on the mental health of children and adolescents is of great concern to child and youth psychiatry. Situations such as fear, anxiety, panic, depression, sleep and appetite disorders, as well as impairment in social interactions caused by psychic stress, are punctual markers of pain and psychic suffering, which have increasing impacts on the mental health panorama of children and adolescents globally, particularly in vulnerable and socially at-risk populations.


**Key Words:** Child psychiatry; Adolescent psychiatry; Mental health; COVID-19; Kids; Teens

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**Core Tip:** Fear, anxiety, panic, depression, sleep, and appetite disorders, as well as impairment in social interactions caused by psychic stress are punctual markers of pain and psychic suffering, which have increasing impacts on the mental health panorama of children and adolescents in the coronavirus disease 2019 pandemic.

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## INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) has caused pain and psychological suffering in children and adolescents, particularly considering the new variants of the disease[1]. Psychologically stressful situations are the main effects caused to populations under the influence of COVID-19, which can contribute to the development of post-traumatic stress symptoms, especially for vulnerable children/adolescents (C-A) in critical developmental stages, with variable prevalence, risk factors, and severity[2]. Recent studies highlight that C-A are more likely to have high rates of depressive or anxiety disorders, impairing family, school, cultural, and social interactions, with multiple and adverse consequences to mental health in the medium and long term[3,4].

Current studies have observed that parental stress, co-parenting, emotional well-being, and children and adolescents' adjustment were impacts that acted unfavorably in the COVID-19 pandemic[5,6]. These findings highlight the psychic burden and stress faced by caregivers of C-A with disabilities and compromised psychiatric development during the pandemic.

In this context, C-A with neurodevelopmental disorders (NDD) have higher levels of distress compared to typically developing children. Distress levels may be heightened by restrictions associated with the COVID-19 pandemic[7,8]. Parents' perceptions of how the pandemic has mitigated their mental health have implications for their well-being and that of their children, with a stronger association for low-income families[9].

Although parenting is essential for positive development, increased parental distress interferes with children's well-being. Sesso *et al*[10] warn that internalization problems in C-A with NDD were among the strongest predictors of parental stress during the pandemic lockdown. The dysfunctional interactions of a child are usually mediated by their internalizing/externalizing problems[11,12]. In this context, parents of children with NDD should be valued groups in public policies to promote mental health in the post-pandemic period[13].

It is also important to highlight that the prevalence of anxiety generally varies from 19% to 64% and depression from 22.3% to 43.7% among adolescents. Among children aged 5 to 12 years, the prevalence of anxiety ranges from 19% to 78%, while depression among adolescents ranges from 6.3% to 22.6%[14]. Among preschool-age children, some studies have found that behavioral and emotional problems worsen during the pandemic[4,15].

This paper aims to summarize the most relevant data on the impact of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic on C-A through a systematic review, particularly analyzing its psychiatric effects.

## METHODS

A systematic review was carried out using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol from 2021 to 2022. Qualitative studies, quantitative studies (*e.g.*, prospective/retrospective cohorts, case-control studies), and experimental studies (randomized, pooled or individual, and non-randomized controlled trials) were included. Case reports, case studies, opinions, editorials, letters, and conference abstracts were excluded.

The following descriptors were used with the respective Boolean operators: "2019 nCoV" OR # 2019 nCoV OR "2019 novel coronavirus" OR "COVID 19" OR "COVID19" OR "new coronavirus" OR "novel coronavirus" OR "SARS CoV-2" OR "Mental health" OR "depression" OR "Anxiety" OR "Child Psychiatry" OR "Adolescent Psychiatry".

### Search strategy

We searched the Web of Science Index Medicus, MEDLINE, WHO COVID-19 databases, EMBASE, Scopus, and Cochrane Library. Non-indexed databases, including MedRxiv preprint and Google Scholar, were also used. To identify missing documents, all systematic reviews and relevant comments were manually searched.

### Types of participants

Studies on children and adolescents aged 3 to 19 years from 2021 to 2022, and which focused on psychiatric interventions in children and adolescents during the SARS-CoV-2 pandemic were included.

### Selection of studies

Articles were included only if the study exclusively examined the mental health impacts of COVID-19 on children and adolescents from 2021 to 2022. Detailed inclusion and exclusion criteria are shown in Table 1. Using Covidence, a web-based tool that helps to identify studies and involves data extraction processes, two reviewers (MLRN and JPP) independently examined all potential articles. In the case of disagreement, both reviewers read the article and discussed it until a consensus was reached.

### Data extraction

Relevant data were extracted from each study, including year and country of publication, study design, target population, pandemic exposure, interventions, and outcomes (Table 2). One reviewer (NNRL) used a form that the research team developed to extract the data. A second reviewer (AOAR) verified the entire data extraction activity and verified its accuracy and completeness. Disagreements were resolved through discussion.

### Quality assessment

The methodological quality of the studies was assessed using the Mixed Methods Assessment Tool.

### Data analysis/synthesis

Data were aggregated and analyzed according to the results and objectives of the study. Therefore, the results were summarized according to the reported results and the study design (Table 2).

**Table 1 Inclusion and exclusion criteria**

| Inclusion criteria | Exclusion criteria |
|---|---|
| Types of studies: Quantitative, qualitative, mixed methods, experimental and observational studies, human studies | Articles that were not in English; studies that did not report age; studies that included participants with mental health issues prior to COVID-19 |
| Types of Participants: Studies carried out with children and adolescents (3 to 19 years old) from 2021 to 2022 | |
| Interventions: Children and adolescents impacted by COVID-19 and its repercussions on mental health | |
| Types of results: Rates of psychiatric disorders in children and adolescents in times of COVID-19 | |
| Secondary outcomes: Fear, anguish, pain and psychic suffering related to the pandemic | |

COVID-19: Coronavirus disease 2019.

### *Risk of publication bias*

The likelihood of a treatment effect reported in systematic reviews resembling the truth depends on the validity of the studies included in the analysis as certain methodological characteristics may be associated with effect sizes. Therefore, it was important to determine in the systematic reviews whether the sample of studies obtained was representative of all the research carried out on depression in childhood and adolescence in times of COVID-19. The possibility of bias resulting from a trend of only positive findings being published-known as the "file drawer effect"-was addressed using two methods: Calculating the fail-safe N and the p-curve approach.

The fail-safe N is determined by calculating the number of studies with a mean null result needed to make the overall results insignificant. The p-curve was introduced to account for "p-hacking", a theory stating that researchers may be able to get most studies to find positive results across different reviews. The p-curve assesses the slope of the reported p-values to determine whether p-hacking has occurred.

The most significant findings of depression in children and adolescents impacted by COVID-19 were found in 24 studies, which required the p-value to be set at > 0.05. In addition, quarantine, sleep disturbances, post-traumatic stress symptoms, and the prevalence of anxiety were findings that validated the results. The p-curve was applied to explain p-hacking-to guarantee positive results. When calculating the p-curve, only 13 studies were included that examined the psychiatric impact on adolescents and children during the COVID-19 pandemic[2,3,6,7,15-23]. The studies existing in the literature ($P$ = 0.5328) indicating depression among children and adolescents have sufficient evidence in their findings, particularly because there were 11 studies on potential interventions to improve the mental health of children and adolescents[1,4,5,8,9-13,23,24].

Clearly, solutions to the file drawer problem present an irritating and challenging issue for meta-analytic research and it will likely take a paradigm shift to truly address this problem, as authors who submit their literature reviews and methods only, abandoning conventional inferential statistics in favor of Bayesian Approaches, or the registration of studies and protocols online before conducting a study.

## RESULTS

The search identified 325 articles, but 125 duplicates were removed. Therefore, 200 articles were selected, chosen by the title and abstract. Fifty articles were excluded after screening the titles and abstracts, as they did not meet the inclusion criteria. Consequently, a total of 150 articles were selected to be read in full. After that, 91 text articles were excluded, with 24 being selected for the final (n) (Figure 1).

### *Study results*

We analyzed the studies thematically and divided them into two categories: (1) Psychiatric impact on children and adolescents in times of COVID-19; and (2) potential interventions to improve the mental health of children and adolescents.

### *Psychiatric impact on children and adolescents in times of COVID-19*

Among the studies included, 13 examined the psychiatric impact on children and adolescents in times of COVID-19[2,3,6,7,14-22].

A research study by Demaria and Vicari[2] and Sayed *et al*[3] showed that quarantine is a psychologically stressful experience. For children, missing school and interruptions in daily routines can have a negative impact on their physical and mental health. In this perspective, they pointed out that parents

**Table 2 Characteristics of included studies (*n* = 24)**

| Ref. | Country | Study design | Target population | Total participants | Exposure | Outcomes |
|---|---|---|---|---|---|---|
| Barros *et al*[19], 2022 | Brazil | Cross-sectional-electronic questionnaire | 12-17 years | 9470 adolescents | COVID-19 | The data showed that factors such as: Family problems, female gender, age 15-17 years, learning disabilities, relatives infected with COVID-19, and death of close friends from COVID-19 were factors associated with worsening mental health |
| Okuyama *et al* [1], 2021 | Japan | Review | Children under 18 years | Studies included (*n* = 28) | COVID-19 | Studies have shown correlation between physical activity and psychological health and sedentary time leading to mood disorders. Some studies on adolescents reported a correlation between physical activity and psychological health and others did not |
| Demaria and Vicari[2], 2021 | Italy | Commentary | NA | NA | COVID-19 | The pandemic context, with regard to quarantine, proved to be a psychologically stressful experience |
| Sayed *et al*[3], 2021 | Saudi Arabia | Cross-sectional-online *via* social media | 12.25 ± 3.77 years | 537 children (263 boys and 275 girls) | COVID-19 | The data showed that Post-traumatic stress disorder symptoms were not correlated with school grade, sex, age or having a close relative working with people infected by COVID-19 |
| Meherali *et al*[4], 2021 | Canada, Pakistan, Australia | Systematic reviews | 5-19 years | Studies included (*n* = 18) | COVID-19 | These studies reported that pandemics cause stress, worry, helplessness, and social and risky behavioral problems among children and adolescents |
| Bussières *et al*[5], 2021 | Canada | Meta-analysis | 5-13 years | Studies included (*n* = 28) | COVID-19 | During the COVID-19 pandemic, the restriction measures imposed had an impact on children's mental health. During this period, there was also a change in sleep habits. Even so, the results do not show significant differences in relation to the general population |
| Bentenuto *et al* [6], 2021 | Italy | Retrospective | Children with NDD and TD | Total 164 (NND 82 and TD 82) | COVID-19 | Quantitative analyzes demonstrated an increase in children's externalizing behaviors and parental stress. However, they also showed that parents enjoyed spending more time with their children and strengthening the parent-child relationship. Furthermore, in children with NDD, the reduction in therapeutic measures predisposes to high externalizing behaviors |
| Burnett *et al*[7], 2021 | Sweden, Australia, Italy | Cross-sectional-online self-reported survey | Parents of children aged 3-18 years | Australia (*n* = 196); Italy (*n* = 200) | COVID-19 | When compared to other developmental disorders among parents in Australia and Italy, intellectual or learning disorders are the ones that bring them the most suffering |
| Raffagnato *et al* [8], 2021 | Italy | Longitudinal | Psychiatric patients age between 6 and 18 years and their parents | 39 patients and their parents (25 girls and 14 boys) | COVID-19 | Patients with behavioral disorders were more impacted when compared to patients with internalizing disorders, who were shown to have adapted better to the pandemic context. In parents, it was possible to observe a protective factor against psychological maladjustment. A decrease in mothers' anxiety and fathers' stress over time was also observed |
| Kerr *et al*[9], 2021 | United States | Cross-sectional-online survey | Parents with at least one child 12 years old or younger | 1000 participants | COVID-19 | As for the psychological impacts, the data show high levels of stress and low levels of positive behavior in children, and a high rate of parental exhaustion. Still, there is an indirect association between parental behavior and the psychological impacts of COVID-19 and children's behaviors. The data also showed that the difference in income is a factor that can increase this indirect |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | association |
| Sesso *et al*[10], 2021 | Italy | Cross-sectional-online questionnaire | Parents of children 6.62 ± 3.12 years with neuropsychiatric disorders | 77 participants | COVID-19 | Internalizing problems in children during quarantine were the strongest predictor of parental stress |
| Li and Zhou[11], 2021 | China | Cross-sectional-online questionnaire | 5-8 years: 647 children; 9-13 years: 245 adolescents | 892 valid questionnaires (mothers 662 and fathers 230) | COVID-19 | Concerning the data, it was possible to observe that parents are worried about their children's internalization and externalization problems. It was observed that, in elementary school, significant and negative relationships were observed between family-based disaster education and internalizing and externalizing problems |
| Bate *et al*[12], 2021 | United States | Cross-sectional-online *via* social media | Parents of children (6-12 years) | 158 parents of children (151 mothers and 7 fathers) | COVID-19 | It was observed that the biggest EH problems of parents were due to the impact of COVID-19. Parents' EH was a positive predictor of children's EBH |
| Kim *et al*[13], 2021 | Suwon, South Korea | Cross-sectional-web based questionnaire | Parents of children aged 7-12 years | 217 parents | COVID-19 | With schools closed, children had body weight gain, spent less time doing physical activities and more time using the media. In addition, an association can be observed between parental depression and children's sleep problems, TV time, tablet time and behavior problems |
| Minozzi *et al* [14], 2021 | Italy | Systematic review | Pre-school children, children 5-12 years and adolescents | Studies included (*n* = 64) | COVID-19 | Studies have reported an increase in suicides, reduced access to psychiatric emergency services, reduction in allegations of maltreatment. The prevalence of anxiety among adolescents varied considerably, as did depression, although in a lower percentage |
| Backer *et al*[15], 2021 | Netherlands | Cross-sectional-questionnaire | 0-4, 5-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89 and ≥ 90 years | 7250 participants | COVID-19 | During the physical distancing restriction measures, it is possible to observe that community contacts in all age groups were restricted to an average of 5 contacts. After relaxation, it was observed that the children returned to maintain their normal contact number, while the elderly maintained their restricted contact numbers |
| Qin *et al*[16], 2021 | Guangdong province, China | Cross-sectional-electronic questionnaire | School-aged students [12.04 (3.01) years] | 1 199 320 children and adolescents | COVID-19 | Among those who reported psychological distress, the risk of psychological distress was analyzed among high school and elementary school students, among students who never used a mask and those who did, and among students who spent less than 0.5 h exercising and those who spent more than 1 h |
| Lu *et al*[17], 2021 | China, United Kingdom | Systematic review and meta-analysis | children and adolescents (0-18 years) | Studies included (*n* = 23) | COVID-19 | Studies show a combined prevalence of depression, anxiety, sleep disorders, and post-traumatic stress symptoms |
| Ma *et al*[18], 2021 | China, United States | Cross-sectional-online self-report questionnaires | 6-8 years | 17740 children and adolescents | COVID-19 | The data reported that depressive, anxiety, compulsive, inattentive and sleep-related problems were more expressive when compared to before the COVID-19 outbreak |
| Spencer *et al*[23], 2021 | United States | Cohort study | 5-11 years | Caregivers of 168 children (54% non-Hispanic black, 29% Hispanic, and 22% non-English speaking) | COVID-19 | Children had significantly higher emotional and behavioral symptoms mid-pandemic *vs* pre-pandemic in all scenarios |
| Han and Song [20], 2021 | South Korea | Retrospective | Middle and high school students | 54948 students | COVID-19 | The data showed, through multivariate logistic regression, that there was a correlation between the perception of the economic situation of the family and the prevalence of depressive symptoms and suicidal ideation |

| | | | | | | |
|---|---|---|---|---|---|---|
| Giannakopoulos *et al*[21], 2021 | Greece | Quality study-interviews | 12-17 years | 09 psychiatric inpatients | COVID-19 | Patients identified that the state of quarantine caused negative changes in personal freedom and social life, as well as excessive contact with family members during social isolation |
| Almhizai *et al* [22], 2021 | Saudi Arabia | Cross sectional study-online self-administered questionnaire | 0-17 years | 1141 respondents, 454 were < 18 years old and 688 children's parents | COVID-19 | Among the data presented, age was a factor for sleep disorders, nervousness and malaise; aggressive behaviors were also associated with an increase in negative behaviors during the pandemic compared to the previous period |
| Maunula *et al* [24], 2021 | Northern prairie communities, Canada | Multi-method study, focus groups, and interviews | Children grade 4-6 and their parents | 31 patients (16 children and 15 parents) | COVID-19 | Children were subjected to sudden and stressful changes in their routines. In addition, loneliness and increased screen time were a result of limited social interaction |

NDD: Neurodevelopmental disorder; TD: Typical developing; EBH: Emotional and behavioral health; EH: Emotional health; COVID-19: Coronavirus disease 2019.

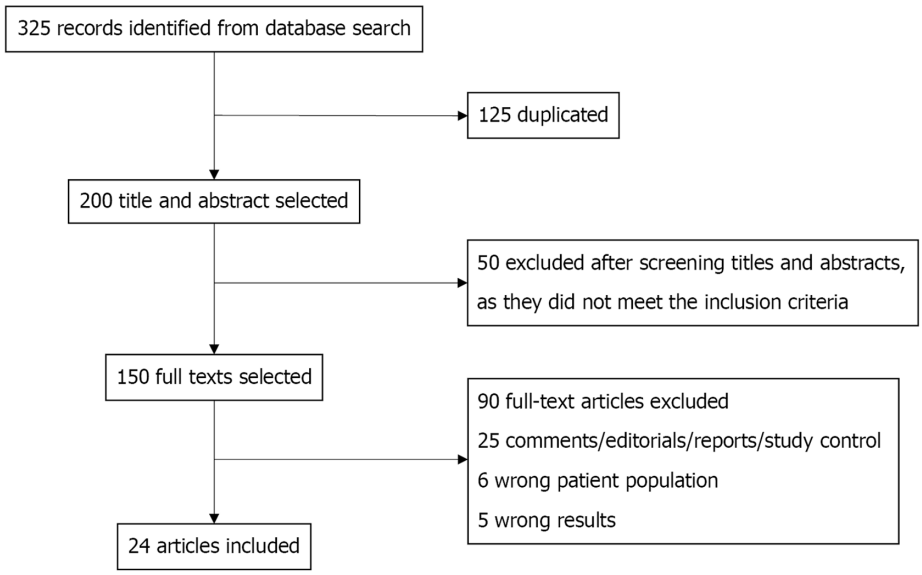


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**Figure 1 Diagram of preferred reporting items for systematic reviews and meta-analyses (PRISMA).**

could also pass on their psychological suffering to children and parent them inappropriately, contributing to the development of post-traumatic stress symptoms. In addition, if the C-A has a mental disorder, the psychic suffering of the parents tends to be greater and depends on the way children externalize their emotions[6,7].

Minozzi *et al*[14] highlight high rates of anxiety and depression among C-A. Among preschool children, they found aggravation of behavioral and emotional problems, while others did not. They found that psychological well-being had significantly worsened, especially among adolescents. Backer *et al*[15] demonstrate that the reduced number of social contacts associated with strict social distancing measures contributes to inflicting pain and psychic suffering in children and adolescents. The authors also point out that not wearing a mask; being a high school student[15] and spending less than 0.5 h exercising were positively associated with increased psychological distress[16].

A meta-analysis of 23 studies ($n$ = 57927 children and adolescents from Turkey and China) showed combined prevalence of anxiety, post-traumatic stress symptoms, sleep disorders and depression. In addition, female sex and adolescents were more associated with depressive and/or anxious symptoms when compared to male sex or children, respectively[18].

Barros *et al*[19] showed high rates of nervousness (48.7%) and sadness (32.4%) among Brazilian adolescents. Individuals aged between 15-17 years; being female; having learning difficulties during the pandemic; having a family that faces financial difficulties; and individuals who previously had trouble sleeping or poor health were the most affected. In the study by Han and Song[20] economic difficulties during the pandemic were correlated with depression and suicidal ideation. Concerning their emotions, adolescents recognized anxiety about self-harm and harm to their loved ones, as well as mood swings in

the family nucleus[21].

Globally, the increase in drug abuse has also been mapped in the literature, with alcohol and marijuana being the most used[7]. Almhizai *et al*[22] showed that the older age of children and adolescents was a risk factor for sleep disorders, malaise, and nervousness. The presence of a relative infected with COVID-19 was also associated with higher rates of anxiety, irritability, sadness, and sleep disorders. Finally, physical punishment and verbal threats had a more negative impact on the mental health promotion of C-A when compared to the pre-pandemic period.

### *Impact of control measures to contain the effect on the mental health of children and adolescents*

Eleven studies reported potential interventions to improve the mental health of children and adolescents[1,4,5,8-13,23,24].

Bussières *et al*[5] showed no association between the presence of previous chronic diseases (including NDD) and negative symptoms during the pandemic. Raffagnato *et al*[8] highlight that patients with internalizing disorders had better adaptation and lower rates of psychological distress when compared to patients with psychological distress.

In addition, the worsening of parents' mental health[10], school-age children belonging to urban racial and ethnical minorities[23], and physical inactivity[1,17] had a negative impact on the health of children and adolescents. Data from Li and Zhou[11] suggest that children less exposed to parental concerns (*e.g.*, about finances, health and education) were less likely to have internalizing and externalizing problems[11]. It is crucial to promote family well-being through political practices and initiatives, including providing financial and care assistance to parents and supporting the mental and behavioral health of families[9]. In addition to focusing on symptom management, families can benefit from support aimed at the parent-child relationship. Insights and implications for practitioners are discussed[12]. Finally, promoting coping strategies for children and adolescents to deal with extreme situations (*e.g.*, pandemics, wars, and natural disasters) is fundamental. Especially if the strategies encompass the communities/schools the children/adolescents attend[24].

## DISCUSSION

The rapid spread of COVID-19 has significantly influenced the psychological state of children and adolescents. It is clear that poverty[19,20], hunger, housing insecurity, domestic violence, and sexual abuse[19], black children and adolescents, and homeless people living in *favelas*, especially older adolescents, need urgent mental health support. The physical restrictions of the COVID-19 pandemic and the social distancing measures have affected all domains of life. Anxiety, depression, drug abuse, sleep and appetite disorders, as well as impaired social interactions, are the most common presentations [4,13].

The frequency of mask use and time spent on schoolwork were factors associated with good mental health[16]. The prevalence of depression ranges from 13.5% to 81.0%. Analysis by age indicated that the prevalence of depression is higher in children aged 5-9 years and adolescents aged 12-18 years. Analysis by gender showed that the prevalence of depression in females was higher than in males. The prevalence of anxiety among children and adolescents was 45.6%. The prevalence of post-traumatic stress symptoms is statistically higher in vulnerable and/or socially at-risk children and adolescents. The prevalence of sleep disorders varies according to the stressor involved in family ties and the way they face COVID-19, as well as the economic situation and the healthcare system, which vary greatly between countries[17]. Parental anxiety has the greatest influence on a child's psychological symptoms, explaining about 33% of the variation in a child's overall symptoms[18,23].

Most studies point to negative symptoms being caused by social distancing in children and adolescents of vulnerable families, including restrictions on social life and personal freedom, as well as excessive contact with family members during stay-at-home periods[1,2,21].

It is important to highlight that children and adolescents in extreme poverty report a wide range of negative thoughts associated with the pandemic (for example, abandonment, helplessness, sadness, anguish, anxiety, and feelings of panic). The thoughts and feelings of such teenagers can be triggered by the fact that their survival is threatened[4,5].

Special populations, especially lesbian, gay, bisexual, transgender, and queer (LGBTQ) adolescents, have higher rates of pain and psychological distress that lead to anxiety, depression, compulsion, and post-traumatic stress disorder (PTSD). Additionally, coming into conflicts with parents due to gender issues is observed in the literature as a factor that worsens mental health in this population[7,22].

## LIMITATIONS

Due to the short data collection period, from 2021 to 2022, relevant studies on how to care for the mental health of children and adolescents may be lacking. In addition, there is the possibility of publication bias, *i.e.*, only significant findings being published.

## CONCLUSION

Fear, anxiety, panic, depression, insomnia and appetite disorders, as well as impaired routine caused by psychic stress, are individual markers of pain and psychic suffering, which have increasing impacts on the mental health panorama of children and adolescents. A better understanding of the psychological pathways available is necessary to help clinicians, researchers, and decision makers prevent the deterioration of mental and general functioning disorders, as well as other stress-related disorders in children and adolescents[2,4,6,13].

Agreeing with Giannakopoulos *et al*[21] and Barros *et al*[19] professionals should continue to provide strategies to mitigate the impact of the pandemic on the mental health of children, adolescents and their families, aiming at improving the quality of life and rehabilitation in the post-pandemic period. It is necessary to emphasize the need to build resilience and promote strategies to manage negative feelings during crises (environmental, social, political, and economic)[24].

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## FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

# Investigating adolescent mental health of Chinese students during the COVID-19 pandemic: Multicenter cross-sectional comparative investigation

Bo-Wen Huang, Pei-Han Guo, Jian-Zhou Liu, Sean X Leng, Li Wang

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## Abstract

### *BACKGROUND*

The coronavirus disease 2019 (COVID-19) pandemic has caused significant challenges for adolescent mental health.

### *AIM*

To survey adolescent students in China to determine the effects of the COVID-19 pandemic on their mental health.

### *METHODS*

A multicenter cross-sectional comparative investigation was conducted in March 2022. We collected demographic information and survey data related to the COVID-19 pandemic. The Patient Health Questionnaire-9 and Generalized Anxiety Disorder Screener scales were used for objective assessment of depression and anxiety.

### *RESULTS*

We collected mental health questionnaires from 3184 students. The investigation demonstrated that adolescents most strongly agreed with the following items: Increased time spent with parents, interference with academic performance, and less travel. Conversely, adolescents most strongly disagreed with the following items: Not having to go to school, feeling an increase in homework, and not socializing with people; 34.6% of adolescents were depressed before COVID-19, of which 1.9% were severely depressed. After COVID-19, 26.3% of adolescents were prone to depression, of which 1.4% were severely depressed. 24.4% of adolescents had anxiety before COVID-19, with severe anxiety accounting for 1.6%. After COVID-19, 23.5% of adolescents were prone to anxiety, of which 1.7% had severe anxiety.

***CONCLUSION***

Chinese adolescents in different grades exhibited different psychological characteristics, and their levels of anxiety and depression were improved after the COVID-19 pandemic. Changes in educational management practices since the COVID-19 pandemic may be worth learning from and optimizing in long-term educational planning.

**Key Words:** Adolescents; Mental health; Chinese students; Grade analysis; COVID-19

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**Core Tip:** Our investigation found that the Chinese adolescents have different psychological characteristics at different grades, and their levels of anxiety and depression have improved since the coronavirus disease 2019 (COVID-19) pandemic. The partial educational management practices that have changed since the COVID-19 pandemic may be worth learning from and optimizing long-term educational planning.

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## INTRODUCTION

As of May 13, 2022, China had 1123709 confirmed cases of coronavirus disease 2019 (COVID-19), including 7247 cases in Guangdong, 2983 cases in Heilongjiang, and 2675 cases in Beijing (http://www.nhc.gov.cn/). The COVID-19 pandemic has dramatically impacted people's lives, affecting teenagers to the same extent as adults. A survey conducted in Shanghai revealed that some policy changes implemented in response to the COVID-19 pandemic had a range of impacts on students. Positive factors included an increase in the amount of time spent with parents, and the amount of time spent on personal matters. Negative impacts included not being able to go out to play and not seeing friends or classmates[1].

A meta-analysis of 5153 COVID-19 patients in 31 studies reported that the overall prevalence rates of depression, anxiety, and sleep disorders among individuals with COVID-19 were 45%, 47%, and 34%, respectively[2]. Lockdown measures in response to the coronavirus pandemic may have affected university students more than workers, with a survey of 400 people in Italy reporting that approximately one third of the sample exhibited symptoms of depression or anxiety[3]. Thus, students may represent a population that requires special care.

In a survey of 2031 college and graduate students in the United States, 48% reported experiencing depression, 38% reported experiencing anxiety, and 18% reported experiencing suicidal thoughts[4]. A British study of 2850 young people using the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder Screener (GAD-7) scales also found a significant increase in anxiety during the COVID-19 pandemic[5]. A GAD-7 online questionnaire answered by 89588 college students in Hainan, China, found that approximately two-fifths of college students experienced anxiety symptoms during the COVID-19 pandemic[6]. However, few large-sample multicenter investigations have examined mental health among primary school, junior high school, and senior high school students. No previous study has conducted a detailed subgroup analysis of the changes in the psychological health of samples of students in three different grades before and after the COVID-19 pandemic.

Therefore, we designed an online questionnaire that was administered to respondents in Heilongjiang, Beijing, and Guangdong, three provinces that run from north to south in China. We

examined respondents' basic information, changes in daily habits, and positive and negative impacts of the COVID-19 pandemic on study and life to determine whether the pandemic had worsened or improved depression and anxiety among students, and to understand the impact of the COVID-19 pandemic on adolescents using a systematic survey with a large sample.

## MATERIALS AND METHODS

### Recruitment

An online cross-sectional comparative survey was designed and conducted during a relatively steady phase of the COVID-19 pandemic in the late Spring 2022 semester in Beijing, Guangdong, and Heilongjiang. Our study population comprised primary school students, junior high school students, and senior high school students. An electronic form in the survey was used to obtain informed consent from all participants. We designed, conducted, and reported this survey following the acknowledged guidelines[7]. Respondents were recruited from the teenage population. Since the COVID-19 pandemic, some schools have adopted a combination of online and offline classes. Depending on the number of confirmed COVID-19 cases, provinces issued stay-at-home orders if necessary. The survey was published using the online survey platform WenJuanXing (WJX, https://www.wjx.cn/) in March 2022. WJX is a professional online questionnaire survey, examination, evaluation, and voting platform, which focuses on providing users with robust and humanized online questionnaire design, data collection, custom reports, and survey results analysis. The survey was released to more than 30000 students through WeChat groups or websites in several school districts.

### Investigation design

The investigation comprised multiple-choice questions and free-text fields for elaboration. The questionnaire consisted of the following four sections.

**Demographics:** This section included questions regarding participants' age, gender, and grade classification, which included primary school students, junior high school students, and senior high school students.

**Questions about changes in learning and life before and after the COVID-19 pandemic:** This section was designed to identify the positive and negative impacts of the pandemic, including the following items: Live with whom, time distribution, positive effects, and negative impacts. Because our preliminary survey results indicated that the COVID-19 pandemic had more negative than positive impacts, we divided the negative impacts into learning and life influences.

**PHQ-9:** The PHQ-9 is a validated and widely used measure of depression severity in mental health care, comprising nine items based on depression symptoms[8]. Respondents reported the frequency of symptoms experienced before and after the COVID-19 pandemic.

**GAD-7:** The GAD-7 is a validated questionnaire for major anxiety disorders, such as generalized anxiety disorder and panic disorder, consisting of seven items, on the basis of GAD symptoms[9]. Respondents rated the frequency of experiencing these symptoms before and after the COVID-19 pandemic.

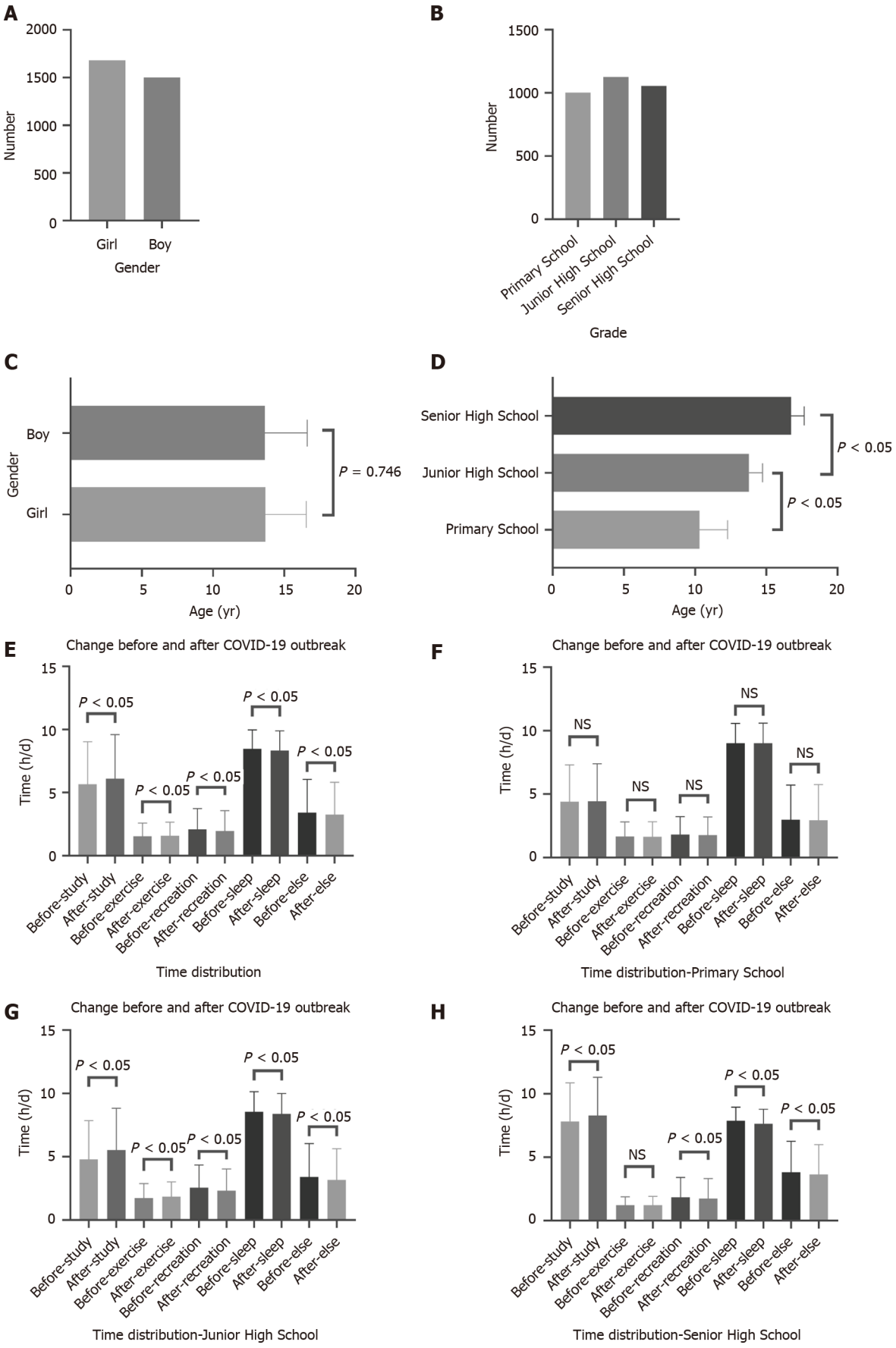
### Statistics analysis

Student's *t*-test, $\chi^2$ analysis, and Fisher's test were conducted, and a threshold of $P < 0.05$ was considered to indicate significant differences. The visualization tool used GraphPad Prism 8 and R 4.1.2.

## RESULTS

### Sample demographics

We collected 3273 questionnaires, of which 3184 were included in the analysis, with an effective rate of 97.28%. The sample included 1682 (52.8%) female respondents (Figure 1A). The sample included students in primary school ($n$ = 1002, 31.47%), junior high school ($n$ = 1126, 35.36%), and senior high school ($n$ = 1056, 33.17%) (Figure 1B). Participants' ages ranged from 6 to 19 years (mean: 13.67; SD: 2.92) (Figure 1C). Primary school students' ages ranged from 6–15 years of age (mean: 10.31; SD: 1.97), junior high school students' ages ranged from 9–18 years (mean: 13.79; SD: 0.95), and senior high school students' ages ranged from 13–19 years (mean: 16.74; SD: 0.93). There were significant differences in age distribution among the three cohorts (Figure 1D).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After-exercise
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After-recreation
Before-sleep
After-sleep
Before-else
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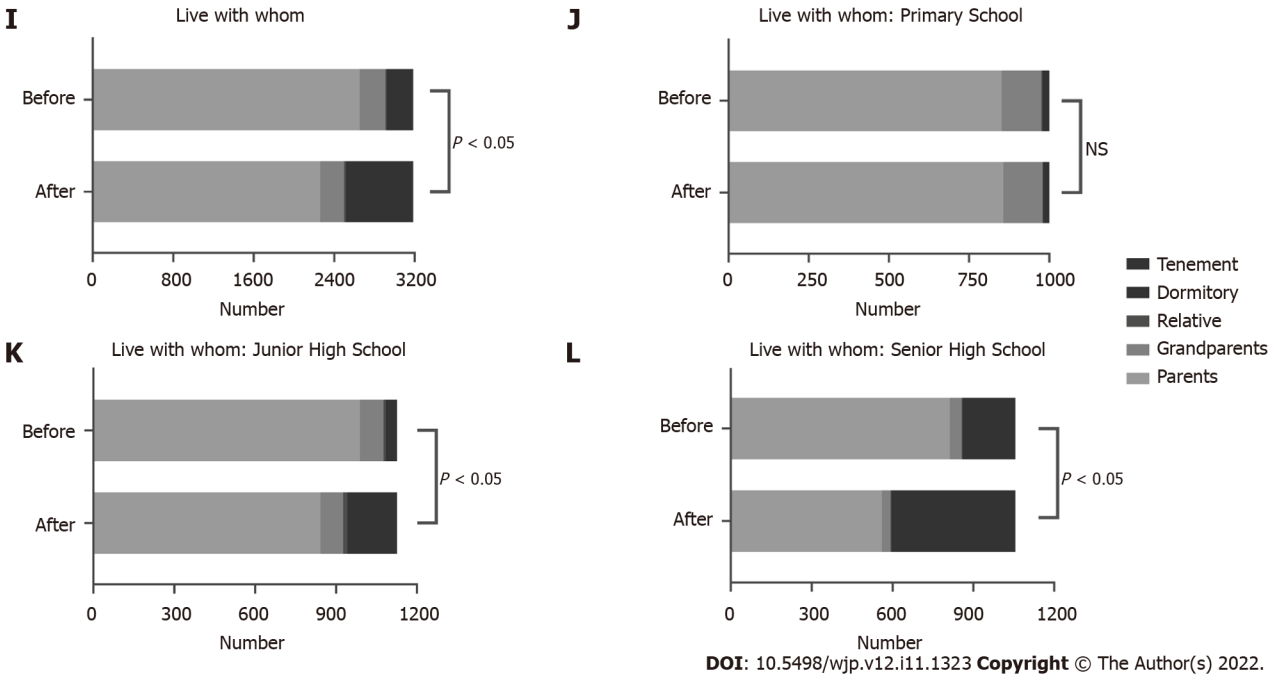


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**Figure 1 Basic characteristics of adolescents before and after the coronavirus disease 2019 pandemic.** A: Participants' gender; B: Participants' grade; C and D: Participants' age; E–H: Participants' time distribution; I–L: The teenagers lived with whom. COVID-19: Coronavirus disease 2019; NS: No significant.

### *Time distribution*

The time distribution of the study, exercise, recreation, sleep, and else exhibited a significant difference between before and after COVID-19 (Figure 1E). We further analyzed the different grades' subgroups and found no difference among primary school students (Figure 1F). Among junior high school students, more time was spent studying and exercising after the COVID-19 pandemic compared with before, whereas less time was spent on recreation, sleep, and else (Figure 1G). The same tendency was observed among senior high school students, except for exercise (Figure 1H).

### *Live with whom*

There has a significant difference in living with whom between before and after the COVID-19 pandemic (Figure 1I). Further analysis demonstrated no differences among primary school students (Figure 1J), but there are significant differences between junior high school and senior high school students (Figure 1K and L). The main change was that fewer students lived with their parents, and most lived on campus.

### *Positive effects*

Despite all of the inconveniences caused by COVID-19, the results revealed some positive impacts of the pandemic for adolescents (Table 1). Scores of −1 denoted "strongly disagree", −0.5 denoted "slightly disagree", 0 denoted "neutral", 0.5 denoted "slightly agree", and 1 denoted "strongly agree". We calculated approval scores for each item, and the proportion of people giving each response. The survey showed that participants in all grades unanimously approved of the following items: Increased time staying at home, increased time spent with parents, and increased time spent on personal matters. Conversely, the following items were unanimously disagreed with by participants in all grades: Do not have to go to school, and decreased monitoring by teachers.

### *Negative effects*

Ratings of −1 denoted "strongly disagree", −0.5 denoted "slightly disagree", 0 denoted "neutral", 0.5 denoted "slightly agree", and 1 denoted "strongly agree". We calculated statistical approval scores for each item, and the proportion of people giving each response.

### *Learning effects*

We examined the main academic-related concerns of adolescents (Table 2). The investigation demonstrated that the following items were unanimously approved of by participants in all grades: Worry about the future, and interference with academic performance. Conversely, all grade members unanimously disagreed with the following items: Difficulty concentrating, unable to adapt to online classes, and feeling an increase in homework. Regarding increased parents' monitoring, with age, adolescents gradually shifted from agreeing to disagreeing with this item.

**Table 1 The positive effects of the adolescents**

| | Mean point [-1,1] | Disagree | Agree |
|---|---|---|---|
| Do not have to go to school | | | |
| All | -0.307 | 50.5% | 15% |
| Primary school | -0.370 | 55.4% | 12.8% |
| Junior high school | -0.256 | 47.5% | 19% |
| Senior high school | -0.303 | 49.1% | 13.0% |
| Increased time staying at home | | | |
| All | 0.082 | 23.4% | 37.9% |
| Primary school | 0.021 | 27.2% | 34.4% |
| Junior high school | 0.149 | 21.7% | 43.2% |
| Senior high school | 0.070 | 21.7% | 35.6% |
| Increased time spent with parents | | | |
| All | 0.232 | 15.5% | 49.6% |
| Primary school | 0.157 | 18.0% | 43.8% |
| Junior high school | 0.342 | 13.1% | 58.0% |
| Senior high school | 0.185 | 15.9% | 46.0% |
| Increased time spent in personal stuff | | | |
| All | 0.159 | 18.7% | 42.9% |
| Primary school | 0.059 | 23.2% | 35.4% |
| Junior high school | 0.246 | 16.3% | 48.6% |
| Senior high school | 0.161 | 17.1% | 43.8% |
| Decreased teachers' monitoring | | | |
| All | -0.182 | 42% | 20.6% |
| Primary school | -0.248 | 47.6% | 18.4% |
| Junior high school | -0.163 | 41.4% | 22.3% |
| Senior high school | -0.140 | 37.2% | 20.9% |

### *Life influence*

Various lifestyle-related concerns are presented in Table 2. The results revealed that the following items were unanimously approved of by participants in all grades: Pay more attention to news reports, change in living environment, less travel, increased inconvenience of traffic, more difficulty in accessing hospital care. Conversely, the following items were unanimously disapproved of by participants in all grades: Do not socialize with people, reduce pocket money. Participants in different grades expressed different views on the following items: Distance from friends and less entertainment.

### *Severity of depression*

The PHQ-9 survey results are shown in Table 3. 34.6% of adolescents were depressed before the COVID-19 pandemic, of which 1.9% were severely depressed. The proportion of adolescents with depression was highest among senior high school students, at 39.8%. The proportion of adolescents with severe depression was highest among junior school students, at 3.5%. After the COVID-19 pandemic, 26.3% of adolescents exhibited depression, of which 1.4% were severely depressed. The highest proportion of adolescents with severe depression was observed among junior high school students, at 2.8%. The highest proportion of depressed students was observed among senior high school students, at 28.9%. Overall, depression improved among adolescents after the COVID-19 pandemic.

### *Severity of anxiety*

The GAD-7 scale results are shown in Table 4, 24.4% of adolescents had anxiety before the COVID-19 pandemic, with severe anxiety accounting for 1.6%. The highest rate of anxiety was among senior high school students, at 29.4%. The proportion of adolescents with severe anxiety was highest among junior

**Table 2 The negative factors of the adolescents**

| Learning effects | Mean point [-1,1] | Disagree | Agree | Life influence | Mean point [-1,1] | Disagree | Agree |
|---|---|---|---|---|---|---|---|
| Increased parents' monitoring | | | | Distance from friends | | | |
| All | 0.073 | 20.1% | 33.2% | All | -0.111 | 34.0% | 23.0% |
| Primary school | 0.165 | 17.5% | 44.4% | Primary school | 0.017 | 25.2% | 32.2% |
| Junior high school | 0.090 | 19.9% | 34.0% | Junior high school | -0.204 | 42.6% | 20.3% |
| Senior high school | -0.031 | 22.7% | 21.6% | Senior high school | -0.134 | 33.0% | 17.1% |
| Difficulty concentrating | | | | Don't socialize with people | | | |
| All | -0.098 | 34.3% | 24.6% | All | -0.243 | 44.5% | 14.6% |
| Primary school | -0.051 | 31.1% | 27.6% | Primary school | -0.160 | 38% | 18.3% |
| Junior high school | -0.185 | 42.2% | 21.0% | Junior high school | -0.353 | 54.3% | 12.7% |
| Senior high school | -0.051 | 28.9% | 25.6% | Senior high school | -0.205 | 40.2% | 13.1% |
| Worry about the future | | | | Less entertainment | | | |
| All | 0.065 | 25.3% | 37.1% | All | -0.02 | 27.1% | 26.7% |
| Primary school | 0.031 | 27.9% | 34.4% | Primary school | 0.076 | 21.1% | 34.1% |
| Junior high school | 0.101 | 25.8% | 42.0% | Junior high school | -0.119 | 36.4% | 21.9% |
| Senior high school | 0.058 | 22.2% | 34.5% | Senior high school | -0.005 | 22.9% | 24.7% |
| Interference with academic performance | | | | Reduce pocket money | | | |
| All | 0.108 | 23.4% | 40.6% | All | -0.209 | 37.4% | 11.1% |
| Primary school | 0.072 | 26.1% | 37.9% | Primary school | -0.192 | 34.9% | 10.8% |
| Junior high school | 0.160 | 23.3% | 46.2% | Junior high school | -0.243 | 43.9% | 13.9% |
| Senior high school | 0.086 | 21.0% | 37.1% | Senior high school | -0.187 | 33.0% | 8.2% |
| Unable to adapt to online classes | | | | Pay more attention to news reports | | | |
| All | -0.057 | 31.3% | 25.7% | All | 0.236 | 11.9% | 48.2% |
| Primary school | -0.027 | 30.5% | 28.8% | Primary school | 0.193 | 12.0% | 45.0% |
| Junior high school | -0.092 | 35.6% | 25.5% | Junior high school | 0.236 | 14.7% | 46.8% |
| Senior high school | -0.050 | 27.6% | 22.9% | Senior high school | 0.278 | 8.8% | 52.7% |
| Feel an increase in homework | | | | Change of living environment | | | |
| All | -0.167 | 35.3% | 14.4% | All | 0.091 | 18.5% | 35.1% |
| Primary school | -0.242 | 41.5% | 10.8% | Primary school | 0.119 | 15.9% | 37.6% |
| Junior high school | -0.160 | 38.5% | 18.8% | Junior high school | 0.067 | 23.4% | 34.3% |
| Senior high school | -0.105 | 26.0% | 13.3% | Senior high school | 0.090 | 15.7% | 33.6% |
| | | | | Less travel | | | |
| | | | | All | 0.317 | 13.4% | 53.7% |
| | | | | Primary school | 0.407 | 11.7% | 60.9% |
| | | | | Junior high school | 0.258 | 17.4% | 49.5% |
| | | | | Senior high school | 0.295 | 10.8% | 51.4% |
| | | | | Feel the traffic is inconvenient | | | |
| | | | | All | 0.072 | 20.8% | 32.2% |
| | | | | Primary school | 0.108 | 10.7% | 35.3% |
| | | | | Junior high school | 0.030 | 26.6% | 30.6% |

| | | | | |
|---|---|---|---|---|
| | Senior high school | 0.083 | 15.5% | 31.1% |
| | Hospital care is harder | | | |
| | All | 0.145 | 18.5% | 39.7% |
| | Primary school | 0.205 | 17.1% | 44.5% |
| | Junior high school | 0.095 | 23.4% | 37.7% |
| | Senior high school | 0.142 | 14.6% | 37.4% |

**Table 3 Comparison of Patient Health Questionnaire-9 responses before and after coronavirus disease 2019**

| | *n* | Mean (95%CI) | Level of severity, *n* (%) | | | | |
|---|---|---|---|---|---|---|---|
| | | | Minimal (0-4) | Mild (5-9) | Moderate (10-14) | Moderately severe (15-19) | Severe (≥ 20) |
| Before COVID-19 | | | | | | | |
| Whole sample | 3184 | 3.862 (3.685-4.043) | 2083 (65.4) | 779 (24.5) | 183 (5.7) | 78 (2.4) | 61 (1.9) |
| Primary school | 1002 | 3.329 (3.036-3.623) | 702 (70.1) | 227 (22.7) | 37 (3.7) | 24 (2.4) | 12 (1.2) |
| Junior high school | 1126 | 4.211 (3.863-4.560) | 746 (66.3) | 224 (19.9) | 83 (7.4) | 34 (3.0) | 39 (3.5) |
| Senior high school | 1056 | 4.001 (3.726-4.276) | 635 (60.1) | 328 (31.1) | 63 (6.0) | 20 (1.9) | 10 (0.9) |
| Post COVID-19 | | | | | | | |
| Whole sample | 3184 | 2.932 (2.763-3.102) | 2348 (73.7) | 607 (19.1) | 116 (3.6) | 67 (2.1) | 46 (1.4) |
| Primary school | 1002 | 2.277 (2.016-2.539) | 787 (78.5) | 175 (17.5) | 17 (1.7) | 16 (1.6) | 7 (0.7) |
| Junior high school | 1126 | 3.383 (3.046-3.719) | 810 (71.9) | 196 (17.4) | 54 (4.8) | 35 (3.1) | 31 (2.8) |
| Senior high school | 1056 | 3.074 (2.810-3.338) | 751 (71.1) | 236 (22.3) | 45 (4.3) | 16 (1.5) | 8 (0.8) |

**Table 4 Comparison of Generalized Anxiety Disorder Screener responses before and after coronavirus disease 2019**

| | *n* | Mean (95%CI) | Level of severity, *n* (%) | | | |
|---|---|---|---|---|---|---|
| | | | Minimal (0-4) | Mild (5-9) | Moderate (10-14) | Severe (15-21) |
| Before COVID-19 | | | | | | |
| Whole sample | 3184 | 2.465 (2.330-2.600) | 2408 (75.6) | 627 (19.7) | 98 (3.1) | 51 (1.6) |
| Primary school | 1002 | 1.984 (1.766-2.202) | 802 (80.0) | 168 (16.8) | 22 (2.2) | 10 (1.0) |
| Junior high school | 1126 | 2.598 (2.340-2.856) | 860 (76.4) | 186 (16.5) | 49 (4.4) | 31 (2.8) |
| Senior high school | 1056 | 2.780 (2.563-2.997) | 746 (70.6) | 273 (25.9) | 27 (2.6) | 10 (0.9) |
| Post COVID-19 | | | | | | |
| Whole sample | 3184 | 2.273 (2.133-2.412) | 2436 (76.5) | 584 (18.3) | 109 (3.4) | 55 (1.7) |
| Primary school | 1002 | 1.775 (1.557-1.994) | 813 (81.1) | 156 (15.6) | 23 (2.3) | 10 (1.0) |
| Junior high school | 1126 | 2.536 (2.262-2.809) | 856 (76.0) | 182 (16.2) | 48 (4.3) | 40 (3.6) |
| Senior high school | 1056 | 2.464 (2.246-2.682) | 767 (72.6) | 246 (23.3) | 38 (3.6) | 5 (0.5) |

high school students, at 2.8%. After the COVID-19 pandemic, 23.5% of adolescents were prone to anxiety, of which 1.7% were severely anxious. Senior high school students had the highest rate of anxiety, at 27.4%. The highest rate of severe anxiety was observed among junior high school students, at 3.6%. Thus, the results revealed that after the COVID-19 pandemic, the prevalence of anxiety was alleviated among senior high school students, whereas junior high school students were more severely affected. This issue deserves the attention of the education department.

## DISCUSSION

We collected mental health questionnaires from 3184 students. Participants' gender and grade were relatively evenly distributed in the sample. The COVID-19 pandemic led to significant changes in the schedules of junior high school and senior high school students, but had little impact on primary school students, possibly because junior high school and senior high school students are more likely to live in school accommodation. With age, adolescents allocate more time to study and less time to play and sleep. This bias may have been partially caused by the study period of approximately 2 years. Some students begin living in the school dormitory after entering a higher grade. To reduce the flow of students, some schools adopted a closed management mode.

In a survey of positive factors, participants most strongly agreed that they had spent more time with their parents since the COVID-19 pandemic. Additionally, participants disagreed most strongly that they did not have to go to school after the pandemic. Closing schools was not common practice in Chinese schools when the pandemic was not severe. A survey of negative effects revealed that adolescents most strongly agreed that the impact of COVID-19 on academic performance was relatively severe. Students' learning styles and efficiency may have changed significantly after the pandemic outbreak, and most students faced difficulty adapting. The most negatively rated factor was the increase in homework. The results suggested that the amount of homework for students after the outbreak was less than before. In terms of the impact on their lives, students most strongly agreed that they traveled less. After the outbreak of COVID-19, to avoid gathering together, most participants reduced the number of trips they took. As a non-essential entertainment activity, most participants reported having given up traveling. Students disagreed most strongly with the lack of communication with people, especially junior high school students. With the development of science and technology, although offline communication has decreased, online communication through WeChat and QQ may have become more frequent and intimate.

We note that some psychologists use the Patient Health Questionnaire for Adolescents (PHQ-A) scale to assess adolescents' mental health[10]. However, only a few studies have validated the PHQ-A under research conditions[11,12]. In contrast, the PHQ-9 has been extensively validated worldwide and has been confirmed as a practical and rigorous scale for all populations, including adolescents[13-16]. After careful consideration, our team adopted the PHQ-9 scale so that more researchers would be able to interpret the results. The PHQ-9 scale results suggested that the prevalence of depression among adolescents improved after the outbreak of COVID-19 compared with before the pandemic. One possible reason for this finding is that students' academic burden was reduced, and the measures taken to reduce the students' campus contact may have indirectly reduced bullying.

The GAD-7 scale results indicated a similar decrease in panic and anxiety among adolescents after COVID-19. Senior high school students exhibited a significant improvement in GAD symptoms. This finding may have been caused by the greater resilience of high school students as they get older, and the larger number of people living in the dormitory with less parental supervision. Anxiety symptoms among junior high school students were not alleviated after the COVID-19 pandemic, and a higher proportion of junior high school students reported worrying about the future and felt that their academic performance declined after the COVID-19 pandemic.

The current study provided new data regarding the mental health of Chinese adolescents. Several previous studies have examined adolescent mental health in other countries. A study in the United Kingdom of 886 adolescents revealed different effects on adolescents' mental health, depending on their mental health and socio-demographic background prior to the pandemic[17]. A survey conducted in the United States with 682 university students suggested that physical disruption was a significant risk factor for depression during the pandemic. However, short-term interventions to restore these habits were reported to be ineffective for improving mental health[18]. A sample of 1337 adolescents in the United Kingdom revealed a significant association between loneliness and concurrent mental health difficulties among adolescents in the United Kingdom at the start of the COVID-19 pandemic and lockdown. Teens that were closer to their parents had lower levels of emotional distress, and adolescents who spent more time texting others tended to have more symptoms of mental health difficulties[19]. A survey of 2224 people in the United States revealed that income loss during the pandemic adversely affected the worsening of depressive symptoms among adolescents[20]. COVID-19 home quarantine rules were suggested to have protective effects on adolescents' mental health in a survey of 322 predominantly Hispanic/Latinx youth in the United States[21]. A Dutch survey of 239 patients with rheumatoid arthritis reported that the COVID-19 pandemic had little psychological impact on patients with underlying conditions, possibly because general education and health care were available for most patients[22].

Some previous studies of adolescent mental health have been conducted in China. A study of 1241 primary and junior high school students in Anhui, China, reported that mental health was associated with the length of school closures caused by COVID-19, and that enforced social isolation by disease control measures was associated with future mental health problems among children and adolescents [23]. A survey of 687 people in Wuhan, China, revealed that by the end of the lockdown, levels of depression and anxiety had risen among a significant number of Chinese people, with students and other medical staff being most affected, while economic workers also experienced stress[24]. The mental

health of more than one in five middle and high school students in China was affected by the COVID-19 pandemic, according to a survey of a sample of 1025 middle and high school students in Guangzhou, China. The results indicated that resilience and actively responding can improve students' psychological and mental health. In contrast, negative coping is a risk factor for mental health[25]. A sample survey of 4342 primary and secondary school students from Shanghai, China, reported the coexistence of mental health problems and resilience among children and adolescents during the COVID-19 pandemic. Parent–child discussions can play an important role in addressing this issue, and parents and children should be encouraged to communicate openly about the pandemic[1]. An extensive survey of 11681 Chinese adolescents reported that non-only children were more likely than only children to experience symptoms of anxiety and depression during the COVID-19 pandemic, particularly those with fewer parent–child connections, low resilience, and experiences of emotional abuse[26]. However, the studies mentioned above did not completely cover the three grades of primary school, middle, and high school, and conducted systematic analysis of a large sample population of different grades.

Several limitations of this study should be acknowledged. We contacted schools in Beijing, Guangdong, and Heilongjiang provinces and distributed questionnaires online, hoping to collect representative samples in the central, southern, and northern regions. However, our sample is still not representative of all Chinese adolescents. In addition, the questionnaire collected double cross-sectional data before and after the pandemic in a single release, which may be biased compared with a prospective design for collecting data at two time-points. Unfortunately, we were not able to predict the course of the COVID-19 pandemic.

Our study had the following advantages. First, the sample size was relatively large compared with other published studies of adolescents. Additionally, we described the characteristics of the sample in detail and demonstrated the positive factors and negative impacts for adolescents in terms of life and learning before and after the COVID-19 pandemic. At the same time, to avoid subjective bias, we also used the PHQ-9 and GAD-7 scales for objective and quantitative assessment, increasing the reliability of the results. Moreover, we also carried out a statistical analysis of the adolescents divided into three groups according to grade. The characteristics of adolescents in different grades were discussed in detail to provide a theoretical basis for optimizing educational measures in different grades. Furthermore, the current study is the most comprehensive and detailed study of adolescent psychological health characteristics in different grades to date.

## CONCLUSION

The current results revealed a reduction in depression and anxiety among adolescents after the COVID-19 pandemic, except anxiety symptoms in junior high school students. Although this conclusion differs from the findings of most previous studies of this issue, it is supported by a small number of studies suggesting the need for a greater focus on students' mental health, rather than academic performance alone, when the COVID-19 pandemic is over and the public returns to ordinary life[21]. The partial educational management practices that have changed since the COVID-19 pandemic may be worth learning from and optimizing in long-term educational planning.

## ARTICLE HIGHLIGHTS

### *Research background*

The coronavirus disease 2019 (COVID-19) pandemic has severely affected adolescents' mental health.

### *Research motivation*

Based on the results, adolescent mental health interventions would be developed or adjusted.

### *Research objectives*

The study investigated the impact of the COVID-19 pandemic on the mental health of Chinese adolescents.

### *Research methods*

A multicenter cross-sectional comparative survey of Chinese adolescents was conducted in March 2022 to collect demographic information, survey data, Patient Health Questionnaire-9, and Generalized Anxiety Disorder Screener scale scores related to the COVID-19 pandemic.

### *Research results*

The investigation demonstrated that adolescents most strongly agreed with the following items: Increased time spent with parents, interference with academic performance, and less travel. Conversely,

adolescents most strongly disagreed with the following items: Not having to go to school, feeling an increase in homework, and not socializing with people; 34.6% of adolescents were depressed before COVID-19, after COVID-19, 26.3% of adolescents were prone to depression. 24.4% of adolescents had anxiety before COVID-19, and after COVID-19, 23.5% of adolescents were prone to anxiety.

### *Research conclusions*

After the COVID-19 outbreak, the anxiety and depression levels of Chinese adolescents in different grades have improved.

### *Research perspectives*

Changes in educational management practices since the COVID-19 pandemic may be worth learning from and optimizing long-term educational planning.

## FOOTNOTES

**Author contributions:** Huang BW and Guo PH contributed equally to this work; Huang BW conceived the project and wrote the manuscript; Guo PH designed the study and acquired data; Liu JZ analyzed data; Leng SX and Wang L edited the manuscript; and all authors contributed to the article and approved the submitted version.

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*REVIEW*

# Bipolar disorder in the International Classification of Diseases-Eleventh version: A review of the changes, their basis, and usefulness

Subho Chakrabarti

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## Abstract

The World Health Organization's 11th revision of the International Classification of Diseases (ICD-11) including the chapter on mental disorders has come into effect this year. This review focuses on the "Bipolar or Related Disorders" section of the ICD-11 draft. It describes the benchmarks for the new version, particularly the foremost principle of clinical utility. The alterations made to the diagnosis of bipolar disorder (BD) are evaluated on their scientific basis and clinical utility. The change in the diagnostic requirements for manic and hypomanic episodes has been much debated. Whether the current criteria have achieved an optimum balance between sensitivity and specificity is still not clear. The ICD-11 definition of depressive episodes is substantially different, but the lack of empirical support for the changes has meant that the reliability and utility of bipolar depression are relatively low. Unlike the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), the ICD-11 has retained the category of mixed episodes. Although the concept of mixed episodes in the ICD-11 is not perfect, it appears to be more inclusive than the DSM-5 approach. Additionally, there are some uncertainties about the guidelines for the subtypes of BD and cyclothymic disorder. The initial results on the reliability and clinical utility of BD are promising, but the newly created diagnostic categories also appear to have some limitations. Although further improvement and research are needed, the focus should now be on facing the challenges of implementation, dissemination, and education and training in the use of these guidelines.

**Key Words:** ICD-11 guidelines; Bipolar disorder; Utility; Reliability

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**Core Tip:** This review evaluates the clinical utility and the scientific basis for the changes made to the section on bipolar disorders in the 11th version of the International Classification of Diseases. The diagnostic requirements for many categories have changed. However, some of these alterations are still controversial based on the existing evidence. The examination of the reliability and utility of the newly created categories has yielded encouraging results, but certain limitations are evident. Thus, there is scope for further improvement, but the greater challenge will be to implement and disseminate the new guidelines and train the potential users of these guidelines.

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## INTRODUCTION

Bipolar disorder (BD) is a complex condition with several facets that influence its diagnosis and treatment[1,2]. Some of these aspects include early onset, a lifelong course characterized by frequent relapses and recurrences, inter-episodic morbidity consisting of residual symptoms, cognitive dysfunction, and functional impairment, high rates of psychiatric and medical comorbidity, and high risks for self-harm or violence. There is a predominance of depression, from the onset of the illness and throughout its course including the inter-episodic periods. Therefore, distinguishing BD from unipolar depression is difficult. The full spectrum of BD commonly includes milder and subthreshold disorders that overlap with normal variations of mood, personality, and other non-mood disorders. In contrast, the more severe forms such as psychotic BD are often indistinguishable from schizophrenia. These complexities mean that the accurate diagnosis and initiation of treatment are often delayed by several years.

In the absence of laboratory tests, the diagnostic process in psychiatry relies on signs, symptoms, and the course of psychiatric disorders[3-5]. Psychiatric classifications utilize these features to frame operational definitions that enhance the diagnostic accuracy of the disorders. Apart from naming and providing explicit descriptions of the disorders, psychiatric classifications also determine their place in the organizational structure. This provides a theoretical perspective that aids research regarding their scientific basis. The creation of classificatory systems in psychiatry has a long history and much effort is spent on revising them to keep pace with the recent advancements in the field.

The principal psychiatric classifications are the Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association and the International Classification of Diseases (ICD) of the World Health Organization (WHO). The fifth version of the DSM (DSM-5) has been published in 2013[6]. The WHO's 11th revision of the ICD (ICD-11) including the chapter on mental, behavioural, or neurodevelopmental disorders has come into effect from January 2022[7]. The draft versions of the ICD-11 guidelines including the one on mood disorders are available on the Global Clinical Practice Network (GCPN) website[8].

Revising the ICD is a part of the core responsibility of the WHO. Its Department of Mental Health and Substance Abuse was responsible for developing the ICD-11 guidelines for the chapter on mental, behavioural, or neurodevelopmental disorders[9-13]. The benchmarks for the revision of this ICD-11 chapter included attention to several guiding principles and priorities. These are summarized in Table 1.

This review focuses on the "Bipolar or Related disorders" section of the ICD-11, Clinical Descriptions and Diagnostic Requirements (CDDR) on mood disorders. It summarizes the changes that have been made in this section and attempts to evaluate the scientific basis and the usefulness of these changes.

## SUMMARY OF THE CHANGES MADE

### *New nomenclature and revised organizational structure*

The name of the section has been changed from mood (affective) disorders in the tenth revision of the ICD (ICD-10)[14] to mood disorders in the ICD-11 version. Consequently, the term "bipolar affective disorder" has become "bipolar disorder". This is appropriate since the word "affective" was redundant, while the label BD is more precise[15]. Additionally, the part on BD is now labelled "Bipolar or Related Disorders" which is similar to the DSM-5.

During their development, efforts were made to forge a comparable organizational structure for both the DSM-5 and the ICD-11 CDDR[16,17]. Reviews regarding the placement of BD concluded that considering the available evidence, the best possible solution would be an independent cluster for BD

**Table 1 Benchmarks for the revisions of the new classifications[9-13]**

| Principles and priorities | ICD-11-CDDR | DSM-5[1] |
|---|---|---|
| **Guiding principles** | | |
| Public health imperative | The guidelines should be useful in alleviating the global mental health burden, especially the burden in the low-and middle-income countries | The manual is meant to be used as a tool for collecting and communicating accurate public health statistics on mental disorders |
| Clinical imperative | Clinical and public health utility were accorded the greatest priority followed by scientific validity | Clinical utility was accorded the highest priority followed by the scientific evidence |
| Stakeholders | The guidelines are meant for use in all countries, for all professionals, and for all service users | The manual is meant for all professionals and service users |
| Multiple uses | The guidelines are meant for clinical, research, teaching, and training purposes, and for collecting data | The manual is meant for clinical, research, teaching, and training purposes, and for collecting data |
| Settings | The guidelines are meant for all settings including specialist and primary-care settings, with special emphasis on primary-care settings in low-and middle-income countries | The manual should be applicable to all settings including specialist, primary-care, community, and forensic settings |
| Cross-cultural applicability | The revision should be relevant and acceptable to clinicians from all cultures | Cultural aspects relevant to the diagnosis was a key consideration |
| **Priorities** | | |
| Global applicability | Global and universal applicability: The guidelines should be relevant for all countries, all stakeholders, and in all settings | Professionals from 39 countries were involved in developing the scientific basis of the diagnostic criteria |
| Clinical utility | Clinical and public-health utility was accorded the highest priority during the process of revision | The manual is primarily intended for clinical use and should be feasible for clinical practice |
| Scientific validity | The scientific basis should be based on best available evidence. Compromises for the sake of utility should be avoided | The revision was guided by a thorough review of the best scientific evidence |
| Harmonization | Efforts to harmonize the ICD-11 revision with the DSM-5 involved enhancing similarities and minimizing arbitrary differences between the two systems | The APA collaborated with the WHO to develop a common and globally applicable research base for the DSM-5 and the ICD-11 disorders |

[1]The priorities of the DSM-5 classification were quite similar to those of the ICD-11.

APA: American Psychiatric Association; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition[6]; ICD-11-CDDR: International Classification of Diseases, 11th version, Clinical Descriptions and Diagnostic Requirements[8]; WHO: World Health Organization.

[18,19]. The DSM-5 thus created a separate chapter for BD. The ICD-11 organization was also influenced by these efforts and its structure is largely similar to that of the DSM-5[13,20]. However, the ICD-11 configuration was also determined by surveys of mental health professionals and studies examining their conception of a more clinically useful structure[13,21-24]. The structure of mood disorders in the ICD-11 was changed based on these studies. The "Mood Disorders" section was retained to refer to a "superordinate" grouping of bipolar and depressive disorders. This avoided cutting the cord between BD and depressive disorders, which belong to the same spectrum[25,26]. Following the spectrum approach, the ICD-11 has grouped cyclothymia with BD. The "Mood Disorders" section opens with the definitions of mood episodes. The longitudinal pattern of mood episodes determines the diagnosis of either depression or BD[13]. This simpler and more clinically useful "building blocks" approach to diagnosing mood disorders[27] is in line with the DSM-5.

### *Manic and hypomanic episodes*

The descriptions of manic and hypomanic episodes in the ICD-11 guidelines differ substantially from the ones in the ICD-10 but are analogous to those in the DSM-5[6,28]. This is depicted in Table 2.

There are only minor differences between the two classifications. Nevertheless, the ICD-11 definitions are somewhat broader than the DSM-5 ones. This is the result of a flexible diagnostic approach used by the ICD-11 CDDR, which avoids rigid and often arbitrary cut-offs imposed in the DSM-5[29]. The requirements for a minimum number of accessory symptoms for mania and hypomania and a minimum duration of symptoms for hypomania have been avoided. This circumvents many difficulties associated with these diagnoses[30]. Moreover, it places greater emphasis on exercising clinical judgment and therefore resembles the diagnostic process in everyday practice[31,32]. The differences in the two diagnostic approaches also reflect the differences between the prototype-based methods followed by the ICD-11 guidelines in contrast to the operational diagnostic criteria used by the DSM-5[33-37]. Although prototype-based methods are not infallible, they are often more congruent with the clinician's diagnostic practices and therefore preferred by them. They are less complex and cumbersome than the operational criteria, but equally reliable and useful in diagnosing mood disorders. The ICD-11 guidelines attempted

**Table 2 Comparison of diagnostic criteria for manic and hypomanic episodes**

| | ICD-11-CDDR | DSM-5 |
|---|---|---|
| **Manic episode** | | |
| Gate/entry level criteria | Both extreme and persistent mood changes (euphoria, irritability, expansiveness, mood lability) and abnormally increased activity or subjective experience of increased energy | Both abnormal and persistent mood changes (elevated, expansive, or irritable) and abnormal and persistent increase in goal-directed activity or energy[1] |
| Accessory criteria | Significant changes in several of the following seven areas: talkativeness/pressured speech, flight of ideas/racing thoughts, increased self-esteem/grandiosity, decreased need for sleep, distractibility, impulsive/reckless behaviour, increased sexual or social drive/increased goal directed activity | Significant and noticeable changes in three of the seven accessory symptoms; four if mood is only irritable; accessory criteria almost identical to the ICD-11 definition |
| Persistence and duration | Symptoms present most of the day, nearly every day for a minimum of one week unless shortened by treatment | Symptoms present most of the day, nearly every day for a minimum of one week unless shortened by hospitalization |
| Functional impairment | Significant impairment in all the areas of functioning; the patient may require intensive treatment/hospitalization to prevent self-harm or violence; the episode may be accompanied by psychotic symptoms | Significant impairment in all the areas of functioning; the patient may require hospitalization to prevent self-harm or violence; the episode may be accompanied by psychotic symptoms |
| Exclusions | Mania secondary to medical conditions or substance use; mixed episodes excluded | Mania secondary to medical conditions or substance use; manic episodes with mixed features allowed |
| Effects of antidepressant treatment | The episode should be considered a manic one if all the criteria are met even after the effects of treatment have diminished | The episode should be considered a manic one if all the criteria are met even after the effects of treatment have diminished |
| Grading of severity | Severity not graded | Severity graded as mild, moderate, or severe based on the number of symptoms, their intensity, and functional impairment |
| Psychotic symptoms | No distinction between mood-congruent and incongruent symptoms | Mood-congruent and incongruent symptoms distinguished |
| **Hypomanic episode** | | |
| Gate/entry criteria | Both persistent mood changes (elevation, irritability, mood lability) and abnormally increased activity or subjective experience of increased energy that are significantly different from the usual mood state; changes are apparent to others and do not include changes that are appropriate to the circumstances[2] | Both abnormal and persistent mood changes (elevated, expansive, or irritable) and abnormal and persistent increase in activity or energy; changes in mood differ significantly from the usual state and are apparent to others |
| Accessory criteria | Significant changes in several of the seven accessory symptoms that are identical to the definition of mania; these changes are apparent to others | Significant and noticeable changes in three of the seven accessory symptoms, four if mood is only irritable; accessory criteria are the same as those for mania and almost identical to the ICD-11 definition |
| Persistence and duration | Symptoms present most of the day, nearly every day for at least several days | Symptoms present most of the day, nearly every day for a minimum of four consecutive days |
| Functional impairment, hospitalization, and psychotic symptoms | Socio-occupational functioning is not markedly impaired; the patient does not require intensive treatment or hospitalization to prevent self-harm or violence; the episode is not accompanied by psychotic symptoms | Clear change in socio-occupational functioning from the usual state apparent to others, but functioning is not markedly impaired; the patient does not require hospitalization to prevent self-harm or violence; the episode is not accompanied by psychotic symptoms |
| Exclusions | Hypomania secondary to medical conditions or substance use; mixed episodes are excluded | Hypomania secondary to substance use[3]; hypomanic episodes with mixed features allowed |
| Effects of antidepressant treatment | The episode should be considered a hypomanic one if all the criteria are met even after effects of treatment have diminished | The episode should be considered a hypomanic one if all the criteria are met even after effects of treatment have diminished; however, full syndromal manifestation of hypomania is necessary |

[1]Updated in 2015 to persistent increase in activity or energy ("goal-directed" removed)[28].
[2]In the ICD-11 CDDR, the word "extreme" is not used to describe the mood change in hypomania as in manic episodes, possibly denoting a reduced severity of mood alterations; no such distinction is present in the DSM-5.
[3]Updated in 2015 to include hypomania secondary to medical conditions[28].
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition[6]; ICD-11-CDDR: International Classification of Diseases, 11th version, Clinical Descriptions and Diagnostic Requirements[8].

to enhance the utility of the prototype approach by using a standardized content form that contained systematic and consistent diagnostic information for all disorders[10,13].

The expanded gate criterion is the most important alteration in the definitions of mania and hypomania both in the ICD-11 CDDR and the DSM-5. It was not present in the earlier versions of both these classifications including the ICD-10 guidelines. Changes in both mood and activity or energy are mandatory for the diagnosis now. This change was made to improve the diagnostic accuracy, specificity, and reliability of mania and hypomania[13,38-40]. It was also meant to differentiate the diagnoses from normal mood fluctuations, particularly in the case of hypomania. The intention was to prevent the overdiagnosis of manic or hypomanic episodes as well as BD. Simultaneously, this change aimed to facilitate earlier detection of BD by minimizing the under-reporting of hypomania in those with major depression.

Adding overactivity to mood symptoms is evidence-based and considered to be a well-founded change[30,38,41-43]. The empirical support for including hyperactivity as a core criterion derives from factor-analytic investigations of mania and large-scale community studies of BD. Recent reviews of the factor-analytic studies of mania have indicated that overactivity is the most prevalent symptom of this condition[44,45]. It is more common than mood changes and is associated with several other key symptoms of mania. Although community-based studies have also shown that any of the three criteria, euphoria, irritability, and overactivity, are sufficient for diagnosing mania or hypomania, overactivity is the foremost diagnostic criterion with the maximum sensitivity[46-50]. In contrast, there is less evidence for irritability being an entry-level criterion for mania or hypomania. Irritability is common in many other disorders and is not specifically associated with mania or hypomania. Moreover, it is rarely associated with overactivity[30,40,41]. The ICD-11 draft also includes lability of mood as a symptom of mania and hypomania, but its diagnostic role is not clear. Although there is a high prevalence of mood lability during manic episodes[51], very few factor-analytic studies have found it to be an important constituent of mania[45].

Additionally, the inclusion of antidepressant treatment-induced prolonged manic or hypomanic switches is also reasonable because such switches occur mainly in those predisposed to bipolarity[41,49,52]. In contrast, the exclusion of mood episodes secondary to medical conditions or substance use is considered faulty because it is based on causal attributions[53]. Lastly, the ICD-11 guidelines have added functional impairment to the definition of mania to bring it more in line with the DSM-5. The ICD-10 had avoided using functional impairment as a diagnostic requirement because cultural factors were thought to confound socio-occupational performance. However, the ICD-11 has included impaired functioning as a part of the diagnosis because it helps in distinguishing mood disorders from normal mood changes, determining their severity, and improving their clinical utility[5,9,10].

The change that has generated the maximum debate is the diagnostic requirement of combined mood changes and overactivity for mania and hypomania. Proponents of this change have insisted that the combination provides an optimal balance between diagnostic specificity and sensitivity[42,43]. Moreover, the higher diagnostic threshold reduces the chances of a false positive diagnosis of BD. They argue that an incorrect diagnosis of BD may be more harmful than being falsely diagnosed with major depression. However, the majority of the other researchers feel that this requirement is too restrictive [31,39,41,53,54]. They believe that the dyadic criterion decreases the chances of diagnosing mania and hypomania. Consequently, the prevalence of type I BD (BP-I) or type II BD (BP-II) will decline because many patients will be relegated to the categories of subthreshold BD or major depression. They point out that community studies of BD have demonstrated that either mood change or overactivity is sufficient for the diagnosis. Thus, using either mood change or overactivity as entry-level criteria could increase the sensitivity of the manic and hypomanic diagnoses without affecting the prevalence of BD [29,40,53]. These contrasting propositions have been examined in some studies on the prevalence of BD using the DSM-5 and ICD-11 criteria. These are included in Table 3.

This table shows that prevalence studies using the DSM-5 criteria are far more common. Only one study has considered the ICD-11 guidelines. Angst *et al*[31] (2020) used the ICD-10, DSM-5, and the ICD-11 criteria to re-analyse the prevalence of mania and hypomania according to the Zurich cohort study. They proposed that the rate of hypomania will be doubled with the ICD-11 criteria compared to the ICD-10 and the DSM-5. This was presumably because of the broader definition of hypomania in the ICD-11 and the inclusion of patients with antidepressant-induced prolonged hypomanic switches. The lifetime prevalence of DSM-5 defined BD appears to be unchanged[55-58]. In contrast, several DSM-5-based studies have found about a 20%-60% reduction in the point prevalence of manic and hypomanic episodes or BD[38,59-61]. In these studies, patients diagnosed according to the DSM-5 criteria had more severe manic symptoms[40,59,61] than those diagnosed with DSM-IV criteria[62,63]. Moreover, these studies suggested that the prevalence with DSM-5 criteria was lowest early in the course of BD and increased with time[38,58,59]. This was confirmed by the study of newly diagnosed patients with BD, in which the rate of DSM-5 BD was reduced by 62% at the baseline, but only by 50% on long-term follow-up[61]. This is because newly diagnosed patients are a more heterogenous group and are less likely to meet the stricter DSM-5 definitions than those with more chronic illnesses[40]. Thus, the reduction in the prevalence of BD attenuated with time and there were no differences in the lifetime rates or clinical characteristics of mania, hypomania, and BD diagnosed with DSM-5 or DSM-IV criteria[39,40,61]. These findings imply that although the DSM-5 criteria may prevent overdiagnosis of BD as intended, patients with less severe and recent-onset BD may be missed[40]. Extrapolating from these results, it appears that although the short-term prevalence of BD may be reduced, the long-term prevalence of BD is likely

**Table 3 Prevalence of bipolar disorder according to the International Classification of Diseases, 11th version and the Diagnostic and Statistical Manual of Mental Disorder, 5th edition criteria**

| Ref. | Criteria sets | Patients | Bipolar types | Type of prevalence | Results regarding the prevalence of BD |
|---|---|---|---|---|---|
| **No change in the prevalence of bipolar disorder** | | | | | |
| Fassassi *et al* [55], 2014 | DSM-5 | Community-based | BP-I, BP-II, Other BD[1] | 12-mo and lifetime | Prevalence similar to earlier studies of BD |
| Calvó-Perxas *et al*[56], 2015 | DSM-5 | Community-based | BP-I, BP-II, Other BD | Lifetime | Prevalence was within the range of previous reports of BD |
| Blanco *et al*[57], 2017 | DSM-5 | Community-based | BP-I | Lifetime | Prevalence was within the range of previous reports of BD |
| Gordon-Smith *et al*[58], 2017 | DSM-IV and DSM-5 | Community-based and outpatients | BP-I, BP-II | Lifetime | Up to 94% of the patients with DSM-IV BD also met the DSM-5 criteria |
| **Decrease in the prevalence of bipolar disorder** | | | | | |
| Angst *et al*[53], 2013[2] | DSM-5 | Analysis based on a previous community study (BRIDGE) | BD | Lifetime | About 22% reduction in prevalence |
| Machado-Vieira *et al*[38], 2017 | DSM-IV and DSM-5 | Outpatients | Maniaand hypomania | Point prevalence | The prevalence of mania and hypomania according to the DSM-5 criteria was reduced by about 50% |
| Fredskild *et al* [59], 2019 | DSM-IV TR and DSM-5 | Outpatients | Maniaand hypomania | Point prevalence | A reduction of 35% in the prevalence of mania and hypomania with the DSM-5 criteria was noted |
| Faurholt-Jepsen *et al*[60], 2020 | DSM-5 | Patients taking part in trials | Mania and hypomania | Smartphone-based activity assessments over 6-9 mo | The prevalence of hypomania according to the DSM-5 criteria was substantially less (0.12%) than patients not meeting these criteria (24%) |
| Fredskild *et al* [61], 2021 | DSM-IVand DSM-5 | Outpatients | Mania and hypomania | Assessments at baseline and at 3-year follow-up | The prevalence of mania and hypomania according to the DSM-5 criteria was reduced by 62% at baseline and by 50% on follow-up |
| **Increase in the prevalence of type II bipolar disorder** | | | | | |
| Angst *et al*[53], 2013[3] | DSM-5 | Analysis based on a previous community study (BRIDGE) | BP-II | Lifetime | Prevalence of BP-II disorder will be twice as much with the DSM-5 than earlier |
| Angst *et al*[31], 2020[4] | ICD-10, DSM-5, and ICD-11 | Analysis based on an earlier community study (Zurich cohort study) | Mania (BP-I) and hypomania (BP-II) | Lifetime | Prevalence of hypomania (BP-II) will be doubled with the ICD-11 criteria compared to the ICD-10 and the DSM-5 criteria; no change in the prevalence of mania (BP-I) is likely |

[1]The Other BD group refers to the "Other Specified Bipolar and Related Disorders" category of the DSM-5.
[2]This reduction is proposed to be a consequence of the mandatory requirement for both mood changes and overactivity.
[3]The increase in prevalence is proposed to be a consequence of inclusion of patients with antidepressant-induced prolonged hypomanic switches.
[4]The increase in prevalence is proposed to be a consequence of a somewhat broader definition of hypomania in the ICD-11 and the inclusion of patients with antidepressant-induced prolonged hypomanic switches.
BD: Bipolar disorder; BP-I: Type I bipolar disorder; BP-II: Type II bipolar disorder; BRIDGE: Bipolar disorders: Improving diagnosis, Guidance, and Education[49]; DSM-IV/DSM-IV TR: Diagnostic and Statistical Manual of Mental Disorders, 4th edition/Text revision[62,63]; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition[6]; ICD-10: International Classification of Diseases, 10th version[14]; ICD-11: International Classification of Diseases, 11th version[8].

to remain unchanged despite the use of the new definitions in the ICD-11 CDDR[39,40,61].

The description of hypomanic episodes in the ICD-11 draft brings it closer to the DSM-5 definition in several aspects. Both distinguish mania from hypomania based on the lack of marked functional impairment, no requirement for hospitalization, and the absence of psychotic symptoms in hypomania. However, these distinguishing features of hypomania are not without their problems. For example, the lack of marked impairment in functioning is often difficult to make out with certainty[64-66]. There are no clear criteria to determine the level of impairment and it is often a subjective judgement on the part of the clinician. Moreover, many patients with hypomania report an improvement in their functioning. Similarly, the decision to hospitalize someone with hypomania is often determined by several cultural, socioeconomic, or health-service-related factors than simply by the lesser clinical severity of the episode [31,65,67]. In some instances, those with hypomania are more likely to be hospitalized than those with mania[65]. Lastly, there is some evidence of an association between psychosis and hypomania, particularly from longitudinal community-based studies[68,69]. Then again, other studies have shown that

patients with hypomania/BP-II disorder are much less likely to experience psychotic episodes or be hospitalized because of psychosis than those with BP-I disorder[66].

Finally, the issue that has been the bone of contention for a long time is the requirement for a minimum duration of 4 d for hypomania in the DSM-5. The existing evidence derived mainly from large community studies shows that there is no difference between hypomanic episodes lasting less or more than 4 d in terms of prevalence, clinical features, and associated impairment[29,53,54,65,66]. However, the proposal to include short-lasting hypomanic episodes was not accepted by the DSM-5 because of concerns about the overdiagnosis of BD[29]. Nevertheless, the DSM-5 has included some of these short-lasting presentations in the category of "Other Specified Bipolar and Related Disorders" and its section three as a condition for further study. By defining the minimum duration as "several days", the ICD-11 guidelines seem to have avoided this controversy, but they are likely to have the same limitations as the DSM-5 in the other criteria for hypomania[65]. It is also unclear whether the lack of clear thresholds will hamper the clinical utility of the ICD-11 diagnosis[70].

### *Depressive episodes and bipolar depression*

The ICD-11 CDDR has made many changes to the definition of the ICD-10 depressive episode so that the ICD-11 description corresponds to the DSM-5 definition[13,29,30]. These changes are shown in Table 4.

There are certain minor differences between the ICD-11 and DSM-5 definitions, but the major difference is the inclusion of the "bereavement exclusion" criterion while diagnosing depression in the ICD-11 draft[29,30]. The DSM-5 has been widely criticized for removing the (operationally defined) "bereavement exclusion" criterion and supplanting it with the application of clinical judgement. The ICD-11 has followed the DSM-IV approach in setting a higher threshold in terms of duration and severity while diagnosing depression in the context of bereavement. Nevertheless, the subject of "bereavement exclusion" remains controversial, with some justifying its removal[71,72] and others claiming its retention to be more in agreement with the evidence[73,74].

Another problem is that the definitions of depressive episodes in the ICD-11 and the DSM-5 lack empirical support[29,75,76]. These definitions arbitrarily impose a categorical threshold on what is essentially a dimensional concept. Accordingly, the distinction between major depression and normality, minor depression, and severe melancholic depression is unclear. The functional impairment criterion does not resolve this threshold problem. Therefore, major depression is a heterogenous category both in terms of the diagnostic criteria and the patients meeting these criteria. Moreover, it has been shown that the current definitions do not include the most important symptoms and that simpler definitions of major depression may be more appropriate. All these limitations lead to poor reliability and clinical utility of the current category.

The definitions of unipolar depression and bipolar depression are identical in both the ICD-11 and the DSM-5[29,54]. This is primarily because the existing evidence indicates that there are no characteristic features that could distinguish the two categories[77-79]. However, certain symptoms, course characteristics, and family history are more common in either unipolar or bipolar depression and in those with unipolar depression who convert to BD. These features could be used to distinguish between unipolar or bipolar depression[77]. Although this "probabilistic" approach might have reasonable predictive power[80,81], there are obvious difficulties in incorporating such a scheme in the current classifications. Nevertheless, the lack of distinction between unipolar and bipolar depression is problematic, because one of the reasons that the diagnosis of BD is often missed is the inability to distinguish between the two types of depression[82].

### *Mixed episodes*

Mixed states consist of an admixture of the usual manic and depressive symptoms along with certain characteristic features such as agitation, irritability, and hostility[83-87]. More than a third (30%-70%) of the patients with BD present with mixed mania or mixed depression. Mixed states are associated with a more severe form of BD, higher comorbidity, poorer course and outcome, inadequate treatment response, higher disability, and greater risk of suicide.

The DSM-IV TR definition of mixed episodes was thought to be too restrictive because it required the concurrent presence of full manic and depressive syndromes. Since the most common presentation of mixed episodes is subsyndromal with a few symptoms of the opposite polarity, the DSM-5 replaced mixed episodes with a "mixed features" specifier[83]. This was defined by the presence of a full mood episode of one polarity accompanied by at least three contrapolar symptoms, excluding those common to both kinds of episodes (overlapping symptoms). The DSM-5 also made it possible to use the specifier for major depressive episodes because of the high rates of subthreshold bipolarity in unipolar depression. It was anticipated that this definition would be better at capturing the subsyndromal manifestations of mixed presentations in BD[82,83]. Indeed, studies showed that with the use of the new DSM-5 specifier, mixed presentations were about three times more common than those with the DSM-IV TR[85,87]. However, several problems with the new specifier have gradually become apparent. The DSM-5 decision to leave out overlapping symptoms has often led to the exclusion of symptoms that are considered to be central to the presentation of mixed states. Several reviews on the subject have pointed out that psychomotor agitation is the principal component of these core features, followed by irritability

**Table 4 Changes to the diagnostic guidelines for bipolar depression in the International Classification of Diseases, 11th version**

| | ICD-11-CDDR | DSM-5 | ICD-10 |
|---|---|---|---|
| Core symptoms | One of the following: Depressed mood or diminished interest or pleasure | One of the following: Depressed mood or loss of interest or pleasure | Two of the following: Depressedmood, loss of interest and enjoyment, and reduced energy leading to increased fatiguability, diminished activity, and marked tiredness |
| | Reported or observed changes | Reported or observed changes | |
| | Change from usual functioning | Change from usual functioning | |
| Accessory symptoms | Eight symptoms including the new symptoms of hopelessness, fatigue, and agitation/retardation | Seven symptoms: Hopelessness is not included, but fatigue and psychomotor changes are included | Seven symptoms: Bleak and pessimistic views of future instead of hopelessness, no psychomotor changes or fatigue that are part of the core symptoms |
| | Other symptoms (unchanged) are inattentiveness, changes in sleep and appetite, low self-worth or guilt, and suicidal ideation | Other symptoms are the same as in the ICD-11 | Other symptoms are the same as in the ICD-11 |
| Persistence and duration | Symptoms occur most of the day, nearly every day during a minimum period of two weeks | Symptoms occur most of the day, nearly every day during a minimum period of two weeks | Minimum duration of two weeks usually required but shorter periods suffice if symptoms are unusually severe and of rapid onset |
| Diagnostic threshold | Five out of ten symptoms | Five out of nine symptoms | Four out of ten symptoms |
| Functional impairment | Part of the diagnostic criteria | Part of the diagnostic criteria | Used to rate severity |
| Exclusions | Depression secondary to medical conditions or substance use and mixed episodes; mixed episodes excluded | Depression secondary to medical conditions or substance use; diagnosis of depressive episodes with mixed features possible | No clear exclusions |
| Bereavement exclusion | Operationalized definition present | Only an explanatory note that advises the use of clinical judgement in such instances | Not mentioned as a part of the diagnostic guidelines |
| Severity ratings | Mild, moderate and severe depressive episodes based on symptom-severity and functional impairment; no requirement for a minimum number of symptoms | Grading similar to the ICD-11; no requirement for a minimum number of symptoms | Grading similar to the ICD-11, but a minimum number of symptoms required for grading different levels of severity; clinical judgement also advised |
| Psychotic symptoms | Moderate depression with psychotic symptoms is a new category | Mood congruent and incongruent symptoms distinguished | Mood congruent and incongruent symptoms distinguished |
| Description of melancholia | Descriptions similar to the ICD-10, but no requirement for a minimum number of symptoms | Description more elaborate; a minimum of four symptoms required | Descriptions similar to the ICD-11; a minimum of four symptoms required |
| Additional specifiers | With prominent anxiety, panic attacks, chronicity, seasonal pattern, puerperal onset | Similar to the ICD-11; additionally mixed features, atypical features, and catatonia | No other specifiers |

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition[6]; ICD-10: International Classification of Diseases, 10th version[14]; ICD-11-CDDR: International Classification of Diseases, 11th version, Clinical Descriptions and Diagnostic Requirements[8].

or hostility (dysphoric mood), mood lability, and distractibility[86-90]. Although these features are more prominent in mixed manic episodes, they are present in both mania/BD and depression/unipolar disorder. Accordingly, the DSM-5 definition of mania or hypomania with mixed features is consistent with the existing evidence[29]. However, the category of major depression with mixed features has been criticized because it leaves out many of these key symptoms while including relatively rare ones such as euphoria and grandiosity[85,88-90]. Leaving out the characteristic symptoms means that a considerable proportion of those with mixed depression will be missed by the DSM-5 criteria. Moreover, it has been demonstrated that patients with major depression and mixed features often convert to BD and therefore should be included with the bipolar spectrum disorders[84,91,92]. Additionally, the minimum number of contrapolar symptoms required for the specifier is unclear[84,87,93]. Lastly, the specifier is likely to have poor clinical utility because of its poor predictive validity and uncertain treatment implications of the symptoms included[91,94].

Therefore, it was suggested that the ICD-11 should retain the mixed episode category rather than adopt the DSM-5 approach[95,96]. Retaining the category allows for further research examining its usefulness and treatment requirements. It also ensures that information about mixed states is properly captured because the category is coded. The ICD-10 definition of mixed episodes only required the

rapid alternation of prominent manic, hypomanic, and depressive symptoms for 2 wk. Although it was less restrictive and more in tune with the existing concepts, it was neither too detailed nor precise. Additionally, the 2-wk duration was considered to be excessive. Consequently, a departure from the ICD-10 approach was also proposed[95,97]. The need to include the core symptoms of agitation, irritability, lability, and distractibility was endorsed, as was the retention of the rapid alternating pattern of symptoms[95,96]. Nevertheless, the ICD-11 draft has essentially followed the ICD-10 approach by including the concurrent presence or rapid alternations of manic or depressive symptoms for 2 wk or less if treatment is initiated[13,29]. Unlike the ICD-10, it has included all the core contrapolar symptoms mentioned above. However, no threshold has been set for the number of such symptoms required for diagnosis. The episodes should cause significant functional impairment. The diagnosis of a mixed episode will automatically signify a diagnosis of BP-I disorder. Therefore, the ICD-11 does not have a category equivalent to major depression with mixed features in the DSM-5. The exclusion of mixed episodes from the BP-II diagnosis is also debatable because of their high prevalence in this subtype[98,99]. Although the concept of mixed episodes in the ICD-11 is not perfect, it may still turn out to be more inclusive than the DSM-5 approach, but this can only be established by further research.

### *Bipolar I disorder*

A history of at least one manic or mixed episode will be sufficient to make a diagnosis of BP-I disorder in the ICD-11 CDDR, unlike the ICD-10 which required the presence of at least two episodes. The reliance on a single episode of mania to define BP-I disorder is based on the current evidence, which demonstrates that the occurrence of mania predicts the typical course of BDs, and separates it from other mood and psychotic disorders[30]. Consequently, an independent diagnosis of a manic episode is no longer possible as it was in the ICD-10. However, like the ICD-10, the ICD-11 draft consigns the illnesses characterized by recurrent manic or hypomanic episodes without depression to the "Other Specified Bipolar or Related Disorders" category. Recently, Angst *et al*[31,53,100] have presented evidence that contradicts the traditional view of recurrent mania as a rare condition indistinguishable from BD[27]. Rather, epidemiological studies have found recurrent mania to be common[101] and clinical studies indicate that about 15%-20% of the patients with BD have this condition[102]. The rates are considerably higher in Asian studies coupled with the predominantly manic course of BD in these countries[103]. Moreover, recurrent mania can be reliably distinguished from BP-I disorder in terms of its diagnostic stability, lifetime course, familial-genetic features, and treatment response[31,53,100,102,104]. Therefore, reviving the recurrent mania diagnosis has been proposed.

### *Bipolar II disorder*

The most noticeable change in the ICD-11 CDDR distinguishing it from the ICD-10, is the inclusion of the BP-II subtype. Similar to the DSM-5, a diagnosis of BP-II disorder will require a history of at least one hypomanic episode and one depressive episode. The BP-II subtype was officially recognized in the DSM-IV, based on its diagnostic stability and familial-genetic links with BD[105]. Although historically perceived to be a milder form of BD, it is now clear that BP-II disorder is a chronic and highly recurrent condition that is equally, if not more disabling than, the BP-I subtype. A predominance of depressive pathology during the acute episodes, subthreshold depression in the inter-episodic periods, and suicidal behavior are more common in BP-II disorder[29,106]. The initial evidence suggested that BP-II disorder could be distinguished from BP-I disorder based on its epidemiology, familial-genetic aspects, longitudinal course, and higher suicidal risk[98,107,108]. However, subsequent reviews concluded that there were more similarities than differences between the two subtypes[109-111]. More recently, this debate has been revived in a slightly different fashion. The essential controversy seems to be whether to use a dimensional or a categorical model of BD. Those who favor a dimensional model have argued that BP-II disorder has to be subsumed under the broader bipolar spectrum diagnosis[70,99,112-114], whereas others who favor a categorical approach maintain that there is sufficient evidence for an independent BP-II category[115-119]. The actual evidence in terms of validators provides almost equal support for both the dimensional and the categorical approaches. Moreover, the size of the evidence base is small and plagued by numerous methodological problems. Additionally, most of the differences seem to arise from the way that BP-II disorder (and hypomania) is defined and assessed across the different studies [32,42,111,120]. Nevertheless, the final verdict seems to be that it would be premature to abandon the BP-II subtype. Rather, it should be retained to encourage further research that may improve its definition and utility[118,119,121-123]. The controversies surrounding the BP-II diagnosis in the ICD-11 and the DSM-5 classifications are detailed in Table 5.

### *Cyclothymic disorder*

The ICD-11 draft has made substantial changes to the diagnostic requirements for cyclothymic disorder compared to the ICD-10 version, bringing the definition closer to the one in the DSM-5. These changes are shown in Table 6.

Unlike the DSM-5, there is no requirement for mood symptoms to be present more than half the time in the ICD-11 version. Moreover, the diagnosis of hypomania can be made at any time after the onset of the disorder, and that of depressive disorder after the first two years. Thus, the definition is less rigid

**Table 5 Controversies about type two bipolar disorder**

| Controversy | For retaining BP-II disorder | Against retaining BP-II disorder |
|---|---|---|
| The definition of hypomania | Current definitions of BP-II disorder in the ICD-11 and the DSM-5 represent an optimal balance between sensitivity and specificity; they will prevent the over-diagnosis and harmful effects of inappropriate treatment of a false positive diagnosis[30,38,42,43] | Current criteria are too restrictive and under-diagnose hypomania and BP-II disorder. The minimum duration required is not evidence-based and should be shorter[32,113,114,120,121] |
| Prevalence of BP-II disorder | The prevalence of BP-II disorder is as high as BP-I disorder, or even higher than the BP-I subtype[98,108-110] | Data on prevalence are mixed. Prevalence is also influenced by factors such as broader definitions, improved recognition, and increased awareness[111, 114] |
| Course of BP-II disorder | Compared to BP-I disorder, BP-II disorder has a more chronic course, greater syndromal and subsyndromal depressive symptoms, and higher episode frequency[98,107-109,112] | The seemingly adverse course of BP-II disorder could be a function of confounding factors such as symptom-severity, comorbidity, and the effects of treatment[32,70,99,114] |
| Diagnostic stability of BP-II disorder | The diagnosis of BP-II disorder remains the same for several years. Only 5%-15% of the patients with BP-II disorder develop BP-I disorder[6,98,105, 109] | The boundaries between BP-II and BP-I disorder, between BP-II disorder and cyclothymia, and between BP-II disorder and personality disorders are unclear [70,99,113,115] |
| The prevalence of psychotic symptoms | Patients with BP-I disorder are more likely than those with BP-II disorder to have psychotic symptoms[66,111,115] | Psychosis is also associated with hypomania, especially in longitudinal community studies[68,69, 113] |
| Suicidal behaviour | Suicide rates are higher in BP-II disorder than BP-I disorder[107-109,120, 121] | The higher suicide rates in BP-II disorder could be a function of comorbid personality disorders and comorbid substance use[98] |
| Family-genetics | BP-II disorder runs in families. Genetic studies help distinguish BP-II disorder from BP-I disorder[98,110,116,118,121] | Genetic studies show that BP-II and BP-I disorders lie on a continuum of genetic risk without any distinction between the two subtypes[106,112,114,120] |
| Neuroimaging | Some studies suggestquantitative or qualitative differences between the two subtypes[116,123] | There are no differences in neuroimaging between the two subtypes[98,111,112,114,120] |
| Neurocognition | Patients with BP-II disorder are less impaired on neuropsychological tests than those with BP-I disorder[98] | There is a great degree of overlap in the neurocognitive performance between the two subtypes[114,116] |
| Treatment response | The treatment requirements of patients with BP-II disorder are different [115,118,119] | There is no difference in treatment response between the two subtypes[98,108,111,114,120] |

BP-I: Type I bipolar disorder; BP-II: Type II bipolar disorder; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition[6]; ICD-11: International Classification of Diseases, 11th version[8].

than the DSM-5 one.

However, the existing literature suggests that cyclothymic disorder is not only characterized by persistent subsyndromal mood changes, but also by mood lability, irritability, increased emotional sensitivity, and a lifelong pattern of impulsivity and interpersonal difficulties that make up the cyclothymic temperament[124-126]. Moreover, cyclothymic temperament seems to be the central part of the presentation of cyclothymia and has been linked to an increased risk of suicide. Accordingly, the selective emphasis on mood changes and the neglect of personality characteristics in the ICD-11 definition may be misplaced. Moreover, the complex diagnostic requirements may reduce the utility of the disorder[127]. The decision to allow hypomanic episodes creates further difficulties. Mixed states are very common in cyclothymia but they have been excluded from the ICD-11 because they denote a diagnosis of BP-I disorder. Therefore, more comprehensive and precise guidelines may be required to improve the reliability and clinical utility of cyclothymia in the ICD-11 CDDR.

### *Bipolar spectrum disorders*

The ICD-11 has followed a somewhat contradictory approach to introducing a dimensional aspect to the BD category. Although it has tacitly accepted the existence of a bipolar spectrum by including BP-II disorder, mixed episodes, cyclothymia, and antidepressant-induced mania and hypomania as a part of BD, it has stopped short of including other categories from this spectrum. This is contrary to the evidence supporting a wider spectrum of BDs[128-132]. This evidence indicates that bipolar spectrum disorders are possibly more common than BP-I and BP-II disorders[133-136]. Additionally, up to half of those with major depression show signs of subthreshold bipolarity. Spectrum disorders are clinically significant forms of BD, often associated with a poor prognosis and enhanced risk of converting to BP-I or BP-II disorders. The failure to detect spectrum disorders often leads to inappropriate or delayed diagnosis and ineffective or harmful treatment. However, the ICD-11 draft chose not to include these disorders. This was because of the concerns about the uncertain boundaries of spectrum disorders and the risk of overdiagnosis and inappropriate treatment[132-135]. The relative lack of external validators,

**Table 6 Changes to the diagnostic guidelines in the International Classification of Diseases, 11th version for cyclothymic disorder**

| | ICD-11-CDDR | DSM-5 | ICD-10 |
|---|---|---|---|
| Core features | Chronic mood instability of more than two years consisting of several hypomanic and depressive periods (irritability in children and adolescents) | Several hypomanic or depressive symptoms for more than two years | A persistent instability of mood, involving numerous periods of mild depression and mildelation (No duration mentioned) |
| | Hypomanic symptoms may meet the criteria for hypomanic episodes | Symptoms do not meet the criteria for hypomanic or major depressive episodes | None of these symptoms meet criteria for mania/BD or depressive episode/recurrent depressive disorder |
| Symptom-free periods | Symptom-free periods are no longer than two months during the course of the disorder | Hypomanic and depressive symptoms are present at least half of the time during the course of the disorder | Mood state may be normal and stable for months (No minimum duration for symptom-free periods specified) |
| | | Symptom-free periods are no longer than two months during this period | |
| Children and adolescents | Duration of one year is appropriate | Duration of one year sufficient | No mention of duration in children and adolescents |
| Manic mixed, and depressive episodes | Criteria for manic and mixed episodes are never met. Depressive episodes cannot be diagnosed during the first two years of cyclothymia. After that, they can be diagnosed if criteria are met | Criteria for manic, hypomanic, or major depressive episodes are never met during the first 2 years. If the person subsequently experiences major depression, mania, or hypomania, the diagnosis is changed to major depressive disorder, BP-I disorder, or other specified or unspecified bipolar and related disorders | Criteria for manic, mixed, and depressive episodes are never met |
| | Criteria for BP-I or BP-II disorder are never met | | Criteria for BD or recurrent depressive disorder are never met |
| Exclusions | Cyclothymia secondary to medical conditions or substance use | Cyclothymia secondary to medical conditions or substance use | No exclusions |
| Functional impairment | Symptoms result in significant distress and/or functional impairment | Symptoms result in significant distress and/or functional impairment | Symptoms are so mild that patients often do not seek treatment |
| Progression to BD | Mentioned | Mentioned | Mentioned |
| Inclusion of additional personality features | Not included-unlike personality disorders, cyclothymia does not include persistent self and interpersonal dysfunction | Included-the person may be temperamental, moody, unpredictable, inconsistent, or unreliable | Included-in some instances, mood changes are less prominent than cyclical disturbances of activity, self-confidence, and social behaviour |

BP-I: Type I bipolar disorder; BP-II: Type II bipolar disorder; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition[6]; ICD-10: International Classification of Diseases, 10th version[14]; ICD-11-CDDR: International Classification of Diseases, 11th version, Clinical Descriptions and Diagnostic Requirements[8].

the problems with diagnostic and prognostic validity, and the absence of controlled data on treatment also proved problematic. Incidentally, the DSM-5 has included some of these disorders in the "Other Specified Bipolar and Related Disorders" category. Moreover, a community study utilizing DSM-5 criteria for BD has shown that the spectrum disorders are as frequent and disabling as BP-I and BP-II disorders[55].

### *Specifiers*

Much like the DSM-5, the ICD-11 CDDR uses several specifiers for mood disorders to create more homogeneous subgroups. These specifiers are also intended to increase diagnostic specificity, assist treatment selection, and help prognostication[29]. They include those related to the course, severity, and descriptive symptom patterns. However, unlike the DSM-5, all specifiers can be coded in the ICD-11 draft so that this information is preserved. The primary specifiers include psychotic symptoms, severity in the case of depressive disorders, and course specifiers such as partial or full remission. Additional specifiers for melancholia and chronicity apply to depressive episodes. The rapid cycling specifier is used to describe BP-I and BP-II disorders. Specifiers common to both depression and BD include the presence of prominent anxiety symptoms, panic attacks, seasonal patterns, and the puerperal onset of episodes. Although most of these specifiers have been included in successive DSM classifications and are evidence-based, there are some uncertainties about their definitions and clinical utility[29]. However, the anxiety symptoms specifier is new to both the ICD-11 and the DSM-5. It is based on the evidence for the frequent occurrence of anxiety symptoms and the influence of these symptoms on the

**Table 7 Considerations guiding the notion of clinical utility in the International Classification of Diseases, 11th version**

| Concept | Application to the ICD-11 CDDR |
|---|---|
| Working definition | Clinical utility of the classification and its categories includes the ability to facilitate communication among clinicians, having characteristics that help clinical practice (diagnostically accurate, easy to use, and feasible), and containing guidance for appropriate treatment choices[141,142] |
| Why clinical utility? | Validity is not a pragmatic goal; enhanced diagnostic reliability has not led to increased validity[143,144]. Current classifications have several shortcomings and are not useful in real-world settings[11,37,142] |
| Levels of utility | Clinical utility has two levels including the architectural or organizational level and the category level[24,141], utility should focus on both the levels and emphasize coverage, description of attributes, and ease of use[145] |
| Application to healthcare settings | The need for utility is the greatest during clinical encounters in routine practice settings. The classification must provide information of value to the clinician in these situations[9-11,13,146] |
| Public health utility | Consideration must be given to the features of the classification that enhance global applicability and reduce global mental health burden[9,147] |
| Contextual aspects | Utility is context-specific; it depends on the purpose for which a classification is used, clinical, research, or for public health[9,10,146] |
| Utility and scientific validity | Clinical utility has to go hand-in hand with the scientific evidence. Moreover, compromising the scientific basis of the classification to meet the needs of clinical utility has to be avoided as far as possible. There is considerable overlap between clinical utility and predictive validity and sometimes it is difficult to distinguish between them[105,145,147] |
| Greater emphasis on clinical utility in the ICD-11 | [1]Clinical utility as the ultimate organizing principle is not a new notion, but the ICD-11 has paid the greatest systematic attention to this aspect[10,147,148] |
| Improving clinical utility in the ICD-11 | Clinical utility has been the guiding principle at all the stages, from the evidence review, to content formation, and to the field trials. The standardized template or content-form was structured to enhance clinical utility. Working Groups were asked to consider the clinical utility of the changes suggested. The protype-based approach contributed to enhanced clinical utility. Cross-cultural usefulness was addressed. The ICD-11 field-trial studies used methodology specifically designed to examine clinical utility in naturalistic settings. The results of these studies have been used to improve the revision further[9-13] |

[1]Similarities between the ICD-11 and the DSM-5 in this regard are shown in Table 1.

ICD-11: International Classification of Diseases, 11th version, CDDR-Clinical Descriptions and Diagnostic Requirements ICD-11[8].

course and outcome of BD[137-140].

### *Clinical utility*

The notion of clinical utility and its examination in the ICD-11 were influenced by different aspects of the concept. These included its working definition[141,142], the need for clinical utility[143-145], levels of utility[141,145], and clinical, research, and public health aspects of utility[146-148]. These are shown in Table 7.

Although clinical utility has been a consideration for the DSM-5 and the earlier versions of both classifications, systematic attention to its study was much greater during the preparation of the ICD-11 CDDR[147,148]. Notably, it was the guiding principle at all stages of the development of the ICD-11 draft, from its adoption as the primary principle, framing an operational definition, using it to guide the evidence review and the description of diagnostic categories, and conducting field trials to examine its relevance[9-11,13,141].

### *The ICD-11 field studies*

The clinical utility of the ICD-11 CDDR categories was examined in a series of studies with a varied methodology in naturalistic settings. These studies were coordinated and conducted by the Field Studies Coordination Group and the GCPN[10,11,149,150]. They included internet-based surveys and clinic-based studies conducted at the field trial centres (FTCs). The formative field trials were conducted early during the guideline development and were meant to provide data to help improve the ICD-11 draft. These included surveys of mental health professionals to elicit their opinions and utilization patterns. Studies on the clinicians' organizational map were meant to inform the structure of the ICD-11 CDDR. Evaluative field studies were designed to assess the utility and reliability of the classification and the individual categories. They included internet-based studies using clinical vignettes and clinic-based FTC studies. The results of these studies regarding BD or mood disorders are shown in Table 8.

At the first glance, the results are encouraging. The clinical utility and utilization of the ICD-11 BD and mood disorders were very high[22,151-154]. The overall structure of the ICD-11 version and the structure of the mood disorders section was endorsed by the clinicians[23,24]. The diagnostic accuracy of BP-II disorders in the ICD-11 CDDR was better than that in the ICD-10 guidelines[155,156]. The clinical utility and inter-rater reliability of BP-I disorder, BD, and mood disorders all proved to be high [142,157-160]. While the clinical utility of these ICD-11 categories was similar to that of the ICD-10[161, 162] and the DSM-5 diagnoses[163], their inter-rater reliability was better than that of the corresponding

**Table 8 The International Classification of Diseases, 11th version field trials on reliability and clinical utility of bipolar disorder[1]**

| Ref. | Manuscript type | Results |
|---|---|---|
| **Formative field trials** | | |
| Surveys of mental health professionals: Opinions and utilization patterns | | |
| Reed *et al*[22], 2011 | Internet-based survey | The ICD-10 category of BD had considerable clinical utility and was commonly used. The category of single depressive disorder was commonly used and should be retained. Functional impairment should be a diagnostic criterion for mood disorders |
| Evans *et al* [151], 2013 | Internet-based survey of psychologists | The ICD-10 category of BD was not as commonly used. BD was rated to have low clinical utility, especially regarding its ease of use |
| Avasthi *et al* [152], 2014 | Internet-based survey | The ICD-10 category of BD was commonly used and was easy to diagnose (high ease of use) |
| Robles *et al* [153], 2014 | Internet-based survey | The ICD-10 category of BD was considered a problematic diagnosis by about 4% of the participants because of its non-specificity. Only about 1% of the participants felt that BP-II disorder should be included in the current version |
| Maruta *et al* [154], 2013 | Internet-based survey | A majority (69%) of the participants felt that BD should be included in a separate category of mood disorders |
| Studies on the clinicians' organizational map for classifications | | |
| Roberts *et al* [23], 2012 | Internet-based survey | Clinicians' concepts were in keeping with the current evidence and similar across all groups and countries. BP-I, BP-II, and cyclothymic disorders were considered to be adult rather than developmental onset disorders. Clinicians' views about the organizational structure corresponded more to the ICD-11 classification than the ICD-10 or the DSM-5 |
| Reed *et al*[24], 2013 | Clinic-based FTC study | Clinicians' concepts were in keeping with the current evidence and similar across all groups and countries. Mood disorders including BP-I, BP-II, cyclothymic, depressive, and dysthymic disorders were grouped together by clinicians. This group was also among the most cohesively organized groups. The results supported the ICD-11 organization of the mood disorders group |
| **Evaluative field trials** | | |
| Studies of clinical vignettes | | |
| Gaebel *et al* [155], 2020 | Internet-based based field study | Diagnostic accuracy of the ICD-11 BP-II disorder category was significantly higher than a modified ICD-10 BP-II category. However, regarding disorders already existing in the ICD-10, *e.g.*, BD, there were no differences between the ICD-11 and the ICD-10. There were no significant differences in overall clinical utility of BD between the ICD-11 and the ICD-10 |
| Kogan *et al* [156], 2021 | Internet-based based field study | Greater diagnostic accuracy was found for the ICD-10 categories of BP-I disorder and a modified category of BP-II disorder on initial analysis. However, there were no significant differences on re-analysis. There were no significant differences between the ICD-11 and the ICD-10 categories of cyclothymic disorder. Clinical utility was somewhat lower for the ICD-11 category of BP-I disorder. Ratings of severity of depression were better with the ICD-10 |
| **Clinic-based FTC studies** | | |
| Reed *et al* [142], 2018 | ICD-11 diagnoses-reliability and utility | The clinical utility of BP-I disorder was higher than schizophrenia, schizoaffective disorder, and depressive disorders on all three parameters including diagnostic accuracy, ease of use, and clarity. Agreement between the raters was also the highest for BP-I disorder ($k$ = 0.85)[2,3] |
| Reed *et al* [157], 2018 | ICD-11 diagnoses-reliability | Agreement between the raters was one of the highest for BP-I disorder ($k$ = 0.84). It was relatively low though adequate for BP-II disorder ($k$ = 0.62)[3,4] |
| Hackmann *et al*[158], 2019 | Qualitative study on patient perceptions of BP-I disorder | The patients commented on several additional features that were missing from the description of BP-I disorder in the ICD-11 CDR. They preferred native language and idioms. A lay language version of the diagnostic descriptions was preferred |
| Medina-Mora *et al*[159], 2019 | ICD-11 diagnoses-reliability and utility | Inter-rater reliability of the mood disorders category was high (percentage agreement-87%). This was higher than schizophrenia and most of the other disorders. Clinical utility was also high |
| Onofa *et al* [160], 2019 | ICD-11 diagnoses-reliability and utility | Inter-rater reliability of BP-I disorder ($k$ = 0.83) was high. Ratings of diagnostic accuracy and ease of use were also high, but the descriptions were felt to be less useful in selecting treatment |

[1]Only those trials that have included results about the categories of bipolar or mood disorders are shown.

[2]The results were very similar to those of two ICD-10 FTC studies of clinical utility[161,162]. They were also similar to those of a clinical utility study of the DSM-5[163].

[3]The inter-rater reliability for a single depressive episode ranged from $k$ values of 0.43 to 0.64. This was lower than the corresponding ICD-10 category ($k$ = 0.66-0.73). Inter-rater reliability of recurrent depressive disorder was higher ($k$ = 0.74) and similar to that of the ICD-10 category ($k$ = 0.69-0.70)[161,162].

[4]The results were comparable to the BD category in the ICD-10 FTC studies ($k$ = 0.81-0.82)[161,162]. Inter-rater reliability was also higher than that found in the DSM-5 FTC studies where reliability for BP-I disorder was 0.56 and for BP-II disorder was 0.40[164,165].

BD: Bipolar disorder; BP I: Type I bipolar disorder; BP II: Type II bipolar disorder; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition[6]; FTC: field trial centre; ICD-10: International Classification of Diseases, 10th version[14]; ICD-11: International Classification of Diseases, 11th

version, CDDR-Clinical Descriptions and Diagnostic Requirements[8]; *k*: Kappa value.

DSM-5 categories[164,165]. However, there were a few limitations. There was a divergence of opinion between psychiatrists and other mental health professionals in certain studies[151,153]. Although the ICD-11 categories were not inferior to the ICD-10 ones in terms of utility and reliability, there were no substantial differences between the two versions[155,156,161,162]. The reliability of BP-II disorder though adequate was relatively low[157]. Certain aspects of the clinical utility, *e.g.*, making treatment decisions based on the diagnoses, were difficult[160]. Patients' perceptions were not invariably favourable[158]. Finally, methodological limitations such as a selection bias towards those positively predisposed to the ICD-11 and inadequate generalization of the results to routine clinical practice could confound these findings[149]. Therefore, there is much scope for improving the utility and reliability of the ICD-11 guidelines as well as conducting further research on the subject.

## CONCLUSION

The ICD-11 guidelines on BD have been more or less finalized following a protracted and complicated process. Many changes have been suggested. Many limitations are also evident, mostly arising from the conflicting nature of the existing evidence. Imperfections are also due to the consensus-based system of creating classifications[166] and the limitations of the current state of knowledge about the aetiology of psychiatric disorders[167-171]. The conservative approach followed may lead to some frustration. However, it has to be accepted that any change can only be incremental and that the scope for paradigmatic shifts is limited at present[30,172]. It is also time to move beyond the endless debates about the necessity of revisions[145,173,174] and focus on the challenges of implementation, dissemination, and education and training of the potential users of these guidelines. A provision for continuous upgrading similar to the DSM-5[175] and a greater focus on treatment-utility are also needed[148]. Although the initial results of clinical utility and reliability of BD seem promising, it will take several years and many studies to evaluate the real impact of the ICD-11 guidelines on the current psychiatric practice. It would be imperative that all stakeholders including the policymakers, professionals, and the people impacted by mental illnesses are engaged in this process[9]. Ultimately, only they will determine if the revision was worth the effort.

## FOOTNOTES

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*MINIREVIEWS*

# Morphological changes in Parkinson's disease based on magnetic resonance imaging: A mini-review of subcortical structures segmentation and shape analysis

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## Abstract

Parkinson's disease (PD) is a neurodegenerative disorder caused by the loss of dopaminergic neurons in the substantia nigra, resulting in clinical symptoms, including bradykinesia, resting tremor, rigidity, and postural instability. The pathophysiological changes in PD are inextricably linked to the subcortical structures. Shape analysis is a method for quantifying the volume or surface morphology of structures using magnetic resonance imaging. In this review, we discuss the recent advances in morphological analysis techniques for studying the subcortical structures in PD *in vivo*. This approach includes available pipelines for volume and shape analysis, focusing on the morphological features of volume and surface area.

**Key Words:** Parkinson's disease; Dopaminergic neurons; Magnetic resonance imaging; Substantia nigra; Morphological

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**Core Tip:** Parkinson's disease (PD) is a neurodegenerative disorder caused by the loss of dopaminergic neurons in the substantia nigra, resulting in clinical symptoms, including bradykinesia, resting tremor, rigidity, and postural instability. The pathophysiological changes in PD are inextricably linked to the subcortical structures. Shape analysis is a method for quantifying the volume or surface morphology of structures using magnetic resonance imaging. In this review, we discuss the recent advances in morphological analysis techniques for studying the subcortical structures in PD *in vivo*. This approach includes available pipelines for volume and shape analysis, focusing on the morphological features of volume and surface area.

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## INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. It is primarily caused by the loss of dopaminergic neurons in the substantia nigra. The classical clinical symptoms of PD include movement symptoms such as bradykinesia, resting tremor, rigidity, and postural instability. Recent studies have shown that symptoms of PD extend beyond motricity and include cognitive and neuropsychiatric symptoms. Non-motor symptoms can be identified at all stages, even before the appearance of motor symptoms[1]. In addition to clinical markers, PD biomarkers include neuroimaging, genetic, and biochemical markers[2]. This review focuses primarily on the use of neuroimaging in PD.

The main pathological features of PD are the degeneration of dopaminergic neurons in the substantia nigra and deposition of Lewy bodies, leading to pathophysiological changes in the downstream basal ganglia circuits. The basal ganglia system includes the striatum, globus pallidus, and structures with functional connections to the striatum, including the subthalamic nucleus, substantia nigra, and red nucleus.

Magnetic resonance imaging (MRI) is one of the most useful noninvasive techniques for examining intracranial structures, showing macroscopic alterations of the subcortical structures, and can visualize their volume and surface morphology. Therefore, MRI-based morphological analysis of the subcortical structures has the potential to be a prominent diagnostic neuroimaging marker for PD. This review focuses on the shape analysis of the striatum, thalamus, and hippocampus, which has been mostly discussed in previous studies.

## METHODS

A literature search was conducted for relevant studies using four databases: PubMed, Web of Science, Google Scholar, and Scopus. The key search terms in the different combinations were "Parkinson's disease, shape analysis, subcortical structures, striatum, thalamus, and hippocampus." The final search was conducted on October 25, 2022.

The inclusion criteria were the studies that included: (1) A background or introduction on PD; (2) the clinical criteria of PD; (3) an introduction to methods of the subcortical structure segmentation; (4) shape analysis of the subcortical or cortical structures; and (5) data utilization of structural MRI sequences.

We excluded studies based on the following exclusion criteria: (1) Articles published in languages other than English; (2) animal model or theoretical articles; (3) studies with a sample size of < 10 patients; (4) studies whose methodology did not involve volumetric or shape analysis; and (5) review or meta-analysis articles of shape analysis.

## RESULTS

Figure 1 shows a flowchart of the study selection. This review included 69 references, of which 2 provided a background/introduction on PD, 5 referred to the segmentation methods, and 62 to the morphology of the subcortical or cortical structures in PD. Subcortical structures mainly included the striatum, thalamus, and hippocampus. Further information on the structures and morphological changes is provided in Table 1.

**Table 1 Morphological studies in Parkinson's disease**

| Subcortical structures | Ref. | Segmentation methods | Analysis type | Results |
|---|---|---|---|---|
| Striatum | | | | |
| | Geng *et al*[12], 2006; Pitcher *et al*[10], 2012; Owens-Walton *et al*[11], 2018 | Manual | Volume | Reduced volume of bilateral caudate and putamen nuclei |
| | Sterling *et al*[13], 2013 | Semi-automatic | Volume | Reduced volume of bilateral caudate and putamen nuclei |
| | Geevarghese *et al*[15], 2015; Vasconcellos *et al*[17], 2018; Tanner *et al*[16], 2017; Melzer *et al*[30], 2012 | Automatic | Volume | Reduced volume of bilateral caudate nuclei |
| | Oltra *et al*[35], 2022 | Automatic | Volume | Reduced volume of bilateral caudate nuclei (with RBD) |
| | Lee *et al*[14], 2014; Garg *et al*[20], 2015 | Automatic | Volume | Reduced volume of bilateral putamen nuclei |
| | Garg *et al*[20], 2015 | Automatic | Volume | Reduced volume of right putamen nuclei |
| | Kamps *et al*[33], 2019 | Automatic | Volume | Reduced volume of right putamen nuclei (with RBD severity) |
| | Kluger *et al*[34], 2019 | Automatic | Volume | Reduced volume of dorsal striatum (with fatigue) |
| | Messina *et al*[18], 2011; Menke *et al*[19], 2014; Nemmi *et al*[21], 2015; Khan *et al*[22], 2019; Gong *et al*[32], 2019 | Automatic | Volume | No significant difference in bilateral striatum |
| | Chung *et al*[31], 2017 | Automatic | Volume | Locally reduction of right caudate nuclei |
| | Devignes *et al*[28], 2021 | Automatic | Shape | Locally reduction of left caudate nuclei (with cognition) |
| | Garg *et al*[20], 2015 | Automatic | Shape | Locally reduction of right putamen nuclei |
| | Gong *et al*[32], 2019 | Automatic | Shape | Locally reduction of bilateral caudate and right putamen nuclei (with RBD) |
| | Tanner *et al*[16], 2017 | Automatic | Shape | Locally reduction of the lateral and medial caudate nuclei |
| | Sterling *et al*[13], 2013 | Semi-Automatic | Shape | Locally reduction of the head and dorsal body of caudate nuclei |
| | Nemmi *et al*[21], 2015 | Automatic | Shape | Locally reduction of the medial surface of left caudate nuclei (with the right UPDRS) |
| | Tanner *et al*[16], 2017 | Automatic | Shape | Locally reduction of the medial surface of putamen nuclei |
| | Sterling *et al*[13], 2013 | Semi- Automatic | Shape | Locally reduction of the caudal and ventro-lateral putamen nuclei |
| | Sigirli *et al*[23], 2021 | Automatic | Shape | Locally reduction of the middle-posterior of right putamen nuclei |
| | Lee *et al*[14], 2014 | Automatic | Shape | Locally reduction of the posterolateral and ventromedial putamen nuclei |
| | Nemmi *et al*[21], 2015 | Automatic | Shape | Locally reduction of the lateral and medial posterior putamen nuclei (with UPDRS) |
| | Khan *et al*[22], 2019 | Automatic | Shape | Locally reduction of the caudal-motor and rostral-motor sub-regions |
| Thalamus | | | | |
| | McKeown *et al*[43], 2008 | Manual | Volume | No significant difference |
| | Garg *et al*[20], 2015 | Automatic | Volume | Significant difference |
| | Vasconcellos *et al*[17], 2018; Mak *et al*[26], 2014; Sivaranjini *et al*[27], 2021; Foo *et al*[45], 2017 | Automatic | Volume | Reduced volume of bilateral thalamus |
| | Niccolini *et al*[46], 2019 | Automatic | Volume | Reduced volume of bilateral thalamus (with non-motor symptom) |

| | | | | |
|---|---|---|---|---|
| | Kamps *et al*[33], 2019 | Automatic | Volume | Reduced volume of left thalamus (with RBD) |
| | Chen *et al*[44], 2020 | Automatic | Volume | Increased volume (20) of right subnuclei |
| | Chen *et al*[44], 2020 | Automatic | Volume | Increased volume (21), reduced volume (2) of left subnuclei |
| | Kaya *et al*[40], 2019 | Manual | Shape | Locally reduction of the dorsolateral of bilateral STN |
| | Devignes *et al*[28], 2021 | Automatic | Shape | Locally reduction of right thalamus (with cognition) |
| | Chung *et al*[31], 2017 | Automatic | Shape | Locally reduction of bilateral thalamus (with cognition) |
| | McKeown *et al*[43], 2008 | Automatic | Shape | Locally reduction of the dorsal surface of bilateral thalamus |
| | Garg *et al*[20], 2015 | Automatic | Shape | Net-inward and outward deformation of left thalamus |
| Hippocampus | | | | |
| | Wang *et al*[55] , 2018 | Automatic | Volume | Reduced volume of right hippocampus |
| | Chen *et al*[56], 2016 | Automatic | Density | Reduced density of left hippocampus |
| | Geevarghese *et al*[15], 2015 | Automatic | Volume | Reduced volume of left hippocampus (with cognition) |
| | Lee *et al*[14], 2014; Tanner *et al*[16], 2017; Radziunas *et al*[53], 2018; Melzer *et al*[30], 2012 | Automatic | Volume | Reduced volume of bilateral hippocampus |
| | Vasconcellos *et al*[17], 2018 | Automatic | Volume | Reduced volume of bilateral hippocampus (with disease duration) |
| | Camlidag *et al*[68], 2014; Xu *et al*[59], 2020 | Automatic | Volume | Reduced volume of bilateral hippocampus (with cognition) |
| | van Mierlo *et al*[64], 2015 | Automatic | Volume | Reduced volume of bilateral hippocampus (with depression) |
| | Rahayel[63], 2019 | Automatic | Volume | Reduced volume of bilateral hippocampus (with REM-RBD) |
| | Wilson *et al*[54], 2019 | Automatic | Volume | Reduced volume of bilateral hippocampus (with cognition, motor and disease duration) |
| | Luo *et al*[60], 2021 | Automatic | Volume | Reduced volume of subfields (with cognition) |
| | Uribe *et al*[61], 2018 | Automatic | Volume | Reduced volume of subfields, especially CA1 |
| | Becker *et al*[62], 2021 | Automatic | Volume | Reduced volume of CA1 (with cognition) |
| | Xu *et al*[59], 2020 | Automatic | Volume | Reduced volume of subiculum, CA2/3, CA4, ML and right GC-DG |
| | Park *et al*[57], 2019 | Automatic | Volume | Volume asymmetry, especially in CA4-DG and CA2-3 |
| | Tanner *et al*[16], 2017 | Automatic | Shape | Locally reduction in the head and CA1 bilaterally |
| | Devignes *et al*[28], 2021 | Automatic | Shape | Locally reduction of right hippocampus (with cognition) |

REM: Rapid eye movement; RBD: Sleep behavior disorder; STN: Subthalamic nucleus; CA: Cornu ammonis (subfields of hippocampus); ML: Molecular layer subfields; GC-DG: Granule cell layer of the dentate gyrus.

### *Parkinson's disease*

The Movement Disorders Society (MDS) has proposed the main diagnostic criteria for PD in clinical settings[3]. The recent version of the MDS diagnostic criteria considers three stages in the progression of PD: Preclinical, prodromal, and clinical. Clinical PD can be diagnosed when typical motor symptoms occur. Neurodegeneration may occur in patients with PD before they reach the clinical stage[3]. Previous studies have been mostly conducted based on clinical diagnosis; therefore, this review focuses

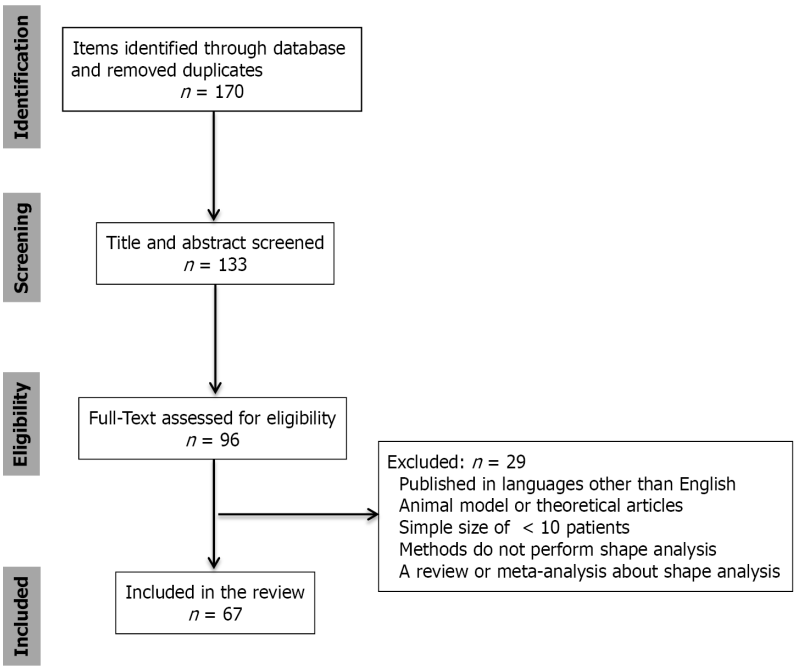


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**Figure 1 A flowchart of the study selection.**

on PD in the clinical stage. The striatum is one of the most affected structures in the nigrostriatal pathway because of the degeneration of dopaminergic neurons. In addition to the striatum, neurons in the substantia nigra project to other basal nuclei, such as the pallidum, substantia nigra, and thalamic nucleus basalis. A decrease in dopamine levels may cause the structural and morphological changes observed in PD.

MRI allows noninvasive observation of morphological changes in the subcortical structures in patients with PD to find changes in neuroimaging characteristics. Hence, it may help in clinical intervention, especially in the preclinical or prodromal stages of the disease. However, the naked eye cannot identify subtle changes in structures; hence, quantitative analysis using a computer may help determine the presence or absence of morphological changes in these structures. Segmentation of subcortical structures based on the images is the prerequisite to performing an accurate analysis. The following sections describe the common segmentation methods and the results of morphological analyses of the subcortical structures obtained from previous studies.

### *Methods of segmentation*

Both manual and automatic segmentation have been used in recent studies. Manual segmentation, usually the gold-standard approach for automatic segmentation, is a tedious and time-consuming task that depends on the subjectivity of the physician. Therefore, many investigators have used publicly available automated segmentation software for efficiency and objectivity. Automatic segmentation methods include voxel-based morphometry (VBM) and surface-based morphometry (SBM). The tools used for segmentation in most studies include FSL and FreeSurfer, among others. The FIRST software, distributed with the FSL package, is a tool that employs manually labeled image data to offer anatomical training information for 15 different subcortical regions using 336 manually labeled T1-weighted MRI images[4]. FreeSurfer is a suite of tools for extensive automated analysis of key features in the human brain that can be used in most MRI sequences and provides an accurate geometric surface model[5]. By minimizing the difference between the original image and the converted target image, large deformation diffeomorphic metric mapping (LDDMM) creates a differential homogenous transformation that has its own inherent smoothness and simulated displacement size. It is often applied in the object-matching segment of medical imaging data processing[6]. This review focuses on the morphological analysis of subcortical structures in PD using the techniques mentioned above in recent years.

Several scholars have compared the effects of manual and automatic segmentation. For the hippocampus and amygdala, segmentation using VBM and FreeSurfer is performed at a level comparable to manual segmentation[7]. In another study, automated segmentation revealed different degrees of variability in the subcortical structures compared to manual segmentation, with particularly pronounced differences found in the FreeSurfer and FSL pipelines for the pallidum and thalamus[8]. From these studies, it can be seen that the efficiency of automatic segmentation is comparable to that of manual segmentation. Automatic methods save more time and display better segmentation results,

which could be used in the shape analysis of the subcortical structures in patients with PD.

### Shape analysis of the striatum

The striatum is a critical component of the brain that controls the motor, reward, and executive functions, and dopamine serves as an important mediator[9]. Decreased dopamine levels have the greatest impact on striatal structures in patients with PD. Several studies have segmented the striatum by manual segmentation of T1-weighted MRI images for its morphology, showing that the volume of the caudate nucleus or putamen was smaller in patients than in normal controls[10,11]. In addition, studies using automatic segmentation showed the same results as those using manual segmentation of the volume of the caudate nucleus and putamen[12-17]. However, some studies have found no significant difference in striatum volume between patients with PD and normal controls[18-21]. Studies that performed further surface morphometric analyses under automated shape analyses showed: (1) A regional contraction of the posterolateral and ventromedial putamen bilaterally in patients with PD[14]; (2) areas of local atrophy in the lateral and medial posterior parts of the bilateral putamen; (3) atrophy locally on the medial surface of the left caudate nucleus[21]; and (4) a reduction in the volume and an inward displacement of the surface of the caudal motor striatum[22]. Studies using other machine learning methods have also found local atrophy in the caudate and putamen nuclei, including the caudal portion of the putamen or the middle-posterior putamen and the head of the caudate[13,23]. A study attempted to distinguish different stages of PD based solely on the shape analysis of the bilateral caudate nucleus and putamen through an automated process, with balanced accuracies in the range of 59%-85%[24].

Dysfunction of the basal ganglia plays a key role in developing motor and non-motor symptoms in PD[25]. When exploring the relationship between volume and symptoms, several studies have shown that greater atrophy of the caudate and putamen in PD is usually associated with more severe motor symptoms and cognitive impairment[11,17,26-28]. Additionally, some correlation analyses did not find a significant correlation between striatal volume and cognitive or motor symptoms[10].

Local morphological analyses provided more details; local atrophy in the left putamen and thalamus correlated with the right Unified Parkinson Disease Rating Scale (UPDRS) motor scale score, which is the most widely used scale for the clinical studies of PD[21,29]. A previous study identified PD with mild cognitive impairment (PD-MCI) with limited atrophy of the right putamen[30]. When PD-MCI converted to dementia, smaller local shape volumes were found in the right caudate nucleus of the patients compared to that of patients with PD-MCI who did not convert[31]. In addition, logistic regression analysis indicated that the local shape volumes in the right caudate nucleus were significant independent predictors of conversion to dementia in patients with PD-MCI. Distinct structural changes in the caudate and/or putamen are associated with performance in the attention or working memory domain, fatigue, the severity of rapid eye movement (REM) sleep behavior disorder (RBD), and excessive daytime sleepiness[26,32-35].

Specifically, volume atrophy of the left caudate nucleus or right putamen was found to be more pronounced in the patient cohort[11,23], which may be due to disease lateralization. Previous studies have shown that the decrease in dopamine capacity in the striatum is more pronounced in the contralateral hemisphere on the side with more severe clinical symptoms of PD[36]. It has been suggested that the onset of motor symptoms may always occur in one limb, and morphological analysis has revealed a greater degree of striatal atrophy on the contralateral side of the limb where motor symptoms occur[16]. Local deformation of the posterior side of the putamen has been reported in several articles. According to the literature, the posterior putamen is directly related to the sensorimotor cortex and is preferentially affected; dopamine depletion is mainly located in this region of the basal ganglia[10,23,37,38]. Therefore, we can also infer that the morphological changes in PD can be detected using MRI. Furthermore, we may be able to assess the severity of some symptoms, such as cognitive function in patients with PD, and provide timely interventions for clinical treatment.

### Shape analysis of the thalamus

The thalamus is composed of several nuclei that regulate various motor and sensory functions and is usually divided into seven nuclei: The anterior, lateral, ventral, intralaminar, medial, and posterior nuclear groups and the reticular nucleus. Among the nuclei of the thalamus, the ventral thalamus, also known as the subthalamic nucleus (STN), plays an important role in extrinsic inputs reaching the basal ganglia circuitry[39]. A study calculated the morphological changes in the STN and found statistically significant differences in the shape of bilateral STN between the PD and control groups, with the largest deformation site located in the dorsolateral parts of bilateral STNs[40]. Patriat *et al*[41] showed that the volume of STN was smaller in PD patients compared to healthy controls, which was further validated in the field of 7T MRI. Although thalamic degeneration may represent a site of dopaminergic degeneration in PD, the thalamus is also influenced by hyperactivity in glutamatergic signaling, which may be caused by the loss of dopaminergic neurons in the substantia nigra and striatum[42]. Thus, various morphological changes occur in the thalamus of patients with PD. Furthermore, several studies on structural and functional imaging have identified morphological or functional changes in the thalamus in patients with PD. Using manual segmentation, scholars found no significant difference in the thalamus volume between patients with PD and healthy controls[43]. They used spherical harmonic-based representation

methods and detected significant differences in shape[43]. A previous study subdivided the left and right thalamus into 25 subnuclei using automatic methods. It was detected that 21 of the left and 20 of the right thalamic subnuclei had increased volume, accompanied by atrophy in two left subnuclei[44].

More studies have been conducted to correlate thalamic shape changes with clinical symptoms. Nemmi *et al*[21] found a significant correlation between local atrophy of the right thalamus and the UPDRS using FSL scripts. However, one study found that surface morphological changes in the thalamus were not associated with disease severity in UPDRS using FreeSurfer segmentation with LDDMM alignment[20]. This may be due to differences in segmentation methods and cohort sizes, and the influence of glutamatergic neurons on thalamic morphology requires further investigation.

Moreover, most studies have concluded that altered thalamic morphology is associated with non-motor symptoms. Several studies have found a relationship between reduced thalamic volume and poor cognitive function in patients with PD[17,26-28,45]. A more detailed correlation analysis showed that the local shape volume of the bilateral thalamus was a significant independent predictor of the conversion of MCI to dementia. However, the local shape volume of the thalamus was associated with semantic fluency and attentional composite scores[31]. In addition, some scholars have found that the severity of other non-motor symptoms in patients with PD is associated with more pronounced thalamic atrophy. Furthermore, they found that such non-motor symptoms include sleep, fatigue, gastrointestinal dysfunction, and REM-RBD[32,46].

The thalamus, one of the output nuclei of the basal ganglia, is markedly affected by dopaminergic and glutamatergic neuronal degeneration. For living subjects, imaging is potentially one of the most practical tools to detect changes in the thalamus. Precise shape analysis shows that the thalamus in PD undergoes major or minor changes. Compared to manual measurements, accurate automated measurements reflect more pronounced variation and more detailed results. Because of the varying progression of neuronal degeneration, thalamus shape analysis in patients with PD presents differently. Hence, future studies using the same methods and similar cohort sizes may show better consistency. Moreover, several studies have demonstrated the relevance of shape alterations and symptoms, especially non-motor symptoms, probably because the thalamic subnuclei play an important role in the transmission of dopaminergic neuronal pathways. However, the sequence in which the onset of symptoms and the changes within the thalamus occur is still unclear. In addition, abnormal STN activity may be associated with motor dysfunction in PD; however, further studies are needed to confirm the relationship between STN shape changes and motor symptoms.

### *Shape analysis of the hippocampus*

As a subcortical structure, the hippocampus is an important brain region that carries the body's cognitive functions and is closely related to learning ability, memory, and emotion regulation. Cognitive impairment is frequently seen in PD; thus, the hippocampus may be an imaging marker of cognitive impairment[47]. Scholars have found a reduction in hippocampal gray matter density or thickness through automatic methods in the elderly or patients with cognitive impairment, especially in the CA1, which is one of the four hippocampal subfields called the cornu ammonis[48-52]. Several studies on hippocampal morphology have been conducted in patients with PD and normal controls. Using automatic shape analysis, some studies have shown smaller hippocampal volumes in patients with PD than in controls[16,17,30,53-55]. There were also reduced local volumes of the hippocampus in patients with cognitive impairment compared with those without cognitive impairment, including the subfields CA1-4[28,30,31,54-62]. Studies have shown that the development of REM-RBD and depression may be associated with a smaller hippocampal volume[33,63,64]. This suggests a close relationship between hippocampal atrophy and cognitive function, in which the CA1 may be one of the most notable subfields.

The hippocampus is the main source of cholinergic input to the cerebral cortex, and most studies have shown that the hippocampal volume shrinks in patients with PD. Hippocampal shape analysis has focused on non-motor symptoms in PD, primarily the cognitive function, which matches the function of the hippocampus. The relationship between hippocampal atrophy and cognitive decline has been confirmed in patients with PD in the majority of studies. However, recent studies mostly showed volume results; thus, the surface morphological analysis may be able to link hippocampal subregions to specific symptoms of cognitive impairment further. The relationship between morphological changes and other symptoms, such as REM-RBD and depression, warrants further investigation.

Furthermore, a large number of studies are also using these automated pipelines to analyze cortical structures in PD. Cerebral cortices are key to human activity and may be altered as a result of unusual activity in PD, such as thinning. Most studies have found atrophy in various parts of the cortex in patients with cognitive impairment. In a longitudinal study, Garcia-Diaz *et al*[65] confirmed the thinning of cortical thickness in PD patients with cognitive impairment *vs* those without. Among some symptoms related to the cerebral cortex, Vignando *et al*[66] reported a general reduction in occipital, parietal, temporal, frontal, and limbic cortical thickness in patients experiencing hallucinations. Changes in visuospatial and visual supraperceptual impairment also correlated with cortical thinning in occipital, parietal, and temporal regions in the study by Garcia-Diaz *et al*[65]. As for motor symptoms, through the calculation of surface area in a study of PD gait disorders, Wei *et al*[67] found that the larger the surface areas of the left lateral temporal cortex and right inferior parietal cortex, the worse the gait

performance.

This review focuses on the results of patients on 3T instruments, and participants were scanned using a 1.5T MRI instrument and used manual planar measurements, revealing that the normalized STN and red nuclei volumes were larger in patients with PD than in controls[68]. Similarly, 7TMRI imaging revealed atrophy of the overall prefrontal cortex and hippocampus, as well as a reduction in STN volume, for patients with PD[41,69]. Although current studies on 7TMRI have focused only on volumetric rather than morphological changes, higher resolution instruments can help us to detect finer structural changes and conduct more structural studies.

## CONCLUSION

Methods for the shape analysis of subcortical structures based on MRI data are becoming increasingly diverse and refined, allowing even minor changes to be detected. This study has reviewed previous research on the application of these techniques in PD. In contrast to manual measurements, most studies employ computational methods to maintain objectivity. Volume atrophy can be found in most structures, including the subcortical and cortical areas. Surface-based morphometry detects structural changes that can be associated with clinical symptoms. We found that pathophysiological changes in PD are closely associated with changes in the subcortical structures and that different sub-structural alterations are consistent with specific clinical phenotypes. Therefore, the shape analysis of the subcortical structures can be used as an imaging biological indicator of PD, helping to explain associated clinical symptoms.

## FOOTNOTES

**Author contributions:** Authors' contributions: Lin F contributed to the conception of the study; Zhang HW, Liu XL, and Deng HZ contributed significantly to analysis and manuscript preparation; Deng JH and Zhang HW performed the data analyses and wrote the manuscript; Zhang HW and Deng JH contributed equally to this study.

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