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Not one thing at a time: When concomitant multiple stressors produce a transdiagnostic clinical picture

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Abstract

A condition of exposure to multiple stressors resulting in a mixed clinical picture spanning conventional categories without meeting any of them in full, encompasses a risk for a list of comorbidities preventing appropriate prevention and treatment. New transformative transdiagnostic approaches suggest changes spanning conventional categories. They base their systems of classification on biomarkers as well as on brain structural and functional dysregulation as associated with behavioral and emotional symptoms. These new approaches received critiques for not being specific enough and for suggesting a few biomarkers for psychopathology as a whole. Therefore, they put the value of differential diagnosis at risk of avoiding appropriate derived prevention and treatment. Multiplicity of stressors has been considered mostly during and following catastrophes, without considering the resulting mixed clinical picture and life event concomitant stressors. We herewith suggest a new category within the conventional classification systems: The Complex Stress Reaction Syndrome, for a condition of multiplicity of stressors, which showed a mixed clinical picture for daily life in the post coronavirus disease 2019 era, in the general population. We argue that this condition may be relevant to daily, regular life, across the lifespan, and beyond conditions of catastrophes. We further argue that this condition may worsen without professional care and it may develop into a severe

mental health disorder, more costly to health systems and the suffering individuals. Means for derived prevention and treatment are discussed.

Key Words: Transdiagnostic; Multiple stressors; Clinical picture; Prevention; Treatment; Interpersonal psychotherapy; Cognitive behavioral therapy

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Core Tip: Multiplicity of stressors has been considered mostly during and following catastrophes, without considering the resulting mixed clinical picture and life event concomitant stressors. We herewith suggest a new category within the conventional classification systems: The Complex Stress Reaction Syndrome, for a condition of multiplicity of stressors, which showed a mixed clinical picture for daily life in the post coronavirus disease 2019 era, in the general population. We argue that this condition may be relevant to daily, regular life, across the lifespan, and beyond conditions of catastrophes.

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INTRODUCTION

Many people with mental health complaints present a mixed clinical picture. Often none of the complaints meet the full criteria of any of the conventional classifications. Possibly, several categories are met (though not completely), leading to a list of comorbidities. This precludes clear diagnosis, prevention and treatment.

There are at least 4 different suggestions to revise classical classifications into transdiagnostic approaches: Hierarchical Taxonomy to Psychopathology[1], Research Domain Criteria[2], Bipolar-Schizophrenia Network on intermediate phenotypes[3,4], and Neuroscience-Based Nomenclature[5]. These suggested new classification systems are based on neuroanatomic findings showing that several brain areas demonstrate similar functionality and structure in various conventional categories[6-9]. However, others have commented on these data that they lack specificity, as the biomarkers show relevance over too many mental disorders[10]. Thus, many current conventional classification categories are gathered in the transformative systems into one pool of psychopathology, preventing consequent application of accurate prevention and treatment per each disorder including the missing clinical attention to individual differences.

Part of the mixed clinical pictures involves the concomitant experience of multiple stressors. As it arises from our literature search using PubMed, Google Scholar and *Reference Citation Analysis* (RCA), the impact of multiple stressors has been discussed by cutting edge papers mostly in the context of disasters such as hurricanes, floods, wars and in drastic conditions experienced by refugees and immigrants including the coronavirus disease 2019 (COVID-19) era, with similarities between the impacts in these types of conditions across the lifespan, *e.g.*[11-14]. The most common psychiatric outcomes reported are post-traumatic stress disorder (PTSD) and depression[15-20]. There are scarce reports on multiple stressors in daily life as related to the development of psychiatric disorders. Some of these reports relate to stressors in the workplace, economic hardships and the impact of urbanization[21-23]. Surprisingly, here also PTSD and depression are the common outcomes. The diagnosis of these two disorders in such different types of multiple stressors calls for attention and re-evaluation. Thus, the aim of the current paper is to suggest a new potential category for the conventional diagnostic system, which will include conditions of mixed clinical pictures with more than one stressor identified.

As clinicians, we encountered a condition in which many patients showed mixed symptomatology, spanning conventional categories, without fully meeting all the conventional criteria of any of these categories during the multi-stressor COVID-19 outbreak. Our literature review supported our observations[24]. In a following empirical bi-national study, using representative, large samples[25], we further found that combinations of several mental health symptoms studied, PTSD, phobia, depression, anxiety and posttraumatic stress symptoms, were more prevalent than combinations of fewer symptoms, with no majorities-minorities differences in both Italy and Israel[25]. We termed this mixed clinical picture the Complex Stress Reaction Syndrome (CSRS). CSRS includes type A (a psychiatric part) and type B (a neuropsychiatric part for the long-COVID component, excluding systemic symptoms)[24,25]. As more cross-cultural studies of the CSRS are warranted, we are currently conducting such an international study with participants from 8 diverse countries located in the Middle East, Europe, Australia and North America.

In this paper we suggest that the CSRS type A (the psychiatric part, not including type B) may explain mixed clinical pictures in conditions of multiplicity of significant stressful life events in the post-COVID era. Thus, we argue that in the general population, experiencing concomitant multiplicity of life events-related stressors may account for the development of a mixed type of mental health disorder, not only in conditions of catastrophes (see Figure 1).

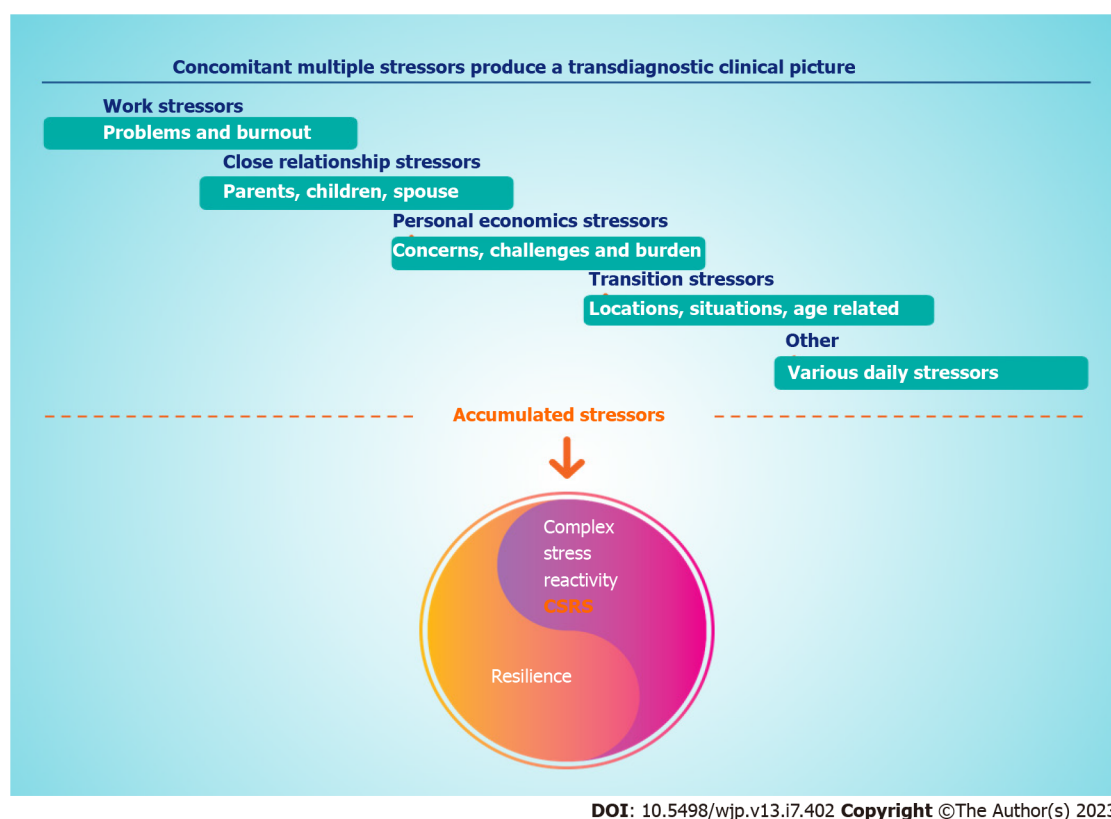


Figure 1 Accumulated stressors in daily life are associated with a mixed clinical picture in the general population. CSRS: Complex Stress Reaction Syndrome.

Differential diagnosis

For differential diagnosis, the CSRS (type A) may be compared to: (1) Diagnosis of adjustment disorder rules out PTSD and bereavement, and it displays a short stressor onset-symptoms occurrence latency; (2) PTSD diagnosis includes exposure to one frightening stressor; (3) Obsessional thoughts are ego-syntonic by definition. The behaviors related to extrinsic stressors are clearly not included in the obsessive-compulsive disorder (OCD) conventional category; (4) Diagnosis of acute stress disorder implies a simpler stressor and a specific symptom response; (5) The criteria for defining generalized anxiety disorder list excessive worrying (on diverse issues) and shifting back and forth among them, thus not implying the multiplicity of stressors and a mixed clinical picture; (6) The diagnosis of major depression disorder includes anhedonia, low affect, psychomotor agitation, unfitting guilt feelings, diminished drive and energy, trouble concentrating, and indecisiveness with no other types of symptomatology which are included in a mixed clinical picture; and (7) C-PTSD is described as the result of a series of traumatic events, which is repetitive and hard to escape but does not include a mixed clinical picture beyond the PTSD conventional criteria. It also describes a series of events and not the simultaneous occurrence of multiple stressors as the possible etiological source for psychopathology.

Prevention

The impact of multiple concomitant stressors depends on individual subjective perception and stress reaction tendencies [26]. The immediate question is what can prevent the emergence of pathological stress reactions, spanning several conventional categories. In a previous study we found that close relationships may protect the individual across the types of psychopathology investigated, spanning anxiety, depression, PTSD and OCD criteria, in conditions of multiple stressors [27]. The means for illness prevention and enhanced coping are therefore suggested as keeping close relationships active. Public and media educational programs for conditions of multiplicity of life stressful events with transdiagnostic potential consequences, aimed at enhancing individual resilience by utilization of social networks, are herewith suggested, evidence-based [27,28].

Treatment

We suggest a combined treatment approach of interpersonal psychotherapy (IPT) and cognitive behavioral therapy (CBT), two evidence-based and cost-effective methods, designed as short-term therapies and found to be equally effective to medications [29] in comparative studies [30,31]. Enhanced close relationships by techniques of problematic interpersonal relations analysis, resolution and role playing adapted from IPT [32], may increase emotional tolerance to accumulating stress emerging from concomitant origins. Our suggested combined psychotherapeutic approach also requires the blending of CBT separate protocols, including techniques for stress reduction and correction of cognitive distortions, rather than following one protocol separately or as recently suggested, one mandatory unified protocol for all

types of symptomology[33-36].

We suggested previously that when exposed to multiplicity of stressors, the lack of clear goals implies the diffusion of actions[37]. This could be a risk factor for effective treatment of patients confronted with this type of condensed stressful experience. To overcome this risk and also to respect individual differences, a patient-specific and session-specific therapeutic strategy of assigning clear goals for adaptive coping is warranted, rather than working through a reparation condition or just attempting to eliminate the identified external stressors.

DISCUSSION

The origins of CSRS

The CSRS emerged from the robust transdiagnostic clinical pictures during and following the pandemic[38]. The World Health Organization indicates a prevalence of 22% of a mixed picture including depression, anxiety, PTSD, and general distress, fatigue, irritability and anger in the general population following the experience of war or natural disaster[39]. Transdiagnostic approaches to classifications were proposed even prior to the COVID-19 pandemic[1-4]. Here we argue that the impact of multiple stressors in daily life is a neglected issue in traditional classifications.

What was probably different about the COVID-19 pandemic compared to previous catastrophes was its global scale and the fact that it was covered extensively by the social, electronic, and print media. This factor may be regarded as an additional stressor in daily life beyond disasters. Whether media use is a source of social support, especially for young people[27,40,41] or a daily life stressor in the form of bombardment of information[42], is still a topic under scientific debate and probably age-related with large inter-individual variance.

Although there is enough evidence to suggest that the mental health of the population deteriorated following the pandemic[43], there are suggestions that the extent of deterioration was less than anticipated[44,45]. In any case, epidemiological studies have shown that anxiety, depression, functional somatic, and even obsessional symptoms can coexist at the population or the community level[38,46,47], supporting our transdiagnostic views and the CSRS.

Inclusion of long COVID symptoms in the CSRS may create the same psychological *vs* physical dispute that we have witnessed with chronic fatigue syndrome or myalgic encephalomyelitis, but we include in the CSRS just neuropsychiatric symptoms, while systemic components of long COVID are excluded. In support of our view, studies that have already started appearing suggest that the long COVID syndrome is more likely to be associated with psychosocial factors rather than the COVID infection itself[48].

Thus, the origins of CSRS are rooted in the multi-faceted stress of the pandemic and its impact on mental health including its residuals in the post COVID era. The relevance of concomitant stressors included in daily life, under regular, non-catastrophic conditions, and their association with a mixed clinical picture, is gradually becoming apparent.

The CSRS within the debate on psychiatric nosology

Our opinion goes beyond conventional approaches for construction of psychiatric taxonomy. Alternative concepts of psychiatric validity include controversies between validation of nosological structures (typical for medicine) as compared to prototype, cluster and dimensional diagnosis of mental disorders[49]. While the field of psychiatry moved towards more medically oriented nomothetic knowledge, alternative groups which we follow in our empirical and review papers, suggest that the field has to move away from this type of knowledge towards a more ideographic and subjective approach to psychopathology[49].

The main differences between the validity of dimensional diagnostics and that of traditional nosology are apparent in several aspects: (1) In traditional approaches, mental pathology is regarded as a strict drift from acceptable norms while the transdiagnostic views, similar to ours, suggest an axis between normal and psychopathological conditions; (2) In dimensional approaches co-existing psychopathological states appear in parallel along with personal strengths and capacities for resilience, unlike traditional nomenclature; (3) Dimensional approaches to the convergent and divergent validity of a cluster or co-existence of different pathologies without meeting a full criteria of any category in the conventional systems, such as the CSRS, do justice to the patient and the entire individual clinical picture he or she describes to the clinician, while traditional approaches prefer multiple comorbidities; and (4) The dimensional approaches such as the CSRS, unlike conventional systems, emphasize subjective complaints of the patient (symptoms) rather than signs judged by the clinician. By that, these dimensional approaches are shifting the focus from the powerful societies of professionals towards the patient's subjectivity, and they recognize that professionals too, have their own subjective perspectives to consider before endorsing a diagnosis based only on signs.

Specifically, the CSRS has shown high reliability, as in two different countries and with two different methodologies similar results were found[25]. Additionally, the CSRS has shown high convergent and divergent validity as a combination of several identified stress symptoms, without meeting any full conventional category. These findings suggest a complex and unique type of reactivity to multiplicity of stressors. Other combinations suggested earlier, as complex anxiety and depression[50] or complex post traumatic stress disorder, showed validity for inclusion of just two conventional categories[51] while others showed a too wide range of inclusion, ruling out the potential judgement of divergent validity[10].

We acknowledge the importance of biological validation of psychiatric illness, but this still cannot be utilized for a treatment per any specified condition until the field of neuropsychiatric science advances considerably. The CSRS implies symptoms more than signs and subjectivity more than objectivity. The treatment derived from the CSRS would be patient-specific and session-specific, as human experience may go back and forth on the axis of elevated symptomology *vs* resilience and adaptive coping. Therefore, the notion of session-specific treatment requires the clinician's diagnostic

effort at every given session to reevaluate the patient's symptomology for progression *vs* regression and to offer treatment accordingly. We propose that the human experience transits along time that elapses and a condition may be judged for a given patient, in a given environment at a given moment, considering how the observed syndrome has been individually experience-shaped[52-55].

It was noted earlier that the empirical validation used as the basis of conventional categories has been mostly regression statistical analyses with a weak basis for causality[49]. Contrary to any etiological arguments, we argue that the CSRS represents an association between multiplicity of stressors and a mixed clinical picture, which is worth treating to avoid further increase in the patient's stress reactivity and future limitations of his or her resilience capacities.

We locate CSRS within the blend of the biopsychosocial model (BPS)[56] and the person-centered medicine (PCM) approach[57], as the novel CSRS is related to exogenic stressors (BPS) and occurs as a subjective complex stress reaction of the patient (PCM). Thus, as outlined here and according to our bi-national research design and findings[25], the CSRS falls within the post-modern dimensional approaches more than within any strict nosology, for better prevention and treatment. CSRS was designed and investigated from a humanistic perspective, arguing that mental health is not represented by the lack of psychopathology, while psychopathology, in turn, is a condition with an indication to treat and may be reversible.

CONCLUSION

Transdiagnostic considerations towards a change in the classification of mental disorders can be accomplished within the existing systems without ruling out the importance of differential diagnosis if these conventional systems will start to include transdiagnostic phenomena as legitimate conditions for treatment and care. This reduces the risk of diagnosing too many comorbidities and by that precluding appropriate prevention and treatment. We argue that the syndrome termed as CSRS better identifies those patients reacting in a manner that spans several conventional diagnostic categories following exposure to concomitant multiple stressors. Unlike approaches that argue for complete transformation of conventional classifications[1-5], we claim that that a specific diagnosis concerning multiplicity of stressors that result in a mixed clinical picture, is a potential contribution to the revised Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Diseases for more accurate derived prevention and treatment. The future will tell if the openness to include post-modern transdiagnostic approaches to accurately serve more patients in need and to facilitate clinical practice of each individual psychiatrist, will be part of the discussions on the next revisions of the Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Diseases or whether the debate and crisis in psychiatry[58] will continue.

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Delivering substance use prevention interventions for adolescents in educational settings: A scoping review

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Abstract

Currently, a proportion of adolescents use alcohol, tobacco, and illicit drugs, which inevitably harms their health and academic progress. Adolescence is a peak period for substance use initiation and a critical time for preventing substance use problems. Various entities, such as families, schools, and communities, have implemented a variety of interventions to alleviate adolescent substance use problems, and schools play a unique role. To explore the types, characteristics, and effectiveness of substance use interventions in educational settings for adolescents, we conducted a scoping review and identified 32 studies after screening. We divided the 32 studies according to intervention type, including curriculum interventions focusing on cognitive-behavioral skill enhancement, exercise interventions, peer interventions and family-school cooperation, and electronic interventions. Except for the mixed results on electronic interventions, the results showed that the other interventions were beneficial to different extents in alleviating adolescent substance use problems. In addition, we analyzed and summarized the advantages and challenges of intervening in adolescent substance use in educational settings. Schools can use equipment and human resources to provide adolescents with various types of intervention measures, but they also face challenges such as stigmatization, ineffective coordination among multiple resources, and poor implementation effects. In the future, school-based intervention measures can fully utilize big data and artificial intelligence technology and collaborate with families and communities to intervene appropriately while paying attention to the comorbidity risks of substance use disorders and psychological health issues.

Key Words: Substance use; Prevention; Adolescents; Educational settings; Artificial intelligence; Digital interventions

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Core Tip: Interventions in educational settings include curriculum interventions, physical activity interventions, peer interventions and family-school cooperation, and electronic interventions. Except for the mixed effectiveness of electronic interventions, all other intervention measures are beneficial in alleviating substance use problems among adolescents. Schools can utilize equipment and human resources to provide various types of interventions but also face challenges such as stigmatization and ineffective coordination between multiple resources. In the future, schools can fully utilize big data and artificial intelligence technologies, jointly intervene with families and communities, and appropriately address the comorbidity risks of substance use disorders and mental health issues.

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INTRODUCTION

Currently, substance use and abuse among adolescents have become important global public health issues. Adolescence is a critical period for physical and psychological development, as well as for experiencing life, pursuing independence, and establishing intimate relationships[1]. Individuals are more susceptible to substance use risks in the adolescent stage than in other stages of life. Research has shown that adolescence is the peak time for the initiation of drug use[2]. The level and frequency of drug use among adolescents begin to increase in mid-adolescence and peak in early adulthood. The median age of onset of alcohol use in most countries is 16-19 years[3]. The global burden of disease study showed that drug use is a significant factor in the health burden in the adolescent and young adult population[4]. Early exposure to alcohol, tobacco, and other drugs may lead to violent or aggressive behavior in adolescents, making it difficult for them to adapt to school, family, and social environments[5]. Such exposure not only causes various negative health outcomes [1], but may also result in psychological health issues such as anxiety and depression in adolescents[6-9]. Therefore, it is essential to identify substance use problems in the adolescent population as early as possible and to take timely intervention measures.

Multiple research results indicate that adolescent substance use problems are the result of the combined action of various risk factors, such as personal, family, school, community, and societal factors. Substance use by parents or relatives in the family environment has an insidious influence on adolescents while also providing a channel for their substance exposure[10]. Adolescents who are in disadvantageous positions in life are more likely to use drugs to escape the pressure of reality[11]. Peer substance use in the school environment may stimulate the curiosity of adolescents or cause them to use drugs to fit in due to “peer pressure”[12]. Implementing intervention plans based on different subjects is an effective strategy to address adolescent substance use problems[13-16]. First, at the social level, clearly defining the scope of legal substance use and adopting strict regulatory measures can effectively reduce adolescents’ negative substance use behavior[17]. For example, alcohol or tobacco price controls can be implemented through taxes[18-22], minimum age laws can be enforced[23], and the availability of inhalants can be minimized[24]. Second, at the family level, factors such as parenting style, family relationships, and family function can significantly predict adolescent drug abuse and related behaviors[25]. Family involvement has been found to be effective in treating adolescent substance use disorders. The basic principle of family-based intervention measures is to directly or indirectly establish more stable family relationships by providing training courses or developing intervention plans for parents and adolescents, thereby reducing the risk of adolescent substance use disorders[26-28]. For example, the Strong African American Families-Teen program effectively prevents drug use and emotional problems in black adolescents by offering 10 h of adolescent skills training courses and family courses[29]. Family matters (FM) helps parents identify family characteristics, behaviors, and attitudes that may affect adolescent drug use by regularly mailing families guidance manuals. Professional health education workers follow up on the use of the manuals by contacting parents after each mailing. The results of a study on FM showed that the complete intervention plans effectively reduced the rates of tobacco and alcohol use in adolescents [13]. Third, at the community level, some studies suggest that the community and its surrounding environment can play a positive role in adolescent substance use problems[16,30]. Community-based intervention plans usually require community leaders, community workers, and other stakeholders and professionals to work together. For example, in the Community Trials Intervention to Reduce High-Risk Drinking, community leaders use local policies and regulations to control the number of bars, retailers avoid selling alcohol to minors, and so on[13]. Clearly, intervention measures based on multiple stakeholders, such as those at the social, family, community, and school levels, can play an essential role in resolving adolescent substance use problems[16]. Multidimensional family therapy (MDFT) integrates family therapy, individual therapy, and drug counseling with multisystem intervention methods[31]. Multiple experiments have shown that MDFT is a more effective treatment method than other methods for adolescent drug abuse and comorbid mental symptoms[32].

In addition, as current adolescents are “digital natives”, they have a “natural” attraction to digital interventions[33-35]. Technology-based intervention measures are mainly interactive digital activities aimed at preventing or delaying adolescent drug use from the aspects of knowledge, attitude, and behavior[36-38]. RealTeen is a web-based intervention measure that places youth in realistic drug use scenarios by using interactive skills-building sessions. Adolescents can

improve their self-awareness and social skills, thereby avoiding drug use[39,40]. Studies have shown that after intervention, participants have lower rates of use of alcohol, marijuana, and multiple drugs[39]. Specific intervention measures based on multiple subjects are shown in Table 1.

Compared with other context, such as families and communities, the educational environment in schools offers unique advantages for intervening in adolescent substance use. Considering the characteristics of adolescence, such as a long duration of schooling, close peer interaction, and intensive education, schools are an excellent place to intervene in adolescent substance use[1]. On the one hand, school can educate adolescents on the characteristics and harms of the use of substances, such as alcohol, tobacco, and illegal drugs, by offering relevant courses. On the other hand, peer interaction and practical activities in the school environment can make adolescents value education, help them form a correct attitude toward life, and prevent substance use problems before they happen[41,42].

Recent research has focused on the importance of schools in addressing adolescent substance use problems and exploring effective intervention measures from different perspectives. For example, intervention models have been constructed based on cultural backgrounds and family relationships, Botvin Life Skills Training has been used to train students in the school environment, and psychological training has been implemented to prevent substance use problems among adolescents. These measures aim to improve adolescent tobacco use problems[43-45].

The existing literature has proposed various intervention measures based on the seriousness of adolescent substance use problems. However, the vast majority of research only discusses school-based intervention as one of many intervention measures[46], and few studies have directly investigated preventive intervention measures for adolescent substance use from the perspective of the educational environment. Considering the changes in adolescent substance use problems before and after the pandemic, this paper, based on a comprehensive review of existing literature in this field, focuses on research results from the past seven years and further explores preventive intervention measures for adolescent substance use in the educational environment.

Objectives

Based on the unique advantages of schools in intervening with adolescent substance use and the richness of research in this field, we conducted a scoping review to understand specific intervention measures and their effectiveness in the current educational environment. Our research questions were as follows: (1) What are the intervention measures currently used in the educational environment to intervene with adolescent substance use? and (2) what are the characteristics and effects of these intervention measures?

LITERATURE REVIEW

Search strategy

To explore the types, characteristics, and effectiveness of intervention measures for adolescent substance use in the educational environment, we conducted a preliminary evaluation of relevant literature in this field. Literature searches were conducted in May 2023 in five databases: Web of Science Core Collection, PubMed, EBSCO, Scopus, and Google Scholar (selecting the top 200 most relevant articles). The following keywords and terms were used: (1) Substance use; (2) adolescent; (3) educational setting; and (4) prevention. The following string was used: ("substance use" [All Fields] OR "alcohol" [All Fields] OR "tobacco" [All Fields] OR "marijuana" [All Fields] OR ("illicit drug" [All Fields]) AND ("youth" [All Fields] OR "teenager" [All Fields] OR "adolescence" [All Fields]) AND ("school" [All Fields] OR "educational setting" [All Fields]) AND ("intervention" [All Fields] OR "prevention" [All Fields]).

Study selection

The full screening process included three stages: (1) EndNote software was used to identify duplicate articles and retain those with more comprehensive information; (2) the first round of screening was conducted based on the inclusion and exclusion criteria, along with titles, abstracts, and keywords in EndNote; and (3) manual screening was performed based on the full text using Rayyan.

The inclusion criteria were as follows: (1) The age of the study subjects was 10-19 years (according to UNICEF, WHO, and UN Population Fund); (2) intervention measures were based in educational settings; (3) there was a specific, clear, and operational intervention plan for substance use problems; (4) the article was easily accessible; and (5) the article was published in English.

The exclusion criteria were as follows: (1) The age of the study subjects was outside the defined range; (2) intervention measures were based on other environments, such as family and community; (3) the article did not belong to the substance use problem category or only mentioned the topic briefly; (4) the article was a literature review, letter to the editor, or opinion piece; (5) the article was from the gray literature; and (6) the article was published in a language other than English. Please see Figure 1 for the specific screening process.

Data analysis

After screening, a total of 32 articles were obtained. Analyses and table summaries of the literature revealed that these articles could be grouped based on the type of intervention strategies used. The two primary themes and their associated subthemes are as follows: (1) Various types of intervention strategies and their effects include interventions that focus on cognitive-behavioral skill building, exercise, peer and family involvement, and electronic interventions; and (2) differences in substance use intervention strategies among adolescents in different educational stages.

Table 1 Multiagent-based adolescent substance use interventions

Implementation subject	Intervention method	Specific measures
Based on social intervention measures	Clarifying the scope of legal substance use and adopting strict regulatory measures	Manage the age, sales timeframe, permissible quantities, and pricing of substances and regulate users[18]
		Levy taxes on the alcohol or tobacco content of goods and tie them to fluctuations in consumer pricing[19]
		Implement and enforce laws mandating a minimum age limit and raise the age threshold for young people to purchase alcoholic beverages[18,23]
Based on family intervention measures	Providing training courses for parents and teenagers	Create community-specific regulations concerning the issuance of tobacco and alcohol licenses to minors and promote their enforcement within localities[24]
		Strong African American Families-Teen program: Deliver skill-building courses and family training sessions spanning 10 h and comprising 5 sessions to both parents and teenagers[29]
	Developing intervention plans	Creating lasting family connections: Offer a 20-wk facilitator training program for parents and teenagers[13]
		Families preparing the new generation plus: Execute a 10-wk prevention plan for nutrition and material use while emphasizing healthy eating and parenting strategies[26]
Based on community intervention measures	Providing community intervention programs	Familias Unidas: Enforce a set of intervention measures aimed at enhancing parents' sense of efficacy and parenting skills (parent support networks), family meetings/home visits, parent-adolescent discussion circles, adolescent activity groups, supervised peer activities, and school counselor meetings[27]
		Risk reduction therapy for adolescents: Intervention measures conducted by a professional therapist with a relevant master's degree at an outpatient clinic. Caregivers are obligated to attend a weekly session lasting between 60 min and 90 min[28]
Based on technology intervention measures	Utilizing innovative intervention methods, such as the internet and big data	Community trials intervention to reduce high-risk drinking: To modify the community's drinking behavior, offer responsible beverage service, reinforce law enforcement, and set up alcohol checkpoints[13]
		Deliver a 10-wk intervention plan for adolescents using the Health Rocks program and multiple disciplinary literacy strategies. Emphasize the effects of substance abuse on health and require adolescents to attend a one-hour theme-based instruction per week[30]
Based on technology intervention measures	Utilizing innovative intervention methods, such as the internet and big data	CLIMATE: Provide 6 lessons based primarily on social influence theories <i>via</i> CD-ROM and the Web. The lessons provide knowledge about how common substance use is as well as the negative outcomes it can lead to and teach methods to avoid substance use and the subsequent hazards[37]
		HeadOn: Require the involvement of students in decision-making related to substance use through interactive simulation scenarios[38]

LITERATURE RESULTS

Each section summarizes the mechanism and effects of various intervention measures (Tables 2-5).

Various types of intervention measures and their effects

Curriculum interventions focused on cognitive-behavioral skill enhancement[47,48]: The mechanism of these interventions involved two parts (Table 2): (1) Using traditional ethnic values and methods to prevent smoking, drug use, *etc.*[49] and connecting the psychological and social concepts of substance use with multicultural values[50] to regulate adolescent substance use behavior; and (2) implementing a series of courses to improve students' cognitive and behavioral skills[51], including knowledge about the characteristics and harms of alcohol, tobacco, and illicit drugs[52], communication[53], decision-making and other life skills[54,55], and methods to resist drug use pressure[56,57]. These interventions had positive effects on adolescent alcohol, cigarette, and marijuana use to varying degrees. A study conducted a randomized field trial with seventh- and ninth-grade students to implement a school-based intervention program, Take Charge of Your Life (TCYL), to prevent adolescent alcohol, tobacco, and drug use. The TCYL program follows the principles of substance abuse prevention programs, using counseling classes to help students understand the negative effects of alcohol, tobacco, and illicit drugs on individuals and society, and it requires students to learn communication, decision-making, assertiveness, and refusal skills. The results of the study showed that TCYL helped reduce the potential motivation for drug use and was beneficial for students who smoked marijuana[58] (Table 2).

Exercise interventions: Exercise is one of many health behaviors associated with good lifestyle habits[59]. Exercise programs to intervene in adolescent substance use problems help adolescents develop good lifestyle habits to reduce the willingness to engage in substance use and the frequency of substance use[60,61]. Werch *et al*[62] and Goldberg *et al*[63] primarily used exercise screening, counseling, and exercise training courses to reduce adolescent drinking behavior and improve health habits. More recently, new forms of exercise intervention have emerged in schools. Some examples

Table 2 Curriculum interventions focusing on cognitive-behavioral skill enhancement

Ref.	Age/gender	Scope of application			Method	Content	Effect	Location
		Alcohol	Tobacco	Illicit drugs				
Diaz Gomez <i>et al</i> [47], 2021	10-12 yr, all genders	Yes	Yes	-	Randomized controlled cluster study	Primavera is a prevention program that focuses on experiences and involves multiple modes of delivery. It spans several years and has a generic approach	Primavera is effective in decreasing alcohol consumption among school students	France
Kimber <i>et al</i> [48], 2009	Grades 7 to 9 (13-16 yrs), all genders	Yes	Yes	Yes	Nonrandomized five-year longitudinal design	Teachers offer weekly lessons on social and emotional training to students	A particular group of people derived benefits from the program	Sweden
Hecht <i>et al</i> [49], 2003	Grade 7, all genders	Yes	Yes	Yes	Randomized controlled trial	Interventions based on culture are conducted through 10 specific lessons and a media campaign utilizing a model of cultural resilience	The intervention had a considerable and noteworthy effect on individual consumption of alcohol, cigarettes, and cannabis	United States
Unger <i>et al</i> [50], 2004	Grade 6, all genders	-	Yes	-	Participatory research	The Project Fun Learning About Vitality, Origins, and Respect is a curriculum that promotes multicultural education	The project successfully stopped hispanic boys from starting smoking but had no impact on other groups	United States
Walker <i>et al</i> [51], 2011	14-19 yr (Grade 9-12), all genders	-	-	Yes	Randomized controlled trial	Motivational enhancement therapy, educational feedback control, and delayed feedback control	Participants stated that they used cannabis less frequently and experienced fewer negative outcomes	United States
Faggiano <i>et al</i> [52], 2010	12-14 yr, all genders	Yes	Yes	Yes	Cluster randomized controlled trial	The program involved a 12-h curriculum that was developed using a thorough social influence approach	Alcohol abuse and marijuana use showed a consistent improvement, whereas smoking displayed no change	Spain, Belgium, Germany, Sweden, Greece, Italy, and Austria
Dent <i>et al</i> [53], 2001	14-17 yr, all genders	Yes	Yes	Yes	Randomized controlled trial	Project Toward No Drug Abuse: Standard care and classroom education program	Over a period of one year after the program, this population saw statistically significant changes in alcohol and illicit drug use	United States
Hanewink <i>et al</i> [54], 2004	Grades 5 and 6 (mean age 11.4 yr), all genders	-	Yes	-	Randomized controlled trial	The smoking prevention program utilized a life-skills approach and included 21 sessions	The program did not have a distinct impact on the current smoking rate (percentage of people who smoked in the past 4 wk)	Austria, Denmark, Luxembourg, and Germany
Botvin <i>et al</i> [55], 2001	Grades 7 to 9, all genders	Yes	-	-	Randomized controlled trial	A proactive approach that educates individuals on resisting alcohol and drug consumption, promoting healthy social norms, and providing material to encourage personal and social skill-building	The prevention program was effective in protecting against episodes of excessive drinking	United States
Botvin <i>et al</i> [56], 1999	Grade 7 (mean age 12.9 yr), girls	-	Yes	-	Randomized controlled trial	This program consists of 15 sessions aimed at teaching social resistance skills within a broader initiative that aims to promote general personal and social competence skills	The number of urban minority girls who started smoking or increased their smoking habits was significantly reduced	United States
Shope <i>et al</i> [57], 1998	Grade 6 (mean age 12 yr), all genders	Yes	Yes	Yes	Participatory research	The students in the curriculum group were taught about alcohol, tobacco (including cigarettes and smokeless	The curriculum achieved short-term effectiveness by considerably decreasing the rising rates of alcohol	United States

						tobacco), marijuana, and cocaine	consumption and addiction, tobacco use, cocaine intake, and other types of substance abuse	
Sloboda <i>et al</i> [58], 2009	Between seventh and ninth grade, all genders	Yes	Yes	Yes	Randomized field trial	TCYL offers students essential life skills, which include communication, decision-making, assertiveness, and refusal skills	TCYL had a negative impact on students' use of alcohol and tobacco as a result of medical treatment	United States

TCYL: Take charge of your life.

Table 3 Exercise interventions

Ref.	Age/gender	Scope of application			Method	Content	Effect	Location
		Alcohol	Tobacco	Illicit drugs				
Werch <i>et al</i> [59], 2005	Ninth and eleventh grade, all genders	Yes	Yes	Yes	Randomized controlled trial	Project SPORT is a short intervention that promotes healthy habits by integrating physical activity and preventing alcohol use	After the treatment and after one year, it was anticipated that the project would have an impact on the drinking and smoking habits of adolescents	United States
Brick <i>et al</i> [60], 2017 and Velicer <i>et al</i> [61], 2013	Grade 6, all genders	Yes	Yes	-	Multiattribute utility measurement approach	An intervention aimed at preventing substance use and promoting a healthy energy balance through physical activity, consumption of fruits and vegetables, and decreasing sedentary behavior	The outcome of every action was a significant decrease in the prevalence of smoking and drinking compared to the existing rates reported by ninth-grade students	United States
Werch <i>et al</i> [62], 2003	Grade 8, all genders	Yes	-	-	Randomized experimental design	Consultation for Sports (Sport): A process of evaluating one's health and fitness followed by discussion and recommendations	The program may boost the frequency of physical activity while decreasing alcohol consumption	United States
Goldberg <i>et al</i> [63], 2000	Grade 9 and grade 10, all genders	Yes	-	Yes	Randomized controlled trial	An education program centered on team collaboration and designed for a specific gender, which includes interactive classroom sessions and exercise training	The program was successful in stopping people from using alcohol and other prohibited drugs	United States
Butzer <i>et al</i> [64], 2017	Grade 7 (with a mean age of 12.64), all genders	-	Yes	-	Preliminary group randomized controlled trial	The curriculum of Kripalu Yoga in the Schools has a version that includes 32 sessions	Practicing yoga in schools can be helpful in reducing the inclination of both males and females towards smoking	United States
Fishbein <i>et al</i> [65], 2016	Grades 9 to 12 (mean age 12 yr), all genders	Yes	-	-	Pilot randomized controlled trial	A 20-session mindfulness yoga program created for students at risk of dropping out from school	The students who took part in yoga sessions showed a reduction in alcohol consumption	United States
Mathews <i>et al</i> [66], 2007	High school students, all genders	Yes	Yes	Yes	Randomized controlled trial	The project SPORT comprises of a brief interactive CD-ROM and a brief group consultation	The project received considerable acceptance among adolescent males and females and could be effective	United States
Horn <i>et al</i> [67], 2013	14-19 yr, all genders	-	Yes	-	Randomized group trial	The physical activity levels of participants in a smoking cessation program for teenagers improved with the addition of a physical activity component	Adolescents in good health are more likely to decrease their amount of smoking	United States

include integrating yoga into students' physical education classes to reduce their smoking habits[64,65] and combining exercise with an interactive CD-ROM to tailor exercise plans for students to execute independently[66]. The results of these studies confirm that exercise interventions are acceptable to adolescents and help reduce substance use behavior.

Table 4 Peer interventions and family-school cooperation

Ref.	Age/gender	Scope of application			Method	Content	Effect	Location
		Alcohol	Tobacco	Illicit drugs				
Paquette <i>et al</i> [68], 2019	Ages 13-17, all genders	Yes	-	Yes	Randomized controlled trial	"Amplifying Our Futures (Amp)" is a temporary intervention program that consists of four phases. It is designed for adolescents who are at low to moderate risk of using substances and is facilitated by trained companions aged 18-28 years old	Young peer intervention was valuable in educational environments	United States
Botvin <i>et al</i> [69], 1990	Grade 7, all genders	Yes	Yes	Yes	Cluster randomized controlled trial	Life skills training is a program designed to improve cognitive and behavioral skills, which is led by both experienced students and teachers in a classroom setting for a total of 20 sessions	Preventative programs have had a quantifiable effect on behavior related to substance use	United States
Furr-Holden <i>et al</i> [70], 2004	Grades 1-8, all genders	Yes	Yes	Yes	Randomized prevention trial	The classroom-centered intervention and the family-school partnership intervention	Two interventions had a clear protective effect against tobacco use	United States
Zavela <i>et al</i> [71], 2004	Grades 4-8, all genders	Yes	Yes	Yes	Control experiments and follow-up questionnaire	Say Yes First-To Rural Youth and Family Alcohol/Drug Prevention: An educational and case management approach to drug prevention	The students who were part of the program consumed less alcohol, tobacco and other drugs and had a lower occurrence of marijuana use throughout their lifetime	United States
Winters <i>et al</i> [72], 2012	Ages 14-17, all genders	Yes	-	Yes	Randomized controlled trial	BIs: Therapists used the principle of motivational interviewing to conduct topical sessions with parents and students	BIs showed a connection with decreased drug usage, with a greater impact when parents were included	United States

Bis: Brief interventions.

Horn *et al*[67] combined physical activity and smoking cessation interventions for adolescents. The research suggested that students who increased their exercise time by 20 min were more likely to reduce their daily smoking quantity (Table 3).

Peer and family-school interventions: On the one hand, peer support is a protective factor for substance use problems in adolescents, and the role of peers can provide screening and intervention measures that are suitable for adolescent development[68]. Botvin *et al*[69] showed that peer intervention programs were more effective than regular classroom teaching. The Amplifying Our Futures program, jointly designed by multiple stakeholders such as schools, communities, and adolescents, is implemented by trained young adults. The results on the program confirmed the value of peers in substance use intervention in adolescents[68]. In addition, some research indicated that forming a partnership between families and schools, strengthening communication and exchange between the two parties, and effectively involving parents in adolescent substance use intervention can help reduce adolescents' early substance use behavior[70-72] (Table 4).

Electronic interventions: Currently, the application of electronic interventions in adolescent substance use is relatively limited. Examples include (1) Having teenagers watch videos and public service announcements[73] or teaching adolescents about alcohol, tobacco, and cannabis using electronic learning modules or programs[74,75]; (2) designing internet-based intervention plans for teenagers[76,77]; and (3) adopting alcohol media literacy programs to enhance teenagers' media literacy skills and reduce the potential impact of substance use-related advertisements on teenagers[78]. However, researchers have not yet reached a consensus on the effectiveness of electronic interventions. It is suggested that internet-based intervention plans are convenient for reducing alcohol and cannabis use, and research results showed that students in the intervention group reduced alcohol use one year after completing the course[76]. However, a web-based program called Consider This, implemented by Buller *et al*[77], was found to be of little value in preventing adolescent substance use (Table 5).

Differences in substance use intervention measures for adolescents at different educational stages

Adolescence is a critical period for preventing substance use. Through a literature review and summary, we found that intervention measures for substance use among adolescents at different educational stages need to focus on different

Table 5 Electronic interventions

Ref.	Age/gender	Scope of application			Method	Content	Effect	Location
		Alcohol	Tobacco	Illicit drugs				
Jennifer <i>et al</i> [73], 2006	Grade 7, all genders	Yes	Yes	Yes, marijuana	Randomized controlled trial	The usefulness of the Drug Resistance Strategies Project's Keepin' it REAL program aimed at preventing adolescent substance use was explored by studying students who participated in it through public service announcements and videotapes	Class videos influenced the use of drugs among teenagers, whereas PSAs did not have an impact	United States
Malmberg <i>et al</i> [74], 2014	11-15 yr, all genders	Yes	Yes	Yes	Randomized clustered trial	Healthy School and Drugs program: Digital modules for e-learning and comprehensive intervention	Both the e-learning and comprehensive intervention failed to prevent the initiation of alcohol, tobacco, or marijuana use	The Netherlands
Kiewik <i>et al</i> [75], 2017	12-16 yr, all genders	Yes	Yes	-	Pre-/post-intervention pilot study with a control group	"Prepared on time": A digital training program that follows the attitude-social influence-efficacy model	This research demonstrated that an electronic learning prevention program is feasible for teenagers with mild or moderate intellectual disability	The Netherlands
Newton <i>et al</i> [76], 2010	13 yr, grade 8, all genders	Yes	-	Yes	Cluster-randomized controlled trial	Internet-based prevention programs for school-age children: The Climate Schools: Alcohol and Cannabis course	After finishing the programs, students' understanding of alcohol and cannabis improved, and it also led to a decrease in the consumption of alcohol for up to twelve months	Australian
Buller <i>et al</i> [77], 2008	Grades 6 to 9, all genders	-	Yes	-	Randomized trials	Consider This: There were a total of 73 online activities divided into six modules: Introduction, media literacy, relationships, mind and body, decision making, and resistance strategies	The activities led to a decrease in smoking and/or a decrease in students' expectations of smoking in the future	Australia and United States
Gordon <i>et al</i> [78], 2017	9-12 yr, all genders	Yes	-	-	Qualitative assessment	Alcohol media literacy programs: Providing children with the necessary skills to question and critically evaluate the information they receive from media sources	Using culturally specific advertisements as a means to educate about the effects of alcohol proved to be a potent strategy	Australia

areas. One demonstration project on minimizing drug harm confirmed this view. In this project, a quasi-experimental intervention was conducted with middle school and high school students for four years. The results showed that education on minimizing drug harm was not suitable for middle school students[79]. We believe that this may be related to the developmental characteristics of adolescents at different educational stages. Adolescents in the upper grades of primary school and in the junior high school stage are in a semimature state and are more prone to imitate behaviors such as smoking and drinking due to curiosity or a psychological desire for conformity. Therefore, at this stage, interventions should focus on guiding adolescents' behavior and values. High school students are relatively mature and have higher levels of cognition and behavioral abilities. Some students in this group may already have varying degrees of substance use disorders. Therefore, interventions should focus on consolidating awareness education and preventing increase substance use.

Advantages and challenges of substance use interventions for adolescents in educational environments

Advantages: Educational environments provide convenient spaces for intervening in substance use among adolescents. The advantages can be summarized in the following five aspects. First, school environments are the context of various interpersonal relationships, including those involving peers, teachers, and administrative personnel. Support from interpersonal relationships is a protective factor against adolescent substance use[80]. Intervention plans for the school context can combine the strengths of multiple stakeholders and maintain a high level of interaction among participants [73]. Examples include peer group pressure interventions[81] and family-school cooperation interventions[70]. Second, schools have unique advantages in terms of facilities and human resources. Evidence suggests that collective interventions are effective in treating adolescent mental health problems and substance use disorders[82]. Schools are

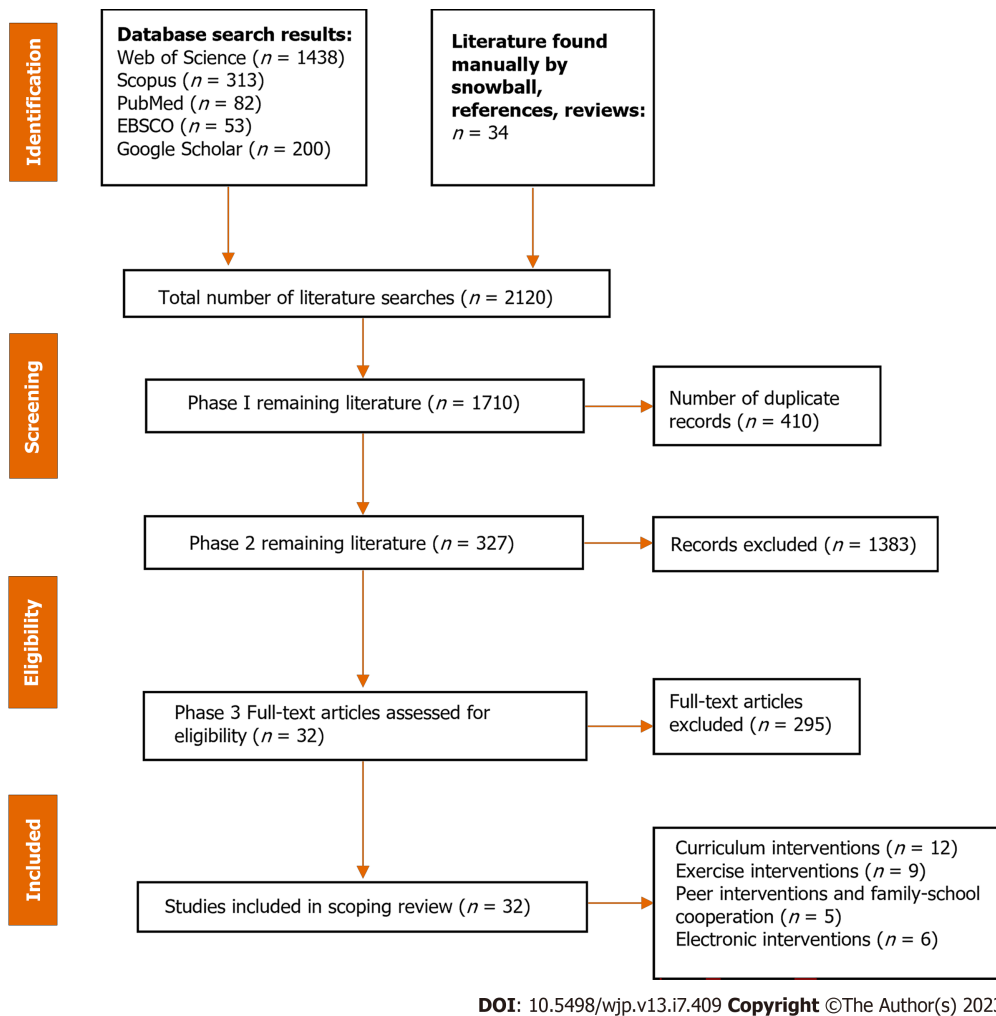


Figure 1 Literature screening process.

ideal places to conduct collective interventions. Teachers can use the school's basic equipment and multimedia devices to conduct general courses to prevent substance use disorders, teach students about the potential risks of substance use, and enhance their decision-making and drug refusal abilities[82]. Third, many behaviors of adolescents, including substance use, are related to their experiences in school. Therefore, intervention plans for the school context can change the external environment to which adolescents are exposed and have external validity[72]. Fourth, it is easy to conduct large-scale screening for substance use in educational environments. Effective early screening for substance use problems is essential for preventing or delaying the use of alcohol, tobacco, and illegal drugs during the vulnerable period of adolescent substance use problems. Schools can use standard screening tools to screen students regularly and universally to identify potential substance use problems as early as possible and implement targeted interventions in a timely manner. Fifth, research shows that there may be a mechanism of mutual influence between students' mental health problems such as anxiety and depression and their substance use behaviors[6,7]. These problems are not conducive to the healthy growth and academic progress of adolescents. Schools provide a favorable environment for addressing these issues. Intervention measures in the school context can alleviate the substance use behavior of at-risk groups, promote the physical and mental health and academic performance of students, and create a virtuous circle, benefiting more adolescents.

Challenges: There is no doubt that education settings face many challenges in providing effective substance use interventions for adolescents. First, intervening with students who already have substance use disorders in schools can potentially compromise their privacy, leading to stigmatization risks. When students are afraid of being labeled as having "drug use problems" and refuse school intervention measures, the work becomes difficult[72]. Second, school-based intervention programs often require approval from the school board and coordination among multiple departments. However, considering the school's image, the board may deny the existence of substance use problems at different levels in the school to avoid affecting its enrollment and future development[83]. In addition, it is difficult for multiple departments to reach a consensus on the design and implementation of an intervention plan, and there may be complex problems such as misunderstandings and slow progress during the implementation process. Third, providing substance use-related courses for adolescents undoubtedly increases the burden and pressure on teachers and administrators, perhaps because they need to receive training from professionals in advance and spend much time and energy on teaching. Teachers and administrators also bear pressure from their own teaching tasks and other administrative work,

which may lead to role conflict and role overload[84]. Therefore, schools may need to provide necessary incentives for the implementers of intervention plans to increase their motivation. Fourth, the school environment increases the availability of alcohol, tobacco, and illegal drugs. In a 2009 study on adolescent risk behavior, 23% of students reported being offered drugs in school[82]. This indicates that in addition to actively formulating intervention plans, schools still need to build a positive, environmentally friendly, and healthy campus environment to prevent the spread of the use of alcohol, tobacco, and illegal drugs in schools. Fifth, as “digital natives”, adolescents have a higher acceptance of electronic interventions than older age groups. However, the effectiveness of electronic interventions for adolescents with substance use disorders is not ideal. In the context of rapid informatization, fully tapping the potential of internet interventions and further introducing digital intervention in educational settings remains a challenge for school health workers and researchers.

DISCUSSION

In the face of the public health challenges posed by adolescent substance use and abuse, schools have an important mission as ideal places to implement intervention plans. In addition to carrying out regular substance use screening and implementing intervention plans according to different categories (such as universal intervention measures for all students, selective intervention measures for students at high risk of substance use, and directive intervention measures for students with substance use disorders), in the future, school-based intervention measures can focus on introducing big data and artificial intelligence technology; integrating advantageous resources from families, schools, and communities; and combining psychological health interventions.

Fully utilizing big data and artificial intelligence technology. In recent years, with the rapid development of artificial intelligence, machine learning, and deep learning, digital intervention methods have rapidly emerged. Schools can use artificial intelligence technology to build a platform for adolescent health management, establish a management mechanism that spans the full process from substance use screening warnings to intervention tracking, and enhance the coverage and accuracy of screening warnings. This platform can also incorporate the psychological health status of adolescents, thereby supporting the creation of personalized health records. In addition, precise assessment and prediction of student substance use problems and hierarchical classification intervention tracking through artificial intelligence technology can reduce the incidence of risky behavior. It is worth noting that when introducing digital intervention methods such as intelligent robots and applications, effectiveness and risk assessments should be conducted, operational procedures should be refined, and the potential of digital interventions should be truly realized.

Resources from families, schools, communities should be integrated to form joint efforts. When schools intervene in adolescent substance use problems, they need to consider protective factors from families, and students also need to recognize the importance of social influences. Currently, there are a variety of diverse intervention measures based on individual entities such as families, communities, and schools, and their effectiveness is significant; however, there is a lack of linkage between these entities. In the future, schools can encourage parents and communities to actively participate in the project while ensuring the integrity of their own intervention plans and managing and coordinating resources.

Psychological health interventions should be integrated, and comorbidity risks should be emphasized. Early substance use in adolescents is related to their psychological health status[85]. Identifying potential psychological health problems in adolescents and intervening in a timely manner can help reduce substance use risks[86]. Therefore, the early identification and intervention of both cannot be separated. When schools screen students for psychological health problems, they should pay attention to substance use, and when implementing substance use interventions, they should pay attention to potential psychological health problems in high-risk groups. This not only maximizes the use of school resources but also prevents adolescents from engaging in risky behavior due to comorbidities.

Furthermore, since this study is a scoping review, we did not calculate specific variable values, nor did we conduct a bias risk analysis. This is a limitation of this study.

CONCLUSION

This article outlines substance use prevention interventions for adolescents in educational environments and their implementation effects. We found that overall intervention measures include curriculum interventions focusing on cognitive-behavioral skill enhancement, exercise interventions, peer interventions and family-school collaboration, and electronic interventions. Except for electronic interventions, which have uneven implementation effects, intervention measures are beneficial in alleviating adolescent substance use problems to varying degrees. In addition, adolescents in different educational stages have different developmental characteristics, and intervention measures should be more targeted and focused. The educational environment has unique advantages for implementing intervention plans, and equipment and human resources can be used to provide adolescents with various types of intervention measures. However, implementation of interventions in the educational environment also faces challenges such as stigmatization, inadequate coordination among multiple resources, and poor implementation effects. In the future, school-based intervention measures can make full use of artificial intelligence technology, jointly intervene with families and communities, and pay attention to the comorbidity risks of substance use disorders and mental health issues.

FOOTNOTES

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Case Control Study

Population-based affective-disorder-related biomedical/biophysical multi-hyper-morbidity across the lifespan: A 16-year population study

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Abstract

BACKGROUND

There are few if any life-span population-based studies of psychiatric disorder-associated biomedical and biophysical disorders and diseases (morbidity).

AIM

To scope the present state of research regarding the biomedical and biophysical morbidity associated with affective and mental disorder in epidemiological samples, and to examine the life-span relationship between affective disorders and biomedical/biophysical disorders to illustrate a novel approach employing the odds ratio to represent the intensity of biomedical and biophysical morbidity associated in time in a population.

METHODS

A repeatable systematic literature search of PubMed was represented in summary. Additionally, a regional population-based dataset was constructed and analyzed to represent the age- and sex-specific diagnoses (International Classification of Diseases Version 9, ICD-9) for those with and without affective disorder. The analysis presents a novel index of the relative age-specific frequency of life-span biomedical and biophysical diagnoses associated with affective disorder.

RESULTS

The volume of biomedical and biophysical morbidity associated with mental disorder literature has increased, yet few studies measure comprehensive temporal hyper-morbidity (over-representation of diseases over time, either

before or after the index diagnostic event) in populations. Further, there have been only a few population-based studies examining the morbidity associated with affective disorder and only one that examines the full diagnostic range of lifespan morbidity. Substantial differences arose between males and females with more females than males having greater frequencies of diagnoses. The age-specific distributions of the maximum proportional diagnosis frequency ratios for each sex illustrate the greatest diagnosis-specific differences when comparing the biomedical and biophysical diagnoses of those with and without affective disorder when the same diagnosis was represented in each grouping at the same age.

CONCLUSION

Clinical research needs to focus on more than one or two comorbid biomedical or biophysical disorders at a time. Comprehensive population-based examination of the lifespan biomedical and biophysical multi-morbidity associated with affective disorder has the potential to directly inform clinical practice. Representing the proportional ratios of age-specific frequency of diagnoses for the full range of ICD-9 diagnoses is a novel analytical model. Diagnostic frequency appears a viable representation of a given disease state, such as affective disorder. Fortunately, the WPA has developed a global education section to better understand the biomedical and biophysical morbidity associated with all psychiatric disorders. This has been identified by the WPA as the psychiatric practice challenge of the 21st century.

Key Words: Biomedical/biophysical morbidity; Temporal hyper-morbidity; Mental disorder; Population; Epidemiology

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Core Tip: The paper presents a scoping review of publications with focus on the biomedical and biophysical morbidities associated with psychiatric disorder and a novel example from a population of the relationship between affective disorder and the frequency of associated biomedical and biophysical morbidities across the lifespan.

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INTRODUCTION

Numerous recent studies have examined the comorbidity of affective disorders and other mental processes[1-5] and disorders[6-9]. Less common is the study of biomedical or biophysical and affective disorder comorbidity. The studies that do address the comorbidity of affective disorders and biomedical diseases and disorders, predominantly focus on one singular biomedical diagnosis, such as diabetes[10-12] and chronic pain[13,14]. A few studies investigated a range of comorbid disorders, such as asthma, diabetes, epilepsy, food allergy, or juvenile arthritis arising within 6 mo of any mental problem[15]. In one study, biomedical markers have been identified indicating links between mental disorder and chronic physical illness[16]. Overall, the study of biomedical and biophysical morbidity in association with mental disorders has been constrained.

To date, while there have been some large sample studies of mental[17-20] and physical disorders[21-24], there have been few large sample studies examining relationship specifically between psychoses, such as affective disorders and biomedical/biophysical disorders. One large sample World Health Organization survey study found the number of medical conditions to increase with the number of psychotic symptoms within a 12 pre-survey month period[25]. In this study, a wide variety of medical conditions and health problems- such as angina, asthma, arthritis, tuberculosis, vision or hearing problems, mouth/teeth problems, alcohol consumption, smoking, and accidents - were reported to be more frequent in individuals with psychotic symptoms.

This altogether brief, focused, literature review outlines the constraints of studies focusing on psychiatric disorder-associated biomedical and biophysical morbidity. There is the need to introduce not only a broader perspective and definitions of morbidity, but also the need to find different approaches to its study.

The purpose of this study is twofold: First to present the current state of the art of biomedical and biophysical morbidity associated with mental disorder in large population-based samples in the published literature (PubMed). Secondly, both as an illustration and an example, we examined the lifespan association with affective psychoses of the full range of biomedical/biophysical diagnoses in a large 16-year regional population sample. We examined the full range of International Classification of Disease (ICD-9) biomedical and biophysical disorders and diseases in a population comparing those with affective disorder and those without any mental disorder. Further the paper presents a novel analysis and graphic representation of the frequency of biomedical and biophysical disorders and diseases of each specific ICD-9 disorder expressed as a ratio comparing the dependent groups.

The dataset in this study was originally compiled to investigate one *a priori* hypothesis in support of the original adverse childhood experience study[26-29]. The hypothesis assumed early adversity to be one gateway to subsequent mental disorder. Based on this assumption the hypothesis was that given the presence of any ICD-9 mental disorder diagnosis, biomedical and biophysical disorders would be proportionally greater than among those without any mental disorder. This proved to be the case with substantial over-representation of biomedical and biophysical disorders in those with any mental disorder[18].

The analysis underpinning the original study of this regional 16-year dataset was a relatively simple representation of the data in terms of odds ratios. Subsequently of interest was the temporal order of biomedical and biophysical disorders in relation to mental disorder and *vice versa*[20,22], in addition to the order of diagnoses in prospective age-defined cohorts[21,23].

MATERIALS AND METHODS

Literature search

Several PubMed searches of mesh and title terms provided an overview of the number of the current population-based psychiatric morbidity research publications (represented in tables associated with each searches' terms). Searching mesh and title terms provided an index of publication frequency with a focus on population, epidemiology, morbidity, and psychiatry. The details of each listed search result in PubMed recorded in Table 1 are repeatable. The results precisely list the total number of papers in each search. The position of the search (*e.g.*, title) indicates the importance of the terms in the search. In the results quotients are expressed in the terms of the results (number of publications) for the numerator expressed as a fraction of the results in generic search (unspecified position) for the denominator (#publications).

Cohort-study

The data for the population-based component of this study were collected under ethics ID REB15-1057. The data represented the health seeking population from the Calgary Health Zone in Alberta, Canada between April 1993 and November 2010. To receive payment all Alberta physicians, even practitioners in private clinics, directly bill the provincial health plan for each patient visit. The data consisted for each patient visit of a record that included an anonymous, encrypted, unique patient identifier, an ICD-9 diagnosis code, age, and sex. The analyzed data was grouped (dependent variable) according to the presence or absence of the ICD-9 diagnosis code 296 representing the affective disorders. The group wherein affective disorders were absent consisted of those without any mental disorders. The independent variable represented all biomedical and biophysical disorders linked within each group (+/- affective disorders). Additionally, the results were stratified on the variable age. The sexes were analyzed separately.

Analysis

The frequency of publications resulting from the PubMed literature searches were tabulated.

From the population-based based, the dependent groups were described in terms of age, sex, total frequency of diagnoses, counts of unique individuals together with the standard deviations and ranges.

The algorithm underpinning the comparative analysis of the groups with and without affective disorders ordered all diagnoses in sequence for individuals stratified by age within groups. Within each group for each diagnosis and each age, the total count of each diagnosis (frequency) was denominated by each age-specific sample size and represented as the proportion of the age-specific sample having a specific diagnosis in each group. For example, if each patient in each age-specific sample received one given diagnosis, the proportional value for that diagnosis would be one. If fewer than the total number of patients in each age-specific sample received a given diagnosis the proportional value would be less than one. If the age-specific sample received the diagnosis more than once each, then the proportional value would be greater than one. Novel in this analysis is the proportional value representing the intensity of any diagnosis within each age-specific strata of each dependent group.

Where age-specific diagnoses occurred in both dependent groups, between groups comparisons of the proportional diagnosis frequency ratio of each age-specific diagnosis for those with and without affective disorders was possible. While similar in formula construction to the odds ratio, the numerator of each group proportion represented each diagnosis' frequency (intensity) within the unique individuals at each specified age.

Ratio of Frequency Proportions of biomedical and biophysical disorders = [With/Without] affective disorder

The ratio of diagnosis frequency between the two groups, when greater than the value one, identifies that the intensity (frequency) of the diagnosis under comparison is greater in the dependent variable group with affective disorder. When the ratio of diagnosis frequency between the two groups is less than one, the diagnosis under comparison is greater in the dependent variable group without affective disorder. Diagnosis frequency within individuals is a way of representing the intensity of the associated disorders in the ratios of the compared groups.

Age-specific diagnoses could also occur in one group but not the other. Diagnoses that occurred only in one or the other group were noteworthy based on the possibility of conferring risk in the affective disorder groups or protection in the group without affective disorders. These diagnoses become asymptotic with the limit of value zero. Where a real frequency was greater in the group without affective disorder the value was between zero and one.

All ICD diagnoses were coded according to the numeric values of their natural codes, with V codes assigned values in the 1200 range and procedures (laboratory, anesthesiology, *etc.*) in the 1500 range.

Table 1 Volume of research publications for repeatable PubMed literature searches

Search condition	Frequency of results
"Consortium in Psychiatric Epidemiology"[Title]	0
"International Consortium in Psychiatric Epidemiology"[Title]	0
"International Consortium in Psychiatric Epidemiology"	6
"Psychiatric Epidemiology"[Title]	245
"ICPE" AND "psych*"	379
"ICPE" AND (psych*[Title])	60
morbid*[MeSH Terms] AND epidemiolog*[MeSH Terms] AND psych*[MeSH Terms]	165364
morbid*[MeSH Terms] AND epidemiolog*[MeSH Terms] AND mental[MeSH Terms]	0
((morbidity[MeSH Terms]) AND (epidemiology[MeSH Terms])) AND (psych*[MeSH Terms])	309
comorbidity[MeSH Terms] AND "epidemiology"[MeSH Terms] AND "psych*"[MeSH Terms]	56
"comorbidity"[Title] AND "epidemiology"[Title] AND "psych*"[Title]	18
((morbidity[Title]) AND (epidemiology[Title])) AND (population[Title])	12
((morbidity[Title]) AND (epidemiology[Title])) AND (psych*[Title])	10
((morbidity[Title]) AND (epidemiology[MeSH Terms])) AND (psych*[MeSH Terms])	8
"International Consortium in Psychiatric Epidemiology" - Articles found by citation matching	6
"morbidity"[Title] AND "epidemiology"[MeSH Terms] AND "psych*"[Title]	2
((morbidity[Title]) AND (epidemiology[Title])) AND (mental[Title])	1
(psych*) or (mental)	3347210

The representation of age-specific diagnoses provides an index of the frequency or intensity of occurrence over lifespan of the biomedical and biophysical diagnoses associated with affective disorder.

RESULTS

Literature Searches

Table 1 shows 17 searches. The last search represents all searchable fields of publications containing the wildcard psych* and mental. The value of this search serves to denominate the largest value with the MeSH term search for the wildcard terms morbid*, epidemiolog*, and psych*. Of note the same search with mental replacing the wildcard term psych* produced zero results. The most generous quotient value indicates that 4.94% (165364/3347210) of the search research results had a precise focus on the MeSH terms. It may also be seen in Table 1 that when the MeSH terms are more precisely constrained (e.g., morbidity, epidemiology, or comorbidity) there are substantially fewer results and even fewer when these terms are searched for in titles alone. Note that the PubMed graphic associated with the search resulting in 165364 articles showed that the articles per year peaked in 2019 with a total of 10239 articles published.

Population sample description

Table 2 describes the distributions of the groups with and without affective disorder. Note that the group without affective disorder consists of individuals without any other mental disorders. As well, there are more females than males with affective disorder and females have in total and on average a higher frequency of biomedical and biophysical diagnoses (mean = 291) compared to males (mean = 239). The average age of females is older than males in the group with affective disorder and younger in the group without affective disorder.

Note in the following graphs when the frequency of diagnosis ratios for each dependent group is equal to the value one, it means that the ratio of each group is equal. When greater than the value one, the ratio is greater in the group with affective disorders. When less than the value one, the ratio is greater in the group without affective disorders. Figure 1 shows the proportional total diagnosis frequency ratios > 1 distribution of associated biomedical and biophysical diagnoses by age comparing males with and without affective disorder. Figure 2 shows the proportional frequency ratios > 1 distribution of maximum values comparing in males comparing those with and without affective disorder. Figure 3 shows the complete proportional ratios > 1 distribution comparing males with and without affective disorder. Figure 4 shows the proportional total diagnosis frequency ratios > 1 distribution of associated biomedical and biophysical diagnoses by age comparing females with and without affective disorder. Figure 5 shows the proportional frequency ratios > 1 distribution of maximum values comparing in females comparing those with and without affective disorder.

Table 2 Demographics and diagnosis frequency of groups with and without affective disorder

Variables	Affective disorder	
Females	With	Without
Unique individuals	23637	141427
Mean age	47	38
SD age	20	24
Range age	(1-104)	(0-103)
Mean diagnoses	291	56
SD diagnoses	253	66
Range diagnoses	(1, 3164)	(1, 2424)
Total diagnoses	6881012	7986931
Males	With	Without
Unique individuals	16164	165527
Mean age	35	46
SD	23	19
Range age	(0, 103)	(0, 102)
Mean diagnoses	239	44
SD diagnoses	257	58
Range diagnoses	(1, 4316)	(1, 1864)
Total diagnoses	3862550	7301122

SD: Standard deviations.

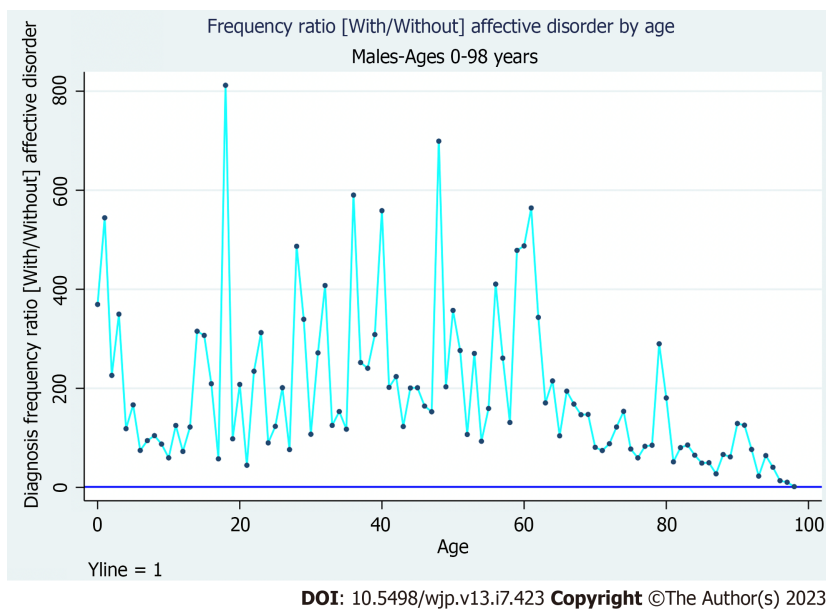
**Figure 1 Proportional total diagnosis frequency ratios > 1 distribution of associated biomedical and biophysical diagnoses by age comparing males with and without affective disorder.**

Figure 6 shows the complete proportional ratios > 1 distribution comparing females with and without affective disorder.

Overall, the reader might take away the following main points of the graphic representations of comparative unique frequency ratios of diagnosis for all ICD-9 diagnoses by age are as follow: (1) Those with affective disorder have greater frequencies of unique ICD-9 diagnoses across age; and (2) Males are substantially different than females.

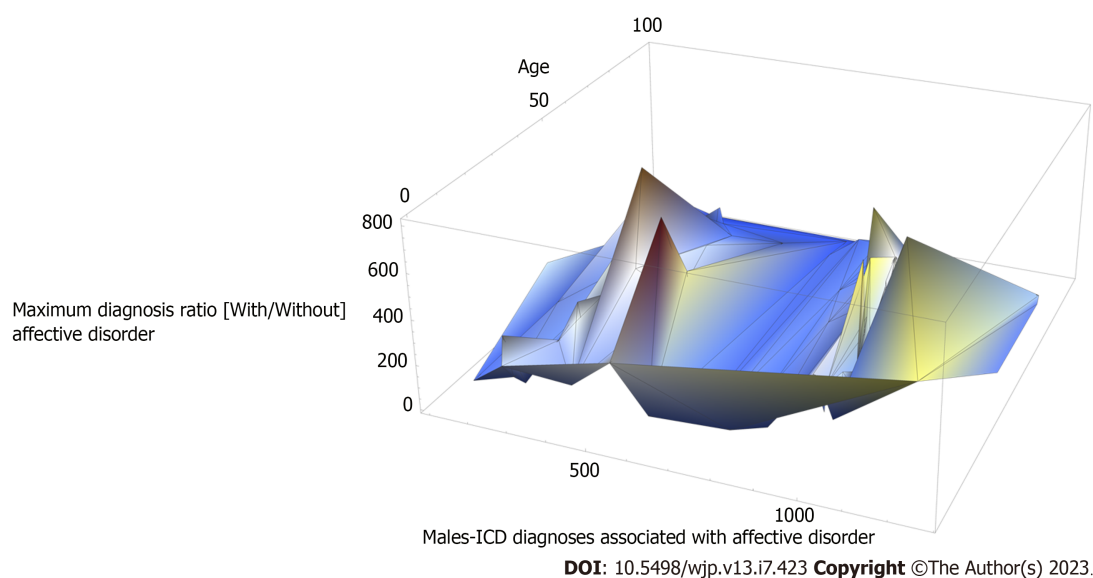


Figure 2 Proportional frequency ratios > 1 distribution of maximum values comparing in males comparing those with and without affective disorder.

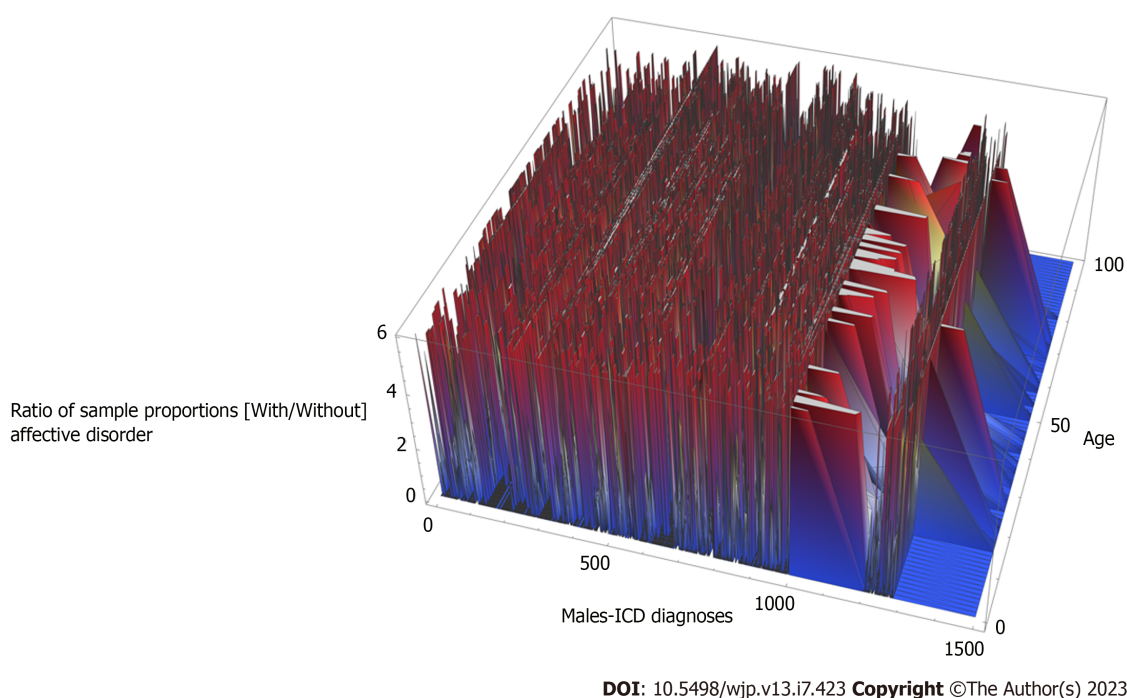


Figure 3 Complete proportional ratios > 1 distribution comparing males with and without affective disorder.

In Figures 1 and 4, the maximum proportional diagnosis frequency ratios' distributions for males and females across all ages most clearly illustrate the sex differences. For example, the age-specific maximum proportional diagnosis frequency ratios are greater for males earlier in life. The maximal values in Figures 1 and 4 are greater than Figures 2 and 5 and more so in Figures 3 and 6, as the values in the latter figures are distributed across the frequency of individual diagnoses for a given sample size, rather than quotients within the summed frequency across the range of all ICD disorders within in a given age-specific sample sizes comparing the groups with and without affective disorder.

Figures 2 and 5 illustrate the sex differences within the subset of age-specific proportional diagnosis frequency ratios distributions for males and females showing the maximum proportional diagnosis frequency ratio values for each age across the full range of ICD diagnoses. Note that the graphs truncate around the proportional diagnosis frequency ratio less than 800 for males and about 100 for females, indicating a much higher proportional frequency of age-specific diagnosis for males.

From the full distribution of age-specific proportional diagnosis frequency ratios distributions shown for males and females in Figures 3 and 6, it is apparent that females have more laboratory testing and procedures, while males have

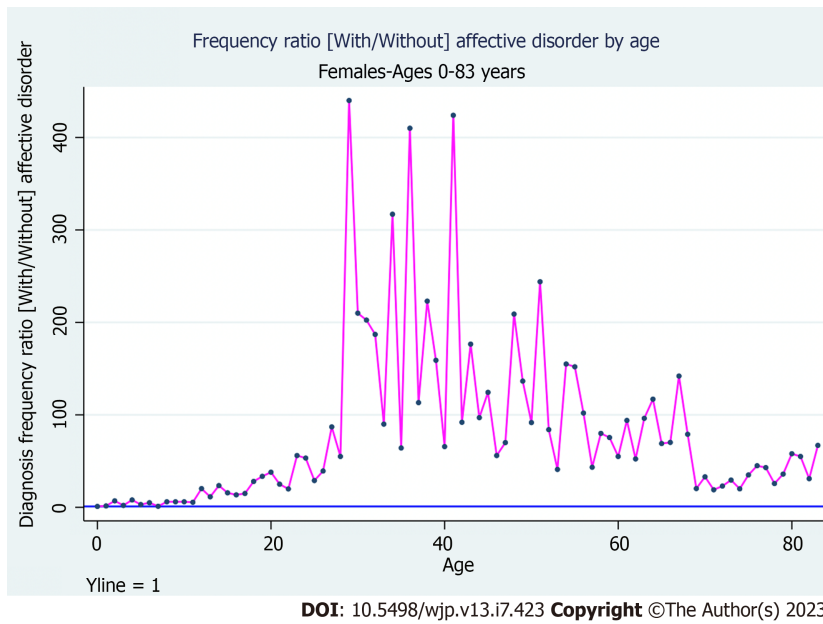


Figure 4 Proportional total diagnosis frequency ratios > 1 distribution of associated biomedical and biophysical diagnoses by age comparing females with and without affective disorder.

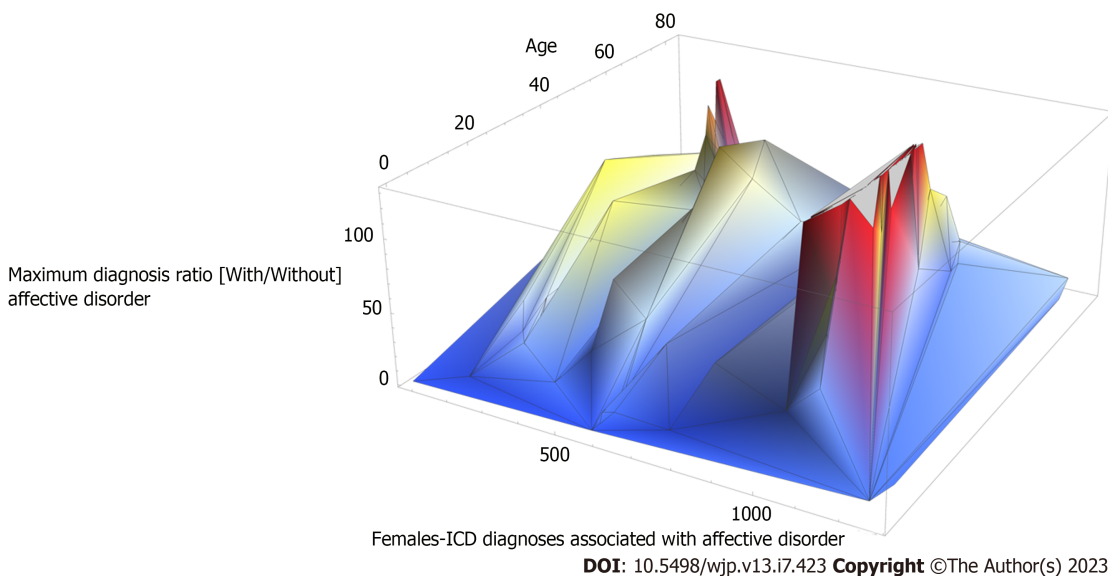


Figure 5 Proportional frequency ratios > 1 distribution of maximum values comparing in females comparing those with and without affective disorder.

more V code diagnoses. Figures 3 and 6 both automatically truncate for visualization at the value 6.0 for both males and females when the full distributions are represented. The areas of the visible plateaus are relative to the height of each where the sequence of disorders by age reach their maximal peaks. Further, Figures 3 and 6 represent the ratios of the average frequency quotients for those with and without affective disorder, rather than the maximum values by age across all ICD disorders. Note the frequency of peaks closer at the value 1200 on the diagnosis axis comparing males and females, the frequency of V-Code peaks is greater for males across all ages. Similarly, note the frequency of peaks closer of the value 1500 on the diagnosis axis comparing males and females, the frequency of Laboratory Testing peaks is greater for females across all ages.

DISCUSSION

Our first purpose, examination of the volume of population-based morbidity literature, yields clear results. The PubMed search scope indicates that there has been a rapid increase in morbidity focused research after 1990 with a peak number of

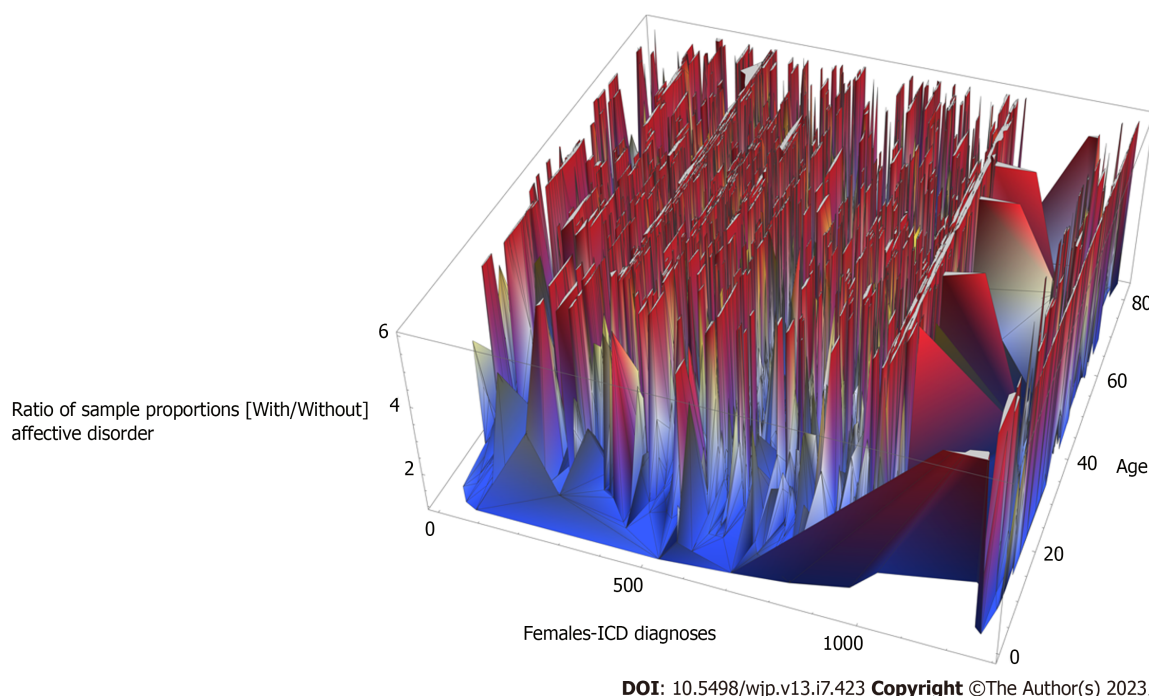


Figure 6 Complete proportional ratios > 1 distribution comparing females with and without affective disorder.

publications ($n = 10238$) in 2019. However, the specific publications cited in this paper indicate that only a minority (4.94%) specifically focus on mental disorder associated temporal biomedical and biophysical hyper-morbidity (Table 1). Even fewer account for the full range of morbidity in populations[18-24].

Our second purpose was the examination of affective disorder associated life-span multi-morbidity of biomedical and biophysical diagnoses in a 16-year population sample. Each age-specific grouping could enter or leave the dataset in any of the 16 years. Other studies of the same dataset focusing on prospective cohort samples (*e.g.*, < 1 year of age before January 1, 1995) in comparison to the same age group across the 16-year sample provide evidence indicating that all ages across the whole 16-year grouping in the current analysis does not unduly bias the results[23]. Thus, we are confident that the cumulative age specific results are similarly unbiased.

As expected, our results illustrate substantial differences between males and females: we found that more females than males were diagnosed with greater frequencies of diagnoses at different ages. This outcome is similar to epidemiological population based studies of affective disorder[30-33].

When comparing the same biomedical and biophysical diagnoses between the two groups at the same age, the age-specific distributions of the maximum proportional diagnosis frequency ratios for each sex showed the greatest diagnosis-specific differences between the two sexes.

Possibly of interest are the biomedical and biophysical diagnoses that do not overlap for males and females between the groups with and without affective disorder. The within group age-specific proportional distributions (not represented as between group ratios) of the non-overlapping diagnoses may in the affective disorder group represent diagnoses associated with increased etiological or sequelae risk over time. It may also be possible that non-overlapping diagnoses may in the group without affective disorder may represent protective diagnoses. These speculations, however, are well beyond the data limits of the present study, albeit such information as is presented may serve as a signpost for future research.

Strengths

Representing the full range of ICD-9 diagnoses as well as examining the proportional diagnosis frequency ratios of overlapping age-specific diagnoses is a novel data representation model. For example, the main difference in comparison to other formula, such as the odds ratio, is that the within-sample intensity of age-specific diagnoses may be represented and compared. The odds ratio generally counts unique individuals, and as such, features such as the frequency of given diagnoses are lost in the comparison. Diagnostic frequency may be an indicator of the severity or chronicity of a particular disease state.

Limitations

The PubMed searches were not thorough or reviewed in terms of content. The searches deviated from typical systematic reviews or meta-analyses. The searches employed a standardized approach only to illustrate the volume of morbidity-focused research.

While proportional diagnosis frequency ratios of overlapping age-specific diagnoses may be a novel form of life-span data representation, it is also important to consider the within group proportions of age-specific diagnoses. It was noted in the methods that when this value exceeded 1.0 the whole within sample had received the diagnosis. The proportional

diagnosis frequency ratios of overlapping age-specific diagnoses reported in this study were not limited to only those disorders having within group proportions greater than the value one. The main reason for this omission was to represent the proportional diagnosis frequency ratios available within the full range of ICD-9 diagnoses. Future work will address this limitation.

Finally, the foregoing novel analyses are a pointer to the complexity of any understanding of the temporal hyper-morbidity of affective disorders, save any mental disorder. For example, a next level of complexity in analysis requires the calculation of the conditional order of diagnoses within individuals. Conditional order is not simply the frequency of diagnoses for the dependent groups of individuals in time, (total of diagnoses on date 1, 2, 3...n) independent of the diagnosis that each individual experiences before or after any given diagnosis. The conditional sequence of diagnoses within individuals may reveal more information that is relevant to the etiology and prognosis of disorders arising before and after an index diagnosis of affective disorder.

CONCLUSION

The study of complex morbidity is emerging as a primary field of research[34] with multiple levels of definition[35]. Despite a rapid increase in morbidity focused research after 1990, a small minority of 4.94% specifically focus on mental disorder associated temporal biomedical and biophysical hyper-morbidity. The publications cited in this paper indicate only a few are focused on lifespan, biomedical and biophysical, population-based, temporal, hyper-morbidity[18-24]. The present study represents to the best of our knowledge the first comprehensive population-based examination of the lifespan biomedical and biophysical multi-morbidity that is associated with affective disorder. By employing a novel model of data representation, we were able to show the intensity of the affective disorder associated diagnoses. Based on the present results, a paradigm shift is required in terms of how in psychiatric and medical practice morbidity is conceptualized, defined, and studied[36,37]. An important step in re-defining morbidity is illustrated in the recent establishment of the World Psychiatric Association Comorbidity Section, wherein the study of morbidity is identified as central 21st century challenge for psychiatry[38,39].

ARTICLE HIGHLIGHTS

Research background

The latest series of publications based on “big-data” leading to this one, have also, in part, contributed to the formation and development of the World psychiatric Association Comorbidity Section.

Research motivation

This overall study was inspired by the Adverse childhood experiences (ACE) study. ACE are associated with lifespan morbidity and many leading causes of death in adulthood. The ACE study is a landmark research effort that investigated the relationship between childhood abuse and household dysfunction, and the leading causes of death in adulthood. The study found that individuals who experienced adverse childhood experiences such as physical, emotional, or sexual abuse, neglect, household dysfunction (*e.g.*, substance abuse, mental illness, incarceration, and divorce), are at higher risk for several chronic health conditions and premature death. The findings of the ACE study demonstrate the far-reaching impact that childhood experiences can have on adult health and well-being. The study's results highlight the importance of addressing childhood trauma and promoting healthy family environments to prevent chronic disease and improve overall health outcomes in adulthood.

Research objectives

To orient all divisions of medicine to the fact that big data has shown important lifespan links between mental disorder and biomedical and biophysical diseases, wherein mental disorder is fundamental linchpin in time, generally leading to hyper-morbidity and hyper-morbidity is a linchpin to mental disorder; and to develop algorithms identifying the precise (conditional) order for individuals and examining how these orders group may prove useful to both clinical practice and research into disease mechanism.

Research methods

We are now developing advanced algorithms for the reduction of data for representation. The example in this paper presents a novel approach to analysis based on the intensity or frequency of total and unique diagnoses by age for all individuals in a large population. In this paper, about 90 million diagnoses for about 0.75 million individuals are reduced to one graphic for each of males and females of age by frequency of diagnosis ratios for each of about 1000 ICD diagnoses.

Research results

It is apparent that there is greater temporal hyper-morbidity for those with affective disorder compared to those without any psychiatric diagnosis. When different publication results are compared, there are different disease vulnerabilities (*e.g.*, cancer and ulcerative colitis) related to different classes of psychiatric disorders and *vice versa*.

Research conclusions

Understanding temporal hyper-morbidity (and perhaps hypo-morbidity) is dependent on large population-based datasets. The results are fascinating in the sense that analyzing whole stable populations over time is more like accounting than statistical analysis and the results from the first population health index paper were intra-ocular (*e.g.*, over 50% of the population has a mental disorder over 16 years and over 3 times the biomedical and biophysical disorders.) This is in line with the World Psychiatry Association's identification of the 21st century's challenge is understanding and responding to mental disorder-related biomedical and biophysical morbidity.

Research perspectives

The conditional groupings are complex (as in the graphics of this paper), and like a classical 'road map' problem, and will likely depend on smart algorithms and artificial intelligence to unravel the clinical meaning for practice related to the next patient who walks through the door and mechanisms underlying groups such as autism, cancers, ulcerative colitis and viral pneumonia). The work to date is largely a signpost, pointing in a future direction. Even so, ChatGPT has already been directed to write several testable algorithms. As it stands, the population health index centered on mental disorder indeed represents an inflation-proof mechanism by which regions and nations may evaluate the cost/benefit impact of universal population-based prevention/promotion and early intervention investments and strategies.

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FOOTNOTES

Author contributions: Cawthorpe DRL collected the data, designed the study, and conducted the analysis and paper draft; Cohen D provided constructive critique, expertise, edited the draft; all authors have reviewed and approved the final version.

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Case Control Study

Glutamate decarboxylase 1 gene polymorphisms are associated with respiratory symptoms in panic disorder

Zhi-Li Zou, Jian Qiu, Xiao-Bo Zhou, Yu-Lan Huang, Jin-Yu Wang, Bo Zhou, Yuan Zhang

Specialty type: Psychiatry**Provenance and peer review:**

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind**Peer-review report's scientific quality classification**

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Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

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Abstract**BACKGROUND**

Genetic factors play an important role in the pathogenesis of panic disorder (PD). However, the effect of genetic variants on PD remains controversial.

AIM

To evaluate the associations between *glutamate decarboxylase 1* (*GAD1*) gene polymorphisms and PD risk and assess the effect of *GAD1* gene polymorphisms on the severity of clinical symptoms in PD.

METHODS

We recruited 230 PD patients and 224 healthy controls in this study. All participants were assessed for anxiety and panic symptom severity using the Hamilton Anxiety Rating Scale (HAM-A) and Panic Disorder Severity Scale (PDSS). *GAD1* gene polymorphisms (rs1978340 and rs3749034) were genotyped and assessed for allele frequencies.

RESULTS

There were no significant differences between cases and controls in the genotype distributions or allele frequencies of *GAD1* (rs1978340 and rs3749034). In addition, the effect of *GAD1* (rs1978340 and rs3749034) on PD severity was not significant. However, regarding respiratory symptoms, patients with the *GAD1* rs1978340 A/A genotype had significantly higher scores than those with the A/G or G/G genotype.

CONCLUSION

Here, we showed that the A/A genotype of *GAD1* rs1978340 was associated with increased severity of respiratory symptoms in patients with PD.

Key Words: Panic disorder; Gene polymorphisms; Respiratory symptoms; Allele frequencies; Pathogenesis; Chinese population

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Core Tip: The study found that the A/A genotype of *glutamate decarboxylase 1* (*GAD1*) rs1978340 was associated with increased severity of respiratory symptoms in patients with panic disorder (PD). However, there were no significant differences between cases and controls in the genotype distributions or allele frequencies of *GAD1* (rs1978340 and rs3749034), and neither did *GAD1* (rs1978340 and rs3749034) have a significant effect on the severity of PD symptoms. These findings suggest that genetic factors may play a role in the pathogenesis of PD, particularly in respiratory symptoms, but further studies with larger sample sizes are needed to confirm these results.

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INTRODUCTION

Panic disorder (PD), the most common anxiety disorder, is characterized by recurrent and unexpected panic attacks and has an estimated 12-mo and lifetime prevalence rates of 2.4% and 3.8%, respectively[1,2]; the lifetime prevalence rate of panic attacks is 13.2%[3]. PD typically occurs in young adults, and women are more likely to be affected than men. However, the etiology of PD is multifactorial and complex, involving genetic, environmental, psychological and neurobiological factors[2,3]. Recent studies examining twins and family shows that the heritability of panic disorder is 30%-40%, suggesting strong evidence for a genetic etiology[4]. To date, genetic studies have reported several susceptibility genes for PD such as *neuropeptide Y*, *catechol-O-methyltransferase* and particularly 5-HT system-related genes[5,6]. For example, a previous study found that patients with PD were characterized by significantly higher frequencies of the LL genotype and L allele variant of the 5-HT transporter-linked promoter region (5-HTTLPR)[7]. However, few of these findings have been replicated by other researchers, and the pathogenesis of PD remains unclear[8-12]. Therefore, other candidate gene polymorphisms in PD should be explored.

γ-Aminobutyric acid (GABA) is an important inhibitory neurotransmitter in the mammalian brain, and abnormalities in the GABAergic system have long been implicated in the pathophysiology of PD[13-15]. For example, a significant decrease in GABA has been detected in the anterior cingulate and medial prefrontal cortices of patients with PD[16]. The *GAD1* gene encodes the 67-kDa glutamic acid decarboxylase isoform (GAD67) and is the rate-limiting enzyme responsible for GABA biosynthesis from glutamic acid. The *GAD1* gene might play an important role in the GABAergic system. A previous study found a significant effect of rs1978340 on cingulate cortex GABA concentrations[17]. In addition, previous studies have indicated that *GAD1* rs3749034 is associated with mRNA expression[18]. Therefore, *GAD1* may be an important candidate gene in PD. Incidentally, previous reports have suggested that the *GAD1* single nucleotide polymorphisms (SNPs) rs3749034 or rs1978340 are significantly related to several psychiatric disorders such as bipolar disorder[19], schizophrenia[20], attention-deficit/hyperactivity disorder[21], and heroin dependence[22]. For instance, the allelic or genotypic frequencies of the rs1978340 polymorphism in heroin addicts significantly differ from those in normal controls[23]. However, few studies have examined the relationship between *GAD1* and PD, particularly in Chinese populations.

Previous genetic and chromosomal studies have yielded inconsistent results. It is likely that most cases of PD have a complex genetic basis. In addition, current data suggest that the genetic architecture underlying PD is heterogeneous and differs among cases[24]. PD is accompanied by various symptoms, including palpitations, accelerated heart rate, dyspnea, sweating, and chest pain. These symptoms may be linked to distinct genetic mechanisms, and genetic polymorphisms have been speculated to be linked to the discrete symptoms of PD. Hence, to test the hypothesis that the *GAD1* polymorphism could be associated with PD, we have conducted a case-control study comparing the frequency of these SNPs (rs1978340 and rs3749034) in PD patients and healthy controls. Additionally, we examined the relationship between the presence of PD symptoms and these polymorphisms.

MATERIALS AND METHODS

Participants

A total of 230 patients with PD were recruited as in- and outpatients at the Department of Psychosomatics, Sichuan Provincial People's Hospital, from July 2012 to January 2016. Patients were qualified based on the following criteria: A primary diagnosis of PD performed by professional psychiatrists according to the standardized structured clinical interview of the diagnostic and statistical manual of mental disorders, fourth edition axis I disorders (SCID-I)[25], and no episodes of other psychiatric disorders in the past or at present. Additionally, 224 healthy controls (HCs) among community volunteers were recruited for the study during the same period. SCID-I was also performed by a trained clinical psychiatrist, and the HCs had no history of any psychiatric disorder or major psychiatric condition in their first-degree relatives. All participants in this study were Han Chinese, aged 18–60 years. None of the patients had acute or chronic somatic disorders, head trauma, or neurological illnesses. The study was approved by the Ethics Committee of the Sichuan Provincial People's Hospital [reference number: (2016) Ethics Review (29)]. All participants provided written informed consent before the initiation of study procedures.

Measures

PDSS: The 7-item PDSS was used to assess the severity of panic symptoms for all patients, and participants were instructed to rate each item from 0 to 4 based on the severity of each symptom, with possible responses ranging from “none” to “extremely severe”[26]. The scale was translated into Chinese by Xiong[27], and the PDSS-Chinese version had good internal consistency (Cronbach's alpha) with an overall score of (0.83).

Hamilton anxiety rating scale

The Hamilton anxiety rating scale (HAM-A) scale comprises 14 items (anxious mood, tension, fear, insomnia, cognitive function, depressed mood, somatic anxiety (muscular system), somatic anxiety (sensory system), cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms, and behavior at interview) with 5-level responses for each item, *i.e.*, scores 0, 1, 2, 3, and 4 indicating not present, mild, moderate, severe, and very severe, respectively[28]. A total score > 17 indicates mild anxiety symptoms; 18–24, mild-to-moderate anxiety symptoms; and 25–30, moderate-to-severe anxiety symptoms.

DNA extraction and SNP genotyping

For each participant, 3 mL of peripheral blood was collected in EDTA tubes. An automatic nucleic acid extractor (TGuide M16; Tiangen Biotech, Beijing, China) was used to extract genomic DNA. SNP genotyping was performed using an improved multiplex ligation detection reaction (iMLDR) technique developed by Genesky Bio-Tech (Shanghai, China). The multiplex polymerase chain reaction (PCR) reaction volume included 1 µL GC-I buffer (Takara Bio Inc., Shiga, Japan), 3.0 mmol/L Mg²⁺, 0.3 mmol/L dNTP, 1 U HotStar Taq Polymerase (Qiagen, Hilden, Germany), 1 µL genomic DNA (5–10 ng/µL), and 1 µL Multiplex-PCR primer mix. The cycling program for PCR was 95 °C for 120 s, followed by 11 cycles of 94 °C for 20 s, 65 °C for 40 s, and 72 °C for 90 s, and each cycle decreased by 0.5 °C. The third step comprised 24 cycles at 94 °C for 20 s, 59 °C for 30 s, and finally, 72 °C for 2 min, and a hold at 4 °C. The PCR product was purified with 5 U SAP and 2 U Exonuclease I at 37 °C for 1 h and then inactivated at 75 °C for 15 min. The primer and probe information is provided in [Supplementary Tables 1 and 2](#), respectively. The ligation reaction included 1 µL of 10× ligation buffer, 0.4 µL 3' ligation primer (2 µM), 0.25 µL Tag DNA ligase, 6 µL ddH₂O mixture, 0.4 µL 5' ligation primer (1 µM), and 2 µL purified multiplex PCR product. The ligation cycling program comprised 38 cycles at 94 °C for 60 s, 56 °C for 4 min, and a hold at 4 °C. Sequencing was conducted in 0.5 µL 500 LIZ Size Standard, 0.5 µL ligation product, and 9 µL Hi-Di mixture (ABI3730XL; Applied Biosystems, Waltham, MA, United States). Raw data were analyzed using GeneMapper v4.1 software (Applied Biosystems). A random sample accounting for approximately 5% of the total DNA samples was directly sequenced using Big Dye-terminator version 3.1 and an ABI3730XL automated sequencer (Applied Biosystems) to confirm the iMLDR results.

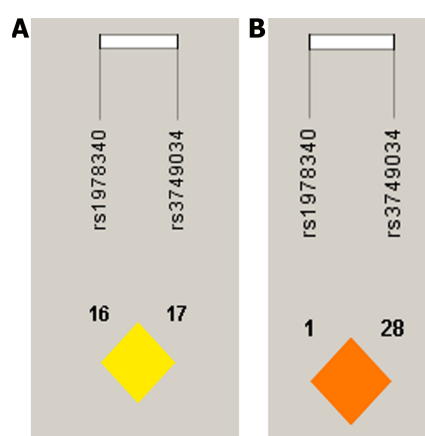
Statistical analysis

SPSS version 13.0 software (SPSS Inc., Chicago, IL, United States) was used to analyze the data. Student's *t*-test was used for intergroup comparisons of continuous variables, and Pearson's chi-square test was used for categorical variables. The Hardy-Weinberg equilibrium (HWE) *P* values were tested using Pearson's chi-square test. Associations between SNPs and PD were determined based on the distribution of allelic frequencies and genetic models (additive, dominant, and recessive models). Odds ratios and 95% confidence intervals were calculated by unconditional logistic regression analysis using PLINK v1.07. Analysis of variance was performed to compare the clinical variables with different *GAD1* SNPs (rs1978340 and rs3749034). Bonferroni's correction was used to avoid Type I errors. For all analyses, statistical tests were two-tailed, and an alpha level of 0.05 was used to define statistical significance.

RESULTS

Demographic data and clinical manifestations

The analyzed sample comprised 230 PD cases (92 men and 138 women; mean age, 35.38 ± 9.55 years) and 224 controls (100 men and 124 women; mean age, 36.57 ± 8.43 years). Of these patients, 54% (*n* = 124) resided in urban locations, and



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Figure 1 Linkage disequilibrium in *glutamate decarboxylase 1* polymorphisms (rs1978340 and rs3749034). A: Data from this study; B: Data from 1000 genomes.

46% ($n = 106$) resided in rural locations. No statistically significant differences were found between the cases and controls in terms of sex, age, or residential location ($P > 0.05$). For the PD patients, the mean course of PD was 2.80 ± 1.68 years, the mean PDSS score was 14.13 ± 3.74 , and the mean HAM-A score was 22.07 ± 6.86 (Table 1).

Association of *GAD1* (rs1978340 and rs3749034) polymorphisms with PD risk

HWE was measured in all genotyped individuals. *GAD1* (rs1978340 and rs3749034) polymorphisms fulfilled the HWE ($P > 0.05$) in both patients and HCs. The linkage disequilibrium evaluated in patients with PD and HCs for variants rs1978340 and rs3749034 of *GAD1* is shown in Figure 1 ($R^2 > 0.9$). The genotype and allele distributions of *GAD1* (rs1978340 and rs3749034) did not significantly differ between PD patients and HCs ($P > 0.05$) (Table 2).

Association of *GAD1* (rs1978340 and rs3749034) polymorphisms with clinical manifestations in PD patients

There were no statistically significant differences in the total PDSS and sub-item scores among the three genotype groups of *GAD1* polymorphisms (rs1978340 and rs3749034; all $P > 0.05$) (Table 3).

However, there was a significant difference among the three groups with different *GAD1* rs1978340 genotypes in item 10 of the HAM-A score for PD ($P < 0.01$). In addition, post hoc analyses indicated that patients with the *GAD1* rs1978340 A/A genotype had significantly higher scores than those with the A/G or G/G genotypes (all $P < 0.001$), and the results remained significant after Bonferroni's multiple comparison adjustment ($P < 0.01$), reflecting a higher score for respiratory symptoms in patients with the *GAD1* rs1978340 A/A genotype than in those with the A/G or G/G genotype. However, there was no statistically significant difference among the three groups with different *GAD1* rs1978340 genotypes for the remaining items or HAM-A total scores ($P > 0.05$). Moreover, there was no significant association between *GAD1* rs3749034 and anxiety severity in PD patients (all $P > 0.05$) (Table 4).

DISCUSSION

In this study, regarding respiratory symptoms, which include chest tightness, choking, and breathing difficulty, we found that patients with the *GAD1* rs1978340 A/A genotype had significantly higher scores than those with the A/G or G/G genotypes. In other words, the present study showed that the *GAD1* rs1978340 A/A genotype was associated with increased severity of respiratory symptoms in patients with PD and demonstrated that the *GAD1* genotype might be related to symptomatic profiles rather than vulnerability to developing PD. In addition, our findings imply that different clinical features in PD patients are closely related to the heterogeneity of heredity. Compared with PD patients of the non-respiratory subtype (non-RS), previous studies have shown that patients with the RS subtype have a more extensive family history of PD[29]. Moreover, experimental animal research has provided evidence of the important role of GABAergic neurotransmission in the amygdala in modulating anxiety-related behaviors. For example, diminished GAD67 expression in the amygdala blunts the anxiolytic-like effects of diazepam in adult mice[30]. Furthermore, *GAD1* SNP rs1978340 is potentially functional because it affects GABA concentrations in the cingulate cortex[22]. In addition, the presence of *GAD1* rs1978340 allele A has been associated with a higher Glu/GABA ratio[31]. Clinical trials have shown that patients with PD and RS have a more rapid response to antidepressants and benzodiazepines than that of non-RS PD patients[32]. These findings contribute to our understanding of the mechanism linking *GAD1* rs1978340 with respiratory-related symptoms.

Similar findings suggest that patients with PD carrying the 5-HTTLPR s-allele experience the most severe panic and depressive symptoms[33]. Another study showed higher anxiety levels among A/G carriers than those among A/A carriers in patients[34]. It is evident that molecular genetics showed inconsistent results across different studies. This may be due to different sample sizes and ethnic differences. In addition, different clinical symptoms may be partly attributed

Table 1 Demographic and clinical characteristics in patients with panic disorder and controls, *n* (%)

Variable	PD (<i>n</i> = 230)	Controls (<i>n</i> = 224)	<i>t/χ²</i>	<i>P</i> value
Sex				
Male	92 (40.0)	100 (44.6)	1.002	0.317
Female	138 (60.0)	124 (55.4)		
Age, yr	35.38 ± 9.55	36.57 ± 8.43	1.410	0.159
Educational level				
< Junior high school	49 (21.3)	43 (19.2)		
High school	95 (41.3)	92 (41.1)	0.412	0.814
College and above	86 (37.4)	89 (39.7)		
Resident location				
Urban	124 (53.9)	126 (56.3)		
Rural	106 (46.1)	98 (43.7)	0.250	0.617
Total duration of PD, yr	2.80 ± 1.68			
PDSS score	14.13 ± 3.74			
HAMA score	22.07 ± 6.86			

PDSS: Panic Disorder Severity Scale; HAMA: Hamilton Anxiety Rating Scale; PD: Panic disorder.

Table 2 *Glutamate decarboxylase 1* gene polymorphisms of patients with panic disorder vs controls in the Chinese population, *n* (%)

SNP	Alleles and genotypes	PD (<i>n</i> = 230)	Controls (<i>n</i> = 224)	Model	OR (95%CI)	<i>P</i> value
rs1978340	A	122 (26.5)	116 (25.9)	Allele ^a	1.003 (0.769-1.389)	0.829
	G	338 (73.5)	332 (74.1)			
	A/A	17 (7.4)	20 (8.9)	Additive ^b	1.031 (0.774-1.373)	0.835
	A/G	88 (38.3)	76 (34.8)	Dominant ^b	1.120 (0.773-1.622)	0.549
	G/G	125 (54.3)	128 (57.1)	Recessive ^b	0.814 (0.415-1.598)	0.550
rs3749034	A	131 (28.5)	129 (28.8)	Allele	0.985 (0.738-1.313)	0.916
	G	329 (71.5)	319 (71.2)			
	A/A	17 (7.4)	15 (6.7)	Additive	0.984 (0.732-1.323)	0.914
	A/G	97 (42.2)	99 (44.2)	Dominant	0.948 (0.656-1.370)	0.777
	G/G	116 (50.4)	110 (49.1)	Recessive	1.112 (0.541-2.286)	0.773

^aChi-square test.

^bLogistic regression analyses.

OR: Odds ratios; CI: Confidence interval; SNP: Single Nucleotide Polymorphism, "A" represent wild type and "a" represent mutant type: allele, a vs A; additive, aa vs Aa vs AA; dominant, aa + Aa vs AA, recessive, aa vs Aa + AA; PD: Panic disorder.

to different genetic backgrounds, leading to difficulties in reaching a consensus on the etiology of PD. Further studies with larger populations are needed to obtain precise results based on different symptom subtypes.

In this case-control study, we examined two SNPs (rs1978340 and rs3749034) in a Chinese population. The results revealed that there was no association between *GAD1* and PD. In addition, we did not observe a modulatory effect of *GAD1* (rs1978340 and rs3749034) on PD severity. Much evidence has indicated that *GAD1* gene polymorphisms may be involved in the etiology of several psychiatric disorders. However, only one study has found that *GAD1* variation is associated with PD in females[35]. The different results of these studies might be partly attributable to differences in sample size and sex. Moreover, samples from different ethnicities and meta-analyses are required to further test this association. The SNP coverage in the present study was limited, and other gene polymorphisms should be considered. In addition, the pathogenesis of PD may involve the interaction of multiple genes and signal pathway regulation, which may incorporate the combined effects of genetic and environmental factors. For example, a previous study suggested the effect of the interaction between 5-HTTLPR and separate life events on PD[36]. Finally, epigenetic mechanisms have been

Table 3 Panic disorder severity scale subdimension scores of panic disorder with different *glutamate decarboxylase 1* rs1978340 and rs3749034 polymorphisms

Variable	rs1978340			F	P value	rs3749034			F	P value
	A/A (n = 17)	A/G (n = 88)	G/G (n = 125)			A/A (n = 17)	A/G (n = 97)	G/G (n = 116)		
PDSS1	2.12 ± 0.93	2.11 ± 1.09	2.14 ± 1.08	0.022	0.978	1.94 ± 0.97	2.06 ± 1.04	2.22 ± 1.10	0.837	0.434
PDSS2	2.41 ± 1.00	2.32 ± 1.00	2.44 ± 1.10	0.349	0.706	2.35 ± 1.41	2.28 ± 1.07	2.49 ± 0.97	1.099	0.335
PDSS3	2.41 ± 1.18	2.08 ± 0.89	2.14 ± 1.05	0.786	0.457	2.18 ± 1.13	1.99 ± 1.00	2.26 ± 0.98	1.934	0.147
PDSS4	1.59 ± 1.28	1.57 ± 1.04	1.66 ± 1.06	0.218	0.804	1.41 ± 1.12	1.76 ± 1.12	1.53 ± 1.00	1.590	0.206
PDSS5	1.71 ± 1.26	1.91 ± 1.01	1.76 ± 1.10	0.581	0.560	2.12 ± 1.22	1.67 ± 0.93	1.89 ± 1.63	1.818	0.165
PDSS6	2.33 ± 1.22	2.15 ± 0.97	2.11 ± 1.03	0.417	0.660	2.18 ± 1.33	2.09 ± 1.03	2.18 ± 0.97	0.206	0.814
PDSS7	1.59 ± 0.94	1.83 ± 1.01	1.97 ± 1.18	1.087	0.339	2.00 ± 1.06	1.85 ± 1.05	1.91 ± 1.15	0.174	0.841
PDSS total	14.18 ± 4.68	13.97 ± 3.39	14.23 ± 3.86	0.132	0.877	14.18 ± 4.99	13.70 ± 3.54	14.47 ± 3.69	1.134	0.323

PDSS1: Panic attack frequency, PDSS2: Panic distress, PDSS3: Severity of anticipatory anxiety, PDSS4: Agoraphobic fear/avoidance, PDSS5: Fear/avoidance of panic-related sensations, PDSS6: Work impairment, PDSS7: Social impairment, PDSS: Panic Disorder Severity Scale.

Table 4 Hamilton Anxiety Rating Scale subdimension scores of panic disorder with different *glutamate decarboxylase 1* rs1978340 and rs3749034 polymorphisms

Variable	rs1978340			F	P value	rs3749034			F	P value
	A/A (n = 17)	A/G (n = 88)	G/G (n = 125)			A/A (n = 17)	A/G (n = 97)	G/G (n = 116)		
HAMA1	1.59 ± 1.06	1.88 ± 1.16	1.81 ± 1.18	0.439	0.645	1.82 ± 1.33	1.81 ± 1.14	1.82 ± 1.17	0.001	0.999
HAMA2	2.00 ± 1.00	2.06 ± 0.94	2.17 ± 1.11	0.402	0.669	2.24 ± 1.30	2.07 ± 1.01	2.13 ± 1.03	0.206	0.814
HAMA3	1.94 ± 1.09	1.66 ± 1.07	1.98 ± 1.08	2.295	0.103	2.24 ± 1.25	1.78 ± 1.01	1.85 ± 1.11	1.260	0.286
HAMA4	1.71 ± 1.11	1.43 ± 1.11	1.58 ± 1.02	0.728	0.484	1.47 ± 0.87	1.48 ± 1.02	1.58 ± 1.12	0.231	0.794
HAMA5	1.59 ± 1.06	1.58 ± 1.04	1.65 ± 1.03	0.121	0.886	1.65 ± 1.17	1.55 ± 1.06	1.67 ± 0.99	0.402	0.670
HAMA6	1.53 ± 1.01	1.25 ± 1.05	1.54 ± 0.99	2.255	0.107	1.65 ± 1.32	1.38 ± 1.07	1.44 ± 0.94	0.498	0.747
HAMA7	1.76 ± 1.03	1.34 ± 0.99	1.62 ± 1.01	2.459	0.088	1.59 ± 1.06	1.46 ± 1.01	1.56 ± 1.02	0.277	0.759
HAMA8	1.06 ± 0.83	1.38 ± 1.10	1.37 ± 1.12	0.644	0.526	1.41 ± 0.94	1.34 ± 1.10	1.34 ± 1.11	0.032	0.969
HAMA9	2.06 ± 1.20	1.91 ± 0.99	1.94 ± 1.03	0.154	0.858	1.82 ± 1.13	2.08 ± 1.07	1.84 ± 0.97	1.647	0.195
HAMA10	2.88 ± 0.93	1.94 ± 0.98	1.90 ± 1.02	7.445	0.001	2.41 ± 1.00	1.94 ± 0.96	1.97 ± 1.08	1.601	0.204
HAMA11	0.76 ± 0.66	0.86 ± 0.79	0.97 ± 0.91	0.672	0.512	1.00 ± 0.94	0.89 ± 0.87	0.92 ± 0.82	0.143	0.867
HAMA12	1.00 ± 1.00	1.20 ± 0.96	1.34 ± 0.92	1.214	0.299	1.41 ± 1.00	1.22 ± 0.93	1.28 ± 0.95	0.340	0.712
HAMA13	1.12 ± 0.93	1.35 ± 0.87	1.30 ± 1.03	0.427	0.653	1.29 ± 1.11	1.25 ± 0.99	1.36 ± 0.92	0.377	0.687
HAMA14	1.59 ± 1.06	1.48 ± 0.98	1.35 ± 0.98	0.693	0.501	1.53 ± 1.28	1.44 ± 0.99	1.38 ± 0.94	0.229	0.796
HAMA total	22.59 ± 5.22	21.34 ± 6.94	22.50 ± 6.97	0.799	0.451	23.53 ± 7.13	21.70 ± 6.93	22.16 ± 6.75	0.535	0.587

HAMA1: Anxious mood; HAMA2: Tension; HAMA3: Fears; HAMA4: Insomnia; HAMA5: Intellectual; HAMA6: Depressed mood; HAMA7: Somatic complaints muscular; HAMA8: Somatic complaints sensory; HAMA9: Cardiovascular symptoms; HAMA10: Respiratory symptoms; HAMA11: Gastrointestinal symptoms; HAMA12: Genitourinary symptoms; HAMA13: Autonomic symptoms; HAMA14: Behavior at interview; HAMA: Hamilton Anxiety Rating Scale.

suggested to play important roles at the intersection of genetic and environmental factors[37]. Environmental factors may influence biological processes through epigenetic mechanisms, particularly DNA methylation[38]. For instance, patients with PD exhibit significantly lower average *GAD1* methylation levels than those of HCs[39]. Another study showed that patients had significantly lower methylation of the *GAD1* promoter region on cytosine-phosphate-guanine 7 than that of HCs, and a significant negative association was found between the cg171674146 site and clinical severity[40]. Therefore,

epigenetic modifications may play an important role and should be further investigated in future studies.

CONCLUSION

In conclusion, the present study showed that the A/A genotype of *GAD1* rs1978340 is associated with increased severity of respiratory symptoms in patients with PD. However, the results of our study should be considered in light of the following limitations: Since this was a small sample investigating the associations between *GAD1* gene polymorphisms and PD, it would be valuable to replicate our findings in a larger cohort. In addition, SNP coverage in the present study was limited, and other gene polymorphisms should be considered.

ARTICLE HIGHLIGHTS

Research background

Genetic factors are known to play a significant role in the development of panic disorder (PD). However, the impact of genetic variants on PD is still a subject of controversy.

Research motivation

γ -Aminobutyric acid (GABA) is an important neurotransmitter that inhibits brain activity. Previous reports have linked the *glutamate decarboxylase 1* (*GAD1*) genetic variants to various psychiatric disorders, including bipolar disorder, schizophrenia, attention-deficit/hyperactivity disorder, and heroin dependence. However, few studies have examined the relationship between *GAD1* and PD, particularly in Chinese populations.

Research objectives

The main objectives of this study were to examine the associations between *GAD1* gene polymorphisms (rs1978340 and rs3749034) and PD risk, and to determine the effect of these polymorphisms on the severity of clinical symptoms, specifically respiratory symptoms, in individuals with PD.

Research methods

The study included a total of 230 PD patients and 224 healthy controls. All participants underwent assessments for anxiety and panic symptom severity using the Hamilton Anxiety Rating Scale (HAM-A) and Panic Disorder Severity Scale (PDSS). The *GAD1* gene polymorphisms (rs1978340 and rs3749034) were genotyped, and allele frequencies were analyzed.

Research results

The study findings revealed no significant differences in the genotype distributions or allele frequencies of *GAD1* (rs1978340 and rs3749034) between the PD cases and the control group. Furthermore, the *GAD1* gene polymorphisms (rs1978340 and rs3749034) did not exhibit a significant effect on the overall severity of PD. However, in relation to respiratory symptoms, PD patients with the *GAD1* rs1978340 A/A genotype demonstrated significantly higher scores compared to those with the A/G or G/G genotype.

Research conclusions

In conclusion, this study demonstrated that the A/A genotype of *GAD1* rs1978340 is associated with increased severity of respiratory symptoms in individuals with PD. However, no significant associations were found between *GAD1* gene polymorphisms and the risk of developing PD or the overall severity of the disorder.

Research perspectives

Further research is needed to explore other potential genetic factors involved in the development and severity of PD. Additionally, investigating the underlying mechanisms through which *GAD1* gene polymorphisms affect respiratory symptoms in PD patients could provide valuable insights for future studies.

FOOTNOTES

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Retrospective Study

Effects of health concept model-based detailed behavioral care on mood and quality of life in elderly patients with chronic heart failure

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Abstract

BACKGROUND

With the intensification of social aging, the susceptibility of the elderly population to diseases has attracted increasing attention, especially chronic heart failure (CHF) that accounts for a large proportion of the elderly.

AIM

To evaluate the application value of health concept model-based detailed behavioral care in elderly patients with CHF.

METHODS

This study recruited 116 elderly CHF patients admitted from October 2018 to October 2020 and grouped them according to the nursing care that they received. The elderly patients who underwent health concept model-based detailed behavioral care were included in a study group (SG; $n = 62$), and those who underwent routine detailed behavioral nursing intervention were included as a control group (CG; $n = 54$). Patients' negative emotions (NEs), quality of life (QoL), and nutritional status were assessed using the self-rating anxiety/depression scale (SAS/SDS), the Minnesota Living with Heart Failure Questionnaire (MLHFQ), and the Modified Quantitative Subjective Global Assessment (MQSGA) of nutrition, respectively. Differences in rehabilitation efficiency, NEs, cardiac function (CF) indexes, nutritional status, QoL, and nursing satisfaction were comparatively analyzed.

RESULTS

A higher response rate was recorded in the SG *vs* the CG after intervention ($P < 0.05$). After care, the left ventricular ejection fraction was higher while the left ventricular end-diastolic dimension and left ventricular end systolic diameter were lower in the SG compared with the CG ($P < 0.05$). The post-intervention SAS

and SDS scores, as well as MQSGA and MLHFQ scores, were also lower in the SG ($P < 0.05$). The SG was also superior to the CG in the overall nursing satisfaction rate ($P < 0.05$).

CONCLUSION

Health concept model-based detailed behavioral care has high application value in the nursing care of elderly CHF patients, and it can not only effectively enhance rehabilitation efficiency, but also mitigate patients' NEs and improve their CF and QoL.

Key Words: Chronic heart failure; Elderly patients; Health concept model; Detailed behavioral care; Patient mood; Quality of life; Nursing effect

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Core Tip: Elderly patients with chronic heart failure (CHF) are prone to negative emotions (NEs) such as depression and anxiety during treatment. Although some drugs can alleviate NEs, they are not conducive to the cardiac function of patients. Therefore, effective means should be explored clinically to improve the mood and quality of life of elderly patients with CHF.

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INTRODUCTION

Chronic heart failure (CHF) is a clinically common cardiovascular disorder that may cause various complications[1,2]. The disease is difficult to treat with a high death rate, re-hospitalization rate, and bleak prognosis, resulting in great clinical attention to its treatment and nursing care[3]. In the current aging society, CHF patients account for a large proportion of the elderly population[4]. CHF in the elderly is characterized by a long course, multiple underlying comorbidities, and declined self-care ability, bringing huge economic burden to patients' families and society[5]. Elderly CHF patients are also predisposed to negative emotions (NEs) due to their age and unpredictable conditions[6]. Although drugs such as duloxetine can be used to relieve depression and other NEs, they may be disadvantageous to patients' cardiac function (CF)[7,8]. Effective nursing intervention is therefore extremely necessary, which is the key to improving patients' quality of life (QoL) and disease prognosis[9].

Conventional nursing intervention, being single and inflexible, cannot meet the actual needs of elderly CHF patients [10]. Health concept model-based detailed behavioral care, on the other hand, formulates nursing intervention programs through behavioral and social psychology, which encourages patients to take the initiative to adopt healthy behaviors, thus improving the treatment effect[11]. In addition, there is a positive correlation between health beliefs and healthy behaviors. Establishing correct health beliefs allows people to accept persuasion, change unhealthy behaviors, and actively adopt healthy behaviors[12]. At present, the health belief model has been widely used in the health education of various diseases with good effects achieved[13]. Besides, chronic and unrelenting symptoms and long treatment process significantly reduces the QoL of CHF patients while causing NEs such as anxiety and depression[14]. Health education can mitigate the NEs of elderly CHF patients and enhance their disease awareness to mitigate their fear of the disease due to insufficient awareness[15].

Based on the above, this study explored the application value of health concept model-based detailed behavioral care in the care of elderly CHF patients.

MATERIALS AND METHODS

Patient information

The clinical data of 116 elderly patients with CHF admitted to the Affiliated Hangzhou First People's Hospital Zhejiang University School of Medicine from October 2018 to October 2020 were analyzed retrospectively. Patients who underwent health concept model-based detailed behavioral care were included in a study group (SG; $n = 62$, male-female ratio 40:22) and those who underwent routine detailed behavioral nursing intervention were included in a control group (CG; $n = 54$, male-female ratio 29:25).

Eligibility criteria

The enrolled patients all were aged ≥ 60 years, with a confirmed diagnosis of CHF[16], complete clinical data, and active cooperation with treatment. Patients and their families were informed and consented to participate in the study.

Patients with chronic obstructive pulmonary disease, cerebral toxicosis, hyperthyroidism, inability to eat normally, cognitive and consciousness disorders, serious infections, malignant diseases, and limited mobility or those who were otherwise unable to complete all care measures were excluded from the study.

Nursing methods

Patients in the CG were intervened by routine detailed behavioral nursing. Following the doctor's advice, patients were instructed to stay in bed or carry out appropriate activities. Besides, their body temperature and pulse were monitored on time until discharge, and their conditions were closely observed.

Patients in the SG received health concept model-based detailed behavioral care. Before carrying out the nursing work, the nursing staff introduced the disease to the elderly patients in detail, and guided them to relax and cooperate with the care. In addition, each patient's condition and physical function were assessed in a timely manner by means of echocardiography and 24-h continuous ECG monitoring, and the corresponding nursing plan was formulated based on the evaluation results. Furthermore, medication management was strengthened. The patient's indicators (*e.g.*, blood pressure and blood lipid) were strictly monitored and controlled within the reference range as far as possible to prevent complications. The emotional status of patients was always concerned during daily care. When they were found to develop NEs, the causes of unhealthy psychological states were analyzed in time, based on which targeted psychological nursing intervention was developed and implemented. During the nursing intervention, patients' bad daily behavioral habits were corrected, and they were guided to keep good hours to reduce the burden on their hearts. In addition, a certain amount of exercise was also ensured, which was realized by developing an appropriate exercise program for each patient to help improve his/her physical fitness and blood circulation. Moreover, a reasonable diet plan was formulated based on the patient's nutritional status and physical function. In the daily diet, patients were advised to take easy-to-digest, crude fiber, and light foods, and avoid oily and high-fat foods.

Outcome measures

The rehabilitation of the two groups of patients after nursing was compared. It was considered markedly effective if the patient had CF improvement $\geq$ grade II, with obviously improved condition. Effective referred to CF improvement $>$ grade I and alleviation of clinical symptoms. Ineffective corresponded to CF improvement $<$ grade I, non-improvement, or disease worsening[17]. Overall response rate was calculated as (markedly effective cases + effective cases)/total cases $\times$ 100%.

Alterations in CF indexes [left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), and left ventricular end systolic diameter (LVESD)] were compared before and after care.

Assessment of patients' anxiety and depression was performed 7 d after nursing using the self-rating anxiety/depression scale (SAS/SDS)[18]. Both scales have a total score of 100, with the scores in direct proportion to anxious and depressive symptoms.

The Minnesota Living with Heart Failure Questionnaire (MLHFQ)[19], which comprises 3 dimensions and 21 items (8, 5, and 8 items in physical field, emotional field, and other fields, respectively), was used for QoL assessment of elderly CHF patients. The total score is 105 points, and the score is inversely proportional to the patient's QoL. Patients' overall nutritional status was evaluated by the Modified Quantitative Subjective Global Assessment (MQSGA) of nutrition[20], with a total score of 35 points, and the score is inversely proportional to the nutritional status.

Nursing satisfaction was investigated using the self-made nursing satisfaction questionnaire (total score: 100) from the aspects of comfort, health knowledge, working ability, service attitude, and comprehensive level. Patients or their families filled it out according to the actual situation. A score of > 90 , 70-90, and < 70 points was considered as very satisfied, satisfied, and dissatisfied, respectively, and the total satisfaction = very satisfied + satisfied. The overall nursing satisfaction was compared.

Statistical analysis

In this study, SPSS 19.0 medical statistical analysis software was used to statistically analyze the collected data, with $P < 0.05$ regarded as the significance level for all analyses. The chi-square test (χ^2) was performed for counting data expressed as percentages (%). The mean $\pm$ SD was used to denote quantitative data, which all followed a normal distribution and were analyzed between groups by the independent sample *t* test and between different time points by the paired *t* test.

RESULTS

Patients' baseline data

Comparing patients' baseline data, it was found that the two patient cohorts were comparable in age, sex, course of disease, body mass index, systolic blood pressure, complications (hypertension, diabetes, coronary heart disease, and atrial fibrillation), CF grade[17], and heart rate ($P > 0.05$), as shown in Table 1.

Comparison of rehabilitation efficacy

Comparing the rehabilitation effects after intervention, it was found that the total rehabilitation effective rate in the SG

Table 1 Baseline data

	Study group (n = 62)	Control group (n = 54)	χ^2/t	P value
Age (years old)	78.16 ± 6.58	77.19 ± 6.94	0.772	0.442
Sex			1.400	0.237
	Male	29 (53.70)		
	Female	25 (46.30)		
Course of disease (years)	5.55 ± 1.34	5.43 ± 1.56	0.446	0.657
BMI (kg/m ²)	23.71 ± 3.27	23.93 ± 3.11	0.370	0.712
Systolic pressure (mmHg)	147.97 ± 12.45	149.94 ± 14.28	0.794	0.429
Complications				
	Hypertension	14 (25.93)	0.717	0.397
	Diabetes mellitus	10 (18.52)	0.694	0.404
	Coronary heart disease	23 (42.59)	0.204	0.652
	Atrial fibrillation	7 (12.96)	1.296	0.255
Cardiac function grade			2.772	0.250
	II	21 (38.89)		
	III	25 (46.30)		
	IV	8 (14.81)		
Heart rate (beats/min)	80.11 ± 5.24	80.98 ± 5.7	0.856	0.394

BMI: Body mass index.

Table 2 Rehabilitation efficacy

	Study group (n = 62)	Control group (n = 54)	χ^2	P value
Markedly effective	38 (61.29)	25 (46.30)		
Effective	21 (33.87)	20 (37.03)		
Ineffective	3 (4.84)	9 (16.67)		
Overall response	59 (95.16)	45 (83.33)	4.354	0.037

was 95.16%, significantly higher than that of the CG (83.33%; $P < 0.05$), as shown in [Table 2](#).

CF improvement

The observation of patients' CF revealed no evident difference in LVEF, LVEDD, and LVESD between the two groups prior to nursing intervention ($P > 0.05$), while elevated LVEF and decreased LVEDD and LVESD were found in both cohorts post intervention ($P < 0.05$). And in comparison with the CG, LVEF was higher while LVEDD and LVESD were lower in the SG ($P < 0.05$; [Figure 1](#)).

Relief of patients' NEs

We comparatively analyzed the relief of patients' NEs and found significantly reduced SAS and SDS scores in both cohorts after intervention ($P < 0.05$), with more significant reductions in the SG compared with the CG ($P < 0.05$; [Figure 2](#)).

Improvement of nutritional status and QoL of patients after nursing

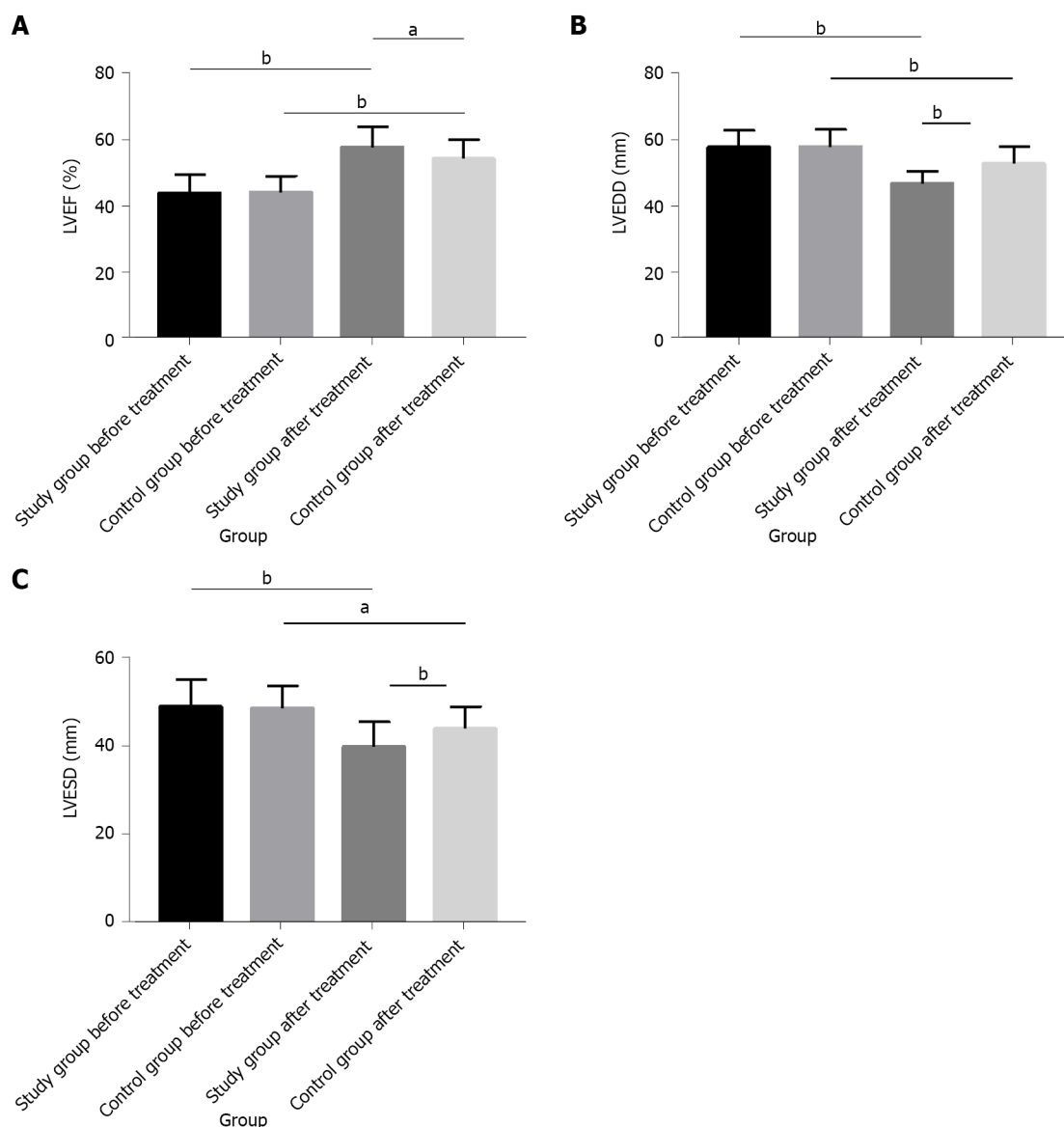
Comparing the MQSGA and MLHFQ scores before and after patient care, it was found that both scores decreased after nursing ($P < 0.05$), with more significant reductions in the SG as compared to the CG ($P < 0.05$; [Figure 3](#)).

Comparison of patients' nursing satisfaction

Statistics on patient satisfaction revealed a nursing satisfaction of 93.55% in the SG, statistically higher than that of the CG (81.48%; $P < 0.05$; [Table 3](#)).

Table 3 Nursing satisfaction

	Study group (n = 62)	Control group (n = 54)	χ^2	P value
Very satisfied	35 (56.45)	27 (50.00)		
Satisfied	23 (37.10)	17 (31.48)		
Dissatisfied	4 (6.45)	10 (18.52)		
Total satisfaction	58 (93.55)	44 (81.48)	3.960	0.047



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Figure 1 Comparison of patients' cardiac function. A: After nursing, the left ventricular ejection fraction of patients in both groups were significantly improved, with a higher level in the study group as compared to the control group; B: Left ventricular end diastolic diameter was significantly reduced in both groups after nursing, and was statistically lower in the study group compared with the control group; C: After nursing, left ventricular end systolic diameter in the two groups dropped obviously and was lower in the study group compared with the control group. ^a $P < 0.01$; ^b $P < 0.001$. LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end diastolic diameter; LVESD: Left ventricular end systolic diameter.

DISCUSSION

Due to CF abnormalities, CHF patients experience many physiological and psychological problems such as restricted daily activities, disordered sleep patterns, and depression, resulting in the need of care from family members in daily life [21]. However, there may be unsatisfactory nursing effects due to inadequate nursing training of family caregivers, and improper care may adversely impact patients both physically and psychologically. Educational interventions can

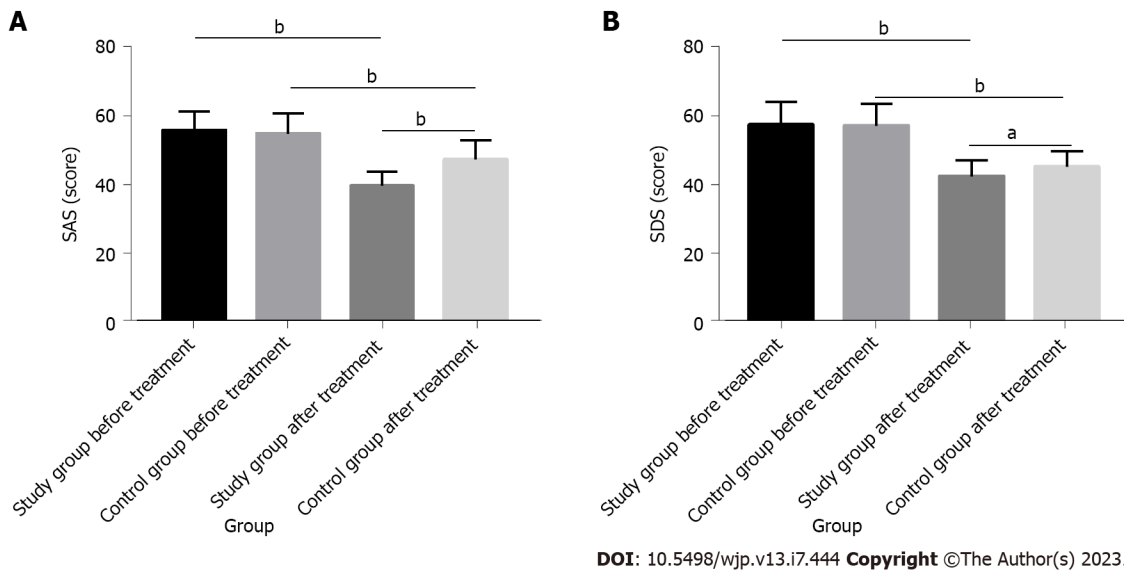


Figure 2 Comparison of patients' negative emotions. A: After nursing, the self-rating anxiety scale score of both groups of patients dropped markedly and was lower in the study group compared with the control group; B: The self-rating depression scale score decreased statistically in both groups after nursing and was lower in the study group compared with the control group. ^a $P < 0.01$; ^b $P < 0.001$. SAS: Self-rating anxiety scale; SDS: Self-rating depression scale.

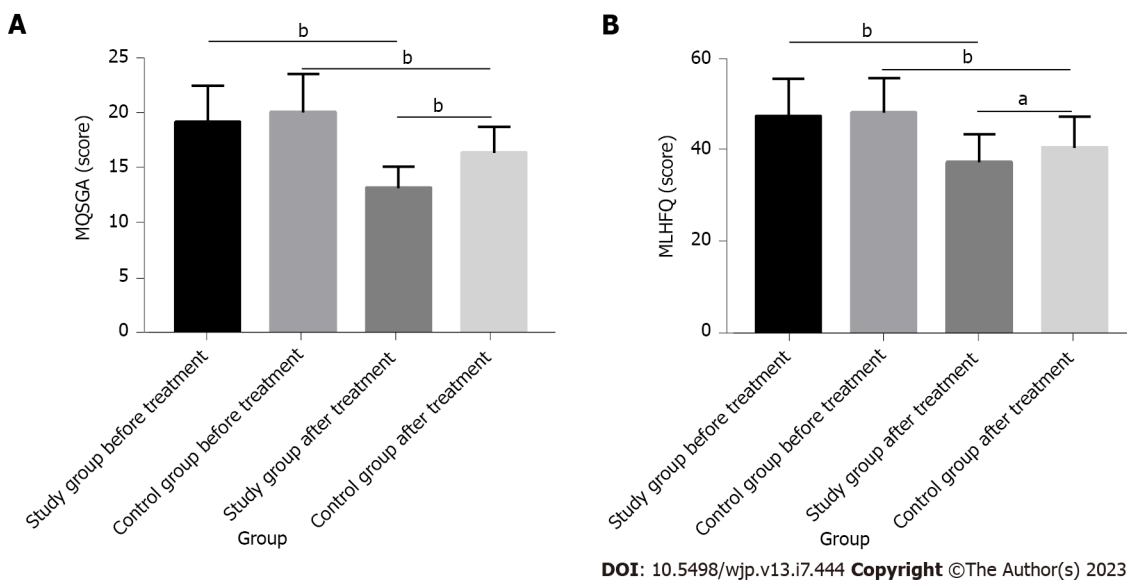


Figure 3 Improvement of nutritional status and quality of life of patients. A: The modified quantitative subjective global assessment score of the two groups dropped statistically after nursing, and was lower in the study group compared with the control group; B: After nursing, the Minnesota living with heart failure questionnaire score of the two groups dropped statistically and was lower in the study group compared with the control group. ^a $P < 0.01$; ^b $P < 0.001$. MQSGA: Modified quantitative subjective global assessment; MLHFQ: Minnesota living with heart failure questionnaire.

effectively improve people's awareness of various health issues, thus affecting patients' detailed behaviors. In recent years, an increasing number of researchers have devoted themselves to exploring a better nursing intervention model for CHF. For example, Taniguchi *et al*[22] adopted a self-monitoring outpatient care model for CHF patients, and Jin *et al*[23] suggested cluster care in their study[22,23].

This study put forward the view that health concept model-based detailed behavioral care can better promote the rehabilitation of elderly CHF patients and improve their CF than the routine one. Previous studies have also shown that interventions based on the health concept model can accelerate recovery from chronic diseases[24]. In addition, under the health concept model-based detailed behavioral care, appropriate exercise programs will be developed for patients, with the exercise intensity gradually increased according to the patient's tolerance, thus facilitating patient recovery. It has been shown that CF recovery in heart failure patients is accelerated with increasing intensity of exercise training. However, too much exercise in a short period of time will lead to poor exercise experience, reduced comfort, and increased NEs, which cannot motivate patients' treatment and compliance[25,26]. Therefore, we increased the amount of exercise step by step to play a better role in rehabilitation.

Middle-aged and aged people are more susceptible to coronary heart disease as their physical fitness will be partially degraded with age, which will affect their physical resistance and psychological status, reducing their QoL[27]. The detailed behavior nursing based on the health concept model can mitigate patients' NEs while enhancing their nutritional status and QoL. The introduction of a more nutritious diet into daily life, coupled with effective rehabilitation, resulted in significant improvements in the patient's nutritional status, QoL, and NEs. Li *et al*[28] mentioned in their study that intervention based on the health concept model can effectively improve the self-management ability of patients and enhance their professional knowledge during the intervention process, contributing to enhanced confidence in treatment and better QoL, which is similar to our research. In addition, detailed nursing can reflect the quality of care services. Nursing disputes arising from nursing defects, errors, and accidents should be effectively avoided during clinical treatment and nursing care. Meanwhile, ward inspections should be strengthened during treatment, so as to ensure nursing safety, enhance nursing service quality, and improve patient satisfaction[29,30]. In our research, health concept model-based detailed behavioral care also significantly outperformed conventional detailed behavioral nursing in terms of patient satisfaction, consistent with the satisfaction results of Smeulders *et al*[31] on patients with heart failure.

The novelty of this study lies in the comparative analysis of the clinical differences in the rehabilitation effect, CF, SAS, SDS, nutritional status, QoL, and nursing satisfaction between health concept model-based detailed behavioral care and routine detailed behavioral nursing in elderly CHF patients. However, this study also has some limitations. CHF is a long-term condition, but patient outcomes have not been explored in this study, resulting in little understanding of the impact of this care model on patient prognosis. Second, we only included patients aged over 60 years, since the elderly were the main patient group of CHF. However, it is still unclear whether our intervention methods are also applicable to those younger than 60 years, which needs to be explored by re-incorporating samples in subsequent studies.

CONCLUSION

In conclusion, health concept model-based detailed behavioral care has high application value in elderly CHF patients, which can improve patients' rehabilitation efficiency, significantly mitigate NEs, and enhance their CF and QoL.

ARTICLE HIGHLIGHTS

Research background

Chronic heart failure (CHF), a clinical condition that affects a large proportion of the elderly population, is characterized by a long course of disease, many complications, and decreased self-care ability, often bringing a huge economic burden to the families of patients and society.

Research motivation

To help people understand CHF in the elderly and provide reference for the clinical optimization of this disease.

Research objectives

To evaluate the application value of health concept model-based detailed behavioral care in elderly patients with CHF.

Research methods

Sixty-two cases of CHF who underwent health concept model-based detailed behavioral care were included in a study group, and patients' rehabilitation efficiency, negative emotions (NEs), cardiac function (CF) parameters, nutritional status, quality of life (QoL), and nursing satisfaction were recorded. In addition, 54 cases who underwent routine detailed behavioral care were included in a control group (CG) for analysis.

Research results

The rehabilitation efficiency and CF parameters of the study group were significantly improved after intervention. In addition, more significant alleviation in NEs and improvement in QoL were recorded in the study group as compared to the CG. A higher degree of overall nursing satisfaction was also noted in the research group.

Research conclusions

Health concept model-based detailed behavioral care has high application value in elderly patients with CHF, which can improve patients' rehabilitation efficiency, significantly relieve NEs, and enhance their CF and QoL.

Research perspectives

This study discusses the application value of health concept model-based detailed behavioral care in the nursing of elderly CHF patients, and focuses on patients' NEs and QoL, hoping to provide some references for improving the clinical care of such patients.

FOOTNOTES

Author contributions: Zheng AD and Xu J carried out the studies, and conceived and designed the study; Zheng AD and Cai LL performed the analyses and collected the data; Zheng AD drafted the manuscript; all authors approved the final manuscript submitted.

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

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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Retrospective Study

Repetitive transcranial magnetic stimulation combined with olanzapine and amisulpride for treatment-refractory schizophrenia

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Abstract

BACKGROUND

Treatment-refractory schizophrenia (TRS), accounting for approximately 30% of all schizophrenia cases, has poor treatment response and prognosis despite treatment with antipsychotic drugs.

AIM

To analyze the therapeutic effectiveness of repetitive transcranial magnetic stimulation (rTMS) combined with olanzapine (OLZ) and amisulpride (AMI) for TRS and its influence on the patient's cognitive function.

METHODS

This study enrolled 114 TRS patients who received treatment at the First Affiliated Hospital of Zhengzhou University between July 2019 and July 2022. In addition to the basic OLZ + AMI therapy, 54 cases of the control group (Con group) received modified electroconvulsive therapy, while 60 cases of the research group (Res group) received rTMS. Data on therapeutic effectiveness, safety (incidence of drowsiness, headache, nausea, vomiting, or memory impairment), Positive and Negative Symptom Scale, Montreal Cognitive Assessment Scale, and Schizophrenia Quality of Life Scale were collected from both cohorts for comparative analyses.

RESULTS

The Res group elicited a higher overall response rate and better safety profile when compared with the Con group. Additionally, a significant reduction was observed in the post-treatment Positive and Negative Symptom Scale and Schizophrenia Quality of Life Scale scores of the Res group, presenting lower scores than those of the Con group. Furthermore, a significant increase in the Montreal

Cognitive Assessment Scale score was reported in the Res group, with higher scores than those of the Con group.

CONCLUSION

The treatment of TRS with rTMS and OLZ + AMI is effective and safe. Moreover, it can alleviate the patients' mental symptoms, improve their cognitive function and quality of life, and has a high clinical application value.

Key Words: Repetitive transcranial magnetic stimulation; Olanzapine; Amisulpride; Treatment-refractory schizophrenia; Therapeutic effectiveness; Cognitive function

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Core Tip: Patients with treatment-refractory schizophrenia always have an unsatisfactory treatment response and prognosis despite antipsychotic therapy, which poses significant challenges to clinical management. Therefore, it is necessary to continuously explore and validate effective treatments for treatment-refractory schizophrenia.

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INTRODUCTION

Schizophrenia, a heterogeneous progressive mental illness that may lead to cognitive impairment in patients, has a great negative impact on the patient's social interaction and work[1]. The etiology of the disease is complicated and has been linked to environmental factors, hereditary factors, cortical excitation-to-inhibition imbalance, and subcortical dopamine dysfunction[2]. Schizophrenia is prone to occur in early adulthood, and its symptoms are classified as positive symptoms, such as hallucinations, delusions, and speech disorders, and negative symptoms, such as emotional retardation, abulia, and social barriers[3]. The overall prevalence of schizophrenia is approximately 0.4%, and the mortality rate of schizophrenia patients is 2-4 times that of the general population[4,5]. Treatment-refractory schizophrenia (TRS), accounting for approximately 30% of the total schizophrenia cases, has a poor treatment response and prognosis despite treatment with antipsychotic drugs, which also poses great clinical challenges[6,7]. Nevertheless, it is a compelling responsibility of physicians to explore effective treatment options for TRS.

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation method, induces local neuronal activation in the brain regions *via* electromagnetic induction of electric fields, thus ameliorating the abnormal connections between the brain regions to a certain extent[8,9]. According to the research by Zhu *et al*[10], rTMS has a significant long-term ameliorating effect on working memory defects in schizophrenia patients. Olanzapine (OLZ) and amisulpride (AMI) are both first-line antipsychotic drugs, which are highly effective in reducing the Positive and Negative Syndrome Scale (PANSS) scores and alleviating the mental symptoms of the patients[11]. OLZ is a 5-hydroxytryptamine 2A/2C antagonist affecting the glucolipid metabolism[12] and an efficient AMP-activated protein kinase activator that enhances the AMP-activated protein kinase activity in the hypothalamus, thus mediating energy homeostasis and metabolic modulation during neuronal activity[13,14]. As for AMI, it is beneficial in relieving depressive symptoms and major negative symptoms as well as enhancing the patient's quality of life (QOL)[15].

We proposed that the combination of rTMS and OLZ + AMI has certain beneficial clinical effects in TRS patients.

MATERIALS AND METHODS

Patient information

This study selected 114 TRS patients who received treatment at the First Affiliated Hospital of Zhengzhou University between July 2019 and July 2022. Among them, 54 cases were included in the control group (Con group) treated with modified electroconvulsive therapy (mECT) and 60 cases in the research group (Res group) treated with rTMS; the patients in both groups received OLZ + AMI therapy. The patients in the Res and Con groups presented similar demographic data ($P > 0.05$), suggesting clinical comparability and feasibility during follow-up research.

Inclusion criteria: The inclusion criteria for this study were that patients of both groups fulfill the TRS diagnostic criteria and present complete medical records with no treatment-associated contraindications.

Exclusion criteria: Patients with a history of allergy to the study medications, serious diseases such as heart, lung, or kidney dysfunction, and mental retardation that hindered compliance and cooperation were excluded. Furthermore, pregnant and lactating women and drug abusers were excluded from this study.

Methods

The Con group patients were treated with mECT and OLZ + AMI, as described here. The patients received mECT 2-3 times a week using a Thymatron ECT therapeutic apparatus. The treatment frequency could be adjusted to once weekly according to the treatment effect up to a maximum of 8 times during the treatment course. The initial oral dose of OLZ was 5 mg once daily, and the drug dose could be gradually increased to 10-15 mg/d, depending on patient tolerance, for a total period of 8 wk. AMI was administered orally at an initial dose of 200 mg/d and increased according to patient tolerance and efficacy but not beyond a maximum daily dose of 1200 mg for a total period of 8 wk.

The Res group received rTMS combined with OLZ + AMI. An rTMS therapeutic instrument was used for treatment. The coil of the instrument was placed on the patient's forehead on the left, tangential to the scalp. The dorsolateral left frontal lobe was stimulated according to the threshold stimulation intensity of 80%-110% of the motor threshold, and the frequency was set at 20 Hz. The treatment time was 20 min, once a day, 5 times a week for 8 wk. OLZ and AMI were administered in the same way as that in the Con group.

Outcome measures

Clinical effectiveness: The PANSS scores were compared before and after treatment between the Res and Con groups. A decrease of more than 80% in the PANSS score was considered a "marked response," a decrease of 50%-79% was considered a "response," and failure to meet the above reduction criteria was considered as "non-response." The overall response rate (ORR) was the percentage of the sum of the number of "marked response" and "response" patients among the total number of cases.

Safety: We observed and recorded the number of cases of drowsiness, headache, nausea, vomiting, and memory impairment and calculated the overall incidence.

Severity of schizophrenia: All patients were assessed for schizophrenia severity using the PANSS (total score: 98) with positive and negative subscales. The higher the score, the more serious the symptoms of schizophrenia.

Cognitive function: The cognitive function (CF) of patients was evaluated using the Montreal Cognitive Assessment (MoCA), comprising eight items such as visuospatial/executive ability, memory, naming, and attention. On the 30-point scale, lower scores suggested worse CF.

QOL: The QOL of schizophrenia patients was evaluated using the Schizophrenia Quality of Life Scale (SQLS), comprising psychosocial factors (15 items, total score: 60), motivation and energy (7 items, total score: 28), and symptoms and adverse reactions (8 items, total score: 32). The score was inversely associated with the patient's QOL.

Statistical analysis

This study used Statistical Product and Service Solutions version 19.0 for data analysis; P -values < 0.05 were considered statistically significant. Sex and other categorical variables, expressed as the number of cases/percentages ($n/\%$), were compared between the groups using the χ^2 test. Continuous variables, such as the PANSS scores, expressed as means $\pm$ standard error, were compared between the groups using the t -test.

RESULTS

General information

Sex, age, course of the disease, family history, marital status, and educational level did not differ significantly between the Res and Con groups, indicating possible comparability between them ($P > 0.05$) (Table 1).

Comparison of therapeutic effectiveness

The ORRs of the Con and Res groups were 72.22% and 93.33%, respectively, demonstrating significantly higher efficacy of rTMS and OLZ + AMI than that of mECT and OLZ + AMI ($P < 0.05$) (Table 2).

Comparison of safety

Observation and records of the occurrence of drowsiness, headache, nausea, vomiting, and memory impairment in both cohorts showed that the incidence of adverse events was statistically higher in the Con group than in the Res group (25.93% vs 8.33%, $P < 0.05$) (Table 3).

Comparison of mental symptoms

Analysis of the mental symptoms using the PANSS revealed that the scores did not differ significantly between the groups before treatment ($P > 0.05$). However, the scores reduced significantly after treatment in both groups ($P < 0.05$), with the Res group exhibiting lower scores than those of the Con group ($P < 0.05$) (Figure 1A).

Comparison of CF

CF, analyzed using the MoCA, did not differ significantly between the groups before treatment ($P > 0.05$). However, the MoCA scores increased significantly in both cohorts after treatment ($P < 0.05$), with higher scores in the Res group than in the Con group ($P < 0.05$) (Figure 1B).

Table 1 Demographic information

Categories	Control group, <i>n</i> = 54	Research group, <i>n</i> = 60	χ^2/t value	<i>P</i> value
Sex			0.069	0.793
Male	32 (59.26)	37 (61.67)		
Female	22 (40.74)	23 (38.33)		
Age in yr	40.07 ± 7.01	41.28 ± 8.74	0.810	0.420
Course of the disease in yr	19.56 ± 7.55	18.93 ± 5.83	0.501	0.617
Family medical history			0.252	0.616
Yes	6 (11.11)	5 (8.33)		
No	48 (88.89)	55 (91.67)		
Marital status			0.381	0.537
Married	33 (61.11)	40 (66.67)		
Single	21 (38.89)	20 (33.33)		
Educational level			1.481	0.224
Below high school	30 (55.56)	40 (66.67)		
High school and above	24 (44.44)	20 (33.33)		

Data are presented as *n* (%), unless otherwise indicated.

Table 2 Comparison of the therapeutic effectiveness of the two treatment methods

Indicators	Control group, <i>n</i> = 54	Research group, <i>n</i> = 60	χ^2 value	<i>P</i> value
Marked response	19 (35.19)	36 (60.00)	-	-
Response	20 (37.04)	20 (33.33)	-	-
Non-response	15 (27.78)	4 (6.67)	-	-
Overall response	39 (72.22)	56 (93.33)	9.120	0.003

Data are presented as *n* (%).

Table 3 Comparison of the safety of the two treatment methods

Indicators	Control group, <i>n</i> = 54	Research group, <i>n</i> = 60	χ^2 value	<i>P</i> value
Drowsiness	4 (7.41)	1 (1.67)	-	-
Headache	4 (7.41)	1 (1.67)	-	-
Nausea	3 (5.56)	2 (3.33)	-	-
Vomiting	2 (3.70)	1 (1.67)	-	-
Memory impairment	1 (1.85)	0 (0.00)	-	-
Total	14 (25.93)	5 (8.33)	6.333	0.012

Data are presented as *n* (%).

Comparison of QOL

The QOL assessment using the SQLS showed that the two groups did not differ statistically in the QOL before treatment ($P > 0.05$). However, the post-treatment QOL improved significantly, manifesting as significantly reduced SQLS scores in various dimensions ($P < 0.05$), with the Res group exhibiting better QOL (lower SQLS scores) than that of the Con group ($P < 0.05$) (Figure 2).

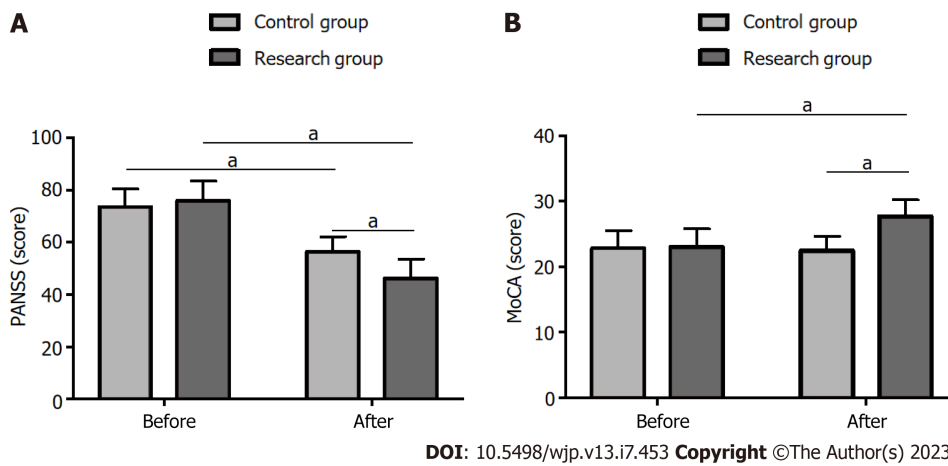


Figure 1 Comparison of the mental symptoms and the cognitive function between the groups. A: Comparison of the mental symptoms; B: Comparison of the cognitive function. MoCA: Montreal Cognitive Assessment; PANSS: Positive and Negative Syndrome Scale. ^a $P < 0.05$.

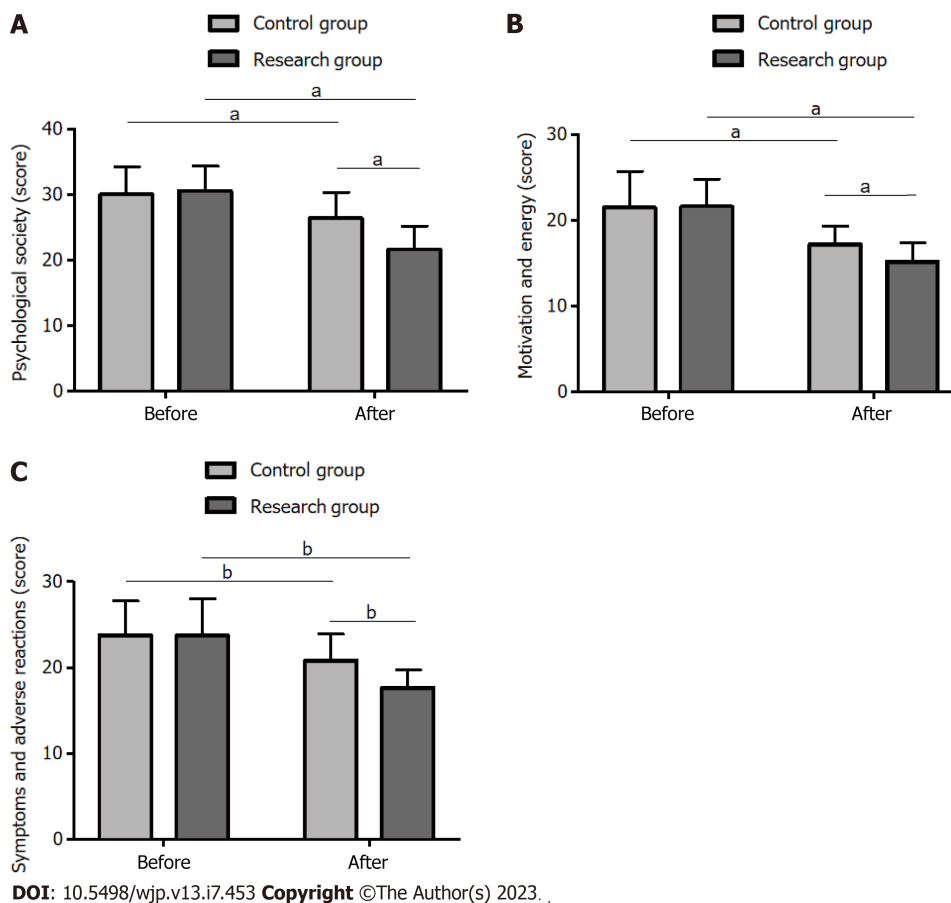


Figure 2 Comparison of the quality of life between the groups. A: Comparison of the quality of life between the two groups from the psychosocial society aspect; B: Comparison of the quality of life between the two groups from the motivation and energy aspect; C: Comparison of the quality of life between the two groups from the aspect of symptoms and adverse reactions. ^a $P < 0.05$; ^b $P < 0.01$.

DISCUSSION

TRS, a chronic mental disorder, is associated with an increased risk of metabolic syndrome, including hypertension and diabetes, as well as cardiovascular diseases and death in patients[16]. The difficulty in treating this disease lies in the fact that a significant proportion of patients do not respond well to non-clozapine antipsychotic drugs, ECT, or other enhancement strategies, imposing an economic burden on families and the healthcare system[17,18].

This study comparatively analyzed the effectiveness and safety of two treatment modalities for TRS, mECT and OLZ + AMI (Con group) *vs* rTMS and OLZ + AMI (Res group), to provide clinical support and references for the formulation of effective treatment strategies for TRS patients to improve their clinical outcomes and reduce medical costs. Our research results identified a significantly higher ORR in the Res group than in the Con group (93.33% *vs* 72.22%), indicating the superior therapeutic effectiveness of rTMS and OLZ + AMI than that of mECT and OLZ + AMI for TRS. Kahn *et al*[19] reported that 45% of the 93 patients receiving AMI and 44% of those receiving OLZ achieved “response” in the first stage of treatment, indicating that AMI or OLZ monotherapy induced less than satisfactory effects in TRS patients.

Currently, there are limited studies on AMI + OLZ combination therapy, most of which focus on the comparison of AMI or OLZ monotherapy. For instance, Men *et al*[20] demonstrated equivalent clinical efficacy and safety of AMI and OLZ in the treatment of schizophrenia. In our study, the total incidence of drowsiness, headache, nausea, vomiting, and memory impairment was significantly lower in the Res group than in the Con group (8.33% *vs* 25.93%), suggesting that rTMS contributes to fewer adverse events and is more cost-effective when compared with mECT in the treatment of TRS patients.

Additionally, we analyzed and compared the mental symptoms, CF, and QOL of the cohorts before and after treatment using the PANSS, MoCA, and SQLS, respectively. The Res group showed significantly reduced PANSS and SQLS scores after treatment. Moreover, the post-treatment scores in the Res group were significantly lower than those before treatment and those in the Con group. On the other hand, the MoCA scores increased significantly in the Res group, and the post-treatment scores were higher than those before treatment and those in the Con group. This suggests that the combination of rTMS and OLZ + AMI has a significant effect on the improvement of mental symptoms, CF, and QOL in TRS patients.

An open-label clinical study indicated that OLZ and AMI have positive and equivalent effects on ameliorating the negative symptoms and cognitive impairment in schizophrenia patients[21]. Currently, antipsychotics alone cannot fully relieve social cognitive impairment and enhance functional outcomes in patients with mental illnesses, while rTMS is highly effective in improving their CF and mental symptoms[22]. Li *et al*[23] reported that a combination of rTMS and family intervention plays a synergistic role in schizophrenia patients, which is conducive to ameliorate the patients’ negative symptoms and CF.

Additionally, an animal study confirmed that rTMS elicits an antidepressant effect by enhancing the endogenous cannabinoid signaling transduction and upregulating the endogenous cannabinoid 1 receptor and diacylglycerol lipase- α in the hippocampal astrocytes and neurons in rats under chronic and unpredictable stress[24]. It has also been noted that rTMS may modulate the cortical plasticity by affecting the permanent changes in the excitability of the cerebellar-thalamic-cortical pathway and that its mechanism of action in TRS could be related to its promotion of interconnection of the remote areas in the neural network system[25].

This study had several limitations that require further consideration. First, this was a single-center retrospective study; hence, the inclusion of more cases from multiple centers would be beneficial to improve the accuracy of the research results. Second, basic experiments should be supplemented to explore the underlying mechanism of the combination of rTMS and OLZ + AMI in treating TRS to understand this therapy and TRS better. Finally, the supplement of multivariate analyses influencing the efficacy of rTMS and OLZ + AMI in the treatment of TRS will help gain deeper insights regarding the pathways to enhance treatment efficacy. Future studies improving the aforementioned limitations are warranted.

CONCLUSION

rTMS in combination with OLZ + AMI may be preferred over the combination of mECT and OLZ + AMI for treating TRS, as the former has a clinical ORR as high as 93.33% and an adverse event rate as low as 8.33%. Moreover, this therapy has outstanding effects in relieving mental symptoms and improving CF and QOL; hence, it should be considered widely in clinical practice.

ARTICLE HIGHLIGHTS

Research background

Treatment-refractory schizophrenia (TRS) accounts for approximately 30% of all patients with schizophrenia, with unsatisfactory treatment response and poor patient prognosis despite antipsychotic therapy.

Research motivation

The treatment of TRS is difficult and challenging, but it is still the responsibility of doctors to explore effective treatment options for the disease.

Research objectives

To analyze the therapeutic effectiveness of repetitive transcranial magnetic stimulation (rTMS) combined with olanzapine (OLZ) and amisulpride (AMI) for TRS and its influence on the patients’ cognitive function (CF).

Research methods

First, 114 TRS patients who received treatment between July 2019 and July 2022 were selected. On the basis of OLZ + AMI therapy, 54 cases in the control group (Con group) received modified electroconvulsive therapy, and 60 cases in the research group (Res group) were given rTMS. Information on the therapeutic effectiveness, safety (drowsiness, headache, nausea, vomiting, and memory impairment), Positive and Negative Symptom Scale, Montreal Cognitive Assessment Scale, and Schizophrenia Quality of Life Scale were collected from both patient cohorts for competitive analyses.

Research results

A higher overall response rate and a better safety profile of treatment were determined in the Res group compared with the Con group. In addition, marked reductions in the Positive and Negative Symptom Scale and Schizophrenia Quality of Life Scale scores were found in the Res group after treatment, which were lower compared with the Con group. A significant increase in the Montreal Cognitive Assessment Scale score was observed in the Res group, with higher scores than the Con group.

Research conclusions

rTMS plus OLZ + AMI was effective and safe in the treatment of TRS, which can alleviate the patients' mental symptoms and improve their CF and quality of life, with clinical promotion value.

Research perspectives

rTMS plus OLZ + AMI, with both clinical efficacy and safety, may be more suitable for TRS patients than modified electroconvulsive therapy plus OLZ + AMI. This therapy has significant advantages in relieving psychiatric symptoms and improving CF and quality of life, which is worth promoting clinically.

FOOTNOTES

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Observational Study

Effects of cumulative COVID-19 cases on mental health: Evidence from multi-country survey

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Abstract

BACKGROUND

Depression and anxiety were both ranked among the top 25 leading causes of global burden of diseases in 2019 prior to the coronavirus disease 2019 (COVID-19) pandemic. The pandemic affected, and in many cases threatened, the health and lives of millions of people across the globe and within the first year, global prevalence of anxiety and depression increased by 25% with the greatest influx in places highly affected by COVID-19.

AIM

To explore the psychological impact of the pandemic and resultant restrictions in different countries using an opportunistic sample and online questionnaire in different phases of the pandemic.

METHODS

A repeated, cross-sectional online international survey of adults, 16 years and above, was carried out in 10 countries (United Kingdom, India, Canada, Bangladesh, Ukraine, Hong Kong, Pakistan, Egypt, Bahrain, Saudi Arabia). The online questionnaire was based on published approaches to understand the psychological impact of COVID-19 and the resultant restrictions. Five standardised measures were included to explore levels of depression [patient health questionnaire (PHQ-9)], anxiety [generalized anxiety disorder (GAD) assessment], impact of trauma [the impact of events scale-revised (IES-R)], loneliness (a brief loneliness scale), and social support (The Multi-dimensional Scale of Perceived Social support).

RESULTS

There were two rounds of the online survey in 10 countries with 42866 participants in Round 1 and 92260 in Round 2. The largest number of participants recruited from the United Kingdom (112985 overall). The majority of participants reported receiving no support from mental health services throughout the pandemic. This study found that the daily cumulative COVID-19 cases had a statistically significant effect on PHQ-9, GAD-7, and IES-R scores. These scores significantly increased in the second round of surveys with the ordinary least squares regression results with regression discontinuity design specification (to control lockdown effects) confirming these results. The study findings imply that participants' mental health worsened with high cumulative COVID-19 cases.

CONCLUSION

Whilst we are still living through the impact of COVID-19, this paper focuses on its impact on mental health, discusses the possible consequences and future implications. This study revealed that daily cumulative COVID-19 cases have a significant impact on depression, anxiety, and trauma. Increasing cumulative cases influenced and impacted education, employment, socialization and finances, to name but a few. Building a database of global evidence will allow for future planning of pandemics, particularly the impact on mental health of populations considering the cultural differences.

Key Words: COVID-19; Mental health; Global research; International; Pandemic; Impact

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Core Tip: This study explores the effect of cumulative coronavirus disease 2019 cases on mental health, more specifically on anxiety, depression, and trauma. Negative impact on mental health was found internationally, with individuals struggling to receive support from mental health services. Results also show that as the pandemic continued, mental health scores got worse.

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INTRODUCTION

Depression and anxiety conditions both ranked among the top 25 leading causes of global burden of diseases in 2019 prior to the coronavirus disease 2019 (COVID-19) pandemic[1]. On January 30, 2020, the World Health Organization (WHO) declared a public health emergency of international concern and governments were urged to prepare for the global spread of COVID-19 from East Asia[2]. The COVID-19 pandemic affected, and in many cases threatened the health and lives of millions of people across the globe[2].

In the first year of the COVID-19 pandemic, global prevalence of anxiety and depression increased by 25%, and overall, the pandemic was estimated to have caused 137.1 (95%UI: 92.5–190.6) additional disability adjusted life years per 100000 population for Major Depressive Disorder and 116.1 per 100000 population (95%UI: 79.3–163.80) for anxiety disorders according to a scientific brief released by the WHO[3]. A number of factors have been implicated including, but not limited to, the stress of social and self-isolation, loneliness, restrictions due to lockdowns[4,5], fear of infection and death of self and near ones, grief and bereavement, worries regarding jobs and finances, as well as impact on education, relationships and on careers[6].

Long COVID described the presence of persistent symptoms following infection from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus[7]. This can last weeks or months after initial infection[7,8]. Common symptoms of long COVID include breathlessness, fatigue, headaches, and weakness as well as reduced quality of life[7, 9]. The most common mental health problems experienced by individuals with long COVID were anxiety, depression, and post-traumatic stress disorder (PTSD)[9,10]. A scoping review of 239 patients found that 3-mo post-COVID, 37.2% experienced PTSD, 35.6% experienced anxiety, and 46.9% were experiencing depression[11,12]. These effects were maintained at 6-mo[11]. Overall, symptoms were more prevalent in women and hospitalized patients[9]. A number of population groups have been shown to have been more adversely affected, including young people and women[7], individuals with vulnerabilities and pre-existing mental health conditions[9,11]. Evidence on healthcare workers, who were frontline during the pandemic has been equivocal with different studies showing a range of impact in this group[11, 13]. The greatest increases in depression and anxiety were found in places highly affected by COVID-19 as indicated by decreased human mobility and daily COVID-19 infection rates[3].

Each country across the globe has responded to the pandemic guided by their population, resources, number of cases, socio demographics, political landscape, and culture[14]. Given the unique situation we faced, the authors sought to explore the psychological impact of the pandemic and resultant restrictions in different countries, using an opportunistic sample and online questionnaire that was established at the beginning of the pandemic.

MATERIALS AND METHODS

Study design

This international study aimed to investigate and report the psychological impact of cumulative COVID-19 cases in the participant sites. A repeated, cross-sectional online international survey of adults, 16 years and above, was carried out in 10 countries (United Kingdom, India, Canada, Bangladesh, Ukraine, Hong Kong, Pakistan, Egypt, Bahrain, Saudi Arabia). The online questionnaire was based on published approaches, to understand the psychological impact of COVID-19 and the resultant restrictions. Five standardised measures were included to explore levels of depression [patient health questionnaire-9 (PHQ-9)][15], anxiety [generalized anxiety disorder (GAD)-7; Generalised Anxiety Disorder Assessment][16], impact of trauma [the impact of events scale-revised (IES-R)][17], loneliness (a brief loneliness scale)[18], and social support (The Multi-dimensional Scale of Perceived Social support)[19]. Further details of the methodology are documented in earlier publications by the group[9,13].

Materials

The survey was repeated to capture the dynamic impact of the pandemic. The questionnaire was changed for each round depending on the stage of pandemic, government policies, and circumstances in each country at the time. In order to make the questionnaire relevant to each country, it was available in different languages and various adaptations were made to ensure that local culture and responses to the pandemic were considered. For this reason, each country published the questionnaire at a slightly different time and some of the questions were variable. As an example, the “Keyworker” status did not exist in many countries and was only used where relevant. Another example, in the Ukraine questionnaire version, the question about exceeding the recommended limits of alcohol was excluded because of the absence of such recommended limits.

Study distribution

In the United Kingdom, the survey was conducted thrice with the corresponding two rounds of the survey in the other countries. The dates of the surveys in the participant countries are noted below. The surveys were publicised to the general population including students and healthcare professionals through social media. Most countries collaborated internally to capture a wide population. As an example, the leads in Ukraine collaborated with Ukrainian organizations including Mental health for Ukraine Project, National Psychological Association of Ukraine, Ukrainian Association of Cognitive-Behavioural Therapy, and Zhytomyr State University to help further with dissemination. Due to the unusual circumstances of the time, this was the best way to disseminate the survey.

Southern Health NHS Foundation Trust in the United Kingdom led and co-ordinated the online survey with support from the participant countries. The survey was advertised to staff, patients, and the public with a weblink to the survey platform.

Data analysis

Cumulative COVID-19 case data has been derived from Microsoft Azure Open dataset, which is a population open dataset[20]. Mental health scores are derived from the online survey and is sample data. In both data, time is day. Although cumulative COVID-19 cases data is available daily (for around last two years), mental health scores in the study were not available for each day during that time. The availability of mental health scores on a specific day depended on whether the survey was conducted on that day by a participant.

The study has used regression analyses, using cross section data of all countries that participated in the study. Separate regression analysis was conducted for survey round 1 and 2. In both regressions, we used dummies for all individual characteristics listed in Table 1 as control variables. Vulnerabilities including requiring shielding, experience of coronavirus, pre-existing mental health conditions, and mental health support, had extremely low response rates therefore, we have recoded missing values into no category, to increase sample sizes in regressions.

In both regressions, the main independent variable, daily cumulative COVID-19 cases, is converted into million unit (by dividing COVID-19 case by 1000000). The purpose is to scale up its coefficients.

The relationship between average mental health scores and average cumulative COVID-19 cases maybe be contaminated or biased by lockdown effects. To control for such effects, we added lockdown dummy, trend and their interaction following the specification in regression discontinuity design (RDD).

RESULTS

Demographics

There were two rounds of the online survey in eight country groups as shown in Table 1. Egypt, Saudi Arabia, and Bahrain were analysed as a single group (labelled Arabic speaking countries). Hong Kong did not participate in the second round due to difficulties in recruitment. While there were three rounds in the United Kingdom, we have only used data from the corresponding two rounds with other participant countries. The United Kingdom has the largest number of participants in both rounds (29134 and 83851, respectively).

In the first round of the survey, participants who reported being healthcare professionals are higher in the United Kingdom (43%). In the second round, Arabic speaking countries had the highest number of participants who reported as healthcare professionals (66%), with a sample size of 909.

Age follows a bell shaped or downward distribution. Female participants were higher than male in most countries. In Canada, United Kingdom and Ukraine, most participants were White. Christian religion was reported the dominant religion in the Western countries. In round one in the Arabic speaking countries, most survey participants reported as Christians too. In most countries, survey participants did not report University education. Most survey participants lived in their own homes. Low proportion of participants reported experiencing COVID-19, but a high percent of participants followed social distancing guidelines. Most of the participants did not report any pre-existing physical health conditions. Alcohol consumption was reported by participants in Canada, United Kingdom, and Ukraine. Most participants did not report taking drugs. Majority participants did not report receiving support from mental health services. Where received, mental health support was reported through general practitioners and many participants did not respond to this question as it was only relevant if they reported experiencing mental health problems.

Mental health scales

Table 2 shows means and SD of PHQ-9, GAD-7 and IES-R by country and survey rounds, with number of respondents (*n*), missing observations and nonrespondents. In both rounds in each country, there were fewer respondents of PHQ-9 compared to nonrespondents. For the other two mental health scales, the gap between respondents and nonrespondents is not that large, with respondents being higher than nonrespondents in some cases. PHQ-9 can vary from 0 to 27, GAD-7 from 0 to 21, and IES-R from 0-88; however, average figures of PHQ-9 are lower than those of other two. IES-R has higher mean scores than others. Hong Kong, Indian, and Ukrainian participants have reported lower scores on the three scales compared with other countries. Bangladesh has highest mean scores on PHQ9, GAD7 and IES -R. All scores increased in round 2 of the surveys.

Cumulative COVID-19 cases

For each country, cumulative COVID-19 cases (the cumulative number of people who suffered coronavirus in official records) varied over time. Mental health scores (on the 3 scales: PHQ-9, GAD-7 and IES-R) in each country varied over time and by individuals' responses during the survey period.

Figure 1 shows a histogram of day/time by country. Two long bars in Bangladesh indicate that survey responses in both rounds were received during short windows, although the survey was open for three months each time in each site. The same pattern is seen in Canada and Hong Kong. Survey periods in Arabic speaking sites and Ukraine seem longer but scattered, meaning that for several days, survey data including mental health scores were not available during the three month period. India and Pakistan showed good density for moderately wider periods in round 1. United Kingdom showed the longest periods of survey responses in both rounds, which indicates that survey data including mental health

Table 1 Percent of categories in individual characteristics by country and survey rounds (1 and 2)

	Arabic		Bangladesh		Canada		China		India		Pakistan		United Kingdom		Ukraine	
	1	2	1	2	1	2	1	1	2	1	2	1	2	1	2	
Observations	1121	909	299	746	8648	5920	178	1427	68	803	160	29134	83851	1256	606	
Percent of above observations																
Healthcare professional																
No	40	9	67	69	88	91	65	65	40	44	41	47	66	79	74	
Yes	38	66	4	5	7	9	19	19	44	0	34	43	22	9	10	
Missing	22	25	29	26	5	0	16	16	16	56	25	10	12	12	16	
Age category																
Under 25	10	4	69	68	8	16	2	20	7	20	51	6	6	35	15	
25-44	44	61	14	14	36	36	43	44	44	35	26	36	31	43	54	
45-54	16	9	2	1	15	16	12	11	16	3	4	23	19	9	13	
55 and over	7	3	1	1	37	32	26	13	21	2	1	26	34	2	3	
Missing	22	22	14	17	5	0	17	13	12	40	18	10	11	11	15	
White ethnicity																
No	77	21	92	89	20	21	9	88	88	81	73	9	15	3	3	
Yes	1	57	0	0	76	78	79	0	0	0	0	82	74	88	82	
Missing	22	22	8	11	4	0	12	12	12	19	27	10	11	9	15	
Christian religion																
No	8	73	92	87	48	52	8	80	78	81	75	48	46	21	22	
Yes	70	4	0	0	47	47	32	7	9	0	0	41	39	69	62	
Missing	22	22	8	13	5	1	60	13	13	19	25	11	15	11	16	
Gender																
Female	50	27	22	23	56	54	61	60	56	49	61	74	61	77	74	
Male	28	51	68	63	39	45	24	27	31	31	18	15	26	13	9	
Missing	22	22	10	14	5	1	15	13	13	20	21	11	13	11	16	
Attended university																
No	78	79	91	88	51	53	85	38	79	80	83	90	89	90	85	
Yes	0	0	0	0	43	47	0	50	9	0	0	0	0	0	0	
Missing	22	21	9	12	6	0	15	13	12	20	18	10	11	10	15	
Living at own home																
No	43	52	64	53	35	41	37	49	0	43	41	25	29	54	41	
Yes	35	26	26	35	61	59	51	39	0	38	40	66	61	36	44	
Missing	22	22	10	12	5	0	13	12	100	19	19	10	11	10	15	
Vulnerable according to government category																
No	63	34	74	52	63	66	71	68	0	68	46	70	67	76	54	
Age ≥ 70	1	40	9	36	15	34	5	7	0	2	31	4	21	1	29	
Chronic disease	2	0	1	0	6	0	2	1	0	2	0	6	0	4	0	
Diabetes	2	0	0	0	3	0	4	1	0	0	0	2	0	0	0	
Other	3	0	3	0	7	0	1	2	0	3	0	5	0	3	0	
Missing	28	26	13	12	6	0	16	19	100	25	23	13	12	16	17	
Vulnerable according to government category and require shielding																

No	64	0	85	0	75	0	77	72	0	67	0	77	0	72	0
Yes	6	0	2	0	13	0	5	6	0	6	0	7	0	11	0
Missing	30	100	14	100	12	100	18	22	100	26	100	16	100	17	100
Whether experienced coronavirus															
No	23	0	42	0	28	0	58	35	0	28	0	22	0	31	0
Yes	49	29	40	23	63	12	26	43	25	43	48	64	25	52	47
Missing	28	71	17	77	8	88	16	22	75	29	53	14	75	17	53
Pre-existing mental health condition															
No	42	0	46	1	62	1	74	67	3	40	0	53	0	60	0
Yes	28	3	41	5	31	21	8	11	4	35	11	31	18	23	9
Missing	30	97	13	95	7	79	18	22	93	25	89	16	82	17	91
Drinking alcohol															
No	68	64	76	77	20	54	28	57	47	0	0	13	75	17	0
Yes	5	1	12	6	74	22	56	24	35	0	5	75	11	69	1
Missing	27	35	13	17	5	24	16	19	18	100	95	12	14	14	99
Whether taking drug															
No	71	65	81	73	83	86	79	78	82	71	69	85	83	83	77
Yes	0	4	8	11	12	14	6	2	1	3	6	2	3	3	2
Missing	28	31	11	15	5	0	15	20	16	26	25	13	13	14	21
Ever experienced suicidal thoughts															
No	9	61	70	69	67	77	74	68	66	55	55	59	60	60	53
Yes	62	7	18	16	27	23	10	12	16	19	18	27	26	24	28
Missing	29	32	13	15	6	1	16	21	18	26	27	13	14	16	19
Having mental health support from															
No support	18	1	27	3	13	4	6	5	3	30	4	14	5	13	2
Health service provider	6	1	5	1	11	6	2	3	1	8	3	12	8	6	5
Other	3	1	7	1	7	10	2	2	1	4	3	5	4	7	1
Missing	73	97	61	95	69	80	90	89	94	58	90	69	83	75	91

Each panel in a column shows percentages of categories/responses of a characteristic/question. Total respondents in each category were divided by observations shown at the beginning of the table and then multiplied by 100, to get the percentage.

scores were available for relatively more days in United Kingdom despite the fact that the survey was available for the same number of months at each site.

Daily cumulative COVID-19 cases (in million) have been plotted for each country, from April 1, 2020 to April 1, 2021 (Figure 2). As India had high COVID-19 cases, we have scaled down the COVID-19 cases by converting its unit into million, to raise the coefficients of cumulative COVID-19 case in regressions. United Kingdom also had high figures (reached nearly 10 million in March 2021). Ukraine and Canada reached relatively high figures. Other countries including Hong Kong had lower figures for cumulative COVID-19 cases. Therefore, the lines are relatively flat (near zero). Hong Kong had low figures at those periods as different countries had their spikes at different times. The figure shows downward movement of lines in India and United Kingdom, because COVID-19 cases were revised.

In survey data of the countries, scores of three mental health scales were available for several individuals in a day. They are reported as averages in a day. Country averages of those averages are taken to get single values in each day. Country average of cumulative COVID-19 cases are also taken. In Figure 3, scatter plots of average values of PHQ-9, GAD-7 and IES-R are shown in three different subplots. Average cumulative COVID-19 cases are plotted in line with three subplots. While left vertical axes measure the average cumulative COVID-19 cases, the right vertical axes measure three average values of mental health scores/indices. As mental health is an individual characteristic, average mental health scores fluctuated over time, and were not uniform like average cumulative COVID-19 cases. However, average mental health scores had less fluctuation/scatter at the beginning of each round (especially at the beginning of the second round). At that time, average mental health scores showed upward movement with average cumulative COVID-19 cases.

Table 2 Summary statistics of mental health scores by country and survey rounds

		PHQ-9		GAD-7		IES-R	
		Round 1	Round 2	Round 1	Round 2	Round 1	Round 2
Arabic	Mean	7.85	6.27	5.28	4.56	20.81	17.14
	SD	6.97	6.88	5.78	5.56	18.79	19.12
	<i>n</i>	596	481	596	486	539	430
	Missing	525	428	525	423	582	479
Bangladesh	Mean	8.07	7.45	5.76	5.45	23.28	21.86
	SD	5.79	6.91	5.38	5.69	18.08	20.35
	<i>n</i>	205	462	205	485	179	419
	Missing	94	284	94	261	120	327
Canada	Mean	6.11	6.97	4.40	4.94	15.10	16.96
	SD	6.44	6.70	5.32	5.46	17.87	18.24
	<i>n</i>	7653	5721	7684	5770	7329	5554
	Missing	995	199	964	150	1319	366
China	Mean	4.38		3.25		11.61	
	SD	4.91		4.20		13.63	
	<i>n</i>	127		124		117	
	Missing	51		54		61	
India	Mean	4.99	4.07	3.46	2.43	14.65	10.24
	SD	5.56	5.34	4.38	3.31	16.49	12.00
	<i>n</i>	820	41	823	42	741	38
	Missing	607	27	604	26	686	30
Pakistan	Mean	8.55	8.64	5.10	5.37	19.02	19.59
	SD	7.34	7.51	5.56	5.42	17.26	19.18
	<i>n</i>	412	85	413	90	376	75
	Missing	391	75	390	70	427	85
United Kingdom	Mean	7.70	8.21	5.46	6.04	17.01	19.19
	SD	6.47	7.03	5.51	5.92	17.51	18.93
	<i>n</i>	22166	64382	22343	65056	20780	59966
	Missing	6968	19469	6791	18795	8354	23885
Ukraine	Mean	6.63	7.81	4.17	5.02	14.93	15.55
	SD	6.10	6.51	4.65	5.20	15.34	15.41
	<i>n</i>	860	421	863	426	782	382
	Missing	396	185	393	180	474	224
Total	Mean	7.24	8.09	5.11	5.93	16.55	18.98
	SD	6.49	7.01	5.45	5.88	17.57	18.88
	<i>n</i>	32839	71593	33051	72355	30843	66864
	Missing	10027	20667	9815	19905	12023	25396

PHQ-9: Patient health questionnaire-9; IES-R: Impact of Events Scale-Revised; GAD-7: Generalized anxiety disorder-7.

In more scatter areas, such positive relation between average cumulative COVID-19 cases and average mental health scores is not seen. As less scatter zones showed a positive relation, we can expect an overall positive relation between them. To control for bias or contamination effect of lockdown, we added lockdown dummy, trend and their interaction



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Figure 1 Distribution of survey respondents over time, by country.

following the specification in RDD.

Table 3 shows lockdown and survey periods of participant countries in the study. In each round, we have made normalized trend by subtracting lockdown easing/withdraw dates of countries (as lockdown start dates do not fall in survey periods) from trend. Zero is a common cut-off date; based on that we made a discontinuity dummy (1 = above cut-off, 0 = below cut-off), that captured negative effects of lockdown or withdraw on mental health. To capture different slopes on either side of the cut-off, we took interaction of normalized trends and the discontinuity dummy.

Regression results

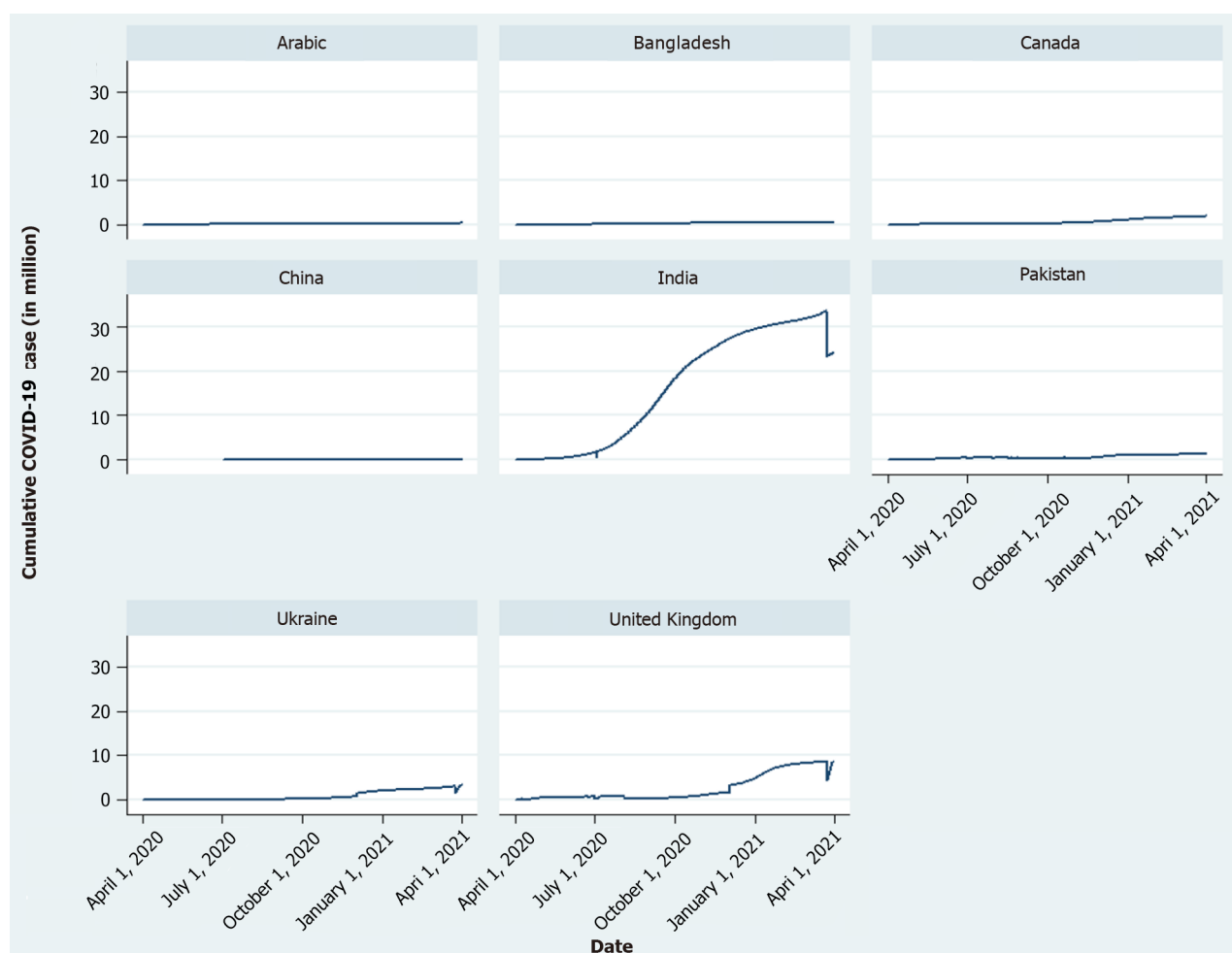
Table 4 shows regression results for round 1 and **Table 5** for round 2. Both tables show two regression results for each mental health score/index, the dependent variable. The first one does not include RDD specification, while the second one does. When RDD specification is included, the results are for United Kingdom only.

In round 1, the cumulative COVID cases had statistically significant effect on all three mental health scores with RDD specification. For example, as United Kingdom had 7.70 average GAD-7, the increase size 1.75 in regression was nearly 23% ($1.75 \times 100/7.70$). So, for a one million increase in cumulative daily COVID cases, GAD-7 increased by 23 percent.

In round 2 (**Table 5**), all three mental health indices increased statistically and significantly due to increase in cumulative COVID cases, with and without RDD specification. Without RDD specification, for a one million increase in cumulative COVID cases, the increase in PHQ-9 was 0.195 (2.38%), GAD-7 0.129 (2.14%), and IES-R 0.454 (2.37%). With RDD specification, for a one million increase in cumulative COVID cases, the increase in PHQ-9 was 0.433 (5.27%), GAD-7 0.577 (9.55%), and IES-R 1.265 (6.59%). Results with RDD specification implied that United Kingdom had higher effects than other countries.

Table 3 Lockdown and survey dates by country

Country	First lockdown		Second lockdown		Survey period		Can we capture lockdown effects?
	Start	End	Start	End	Round 1	Round 2	
Bangladesh	March 26, 2020	May 16, 2020	April 5, 2021	July 14, 2021	July 1, 2020-July 25, 2020	January 19, 2021-March 18, 2021	No
Canada	March 18, 2020	May 18, 2020	November 7, 2020	January 8, 2021	August 18, 2020-October 2, 2020	December 21, 2020-March 30, 2021	No
China	January 23, 2020	April 8, 2020			June 24, 2020-August 7, 2020		No
India	March 25, 2020	June 7, 2020	April 19, 2021	May 31, 2021	July 1, 2020-September 20, 2020	January 22, 2021-April 1, 2021	No
Pakistan	March 24, 2020	May 9, 2020	May 8, 2021	May 18, 2021	June 10, 2020-September 24, 2020	February 2, 2021-March 29, 2021	No
Saudi Arabia	March 29, 2020	June 21, 2020			June 3, 2020-October 7, 2020	January 16, 2021-April 1, 2021	Yes, in round 1
Ukraine	March 17, 2020	April 24, 2020			June 11, 2020-September 30, 2020	January 7, 2021-March 25, 2021	No
United Kingdom	March 23, 2020	July 4, 2020	November 5, 2020	December 2, 2020	April 28, 2020-August 6, 2020	November 12, 2020-February 18, 2021	Yes, in both rounds



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Figure 2 Cumulative coronavirus disease 2019 case (in million) over time, by country. COVID-19: Coronavirus disease 2019.

Table 4 Ordinary least squares regression of mental health scores on cumulative coronavirus disease 2019 case, lockdown, and individual characteristics (survey round 1)

	PHQ-9		GAD-7		IES-R	
	Round 1	Round 2	Round 1	Round 2	Round 1	Round 2
Daily cumulative COVID-19 case/1000000	0.075 ^a [-0.01, 0.16]	2.121 ^c [1.58, 2.66]	0.041 [-0.03, 0.11]	1.750 ^c [1.28, 2.22]	0.225 ^a [-0.02, 0.47]	1.543 ^a [-0.05, 3.14]
Dummy for first lockdown withdraw		-0.658 ^c [-0.97, -0.34]		-0.450 ^c [-0.73, -0.17]		-1.224 ^b [-2.16, -0.29]
Dummy for first lockdown withdraw ¹ (date-first lockdown withdraw date)		-0.018 ^c [-0.03, -0.01]		-0.014 ^c [-0.02, -0.01]		-0.043 ^c [-0.07, -0.02]
Date-first lockdown withdraw date		0.006 ^b [0.00, 0.01]		0.000 [-0.00, 0.01]		0.004 [-0.01, 0.02]
Healthcare professional (1 = yes, 0 = no)	-0.402 ^c [-0.54, -0.26]	-0.737 ^c [-0.89, -0.58]	-0.328 ^c [-0.45, -0.21]	-0.631 ^c [-0.77, -0.49]	-1.394 ^c [-1.81, -0.98]	-2.185 ^c [-2.65, -1.72]
Age (base: Below 25)	0.000	0.000	0.000	0.000	0.000	0.000
25-44	-1.084 ^c [-1.34, -0.83]	-1.428 ^c [-1.75, -1.11]	-0.482 ^c [-0.71, -0.26]	-0.713 ^c [-0.99, -0.43]	-2.350 ^c [-3.10, -1.60]	-2.091 ^c [-3.02, -1.16]
45-54	-1.958 ^c [-2.24, -1.68]	-2.345 ^c [-2.69, -1.99]	-1.456 ^c [-1.70, -1.21]	-1.737 ^c [-2.05, -1.43]	-3.992 ^c [-4.83, -3.15]	-3.366 ^c [-4.39, -2.34]
55 and over	-2.956 ^c [-3.24, -2.67]	-3.108 ^c [-3.47, -2.75]	-2.179 ^c [-2.43, -1.93]	-2.284 ^c [-2.60, -1.97]	-5.568 ^c [-6.42, -4.72]	-4.085 ^c [-5.15, -3.02]
White (1 = yes, 0 = no)	0.360 ^c [0.17, 0.55]	0.482 ^c [0.23, 0.74]	0.299 ^c [0.13, 0.47]	0.413 ^c [0.19, 0.64]	-1.120 ^c [-1.69, -0.55]	-0.054 [-0.80, 0.69]
Christian (1 = yes, 0 = no)	-0.206 ^c [-0.34, -0.07]	-0.036 [-0.19, 0.12]	0.018 [-0.10, 0.13]	0.222 ^c [0.08, 0.36]	0.522 ^c [0.13, 0.91]	0.829 ^c [0.37, 1.29]
Male (1 = yes, 0 = no)	-1.189 ^c [-1.34, -1.03]	-1.231 ^c [-1.43, -1.03]	-1.039 ^c [-1.18, -0.90]	-1.042 ^c [-1.22, -0.86]	-2.997 ^c [-3.46, -2.53]	-3.719 ^c [-4.31, -3.13]
Attended university (1 = yes, 0 = no)	-1.141 ^c [-1.34, -0.94]	0.000 [0.00, 0.00]	-0.545 ^c [-0.72, -0.37]	0.000 [0.00, 0.00]	-1.254 ^c [-1.85, -0.65]	0.000 [0.00, 0.00]
Living at own home (1 = yes, 0 = no)	-0.885 ^c [-1.04, -0.73]	-1.105 ^c [-1.30, -0.91]	-0.489 ^c [-0.63, -0.35]	-0.692 ^c [-0.86, -0.52]	-1.432 ^c [-1.89, -0.97]	-2.270 ^c [-2.83, -1.71]
Vulnerable according to government category (base: Not vulnerable)	0.000	0.000	0.000	0.000	0.000	0.000
Aged 70 or above	-0.898 ^c [-1.18, -0.62]	-1.105 ^c [-1.52, -0.69]	-0.764 ^c [-1.01, -0.52]	-0.985 ^c [-1.35, -0.62]	-1.954 ^c [-2.81, -1.10]	-2.909 ^c [-4.19, -1.63]
Chronic disease	0.361 ^b [0.08, 0.64]	0.345 ^b [0.03, 0.66]	0.533 ^c [0.29, 0.78]	0.543 ^c [0.26, 0.83]	1.245 ^c [0.41, 2.08]	1.644 ^c [0.70, 2.59]
Diabetes	0.034 [-0.43, 0.49]	-0.064 [-0.63, 0.50]	0.102 [-0.30, 0.50]	0.139 [-0.36, 0.64]	0.867 [-0.50, 2.23]	1.185 [-0.49, 2.86]
Other	0.915 ^c [0.62, 1.21]	0.846 ^c [0.49, 1.20]	0.390 ^c [0.13, 0.65]	0.355 ^b [0.04, 0.67]	0.811 ^a [-0.07, 1.70]	1.208 ^b [0.15, 2.27]
Vulnerable according to government category and require shielding (1 = yes, 0 = no)	1.087 ^c	1.096 ^c	0.909 ^c	0.945 ^c	4.281 ^c	3.513 ^c

	[0.83, 1.34]	[0.76, 1.43]	[0.68, 1.13]	[0.65, 1.24]	[3.51, 5.05]	[2.52, 4.50]
Experienced coronavirus (1 = yes, 0 = no)	0.324 ^c	0.220 ^b	0.237 ^c	0.181 ^b	0.410 ^a	0.547 ^b
	[0.18, 0.47]	[0.05, 0.39]	[0.11, 0.36]	[0.03, 0.33]	[-0.01, 0.83]	[0.05, 1.05]
Pre-existing mental health condition (1 = yes, 0 = no)	3.447 ^c	3.256 ^c	3.158 ^c	3.091 ^c	8.608 ^c	8.227 ^c
	[3.26, 3.63]	[3.04, 3.47]	[3.00, 3.32]	[2.90, 3.28]	[8.06, 9.16]	[7.60, 8.86]
Drinking alcohol (1 = yes, 0 = no)	0.251 ^c	-0.082	0.234 ^c	-0.101	0.410	-0.277
	[0.08, 0.42]	[-0.30, 0.13]	[0.08, 0.38]	[-0.29, 0.09]	[-0.10, 0.92]	[-0.91, 0.36]
Taking drug (1 = yes, 0 = no)	0.794 ^c	1.303 ^c	0.725 ^c	0.729 ^c	2.262 ^c	2.527 ^c
	[0.48, 1.11]	[0.76, 1.84]	[0.45, 1.00]	[0.25, 1.21]	[1.33, 3.19]	[0.95, 4.11]
Ever experienced suicidal thoughts (1 = yes, 0 = no)	3.101 ^c	2.976 ^c	1.623 ^c	1.503 ^c	6.054 ^c	5.812 ^c
	[2.95, 3.25]	[2.80, 3.15]	[1.49, 1.75]	[1.35, 1.66]	[5.61, 6.50]	[5.30, 6.32]
Mental health support from (base: No support)	0.000	0.000	0.000	0.000	0.000	0.000
Health service provider	0.134	0.245 ^a	-0.052	-0.021	0.008	-0.030
	[-0.11, 0.37]	[-0.03, 0.52]	[-0.26, 0.16]	[-0.26, 0.22]	[-0.71, 0.72]	[-0.85, 0.79]
Other	1.072 ^c	1.269 ^c	0.521 ^c	0.666 ^c	3.042 ^c	3.542 ^c
	[0.77, 1.38]	[0.91, 1.63]	[0.25, 0.79]	[0.35, 0.98]	[2.14, 3.95]	[2.49, 4.59]
Constant	7.050 ^c	7.213 ^c	4.651 ^c	4.590 ^c	16.577 ^c	16.791 ^c
	[6.73, 7.37]	[6.69, 7.73]	[4.37, 4.93]	[4.13, 5.05]	[15.62, 17.54]	[15.26, 18.32]
Observations	28560	21077	28710	21202	26913	19785
Adjusted R ²	0.279	0.261	0.214	0.203	0.180	0.172

^a*P* < 0.10.^b*P* < 0.05.^c*P* < 0.01.¹See Table 3 for dates of first lock down period.

95% confidence intervals are in brackets. PHQ-9: Patient health questionnaire-9; IES-R: Impact of Events Scale-Revised; GAD-7: Generalized anxiety disorder-7; COVID-19: Coronavirus disease 2019.

In both regression tables, lockdown withdraw dummy in RDD specification showed that lockdown withdraw had statistical and significant effects on mental health indices, which supported the findings of our previous paper that showed that lockdown increased participants mental health scores, or worsened participant's mental health[8].

In both regression tables, compared to the youngest age group (under 25), other age groups had lower scores on the mental health scales, meaning better mental health. Non-White participants reported better mental health than White participants, in most cases. Non-Christians reported better mental health than Christians in both rounds. In both rounds, higher educated participants had better mental health than the lowest educated group.

Heterogenous effects

To demonstrate heterogeneous effects of cumulative COVID cases on mental health scores for different countries, we ran regressions without RDD specification for each country separately, but we included all characteristics used in previous regressions. RDD specification was only applicable to United Kingdom data.

For China (Hong Kong), cumulative COVID cases was extremely low, and therefore, the coefficients of daily cumulative COVID cases were extremely high. Similarly high and low coefficients in different countries depended on scales of cumulative COVID cases in the relevant countries.

Most countries did not show any significant effects. United Kingdom had very good distribution of survey respondents over a long period of time. Therefore, regression results for United Kingdom are more reliable than others. The results are statistically positive in both rounds in the United Kingdom. The first round in the United Kingdom showed statistically and significantly higher positive results. As we have seen in Table 4, such significance vanishes with the inclusion of RDD specification.

DISCUSSION

Using repeated cross sectional survey data of eight country groups and cumulative COVID-19 cases of same countries from Microsoft AZURE, this study found that the daily cumulative COVID-19 cases had a statistically significant effect on

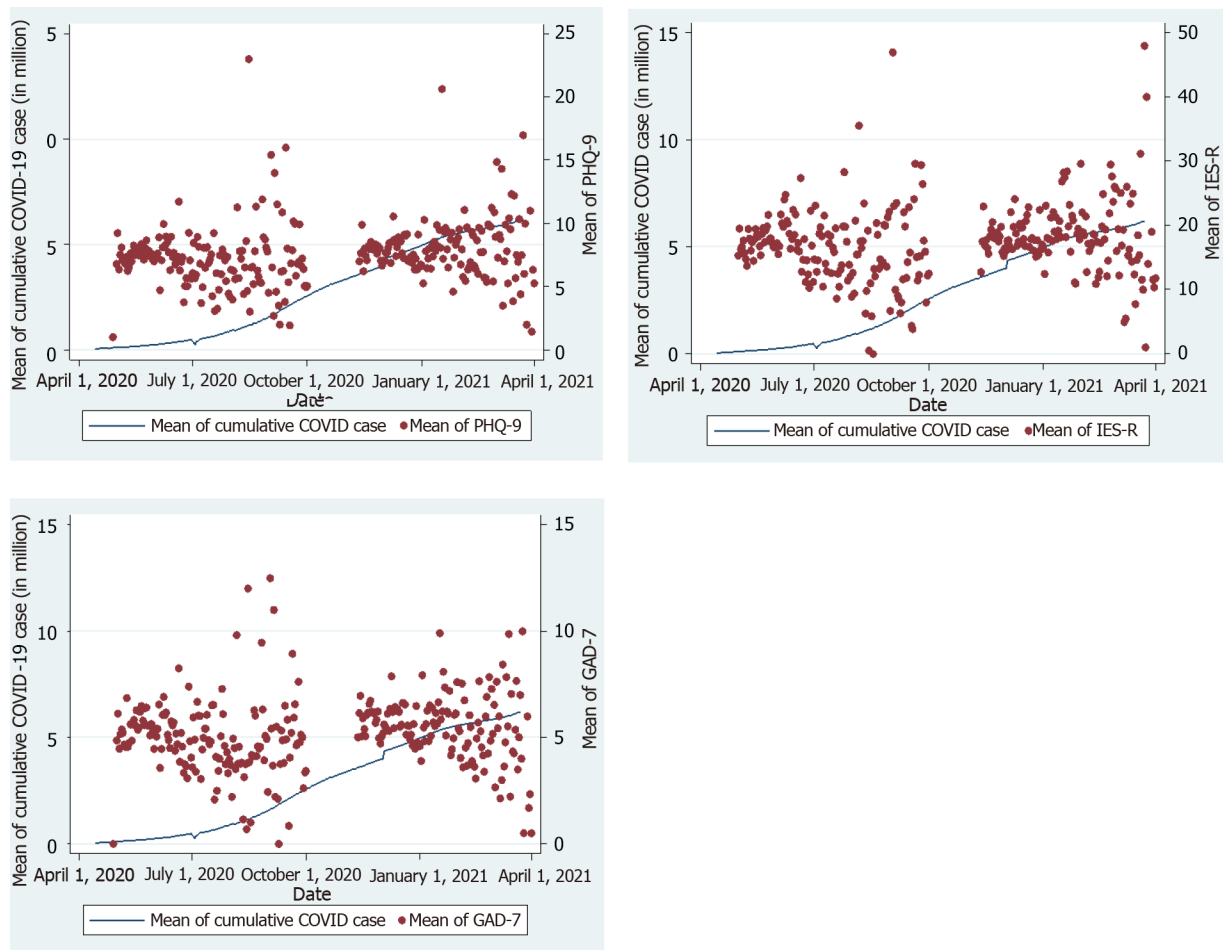
Table 5 Ordinary least squares regression of mental health scores on cumulative coronavirus disease 2019 case, lockdown, and individual characteristics (survey round 2)

	PHQ-9		GAD-7		IES-R	
	Round 1	Round 2	Round 1	Round 2	Round 1	Round 2
Daily cumulative COVID-19 case/1000000	0.195 ^c [0.18, 0.21]	0.433 ^c [0.23, 0.63]	0.129 ^c [0.11, 0.15]	0.557 ^c [0.38, 0.74]	0.454 ^c [0.40, 0.51]	1.265 ^c [0.67, 1.86]
Dummy for second lockdown withdraw		-0.507 ^c [-0.83, -0.18]		-0.343 ^b [-0.63, -0.05]		-1.077 ^b [-2.04, -0.11]
Dummy for second lockdown withdraw ¹ (date-second lockdown withdraw date)		-0.034 ^c [-0.06, -0.01]		-0.038 ^c [-0.06, -0.02]		-0.104 ^c [-0.18, -0.03]
Date-second lockdown withdraw date		0.013 [-0.01, 0.03]		-0.002 [-0.02, 0.02]		0.034 [-0.03, 0.10]
Healthcare professional (1 = yes, 0 = no)	-0.693 ^c [-0.80, -0.58]	-0.747 ^c [-0.86, -0.63]	-0.540 ^c [-0.64, -0.44]	-0.587 ^c [-0.69, -0.48]	-2.325 ^c [-2.65, -2.00]	-2.551 ^c [-2.89, -2.21]
Age (base: Below 25)						
25-44	-1.147 ^c [-1.34, -0.96]	-1.339 ^c [-1.55, -1.13]	-0.333 ^c [-0.50, -0.16]	-0.445 ^c [-0.63, -0.26]	-1.043 ^c [-1.60, -0.49]	-0.715 ^b [-1.33, -0.10]
45-54	-2.059 ^c [-2.27, -1.85]	-2.245 ^c [-2.47, -2.02]	-1.310 ^c [-1.50, -1.12]	-1.421 ^c [-1.63, -1.22]	-2.263 ^c [-2.88, -1.65]	-1.750 ^c [-2.42, -1.08]
55 and over	-3.455 ^c [-3.66, -3.25]	-3.639 ^c [-3.87, -3.41]	-2.424 ^c [-2.61, -2.24]	-2.521 ^c [-2.72, -2.32]	-4.792 ^c [-5.40, -4.18]	-4.223 ^c [-4.89, -3.55]
White (1 = yes, 0 = no)	-0.291 ^c [-0.42, -0.16]	-0.243 ^c [-0.38, -0.11]	-0.326 ^c [-0.44, -0.21]	-0.249 ^c [-0.37, -0.13]	-2.114 ^c [-2.49, -1.74]	-1.667 ^c [-2.07, -1.27]
Christian (1 = yes, 0 = no)	-0.017 [-0.11, 0.08]	0.018 [-0.08, 0.12]	0.174 ^c [0.09, 0.26]	0.183 ^c [0.10, 0.27]	0.752 ^c [0.47, 1.03]	0.795 ^c [0.50, 1.09]
Male (1 = yes, 0 = no)	-1.470 ^c [-1.57, -1.37]	-1.476 ^c [-1.58, -1.37]	-1.491 ^c [-1.58, -1.40]	-1.523 ^c [-1.62, -1.43]	-4.418 ^c [-4.72, -4.12]	-4.798 ^c [-5.12, -4.48]
Attended university (1 = yes, 0 = no)	-0.699 ^c [-0.96, -0.43]	0.000 [0.00, 0.00]	-0.543 ^c [-0.78, -0.31]	0.000 [0.00, 0.00]	-0.174 [-0.95, 0.60]	0.000 [0.00, 0.00]
Own home (1 = yes, 0 = no)	-1.328 ^c [-1.44, -1.22]	-1.391 ^c [-1.51, -1.27]	-0.899 ^c [-1.00, -0.80]	-0.957 ^c [-1.06, -0.85]	-2.985 ^c [-3.32, -2.65]	-3.338 ^c [-3.69, -2.99]
Vulnerable according to government category and require shielding (1 = yes, 0 = no)	1.355 ^c [1.25, 1.46]	1.393 ^c [1.28, 1.51]	1.083 ^c [0.99, 1.18]	1.124 ^c [1.02, 1.23]	3.932 ^c [3.61, 4.26]	3.929 ^c [3.59, 4.27]
Experienced coronavirus (1 = yes, 0 = no)	0.747 ^c [0.64, 0.85]	0.715 ^c [0.61, 0.82]	0.566 ^c [0.47, 0.66]	0.535 ^c [0.44, 0.63]	2.601 ^c [2.30, 2.91]	2.398 ^c [2.08, 2.71]
Pre-existing mental health condition (1 = yes, 0 = no)	2.808 ^c [2.62, 2.99]	2.745 ^c [2.55, 2.94]	2.278 ^c [2.11, 2.44]	2.266 ^c [2.10, 2.44]	7.150 ^c [6.60, 7.70]	7.160 ^c [6.60, 7.73]
Drinking alcohol (1 = yes, 0 = no)	2.300 ^c [2.17, 2.43]	2.506 ^c [2.36, 2.65]	1.714 ^c [1.60, 1.83]	1.875 ^c [1.75, 2.00]	5.976 ^c [5.59, 6.37]	6.400 ^c [5.98, 6.82]
Taking drug (1 = yes, 0 = no)	1.232 ^c [1.01, 1.46]	1.359 ^c [1.10, 1.62]	0.539 ^c [0.34, 0.74]	0.562 ^c [0.33, 0.79]	3.126 ^c [2.46, 3.79]	3.270 ^c [2.51, 4.03]
Ever experienced suicidal thoughts (1 = yes, 0 = no)	4.405 ^c	4.379 ^c	2.749 ^c	2.716 ^c	9.625 ^c	9.747 ^c

	[4.29, 4.52]	[4.26, 4.49]	[2.65, 2.85]	[2.61, 2.82]	[9.30, 9.95]	[9.41, 10.09]
Mental health support from (base: No support)						
Health service provider	0.322 ^c	0.342 ^c	-0.024	-0.051	-0.124	-0.288
	[0.10, 0.55]	[0.11, 0.57]	[-0.22, 0.17]	[-0.26, 0.15]	[-0.79, 0.54]	[-0.97, 0.39]
Other	1.041 ^c	1.300 ^c	0.686 ^c	0.854 ^c	2.979 ^c	3.572 ^c
	[0.78, 1.31]	[1.02, 1.58]	[0.45, 0.92]	[0.61, 1.10]	[2.20, 3.76]	[2.75, 4.40]
Constant	8.201 ^c	8.292 ^c	6.023 ^c	5.496 ^c	17.577 ^c	16.168 ^c
	[7.98, 8.42]	[7.84, 8.74]	[5.83, 6.22]	[5.10, 5.90]	[16.94, 18.21]	[14.84, 17.50]
Observations	62938	57985	63545	58547	58966	54202
Adjusted R²	0.315	0.318	0.228	0.230	0.222	0.228

^b $p < 0.05$.^c $p < 0.01$.¹See Table 3 for dates of first lock down period.

95% confidence intervals are in brackets. PHQ-9: Patient health questionnaire-9; IES-R: Impact of Events Scale-Revised; GAD-7: Generalized anxiety disorder-7; COVID-19: Coronavirus disease 2019.



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Figure 3 The association between mental health scores and coronavirus disease 2019 case. A: Mean of patient health questionnaire-9; B: Mean of impact of events scale-revised; C: Mean of generalized anxiety disorder-7. PHQ-9: Patient health questionnaire-9; IES-R: Impact of Events Scale-Revised; GAD-7: Generalized anxiety disorder-7; COVID-19: Coronavirus disease 2019.

three mental health scale indices: Depression, anxiety, and trauma. Ordinary least squares regression results with RDD specification to control for lockdown effects confirms the results. The results are dominated by data in the United Kingdom, which has the largest number of respondents with wider distribution over time. The study findings imply that

participants' mental health worsened with high cumulative COVID-19 cases. Daily cases did not show any impact on mental health scores of participants. The study also highlights other important demographic information and differences due to impact of the COVID-19 pandemic on different countries' participants.

These findings are understandable, considering the significant impact of COVID-19 pandemic on the lives of people across the globe and similar results from other data. Evidence from the Centre for Disease Control and Prevention has shown that fear and stress related to the COVID-19 has led to symptomatology, including change in sleep and eating patterns, worsening of premorbid psychiatric conditions, and increased use of substances (*e.g.*, alcohol, tobacco, drugs), which add to the mental health burden[21]. Quadros *et al*[22] conducted a scoping review and concluded that females, younger adults, urban residents, divorcees, healthcare workers, those in quarantine settings, those in suspicion of being infected, and those with mental health problems, were found to be at an increased risk of COVID-19-related fear[22].

High cumulative COVID-19 cases not only presented a fear of infection and mortality, especially in vulnerable groups, but also impacted on education, jobs, ability to socialize, relationships, loneliness, and other socio-cultural and socioeconomic variables. Most studies have shown an impact on young people's mental health as does this study and the same study in United Kingdom participants has shown an increase in suicidal thoughts[23,24]. High cumulative cases additionally meant the implementation of public health interventions and lockdowns restricting activities. Our findings from the United Kingdom data of the same study demonstrate the positive association of lockdown relaxation and face covering policies on the mental health of participants evidencing the impact of these interventions on mental health of populations as also demonstrated by the international data in this study[9].

These results add to existing global evidence of the psychological impact of the COVID-19 pandemic and previous studies that have demonstrated the adverse impact of population shocks on population mental health[25-27]. A systematic review of data published between January 2020 to January 2021 during the COVID-19 pandemic found that daily SARS-CoV-2 infection rates and reductions in human mobility were associated with increased prevalence of major depressive disorder[28]. These findings have been confirmed by the WHO[3].

In our study, participants from Hong Kong, India and Ukraine had lower mental health scores than other countries' participants. It is not possible to make conclusions on these findings as the number of participants were small and there would be an element of time of participation in the survey.

Different countries had their case number surges and lockdowns at different times during the pandemic. Similarly different countries followed a different trajectory depending on their populations, readiness to respond, political, cultural, financial, and technical landscape. As an example, Ukraine underwent change in ministers three times during the pandemic. There were other determinants of response to the pandemic including levels of awareness, stigma, fear in the early phases of pandemic and attributions to the illness based on cultural explanations[11].

Since the COVID-19 pandemic, the need for mental health support services has increased significantly[29]. This has been particularly difficult due to isolation and distancing measures, causing a physical barrier to help-seeking and treatment implementation[29,30]. Mental health rehabilitation interventions aim to increase social skills and teach coping strategies through training and increased social interactions[29]. This can help individuals with various mental health conditions but is especially useful for those with anxiety or depression[30]. Social and peer support is an integral part of mental health rehabilitation, yet the isolating protection measures of the COVID-19 pandemic pose a barrier[30].

Measures, such as regular testing or online programmes, are some actions which help to overcome these unprecedented circumstances[30,31]. Many organisations and facilities moved their services online in order to provide continuous psychological support for their clients[30,31]. This will ensure that services can continue to operate whilst controlling the spread of the pandemic[31]. The United Kingdom government has published a COVID-19 Mental Health and Wellbeing Recovery Action Plan to accommodate for mental health interventions throughout and post-pandemic [32]. The plan outlines various measures including support for young people, assistance within the employment sector, and accessible and widely available support for frontline healthcare workers[32]. Whilst mental health has always been a pressing matter, the pandemic has amplified its prevalence and affects across all demographic groups[32]. As there were rigid isolation regulations in place, this made the implementation of support difficult so organisations had to be innovative with the ways in which they would continue to assist clients[33]. Likewise, the pandemic also helped to highlight vulnerable groups, leading to the implementation of better support strategies and frameworks for these groups [33].

The results of this study should be interpreted considering its limitations. The timing of the study was such that most countries were in different phases of the pandemic. To conduct a study in that unusual environment meant that some may not consider this a cross sectional study in the epidemiological sense, and it could be difficult to judge the true population prevalence and make international comparisons. For this reason, we have explained the landscape of the different countries separately. This limitation could not have been avoided given the unpredictable nature of the spread of virus, even if confined parameters had been used. Additionally, where many cultural adaptations were made to account for the differences in the countries, it may still be difficult to draw conclusions about the differences in these populations which might be attributable to COVID as the measures are all taken after the onset of the pandemic. Another limitation concerning cumulative cases is that in many low and middle income countries, public health infrastructures and disease notification are very different to those used in high income countries, meaning that the potential for under-ascertainment of cases is much higher. The study has a high number of missing cases and non-random selection of participants are further limitations. In some participating centres the numbers are small. Many surveys were in circulation during this time in all the participating countries, especially during the second round, which may have affected the participation in the survey. Most studies of similar kind have reported small numbers.

CONCLUSION

The results from the current study add to developing evidence of the psychological impact of COVID-19, especially daily cumulative cases on three mental health indices. Building a database of evidence will allow for future planning of pandemics, particularly the impact on mental health of populations and the cultural differences.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) pandemic had a huge effect on mental health across the globe. As the pandemic developed over time, international rates of mental health conditions increased. It would be insightful to explore how the increasing cases of COVID-19 impacted mental health throughout the pandemic.

Research motivation

Exploring the impacts of COVID-19 on mental health with help construct a better understanding of the current mental health situation across the globe. It will also help to inform pandemic preparedness policies around mental health services.

Research objectives

This study aimed to explore the psychological implications of the increasing COVID-19 case throughout the pandemic across various countries.

Research methods

A repeated, cross-sectional online international survey of adults was carried out in 10 countries. Five standardised psychological measures were included to explore the psychological impact of cumulative COVID-19 cases. This was carried out at two timepoints in all countries, aside from the United Kingdom which collected data at 3 timepoints.

Research results

There were two rounds of the online survey in eight country groups with 42866 participants recruited in Round 1 and 92260 recruited in Round 2. This study found that the daily cumulative COVID-19 cases had a statistically significant effect on three depression, anxiety, and trauma. Trauma scores were higher across all countries compared to those for anxiety and depression. All scores increased in Round 2 in all countries.

Research conclusions

Considering the significant impact of COVID-19, understanding the effects will enable for adequate services and support to be put in place. This evidence dataset will also help inform the policies and strategies for pandemic preparedness.

Research perspectives

COVID-19 has had enduring effects in all aspects of life including physical and mental health.

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FOOTNOTES

Author contributions: Rathod S, Rathod P and Phiri P developed the study protocol and questionnaire; Rathod S, Phiri P, and Rahman MM contributed to the manuscript development; All authors reviewed and approved the final manuscript.

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Informed consent statement: All participants gave informed consent.

Conflict-of-interest statement: Professor Shanaya Rathod declares in the past 5 years to have received sponsorship for educational events

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STROBE statement: The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

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Observational Study

Role of comprehensive geriatric assessment in screening for mild cognitive disorders

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Abstract

BACKGROUND

The role of comprehensive geriatric assessment (CGA) in screening for mild cognitive disorders was not known.

AIM

To evaluate the role of CGA in screening for mild cognitive disorders.

METHODS

A total of 100 elderly people who underwent health examinations in our hospital and community between January 2020 and December 2021 were included for analysis. Using Petersen as the diagnostic gold standard, healthy individuals were included in the control group and patients with mild cognitive impairment were assigned to the study group. The correlation between the cognitive function of the patients and their baseline clinical profiles was analyzed. Patients' Montreal Cognitive Assessment (MoCA) and CGA screening results were compared, and the sensitivity and specificity were calculated to assess the screening role of CGA.

RESULTS

CGA assessment yielded higher diagnostic accuracy than MoCA. The results of the multivariate regression analysis showed no correlation of gender, age, body mass index and literacy with cognitive function. Patients with mild cognitive impairment obtained significantly lower MoCA scores than healthy individuals ($P < 0.05$). In the CGA scale, patients with mild cognitive impairment showed significantly lower Mini-mental State Examination, Miniature Nutritional Assessment and Berg Balance Scale scores, and higher Activity of Daily Living, Instrumental Activities of Daily Living Scale and Frailty Screening Inventory scores than healthy individuals ($P < 0.05$), whereas the other assessment scales showed no significant differences ($P > 0.05$). The CGA provides higher diagnostic sensitivity and specificity than the MoCA ($P < 0.05$).

CONCLUSION

CGA allows accurate identification of mild cognitive impairment with high sensitivity and specificity, facilitating timely and effective intervention, and is thus recommended for clinical use.

Key Words: Comprehensive geriatric assessment; Mild cognitive impairment; Screening; Montreal Cognitive Assessment; Sensitivity; Specificity

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Core Tip: Comprehensive geriatric assessment allows accurate identification of mild cognitive impairment with high sensitivity and specificity, facilitating timely and effective intervention, and is thus recommended for clinical use.

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INTRODUCTION

Mild cognitive impairment (MCI) is the transitional state between normal aging and mild dementia and is an early stage of dementia[1,2]. People with MCI present with memory impairment that exceeds the allowable range for their age and culture. However, they experience normal social work or daily functioning and do not meet the diagnostic criteria for dementia. Evidence suggests that within the following 2-5 years, mild cognitive impairment is associated with a higher risk of developing dementia compared to age-appropriate non-mild cognitive impairment, which may be attributable to multiple diseases[3]. There is a prevalence of mild cognitive impairment of over 15% in people over 65 years of age, with 10%-15% of the population deteriorating to Alzheimer's disease within one year per year, whereas the prevalence in the normal population averages only 1%-2%. Therefore, enhanced detection, intervention, or delay of the onset of cognitive impairment in mild cognitive impairment at an early clinical stage is necessary[4,5]. Timely diagnosis of patients with mild cognitive impairment is a prerequisite for treatment and can efficiently mitigate the progression of the disease. Screening for mild cognitive impairment is normally performed using the Montreal cognitive assessment (MoCA)[6,7], a scale that references the cognitive elements and scores of the Mini-mental State Examination (MMSE) to assess mild cognitive impairment[8]. However, the results of studies related to the cut-off point, sensitivity and specificity of the scale vary considerably. Comprehensive geriatric assessment (CGA)[9] is a multidisciplinary approach that assesses the physical health, functional status, mental health and social-environmental status of older people[10]. CGA can facilitate timely treatment, slow down the disease process and reduce dementia through multidimensional analysis of MCI[11,12]. To this end, the current research was performed to evaluate the role of CGA in screening for mild cognitive disorders.

MATERIALS AND METHODS

Case selection

A total of 100 elderly people who underwent health examinations in our hospital and community between January 2020 and December 2021 were included for analysis. Written informed consent was obtained from all patients in this study.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with objective signs of impairment in one or more areas of cognitive function; (2) patients met the relevant diagnostic criteria in the Diagnosis and Treatment of Mild Cognitive Impairment; and (3) clinical information was complete, with no restriction on gender, and age no less than 60 years.

Exclusion criteria: (1) Patients met the diagnostic criteria for clinical dementia; (2) physical organ disability, including vision and hearing; and (3) inability to cooperate with the completion of this study for psychiatric reasons.

Methods

Using Petersen as the diagnostic gold standard, healthy individuals were included in the control group and patients with mild cognitive impairment were assigned to the study group. The correlation between the cognitive function of the patients and their baseline clinical profiles was analyzed. Patients' MoCA and CGA screening results were compared, and the sensitivity and specificity were calculated to assess the screening role of CGA.

Outcome measures

Petersen diagnosis: The patient reported memory loss for no less than 3 mo, which was confirmed by others; age-incompatible objective memory decline, with overall normal cognitive function and a Geriatric Depression Scale (GDS) score of 2-3; patients had essentially normal activities of daily living and an Activity of Daily Living (ADL) score no higher than 18; patients did not meet the US NIA-AA dementia diagnostic criteria for dementia, with a CDR score = 0.5.

MoCA: The Chinese version of the MoCA scale developed by Peking Union Medical College Hospital and Professor Nasreddine was used for assessment. The scale has a total score of 30 and includes eight cognitive domains, namely time, positional orientation, language, calculation, memory and delayed memory, visuospatial ability, executive function, attention and abstract thinking. Scores are proportional to cognitive functioning, with scores below 26 indicating impaired cognitive functioning[13].

CGA: The CGA assesses the cognitive status of patients through the General Medical Assessment, Physical Functioning Assessment, Psychosocial Assessment, Social Health Assessment, Environmental Assessment, Quality of Life Assessment and Assessment of Common Symptoms or Problems in Older Adults. It includes the GDS, Geriatric Anxiety Inventory (GAI), MMSE, Miniature Nutritional Assessment (MNA), ADL, Instrumental Activities of Daily Living Scale (IADL), Frailty Screening Inventory (FRAIL), Berg Balance Scale (BBS), Falls Risk Factor Assessment (FRAF), and PAGAR. GDS, GAI, MMSE, MNA, BBS, FRAF, and PAGAR were proportional to the CGA score, and ADL, IADL, and FRAIL were inversely proportional to the CGA score.

Statistical analysis

SPSS 26.0 was used for data analyses. Measurement data were expressed as mean $\pm$ SD and tested using independent samples *t*-test. Count data were expressed as number of cases (%) and tested using χ^2 test. Pearson correlation analysis was applied for multiple regression analysis. Statistical significance was indicated by $P < 0.05$.

RESULTS

Screening results

Petersen diagnosed 62 healthy individuals as controls and 38 patients with mild cognitive impairment as the study group. The MoCA diagnosed 30 cases of healthy individuals and 38 cases of patients with mild cognitive impairment, while the CGA assessment showed 58 cases of healthy individuals and 36 cases of patients with mild cognitive impairment. CGA assessment yielded higher diagnostic accuracy than MoCA (Table 1 and Table 2).

Baseline patient profiles

The control group consisted of 41 males and 21 females, aged 62-80 (71.84 ± 7.21) years, with a body mass index (BMI) of 20-26 (24.18 ± 2.11) kg/m². There were 5 cases of illiteracy, 18 cases with an education level of primary school, 25 cases of junior high school, and 14 cases of high school and above. The study group consisted of 25 males and 13 females, aged 61-79 (71.52 ± 7.36) years, with a BMI of 20-26 (24.21 ± 2.07) kg/m². There were 2 cases of illiteracy, 11 cases with an education level of primary school, 16 cases of junior high school, and 9 cases of high school and above. The two arms were well-balanced in terms of baseline patient profiles ($P > 0.05$, Table 3).

Correlation

The results of the multivariate regression analysis showed no correlation of gender, age, body mass index and literacy with cognitive function ($P > 0.05$, Table 4).

MoCA scores

MoCA score in the control group was 26.88 ± 2.14 and the MoCA score in the study group was 20.86 ± 2.56 . Patients with mild cognitive impairment obtained significantly lower MoCA scores than healthy individuals ($P < 0.05$, Table 5).

CGA scores

In the CGA scale, patients with mild cognitive impairment showed significantly lower MMSE, MNA and BBS scores, and higher ADL, IADL and FRAIL scores than healthy individuals ($P < 0.05$), whereas the other assessment scales showed no significant differences ($P > 0.05$) (Table 6).

Application value of CGA vs MoCA

The sensitivity and specificity of MoCA was 0.761 and 0.714, while the sensitivity and specificity of CGA was 0.882 and 0.964. The CGA provides higher diagnostic sensitivity and specificity than the MoCA ($P < 0.05$) (Table 7).

DISCUSSION

Cognitive impairment can affect learning, memory, social functioning, language, visuospatial function, and attention, and severe cognitive impairment can lead to dementia. Statistics show that 5%-10% of people with mild cognitive impairment

Table 1 Montreal cognitive assessment results

MoCA results	Study group	Control group
Normal	30	7
Mild cognitive impairment	8	55
Total	38	62

MoCA: Montreal cognitive assessment.

Table 2 Comprehensive geriatric assessment results

CGA results	Study group	Control group
Mild cognitive impairment	36	4
Normal	2	58
Total	38	62

CGA: Comprehensive geriatric assessment.

Table 3 Baseline patient profiles

	Control group, <i>n</i> = 62	Study group, <i>n</i> = 38	<i>t</i> value	<i>P</i> value
Sex				
Male	41	25	-	-
Female	21	13	-	-
Age (yr) (mean)	62-80 (71.84 ± 7.21)	61-79 (71.52 ± 7.36)	0.214	0.831
BMI (kg/m ²) (mean)	20-26 (24.18 ± 2.11)	20-26 (24.21 ± 2.07)	0.070	0.944
Education level				
Illiterate	5	2	-	-
Primary school	18	11	-	-
Junior high school	25	16	-	-
High school and above	14	9	-	-

BMI: Body mass index.

Table 4 Correlation of baseline profiles and cognitive function

	B	SE	B'	<i>t</i> value	<i>P</i> value
Sex	-1.612	2.705	-0.079	-0.521	0.511
Age	-0.154	0.088	-0.227	1.794	0.094
BMI	0.012	0.069	0.034	0.314	0.807
Education level	0.714	0.763	0.185	0.894	0.352

BMI: Body mass index.

develop dementia each year, which is higher than the 1%-2% annual prevalence in the general population. Nearly 50 million people worldwide suffered from dementia in 2016, and its prevalence has been increasing[14]. The aging population and the increasing prevalence of dementia are the primary contributors to the expected increase in the cost of dementia. Few clinically effective medications are available for the treatment of cognitive impairment. However, studies have shown that 30%-50% of patients initially diagnosed with mild cognitive impairment recover to a normal cognitive

Table 5 Montreal cognitive assessment scores

	Control group	Study group	t value	P value
n	62	38	-	-
MoCA scores	26.88 ± 2.14	20.86 ± 2.56	12.663	< 0.001

MoCA: Montreal cognitive assessment.

Table 6 Comprehensive geriatric assessment scores

	Control group, n = 62	Study group, n = 38	t value	P value
GDS	9.61 ± 3.98	10.05 ± 3.88	0.542	0.589
GAI	3.62 ± 3.25	3.44 ± 3.18	0.271	0.787
MMSE	28.85 ± 1.85	26.05 ± 1.27	8.212	< 0.001
MNA	22.51 ± 4.14	19.14 ± 3.52	4.176	< 0.001
ADL	17.25 ± 2.62	19.58 ± 2.14	4.616	< 0.001
IADL	10.52 ± 3.51	12.88 ± 3.54	3.253	0.002
FRAIL	1.25 ± 0.25	1.89 ± 0.57	7.728	< 0.001
BBS	44.52 ± 7.98	39.21 ± 8.11	3.210	0.002
FRAF	2.62 ± 1.25	2.68 ± 1.31	0.229	0.819
PAGAR	8.29 ± 2.58	8.33 ± 2.49	0.076	0.940

CGA: Comprehensive geriatric assessment; GDS: Geriatric depression scale; GAI: Geriatric anxiety inventory; MMSE: Mini-mental state examination; MNA: Miniature nutritional assessment; ADL: Activity of daily living scale; IADL: Instrumental activities of daily living scale; FRAIL: Frailty screening inventory; BBS: Berg balance scale; FRAF: Falls risk factor assessment.

Table 7 Sensitivity and specificity of Montreal cognitive assessment and comprehensive geriatric assessment

	MoCA	CGA
Sensitivity	0.761	0.882
Specificity	0.714	0.964

MoCA: Montreal cognitive assessment; CGA: Comprehensive geriatric assessment.

level during postoperative care. Therefore, timely screening and prevention will contribute to improving the standard of living of patients and reducing the family, social and economic burden[15,16]. Patients with mild cognitive impairment show no typical clinical manifestations in the early stages, which poses difficulties in the clinical diagnosis of the disease and is detrimental to the early identification and targeted treatment of the condition.

The MoCA is an assessment scale for mild cognitive impairment developed by Canadian scientists based on clinical experience and with reference to the cognitive elements and scores of the MMSE[17,18]. In the present study, patients with mild cognitive impairment showed significantly lower MMSE, MNA, and BBS scores, and higher ADL, IADL and FRAIL scores than healthy individuals, whereas the other assessment scales showed no significant differences, and the CGA provides higher diagnostic sensitivity and specificity than the MoCA, which was consistent with the findings of previous studies. It has been reported that the relative risk of conversion to dementia in those with cognitive abnormalities is 6.4 times higher than in those with normal cognition. Mild cognitive impairment is an early manifestation of dementia, and the MMSE is a scale that has been used to assess cognitive ability. It has been proposed that the dietary patterns of patients have implications for future perceptions in life, and that most older people require treatment for nutritional deficiencies to prevent cognitive decline. As a result, greater emphasis should be placed on screening for nutritional status in patients with mild cognitive impairment to ensure adequate nutritional support. In 2013, the International Academy of Nutrition and Aging and the International Association of Geriatrics introduced the concept of 'cognitive deprivation', linking cognition to deprivation. The present study also found that the results of the multiple regression analysis showed that gender, age, BMI and literacy were not correlated with cognitive function. However, this is inconsistent in previous studies and may be the result of the large variation in sample size from one study to another, with increased sample size contributing to the analysis of cognitive function factors.

The MoCA scale focuses on a single disease and fails to fully address the healthcare needs of older people. CGA was originally proposed by British scientists in 1946 as an intervention to comprehensively assess the illness, physical ability, cognitive, psychological, social and economic status of elderly patients at multiple levels, so as to comprehensively assess older people with a function-oriented approach during the recovery phase of chronic disease to guide treatment and health maintenance. Currently, it is widely used to determine the level of health functioning of older people and is recognized for its effectiveness in improving diagnosis, prognosis and quality of life of patients. Nevertheless, no consensus has been reached on the content of their specific assessments. Heterogeneity in the size of different research institutions precludes the comparison of different findings, for which the identification of standardized comprehensive CGA assessments for older people is an effective approach. However, a large body of evidence is required[19,20].

Limitations

Research suggests that all people over the age of 70 years ought to undergo annual subjective or objective cognitive testing with their healthcare provider. However, this has significantly increased the workload of medical staff, resulting in high human costs. This could be improved in the future through the development of a fee schedule for comprehensive assessments, including health insurance, changes to the writing of health records, the addition of a "comprehensive assessment and diagnosis for older people" and the conversion of different assessment scales into electronic health records. Limitations of the current study include the risk of bias due to insufficient sample size and lack of sample diversity. Future studies will expand the sample to further improve the protocol and provide more references for future relevant diagnostic treatments.

CONCLUSION

CGA allows accurate identification of mild cognitive impairment with high sensitivity and specificity, facilitating timely and effective intervention, and is thus recommended for clinical use.

ARTICLE HIGHLIGHTS

Research background

Comprehensive geriatric assessment (CGA) is a multidisciplinary approach that assesses the physical health, functional status, mental health and social-environmental status of older people. CGA can facilitate timely treatment, slow down the disease process and reduce dementia through multidimensional analysis of Mild cognitive impairment.

Research motivation

This study found that CGA allows accurate identification of mild cognitive impairment with high sensitivity and specificity, facilitating timely and effective intervention.

Research objectives

This study was conducted to evaluate the role of comprehensive geriatric assessment in screening for mild cognitive disorders.

Research methods

Using Petersen as the diagnostic gold standard, healthy individuals were included in the control group and patients with mild cognitive impairment were assigned to the study group. The correlation between the cognitive function of the patients and their baseline clinical profiles was analysed. Patients' Montreal Cognitive Assessment (MoCA) and CGA screening results were compared, and the sensitivity and specificity were calculated to assess the screening role of CGA.

Research results

CGA assessment yielded higher diagnostic accuracy than MoCA. The results of the multivariate regression analysis showed no correlation of gender, age, body mass index and literacy with cognitive function. Patients with mild cognitive impairment obtained significantly lower MoCA scores than healthy individuals. In the CGA scale, patients with mild cognitive impairment showed significantly lower Mini-mental State Examination, Miniature Nutritional Assessment and Berg Balance Scale scores, and higher Activity of Daily Living, Instrumental Activities of Daily Living Scale and FRAIL scores than healthy individuals. The CGA provides higher diagnostic sensitivity and specificity than the MoCA.

Research conclusions

CGA allows accurate identification of mild cognitive impairment with high sensitivity and specificity, facilitating timely and effective intervention, and is thus recommended for clinical use.

Research perspectives

Future studies will expand the sample to further improve the protocol and provide more references for future relevant diagnostic treatments.

FOOTNOTES

Author contributions: Yu J and Lu SR contributed equally to this work; Wang Z, Yang Y designed the research study; Zhang BS performed the research; Hong K contributed new reagents and analytic tools; Xu Q analyzed the data and wrote the manuscript; and all authors have read and approve the final manuscript.

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Observational Study

Factors influencing postoperative anxiety and depression following Iodine-131 treatment in patients with differentiated thyroid cancer: A cross-sectional study

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Abstract

BACKGROUND

Differentiated thyroid cancer (DTC) often seriously impacts patients' lives. Radionuclide Iodine-131 (¹³¹I) is widely used in treating patients with DTC. However, most patients know little about radionuclide therapy, and the treatment needs to be performed in a special isolation ward, which can cause anxiety and depression.

AIM

To explore anxiety and depression status and their influencing factors after ¹³¹I treatment in patients with DTC.

METHODS

A questionnaire survey was conducted among postoperative patients with DTC who received ¹³¹I treatment at our hospital from June 2020 to December 2022. General patient data were collected using a self-administered demographic characteristics questionnaire. The self-rating depression scale and self-rating anxiety scale were used to determine whether patients were worried about their symptoms and the degree of anxiety and depression. The patients were categorized into anxiety, non-anxiety, depression, and non-depression groups. Single-variable and multiple-variable analyses were used to determine the risk factors for anxiety and depression in patients with thyroid cancer after surgery.

RESULTS

A total of 144 patients were included in this study. The baseline mean score of self-rating anxiety and depression scales were 50.06 ± 16.10 and 50.96 ± 16.55 , respectively. Notably, 48.62% (70/144) had anxiety and 47.22% (68/144) of the

patients had depression. Sex, age, education level, marital status, household income, underlying diseases, and medication compliance significantly differed among groups ($P < 0.05$). Furthermore, multivariate logistic regression analysis showed that education level, per capita monthly household income, and medication compliance level affected anxiety ($P = 0.015, 0.001, \text{ and } 0.001$ respectively). Patient's sex, marital status, and underlying diseases affected depression ($P = 0.007, 0.001, \text{ and } 0.009$, respectively).

CONCLUSION

Nursing interventions aiming at reducing the risk of anxiety and depression should target unmarried female patients with low education level, low family income, underlying diseases, and poor adherence to medications.

Key Words: Iodine-131; Thyroid gland; Neoplasms; Anxiety; Depression; Prognosis

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Core Tip: Differentiated thyroid cancer (DTC) seriously impacts the patient's life and induces more adverse emotions. This study investigated anxiety and depression in 144 patients with DTC. Sex, education level, family factors, and basic diseases were the risk factors for anxiety and depression. Better intervention nursing measures can be proposed for clinical practice by observing and proposing indicators that affect patients' mood risk factors and by comparing them with previous studies, thereby reducing the risk of developing anxiety and depression and improving their prognosis.

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INTRODUCTION

Thyroid cancer is a common malignant head and neck tumor, and its incidence has been annually increasing in recent years[1]. According to the International Agency for Research on Cancer, the worldwide incidence of thyroid cancer is approximately 6.7/100000, and the number of new cases in China is 190000 in 2022[2]. Among them, differentiated thyroid cancer (DTC) accounts for approximately 90%. Currently, DTC is treated with a three-step comprehensive treatment approach consisting of surgery, Iodine-131 (¹³¹I) treatment and thyroid hormone suppression[3], which can significantly reduce the tumor recurrence rate and improve disease prognosis. However, the complications of tumor surgery and lack of understanding of ¹³¹I treatment, especially the fact that ¹³¹I treatment is a type of internal radiotherapy, may result in patients experiencing anxiety, fear, depression, and other negative emotions[4]. In clinical practice, several patients with DTC exhibit anxiety or poor mental state before radiotherapy, which leads to poor compliance with radiotherapy and ultimately affects the clinical treatment effect[5]. Therefore, it is crucial to analyze the anxiety status and related influencing factors of patients with thyroid cancer after surgery. This analysis can guide the formulation of clinical preventive nursing strategies and improve patient outcomes. Along those lines, this study aims to explore the anxiety states and associated risk factors in patients with DTC after ¹³¹I treatment.

MATERIALS AND METHODS

Patient characteristics

A questionnaire survey was conducted among postoperative patients with DTC who received ¹³¹I treatment at our hospital from June 2020 to December 2022.

Inclusion criteria were as follows: Pathological diagnosis of DTC; clinical indications for surgical treatment and completed surgical treatment; age ≥ 18 years; ability to read and independently complete the questionnaire, the patients were informed, cooperated well, and had complete clinical pathological data. Comply with medical advice, regular postoperative review at our hospital.

The exclusion criteria were as follows: Previous or concurrent malignant tumors combined with anxiety; depression; history of dementia; history of drug abuse; alcoholism; failure of the heart, liver, kidney, and other important organs; hearing and language dysfunction; and inability to cooperate.

A total of 144 patients met the inclusion standard. The patients were divided into anxiety, non-anxiety, depression, and non-depression groups based on their reported anxiety or depression status.

General information collection

General patient data, collected using a self-administered demographic characteristics questionnaire, mainly included age, sex, cultural background, marital status, family per capita monthly income, presence or absence of underlying diseases, and medication compliance. At the same time, the anxiety self-rating scales (SAS) and the self-rating depression scale (SDS) were used to evaluate the anxiety and depression of the patients one month after operation.

Anxiety status assessment

Trained healthcare professionals used SAS to assess anxiety in all patients. The SAS includes 20 items, of which 15 are scored positively, and 5 are scored negatively. Twenty entries add up to a total score of 20. The integer part of the total score was multiplied with 1.25 to obtain the standard score. The threshold was set to 50 points based on the Chinese scoring standard. The degree of anxiety was categorized as mild (50–60 points), moderate (60–80), and severe (80–100).

Depression status assessment

SDS was used to evaluate the depression status of the patients. All patients were evaluated by a professional medical staff member who had undergone systematic training. The SDS includes 20 items, and each item was evaluated using a 4-point Likert scale, with a score of 1–4 points. The rough score was obtained by adding the scores of each item (the reverse item is the reverse score); the coarse fraction was multiplied with 1.25 and the integer part was considered as the standard score. The threshold of the standard SDS score was 53 points, and the normal score was 53 points. Depression was classified as mild (53–60 points), moderate (60–70), or severe (70–100).

Statistical Methods

Descriptive analysis, and single-factor and multi-factor analyses were performed. Descriptive analysis was performed on the number of samples and their compositions. The histogram shows the basic characteristics of anxiety and depression. Univariate chi-square tests and single-factor logistic regression analyses were used to evaluate the influencing factors of anxiety and depression. Anxiety and depression (yes = 1; no = 0) were assigned as the dependent variables. All statistical tests were two-sided, with a statistically significant difference of $P < 0.05$. The data obtained were statistically analyzed using SPSS26.0 (IBM SPSS Inc., Chicago, United States).

RESULTS

Survey population

A total of 144 participants were included in this study, comprising 70 men (48.61%) and 74 women (51.39%). Their age was 18–60 (34.81 ± 4.92) years; and education level was 68 (47.22%) above high school, 76 (52.78%) below high school. **Table 1** presents additional basic information collected in this study.

Anxiety and depression

The baseline mean scores of SAS and SDS were 50.06 ± 16.10 and 50.96 ± 16.55 , respectively. Further, 51.38% (74/144) of the patients were in a non-anxiety state and 48.62% (70/144) were anxious. The proportions of mild, moderate, and severe anxiety were 21.52%, 24.30%, and 2.78%, respectively. Moreover, 52.78% (76/144) of the patients were non-depressive and 47.22% (68/144) experienced depression. The proportions of mild, moderate, and severe depressive loops were 20.83%, 22.92%, and 3.47%, respectively (**Table 2**).

Influencing factors of anxiety

Single-factor analysis of anxiety symptoms: The results of single factor showed that there were significant differences between the two groups in education level, family monthly average income and medication rule ($P < 0.05$) (**Table 3**).

Multivariate analysis of anxiety symptoms: Logistic regression analysis was performed with the dependent variable anxiety. Independent variables included age, sex, marital status, educational level, family income, basic diseases, and medication compliance. The detailed variables assignments are listed in **Table 4**.

Multivariate analysis showed that education level, monthly average family income, and medication compliance were factors influencing patients' possible anxiety ($P < 0.05$; **Table 5**). Patients with a high educational level were 0.28 times more likely to experience anxiety than that those with a low educational level. Patients with high family income were 0.09 times more likely to experience anxiety than those with low family income. Patients who took medications regularly were 0.03 times more likely to be anxious than those who missed medications occasionally.

Influencing factors of depression

Single-factor analysis of depression: The results of single factor showed that there were significant differences between the two groups in gender, marital status and basic diseases ($P < 0.05$) (**Table 6**).

Multivariate analysis of depression: Logistic regression analysis was performed with depression as the dependent variable. Independent variables included age, sex, marital status, educational level, family income, basic diseases, and medication compliance. The variables assignments are listed in **Table 4**.

Table 1 Characteristics of the survey population

Category	Variable	Number of samples	Percentage (%)
Age	< 30	66	45.83
	≥ 30	78	54.17
Sex	Male	70	48.61
	Female	74	51.39
Education	High school or above	68	47.22
	High school and below	76	52.78
Marital status	Have a spouse	69	47.92
	no spouse	75	52.08
Monthly household income	≥ 5000	70	48.61
	< 5000	74	51.39
Underlying medical conditions	Yes	71	49.31
	No	73	50.69
Medication adherence	Regular	67	46.53
	Irregular	77	53.47

Table 2 Overall status of anxiety and depression in patients undergoing ¹³¹I treatment after surgery for differentiated thyroid cancer

Category	Normal	Mild	Moderate	Severe
Anxiety	74 (51.39)	31 (21.52)	35 (24.30)	4 (2.78)
Depression	76 (52.78)	30 (20.83)	33 (22.92)	5 (3.47)

Table 3 Single factor analysis of anxiety in survey participants

Category		Anxiety (n = 70)	Non-anxiety (n = 74)	χ^2	P value
Age	≤ 40	31 (44.29)	35 (47.30)	0.131	0.717
	> 40	39 (55.71)	39 (52.70)		
Sex	Male	33 (47.14)	41 (55.40)	0.983	0.321
	Female	37 (52.86)	33 (44.59)		
Education	High school or above	48 (68.57)	20 (27.03)	24.911	0.001
	High school and below	22 (31.43)	54 (72.97)		
Marital status	Have a spouse	38 (54.29)	35 (47.30)	0.703	0.402
	No spouse	32 (45.71)	39 (52.70)		
Monthly household income	≤ 5000	51 (72.86)	19 (25.68)	32.065	0.001
	> 5000	19 (27.14)	55 (74.32)		
Underlying medical conditions	Yes	37 (52.86)	34 (45.95)	0.687	0.407
	No	33 (47.14)	40 (54.05)		
Medication adherence	Irregular	56 (80.00)	11 (14.86)	61.342	0.001
	Regular	14 (20.00)	63 (85.14)		

Logistic multivariate regression analysis showed that the factors influencing depression were sex, marital status, and basic diseases ($P < 0.05$). Female patients were more likely to have depression than male patients. Patients without a spouse were more likely to experience depression than those with a spouse. Patients with underlying diseases were more likely to have depression than those without. Detailed data analysis is presented in [Table 7](#).

Table 4 Assignments

Category	Assignment
Age	≤ 40 = 1; > 40 = 0
Education	High school or above = 1; High school and below = 0
Sex	Male = 1; Female = 0
Marital status	Have a spouse = 1; No spouse = 0
Monthly household income	> 5000 = 1; ≤ 5000 = 0
Underlying medical conditions	Yes = 1; No = 0
Medication adherence	Regular = 1; Irregular = 0
Anxiety	Anxiety = 1; Non-anxiety = 0
Depression	Depression = 1; Non-depression = 0

Table 5 Multivariate logistic analysis of anxiety in differentiated thyroid cancer patients after ¹³¹I treatment and surgery

Factors	β	SE	Wald χ^2 value	P value	OR	95%CI
Education	-1.256	0.518	5.872	0.015	0.285	0.103–0.786
Family monthly income	-2.402	0.587	16.719	0.001	0.091	0.029–0.286
Medication compliance	-3.292	0.585	31.617	0.001	0.037	0.012–0.117

SE: Standard error

Table 6 Univariate analysis of the depression in patients with differentiated thyroid cancer after ¹³¹I treatment and surgery

Catalog		Depression (n = 68)	Non-depression (n = 76)	χ^2 value	P value
Age	≤ 40	34 (50.00)	32 (42.11)	0.901	0.343
	> 40	34 (50.00)	44 (57.89)		
Sex	Male	27 (39.71)	47 (61.84)	7.040	0.008
	Female	41 (60.29)	29 (38.16)		
Education	High school and below	34 (50.00)	34 (44.74)	0.399	0.528
	High school or above	34 (50.00)	42 (55.26)		
Marital status	Have a spouse	22 (32.35)	51 (67.11)	17.341	0.001
	No spouse	46 (67.65)	25 (32.89)		
Monthly household income	≤ 5000	37 (54.41)	33 (43.42)	1.735	0.188
	> 5000	31 (45.59)	43 (56.58)		
Underlying medical conditions	Yes	44 (64.71)	27 (35.53)	7.614	0.006
	No	24 (35.29)	49 (64.47)		
Medication adherence	Irregular	36 (52.94)	31 (40.79)	2.130	0.144
	Regular	32 (47.06)	45 (59.21)		

DISCUSSION

DTC is a common thyroid gland malignancy that occurs in young and middle-aged women[6]. DTC has a serious impact on the lives of patients and also induces more adverse emotions. Radionuclide ¹³¹I has been widely used to treat patients with DTC and has contributed to continuous progress in medical technology in China[7]. However, most patients know little about radionuclide therapy, and the treatment needs to be performed in a special isolation ward, which can easily cause anxiety and depression[8]. Thus, it is important to consider the mental health of patients, which is conducive to better recovery.

Table 7 Multivariate Logistic analysis of depression in differentiated thyroid cancer patients after ¹³¹I treatment and surgery

Factors	β	SE	Wald χ^2 value	P value	OR	95%CI
Sex	-1.096	0.405	7.323	0.007	0.334	0.151–0.739
Marital status	-1.616	0.401	16.210	0.001	0.199	0.091–0.436
Underlying diseases	-1.027	0.396	6.737	0.009	0.358	0.165–1.038

SE: Standard error; OR: Odds ratio.

The findings of this study showed that 48.61% of patients with DTC exhibited anxiety and 47.22% exhibited depression, one month following their ¹³¹I treatment initiation. These elevated percentages could be attributed to patients having concerns about the problems associated with radiation involved in ¹³¹I treatment during isolation, due to a limited understanding of ¹³¹I treatment. These patients are prone to panic, anxiety, and other serious passive moods, which reduce their compliance with treatment and affect the overall treatment outcomes. Therefore, the assessment of anxiety and depression in patients undergoing ¹³¹I treatment facilitates the provision of timely counseling intervention to alleviate these negative emotions, and improve patients' treatment compliance, prognosis, and quality of life[9]. Moreover, these negative emotions in patients with thyroid cancer are reported to be associated to age, educational level, and family income[4,10].

In the present study, the anxiety and depression symptom scores of postoperative patients after ¹³¹I treatment were 50.06 ± 16.10 and 50.96 ± 16.55 , respectively. It has been reported that the main reasons for the high scores of anxiety and depression were the lack of trust in the professional level of the medical staff, lack of understanding of treatment methods, and concerns regarding recurrence and adverse reactions during surgery, as well as the resulting economic burden[11,12]. The superposition of these factors inadvertently leads to high psychological pressure and stress responses in patients, thereby resulting in anxiety and depression[13].

Further multivariate logistic regression analysis showed that patient's education level, family income, and medication regularity were the independent influencing factors of anxiety. Therefore, our results suggest that patients with a low education level, low family income, and irregular adherence to medication were more prone to anxiety. These findings are consistent with those of Yang *et al*[14] and Tsartsalis *et al*[15]. Possible reasons for these results may include the limited knowledge levels among people with low education levels, less access to disease information, a lack of understanding of important stressors, and a difficulty in effectively reducing stress using corresponding methods. Such patients are sensitive to possible threats caused by diseases and operations and are prone to anxiety and depression[16]. Patients with higher education levels have a stronger learning ability and thorough understanding of medical staff's knowledge and educational status. Patients who are able to actively collect information about the disease and its treatment from books, networks, and other means, are better equipped to reduce the psychological burden and eliminate negative emotions. On the other hand, patients with low education levels require repeated explanations, even through the use audiovisual aids to increase their understanding of their diseases, thereby eliminating the uncertainty of the disease or treatment, and improving their confidence in the healing process[17].

Thyroid cancer requires long-term treatment, which is expensive and increases the economic burden of patients. Therefore, family income has also become an independent risk factor for patients' concerns. Patients with thyroid cancer with a family monthly income ≤ 5000 yuan have often face financial difficulties. They experience significant psychological pressure because they worry about becoming a burden on their families, and they may feel anxious about being unable to afford the long-term medical expenses. The consequent uncertainty of follow-up treatment can easily lead to negative emotions, such as guilt and anxiety. Indeed, patients from low-income families can choose effective and low-cost drug treatment to reduce their families economic burden[18].

Occasionally missed medications are also a risk factor for anxiety in patients with DTC after surgery. Long-term and occasionally missed medication increases the fear of disease recurrence, resulting in anxiety symptoms. Therefore, family members should ensure that patients take their medications on time.

In the present study, sex, marital status, and underlying diseases were independent risk factors for depression. The incidence of depression was higher in women than that in men, which is consistent with previous studies[19]. This reason may be related to cyclical fluctuations in female endocrine hormone levels[20]. In addition, women now play multiple roles in social responsibility, leading to increased stress in life; they are relatively more sensitive, tend to have more physical and emotional pain, which may lead to a poor prognosis[21]. More attention should be paid to the feelings of female patients, and their symptoms should be actively improved to enhance their quality of life. Studies[19] have shown that marital status is an independent risk factor for depression. Although unmarried patients are accompanied by their parents, they lack active support from their spouses or children, and consequently experience greater loneliness than married patients. On the other hand, patients with spouses can receive family support to reduce their risk of anxiety and depression. Studies[22] have also reported that patients with cancer undergoing long-term treatments, such as radiotherapy and chemotherapy, are affected by irreversible damage to fertility and reproductive performance, resulting in depression, especially in unmarried and childless patients. In addition, ¹³¹I treatment should be isolated in a separate closed ward for one week. This lack of social connection which has serious consequences, such as social isolation and interruption of important interpersonal relationships[23]. The present study shows that medical staff should pay more attention to such patients and mobilize social and family members to provide them with psychological support and emotional comfort. In addition, compared with patients without underlying diseases, patients with underlying diseases

tend to have higher levels of depression. First, patients with underlying diseases have higher medical costs than those without such conditions, and consequently exhibit a greater economic and psychological burden. Second, patients with underlying diseases often have severe physical pain and functional impairment, which can cause more severe depression than patients without such conditions[24]. In particular, this phenomenon is more common in patients with hypertension [25], cardiovascular disease[26], and brain edema[11]. Therefore, medical staff and family members should provide more care and companionship to such patients.

Notably, this was a single-center study with a small sample size and did not analyze the long-term concerns of the patients. The risk factors associated with anxiety in patients after DTC surgery must be further verified in large multicenter studies.

CONCLUSION

The anxiety scores of patients with DTC were higher after ¹³¹I treatment. Among them, female sex, no spouse, low education level, low family income, basic underlying diseases, and irregularity in taking medicine were influencing factors of anxiety and depression in these patients. In clinical practice, providing patients with targeted nursing interventions according to the aforementioned factors could decrease the risk of anxiety and depression and eventually improve patient prognosis.

ARTICLE HIGHLIGHTS

Research background

Patients were investigated using the self-rating depression scale (SDS) and self-rating scales (SAS). Patients were grouped according to the presence and degree of anxiety and depression. The influencing factors were analyzed, and the appropriate intervention was suggested.

Research motivation

Patients with differentiated thyroid cancer (DTC) after ¹³¹I treatment were more prone to anxiety and depression. Clinically, female patients with no spouse, low education level, and low family income, accompanied by basic diseases, and medication irregularity should receive intervention care, thereby reducing the risk of anxiety and depression and improving their prognosis.

Research objectives

The original mean score of SAS and SDS was 50.06 ± 16.10 and 50.96 ± 16.55 , respectively; 48.62% (70/144) and 47.22% (68/144) of the patients experiences anxiety and depression, respectively. Educational level, average monthly family income, and medication compliance influenced anxiety. Sex, marital status, and underlying diseases influenced depression ($P < 0.05$).

Research methods

We analyzed 144 patients with thyroid cancer after surgery who received ¹³¹I treatment in our hospital from June 2020 to December 2022. The patients were grouped according to their SDS and SAS scores. Single factor and multivariate analyses were used to determine the factors influencing anxiety and depression in patients with DTC after surgery.

Research results

It is crucial analyze the anxiety status and the related risk factors in patients with DTC after surgery, in order to formulate clinical preventive nursing strategies to improve the prognosis of patients.

Research conclusions

This study discussed the anxiety and depression status of patients with DTC after ¹³¹I treatment and analyzed their influencing factors.

Research perspectives

Patients with DTC do not comprehend ¹³¹I treatment, which is a type of internal radiotherapy, and they easily experience anxiety, fear, depression, and other negative emotions.

FOOTNOTES

Author contributions: Su YR designed and performed the study and wrote the paper; Zha JS designed the study and supervised the report; Su YR designed the study and contributed to the analysis; Yu XP, Huang LQ, and Xie L provided clinical advice.

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