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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

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

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.

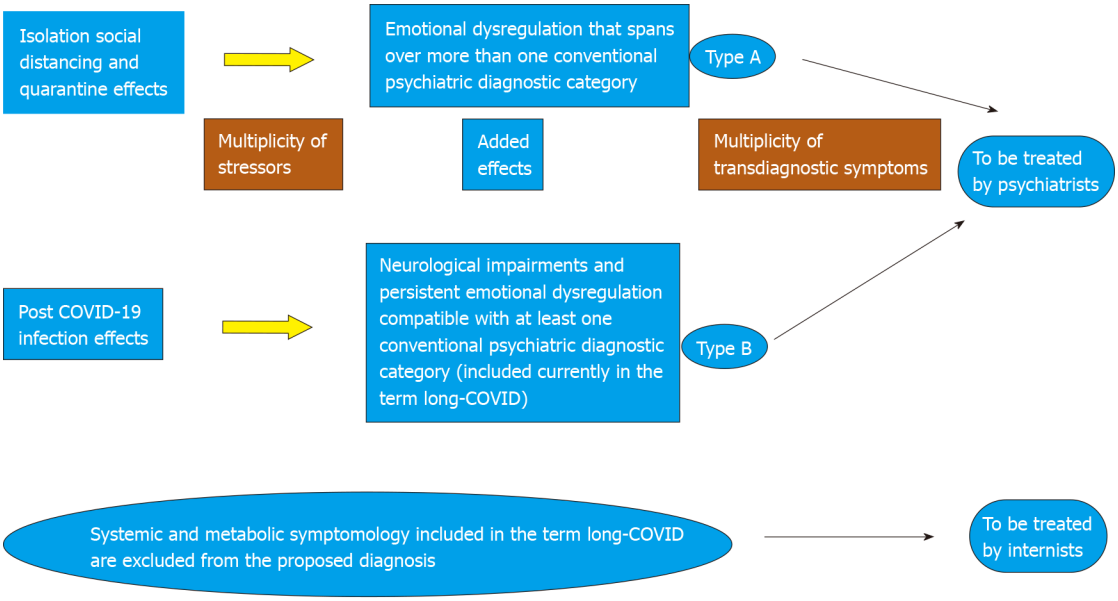

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Figure 1 Outline of the Complex Stress Disorder Syndrome hypothesis and pathways for future treatment as a diagnosis-derived expected development. COVID-19: Coronavirus disease 2019.

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

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

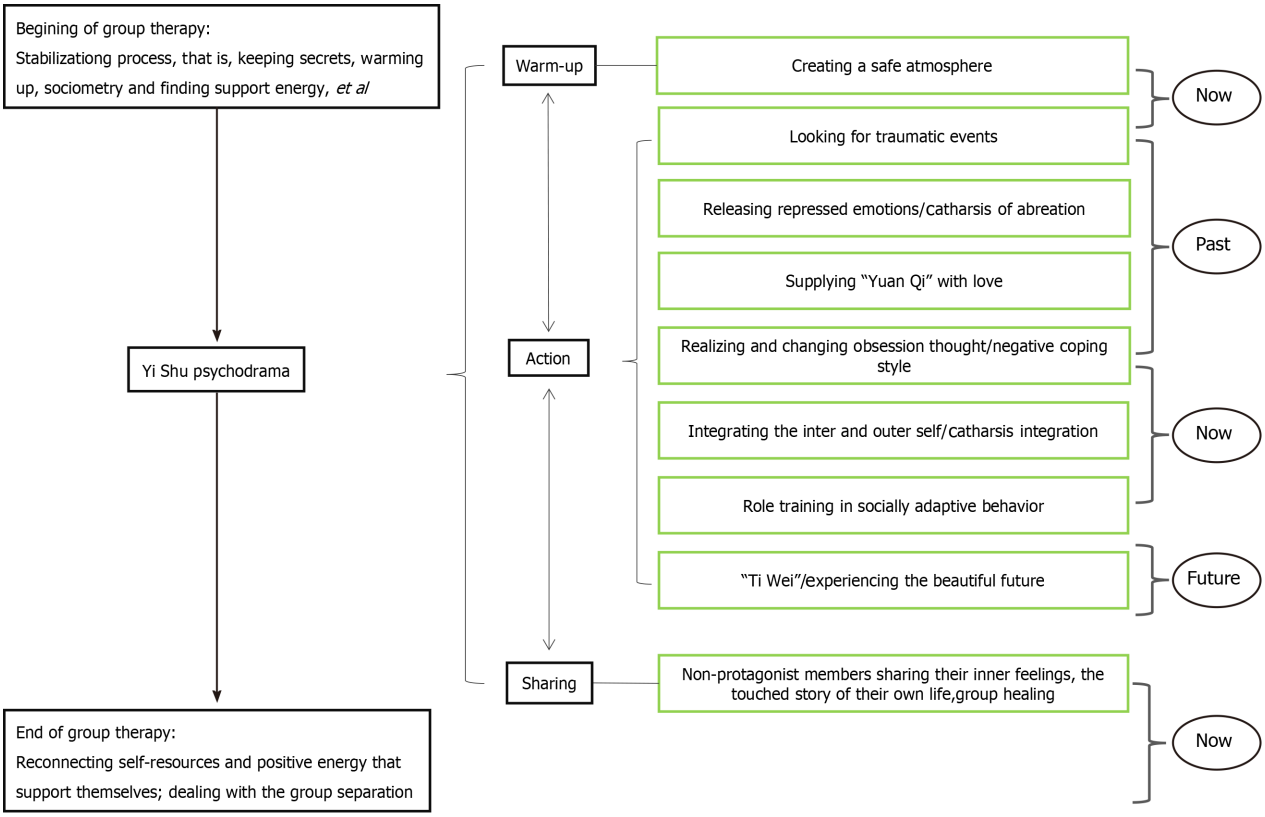

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Figure 1 Model of Yi Shu psychodrama for patients with major depressive disorder.

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 χ^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 χ^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/χ^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)
χ^2			0.022
P value			0.881

Data are *n* (%). Due to rounding, the total % might be more than 100%.

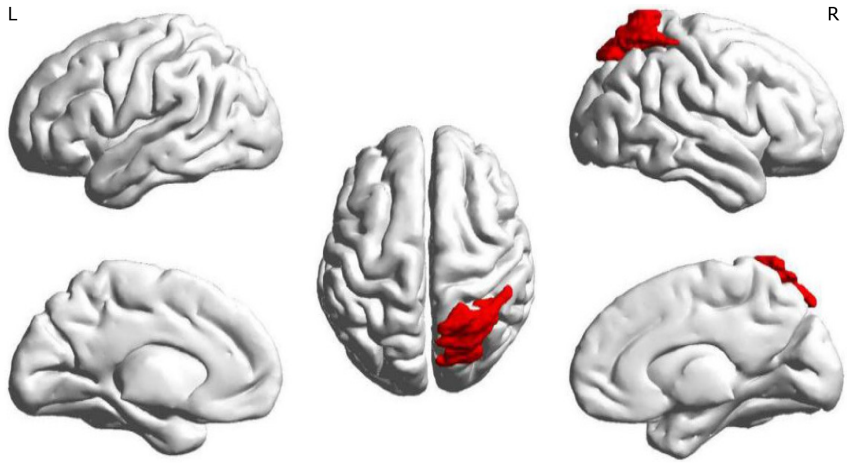

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Figure 2 Location of brain regions with interactions of node efficiency. The red brain area marked in the figure is the right superior parietal gyrus, the brain region where the node efficiency interacts after intervention in the two groups.

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 χ^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.

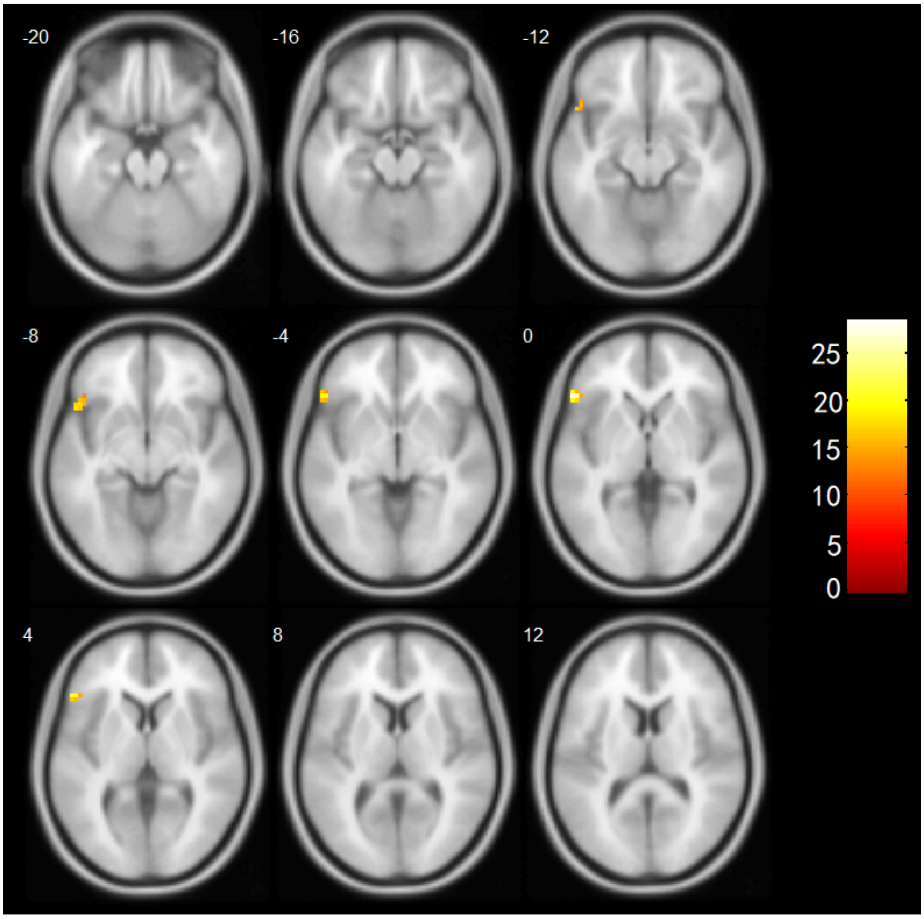

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Figure 3 Increased connectivity with the right superior gyrus after intervention. The numbers in the figure represent the axial coordinates of the brain profile in Montreal Neurological Institute space, and the brightness of the color represents the 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

Author contributions: All authors have materially participated in the research and article preparation; Yu RQ and Tan H participated in data collection, analysis, paper writing, and have equally contributed to this work; Wang ED implemented psychodrama intervention; Huang J, Wang PJ, Li XM, Zheng HH, and Lv FJ participated in data collection and analysis; Hu H, in charge of the research, was responsible for project application, implementation, and article writing; All authors approved the final manuscript.

Institutional review board statement: All patients provided written informed consent, and the study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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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

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 (ε_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 χ^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.

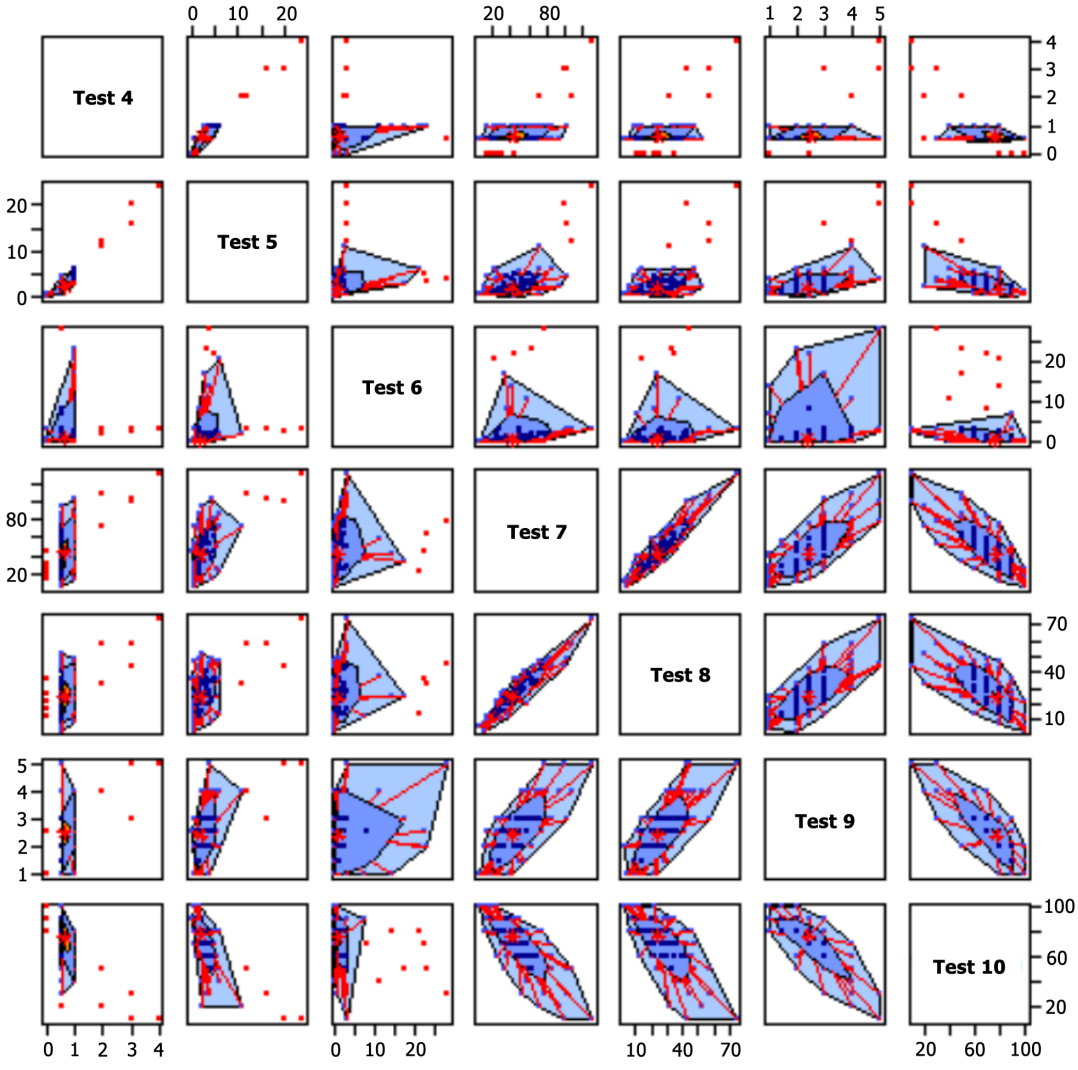

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Figure 1 A bagplot that visualizes the location, spread, skewness, and outlier of the test results. Test 4 = Global Clinical Dementia Rating score; Test 5 = Sum of boxes in Clinical Dementia Rating; Test 6 = Korean Instrumental Activities of Daily 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.

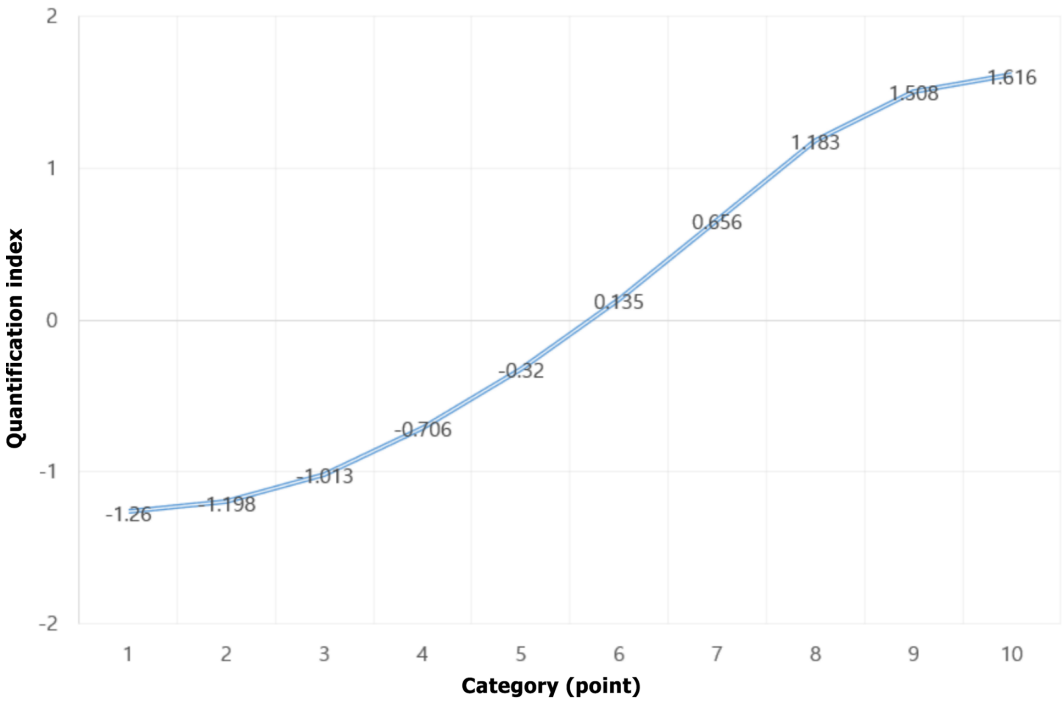

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Figure 2 Quantification score graph among Korean Mini-Mental State Examination. Category 1 = 3-14 point; Category 2 = 15-18 point; Category 3 = 19-20 point; Category 4 = 21-22 point; Category 5 = 23-24 point; Category 6 = 25 point; Category 7 = 26 point; Category 8 = 27 point; Category 9 = 28 point; Category 10 = 29-30 point.

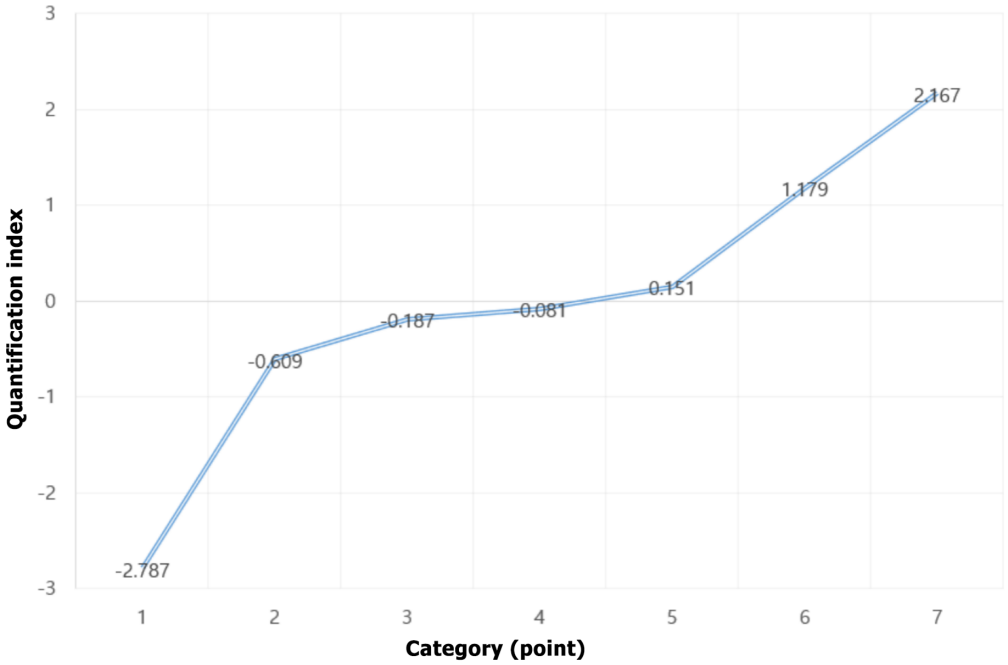

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Figure 3 Quantification score graph among Hoehn and Yahr staging. Category 1 = 1.0 point; Category 2 = 1.5 point; Category 3 = 2.0 point; Category 4 = 2.5 point; Category 5 = 3.0 point; Category 6 = 4.0 point; Category 7=5.0 point.

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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Worldwide suicide mortality trends (2000-2019): A joinpoint regression analysis

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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

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

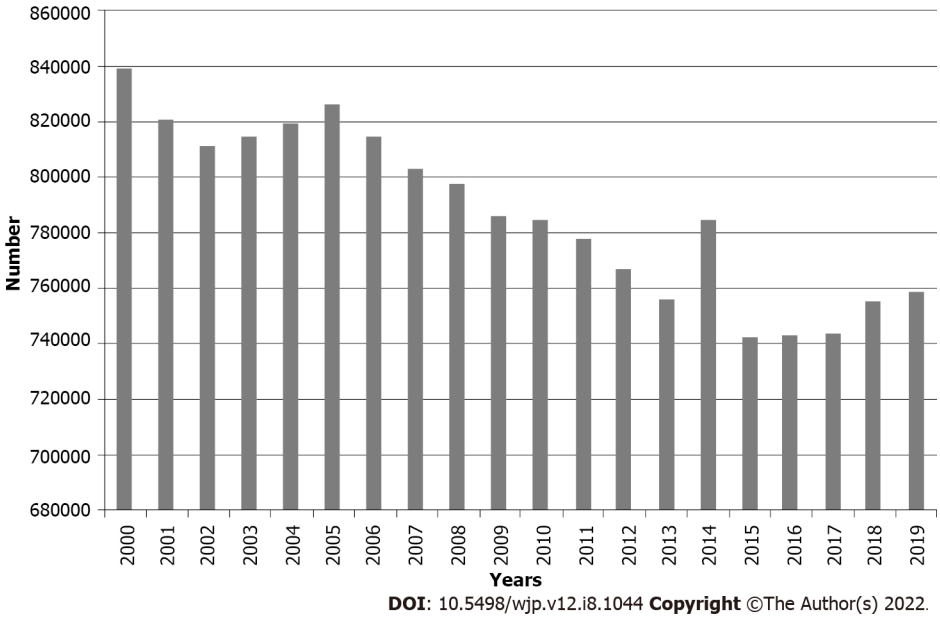

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Figure 1 Global suicide deaths, 2000-2019. Source: World Health Organization[6] and Global Burden of Disease estimates[7].

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

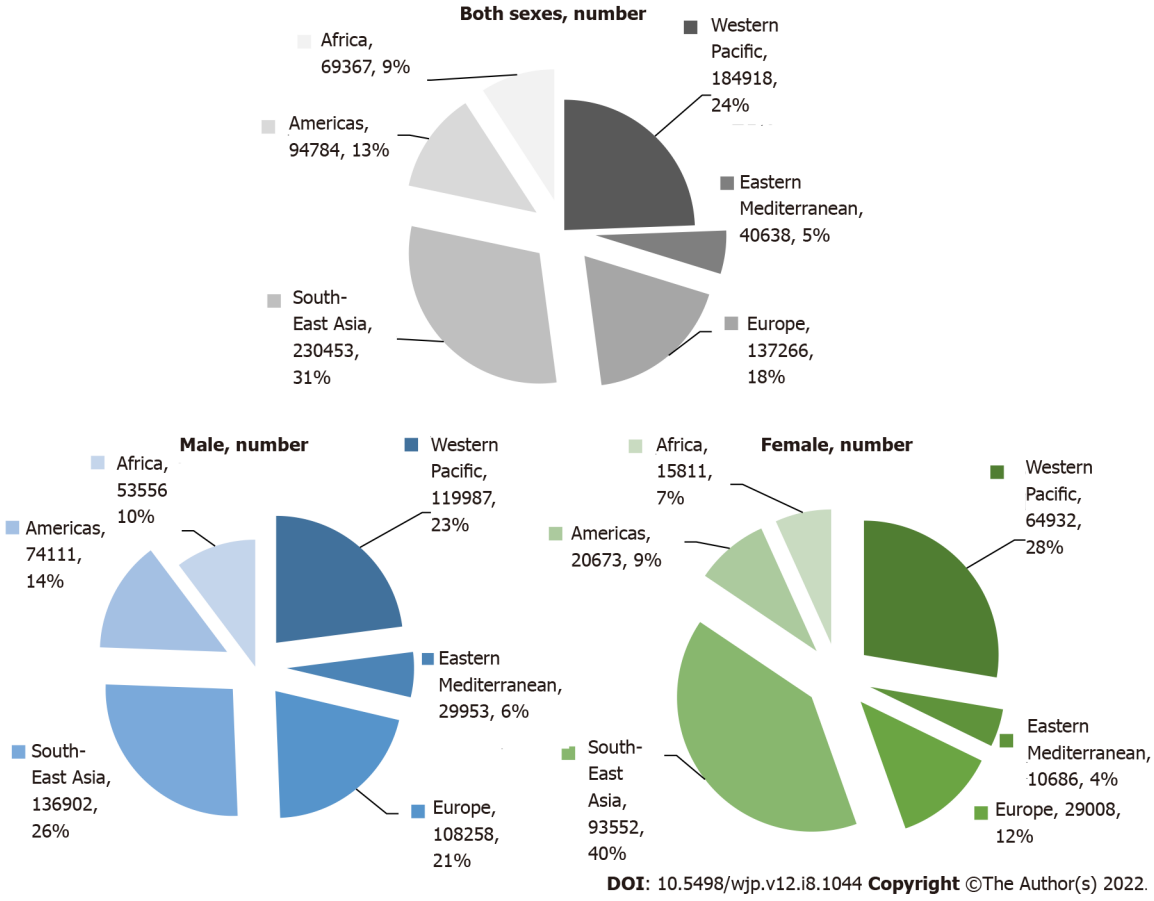

Figure 2 Number of suicide (global and by World Health Organization regions), by sex, 2019. Source: World Health Organization[6] and Global Burden of Disease estimates[7].

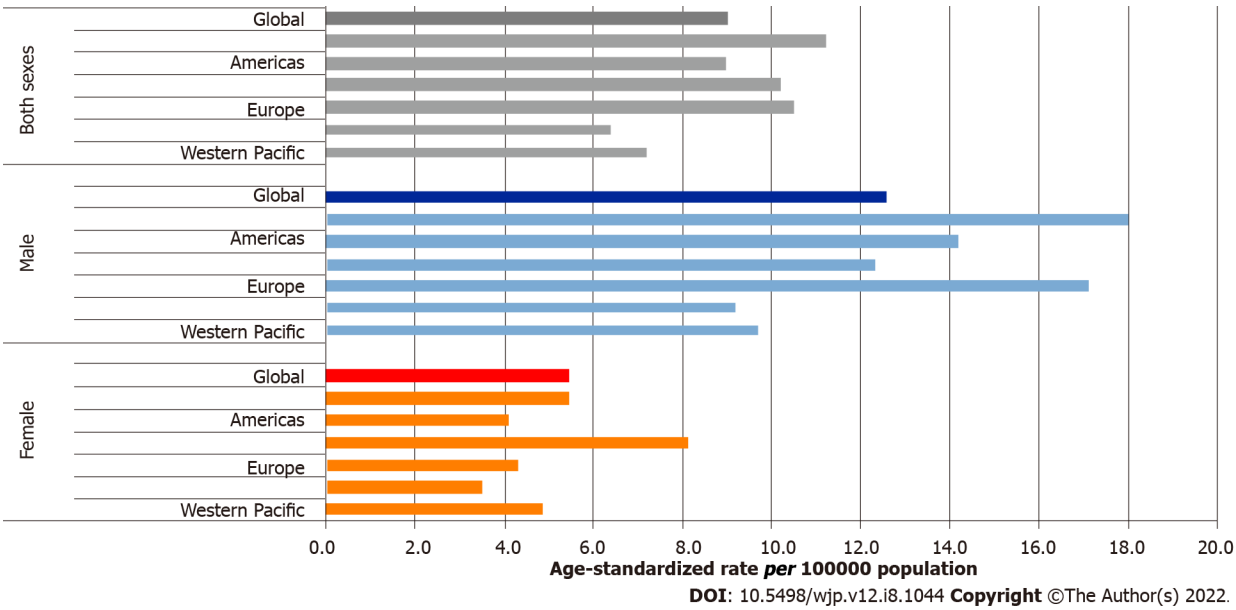

Figure 3 Age-standardized suicide mortality rates (global and by World Health Organization regions), by sex, 2019. Source: World Health Organization[6] and Global Burden of Disease estimates[7].

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)]

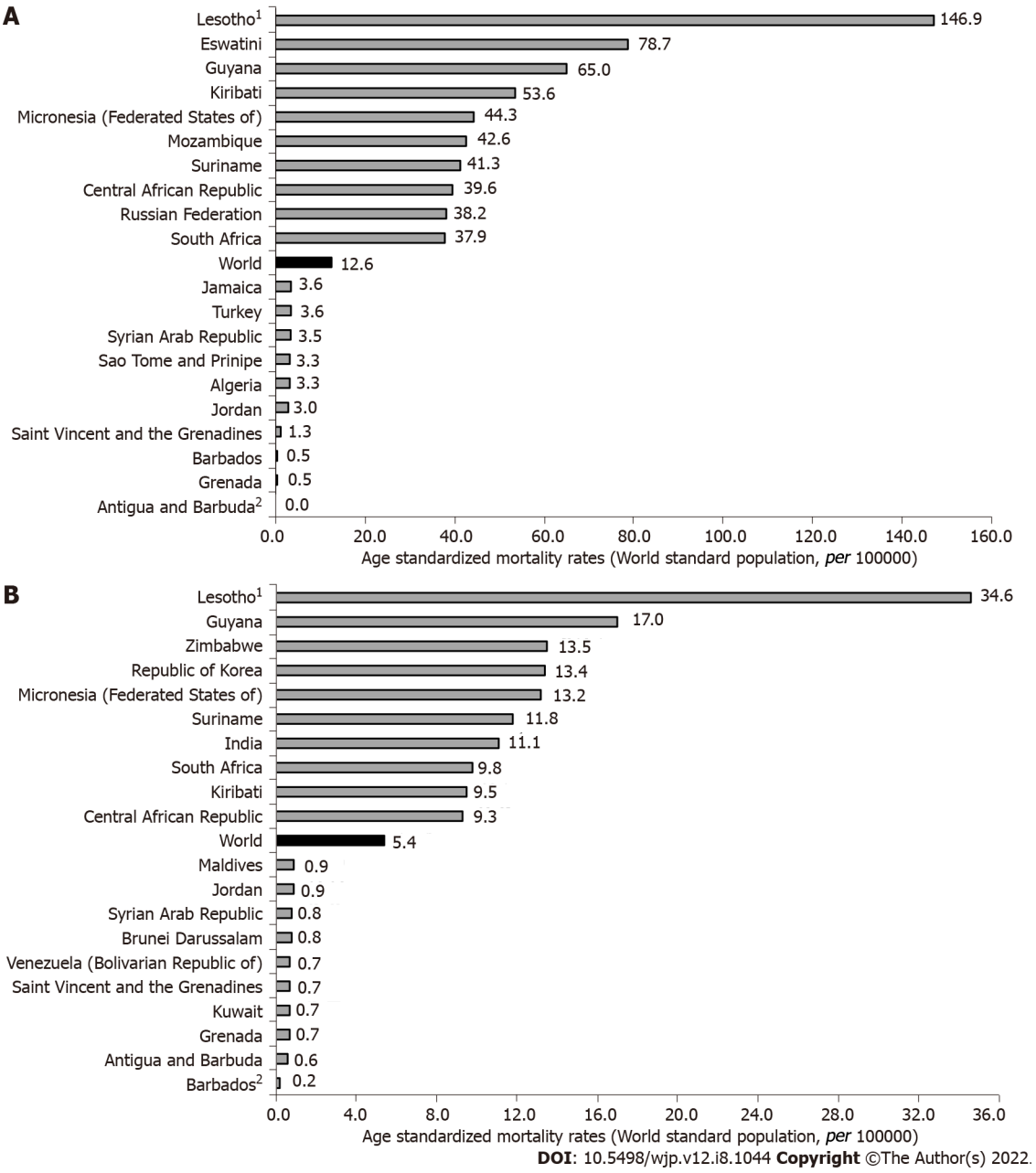

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Figure 4 Suicide mortality, by countries, 2019. [1]Country with the highest rates; [2]Country with the lowest rate. A: Men; B: Women. Source: World Health Organization[6] and Global Burden of Disease estimates[7].

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

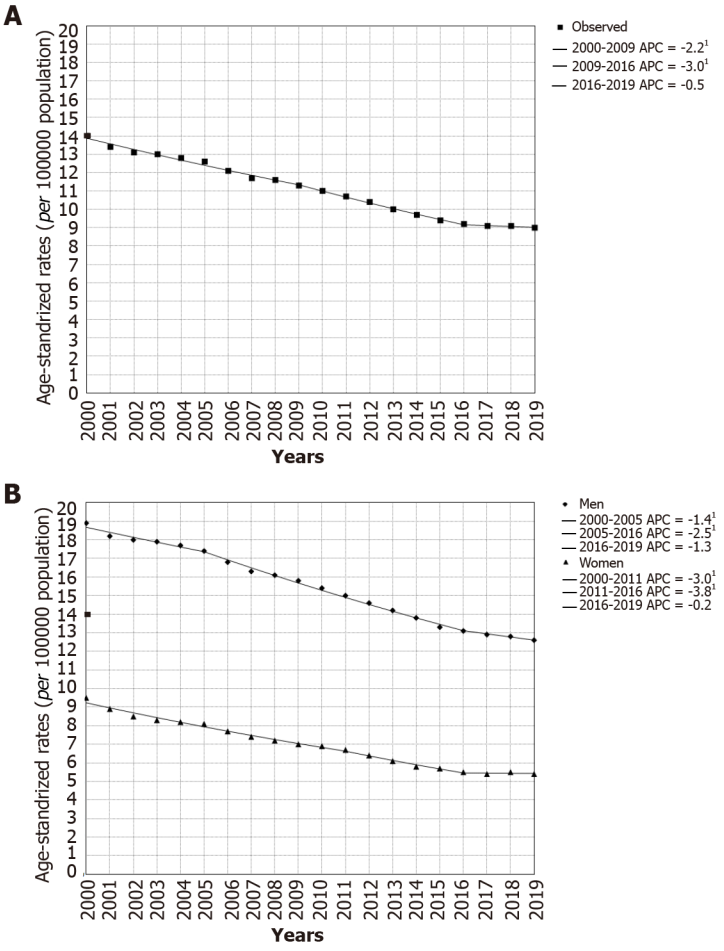

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Figure 5 Joinpoint regression analysis of global suicide mortality. [1]Indicates that the Annual Percent Change is significantly different from zero at the alpha = 0.05 level. Final selected model: 2 joinpoints. A: Both sexes, 2019: 2 joinpoints; B: 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

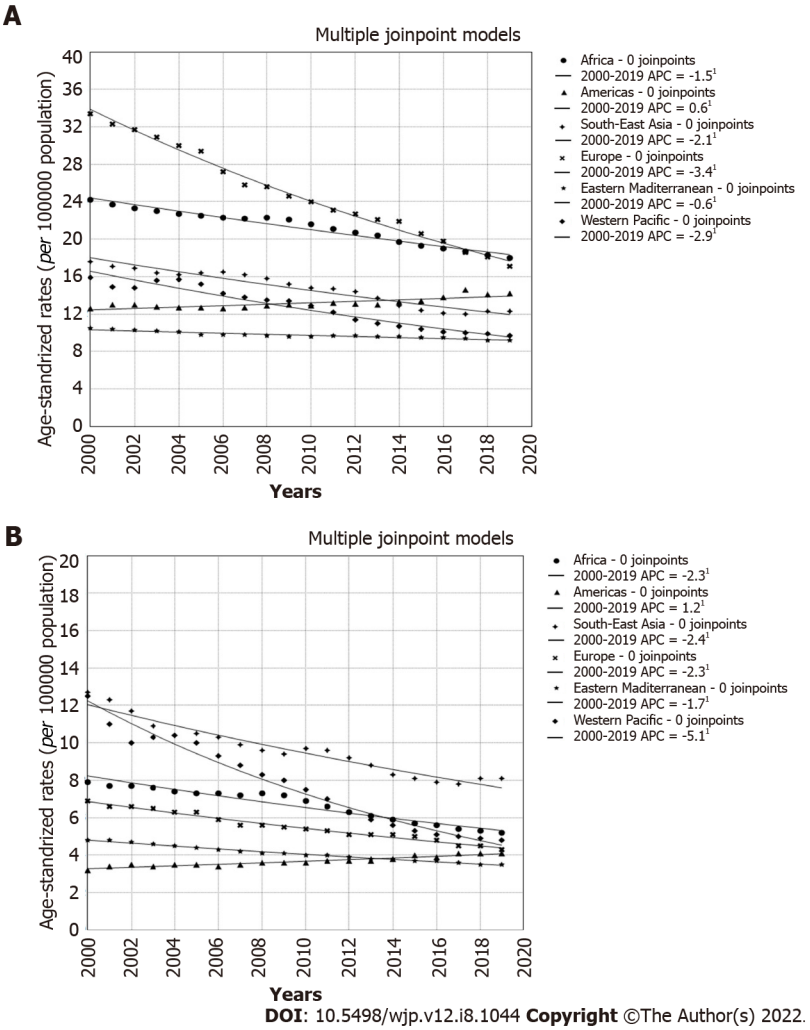

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Figure 6 Suicide mortality trends (World Health Organization regions), 2000-2019; a joinpoint analysis. [1]Statistically significant trend. A: In males; B: In females. APC: Annual percent change. Source: World Health Organization[6] and Global Burden 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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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 10th week to 12th 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

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 1st 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 10th 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 3rd trimester, with 13.5% (n = 27) in the 2nd and 8.5% (n = 17) in the 1st 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.

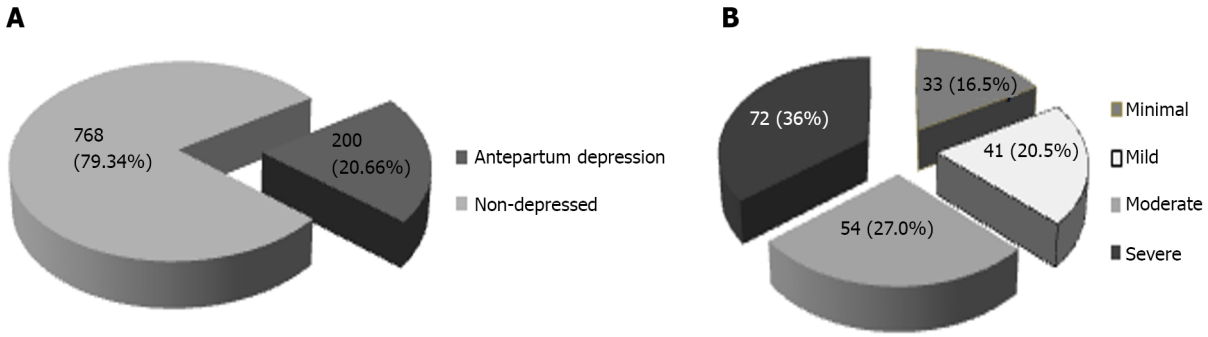

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Figure 1 Antepartum depression. A: Prevalence rate of antepartum depression. B: Severities of antepartum depression.

(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

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, χ^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 (χ^2 = 0.319, P = 0.956), HADS-A score (χ^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 (χ^2 = 1.049, P = 0.789); total ASDS score (χ^2 = 0.528, P = 0.913); and total ISI score (χ^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) (χ^2 = 7.654, P = 0.022), difficulty in falling asleep (χ^2 = 6.793, P = 0.033), and difficulty staying asleep (χ^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 (χ^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			χ^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 (χ^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

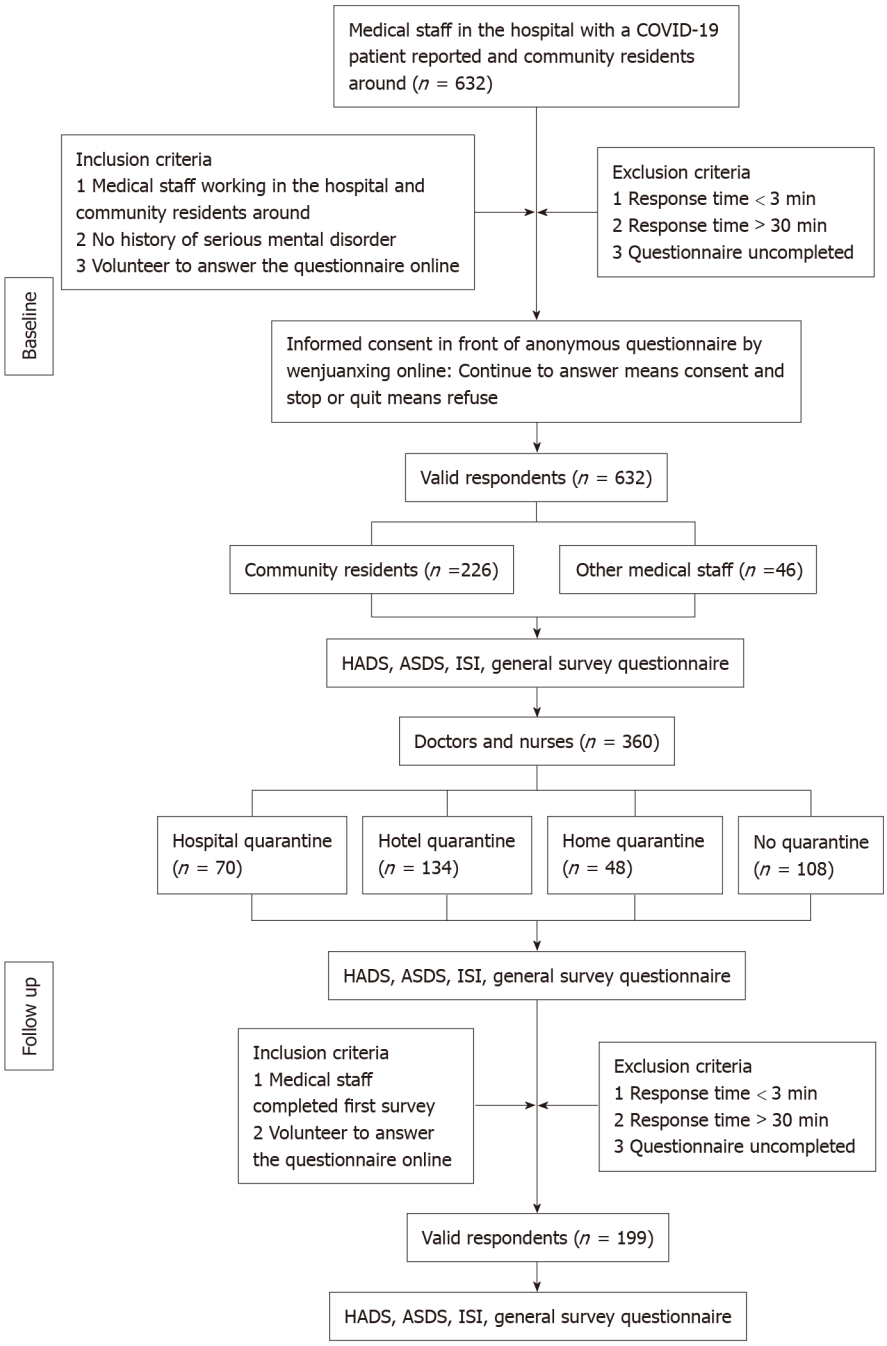

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Figure 1 Cross-sectional survey and follow-up study on psychological problems and insomnia in hospital staff and surrounding community residents of sporadic COVID-19 cases. COVID-19: Coronavirus disease 2019; HADS: Hospital anxiety and depression scale; 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

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.

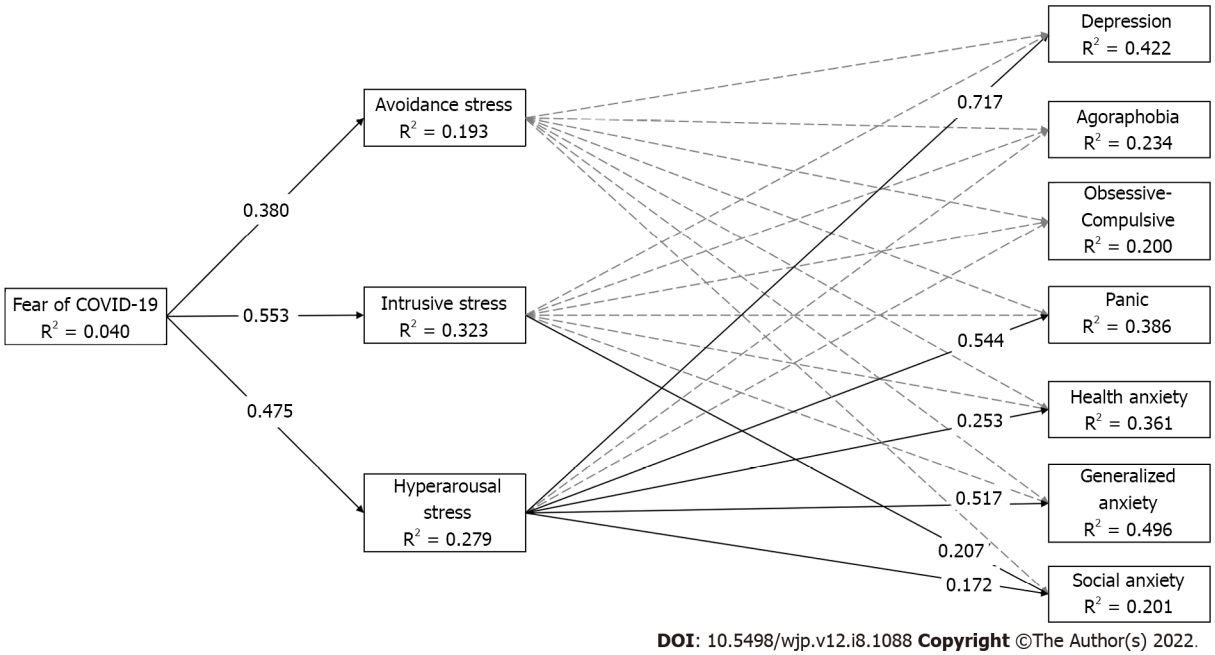

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Figure 1 Estimated path mediation model. Significant associations are indicated by the solid line for emphasis and were determined by a 99% bias-corrected standardized bootstrapped confidence interval (based on 10000 bootstrapped samples) that does 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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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

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

Author contributions: Tseng PT and Chen MH designed research; Chen MH and Liang CS performed research; Tseng PT and Liang CS analyzed data; Tseng PT wrote the letter; and Chen MH and Liang CS revised the letter.

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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

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.

FOOTNOTES

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LETTER TO THE EDITOR

Cardiotoxicity of current antipsychotics: Newer antipsychotics or adjunct therapy?

Zheng Liu, Mo-Lin Zhang, Xin-Ru Tang, Xiao-Qing Li, Jing Wang, Li-Liang Li

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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

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 ω-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

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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