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REVIEW

Influencing factors, prediction and prevention of depression in college students: A literature review

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Abstract

The high prevalence of depression among college students has a strong negative impact on individual physical and mental health, academic development, and interpersonal communication. This paper reviewed the extant literature by identifying nonpathological factors related to college students' depression, investigating the methods of predicting depression, and exploring nonpharmaceutical interventions for college students' depression. The influencing factors of college students' depression mainly fell into four categories: biological factors, personality and psychological state, college experience, and lifestyle. The outbreak of coronavirus disease 2019 has exacerbated the severity of depression among college students worldwide and poses grave challenges to the prevention and treatment of depression, given that the coronavirus has spread quickly with high infection rates, and the pandemic has changed the daily routines of college life. To predict and measure mental health, more advanced methods, such as machine algorithms and artificial intelligence, have emerged in recent years apart from the traditional commonly used psychological scales. Regarding nonpharmaceutical prevention measures, both general measures and professional measures for the prevention and treatment of college students' depression were examined in this study. Students who experience depressive disorders need family support and personalized interventions at college, which should also be supplemented by professional interventions such as cognitive behavioral therapy and online therapy. Through this literature review, we insist that the technology of identification, prediction, and prevention of depression among college students based on big data platforms will be extensively used in the future. Higher education institutions should understand the potential risk factors related to college students' depression and make more accurate screening and prevention available with the help of advanced technologies.

Key Words: Depression; Prediction; Prevention; Artificial intelligence; Big data; Machine learning

Core Tip: This study reviewed the extant literature by identifying nonpathological factors related to college students' depression, investigating the methods of predicting depression, and exploring nonpharmaceutical interventions for depression among college students. The influencing factors can be categorized into students' demographic characteristics, college experience, lifestyle, and social support. For the prediction of depression, methods such as machine algorithms and artificial intelligence have been employed together with the traditional psychological scales. This study summarizes general and professional measures that can be taken for the prevention and treatment of college students' depression.

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INTRODUCTION

The prevalence of depression among college students has gradually increased in recent years, even exceeding that of the general public, which has become a global phenomenon[1]. Mounting research has focused on the topic, and the consensus is that the high prevalence of depression among college students cannot be ignored. For instance, in Asia, a follow-up survey and analysis based on 1401 undergraduates in China over four consecutive years showed that approximately 20% to 40% of undergraduates suffered from depression, anxiety and stress to different degrees, and approximately 35% of them had higher depression levels than the normal population[2]. An online survey based on 7915 freshmen students at Hong Kong University in China showed that 21%, 41% and 27% of individuals had moderate or higher levels of depression, anxiety and stress, respectively, far exceeding the average in the general population[3]. The median prevalence rate for depression among 15859 college students in six ASEAN countries (Cambodia, Laos, Malaysia, Myanmar, Thailand and Vietnam) was 29.4%, and 7% to 8% of students committed suicide; despite the high prevalence of mental illness, their willingness to seek professional help was relatively low[4]. Among 642 college students in Saudi Arabia, the proportions of moderate depression, anxiety and stress were 53.6%, 65.7% and 34.3%, respectively[5]. In Africa, among 1206 Nigerian college students, 5.6% had mild depression, and 2.7% suffered severe depressive disorder[6]. In North America, 53% of 1455 American college students reported that they had experienced depression since the beginning of college, and 9% said they had considered suicide since the beginning of college[7]. Thirty percent of 7800 Canadian undergraduates reported that their psychological stress increased, and the degree of depression was significantly higher than that of the general population[8]. In Europe, more than one-third of college students from three higher education institutions in the United Kingdom suffered from long-term mental health diseases, the prevalence rate of which was higher than the average level of national surveys, and the scores of the eight dimensions of mental health, measured by the MOS 36-item short-form health survey, were all significantly lower than those of local peers aged 18 to 34[9]. In Oceania, 21.8% of 751 Australian college students reported depression, and their depression scores were higher than the standard scores of the general Australian population[10].

The global outbreak of the coronavirus disease 2019 (COVID-19) pandemic in 2020 brought in additional pressure and challenges for the prevention and treatment of depression among college students. Many reports worldwide voiced that college students had a greater probability of struggling with higher levels of depression after the pandemic. The data show that after the outbreak of the pandemic, acute stress, anxiety, and depressive symptoms were widespread among Chinese college students, and the incidence rate was significantly higher than before[11]. The prevalence rates of moderate depression and suicide-related symptoms among 212 Japanese college students were 11.7% and 6.7%, respectively[12]. Among 2031 American college students, 48.14% suffered from moderate to severe depression, 38.48% experienced moderate to severe anxiety, 18.04% had suicidal thoughts, and 71.26% reported that their stress/anxiety levels increased during the pandemic[13]. More than a quarter of Swiss university students had depressive symptoms during the pandemic, which was much higher than that of the general population and higher than that before the pandemic[14].

The transition from high school to university is full of tension and adaptation. It is a critical period for the shift from late adolescence to adulthood or emerging adulthood, which is neither adolescence nor young adulthood but theoretically and empirically distinct from both periods[15]. Arnett stressed that

this is a stage full of self-exploration, instability, possibility, self-focus, and something in between[16]. At this phase, individuals will face the challenges of identity and role transformation and more diversification and complexity from families and institutions. Specifically, compared with middle schools, universities put forward higher requirements for freshmen's independence and self-regulation, such as the independence of living in a new place, the autonomy of learning patterns, and the complexity of social networks. However, confronted with these challenges, college students entering the campus for the first time often wander between independence and dependence. On the one hand, they are eager to enjoy new freedoms; on the other hand, it is difficult to eliminate their attachment and economic dependence on their parents; thus, they are often in a state of "pseudo independence"[17].

In summary, compared with teenagers and adults, college students are the key group at significantly higher risk of poor mental health. A series of factors, including family, college, studies, and social interactions, are likely to induce college students' depression. However, few publications have reviewed the literature on risk factors for college students' depression. Given that most studies examined individual risk factors based on samples from a certain country or region, this paper reviewed the extant literature related to college students' depression and aimed to systematically present the nonpathological factors, predictions and nonpharmaceutical interventions for college students' depression to provide a reference for stakeholders worldwide.

NONPATHOLOGICAL INFLUENCING FACTORS OF DEPRESSION

The related factors can be roughly divided into four categories: biological factors, personality and psychological state, college experience, and lifestyle. The literature review presented the specific risk factors under four categories in Table 1. Subsequently, this paper explained certain factors with controversial research conclusions.

Sex

Some studies have asserted that the risk of depression in female college students is significantly higher than that in male students[24,26,40,41]. The possible mechanism lies in physiological differences between the sexes (such as genetic vulnerability, hormone, and cortisol levels), differences in self-concept, and different role expectations from society leading to different emotional responses and behavior patterns. Females are more likely to internalize their negative feelings, whereas males resort to externalizing behaviors such as smoking and alcoholism[42-44]. However, some analyses did not find significant sex differences[28,45,46]. Other studies have shown that men have a higher prevalence of depression[20,47]. This may be ascribed to their conservative attitudes toward mental health counseling and treatment under certain social expectations. For instance, women are more help-seeking than men and therefore tend to have more diagnoses and treatment. In particular, gregarious women are more likely to discuss their difficulties with others, such as family and friends, as a form of coping. Nevertheless, considering that societal expectations for men might be different, with those who express vulnerable emotions being regarded as weak, the depressive symptoms of men may manifest as anger and excessive indulgence in smoking and drinking, which are more acceptable masculine expressions in society[43,44].

Year of study

Most studies have found significant differences in the depression level of college students in different years of their education, although some found the difference to be insignificant[28]. Some research has suggested that undergraduates with lower grades suffer more from depression, which can be attributed to separation from relatives and friends, social adaptation, academic pressure, and increased investment in social activities. A survey of Chinese students showed that the highest scores for depression, anxiety and stress all appeared in the first three years of college, and students' mental health status was relieved in the fourth year with the passage of time[48]. A survey of medical students in Saudi Arabia found that students' depression levels continued to rise from the first year of enrollment, reached maximum intensity in the third year, and then dropped significantly with graduation in the last year[22]. However, other studies found that compared with other undergraduates, senior students had a higher risk of depression. The graduation year is a critical period for individuals to further their studies or go into society, and students are faced with many new stressors, such as graduation pressure, pressure from grades and applications to other institutions, difficulties in future career planning and employment discrimination in the labor market[49]. Compared with undergraduates, postgraduates may be exposed to greater pressure in obtaining financial security, stable employment, getting married and other aspects of life, which results in a higher risk of depression[19,41].

Lifestyle

The depression issues of college students can largely be attributed to their lifestyles. First, the lack of regular physical activities increases the risk of depression[11,14], particularly for individuals whose amount of weekly physical activity fails to meet the standards of the World Health Organization[20].

Table 1 Factors related to depression in college students

Category	Specific variable	Factor positively correlated with high levels of depression
Biological factors	Sex	Inconclusive
	Nationality	Ethnic minorities[18], international student[14,19]
	Family	Low family socioeconomic status[14,18,26,27]
		Non-only child[19], too many siblings[6]
		Parents divorced or having mental problems[29,30], family dysfunction[11]
		Adverse childhood experiences such as injury, physical violence, psychological abuse and lack of family care [30,31]
		Insufficient social support especially family support[11,14,36,39]
Personality and psychological state		Neuroticism[20]
		Presence of psychological illness[21,22]
		High level of psychological stress (including value, aspiration, deprivation, or coping)[23]
		Low self-efficacy[14,24]
		Solitude[25]
College experience	Year of study	Inconclusive
	Academic performance	Poor academic performance[21,30]
	Financial support	Lack of financial resources and support[21]
	Living arrangement	Do not have own room[6,26]
	College satisfaction	Low satisfaction with teachers and low satisfaction with college major[26], low satisfaction with university facilities[22]
Lifestyle	Physical exercise	Lack of physical exercise[11,14,20]
	Substance abuse	Smoking and drinking[6,12,21] (especially alcohol intake[32,33])
	Sleep	Daytime drowsiness[20,34], poor sleep quality[21], sleep too short[35] or too long[10]
	Diet	Unhealthy food intake[30], gluttony[14], skipping breakfast[10], malnutrition[36]
	Network usage	Social networking sites, online game addiction[37,38]

Second, substance abuse, such as excessive smoking, alcohol abuse[6,12,21], or alcohol intake[33], can cause depressive disorders, and it should be noted that their relationship might be bidirectional. Studies have shown that individuals with depression are more likely to drink obsessively to relieve their negative emotions due to their poor self-control, which will in turn trap them in a vicious cycle between excessive drinking and depressive disorders[32]. Third, unhealthy sleeping habits such as daytime sleepiness[20,34], poor sleep quality[21], and short[35] or long sleep duration[10] may lead to depressive symptoms. Fourth, unhealthy nutritional habits are also among the crucial factors that are strongly correlated with depression[36]. From the perspective of dietary structure and nutritional habits, individuals with depression often report excessive intake of high-fat snacks and margarine/butter/meat fat and inadequate intake of fruits, vegetables, and lean protein[30]. Overeating[14] and skipping breakfast[10], especially for males, are also related to depressive disorders.

Network usage

Relevant studies have indicated that depression in college students is associated with their time spent on the internet[50,51]. Those who suffer from internet addiction and dependence are more likely to struggle with depression[52], and phubbing (a portmanteau of the words "phone" and "snubbing") has been proven to be a mediator of the relationship between depression and problematic internet use[53], mainly focusing on social networking and entertainment[54].

Social software

Some researchers believe that social software, as a complementary mode of providing social support, can provide more help for people with low social support, thus reducing the occurrence of depression [55]. However, there is increasing recognition that social networks, especially the excessive use of social media, are closely related to depression[56-60]. Regarding the possible contributing factors, first, individuals who frequently use social software are more likely to have a fear of missing out, and they

are always worried that they will miss some important information if they do not refresh the social platform dynamics frequently. This persistent social anxiety will increase the risk of depression[61]. Second, college students who are addicted to social media are more likely to have a comparison mentality when checking the status updates of others on social network platforms, especially when they feel that others' lives are better than their own, which can result in symptoms of depression[62]. Third, it is quite impossible for those who struggle with depressive disorders to establish satisfactory interpersonal relationships in virtual space since they usually maintain poor relationships in the real world. The lack of expected support from social networks undoubtedly aggravates their depression[63].

In addition, because the COVID-19 pandemic has aggravated the depression of college students worldwide, we further analyzed the influencing factors of college students' depression against the background of the COVID-19 pandemic, apart from the general factors mentioned above: (1) Given that COVID-19 is highly contagious and uncertain, the higher risk of becoming infected with COVID-19 is closely related to individuals' level of depression. Research has indicated that individuals who live in high-risk areas for COVID-19, have close contact with the COVID-19 virus, or have acquaintances or relatives infected with COVID-19[19,41] often have a higher prevalence of depression; (2) Considering that the internet serves as the main channel for college students to obtain information about COVID-19, those who browse the internet for a short time will not suffer from too much anxiety because of the small amount of information they receive. Meanwhile, students surfing the internet for a long time will be able to obtain more accurate details about COVID-19, which can prevent misunderstanding relevant information. Nevertheless, individuals with shorter browsing times often have a higher risk for depression given that they may be easily misled by the rumors and have limited time to verify the authenticity of relevant information[64]; (3) Academic stress increases the degree of depression of college students with the closure of schools, the challenges of online courses and the risk of graduation delay[13,65]; (4) Financial pressures include the impact of the pandemic on family economic resources [49] and the increasing uncertainty of individuals about future employment[13]; (5) Environmental changes, home study, self-isolation, isolation from relatives and friends, decreased exercise frequency, uncertainty of school reopening, regular temperature measurement, wearing masks for a long time, cancellation of package deliveries and take-out supplies and other forced changes in daily study and living habits all increase the risk of depression among college students[13,49]; (6) There is less family support, social support and deteriorating family relations[65]; and (7) Social confidence wanes. Research has shown that the prevalence of depression also increases when individuals lack confidence in the government[66].

PREDICTING DEPRESSION

Traditional depression prediction methods are based on various self-rated psychological scales, such as the 21-item depression, anxiety and stress scale (DASS-21) and the self-rating depression scale (SDS). A growing body of research on the reliability and validity of the DASS-21 scale has been published from throughout the world (such as in Britain, Portugal, The Netherlands, Italy, the United States, and Nepal), all of which show that the DASS-21 is a mature tool that can accurately measure the symptoms of depression, anxiety and stress in adult clinical and nonclinical samples and identify and screen people at high risk of depression[67-70]. Similar to the DASS-21, the prediction reliability and validity of the SDS scale for depression have also been confirmed and recognized by relevant studies[71-73]. These are screening tools, and when elevated scores are detected, further evaluation is needed by a clinician. Moreover, the measurement often needs to rely on the patient's own active consultation and cooperation, which is costly, time-consuming, and inaccurate, and there is a risk of social stigma for patients. In recent years, with the progress of science and technology, a series of more advanced methods of depression risk prediction and identification, such as machine learning and artificial intelligence, has emerged, which can deeply learn all types of social and behavioral characteristics of people with potential mental illness risk based on big data and then accurately simulate, identify and predict who they are. Typical methods include support vector machines, decision trees, naïve Bayes classifiers, K-nearest neighbor classifiers and logistic regression[74]. More specifically, support vector machines are applied to classify handwritten digits and organize cancer tissue samples using microarray expression data[75,76]. Decision trees serve as a hierarchical classifier, employing certain rules to divide the predictor space. The naïve Bayes classifier is based on Bayes' theorem and is employed to predict class membership probabilities. K-nearest neighbor classifiers are instance-based learning classifiers that compare a new datapoint with the k nearest sample datapoints, regarding the class with the nearest neighbors to the new datapoint as the class of the datapoint. Logistic regression, as a probabilistic linear classifier, directly estimates class probabilities with the logit transform[74].

The gait feature analysis method based on machine learning has been developed as a supplementary tool to identify depression among college students. Relevant research found that the gait of depressed and nondepressed college students showed significant differences. The specific gait performance of depressed patients included reduced walking velocity, arm swing, vertical head movement and stride length, increased body sway and a slumped head posture. When the above series of features were

applied to classifiers with different machine learning algorithms, the accuracy of depression screening and recognition reached 91.58%[77]. A study collected 121 campus behaviors of college students, including basic personal information, academic achievements, poverty subsidies, consumption habits, daily life, library behaviors, and eating habits, and found that 25 campus behaviors are related to depression, such as failing exams, having bad eating habits, increasing night activities, decreasing morning activities, and seldom participating in social activities (such as eating with friends). On this basis, a depression recognition method was developed by combining machine learning algorithms[78]. There is also research and development of a machine learning method to identify depression based on college students' smartphone and fitness tracker data (*e.g.*, Bluetooth, calls, location, campus map, phone usage, steps, sleep), which extracts many features that can effectively identify depression, such as long-term inactivity and restless sleep at night; the recognition accuracy of this method for college students' depression can reach over 80%[79].

In addition, it is worth noting that social software has increasingly become a nonpathological risk factor for depression among college students. Addiction to social software is often more likely to induce depression, while college students at high risk of depression are more inclined to vent their negative emotions and relieve stress on various online social platforms. In this way, social network behavior analysis was developed based on machine learning as another effective way to identify and predict depression[80,81]. Through mining, emotion analysis and emotion recognition of personal user information data on social network platforms, we can capture the abnormal behavior patterns of people with depression, among which the most frequently used communication methods are text, emoticons, user log-in information and pictures. The selected research usually uses classic off-the-shelf classifiers to analyze the available information and combines words, such as National Research Council Canada (NRC) Word-Emoticon Association Lexicon, WordNet-Affect, Anew, and Linguistic Inquiry and Word Count tool. It is challenging to analyze the combination of temporal information and different types of information[82]. For example, some studies have conducted text analysis on the Sina Weibo data of Chinese college students. First, the behavioral differences between depressed and nondepressed individuals in language style, emoji usage, number of Weibos, followers and so on were obtained. Then, a deep neural network was applied to feature extraction and dimension reduction for college students with depression, and input data suitable for the classifier were constructed. Finally, a deeply integrated support vector machine was introduced to classify the input data, and more stable and accurate depression identification was realized[83]. Some studies collected historical behavior data of American college students using Google search and YouTube during the COVID-19 pandemic and found that there were strong correlations between depression and the following online behavior changes: long use sessions (multiple comprehensive activities with short time intervals), more online activities in the middle of the night or even staying up late, and searching for more authentic and realistic topics related to work, money or death, which verifies the feasibility of building a machine learning model based on individual behavior signals to predict college students' depression[84].

Generally, machine learning has been widely used in a series of mental health risk predictions about college students' depression, stress[85] and suicidal behavior[86,87]. Big data brings many benefits to the prediction of psychological states by reducing the subjectivity of human judgment or human operations to a certain extent and relieving the concerns of patients about possible social stigma and discrimination. In other words, big data and machine learning result in no prejudice in predictions. Thus, confirming depression through data and behavioral performance may be the developing trend in identifying and predicting depression among college students and an even broader population in the future. However, issues such as data privacy and data protection are unavoidable. The government needs to set stricter privacy protection policies, while a more extensive collection of personal data needs to be confirmed and approved by the collectors.

NONPHARMACEUTICAL PREVENTION OF DEPRESSION

Both general and professional measures for the prevention and treatment of depression were explored in this study. The former emphasizes the importance of multi-subject participation in the prevention and treatment of depression among college students, while the latter focuses on measures with the theoretical support of professional disciplines such as psychology.

General intervention measures

The general interventions are summarized in Table 2 and can be coarsely categorized into support from family, interventions by colleges and universities, cultivation of personal lifestyles, and resilience therapy.

High level of family support

A high level of family support can be used as a buffer against the influence of a high-stress reaction to prevent the development of depression[91]. In a study of 62 patients who recovered from depression, a high level of perceived emotional support from their families indicated that family support, especially

Table 2 General intervention measures

General intervention	Specific measures
High level of family support	Emotional support from family
Interventions by colleges and universities	Mental health services from the faculty, peers, and psychological counseling centers
Cultivation of healthy lifestyles	Proper physical exercise, healthy sleep and diet, and regular sun exposure
Resilience therapy	Self-healing for positive emotional and cognitive outcomes, and increasing life satisfaction and resilience[88-90]

emotional support, was very important for the relief and even rehabilitation of depression[92]. However, it should be noted that family support and perfect family functioning depend more on objective characteristics related to family socioeconomic status, such as parents' level of education[93]. In addition, some studies have found that the role family support plays in the prevention and treatment of depression also depends on the levels of perceived stress reactivity of individuals. Specifically, family emotional support can significantly alleviate the symptoms of depression when the perceived stress reactivity is low, but when the individual shows a high level of the perceived stress response, the effect of family emotional support in preventing depression will be greatly reduced[94].

The intervention from colleges and universities

Prior literature has shown that the faculties, peers, and social clubs on campus can help alleviate the negative effects of online games on depression. Students may seek social support from their teachers, peers, or psychological counseling centers to prevent addiction to online video games that may lead to depressive disorders[38]. Therefore, colleges and universities should build mental health services involving faculty, students, and psychological counseling centers. In addition, some studies have indicated that the implementation of related courses and projects in universities, such as resilience programs (including goal-building, mindfulness, and resilience skills), might be effective in improving college students' mental health[95].

Cultivation of healthy lifestyles

Apart from external support from family and intervention by higher education institutions, the prevention of depression also needs to rely on the patient's own efforts. Studies have shown that healthy lifestyles, including proper physical exercise, healthy sleep and diet, and regular sun exposure, can help prevent or reduce the occurrence of depression in college students[96]. For instance, students with a consistent sleep schedule and sufficient sleep duration are less likely to suffer from depression. Meanwhile, regular sun exposure aids in the synthesis of vitamin D in the body, which is crucial to release fatigue and change the negative moods that individuals with mild or moderate depression may experience[46]. Proper physical activities are also important for stress and depression relief among college students[97,98]. Additionally, improving diet and overall nutrition is also an effective way to treat depression[99]. In particular, eating breakfast on time helps reduce the risk of depression[46]. Certain nutrients, including zinc, magnesium, B vitamins, and cooking fats, have also been proven to be associated with depressive symptoms[100-102]. Therefore, colleges and universities can help prevent the occurrence of depression in college students by providing a regular diet with an adequate intake of vitamins and nutrients[103].

Resilience therapy

Some research has shown that resilience therapy can help individuals maintain mental health in the face of negative emotions and stressful events, thereby reducing the occurrence of depression[104]. Others have also found that it can reduce depressive symptoms by modulating the effects of timing and sleep quality on depression[105].

Professional intervention measures

Cognitive behavioral therapy, which aims to change individual thoughts and behaviors, has been the most widely used treatment method for depression thus far[106-110,113-115]. Mindfulness intervention programs[111] based on cognitive behavioral therapy and dialectal behavior group therapy[112] can effectively alleviate the depressive symptoms of college students.

In recent years, a growing number of online technologies have been applied to the treatment of depression among college students thanks to the rapid development of internet technology and mobile terminal devices[116-120], and some of the technologies were even skillfully combined with cognitive behavioral therapy[121,122]. For example, there are many apps that incorporate elements of cognitive behavioral therapy and mindfulness. A study from Switzerland revealed that apps such as MoodKit, MoodMission and MoodPrismying can successfully deliver ecological momentary interventions (EMIs) based on cognitive behavioral therapy principles to users through smartphones, thereby improving their well-being and effectively reducing the symptoms of depression. The study also noted that EMI

has been generally accepted by users of different ages, sex, educational backgrounds and occupations and is expected to provide scalable global mental health solutions[123]. Compared with behavioral cognitive therapy and online interventions, the efficacy of traditional educational/personalized feedback interventions in the past has been slightly inferior. Some projects have evaluated the effectiveness of mailing personalized standardized alcohol surveys for college students' depression prevention, but unfortunately, there is no obvious improvement[124].

LIMITATIONS

Limitations of this study include the following. First, this paper analyzed relevant literature written in English, but research in other languages, such as Chinese, Japanese, German, and Italian, was not included. Second, the paper is a narrative review of extensive studies including the influencing factors, prediction, and prevention of depression in college students. We did not undertake explicit methods such as systematic reviews, nor did we involve substantial clinical results and corroborate the evidence in prior literature such as retrospective reviews. The study merely presents studies in the pertinent field by summarizing their main conclusions, which cannot be directly applied to clinical treatment.

CONCLUSION

This paper reviewed the extant literature by identifying nonpathological factors related to depression among college students, investigating methods of predicting their depressive symptoms, and summarizing nonpharmaceutical interventions. The nonpathological related factors of college students' depression mainly fell into four categories: biological factors, personality and psychological state, college experience, and lifestyle. The outbreak of COVID-19 exacerbated the severity of depression among college students worldwide and posed grave challenges to the prevention and treatment of depression, given that the coronavirus spread quickly with high infection rates, changing the daily routines of college life and creating financial stress, academic stress, and long-term home isolation. Regarding the prediction of vulnerability to depression, machine algorithms and artificial intelligence based on big data have emerged in addition to the commonly used psychological scales. A series of big data, such as text, pictures, video and audio, based on individual social network behaviors was widely discussed and applied to identify and predict college students' depression. Regarding preventive measures, both general measures and professional interventions were discussed for the prevention and treatment of college students' depression, which required not only help from family, professionals, and institutions (cognitive behavioral therapy and online therapy) and society but also the individuals themselves through the cultivation of healthy habits.

Technology based on the internet and big data platforms will become more widely used in the future to identify, predict, and prevent depression among college students. Higher education institutions should clearly understand the potential risk factors related to college students' depression and employ advanced technology for more accurate screening and prevention. They should also work on increasing access to resources and clinical support considering the common difficulties in making appointments and long-term waits for psychological consultation.

Furthermore, this paper proposed two prospects for the future development of nonpharmaceutical interventions for college students' depression. First, the risk of stigma should be minimized. Many traditional precautionary measures are used to help students identify whether they suffer from depression, including e-mail, posters, campus activities, pamphlets, and first aid training courses about mental health. However, these measures may result in further concerns about the risk of stigmatization and psychological worries of students[125]. Therefore, in the future, we should avoid stigmatizing issues in the prevention of depression among college students and pay more attention to personalization and privacy in the development and application of precautionary measures. Second, the importance of general measures for the prevention and treatment of college students' depression should be combined with professional interventions such as cognitive intervention therapy and other evidence-based treatment. A meta-analysis showed that apart from cognitive behavioral therapy and mindfulness-based interventions, other measures, such as art, exercise, and peer support, are also effective in relieving depressive symptoms in college students[126].

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MINIREVIEWS

SARS-CoV-2 consequences for mental health: Neuroinflammatory pathways linking COVID-19 to anxiety and depression

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has been linked to an increased prevalence of mental health disorders, particularly anxiety and depression. Moreover, the COVID-19 pandemic has caused stress in people worldwide due to several factors, including fear of infection; social isolation; difficulty in adapting to new routines; lack of coping methods; high exposure to social media, misinformation, and fake reports; economic impact of the measures implemented to slow the contagion and concerns regarding the disease pathogenesis. COVID-19 patients have elevated levels of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α, and other inflammation-related factors. Furthermore, invasion of the central nervous system by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may potentially contribute to neuroinflammatory alterations in infected individuals. Neuroinflammation, a consequence of psychological stress due to the COVID-19 pandemic, may also play a role in the development of anxiety and depressive symptoms in the general population. Considering that neuroinflammation plays a significant role in the pathophysiology of depression and anxiety, this study investigated the effects of SARS-CoV-2 on mental health and focused on the impact of the COVID-19 pandemic on the neuroinflammatory pathways.

Key Words: Anxiety disorders; COVID-19 pandemic; Depression; Mental health; Neuroinflammation; Stress

Core Tip: The coronavirus disease 2019 pandemic has impacted the mental health of the population worldwide. This review summarizes the evidence of the role of neuroinflammation, either as a result of chronic stress caused by the pandemic or severe acute respiratory syndrome coronavirus 2 infection, in the development of anxiety and depressive disorders.

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INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared the outbreak of the coronavirus disease 2019 (COVID-19) as a pandemic[1]. More than two years have passed since the emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and its ramifications have changed human lives worldwide. In response to the COVID-19 outbreak, the scientific community has collaborated to provide information on all aspects of the disease, including the devastating sequelae in survivors. The pandemic has directly affected people through infections and resulted in increased psychological stress in the general population.

Several factors contributed to the psychological consequences of the pandemic in the affected population, such as poor knowledge about the disease, previously undiagnosed mental health disorders, lack of a healthy lifestyle, no prior mental health assessment, economic problems, changes in eating and sleeping habits, difficulty in adapting to new routines, lack of coping methods, high exposure to social media, misinformation and fake reports, and social isolation during quarantine[2,3]. Quarantine and lockdowns have severely impacted everyday life worldwide, ranging from student education to the immense workload on health professionals[4]. Social distancing has isolated people inside their houses and significantly impacted the economy[5-7]. People with an infected household or a close contact with COVID-19 patients or those with a history of chronic illnesses have been shown to a higher risk of developing psychiatric distress[8,9].

Another concern is related to patients hospitalized due to COVID-19. Hospitalized patients are at risk of experiencing depression, anxiety, insomnia, and delirium[10]. Among all sequelae resulting from the disease, those of psychopathological nature can be induced either directly through the invasion of the virus in the central nervous system (CNS) or indirectly as a consequence of systemic inflammation and immune response[11]. Neuroinflammatory alterations have been postulated to cause depression and anxiety[12]. Although there are several comprehensive literature reviews on the impact of SARS-CoV-2 on human health, in this minireview, we have discussed how neuroinflammation caused by chronic stress or SARS-CoV-2 infection can lead to anxiety and depression. We hypothesized that the neuroinvasion of SARS-CoV-2 in the brain, peripheral pro-inflammatory cytokines that may enter the brain after SARS-CoV-2 infection, and psychological stress associated with the pandemic, alone or in combination, could cause neuroinflammation and contribute to the development of anxiety and depression disorders.

COVID-19-RELATED STRESS AND THE HIGH PREVALENCE OF DEPRESSION AND ANXIETY

The increase in depression and anxiety during the COVID-19 pandemic has become a major health concern[2-4]. Depression and anxiety frequently co-occur and are prevalent and burdensome psychiatric disorders[13]. Depression was the second largest cause of disease burden in 2020[14-16] and has been projected to take precedence by 2030[17]. The most recent Atlas of Mental Health published by the WHO in 2020 revealed the indicators of mental health and Comprehensive Mental Health Action Plan, which has been extended till 2030 to assist individuals whose mental health has been affected by the COVID-19 pandemic[17]. Generally, anxiety disorders have a high annual prevalence at approximately 14%, with the United States and Europe presenting a higher rate than other areas[18,19]. One in four individuals is likely to develop or has already developed anxiety disorders[20]. Of note, the risk of developing anxiety and depression has been closely associated with exposure to chronic stress[21] such as that in the COVID-19 pandemic[22].

Coronaphobia, or excess anxiety about COVID-19, is strongly associated with elevated reports of depression, general anxiety, a lack of hope, and suicidal ideation[14,15,23]. A systematic review and

meta-analysis of 13 studies with a total of 33062 participants indicated a 23.2% and 22.8% prevalence of anxiety and depression, respectively, in healthcare workers in China during the beginning of the pandemic, with a higher prevalence in female nurses[4]. In addition, the prevalence of depression and anxiety has increased in the general population, especially in young adults. During the initial stages of the COVID-19 pandemic in the United States, at least one-third of participants in a cross-sectional study reported high levels of depression (43.3%), anxiety (45.4%), and post-traumatic stress (31.8%)[24]. These rates were higher than those found in a previous study conducted in 2009 using the same assessment tools, showing a prevalence rate of 6.2% among young adults aged 18–24 years and 13.1% among those aged 25–34 years[25]. These symptoms were also associated with loneliness and low resilience to stress, whereas a higher tolerance to stress was associated with lower anxiety. Family support has been previously associated with lower levels of depression and post-traumatic stress disorder[24].

Another Chinese study conducted in 2020 reported a four times higher prevalence of depression, anxiety, or both, than a study published in 2019 (20.4% in 2020 *vs* 4% in 2019)[26,27]. This study associated the development of depressive and anxiety symptoms with some common pandemic stressors, including worrying about oneself or loved ones being infected; concerns about income, jobs, school, and ability to pay loans; and hardships involving home quarantine in everyday life[26]. Depression and anxiety reported by Bangladeshi University students during the pandemic were associated with uncertainty about their academic or professional future and financial instability[28]. Early reports between mid-February and mid-March 2020 showed an increase of 34.1% in the demand for anxiolytic drugs, followed by 18.6% for antidepressants and 14.8% for sleep medications[29].

Studies on youth population have suggested that children and adolescents have also been affected by the pandemic. During the first year of the pandemic, one in four young adults experienced a clinical increase in depressive symptoms, with older children being the most affected. In addition, one in five children and adolescents had clinically elevated anxiety levels. The prevalence rates of depression and anxiety in children and adolescents increased over time and doubled compared to estimates before the pandemic according to a recent meta-analysis[30]. Further, the global prevalence of depression and anxiety increased by 25% and 27.6% due to the COVID-19 pandemic in 2020, indicating the negative impact of COVID-19 on the mental health of people of all ages worldwide[31].

NEUROINFLAMMATION AND PSYCHOLOGICAL MANIFESTATIONS

Several studies have shown that inflammation plays a key role in the pathophysiology of depressive disorders[12]. Preclinical studies have provided consistent evidence that exposure of rodents to chronic unpredictable and/or inescapable stress situations induces depressive-like behavior accompanied by peripheral and central activation of the immune, inflammatory, and oxidative and nitrosative stress pathways. Furthermore, chronic administration of antidepressants attenuates these effects[32]. Chronic stress can also induce neurotoxic effects on specific brain regions, either directly or indirectly, through the kynurenine pathway[33], causing a reduction in brain-derived neurotrophic factor with consequent impairment of adult hippocampal neurogenesis[32].

Individuals with depression present with high serum levels of pro-inflammatory cytokines and acute-phase proteins and an increased expression of adhesion molecules and chemokines[34-38]. These protein alterations suggest an association between depression and activation of pro-inflammatory responses. Depression has been associated with increased levels of peripheral and central tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, and C-reactive protein[34,37,39]. Furthermore, studies have reported an increase in the levels of other acute-phase proteins (*i.e.*, α-1-acid glycoprotein, α -1-antichymotrypsin, and haptoglobin) in the plasma of patients with depression[37,40-42]. Elevated levels of human macrophage chemoattractant protein-1, soluble intracellular adhesion molecule-1, and E-selectin have also been reported[43]. An apparent association between the severity of depressive symptoms and level of inflammatory mediators in the plasma of patients has also been shown[34,44]. In addition, functional variants of alleles of IL-1β and TNF-α genes influence different factors, either elevating the risk of depression or reducing the response to antidepressants[40,45,46].

Despite the frequent co-occurrence of anxiety and depression and their common association with cardiovascular[47] and metabolic diseases[48], the role of neuroinflammation in the pathophysiology of anxiety disorders has not been studied as extensively as that in depression[49]. Neuroinflammation may cause alterations in the structure or function of anxiety-related brain circuits (mainly the limbic and prefrontal regions), priming the brain to become vulnerable to anxiety disorders[33]. Studies have reported increased inflammation in patients of both sexes with late-onset anxiety disorder; however, they were unable to confirm it as an etiological factor[49]. Other studies have linked the immune system and CNS through key interactions that can influence behavioral changes; however, a causal relationship between anxiety and inflammation needs extensive investigation[49]. In preclinical studies, activation of the nucleotide-binding oligomerization domain-like receptor pyrin domain-containing-3 (NLRP3) inflammasome has been associated with anxiety-like behavior[50,51]. Clinical findings have suggested that increased cytokine levels affect neurotransmitters, such as monoamines and glutamate, in the amygdala, insula, and anterior cingulate cortex, which are brain regions related to anxiety[52].

Accordingly, inhibition of neuroinflammation has been accompanied by anxiolytic effects[51].

Increased levels of TNF-α, a cytokine important for cellular regulation and apoptosis, have been consistently associated with depression and anxiety in humans[53]. Similarly, central administration of TNF-α in mice resulted in depressive-like behavior, whereas TNF-α receptor 1 knockout mice exhibited antidepressant-like behavior in the forced swimming test and tail suspension test[54]. In addition, administration of TNF-α induced anxiety-related behavior in mice[55]. Administration of etanercept, a TNF-α blocker, reduced anxiety and depressive-like behavior in db/db mice exhibiting type-2 diabetes-related inflammation and mood alterations[56]. TNF-α blockade also caused an anxiolytic effect in mice with experimental autoimmune encephalomyelitis[55] and mice subjected to peripheral immune challenge with lipopolysaccharide[57]. Furthermore, administration of the TNF-α-neutralizing antibody infliximab in the basolateral amygdala reversed anxiety-like behaviors in mice with persistent inflammatory pain[58].

During the initial phases of inflammation, IL-6 is induced along with TNF-α and may represent a key inflammatory mediator in patients with COVID-19[59-61]. Similarly, IL-1β is the major cytokine (in association with IL-18) produced by the activation of the NLRP3 inflammasome and increases in depression. These cytokines modulate the neuroimmune pathways that regulate critical brain circuits involved in cognition, mood, and reward[62-64]. Notably, SARS-CoV-2 is postulated to directly activate the NLRP3 inflammasome, and patients with dysregulated NLRP3 inflammasome activity may develop COVID-19 with severe tissue damage and a cytokine storm[65].

Increased levels of pro-inflammatory cytokines such as IL-6 may repress brain-derived neurotrophic factor, contributing to the development of depressive behavior[66,67]. IL-6 is also associated with lymphocyte exhaustion, and its role in COVID-19 inflammation has propelled the use of IL-6 inhibitors, corticosteroids, antimalarial drugs, and intravenous immunoglobulin to oppose the effects of cytokine storms in individuals with COVID-19[68]. Therefore, a strong inflammatory response can be related to disease severity and death in patients with COVID-19[68]. In severely affected patients, increased levels of peripheral cytokines can cause lymphopenia and invasion of mononuclear cells in the heart, lungs, lymph nodes, spleen, and kidneys[69]. A study on COVID-19 survivors revealed elevated depression, anxiety, insomnia, post-traumatic stress disorder, and obsessive–compulsive symptoms one month after hospitalization[70]. These findings are consistent with those reported during the previous coronavirus outbreaks, in which 10%-35% patients in the post-disease recovery stage presented psychiatric comorbidities[10]. These psychiatric outcomes may be a consequence of neuroinflammation caused by COVID-19. Moreover, neuroimaging and CSF marker elevations in patients with COVID-19 have suggested that SARS-COV-2 causes CNS inflammation[71].

NEUROINVASION BY SARS-COV-2

Individuals infected with SARS-CoV-2 can remain asymptomatic or develop COVID-19 symptoms. Hospitalized patients with COVID-19 commonly present with clinical sequelae that appear up to three months after discharge[72]**.** These sequelae are not limited to respiratory issues because patients can manifest cardiovascular, neurological, and psychosocial symptoms after discharge[11,72,73].

The neurological symptoms after COVID-19 may be associated with direct SARS-CoV-2 invasion of the CNS, where the virus has a high potential for replication, causing significant neuronal death[74]. Patient autopsies have revealed neuronal loss[75], often associated with an immune response against the virus in the CSF. Few reports showed that patients who tested positive for SARS-CoV-2 in their CSF but did not have any significant risk factors or a history of neurological diseases manifested neurological symptoms, such as seizures and loss of consciousness[76].

Most *in vitro* and *in vivo* experiments support the hypothesis that neuroinvasion by SARS-CoV-2 causes neurological symptoms in patients with COVID-19. The presence of the virus within neurons in multiple brain areas of infected animals resulted in a neuropathology similar to that observed in hospitalized patients[77]. Importantly, these alterations are not limited to adult patients; children also manifest the same critical developments after COVID-19, including thrombosis, inflammation, and secondary tissue ischemia[78,79]. Severe COVID-19 is rarely reported in children; however, there have been reports of children who developed acute fulminant cerebral edema, severe encephalopathy, and ischemic stroke despite being previously healthy[80,81].

Animal experiments have provided detailed information regarding the neuroinvasive potential of SARS-CoV-2. A study by Song *et al*[74] revealed that SARS-CoV-2 infects animal lungs at early time points, while it infects the brain much later. In the same study, electron microscopy to identify viral particles sprouting from the endoplasmic reticulum indicated that the virus could use cellular machinery for replication. Unlike other neurotropic viruses such as Zika, SARS-CoV-2 causes metabolic changes in the brain, as demonstrated using human brain organoids[74].

The literature further suggests SARS-CoV-2 neuroinvasion occurs through the trans-neuronal route, especially during the early stages of infection, in which SARS-CoV-2 invades the brain *via* the cranial nerve pathways such as the olfactory, gustatory, and trigeminal nerves[77]. This infiltration route is also associated with the severity of infection and neurological manifestations that lead to a higher risk of

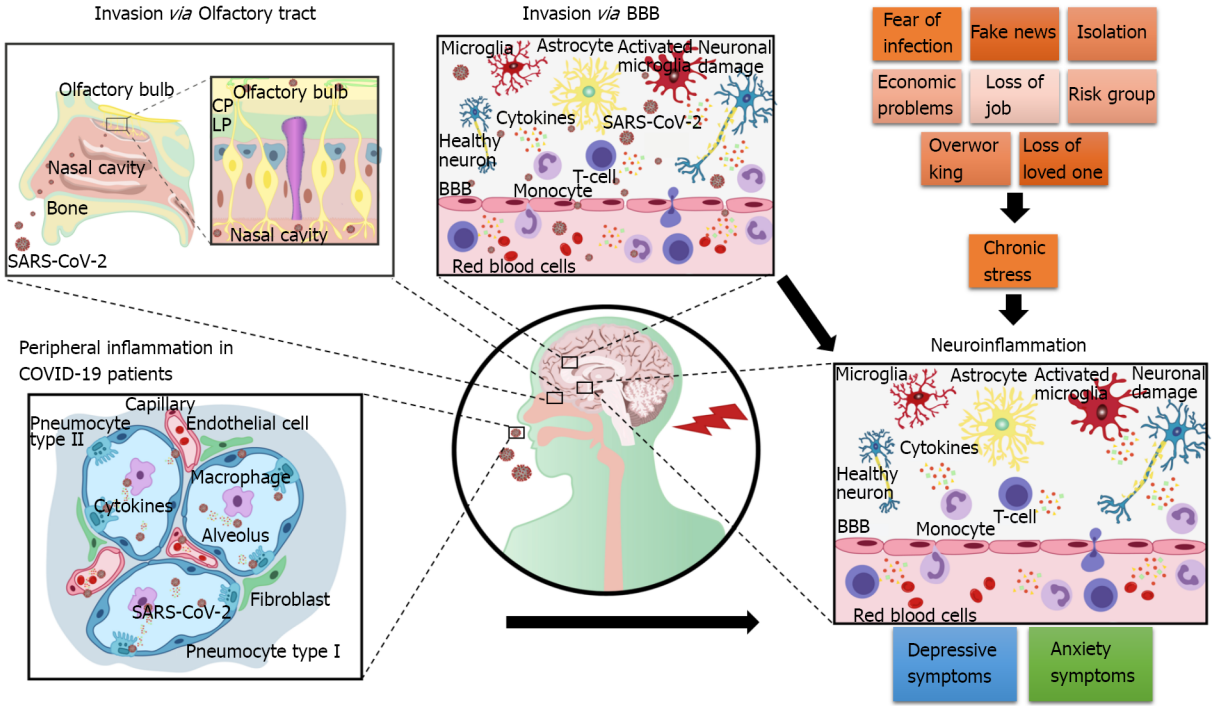

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Figure 1 Role of neuroinflammation in the development of anxiety and depressive disorders due to coronavirus disease 2019. Peripheral inflammation experienced by patients with coronavirus disease 2019 (COVID-19) and severe acute respiratory syndrome coronavirus 2 neuroinvasion, either *via* the olfactory tract or blood-brain barrier, contribute to neuroinflammatory alterations in infected individuals. Chronic stress resulting from several factors associated with the COVID-19 pandemic can also induce neuroinflammation. By activating astrocytes and microglia, causing neurotoxicity, and affecting synaptic plasticity and neurogenesis, neuroinflammatory alterations may play a role in the development of anxiety and depression. BBB: Blood-brain barrier; COVID-19: Coronavirus disease 2019; CP: Cribriform plate; LP: Lamina propria; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

mortality in patients with COVID-19. Liu *et al*[77] reported that death occurred only in infected animals with neurological deficits, suggesting that disease progression is associated with the severity of neurological impairment.

Involvement of the trans-neuronal route suggests that SARS-CoV-2 enters the CNS through the olfactory nerves *via* angiotensin-converting enzyme 2 (ACE2; a part of the renin-angiotensin-aldosterone system) present on the cell membrane. The virus then migrates through the neuroepithelium and reaches the brain, consistent with the loss of smell observed in patients with COVID-19[82,83]. This route of SARS-CoV-2 neuroinvasion has been demonstrated by Song *et al*[74] in mice overexpressing human ACE2[74]. Accordingly, COVID-19 respiratory distress has been associated with increased nasopharyngeal expression of ACE2 and transmembrane serine protease 2[84]. In addition, clinical studies and *post-mortem* analyses have reported the presence of viral antigens in the olfactory tract[85-88]. Magnetic resonance imaging examination of patients with COVID-19 revealed structural changes throughout the olfactory pathway, including the nerve, bulb, and cerebral cortex, and supports the olfactory bulb route hypothesis[83,89,90]. Immunostaining for SARS-CoV-2 in animal models has revealed extensive staining in these regions[91,92].

Another plausible entry route for SARS-CoV-2 could be through the blood-brain barrier (BBB) by binding to ACE2 on endothelial cells[82]. This route, previously linked to infected individuals with high fever, may cause cytokine storms and increase the BBB permeability[93,94], thereby facilitating the access of SARS-CoV-2 to the brain[95]. As a consequence of BBB impairment, peripheral immune cells can enter the brain, increase the release of pro-inflammatory cytokines by microglial cells and sustain neuroinflammation[96].

Finally, *post-mortem* studies have reported the presence of ischemic damage and microinfarcts in brain samples of patients with COVID-19, supporting the assumption of SARS-CoV-2 neuroinvasion into the CNS[74].

CONCLUSION

As illustrated in Figure 1, the increased prevalence of depression and anxiety during the COVID-19 pandemic may be attributed to SARS-CoV-2 neuroinvasion and its harmful consequences on the CNS. Depression and anxiety may also occur because of peripheral inflammation caused by the virus and

indirect negative effects on the brain function. Moreover, long-lasting social stressors linked to the pandemic may contribute to neuroinflammation and, consequently, to the development of these psychiatric symptoms. Therefore, anxiety and depression can affect the infected individuals and general population exposed to long-lasting pandemic stress. In the future, epidemiological studies should be conducted to elucidate the COVID-19 psychiatric burden, and public health control measures to help manage this burden must be provided.

FOOTNOTES

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MINIREVIEWS

Genetic variables of the glutamatergic system associated with treatment-resistant depression: A review of the literature

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Abstract

Depression is a common, recurrent mental disorder and one of the leading causes of disability and global burden of disease worldwide. Up to 15%-40% of cases do not respond to diverse pharmacological treatments and, thus, can be defined as treatment-resistant depression (TRD). The development of biomarkers predictive of drug response could guide us towards personalized and earlier treatment. Growing evidence points to the involvement of the glutamatergic system in the pathogenesis of TRD. Specifically, the N-methyl-D-aspartic acid receptor (NMDAR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor

(AMPAR), which are targeted by ketamine and esketamine, are proposed as promising pathways. A literature search was performed to identify studies on the genetics of the glutamatergic system in depression, focused on variables related to NMDARs and AMPARs. Our review highlights *GRIN2B*, which encodes the NR2B subunit of NMDAR, as a candidate gene in the pathogenesis of TRD. In addition, several studies have associated genes encoding AMPAR subunits with symptomatic severity and suicidal ideation. These genes encoding glutamatergic receptors could, therefore, be candidate genes for understanding the etiopathogenesis of TRD, as well as for understanding the pharmacodynamic mechanisms and response to ketamine and esketamine treatment.

Key Words: Genetics; N-methyl-D-aspartic acid receptor; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Treatment-resistant depression; Ketamine; Esketamine

Core Tip: Depression is a common mental disorder and one of the leading causes of disability worldwide. Up to 15%-40% of cases are considered treatment-resistant depression, which seems to be conditioned by environmental and genetic factors. The glutamatergic system, specifically N-methyl-D-aspartic acid receptor (NMDAR) dysfunction, has been proposed to be involved in the pathogenesis of treatment-resistant depression (TRD). A literature search was performed to identify studies on the genetics of the glutamatergic system in depression, focused on NMDAR and the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor. Our review highlights *GRIN2B*, which encodes the NR2B subunit of NMDAR, as a candidate gene in the pathogenesis of TRD.

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INTRODUCTION

Depression: An overview

Depression is characterized by sustained low mood, anhedonia, psychomotor inhibition and, frequently, somatic alterations that significantly affect an individual's functioning and, as such, poses a social and economic problem, as well as a health problem. It is, according to the World Health Organization, a common, recurrent mental disorder and one of the leading causes of disability and global burden of disease worldwide[1]. Thus, it has been highlighted as one of the priority conditions covered by the Mental Health Gap Action Programme. The 12-mo prevalence of major depressive disorder (MDD) is estimated to be approximately 6%[2], whereas the lifetime risk of depression is between 15% and 18%[3]. Thus, MDD is common, with almost one in five people experiencing one episode at some point in their lifetime. Between 2005 and 2015, the incidence of depression increased by 18.4% worldwide[4]. Regarding gender differences, the lifetime-incidence of a major depressive episode in females has been reported to be twice that of males[5].

Depression significantly affects family, social, and occupational functioning and is, therefore, a health, social and economic problem. A recent review calculated that the direct costs of depression, due to the higher use of healthcare services, may be up to 24,069€ *per* patient/year, depending on the jurisdiction wherein the analyses were performed[6]. Productivity losses, for their part, were estimated to be between 1963€ and 27364€ *per* person *per* year[6]. It is among the leading causes of loss of disability-adjusted life years, mainly in the age range between 10 and 49 years[7], and is the most frequently identified diagnosis in people who have died by suicide[8]. Thus, in recent years, depression has become a major target of public health policies[9,10] due to the consequences that both depression itself, as well as associated events such as suicide, have on society.

If depression is untreated or inadequately treated, it is associated with higher rates of medical morbidity, lower productivity, decreased life expectancy, higher rates of suicide, and higher rates of functional disability. However, sometimes, despite evidence-based treatment, the patient may not respond favorably to treatment. Even though we have a growing number of therapeutic alternatives available to treat depression, approximately half of patients do not respond, and up to two-thirds do not achieve remission after first-line treatment[11]. In this context, the development of biomarkers

predictive of drug response, which could guide us towards personalized treatment for each patient, is a challenge for the future.

TREATMENT-RESISTANT DEPRESSION

Although there is no consensus on the definition of treatment-resistant depression (TRD), it is a useful concept to characterize a group of patients with MDD that do not respond to traditional monoaminergic antidepressants. The European Medicines Agency considers TRD to be that which has not responded to two antidepressants of different classes, prescribed at adequate doses (within a therapeutic range), for the appropriate time (> 6 wk) and ensuring correct adherence to the protocol[12,13]. Some authors add that potentiation strategies, such as lithium, neuroleptic drugs, or electroconvulsive therapy, also need to have been used.

According to the well-known Sequenced Treatment Alternatives to Relieve Depression study, one-third of patients with depression could be classified as TRD, as they do not respond to two different antidepressant treatments[11]. Along the same lines, other works have described that 15%-40% of patients with MDD do not respond to multiple pharmacological treatments[14].

Patients with MDD are more likely to make attempts and/or complete suicide, as well as to experience more frequent relapses and hospitalizations, and to have a worse overall prognosis. In other words, they form a subgroup of depressive patients characterized by clinical severity and higher health and social costs[15].

Resistance to treatment seems to be conditioned by genetic and environmental factors[16]. The underlying genetic factors of individuals cannot be modified, but genetic information could be used to predict response and tailor treatments to the idiosyncrasies of each patient. Emerging evidence has shown that genetic variations associated with antidepressant responses appear to cluster in families, supporting the importance of these variations in the underlying mechanism of depression, especially in TRD[17].

Identifying biomarkers that can predict the antidepressant response could be helpful in designing the initial treatment, decreasing the need for trial-and-error testing, and also avoiding suffering and possible chronicity. Single nucleotide polymorphisms (SNPs) have been suggested to be a decisive factor in the antidepressant response; numerous genetic polymorphisms have been described as possible risk factors for MDD and TRD[18-21].

GENETICS OF DEPRESSION

Albeit a clinically heterogeneous pathology, there is consistent evidence, based on twin and adoption studies, that there is a heritability of 29%-49% in MDD (reviewed in[22]). Research has also been performed to identify more genetically homogeneous groups of MDD, indicating that clinical severity, the need for certain therapeutic strategies, recurrent episodes, and postpartum depression show differences in heritability[23,24].

It is a polygenic disease caused by the combined effect of polymorphisms, common to the general population, in different genes[25]. The genetics of depression has been studied for years *via* a candidate gene approach, mainly focusing the study on genes involved in the serotonergic, noradrenergic, and dopaminergic pathways, targets of the usual treatments[26-28]. A recent literature review of 18 candidate genes showed that most of the studies performed lacked sufficient statistical power and, thus, questioned previous depression candidate gene findings[29]. More recent work has begun to focus on the glutamatergic pathway as a candidate in the study of genetic factors involved in depression[30].

In recent years, genome-wide association studies (GWAS) have proliferated in an attempt to identify genes involved in various pathologies, including depression. A recent GWAS identified 102 independent variants, 269 genes, and 15 gene-sets associated with depression, including both genes and gene pathways associated with synaptic structure and neurotransmission, providing further evidence of the importance of prefrontal brain regions. A previous GWAS implicated voltage-gated calcium channels, the D2 dopamine receptor and, interestingly, glutamate receptors[31]. The authors stated that all humans carry a lesser or greater number of genetic risk factors for MDD.

Along this line, many authors have investigated the interaction between genetics and environment in the pathogenesis of depression. Recent reviews concluded that various genetic polymorphisms in the serotonergic system moderate the association between adverse childhood experiences and depression [32], and that early-life stress produces transcriptomic changes that are moderated by the female sex[33].

Finally, postmortem studies have also been conducted to investigate differential gene expression in human brains. *GluR* gene expression in the dorsolateral prefrontal cortex has been studied in small postmortem cohorts of MDD subjects and controls, with inconclusive results to date[34,35]. Nonetheless, the data seemed to indicate a fundamental dysfunction of the glutamatergic system in the frontal cortex in MDD[36].

THE GLUTAMATERGIC SYSTEM AND TRD

The neurotransmitter systems most studied in the etiopathogenesis of depression have been the serotonergic, noradrenergic, and dopaminergic systems, which are targeted by the most commonly used antidepressant drugs. However, another system involved is the glutamatergic system. Glutamate exerts its action *via* ionotropic receptors [N-methyl-D-aspartic acid receptor (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), and 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine kainate receptors (KAR)] and metabotropic receptors. In the last two decades, the glutamatergic system, specifically NMDAR dysfunction, has been shown to be involved in the pathogenesis of TRD[37]. In particular, NMDAR antagonism has been highlighted, marking it a target of numerous drugs indicated for TRD[38], such as ketamine and esketamine[39,40].

Intravenous ketamine and intranasal esketamine, rather than inhibiting, activate glutamate release [41], resulting in a rapid antidepressant effect, a prompt disappearance of suicidal ideation[42,43], and a reduction of anhedonic symptoms[44]. This emerging hypothesis suggests that NMDAR antagonism in GABAergic interneurons (the mechanism of action of ketamine and esketamine) leads to glutamate release[45]. Regarding this gamma-amino butyric acid (GABA)-glutamate neurotransmitter system, animal and human studies have described that intravenous ketamine administration reduces GABA concentration in several brain areas, such as the frontal cortex[45-47].

Treatment with ketamine and esketamine has proven particularly useful in cases of TRD[48], thus their mechanism of action in glutamatergic pathways, being the major difference with respect to usual antidepressant treatments, is an interesting starting point for understanding the etiopathogenesis of TRD.

Central glutamatergic activity is measured at the peripheral level *via* plasma levels of glutamate (pGlu) and GABA (pGABA). pGlu and pGABA levels have been described to significantly correlate with cerebrospinal fluid glutamate levels[49,50], indicating that, although the plasma levels assessed derive from both the brain and the periphery, the plasma levels of these amino acids reflect brain concentrations[51]. Previous studies reported altered levels of pGlu in blood, cerebrospinal fluid, and prefrontal, frontal, and occipital cortical areas of patients with depression compared with healthy volunteers[52-55].

In relation to GABA, as a neurotransmitter system closely related to the glutamatergic, a recent meta-analysis indicated a decrease in pGABA levels in patients with depression compared with healthy controls, although the heterogeneity was significant[56].

All these findings indicate that alterations in the glutamatergic system may play a key role in the development of TRD. Therefore, it has been proposed that genes involved in glutamatergic transmission could be candidate genes to explain the neurobiological basis of TRD, *i.e.*, genetic risk factors for the development of depression, especially TRD[55,57].

GENETIC VARIABLES OF THE GLUTAMATERGIC SYSTEM ASSOCIATED WITH TRD

Literature search

A literature search was performed to identify studies regarding the genetics of the glutamatergic system in depression. A total of 118 articles, published up to October 15, 2021, were retrieved from the PubMed and Reference Citation Analysis (https://www.referencecitationanalysis.com/) databases using broad search terms in order to identify as many potentially eligible studies as possible: [(NMDA receptor OR AMPA receptor) AND gene* AND depression]. An age filter was added: "Adults: 19+ years". Studies were included according to three criteria: (1) They investigated the influence of genetics/epigenetics on glutamate receptors in depression; (2) They were systematic reviews, meta-analyses, narrative reviews, or original research studies; and (3) They were written in English or Spanish. The reference lists of the selected studies and reviews were also checked to identify additional relevant articles using a snowballing approach. Finally, 46 papers were included in the review.

This is not a systematic review, but a narrative one; it summarizes the findings described in the selected reports and, in this way, provides an overview of the subject. The main results are summarized in Table 1.

NMDA receptor

NMDAR, indicated as a therapeutic target in TRD[58], consists of four subunits (Figure 1). Two of them must be the NR1 subunit, mandatory for the receptor to be functional, while the other two subunits can be any of the four NR2 subunits (NR2A-D), or two NR3[59]. The NR2A-D subunits bind glutamate[60]. These subunits are encoded by the *GRIN1*, *GRIN2A-D*, and *GRIN3* genes[61,62].

NR2B subunit: The GRIN2B gene

Associations between the functionality of these subunits and depression or response to antidepressant molecules were mostly found with the NR2B subunit. This is encoded by the *GRIN2B* gene, which is located on chromosome 12p12 and consists of 13 exons. Three potentially functional SNPs have been

Table 1 Summary of studies on main candidate genes of the glutamatergic system related to depression

Receptor	Gene	Marker	Ref.	Result
NMDA	*GRIN2A*	rs16966731	Chen *et al*[79], 2021	T allele associated with antidepressant effect of ketamine
	GRIN2B	rs1805502	Zhang *et al*[69], 2014	G allele associated with TRD
			Arnold *et al*[70], 2009	GT haplotype increased risk of TRD
		rs890	Zhang *et al*[69], 2014	C allele associated with TRD
			Arnold *et al*[70], 2009	
		rs2268115	Sokolowski *et al*[72], 2013	Associated with suicide attempts
		rs220557	Sokolowski *et al*[72], 2013	Associated with suicide attempts
AMPA	*GRIA2*	rs4302506	Chiesa *et al*[91], 2012	C allele associated with a lower age of onset in MDD
		rs4400397	Chiesa *et al*[91], 2012	C allele associated with a lower age of onset in MDD
	GRIA3	rs4825476	Laje and McMahon[17], 2007	G allele associated with suicidal ideation
Kainate	*GRIK4*	rs1954787	Horstmann *et al*[94], 2010	CC haplotype associated with response to antidepressants
			Serretti *et al*[95], 2012	No significant associations
		rs12800734	Horstmann *et al*[94], 2010	GG haplotype associated with response to antidepressants
			Serretti *et al*[95], 2012	No significant associations

NMDA: N-methyl-D-aspartic acid; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; TRD: Treatment-resistant depression; MDD: Major depressive disorder; T: Thymine; G: Guanine; C: Cytosine.

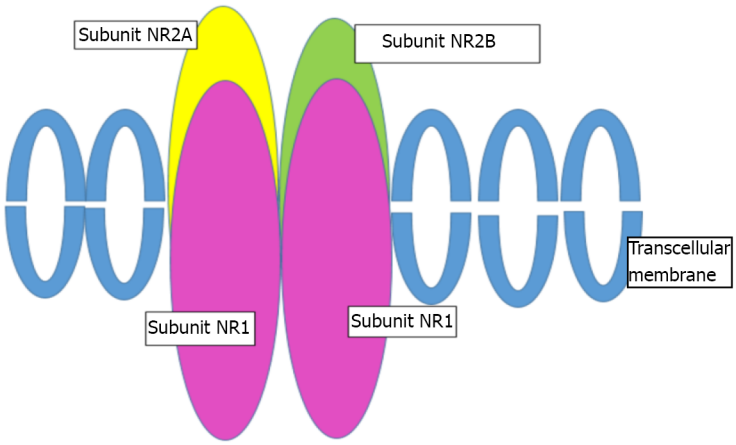

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Figure 1 Structure of the N-methyl-D-aspartic acid receptor, which consists of four subunits [NR1, and either two of the four NR2 subunits (NR2A-D) or two NR3].

identified in this gene, all located in the 3'-untranslated region (UTR) that governs gene expression: rs1805502 (A to G), rs1806201 (T to C), and rs890 (A to C). They may contribute to the regulation of *GRIN2B* gene expression and influence glutamate release activity in the brain.

Ketamine users have also been reported to have a higher frequency of the rs1806201 TT genotype and a lower frequency of the CC genotype than controls, suggesting that this polymorphism may play a role in ketamine abuse[63]. Clinical trials report the superior therapeutic efficacy of NMDAR NR2B subunit antagonists over conventional antidepressants in patients with TRD[64,65].

Different GWAS have revealed a relationship between SNPs in the *GRIN2B* gene and depression[38,66,67]. *In vivo* studies evaluating glutamatergic activity at the brain level have shown that carriers of the rs1805502 G, rs1806201 T, or rs890 C allele have decreased glutamate concentrations in the anterior cingulate cortex. These alleles have been related to several psychiatric disorders[68-70], suggesting that they be a risk factor (genetic predictor) for TRD[69] in MDD patients. Recently, in a preclinical study in

transgenic mice with selective mutations in the NR2B subunit in GABAergic interneurons, deletion of NR2B was found to block the antidepressant action of ketamine[71].

These *GRIN2B* gene polymorphisms have been described both as risk variables for MDD and predictors of TRD. An association was reported between the GT haplotype (rs1805502-rs890) and increased TRD risk compared with controls, as well as between the rs1805502 G allele and TRD (compared with non-resistant depression)[69].

A GWAS-based study reported a significant association between GRIN2B and suicide attempts, as well as a gene-environment relationship with a history of physical abuse in childhood and adolescence, which also increases the risk of suicide[72]. Indeed, they found that *GRIN2B* and *ODC1* (encoding ornithine decarboxylase, a rate-limiting enzyme of the polyamine synthesis pathway) seem to be associated with severe suicide attempts, as well as with serious physical assault in childhood and adolescence[73,74], which in turn increases the risk of suicide attempts, thereby configuring a gene-by-environment interaction.

Finally, human postmortem studies found *GRIN2B* expression to be higher in suicidal MDD patients, compared with non-suicidal MDD patients[36], and in the locus coeruleus of depressed individuals[75]. It is therefore postulated that *GRIN2B* mRNA level may be a biomarker of suicide; indeed, *GRIN2B* genetic polymorphisms in MDD have been reported to predict treatment resistance, suicide attempts, and reasoning ability[72].

Based on the data described, *GRIN2B* is considered a promising candidate gene for MDD susceptibility, and more specifically for TRD, supporting the contention that TRD can be classified as a specific subtype of MDD[69].

Other NMDAR subunits: GRIN1, GRIN2A, C, and D, and GRIN3

Regarding other NMDAR subunits, postmortem studies in rodents using depression models have observed that chronic stress, besides increasing NR2B subunit mRNA, also increases NR1 and NR2A in several brain regions[76,77]. Postmortem studies in humans reported higher expression levels of GRIN1 and GRIN2A in the brains of depressed patients than in controls, and of GRIN2B in suicidal compared with non-suicidal MDD patients[36,78]. Likewise, the *GRIN2A* rs16966731 polymorphism (T to C, intron area) has been associated with the rapid and persistent antidepressant effect of ketamine[79]. Chandley *et al*[75] also reported altered expression of the *GRIN2C* gene at the locus ceruleus in depressed patients [75]. Finally, one paper reported that women with MDD had higher expression levels of all the NMDAR subunit genes; the only one not reaching statistical significance was GRIN3A[36].

From a gene-environment interaction perspective, an epigenetic study showed that *GRIN1* methylation was a significant predictor of depression in a sample of abused children[80]. In one study, *GRIN2A* hypermethylation in the hippocampus and prefrontal cortex in postmortem studies was related to overexpression of the GluN2A subunit[81,82]. Interestingly, maternal separation increases the expression of this subunit in the hippocampus of adult rats, but not of subunit 2B. Numerous rat stress models have evaluated GRIN1A, GRIN2B, and GRIN2A with results similar to those described above [77,83,84].

AMPA receptor: The GRIA2 and GRIA3 genes

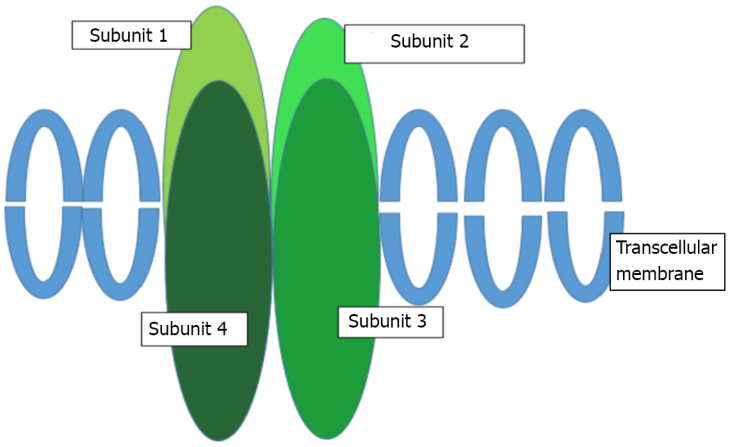
AMPARs are transmembrane ionotropic glutamatergic receptors and the main receptors mediating rapid synaptic neurotransmission in the brain. They consist of four subunits (GluR1-4) encoded by four genes (*GRIA1-4*)[85] (Figure 2). Evidence also suggests that the antidepressant mechanism of action of ketamine and esketamine involves the activation of AMPARs, with a subsequent increase in brain-derived neurotrophic factor levels (usually reduced in patients with depression)[45], as has been observed in rodent models[86]. Therefore, AMPARs have been proposed to play a key role in the antidepressant effect associated with ketamine[87].

Ketamine and its enantiomer, esketamine, lead to the disinhibition of glutamatergic neurons that modulate AMPARs by antagonizing the NMDAR of GABAergic interneurons[45,88]. In addition, ketamine metabolites such as hydroxynorketamine seem to exert their antidepressant effect *via* AMPAR activation[84,89].

In mouse models reproducing depression and stress, increased expression of AMPARs has been observed[76,90]. Postmortem studies described increased GRIA2-4 expression in the prefrontal cortex of MDD patients *vs* controls[36], and of GRIA3 in suicidal *vs* non-suicidal patients with MDD. As regards the *GRIA2* gene, several authors have observed an association between carriers of the C allele (rs4302506; C to T, located in the coding exon) and carriers of the T allele (rs4400397; C to T, 3'-UTR), and a lower age of MDD onset[91]. Also, the G allele (rs4825476; G to A, intron 3) of the *GRI3A* gene has been associated with suicidal ideation in patients with major depression treated with monoaminergic antidepressants[17]. The AMPAR subunits GluA2-4 had significantly higher expression in female MDD patients[36].

Other glutamatergic receptors associated with treatment response

Animal studies have suggested that ionotropic glutamate receptors play a role in the action of antidepressant drugs[92,93]. Another widely investigated gene is *GRIK4*, which encodes subunit 4 of the ionotropic glutamate KAR. Here, an association was observed between the rs1954787 polymorphism



DOI: 10.5498/wjp.v12.i7.884

Figure 2 Structure of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, which consists of four subunits (GluR1-4).

and antidepressant response[94]; however, the *GRIK4* polymorphism with the highest predictive value for treatment outcome was rs12800734. Nonetheless, these findings have not been replicated in other studies, probably due to design differences[95]. Existing data also revealed increased expression of the KAR subunits, GluK1 and GluK2. In addition, the strongest predictor of suicide was GRIK3 (GluK3) expression in both sexes[36]. KARs appear to regulate L-glutamate release by functioning as facilitatory or inhibitory autoreceptors during repetitive synaptic activation. The KAR activity may contribute to excitotoxic cell death; however, the role of these receptors in the dorsolateral prefrontal cortex of MDD subjects remains to be elucidated. Genetic variation in *GRIK3* has been associated with recurrent MDD [36].

In addition to ionotropic glutamatergic receptors, metabotropic receptors have also been involved in the genesis of MDD. Increased expression of *GRIN1, GRIN2A-D, GRIA2-4, GRIK1-2, GRM1, GRM4, GRM5*, and *GRM7* has been observed in female MDD patients. In contrast, *GRM5* expression was lower in male MDD patients relative to male controls. When suicidal MDD patients were compared with non-suicidal patients, *GRIN2B, GRIK3,* and *GRM2* were expressed at higher levels in suicidal patients[36]. Recent studies showed that mGluR4 regulation is altered in male suicidal individuals, leading to higher expression of mGluR. Higher expression levels of the mGluR2 encoding gene, *GRM2*, were also detected; *GRM2* has been proposed as a biomarker of suicide[36].

Repeated stress in male rats has been reported to be associated with lower expression of AMPARs and NMDARs, and, also, with a lower activity of these receptors. In contrast, in female rats exposed to stress, the expression of AMPARs and NMDARs was normalized *via* the activation of estrogen receptors, resulting in a neuroprotective and procognitive effect[96]. The authors proposed that, in female patients, estrogenic activity may lead to a differential response to ketamine; it should be noted that two-thirds of MDD patients are women.

Finally, there is downregulation of metabotropic receptors in mice reproducing models of depression, especially in the mGlu2 subunit, which is completely restored by ketamine administration[97].

LIMITATIONS AND STRENGTHS

The main limitation of this review is the scarcity and heterogeneity of the literature available on the topic. Few studies have employed similar methodology and, thus, there is limited replication of the described findings. Due to the small number of studies, all research conducted in humans and animals has been included in the review, although the extrapolation of the results, in this case, is limited. As we have noted, this is a narrative review, and limitations inherent to this type of review should also be mentioned: Study selection, data extraction, and synthesis were not protocol-based and, thus, could be prone to bias.

Nonetheless, it should also be noted that this is the first review, to our knowledge, of this specific topic, making it possible to summarize the current state of the art, highlighting the need to advance research in this field.

CONCLUSION

Patients with TRD often experience long periods of therapeutic trials with different antidepressant

medications, resulting in a worse outcome, a delay in symptomatic remission, and an increased risk of fatal events, such as suicide. Therefore, the management of TRD with appropriate therapy could be facilitated by the identification of biological markers of TRD, which could guide treatment choice from the outset.

Although the serotonergic, noradrenergic, and dopaminergic pathways were those historically studied, more recent work indicates the involvement of the glutamatergic pathway. This proposal is consistent with new therapeutic strategies in TRD, such as ketamine and esketamine, which act mainly on glutamatergic receptors.

Our review highlights *GRIN2B*, which encodes the NR2B subunit of NMDAR, as a candidate gene in the pathogenesis of TRD. In addition, several studies have associated genes encoding AMPAR subunits with symptomatic severity and suicidal ideation. These genes encoding glutamatergic receptors could, therefore, be candidate genes for understanding the etiopathogenesis of TRD, as well as for understanding the pharmacodynamic mechanisms and response to ketamine and esketamine treatment. However, further empirical work is required to replicate the observed associations and to confirm the involvement of these genes in the pathogenesis of TRD.

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MINIREVIEWS

Social media and schizophrenia: An update on clinical applications

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Abstract

Social media has redesigned the landscape of human interaction, and data obtained through these platforms are promising for schizophrenia diagnosis and management. Recent research shows mounting evidence that machine learning analysis of social media content is capable of not only differentiating schizophrenia patients from healthy controls, but also predicting conversion to psychosis and symptom exacerbations. Novel platforms such as Horyzons show promise for improving social functioning and providing timely access to therapeutic resources. Social media is also a considerable means to assess and lessen the stigma surrounding schizophrenia. Herein, the relevant literature pertaining to social media and its clinical applications in schizophrenia over the past five years are summarized, followed by a discussion centered on user feedback to highlight future directions. Social media provides valuable contributions to a multifaceted digital phenotype that may improve schizophrenia care in the near future.

Key Words: Social media; Schizophrenia; Digital phenotype; Facebook; YouTube; Instagram

Core Tip: Recent literature demonstrates that social media data analysis guided by machine learning can differentiate users with schizophrenia from healthy controls as well as predict conversion to psychosis and symptom exacerbations. Novel platforms such as Horyzons can improve social functioning in schizophrenia patients, but long-term engagement is a challenge that may be addressed by streamlining the user experience.

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INTRODUCTION

Although the increased prevalence of social media has already transformed daily life, these platforms are poised to further improve the management of various medical conditions. Schizophrenia presents a unique opportunity for advancement in diagnosis and management. Prior studies have established the feasibility and acceptability of social media in patients with schizophrenia[1-3], and the recent research discussed within this article demonstrate that potential benefits are within reach.

The intrinsic sociality of social media platforms such as Facebook and YouTube offers the capability to not only assess and reform the stigma surrounding the condition, but also provides a manner of communication and community that may be more agreeable to individuals with schizophrenia who are likely to self-isolate.

The aim of this article is to review the recent literature on social media with a focus on clinical applications in schizophrenia. A literature search for (social media) AND [(psychosis) OR (schizophrenia)] was conducted on PubMed and Reference Citation Analysis (https://www.referencecitationanalysis.com/) from 2017 to present, and the most relevant articles were selected for discussion. The contributions of the subsequent studies to schizophrenia diagnosis and clinical management will be reported, followed by a discussion on future directions that details necessary changes and further avenues of research that may augment the promising advances in schizophrenia management.

SOCIAL MEDIA

Diagnosis

The content of several social media platforms was analyzed, and findings will be organized by platform in consideration of the inherent differences between media types (*i.e.*, typed posts on Facebook, Twitter, Reddit; visual content on Instagram). These findings are summarized in Table 1.

Kelly *et al*[4] performed a study that offers insight into the clinical utility of Facebook posts. Blinded clinical raters assessed eight participants with schizophrenia, seven with depression, and eight health controls using symptom severity scales, including the Brief Psychiatric Rating Scale for psychotic symptoms and the Community Assessment of Psychotic Experiences for global functioning. The clinical raters included psychiatrists and other mental health clinicians, who rated participants on the corresponding scales by both de-identified Facebook posts and in-person assessments. The ratings for the Facebook posts were significantly correlated with in-person assessments across all three categories of psychotic symptoms, depressive symptoms, and global functioning. These results validate the clinical relevance of social media posts.

Birnbaum *et al*[5] analyzed Twitter posts by combining clinical appraisals with machine learning and found significant linguistic differences between individuals who self-disclosed as having schizophrenia from healthy controls. The clinicians evaluated the self-disclosed Twitter users' posts to determine authenticity of the diagnosis. Their appraisals were used to strengthen the machine learning algorithm to achieve an accuracy of 88% in identifying users with schizophrenia. In addition, the schizophrenia group were found to have significantly greater use of interpersonal pronouns, decreased attention on friendship, and increased preoccupation with biological processes. In other studies, machine learning analysis of Twitter posts have also revealed that users with schizophrenia are more likely to tweet about depression, anxiety, and suicidality than control groups, which highlights the importance of social media as a facet of digital phenotyping that may lead to earlier detection of symptoms[6,7].

Machine learning has been found to be similarly capable of identifying users with schizophrenia with up to 93% accuracy in Rezaii *et al*[8], in which 30000 Reddit posts were analyzed. The authors emphasize that low semantic density and content about voices and sounds were essential factors in predicting conversion to psychosis. Although outside the scope of the present discussion, the study used a

Table 1 Summary of findings across social media platforms related to schizophrenia diagnosis

Ref.	Social media platform	Findings
Kelly *et al*[4]	Facebook	Blinded clinical raters assessed Facebook posts using standardized symptom scales that correlated with in-person assessments
Birnbaum *et al*[5]	Twitter	Combined clinical appraisals with machine learning to achieve accuracy of 88% differentiating users with schizophrenia from controls
Hswen *et al*[6, 7]	Twitter	Users with schizophrenia tweet more frequently about depression, anxiety, and suicidality
Rezaii *et al*[8]	Reddit	Low semantic density and content about voices and sounds in users' posts were core variables in differentiating users with schizophrenia
Bae *et al*[9]	Reddit	Machine learning differentiated users with schizophrenia through increased third person plural pronouns, negative emotion words, and symptom-related topics
Kim *et al*[10]	Reddit	Machine learning able to analyze users' posts and categorize into range of psychiatric diagnoses
Hänsel *et al*[11]	Instagram	Users with schizophrenia spectrum disorders found to have significantly lower saturation, colorfulness, and decreased number of faces in posted images

mathematical method called vector unpacking that breaks down the meaning of a sentence into a simplified set of core ideas. Further expanding on linguistic features, Bae *et al*[9] used machine learning and Reddit posts focusing on schizophrenia to highlight significant differences from the control group, including increased frequency of third person plural pronouns, words representing negative emotions, and topics related to their symptoms. Lastly, Kim *et al*[10] was likewise able to use machine learning to tie the contents of user posts in Reddit mental health communities with schizophrenia, but expanded its classification to include a range of diagnoses including depression, schizophrenia, borderline personality disorder, and autism. All the above studies demonstrate that social media posts can be used to differentiate schizophrenia patients from healthy controls, forming the foundation for diagnostic relevance in the future.

In addition to the linguistic features of social media posts, the clinical utility of visual content on Instagram has also been explored. Hänsel *et al*[11] extracted image features such as color composition and the number of faces depicted from nearly 12000 Instagram posts from 68 individuals with schizophrenia spectrum disorders and 34 healthy controls. The study found that users with schizophrenia posted images with significantly lower saturation, colorfulness, and number of faces. Individuals with schizophrenia also had significantly lower ratios of followers to the number of accounts being followed compared to the control group. The study proves that visual Instagram data can be another clinically relevant component that can ultimately contribute to a digital phenotype with a diagnostic signature.

Management

One of the most researched benefits offered by social media may be found in their characteristic ability to provide users with an alternative form of socializing. Several studies have evaluated the capacity of these platforms to encourage social behaviors in the schizophrenia population, who commonly tend to self-isolate.

Although not in schizophrenia patients, a study by Alvarez-Jimenez *et al*[12] sets the stage for the discussion by investigating social media interventions in young people considered high risk for transition to psychosis. Researchers developed a platform called MOMENTUM, which highlights mindfulness, personal strengths, and self-efficacy. Thirteen of the fourteen participants reported that the platform was helpful, and data showed significant improvements in social functioning and subjective wellbeing, as well as significant increases in mindfulness skills and use of strengths that were both highlighted by the intervention. Thus, the platform MOMENTUM was not only used widely by participants, but also led to measurable improvements in sociality.

Alvarez-Jimenez *et al*[13] also led the first intervention in first-episode psychosis patients *via* a similar platform called Horyzons, which aims to incorporate social networking, psychotherapy, moderation by experts and peers, and the aforementioned emphasis on mindfulness and personal strengths[13]. The primary outcome was social functioning, using the Personal and Social Performance Scale at the final follow-up at 18-mo. The study recruited 170 participants between the ages of 16 and 27, who were randomly assigned to the Horyzons intervention in addition to treatment as usual (TAU) or solely TAU, which consisted of generic medical and mental health services.

While no significant effects were found, participants in the intervention group demonstrated a 5.5 times greater increase in their odds of finding employment or furthering their education compared to the control group. Participants can choose from a selection of activities, and topics related to occupational preparation were among the most selected. This included activities such as "Nailing the interview," "How to write a resume," and "Getting your public persona ready." This content likely

contributed to the improved vocational and educational attainment compared to the TAU group, in which vocational/educational measures declined over the length of the study. Likewise, 13% of the Horyzons group were hospitalized due to psychosis compared to 27% of the control group, but again this difference was not significant. The level of engagement with the Horyzons platform may play a role, as 55.5% of intervention participants logged on for at least 6 mo, and 47% logged on for at least 9 mo[14]. Although medication adherence was not a target measure in these studies, it is likely that the reduced hospitalization rates and other benefits are in part due to treatment adherence reinforced through platform participation. The awareness of symptom exacerbations to both participants and moderators may identify medication nonadherence and allow for timely dose adjustments as well. Overall, the Horyzons platform continues to hold promise as a feasible opportunity to prevent relapse and bridge patients from early psychosis treatment to multiple fundamental resources[14,15]. The study was originally developed and performed in Australia, but has since expanded to several other countries as well[15-17], further supporting the accessibility of social media interventions.

From a clinical perspective, Birnbaum *et al*[18] used machine learning models to analyze over 50000 Facebook posts from 51 patients with first-episode psychosis. The study captured behavioral and linguistic markers associated with predicting relapse, including significant differences in the wording of Facebook posts that preceded relapse hospitalization by one month. These differences included increased use of first and second person and more frequent use of words related to swearing, anger, and death. The related posts showed significantly less mentions of work, health, and friends, yet also involved more frequent co-tagging of friends. The study demonstrates the predictive value that social media can offer in identifying patients most susceptible to relapse. Similarly, patients who displayed increased, above-median Twitter posts related to schizophrenia had a 15% increase in mental health episodes[19]. Temporal analyses showed a seven-day pattern of positively associated Twitter posts and mental health fluctuations on day 1, negative association by day 4, and a return to negative association at day 7. The identified pattern illustrates the potential predictive value of Twitter posts on the symptomatic course of schizophrenia and may be valuable in identifying individual risks for symptom exacerbation.

Lastly, social media can provide additional benefits that improve patients' daily life in unique ways. Pertaining to physical health improvements, Naslund *et al*[20] investigated the role of a Facebook group to support health goals in patients with severe mental illness (SMI). Group participants who achieved weight loss of at least 5% of body weight or improved physical activity had contributed increased Facebook interactions, though this relationship neared but did not surpass the threshold for significance. Nevertheless, when participants posted about their personal successes and challenges, it generated significantly more platform interactions in comparison to motivational content, health information, and program reminders. This study exemplifies the impact that social media can have on patients' medical health outside of psychiatric care.

On a similar note, social media can be used to identify habits detrimental to health, such as smoking. Hswen *et al*[21] found that Twitter users with schizophrenia had significantly more posts containing tobacco-related keywords, which parallels the reality that smoking is more common in the schizophrenia community relative to the general population. Thus, these two studies demonstrate the capability of social media to not only identify areas to improve physical health, but also provide a reasonable intervention buffered by social support. Apart from physical health benefits, Sangeorzan *et al*[22] found that patients with SMI who vlog through YouTube receive peer support, increased self-efficacy, and diminished self-stigma. These benefits are likely to contribute to an improved sense of well-being, as would reducing overall stigma through public health education.

Public health education

While not a directly clinical application, it is worthwhile to briefly note the impact of social media in removing stigma through educational efforts targeting the general population. Robinson *et al*[23] examined over one million tweets and found schizophrenia to be the most stigmatized condition among mental health illnesses. Likewise, 68.3% of Turkish Twitter posts containing schizophrenia were deemed stigmatizing[24]. Several efforts have been made to assess public perception and improve awareness through Twitter[23-25], YouTube[26-28], Facebook[29,30], Instagram[30,31] and Weibo[32] (a Chinese social media platform). Social media has demonstrated potential to reduce stigma of schizophrenia, which may indirectly benefit patients' daily interactions and sense of well-being.

FUTURE DIRECTIONS

Although the above results are undoubtedly promising, one concern that must be addressed is whether these benefits apply to all age groups. Rekhi *et al*[33] reported the results of a survey of 265 individuals with schizophrenia to determine the characteristics of social media users. 52% of individuals used social media in the past week. However, patients that more frequently used social media were of younger age, higher family income, decreased symptom severity, and education above secondary school. Similarly, in a survey of patients from early psychosis and recovery units, age accounted for differences in use and

access of technology[34]. The use of technology and interest in internet-based interventions were nevertheless primarily positive, suggesting that with improvements, the interventions can become even more appealing to the broader population. These statistics are also improved compared to a 2015 survey that reported on 80 patients of ages 18-70 with schizophrenia, in which only 27% of individuals used social media[35]. At that time, participants reported that social media assisted them in increasing socialization, further supporting that the underlying interest is present and growing, but peak usage may depend on improvements in appeal and functionality.

To better understand what these improvements may be, a suitable starting point is patient feedback. Twelve participants with a mean age of 23 years were interviewed from the original Horyzons study. While some participants reported that the strengths of the intervention were on-demand support and flexibility, others felt overwhelmed by the options available to them that resulted in decreased motivation to engage with the platform[36]. Additional feedback was given by 26 participants involved in an open trial of the Horyzons platform in the United States. These users recommended the development of a smartphone application, the functionality to allow users to send private messages to each other, and the expansion of the Horyzons community to incorporate a greater number of users[15]. Integrating user suggestions such as simplifying the users' choices and increasing ease of use with a smartphone application may increase motivation to engage with the platform and ultimately expand the diversity of the userbase. Lastly, future updates to the Horyzons platform may benefit from employing artificial intelligence to automate delivery of therapy content tailored to users by analysis of individual data, further streamlining the user experience[37].

The negative effects of platforms such as Horyzons should also be taken into consideration for future research. Social media users with SMI report various concerns about privacy vulnerabilities. Specifically, these concerns involve the fear of stigma and judgment by others, impact on personal relationships, hostility towards participants, being hurt, and endangering employment. In a survey of 90 social media users with SMI, approximately one-third reported being concerned about privacy[38]. These concerns are legitimate, and platform developers should continue to involve participants in the development of their systems and ensure that privacy is prioritized. Likewise, enrolled participants should be educated on how to protect themselves from the potential risks related to stigma, self-disclosure, and other related concerns. These platforms must also take precautions to prevent spreading misinformation, worsening participant symptoms, and delaying professional help when necessary[38]. Lastly, the aforementioned improvement in vocational and educational outcomes seems to be dependent on user engagement, as those in the top quartile of logins (greater than 77 times over the course of the study) demonstrated significantly greater effects compared to those in the bottom quartile of logins (less than 9 times)[14]. Since these improvements seem to follow a dose-response relationship, platforms should screen for participants in this lower quartile of engagement, as they are not receiving the intended intervention effects, but may benefit from additional one-on-one time with moderators or specifically designed interventions.

CONCLUSION

Social media has transformed daily life and is on the cusp of extending an equal impact to psychiatric diagnosis and management. Studies have consistently shown the capability of machine learning to distinguish users with schizophrenia through social media data, whether it be typed language or visual content. These technologies showcase the emerging predictive value in first-episode psychosis and episodes of symptom exacerbation. Novel platforms such as Horyzons improve social functioning and increase timely access to resources such as peer support and psychotherapy. With platform improvements that streamline the user experience and augment patient engagement, all users stand to benefit from the contribution of social media to a multifaceted digital phenotype.

FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

ABCB9 polymorphism rs61955196 is associated with schizophrenia in a Chinese Han population

Xin-Wei Li, Ming-Yuan Zhang, Zhi-Jun Li, Li-Zhe Ai, Meng-Di Jin, Ning-Ning Jia, Meng-Tong Xie, Yu-Qing Yang, Wei-Zhen Li, Lin Dong, Qiong Yu

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Abstract

BACKGROUND

Schizophrenia (SCZ) is a complex disease which can be affected by both genetic and environmental factors. Prenatal famine exposure may cause changes in DNA methylation levels of genes. Meanwhile, maternal nutrition during pregnancy is a pivotal environmental factor in the development of SCZ. DNA methylation may be an intermediate factor mediating exposure to famine during pregnancy and SCZ, and DNA methylation quantitative trait loci might serve as a promising tool for linking SCZ and prenatal famine.

AIM

To analyze the association between prenatal famine exposure and SCZ risk in Northeast Han Chinese through analysis of DNA methylation related loci.

METHODS

A total of 954 Han Chinese from Northeast China were recruited, including 443 patients with SCZ and 511 healthy controls. The participants were further divided into famine (born in 1960-1962) and non-famine (born in 1963-1965) groups to investigate the effect of prenatal famine exposure. Four single-nucleotide polymorphisms (SNPs) selected according to the relevant literature were genotyped, namely, rs11917047 in *PTPRG*, rs2239681 in *IGF2*, rs3842756 in *INSIGF*, and rs61955196 in *ABCB9*. DNA were extracted from peripheral blood samples, and the genotypes of these SNP loci were detected using the improved Multiple Ligase Detection Reaction multiple SNP typing technique. The associations of the DNA methylation related SNPs with SCZ risk and prenatal famine,

and their interactions were analyzed using logistic regression analysis and generalized multifactor dimensionality reduction (GMDR) software.

RESULTS

Based on the sequencing data, genotype distributions and allele frequencies of the four selected SNPs were determined. All genotype frequencies of the four SNPs in the healthy control group were tested for deviation from Hardy-Weinberg equilibrium ($P > 0.05$). Logistic regression analysis showed that rs61955196 was significantly associated with SCZ risk in the log-additive model [odds ratio (OR): 1.22; 95% confidence interval (CI): 1.01-1.48; $P = 0.040$]. We also found that the rs61955196 allele was related with an enhanced risk of SCZ (G>C, OR: 1.22; 95%CI: 1.01-1.47; $P = 0.042$). However, no associations were observed between rs11917047, rs2239681, or rs3842756 and SCZ risk. Under the optimal genetic model, no significant association of famine with the four SNPs was seen. Though the gene–gene interactions between rs2239681 and rs61955196 were found in GMDR analysis, none of the gene-gene interactions and gene-famine interactions were associated with the risk of SCZ.

CONCLUSION

Our study suggested that rs61955196 in *ABCB9* is associated with SCZ susceptibility in Northeast Han Chinese, providing insight into genetic effects on SCZ.

Key Words: Schizophrenia; Prenatal famine; rs61955196; DNA methylation; *ABCB9* polymorphism

Core Tip: Prenatal famine exposure may cause changes in DNA methylation levels of genes, while maternal nutrition is a pivotal environmental factor for schizophrenia (SCZ). To analyze the association between prenatal famine exposure and SCZ risk, we recruited 443 SCZ patients and 511 healthy controls with four single-nucleotide polymorphisms genotyped, which were previously identified as DNA methylation quantitative trait loci. Our study observed significant differences in rs61955196 genotype distribution and allele frequency between SCZ patients and healthy controls for the first time, suggesting that rs61955196 in *ABCB9* was associated with SCZ susceptibility among the Northeast Han Chinese population.

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INTRODUCTION

Schizophrenia (SCZ) is a complex disease affected by both genetic and environmental factors, which is often characterized by symptoms such as hallucinations, social withdrawals, delusions, and cognitive dysfunction[1,2]. The global point prevalence of SCZ was estimated to be 0.28% (0.24%–0.31%) in 2016 which contributes 13.4 (95% uncertainty interval: 9.9–16.7) million years of life lived with disability to burden of disease globally[3]. And China was assessed to show the highest prevalence of 0.42% among global countries, which raises necessity to conduct research enrolling local Chinese participants to reveal the practical status and underlying biological mechanisms of SCZ for its management and treatment.

DNA methylation is a heritable epigenetic modification which alters gene expression[4]. Studies have demonstrated that overall DNA hypomethylation is evident in SCZ patients, while treatment with haloperidol might increase methylation[5,6]. In other words, DNA methylation, which can regulate gene expression, is closely associated with the risk of SCZ [7-10].

Although the peak incidence rate of SCZ appears in adolescence and early adulthood, many believe that its etiological origin exists much earlier in one's life, which includes exposure to environmental and genetic factors. The exposure occurring in the early stages of life development along with a cumulative effect during the later stages may eventually lead to the appearance of symptoms[11]. Among the environmental factors, maternal nutrition during pregnancy plays an early and vital role in the occurrence and development of SCZ[12,13]. Studies have shown that prenatal famine exposure may

cause changes in DNA methylation levels of genes. Malnutrition during pregnancy, especially the lack of maternal protein and folic acid, seriously affects fetal development which will result in changes in DNA methylation[14]. Empirical studies of the Great Famine of China in 1959-1961 and the Dutch famine in 1944-1945 both showed that prenatal famine exposure led to an obviously increased risk of SCZ[15-17]. It was found that those who were born during the famine are twice as likely to have SCZ in their later years as normal people[16]. Therefore, we proposed that prenatal nutritional deficiencies may increase the risk of SCZ by altering DNA methylation status.

In recent years, genome-wide association studies (GWAS) have been effectively used for studying genetic variation associated with SCZ[18,19]. As DNA methylation tends to be sensitive to environmental factors, DNA methylation quantitative trait loci (meQTL) seems more promising. They can be derived by GWAS mapping levels of DNA methylation in genotyped individuals and define loci at which DNA methylation is influenced by genetic variation[20], with a superiority of higher consistency throughout one's life than DNA methylation itself. There have already been reports revealing the role of meQTLs in SCZ risk, which promote the feasibility of them serving as a useful tool for SCZ-related research[21,22]. However, the results from GWAS studies are often not repeatable due to the enormous number for detection and heterogeneity of genetic information regarding people from different races and regions[23]. Given the high SCZ prevalence in China and current lack of available genetic data covering native patients, we find it necessary to conduct research collecting genetic data among Chinese individuals.

Here we intended to analyze the associations between single-nucleotide polymorphisms (SNPs) identified as meQTLs with the risk of SCZ and prenatal famine exposure among a Han population in Northeast China. We recruited SCZ patients and healthy controls (HCs) with comparable age including individuals born between 1959 and 1961 with prenatal famine exposure, and collected their peripheral blood samples for genotyping. We selected four SNPs which were previously reported as meQTLs, and determined their associations with SCZ and prenatal famine along with their interactions. We hope our work may provide more practical reference in management of SCZ.

MATERIALS AND METHODS

Study subjects

A desired sample size of 417 patients was calculated using the software Quanto with a proper power before the recruitment of participants, with a unmatched case-control rate of 1.2, an estimated population risk of 1% for SCZ, a log-additive model gene with allele frequency of 0.1, genetic effect of 1.5, and a type I error rate of 0.05 by two-sided test. According to the desired sample size and the inclusion and exclusion criteria, a total of 954 Han Chinese from Northeast China were finally recruited between 2010 and 2012, including 443 SCZ patients and 511 healthy people. The patients were recruited from the Siping Psychiatric Hospital and Sixth Hospital of Changchun City (Jilin, China). Each patient was diagnosed according to the Tenth Revision of International Classification of Diseases-10 for SCZ and confirmed by at least two experienced psychiatrists. Those with neurological disorders, severe organic lesions, and drug dependence were excluded. Subjects in the HC group matching the patients by gender and age were recruited from the Changchun Municipal Centre for Disease Control and Prevention, in order to get a comparable proportion of famine-exposed individuals between two groups and a similar ratio of gender. The healthy subjects were required to have no history of mental illness and were in good health without any known disease at the time of recruitment. Furthermore, subjects who were in uterus between 1959 and 1961 were regarded to be exposed to famine. And then they were divided into two groups, namely, famine group (born in 1960-1962) and non-famine group (born in 1963-1965), according to whether they were exposed to famine before birth. All methods were performed in accordance with the relevant guidelines and regulations. The study adhered to the tenets of the Declaration of Helsinki, and was approved by the Ethics Committee of the School of Public Health of Jilin University (Approval No: 2014-03-11). All participants provided informed consent.

Genomic DNA extraction and genotyping

In the first step, we collected peripheral blood samples from the participants and extracted genomic DNA. Then, DNA content and purity were determined based on the ratio of OD_{260}/OD_{280}. Combining the feasibility of the detection method and the previous publications, we selected four SNPs (rs11917047 in *PTPRG*, rs2239681 in *IGF2*, rs3842756 in *INSIGF*, and rs61955196 in *ABCB9*) which have been confirmed as meQTLs, and the SNPs themselves or the genes that they belong to were assessed to be associated with SCZ[21,24-26].

Then, the genotypes of these SNP locus were detected using the improved Multiplex Ligase Detection Reaction multiple SNP typing technique (Shanghai Tian Hao Biological Technology Co. Ltd.). Using the Assay Design software 3.1, we successfully designed primers for the four meQTL SNPs. And the primer sequences for each SNP are as follows: rs11917047-F, AGATGAAAGATTGGGGTGTGGGTA and rs11917047-R, GCTGGTACCCAACCAGGAACAC; rs2239681-F, ATGGGCAAATCAGCCTGAAGAG and rs2239681-R, GTGTGCAAGAGGGGTGAAAGGT; rs3842756-F, TCCACAGGGACTCCAT-

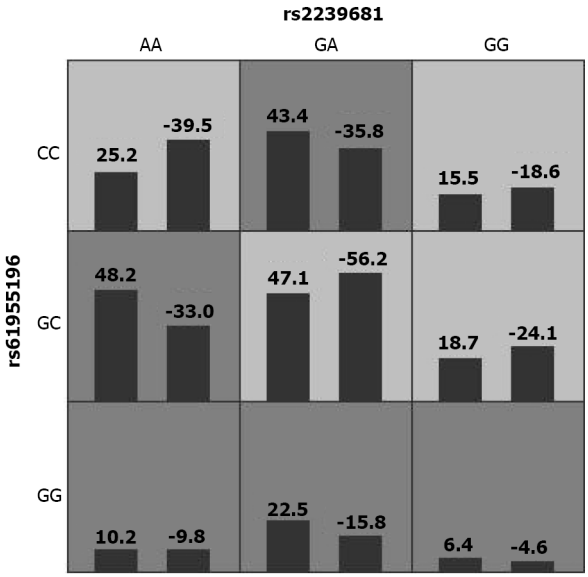

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Figure 1 Generalized multifactor dimensionality reduction 2D interaction model in rs2239681 and rs61955196. The left bar represents the positive score and the right bar represents the negative score.

CAGAAA and rs3842756-R, CCTGTGGCTCAGGGTCCAGTAT; and rs61955196-F, GCTGCAAGGTCG-GAGCTGAG and rs61955196-R TGGGAGGAGTTTGCCACAGG.

Statistical analysis

Deviation of the genotypes from Hardy-Weinberg equilibrium (HWE) between the SCZ patients and healthy individuals was assessed using a χ^2 goodness-of-fit test. Logistic regression analysis was used to examine the relationship between SNPs and the risk of SCZ as well as the association of famine with SNPs with age and sex adjusted as covariates. The online genetic analysis software, SNPStats, was used to select the optimal genetic model according to the Akaike information criterion (AIC) and Bayesian information criterion. Generalized multifactor dimensionality reduction (GMDR) analysis was conducted to analyze the gene-gene interactions, which are rather critical in investigating genetic information for multifactorial diseases, and the gene-environment interactions were analyzed by crossover analysis based on logistic regression analysis. Except for the above specified, all statistical analyses were performed with SPSS 24.0 software. A P-value < 0.05 was considered statistically significant.

RESULTS

Based on the SNP sequencing data, the genotype distributions and allele frequencies of the four selected SNPs in SCZ patients (n = 443) and HCs (n = 511) were determined and the detailed data are shown in Table 1. All genotype frequencies of the four SNPs in the HC group were in accordance with HWE (P > 0.05). Logistic regression analysis showed that, compared with those carrying the wild-type homozygote (CC) of rs61955196, subjects carrying the mutant homozygote (GG) had a higher risk of SCZ [odds ratio (OR): 1.54; 95% confidence interval (CI): 1.03-2.30; P = 0.037]. We also found that the rs61955196 allele was related with an enhanced risk of SCZ (OR: 1.22; 95%CI: 1.01-1.47; P = 0.042). The frequency of the rs61955196 G allele was 40.5% in the case group, which was significantly higher than that of the control group (36.6%; P < 0.05). No associations were observed between SCZ patients and HC subjects regarding different genotypes or alleles of the rest three SNPs.

Based on the findings, we dug into the association between genotypes of rs61955196 and SCZ risk using multiple genetic models. As shown in Table 2, a significant association between rs61955196 and SCZ in the log-additive model was revealed (OR: 1.22; 95%CI: 1.01-1.48; P = 0.040). In the codominant model, we also found the association of rs61955196 with SCZ in the GG *vs* CC genotype comparison. No obvious effect of rs61955196 on the risk of SCZ was found in other models (P > 0.05).

To investigate the relationship of meQTLs and prenatal famine exposure, we analyzed the associations of the four SNPs with famine. Totally, 492 subjects were exposed to prenatal famine, including 220 SCZ patients and 272 HC subjects. As shown in Table 3, based on the AIC, the inheritance model was recessive for rs11917047 and rs2239681, codominant for rs3842756, and overdominant for rs61955196. SCZ patients and HCs were further divided into a famine group and a non-famine group.

Table 1 Association analysis for four target single-nucleotide polymorphisms and schizophrenia risk, *n* (%)[1]

SNP	Genotype/allele	SCZ (*n* = 443)	HC (*n* = 511)	*P* value	OR (95%CI)	HWE test for controls
rs11917047 (*PTPRG*)	AA	219 (49.4)	259 (50.7)		1.00 (ref)	0.151
	AG	183 (41.3)	200 (39.1)	0.431	1.12 (0.85-1.47)	
	GG	41 (9.3)	52 (10.2)	0.713	0.92 (0.58-1.45)	
	A	621 (70.1)	718 (70.3)		1.00 (ref)	
	G	265 (29.9)	304 (29.7)	0.885	1.02 (0.83-1.24)	
rs2239681 (*IGF2*)	AA	156 (35.2)	177 (34.6)		1.00 (ref)	0.104
	AG	211 (47.6)	232 (45.4)	0.667	1.07 (0.80-1.43)	
	GG	76 (17.2)	102 (20.0)	0.447	0.87 (0.59-1.26)	
	A	523 (59.0)	586 (57.3)		1.00 (ref)	
	G	363 (41.0)	436 (42.7)	0.567	0.95 (0.79-1.14)	
rs3842756 (*INSIGF*)	CC	405 (91.4)	475 (93.0)		1.00 (ref)	0.409
	CT	38 (8.6)	36 (7.0)	0.319	1.28 (0.79-2.08)	
	TT	-	-	-	-	
	C	848 (95.7)	986 (96.5)		1.00 (ref)	
	T	38 (4.3)	36 (3.5)	0.329	1.27 (0.79-2.04)	
rs61955196 (*ABCB9*)	CC	157 (35.4)	202 (39.5)		1.00 (ref)	0.513
	CG	213 (48.1)	244 (47.7)	0.297	1.16 (0.88-1.55)	
	GG	73 (16.5)	65 (12.7)	0.037[a]	1.54 (1.03-2.30)	
	C	527 (59.5)	648 (63.4)		1.00 (ref)	
	G	359 (40.5)	374 (36.6)	0.042[a]	1.22 (1.01-1.47)	

[a]$P < 0.05$.

[1]Adjusted for gender.

SCZ: Schizophrenia; HC: Healthy control; OR: Odds ratio; HWE: Hardy-Weinberg equilibrium; SNP: Single-nucleotide polymorphism.

Logistic regression analysis indicated that under the optimal genetic model, there was no significant association of famine with the four SNPs in either the SCZ group or HC group ($P > 0.05$).

In this study, GMDR was used to import and analyze the interactions between rs11917047, rs2239681, rs3842756, and rs61955196. The impact of gene–gene interaction on the risk of SCZ is summarized in Table 4. The multifactor model 2 (rs2239681 × rs61955196) presented the best cross-validation consistency, which had a testing-balanced accuracy of 55.8%. Figure 1 shows the interaction model of this gene–gene interaction between rs2239681 and rs61955196. However, no significant association of gene-gene interaction with the risk of SCZ was found in this model.

Crossover analysis based on a multiplicative model of logistic regression was conducted to determine the interactions between the SNPs and famine in SCZ patients (Table 5). None of the interactions between the genotypes of the four loci of rs11917047/rs2239681/rs3842756/rs61955196 with the risk of famine were statistically significant ($P > 0.05$).

DISCUSSION

Based on existing reports, we selected four susceptibility loci of SNPs related to SCZ as the starting point for analysis, which are rs11917047 in *PTPRG*, rs2239681 in *IGF2*, rs3842756 in *INSIGF*, and rs61955196 in *ABCB9*, respectively. This study analyzed genetic data from representative samples of Northeastern Chinese using meQTL SNPs, and found the difference of rs61955196 genotype distribution with allele frequency between SCZ patients and HC subjects for the first time. rs61955196 is located in the 5' untranslated region of the *ABCB9* gene, encoding the ABCB9 protein which belongs to the ATP-binding cassette (*ABC*) transporter family. The *ABC* gene can be divided into seven different subfamilies (*MRP, ABC1, OABP, ALD, GCN20, MDR/TAP,* and *White*)[27], and the ABCB9 protein is a member of the *MDR/TAP* subfamily. *ABC* family and *ABCB9* are reported to be involved in progression of multiple malignant tumors and chemoresistance[28-31], but little research has been done on the relationship

Table 2 Associations between rs61955196 and schizophrenia based on multiple models, *n* (%)[1]

Model	Genotype	SCZ (%)	HC (%)	OR (95%CI)	*P* value	AIC	BIC
Codominant	CC	157 (35.4)	202 (39.5)	1.00		1279.8	1299.2
	GC	213 (48.1)	244 (47.8)	1.16 (0.88-1.55)	0.297		
	GG	73 (16.5)	65 (12.7)	1.54 (1.03-2.30)	0.037[a]		
Dominant	CC	157 (35.4)	202 (39.5)	1.00	0.120	1279.7	1294.3
	GC + GG	286 (64.6)	309 (60.5)	1.24 (0.95-1.62)			
Recessive	CC + GC	370 (83.5)	446 (87.3)	1.00	0.068	1278.9	1293.5
	GG	73 (16.5)	65 (12.7)	1.41 (0.97-2.04)			
Overdominant	CC + GG	230 (51.9)	267 (52.2)	1.00	0.810	1282.1	1296.7
	GC	213 (48.1)	244 (47.8)	1.03 (0.80-1.34)			
Log-additive	-	-	-	1.22 (1.01-1.48)	0.040[a]	1278	1292.6

[a]$P < 0.05$.
[1]Adjusted for gender.
SCZ: Schizophrenia; HC: Healthy control; OR: Odds ratio; AIC: Akaike information criterion; BIC: Bayesian information criterion.

Table 3 Association analysis for famine and single-nucleotide polymorphisms, *n* (%)[1]

Group	SNP	Genotype	Famine	Non-famine	*P* value	*OR* (95%CI)
SCZ	rs11917047	AA + GA	204 (92.7)	198 (88.8)	0.150	1.00
	(Recessive)	GG	16 (7.3)	25 (11.2)		1.62 (0.84-3.13)
	rs2239681	AA + GA	185 (84.1)	182 (81.6)	0.550	1.00
	(Recessive)	GG	35 (15.9)	41 (18.4)		1.16 (0.71-1.91)
	rs3842756	CC	198 (90)	207 (92.8)	0.270	1.00
	(Codominant)	CT	22 (10)	16 (7.2)		0.68 (0.35-1.34)
	rs61955196	CC + GG	117 (53.2)	113 (50.7)	0.610	1.00
	(Overdominant)	GC	103 (46.8)	110 (49.3)		1.10 (0.76-1.60)
HC	rs11917047	AA + GA	249 (91.5)	210 (87.9)	0.160	1.00
	(Recessive)	GG	23 (8.5)	29 (12.1)		1.50 (0.84-2.68)
	rs2239681	AA + GA	222 (81.6)	187 (78.2)	0.330	1.00
	(Recessive)	GG	50 (18.4)	52 (21.8)		1.24 (0.80-1.92)
	rs3842756	CC	257 (94.5)	218 (91.2)	0.150	1.00
	(Codominant)	CT	15 (5.5)	21 (8.8)		1.65 (0.83-3.27)
	rs61955196	CC + GG	144 (52.9)	123 (51.5)	0.750	1.00
	(Overdominant)	GC	128 (47.1)	116 (48.5)		1.06 (0.75-1.50)

[1]Adjusted for gender.
SCZ: Schizophrenia; HC: Healthy control; OR: Odds ratio; SNP: Single-nucleotide polymorphism.

between *ABCB9* gene and SCZ. Recent evidence suggests that *ABCB9* is positively associated with the risk of SCZ[32], which is in accordance to our findings to some extent.

Increasing studies have shown that epigenetic modifications are associated with the pathogenesis of SCZ, and DNA methylation is a crucial one regulating gene expression, which may be a key factor in the process[33,34]. Our results showed that the methylation locus rs61955196 increased the risk of SCZ in the log-additive model. However, we did not observe the association between the methylation loci located in the other three genes and SCZ, which is inconsistent with existing studies. For example, Cressant *et al*[35] discovered that the *PTPRG* gene containing the rs11917047 locus was associated with SCZ. The receptor protein tyrosine phosphatase PTPRG is a ligand for members of the contact protein

Table 4 Generalized multifactor dimensionality reduction analysis for best interaction combination models

No.	Best combination	CVC	Te-BA	*P* value
1	rs61955196	9/10	0.5097	0.8281
2	rs2239681 × rs61955196	10/10	0.5582	0.0547
3	rs11917047 × rs2239681 × rs61955196	10/10	0.5341	0.1719
4	rs11917047 × rs2239681 × rs3842756 × rs61955196	10/10	0.5449	0.1719

CVC: Cross validation consistency; Te-BA: Testing-balanced accuracy.

Table 5 Crossover analysis of interactions between rs11917047/rs2239681/rs3842756/ rs61955196 and famine factor with schizophrenia

SNP	Genotype	Famine	SCZ	HC	OR (95%CI)	*P* value
rs11917047	AG + GG	+	121	119	1.21 (0.85-1.72)	0.294
	AG + GG	-	103	133	0.92 (0.65-1.31)	0.646
	AA	+	102	120	1.01 (0.70-1.45)	0.958
	AA	-	117	139	1.00 (ref)	
rs2239681	AG + GG	+	144	157	1.13 (0.78-1.65)	0.519
	AG + GG	-	143	177	1.00 (0.69-1.45)	0.986
	AA	+	79	82	1.19 (0.77-1.83)	0.432
	AA	-	77	95	1.00 (ref)	
rs3842756	CT	+	16	21	0.99 (0.50-1.95)	0.974
	CT	-	22	15	1.90 (0.96-3.77)	0.064
	CC	+	207	218	1.23 (0.95-1.61)	0.123
	CC	-	198	257	1.00 (ref)	
rs61955196	CG + GG	+	147	145	1.35 (0.94-1.95)	0.109
	CG + GG	-	139	164	1.13 (0.78-1.63)	0.513
	CC	+	76	94	1.08 (0.71-1.64)	0.724
	CC	-	81	108	1.00 (ref)	

SCZ: Schizophrenia; HC: Healthy control; OR: Odds ratio; SNP: Single-nucleotide polymorphism.

family, which are linked to autism spectrum disorders. The interpretation for these disagreements may be due to the disparity in the target population as what we studied is the Han population in Northeast China, which is different from other studies in race, sample size, and geographic location.

It is a pity that we did not find the association of prenatal exposure to famine with DNA methylation loci. A recent study also reported that maternal risk alleles for neurodevelopmental disorders, primarily attention-deficit/hyperactivity disorder, were associated with prenatal exposures, but nor for SCZ or autism spectrum disorder[36]. Nevertheless, there have been much supportive evidence regarding the positive relationship between SCZ and prenatal famine exposure. Waterland[37] discovered that maternal nutritional deficiency may result in permanent abnormal DNA methylation with the potential to affect gene expression. In addition, since human is unable to synthesize folic acid which is necessary for normal DNA methylation, the lack of folic acid which hinders the production of methyl donors might affect gene expression related to neurodevelopmental processes. Prenatal famine leads to undernutrition during fetal development, which is believed to further promote the risk of SCZ in offspring[38]. Wang and Zhang[39] also used data from a nationally representative sample to analyze the association of prenatal famine exposure with the risk of SCZ. The results showed that famine population had a higher risk of SCZ compared to the non-famine cohorts. This pattern was found throughout different subsamples, such as the urban/rural population[40]. Therefore, we still believe that it is vital to continue exploring the association of prenatal famine exposure with DNA methylation and SCZ in the future. Meanwhile, this study had several limitations. First, we only adjusted for gender as we mainly focused on the genetic variants, and we were not able to explore some underlying

confounders such as medication as we have directly excluded those who had any medical treatment in the past 3 mo before enrollment. Second, as we did not collect sufficient information from the patients regarding illness-related parameters such as the severity or duration of disease, we could not rule out the possibility that the SNPs could be associated with SCZ under some specific conditions although we got negative results. Third, this is a case-control study and the patients were recruited from hospitals, resulting in inevitable selection bias. Finally, limited by the feasibility and applicability of the detection method, we only selected four SNPs in this study, and the constrained selection may leave out other crucial SNPs related to DNA methylation.

CONCLUSION

Our study suggested that rs61955196 in *ABCB9* could be associated with SCZ susceptibility among the Han population in Northeast China. No association was found between the four meQTL SNPs and prenatal famine. These findings provide insight into genetic effects on SCZ. Future research should be devoted to validating the results, and gathering comprehensive information for additional subgroup analyses may help to reveal the association between prenatal famine and SCZ risk.

ARTICLE HIGHLIGHTS

Research background

Schizophrenia (SCZ) is a severe mental disorder bringing heavy burden, which is closely related with genetic and environmental factors. The effect of prenatal exposure of famine on SCZ risk has been reported with intense interest. DNA methylation may be an intermediate factor mediating prenatal famine and SCZ, and DNA methylation quantitative trait locus (meQTLs) can serve as a promising tool.

Research motivation

The lifetime prevalence of SCZ is approximately 1% around the world, and study has reported the highest age-standardized prevalence of SCZ in China. Meanwhile, the Chinese famine of 1959-1961 is a proper source of study subjects to investigate the effect of prenatal famine on SCZ with little available genetic data. As a result, we intended to conduct analyses for SCZ and prenatal famine using native subjects with collected genetic information, which may provide insights specifically for Chinese researchers and patients.

Research objectives

To investigate the associations of four single-nucleotide polymorphisms (SNPs) identified as meQTLs with the risk of SCZ and prenatal famine exposure along with their interactions among Northeast Han Chinese.

Research methods

We recruited 954 Han Chinese from Northeast China including 443 patients with SCZ and 511 healthy controls, and their peripheral blood samples were collected. Among them, 492 born in 1960-1962 were further allocated to a famine group. Four SNPs were selected and genotyped, namely, rs11917047 in *PTPRG*, rs2239681 in *IGF2*, rs3842756 in *INSIGF*, and rs61955196 in *ABCB9*. The associations of the meQTLs with SCZ risk and prenatal famine, and their interactions were analyzed using logistic regression analysis and generalized multifactor dimensionality reduction software.

Research results

The genotype distributions along with allele frequencies of the four SNPs were determined among the Chinese participants. We found that rs61955196 was significantly associated with SCZ risk in the log-additive model [odds ratio (OR): 1.22; 95% confidence interval (CI): 1.01-1.48; $P = 0.040$], and rs61955196 allele was related with an enhanced risk of SCZ (G>C, OR: 1.22; 95%CI: 1.01-1.47; $P = 0.042$). However, the other three SNPs were not associated with SCZ risk. No association was observed between the SNPs and prenatal famine. Gene-gene interactions were seen between rs2239681 and rs61955196, while no gene-gene or gene-famine interactions were associated with the risk of SCZ.

Research conclusions

Our results suggested that rs61955196 in *ABCB9* might be involved in SCZ susceptibility among Northeast Han Chinese.

Research perspectives

Our study provides a potential functional variant rs61955196 for SCZ susceptibility, and we recommend

further research to extend the findings to different populations and verify its function. Although no evidence between SCZ and prenatal famine was found, we believe that gathering comprehensive information for analyses regarding subgroups may help to reveal the association in the future.

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FOOTNOTES

Author contributions: Li XW and Zhang MY performed the majority of experiments and wrote the manuscript; Li ZJ and Ai LZ provided advices to the manuscript correction; Jin MD served as scientific advisor and participated in the collection of human material; Jia NN was involved in analytical tools; Xie MT, Yang YQ, Li WZ and Dong L participated in the collection of the human material; Yu Q designed the study and is the guarantor; all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

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Predicting South Korea adolescents vulnerable to depressive disorder using Bayesian nomogram: A community-based cross-sectional study

Haewon Byeon

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Abstract

BACKGROUND

Although South Korea has developed and carried out evidence-based interventions and prevention programs to prevent depressive disorder in adolescents, the number of adolescents with depressive disorder has increased every year for the past 10 years.

AIM

To develop a nomogram based on a naïve Bayesian algorithm by using epidemiological data on adolescents in South Korea and present baseline data for screening depressive disorder in adolescents.

METHODS

Epidemiological data from 2438 subjects who completed a brief symptom inventory questionnaire were used to develop a model based on a Bayesian nomogram for predicting depressive disorder in adolescents.

RESULTS

Physical symptoms, aggression, social withdrawal, attention, satisfaction with school life, mean sleeping hours, and conversation time with parents were influential factors on depressive disorder in adolescents. Among them, physical symptoms were the most influential.

CONCLUSION

Active intervention by periodically checking the emotional state of adolescents and offering individual counseling and in-depth psychological examinations when necessary are required to mitigate depressive disorder in adolescents.

Key Words: Depressive disorder; Nomogram; Adolescents; Risk factor; Community-based

cross-sectional study; Brief symptom inventory

Core Tip: The early detection and prevention of depressive disorder in adolescents is important because it not only adversely affects interpersonal relationships and academic achievement but also increases the probability of other related mental illnesses such as panic disorder. We developed a nomogram for screening depressive disorder using epidemiological data on 2438 adolescents. Physical symptoms, aggression, social withdrawal, attention, satisfaction with school life, mean sleeping hours, and conversation time with parents were influential factors on depressive disorder in adolescents.

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INTRODUCTION

Depressive disorder causes an emotional response that can make a person feel a sense of failure, a sense of loss, and/or a sense of worthlessness as a result of a negative perception of him/herself[1]. It is defined as a persistent feeling of sadness or hopelessness to the extent of not being able to maintain daily activities for 2 wk in the past year[1]. It has been reported that South Koreans experience depressive disorder most frequently during adolescence compared to other stages of life[2]. A national survey of South Korean adolescents reported that one in four males and one in three females were diagnosed with depressive disorder[3]. In particular, it has been reported that depression during adolescence increases rapidly after middle school[3,4], suggesting that the mental health of adolescents is at risk during this period.

Adolescence involves the most physical, mental, and social changes that occur in a human lifetime [5]. Adolescents experiencing depressive disorder are highly likely to self-torture and/or express delinquent and aggressive behavior[5]. Moreover, if depressive disorder is not identified and managed early, it may progress to become a chronic illness with depression likely to recur during a person's lifetime[6]. The early detection and prevention of depressive disorder in adolescence is an important social issue because it not only adversely affects interpersonal relationships and academic achievement but also increases the probability of developing other mental illnesses such as panic disorder[7].

Although South Korea has developed and carried out evidence-based intervention and prevention programs to mitigate depressive disorder in adolescents[2], the number of adolescents with depressive disorder has increased every year for the past 10 years[2]. Consequently, it is necessary to identify the influential factors causing depression and develop a predictive model with high accuracy that can identify groups highly vulnerable to depressive disorder as soon as possible.

Recently, the naïve Bayesian nomogram has been used as a method for predicting groups at high risk of developing diseases[8,9]. One of the advantages of this method is that it presents the risk probability according to multiple risk factors of a disease visually so that clinicians can easily understand the results [10]. In this study, a nomogram based on a naïve Bayesian algorithm using epidemiological data on adolescents in South Korea was developed and baseline data for screening depressive disorder in adolescents is presented.

MATERIALS AND METHODS

Data source

This is a secondary data analysis study using raw data from the 2019 Korean Children Youth Panel Study (KCYPS) survey from March to June 2019 provided by the National Youth Policy Institute. The study was approved by the Research Ethics Review Board of the National Youth Policy Institute (No. KCYPS-2018).

The survey method for KCYPS is presented in Cho *et al*[11] (2018). Briefly, the KCYPS sampled 7th-grade students attending 162 middle schools across South Korea using a stratified multi-stage cluster sampling method. Schools were selected according to the probability proportional to the size sampling method for 27 clusters across 16 metropolitan cities, small and medium-sized cities, and rural areas. After checking the information on the number of 7th-grade classes and the number of students in each

Table 1 Measurements of explanatory variables

Classification	Variable	Characteristics
Sociodemographic factors	Gender	Male or female
	Number of siblings (including the subject)	1 person, 2 people, 3 people, or 4 people or more
Environmental factors	Mean conversation time with parents *per* day	< 30 min, ≥ 30 min and < 1 h, ≥ 1 h and < 2 h, ≥ 2 h and < 3 h, or ≥ 3 h
Personal factors	Satisfaction with academic achievement	Dissatisfied, not dissatisfied or satisfied, or satisfied
	Satisfaction with school life	Dissatisfied, not dissatisfied or satisfied, or satisfied
	Mean sleeping hours *per* day	< 5 h, 6 h, 7 h, 8 h, 9 h, or ≥ 10 h
	Social withdrawal	Continuous variable
	Aggression	Continuous variable
	Attention	Continuous variable
	Physical symptoms	Continuous variable

class at each school, samples were extracted by randomly selecting classes. The KCYPS collected data using a tablet-assisted personal interview method to compensate for the quality deterioration caused by existing questionnaire input errors or logical errors and to increase the accuracy and efficiency of the survey. In the present study, we analyzed 2438 subjects after excluding 152 cases with missing values in the depressive disorder screening part among 2590 people who completed the KCYPS questionnaire in 2019.

Measurements

Depression, the outcome variable, was defined by using ten items for measuring depression in the brief symptom inventory (BSI) (1984)[12], which was adapted for the South Korean population by standardizing the Symptom Checklist-90-Revision[13]. The BSI is a self-reporting test with each item being measured on a 4-point scale. Moreover, the total score ranges from 10 to 40 points. A higher score indicates more severe depression. Referring to Byeon *et al*[14] (2015), the threshold for depression in this study was 24 points, corresponding to 1 standard deviation (less than the 16th percentile). *AORN J* reported that Cronbach's α (a measurement of reliability) for the BSI was 0.904 (0.882 in the present study)[15].

Explanatory variables included gender, environmental factors (number of siblings and mean conversation time with parents during weekdays), and personal factors (satisfaction with academic achievement, satisfaction with school life, mean sleeping hours during weekdays, social withdrawal, aggression, attention, and physical symptoms). The definitions of the explanatory variables are provided in Table 1.

Social withdrawal was measured by using five items from the Behavior Problem Scale for Children and Adolescence (BPSCA) developed by Kim and Kim[16] (1998) after excluding items overlapping with other sub-domains. Each item was measured on a 4-point scale with the total score ranging from 5 to 20 points. A higher score indicates more severe social withdrawal. *AORN J* reported that Cronbach's α for the tool was 0.850 (0.894 in the present study)[15].

Aggression was measured by using the Emotional or Behavioral Problems Scale (EPS) developed by Cho and Lim[17] (2003). Six items were used and each item was measured on a 4-point scale with the total score ranging from 6 to 24 points, and a higher score indicates a more aggressive condition. Cho and Lim[17] (2003) reported that the Cronbach's α of the tool was 0.760 (0.809 in the present study).

Attention problems were measured by using 7 items in the EPS[17]. Each item was measured on a 4-point scale with the total score ranging from 7 to 28 points. A higher score indicates more severe attention problems. Kim and Song[18] (2014) reported Cronbach's α for the tool was 0.791 (0.813 in the present study).

Physical symptoms are when a person perceives that he or she is frequently ill or tired such as chest tightness or stomach discomfort without a pathological cause. These were measured by using eight items in the EPS[17]. Each item was measured on a 4-point scale with the total score ranging from 8 to 32 points. A higher score indicates more severe physical symptoms. Choi *et al*[19] (2017) reported Cronbach's α for the tool was 0.87 (0.858 in the present study).

Developing the naïve Bayes nomogram for predicting adolescents vulnerable to depressive disorder

A nomogram is used to visually present complex functions or calculations[20,21]. In particular, it is used as a method to visually present the diagnosis, recurrence, and survival prediction of a disease[20,21]. It is expressed graphically (Figure 1) in which a line is assigned to each attribute used as an input item and the possible value of the attribute is displayed on the line[22]. The score corresponding to the position of

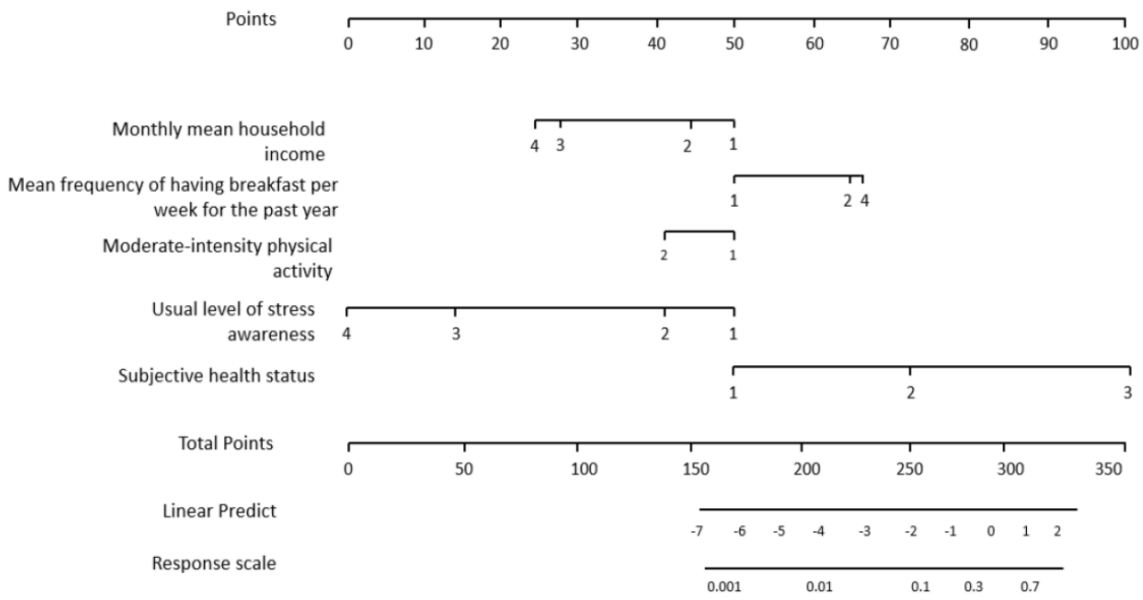

Figure 1 An example of a nomogram[22]. Citation: Byeon H. Developing a nomogram for predicting the depression of senior citizens living alone while focusing on perceived social support. *World J Psychiatry* 2021; 11: 1314-1327. Copyright ©The Authors 2021. Published by Baishideng Publishing Group Inc.

the attribute value becomes the individual score of the point displayed at the top.

We used a naïve Bayes classifier as the algorithm to develop the nomogram. A naïve Bayes classifier model determines the probability for a specific class by applying the Bayesian theorem under the assumption that the attributes of data and events are independent of each other. When the attributes are assumed to be independent, the posterior probability indicating the probability that an object (belongs to class *C* can be expressed as follows:

$$P(c|X) = \frac{P(a_1, a_2, ..., a_m|c)P(c)}{P(X)} = \frac{P(c)\prod_i P(a_i|c)}{P(X)} \quad (1)$$

Where c is the target class of the nomogram. However, if it is a class other than c, and $P(|X)$ represents the probability that object X does not belong to class c[9], then the odds ratio (OR) for these two probabilities can be calculated as:

$$OR = \frac{P(c|X)}{P(\bar{c}|X)} = \frac{P(c)\prod_i P(a_i|c)}{P(\bar{c})\prod_i P(a_i|\bar{c})} \quad (2)$$

We calculated the general accuracy, precision, recall, F-1 score, the area under the curve (AUC), and calibration plot using leave-one-out cross-validation (LOOCV) of the developed Bayesian algorithm-based nomogram to validate its predictive performance.

Precision is defined as the proportion of classifications that are true actually being true:

$$(Precision) = \frac{TP}{TP + FP}$$

Recall is defined as the ratio of the number of model predictions that are true over the number that are actually true:

$$(Recall) = \frac{TP}{TP + FN}$$

Accuracy is an evaluation index that can most intuitively indicate the performance of a model:

$$(Accuracy) = \frac{TP + TN}{TP + FN + FP + TN}$$

However, since using accuracy alone to overcome bias due to data imbalance is limited, it is necessary to present the F-1 score as an additional predictive performance indicator to overcome bias.

The F-1-score is the harmonic mean of Precision and Recall; *i.e.*

$$(F1 - score) = 2 \times \frac{1}{\frac{1}{Precision} + \frac{1}{Recall}} = 2 \times \frac{Precision \times Recall}{Precision + Recall}$$

AUC is an indicator used to evaluate the performance of a binary classifier. The maximum value is 1, and a value close to 1 means that the performance of the model is good (*i.e.*, the recall is larger than the

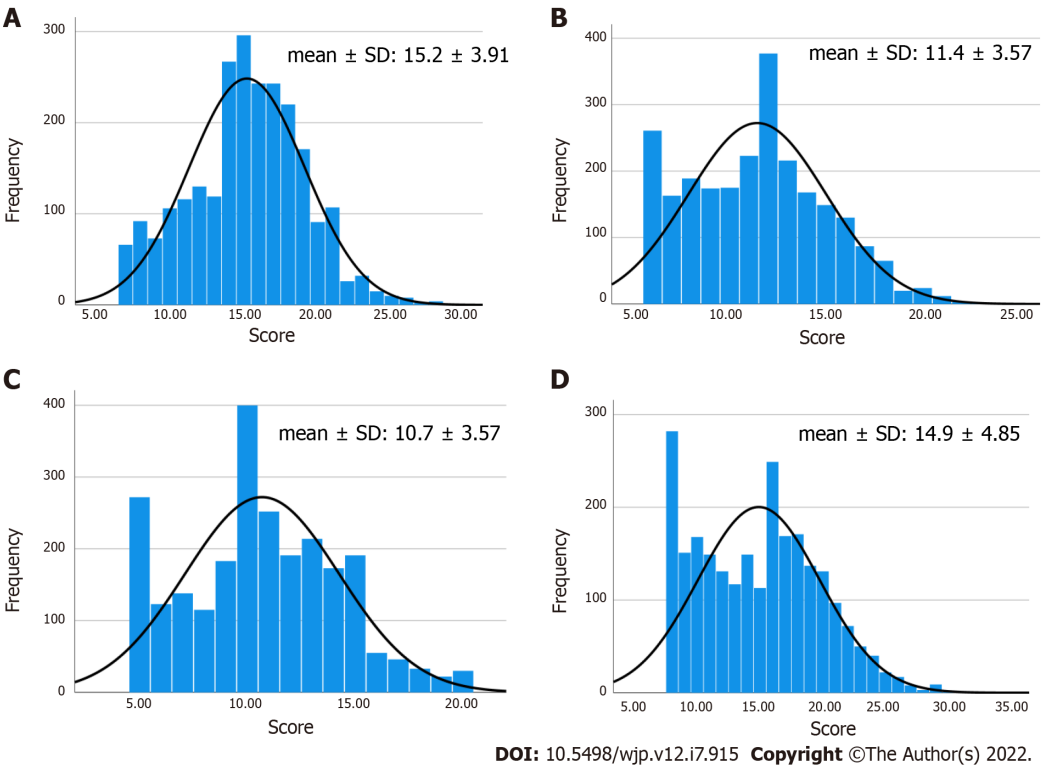

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Figure 2 Test results. A: Subject's attention test; B: Subject's aggression test; C: Subject's social withdrawal test; D: Subject's physical symptoms test.

fall-out). All analyses were performed by using Python version 3.10.0 (https://www.python.org/downloads; accessed on November 28, 2021).

RESULTS

General characteristics of the subjects

Of the 2438 subjects, the majority were male (54.1%) in a family with two siblings including the subject (61%); 32.0% had 30 minutes or more but less than 1 h of mean conversation time with their parents during weekdays; 37.2% were neither satisfied nor dissatisfied with last semester's school performance, 44.2% were satisfied with last semester's school life, and 40.4% slept for an average of 8 h *per* day during weekdays (Table 2). Their aggression, attention problems, physical symptoms, and social withdrawal are presented in Figure 2.

General sample characteristics and prevalence of depressive disorder

The results of Chi-square tests showed significant differences ($P < 0.05$) between the groups with and without depressive disorder in gender, mean sleeping hours *per* day, mean conversation time with parents *per* day, satisfaction with academic achievement, satisfaction with school life, attention, aggression, social withdrawal, and physical symptoms (Table 3).

Correlations between variables

Correlation analysis results between the major variables used in this study are presented in Figure 3. Depressive disorder was significantly and positively correlated with attention, aggression, social withdrawal, and physical symptoms ($P < 0.05$).

Predicting the group of adolescents vulnerable to depressive disorder by using the Bayesian nomogram

Figure 4 shows the Bayesian nomogram for predicting the adolescent group vulnerable to depressive disorder. We developed a nomogram comprising seven variables with high importance: Physical symptoms, aggression, social withdrawal, attention, satisfaction with school life, mean sleeping hours, and conversation time with parents were the major influential factors associated with depression in adolescents. Physical symptoms comprised the most influential factor for predicting depression in this high-risk group. We predicted the depression risk of South Korean adolescents by using the developed nomogram (Figure 4). The high-risk group comprised those who received 15.5 points for physical

Table 2 General characteristics of subjects (mean ± SD)

Characteristic	*n*	%
Depressive disorder		
No	1999	82.0
Yes	439	18.0
Gender		
Male	1318	54.1
Female	1120	45.9
Number of siblings (including the subject)		
1 person	358	14.7
2 people	1487	61.0
3 people	515	21.1
4 people	78	3.2
Mean sleeping hours *per* day		
< 5 h	63	2.6
6 h	236	9.7
7 h	600	24.6
8 h	986	40.4
9 h	454	18.6
≥ 10 h	99	4.1
Mean conversation time with parents *per* day		
< 30 min	456	18.7
≥ 30 min and < 1 h	781	32.0
≥ 1 h and < 2 h	644	26.4
≥ 2 h and < 3 h	351	14.4
≥ 3 h	206	8.4
Satisfaction with academic achievement		
Dissatisfied	577	23.9
Not dissatisfied or satisfied	906	37.6
Satisfied	928	38.5
Satisfaction with school life		
Dissatisfied	144	5.9
Not dissatisfied or satisfied	616	25.4
Satisfied	1666	68.7
Attention	15.2 ± 3.9	
Aggression	11.4 ± 3.5	
Social withdrawal	10.6 ± 3.5	
Physical symptoms	14.9 ± 4.8	

symptoms (EPS test), 11.5 points for aggression (EPS test), 10.5 points for social withdrawal (BPSCA test), and 17.5 points for attention (EPS test) and were dissatisfied with their school life, slept 10 h or more *per* day on average, and talked with parents less than 30 min (84% of developing depression).

The predictive performance of the developed nomogram for predicting the adolescent group highly vulnerable to depressive disorder was validated by using AUC, F-1 score, accuracy, and a calibration plot. The results of the LOOCV evaluation show that the model had an AUC of 0.90 (Figure 5), F-1 score of 0.86, general accuracy of 0.85, precision of 0.88, and recall of 0.86. Adolescents with and without

Table 3 Characteristics by prevalence of depressive disorder, *n* (%) (mean ± SD)

Characteristic	Depressive disorder		*P* value
	No (*n* = 1999)	Yes (*n* = 439)	
Gender			< 0.001
Male	1119 (84.9)	199 (15.1)	
Female	880 (78.6)	240 (21.4)	
Number of siblings (including the subject)			0.671
1 person	301 (84.1)	57 (15.9)	
2 people	1217 (81.8)	270 (18.2)	
3 people	419 (81.4)	96 (18.6)	
4 people	62 (79.5)	16 (20.5)	
Mean sleeping hours *per* day			<0.001
< 5 h	44 (69.8)	19 (30.2)	
6 h	191 (80.9)	45 (19.1)	
7 h	512 (85.3)	88(14.7)	
8 h	841 (85.3)	145 (14.7)	
9 h	350 (77.1)	104 (22.9)	
≥ 10 h	61 (61.6)	38 (38.4)	
Mean conversation time with parents *per* day			< 0.001
< 30 min	240 (74.6)	116 (25.4)	
≥ 30 min and < 1 h	645 (82.6)	136 (17.4)	
≥ 1 h and < 2 h	539 (83.7)	105 (16.3)	
≥ 2 h and < 3 h	293 (83.5)	58 (16.5)	
≥ 3 h	182 (88.3)	24 (11.7)	
Satisfaction with academic achievement			< 0.001
Dissatisfied	434 (75.2)	143 (24.8)	
Not dissatisfied or satisfied	735 (81.1)	171 (18.9)	
Satisfied	812 (87.5)	116 (12.5)	
Satisfaction with school life			< 0.001
Dissatisfied	63 (43.8)	81 (56.3)	
Not dissatisfied or satisfied	470 (76.3)	146 (23.7)	
Satisfied	1457 (87.5)	209 (12.5)	
Attention	14.6 ± 3.8	17.7 ± 3.1	< 0.001
Aggression	10.6 ± 3.1	15.1 ± 3.1	< 0.001
Social withdrawal	10.0 ± 3.3	13.6 ± 2.9	< 0.001
Physical symptoms	13.7 ± 4.2	20.2 ± 3.7	< 0.001

depressive disorder were compared by using a calibration plot (Figure 6) and Chi-square tests based on the predicted and observed probability, between which there was no significant difference (P = 0.683).

DISCUSSION

This study was conducted to present baseline data for preventing depressive disorder in adolescents by identifying multiple influential risk factors. The results reveal that physical symptoms, aggression, social withdrawal, attention, satisfaction with school life, mean sleeping hours, and conversation time

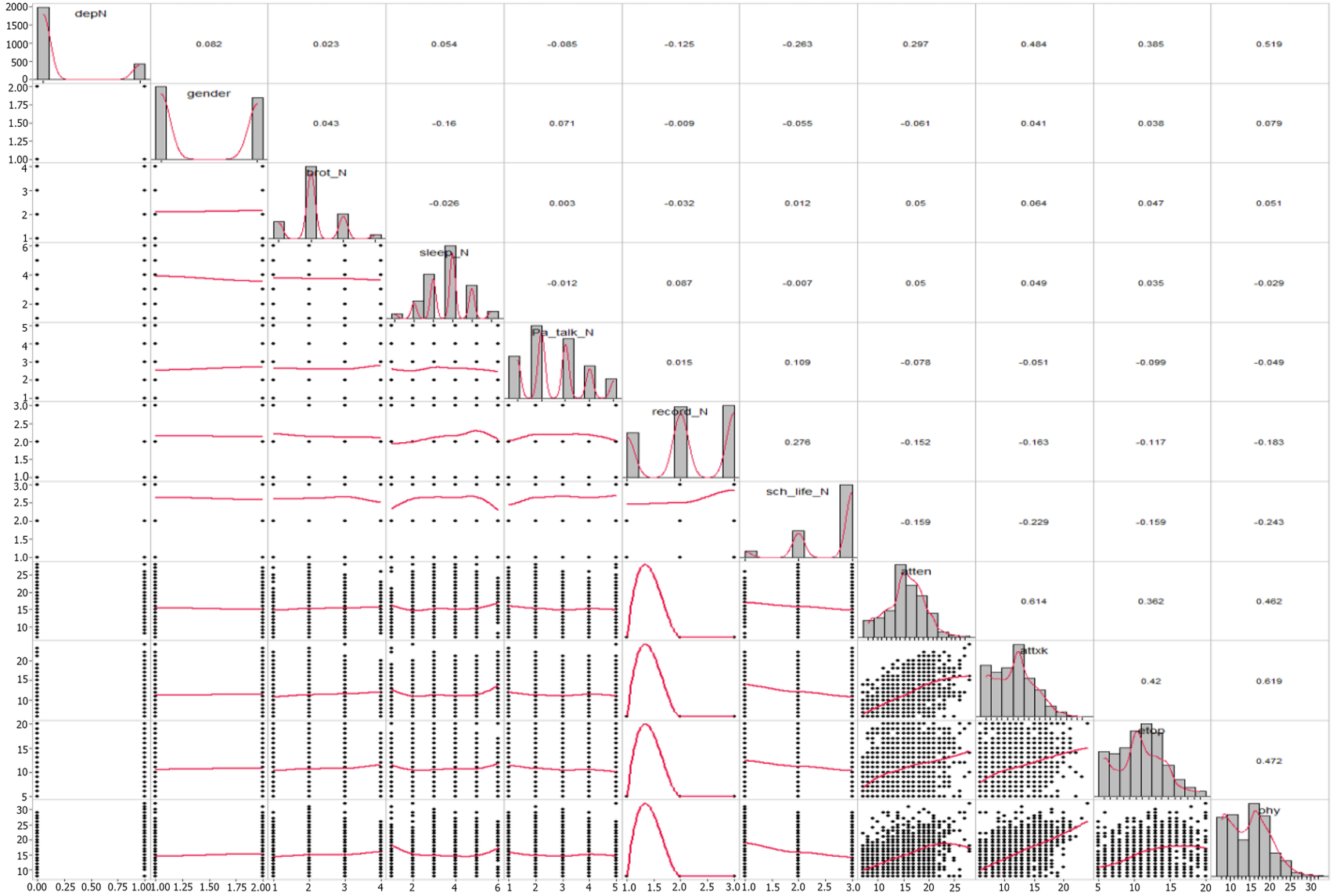

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Figure 3 Correlation between variables: Scatter matrix. depN: Depressive disorder; brot_n: Number of siblings; sleep_N: Mean sleeping hours *per* day; Pa_talk_N: Mean conversation time with parents *per* day; record_N: Satisfaction with

academic achievement; sch_life_N: Satisfaction with school life; atten: Attention; attxk: Aggression; etop: Social withdrawal; phy: Physical symptoms.

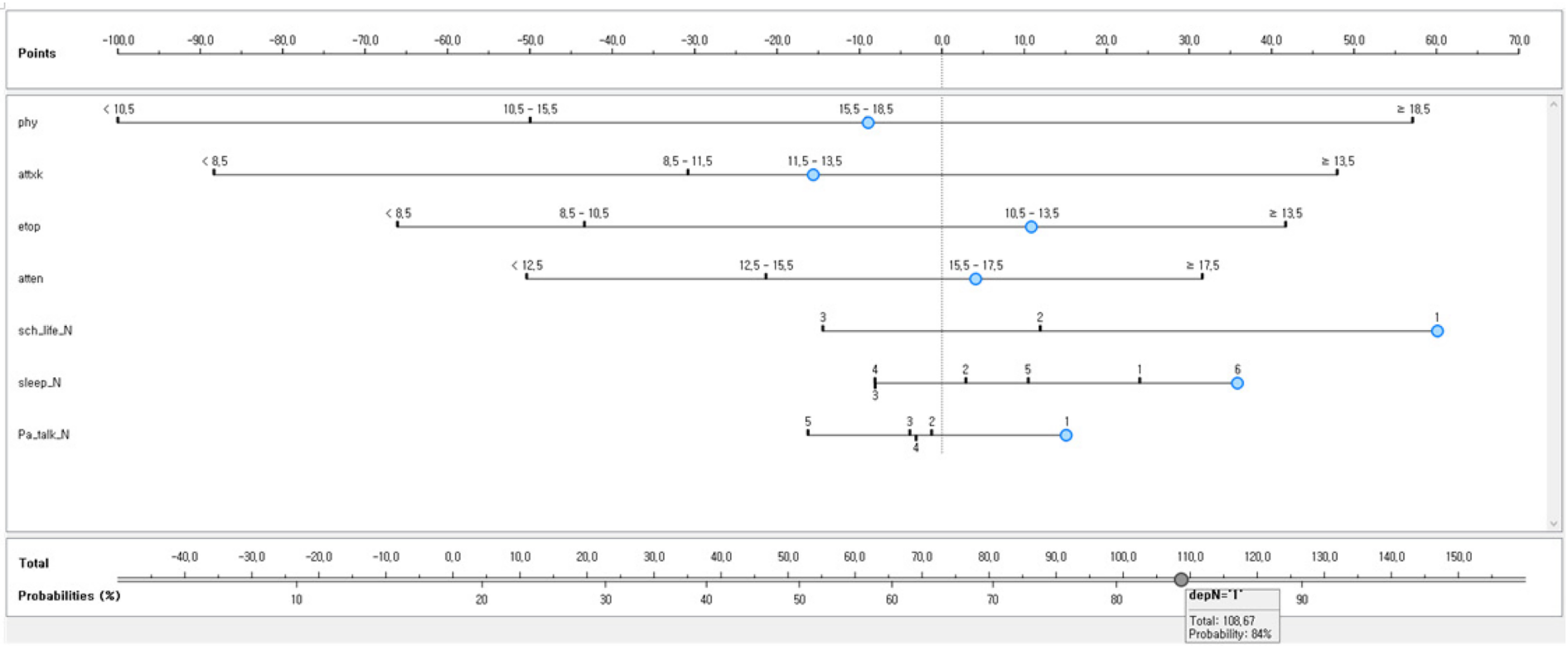

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Figure 4 A model for predicting adolescent groups vulnerable to depressive disorder by using Bayesian nomograms. phy: Physical symptoms; attxk: Aggression; etop: Social withdrawal; atten: Attention; sch_life_N: Satisfaction with school life (1 = dissatisfied, 2 = not dissatisfied or satisfied, 3 = satisfied); Pa_talk_N: Mean conversation time with parents *per* day (1: < 30 min, 2: ≥ 30 min and < 1 h, 3: ≥ 1 h and < 2 h, 4: ≥ 2 h and < 3 h; 5: ≥ 3 h).

with parents were significant predictors. Among them, physical symptoms had the greatest influence on the depressive disorder of adolescents. The outcomes of numerous previous studies on variables associated with depression in adolescents identify peer relationships, the home environment, and the school environment as significant risk factors[23-26], which supports the findings of the present study.

From the perspective of the socioecological model, family, peer group, and school are three major domains directly affecting the mental health of adolescents[27,28]. Since risk and protective factors are generated in these three domains[27,28], the viewpoint of the socioecological model is useful for

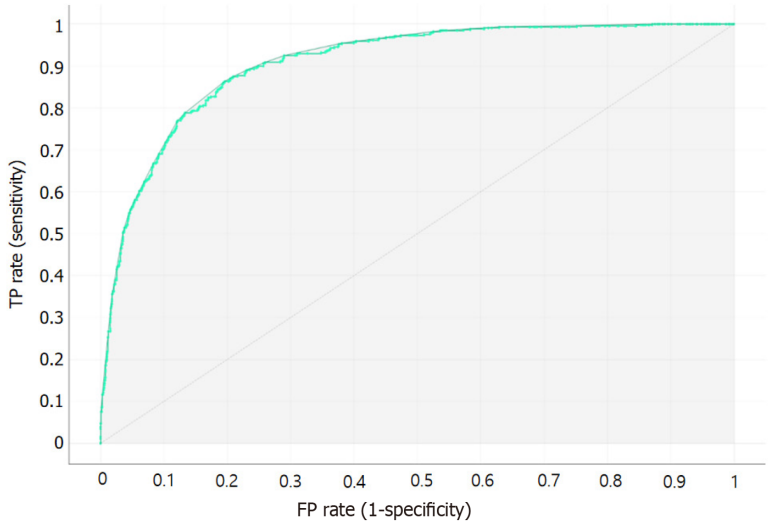

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Figure 5 Receiver operating characteristic analysis result of the developed model.

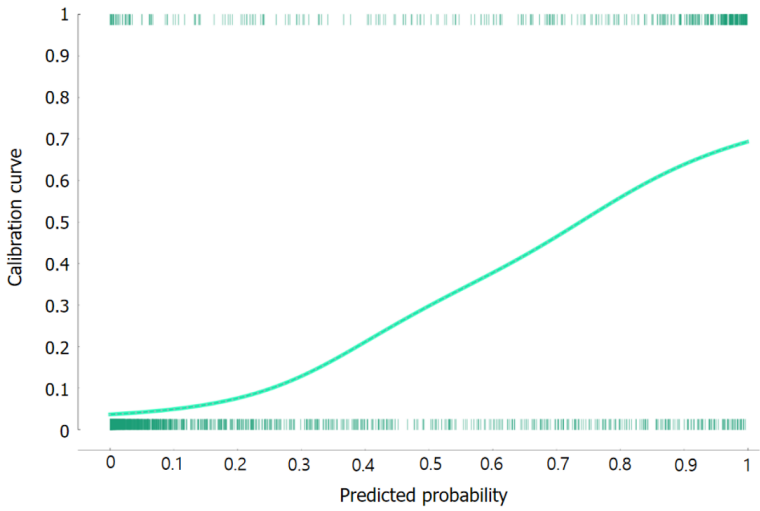

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Figure 6 Calibration plot comparing predicted to actual probability of depressive disorder.

explaining the depressive disorder of adolescents as the outcome of multiple risk factors. Nevertheless, there were limitations in previous studies about explaining the relationship between multiple risk factors and depressive disorder[2,25]. First, researchers mainly used regression models as the method of exploring the risk factors associated with depressive disorder in adolescents. Although calculating ORs by using regression analysis is useful for identifying individual risk factors, its ability to identify complex multiple risk factors is limited. Second, only sociodemographic and environmental factors as risk factors associated with depressive disorder were identified in previous studies[23,25]. Indeed, comprehensive analysis of risk factors associated with depressive disorder in adolescents by using individual factors such as difficulty with attention, social withdrawal, as well as environmental factors, has still not been sufficiently conducted. Third, as normality and independence between the variables are assumed in regression analysis, it is difficult to draw accurate conclusions because the data on many diseases such as depressive disorder are unbalanced, thereby violating the normality assumption.

In summary, there are limitations when utilizing depression prediction models for adolescents based on regression analysis in the primary medical care environment because it is difficult to identify the complex relationships between multiple risk factors solely relying on ORs based on regression models. Thus, we identified an adolescent group highly vulnerable to depressive disorders by using multiple risk factors based on a Bayesian nomogram to overcome these limitations. Our results predicted that adolescents who received 15.5 points in physical symptoms, 11.5 points in aggression, 10.5 points in social withdrawal, and 17.5 points in attention and who were dissatisfied with their current school life, slept for 10 h or more *per* day on average, and talked with their parents less than 30 min have a

depression risk of 84%. Therefore, communities and schools must continually monitor the high-risk group for the early identification and prevention of depressive disorder in adolescents with these multiple risk factors.

Another important finding of the present study is that physical symptoms in adolescents comprised the most influential risk factor in predicting depressive disorder. Ryu and Hong[29] (2019) also explored factors affecting depressive disorder in 1881 middle school students and confirmed that physical symptoms of adolescents comprised the main risk factor influencing depressive disorder. Choi *et al*[19] (2017) also revealed that physical symptoms and depressive disorder had a positive correlation in fourth graders.

Physical symptoms in adolescents, which are related to mental activities and the psychological state, are generally overlooked as an early symptom of depressive disorder because they cannot be found by internal or neurological examination, or even when a physical abnormality is found, the symptoms are insufficient for disease diagnosis. However, although depressive disorder of adolescents is similar to the adult psychopathology, unlike in adults, clinical characteristics are often accompanied by physical symptoms (*e.g.*, fatigue, insomnia, muscle pain, and headache) and aggression[30]. In particular, Jung *et al*[31] (2004) reported that depressed people excessively focus on physical symptoms or amplify their bodily sensations. Therefore, frequent complaints by adolescents of physical symptoms without a known medical cause are likely to be early signs of depressive disorder, even when the physical symptoms seem superficially less severe. Consequently, the community and school must pay attention to them and actively intervene by periodically checking the emotional state of adolescents, as well as providing individual counseling and in-depth psychological testing.

The strength of the present study is that it identified the group at high risk of developing depressive disorder based on multiple risk factors by using epidemiological data on South Korean adolescents and provided evidence for the early screening and management of depression. However, it does have some limitations, with the first being that there could be more potential variables for depressive disorder in addition to the explanatory variables used in this study because we analyzed secondary data. Second, the results cannot be generalized for all high school students because we identified a high-risk group for depressive disorder in seventh graders only. Third, the variables used (including depressive disorder) were measured based on a self-report questionnaire. Thus, future studies are needed to identify groups at high risk of depressive disorder by integrating qualitative research methods such as Delphi analysis and in-depth interviews in addition to self-report questionnaires. Fourth, since the results were based on a cross-sectional approach, it is difficult to determine causal relationships. Hence, additional prospective cohort studies should be conducted to prove causality between the depressive disorder high-risk group and depressive disorder found in the present study.

CONCLUSION

We showed that physical symptoms, aggression, social withdrawal, attention, satisfaction with school life, mean sleeping hours, and conversation time with parents are influential factors associated with depressive disorder in adolescents. Among them, physical symptoms comprise the most influential factor in the prediction of depressive disorder. Therefore, periodically checking on the emotional state of adolescents is required, along with providing individual counseling and conducting in-depth psychological examinations when necessary. Moreover, longitudinal studies based on clinical depressive disorder data targeting depressive disorder in the high-risk group confirmed in this study should be conducted.

ARTICLE HIGHLIGHTS

Research background

Although South Korea has developed and carried out evidence-based intervention and prevention programs to mitigate depressive disorder in adolescents, the number of adolescents with depressive disorder has increased every year for the past 10 years. Consequently, it is necessary to identify the influential factors causing depression and develop a predictive model with high accuracy that can identify groups highly vulnerable to depressive disorder as soon as possible.

Research motivation

Recently, the naïve Bayesian nomogram has been used as a method of predicting groups at high risk of developing diseases. One of the advantages of this method is that it presents the risk probability according to multiple risk factors of a disease visually so that clinicians can easily understand the results.

Research objectives
In this study, a nomogram based on a naïve Bayesian algorithm using epidemiological data on adolescents in South Korea was developed and baseline data for screening depressive disorder in adolescents was presented.

Research methods
We used a naïve Bayes classifier as the algorithm to develop the nomogram. Also, we calculated the general accuracy, precision, recall, F-1 score, the area under the curve, and calibration plot using leave-one-out cross-validation of the developed Bayesian algorithm-based nomogram to validate its predictive performance.

Research results
We showed that physical symptoms, aggression, social withdrawal, attention, satisfaction with school life, mean sleeping hours, and conversation time with parents were influential factors associated with depressive disorder in adolescents.

Research conclusions
Periodically checking on the emotional state of adolescents is required, along with providing individual counseling and conducting in-depth psychological examinations when necessary.

Research perspectives
Longitudinal studies based on clinical depressive disorder data targeting depressive disorder in the high-risk group confirmed in this study should be conducted.

FOOTNOTES

Author contributions: Byeon H designed the study, interpreted the data, preformed the statistical analysis, and wrote the article.

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ORIGINAL ARTICLE

Observational Study

Believing processes during the COVID-19 pandemic in individuals with bipolar disorder: An exploratory study

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Abstract

BACKGROUND

Believing or "credition" refers to psychological processes that integrate the cognitions and emotions that influence our behavior. In the credition model by Angel and Seitz, four parameters are postulated: proposition, certainty, emotion and mightiness. It is assumed that believing processes are influenced by both the individual as well as socio-cultural factors and external circumstances. External or environmental circumstances can include threatening situations such as the ongoing pandemic. It has been hypothesized that believing processes related to the pandemic differ between individuals with bipolar disorder (BD) and healthy controls (HC).

AIM

To investigate credition in individuals with BD during the coronavirus disease 2019 (COVID-19) pandemic.

METHODS

Psychiatrically stable individuals with BD (n = 52) and age- and sex matched HC (

n = 52) participated in an online survey during the first lockdown of the COVID-19 pandemic. The survey took place between April 9th and June 4th, 2020, in Austria. Participants completed the Brief Symptom Inventory-18, the Beck Depression Inventory-II, the Altman Self-Rating Mania Scale, the Pittsburgh Sleep Quality Index and a dedicated Believing Questionnaire assessing four parameters of credition (proposition, certainty, emotion and mightiness). The MAXQDA software was used to analyze the qualitative data. Statistical analyses included analyses of variance, a multivariate analysis of variance and a multivariate analysis of co-variance.

RESULTS

Individuals with BD reported significantly more negative propositions [F (1,102) = 8.89, P = 0.004, η^2_p = 0.08] and negative emotions [Welch´s F (1,82.46) = 18.23, P < 0.001, η^2_p = 0.18], while HC showed significantly more positive propositions [F (1,102) = 7.78, P = 0.006, η^2_p = 0.07] and emotions [F (1,102) = 14.31, P < 0.001, η^2_p = 0.12]. In addition, individuals with BD showed a higher incongruence between their propositions and their emotions [F (1,102) = 9.42, P = 0.003, η^2_p = 0.08] and showed strong correlations between the parameters of the Believing Questionnaire and their psychiatric symptoms (r = 0.51-0.77, all P < 0.001). Positive as well as negative emotions and propositions were associated with scores measuring symptoms of depression, anxiety and sleep quality.

CONCLUSION

Believing parameters were associated with psychiatric symptoms in BD during the pandemic. Findings broaden knowledge about the susceptibility of believing processes for ambient challenges in individuals with BD.

Key Words: COVID-19; Bipolar disorder; Cognition; Emotions; Judgement; Evaluation study

Core Tip: Research concerning believing processes ("creditions") in individuals with bipolar disorder (BD) during the coronavirus disease 2019 pandemic showed that patients reported more negative emotions and propositions than healthy controls who reported more positive emotions and propositions. Individuals with BD had a higher incongruence between their propositions and their emotions and strong correlations between the parameters of the Believing Questionnaire and psychiatric symptoms. These findings provide insight into the attitudes and beliefs of people with BD during a crisis.

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INTRODUCTION

Believing is a fundamental cognitive process involving belief formation, updating and evaluation[1,2]. Importantly, beliefs determine an individual's behavior by allowing predictions of future events[3]. In the past century, believing has widely been neglected as an object of scientific interest since it was associated with spirituality or considered as abnormal[4]. Recently, however, there is growing interest in the processes of believing and beliefs in evolutionary biology, cognitive neuroscience, psychology and psychiatry[5]. This is corroborated by neuroimaging evidence revealing underlying neural correlates of believing[6-10]. To contextualize this research within the realm of cognition and emotion, the term "credition" is derived from the Latin word "credere" (which means "to believe"). This term highlights psychodynamic activities which underpin the believing processes resulting in stable but still modifiable states of belief[4].

Creditions are understood as dynamic processes that can activate at any time and influence existing states of belief which were constructed by a person's prior experiences[4]. Accordingly, creditions are an important part of our lives as they influence our thinking, feeling and acting and vice versa[11]. Sacks and Hirsch[12] postulated that people tend to accept something as reality until they are proven wrong and that belief formation can be understood as the result of perceptual and affective information processing. Supporting this notion, prior work demonstrates that integration of cognition and emotion

occurs in the lateral prefrontal cortex[13]. In the credition model, four characteristic parameters are differentiated: proposition, certainty, emotion and mightiness[1]. "Proposition" represents the content of the statement. "Certainty" reflects the person's inclination to believe the proposition. "Emotion" reflects the affective valence of the proposition for a person. "Mightiness" reflects the degree of relevance of the proposition. It is assumed that believing processes are influenced by the individual themself as well as by socio-cultural factors and external circumstances[14]. Such external or environmental circumstances can include threatening situations including the ongoing pandemic.

The coronavirus disease 2019 (COVID-19) pandemic has deeply influenced the lives of the global population. Caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it was labelled as a pandemic by the WHO on March 11th, 2020[15]. Since its outbreak, the virus has infected over 274 million and claimed the lives of more than five million people (December 2021)[16]. To contain the virus spread, several periods of lockdown have been implemented across the world contributing to far-reaching effects of the pandemic on the environment[17], economy, social life[18] and mental health [19]. The psychological consequences have been numerous[20], particularly for individuals with pre-existing psychiatric disorders including affective disorders[21].

Bipolar disorder (BD) is a neuropsychiatric affective disorder characterized by severe changes in mood ranging from depression to mania. Typically emerging in early adulthood, bipolar spectrum disorders have a prevalence of 1% to 6%[22,23]. Stressful events and exposure to life stress increase the recurrence of affective episodes in BD[24], making individuals with BD a vulnerable group during the COVID-19 pandemic[25]. Increased depressive symptoms, fatigue[26], psychological distress[27,28], post-traumatic stress symptoms[29], fear and sleeping problems[29,30] have all been shown in this population during this period. An increase in subjective cognitive dysfunction has also been found in this population and was associated with negative symptoms and poor quality of life[31].

In Beck's cognitive model of depression[32], dysfunctional cognitive schemata are assumed to be the basis for the development of a depressive episode. This leads to a cognitive bias in information processing as attention is selectively directed towards negative aspects and experiences while positive events and memories are blocked[32,33]. Regarding the COVID-19 pandemic, the specific believing processes possibly contributing to the development of a depressive episode remain largely unknown.

The aims of the current study were: (1) To analyze believing processes, in particular the four parameters of proposition, certainty, emotion and mightiness in individuals with BD during the COVID-19 pandemic compared with healthy controls (HC); and (2) to investigate correlations between these parameters and psychiatric symptoms in BD.

Due to the still lacking empirical evidence in this field, this study utilized an exploratory approach. However, based on the literature, it was expected that in accordance with Beck's cognitive theory of depression[32], individuals with BD would show more negative propositions and emotions in their verbalized believing processes than HC. Further, it was expected that HC would show more positive propositions and emotions in their verbalized believing processes compared to individuals with BD. Additionally, it was hypothesized that current psychiatric symptoms would be related to possible differences in parameters between the two groups.

MATERIALS AND METHODS

Participants

In total, 260 individuals were recruited; 208 of these had complete data sets. After matching for sex and age, the final sample was comprised of 52 stable, medicated individuals diagnosed with BD (29 males and 23 females) and 52 HC. The individuals with BD were previously diagnosed at the outpatient center for BD at the Medical University of Graz, Department of Psychiatry and Psychotherapeutic Medicine, using the Structured Clinical Interview for DSM-IV[34]. Exclusion criteria for HC were any psychiatric diagnosis, taking psychiatric medication or first-degree relatives with psychiatric disorders. Inclusion criteria for all participants were voluntary participation and e-mail access. All participants with BD and the majority of HC were recruited from the pool of the ongoing BIPLONG study which assesses lifestyle, metabolism and cognitive function in individuals with BD compared to HC. Additional HC were recruited by word of mouth and social media.

Procedure

An online survey was sent out *via* the survey tool LimeSurvey (Version 3.27.4, Limesurvey GmbH) between April 9th and June 4th, 2020, starting 3 wk after the beginning of the first lockdown in Austria. Participants were thus experiencing travel restrictions, social distancing measures, and the closure of institutions such as schools, leisure venues and nonessential shops while completing measures for this study.

Participants gave informed consent before pseudo-anonymously responding to questionnaires. This study was approved by the local ethics committee in accordance with the current revision of the Declaration of Helsinki, ICH guideline for Good Clinical Practice and current regulations (Medical University of Graz, Austria; individuals with BD were from the BIPLONG study, EK-number: 25-335 ex

12/13; data was collected in the course of a new study, EK number: 32-363 ex 19/20).

Psychological inventories

Analyses in the current study were conducted on the following psychological inventories:

The Brief Symptom Inventory-18 (BSI-18) was constructed by Derogatis and Fitzpatrick[35], a short version of the Symptom-Checklist-90-Revised (SCL-90-R) by Derogatis and Savitz[36]. The BSI-18 was used to measure psychological symptoms during the last week. This measure yields a Global Severity Index (GSI) and three subscales: anxiety, depression and somatization, each with acceptable internal consistency (Cronbach's alpha: GSI $\alpha = 0.93$, anxiety $\alpha = 0.84$, depression $\alpha = 0.87$, and somatization $\alpha = 0.82$).

The Beck Depression Inventory (BDI-II) by Beck *et al*[37] assessed the severity of depressive symptoms within the last week with a score of 18 or higher indicating clinically relevant depression. Assessed quality criteria were Cronbach's alpha ($\alpha \geq 0.84$) and reliability ($r \geq 0.75$)[38].

The Altman Self-Rating Mania Scale (ASRM) is a 5-item questionnaire that determines the extent of manic symptoms in the course of 1 wk[39]. Assessing self-confidence, mood, speech, activity level and need to sleep, each item is rated on a five-point scale (0-4). A score of five or more is considered clinically relevant.

The Pittsburgh Sleep Quality Index (PSQI) was constructed by Buysse *et al*[40] and measures sleep quality in the last month. The 19 items constitute seven components: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication and daytime sleepiness. The sum score has a range of 0-21, with a higher score indicating worse sleep quality. A total score > 5 has diagnostic sensitivity of 89.6% and specificity of 86.5% ($\kappa = 0.75$, $P < 0.001$) when differentiating between poor and good sleepers.

The Believing Questionnaire (BQ) was created by JWS and ND of the Department of Psychiatry and Psychotherapeutic Medicine in consultation with HFA and RS. The BQ assessed the characteristic credition parameters (proposition, certainty, emotion, mightiness) during the COVID-19 pandemic. Consisting of six open-ended questions, the BQ was developed to gain insight in believing processes during such a precarious and challenging situation:

When I think of the current, very special situation, I believe;
When I think of my body, I believe;
When I think of my mental/emotional situation, I believe;
When I think of the coronavirus, I believe;
When I think of what the future holds 3 mo from now, I believe;
When I think of what the future holds 6 mo from now, I believe.

Participants were asked to answer as spontaneously and honestly as possible. Each question was then rated on a scale from 0 (= not sure) to 100 (= very sure) regarding the certainty of belief. Additionally, participants were asked to identify the emotion that arose for them in the context of that belief using an "Emotion Wheel" consisting of three concentric circles. The innermost circle showed the six basic emotions according to Ekman[41]: fear, anger, joy, sadness, disgust and surprise. The surrounding two circles provided options to further differentiate the basic emotion. The intensity of the emotion (sense of mightiness) was rated on a scale from 0 (= not sure) to 100 (= very sure) as well.

Statistical analysis

To analyze the qualitative data of the BQ in a standardized and transparent manner, MAXQDA 2020[42] software was used; this has previously proven useful in research of BD in clinical settings[43,44]. The process of analysis consisted of two independent raters categorizing individuals' propositions and emotions into the three categories positive, negative and indifferent, generating six codes (positive propositions, negative propositions, indifferent propositions, positive emotions, negative emotions and indifferent emotions). The interrater reliability of $\kappa = 0.92$ was satisfactory.

To make data suitable for analysis with the Statistical Package for Social Sciences (SPSS version 26, IBM), six new variables were calculated to reflect the frequency of each code. Additionally, a variable reflecting the frequency of incongruencies between the valence of a person's proposition and the identified emotion was created.

A multivariate analysis of variance (MANOVA) with group (BD *vs* HC) as the independent variable was calculated to test for between-subject differences in the credition parameters. Positive propositions, negative propositions and positive emotions were included in the MANOVA as variables because they were moderately intercorrelated ($r = 0.64$-0.78, all $P < 0.001$). Not all credition parameters were intercorrelated; as such, single ANOVAs were utilized for indifferent propositions, negative emotions, indifferent emotions, incongruence, certainty and mightiness. A multivariate analysis of co-variance with the same design but controlling for psychiatric symptomatology was then conducted. The psychiatric symptomatology consisted of the individual total scores in the BSI-18 (GSI), BDI-II and PSQI. The total score of the ASRM was not included because the two groups did not differ in their manic symptomatology. Spearman correlation analyses were used to test for associations between credition parameters and psychological test scores (BSI-18, BDI-II, ASRM and PSQI). Bonferroni correction ($P < 0.003$) was used to correct for conducting multiple tests. To test for normal distribution for the psychological test scores and credition parameters of both groups, Shapiro-Wilk tests were run and skewness

and kurtosis were calculated. All data met the assumed criteria of linearity. The criterion of normality was not met for several variables (sex, negative propositions, positive emotions, negative emotions, indifferent emotions, and certainty) however, the sample size was adequate ($n \geq 30$) and thus, normal distribution could be assumed, according to the central limit theorem. The criterion of variance was also not met for several variables (GSI, BDI-II, PSQI, negative propositions, positive emotions, negative emotions). However, the analyses were continued given that MANOVAs are relatively robust to violations of equality of variance[45] and for ANOVAs the Welch-ANOVA could be interpreted[46,47].

In addition, word clouds in MAXQDA were used to present propositions and emotions for each item of the BQ. Word clouds are a useful method to simultaneously visualize the actual words as well as their frequency[48]. The word clouds show the most frequently used words for each BQ item. Prepositions and conjunctions were ignored and added to a stop list in MAXQDA. The word clouds were translated from German into English for the present paper. It is noted that a loss of information may occur due to translation.

RESULTS

Sample characteristics

Each group consisted of 29 males and 23 females. Mean age was 50.2 years (individuals with BD; *SD* = 14.5) and 49.0 years (HC; *SD* = 13.3). The individuals with BD showed higher scores of psychiatric symptoms than the HC group [F (3,100) = 11.53, $P < 0.001$, Roy's Largest Root = 0.346, $\eta^2_p = 0.257$; see Table 1 for statistics].

Differences in believing parameters between the individuals with BD and HC

The MANOVA testing for group differences in the believing parameters showed significant differences for the combined dependent variables of positive propositions, negative propositions and positive emotions [F (3,100) = 4.93, $P = 0.003$, $\eta^2_p = 0.13$, Roy´s Largest Root = 0.15]. Specifically, the HC group showed more positive propositions and emotions in their verbal believing processes than the individuals with BD. In contrast, the individuals with BD revealed more negative propositions and emotions compared with HC (Table 1). The individuals with BD showed a stronger incongruence between the valence of their propositions and the valence of their emotions. Furthermore, HC were more certain about their propositions than were individuals with BD. However, this difference did not remain significant after Bonferroni correction. No statistically significant differences emerged between the two groups in indifferent propositions and emotions or in mightiness.

After controlling for psychiatric symptoms (GSI score of the BSI-18, total scores of BDI-II and PSQI), the group differences in credition parameters were no longer significant.

Word clouds

Figures 1-3 show word clouds for the six BQ items. Results of item 2 (“When I think about my body, I believe”) and item 3 (“When I think about my mental/emotional situation, I believe”) are presented in more detail because there were significant differences between the two groups for both the valence of propositions [item 2: $\chi^2(2) = 12.45$, $P = 0.002$, Cramér's V = 0.22 item 3: $\chi^2(2) = 8.03$, = 0.018, Cramér's V = 0.27] and the valence of emotions [item 2: $\chi^2(2) = 10.44$, $P = 0.004$, Cramér's V = 0.31; item 3: $\chi^2(2) = 9.61$, $P = 0.005$, Cramér's V = 0.30]. For item 2, individuals with BD used a total of 352 words and the HC 273 words. For item 3, individuals with BD used a total of 486 words and the HC 292 words. The word frequencies of the different words for the two items are shown in Tables 2 and 3.

For item 2 (Figure 2, Table 2), both groups used the word “I” most often, followed by positive emotional words. The HC predominantly used positive words about their body, such as “fit”, “fitter” and “healthy”. In contrast, the individuals with BD, predominantly used the word “fat” for their body. In addition, the individuals with BD often used negative emotion words such as “fearful” and “unhappy”. For item 3 (Figure 2, Table 3), both groups again used the word “I” most frequently. However, the individuals with BD more frequently utilized self-centered words, such as “me” and “myself”, followed by positive emotion words, such as “good” and “content”. The HC used positive emotion words most often, such as “content”, “good”, “balanced” and “calm”.

For item 4 (“When I think of the coronavirus, I believe") and item 6 (“When I think of what the future holds 6 mo from now, I believe"), it was notable that individuals with BD used the word “I” and the HC the word “We” most frequently (see Figures 1 and 3).

Correlations between believing parameters and psychiatric symptoms

Spearman correlation analyses between the believing parameters and psychiatric symptoms showed significant correlations in individuals with BD ($P < 0.001$ after Bonferroni correction; Table 4) for both positive as well as negative propositions and psychiatric symptoms. Specifically, there were significant negative correlations between the positive propositions and emotions and the BSI-18 scales GSI, depression and anxiety, the BDI-II and the PSQI sum score. Positive correlations were found between

Table 1 Differences in the psychiatric symptoms and the credition parameters between the bipolar individuals and controls

	Bipolar		Control		*F*	*P* value	η^2_p
	M	SD	M	SD			
BSI-18	13.21	13.45	3.83	4.23	23.05	**< 0.001**	0.18
BDI-II	12.08	10.92	2.77	3.54	34.22	**< 0.001**	0.25
ASRM	1.52	2.73	0.94	1.60	1.73[1,2]	0.192	
PSQI	7.08	4.26	4.12	2.34	19.30	**< 0.001**	0.16
Positive propositions	3.15	1.80	4.08	1.57	7.78	**0.006**	0.07
Negative propositions	1.63	1.70	0.81	1.10	8.89	**0.004**	0.08
Indifferent propositions	1.23	1.17	1.12	1.00	0.29	0.590	
Positive emotions	3.10	2.31	4.54	1.49	14.31	**< 0.001**	0.12
Negative emotions	2.65	2.34	1.06	1.34	18.23[2,3]	**< 0.001**	0.18
Indifferent emotions	0.25	0.65	0.38	0.75	0.96	0.329	
Incongruence[4]	2.13	1.39	1.38	1.09	9.42	**0.003**	0.08
Certainty[5]	80.49	15.67	86.35	10.44	5.03	0.027	0.05
Mightiness[5]	78.11	13.91	77.20	15.98	0.10	0.757	

[1]Welch´s *F*.
[2]df_{error} = 82.46.
[3]df_{error} = 80.98.
[4]Incongruence between the propositions and the emotions.
[5]In percent.
Bold letters: Bonferroni corrected significant differences. df = 1; df_{error} = 102; BSI-18: Brief-Symptom Inventory-18; BDI-II: Beck Depression Inventory; ASRM: Altman Self-Rating Mania Scale; PSQI: Pittsburgh Sleep Quality Index.

the negative emotions and the BSI-18 scales GSI, depression and anxiety, the BDI-II and the PSQI sum score. Additionally, a negative correlation was found between negative propositions and depression while GSI, the BDI-II and the PSQI sum score were positively correlated. No correlations were found with the scores in the ASRM.

In HC, there was only one negative correlation between certainty about the proposition and the BSI-18 GSI score (r = -0.48, P < 0.001, after Bonferroni correction).

Correlations between the believing parameters in the Believing Questionnaire

Spearman correlation analyses were used to examine the extent to which the believing parameters depend on each other (Tables 5 and 6). The analyses were calculated for both groups separately. After Bonferroni correction, both groups showed significant correlations between propositions and emotions with a positive and negative valence. There was another significant correlation between certainty and mightiness. Furthermore, the controls showed significant correlations between the positive and negative propositions and incongruence.

DISCUSSION

In this study, creditions of individuals with BD were investigated using questionnaires tapping into beliefs and believing processes during the first wave of the COVID-19 pandemic. Findings showed that individuals with BD differed from controls in the believing parameters of propositions and emotions. Results confirmed our hypothesis that individuals with BD would show more negative propositions and emotions in their verbalized believing processes than HC. This corresponds to Beck's cognitive theory about negative dysfunctional cognitive schemata in depressive disorders[32]. Accordingly, a cognitive bias in information processing renders depressive individuals likelier to focus their attention more on negative aspects of life and to block positive aspects. This change in perception can result in negative believing processes. In addition, we found that individuals with BD showed greater incongruence between the valence of their propositions and the valence of their emotions compared to HC. Carl Rogers[49] has suggested incongruence as the root cause for the development of mental disorders. According to this concept, the actual experience does not match one´s own self-image. Recently, it was proposed that incongruence stems from a mismatch between the internal and external

Table 2 Word frequencies for item 2 ("When I think about my body, I believe") in the Believing Questionnaire for the two groups

BD			HC		
Word	**Frequency**	**%[1]**	**Word**	**Frequency**	**%[1]**
I	31	8.8	I	28	10.3
Optimistic	8	2.3	Good	10	3.7
More	7	2.0	Content	8	2.9
My	7	2.0	Body	6	2.2
Not	6	1.7	Everything	6	2.2
Should	6	1.7	Healthy	6	2.2
Content	5	1.4	More	6	2.2
Could	5	1.4	Exercise	5	1.8
Happy	5	1.4	My	5	1.8
Much	5	1.4	Optimistic	5	1.8
Thick	5	1.42	Fit	4	1.47
Better	4	1.14	Fitter	4	1.47
Expectant	4	1.14	Myself	4	1.47
Good	4	1.14	Should	4	1.47
Age	3	0.85	Unconcerned	4	1.47
Always	3	0.85	Worried	4	1.47
Confident	3	0.85	Calm	3	1.10
Fearful	3	0.85	Could	3	1.10
Fits	3	0.85	Fits	3	1.10
Make	3	0.85	Self-confident	3	1.10
Me	3	0.85	Sports	3	1.10
Myself	3	0.85			
Okay	3	0.85			
Quite	3	0.85			
Unhappy	3	0.85			
Very	3	0.85			
Yr	3	0.85			

[1]Shows what percentage of the total words the word represents. BD: Individuals with bipolar disorder; HC: Healthy controls.

experiences and a person's self-concept, resulting in a state of tension[50]. The high incongruence we found in individuals with BD could therefore reflect an experiential incongruence within the individuals with BD themselves.

Furthermore, we observed that believing parameters were strongly related to psychiatric symptoms in the bipolar group. The correlations were particularly strong between the propositions or emotions and the total scores in the BSI-18, BDI-II and PSQI. The believing parameters related to propositions and emotions were more negative as psychiatric symptoms were more severe and more positive as psychiatric symptoms were less severe. In contrast, only a moderate negative association between GSI and the believing parameter of certainty was observed. One possible explanation for the fact that psychiatric symptoms and believing parameters were highly correlated in individuals with BD could be that individuals with BD generally experienced more psychiatric symptoms during the COVID-19 pandemic. Another possible explanation is that individuals with BD ruminate more on emotional experiences, both negative and positive[51-53]. Consequently, cognitions and emotions appear to have a profound impact on mental health in individuals with BD.

An interesting result of this study was that after controlling for psychiatric symptoms, *i.e.* total scores in BSI-18, BDI-II and PSQI, the differences in believing parameters between the two groups

Table 3 Word frequencies of item 3 ("When I think about my mental/emotional situation, I believe") in the Believing Questionnaire for the two groups

BD			HC		
Word	**Frequency**	**%[1]**	**Word**	**Frequency**	**%[1]**
I	55	11.3	I	32	11.0
Good	12	2.5	Content	13	4.5
Me	11	2.3	Good	11	3.8
Myself	11	2.3	Balanced	7	2.4
Content	10	2.1	Calm	7	2.4
Not	8	1.7	Me	7	2.4
Better	7	1.4	Myself	7	2.4
Everything	7	1.4	Optimistic	7	2.4
Completely	6	1.2	Stable	7	2.4
Happy	6	1.2	Very	6	2.1
My	6	1.23	Reassured	5	1.71
Like	5	1.03	Carefree	4	1.37
Can	4	0.82	Everything	4	1.37
Confident	4	0.82	Expectant	4	1.37
Depressed	4	0.82	Happy	4	1.37
Much	4	0.82	Not	4	1.37
Optimistic	4	0.82	Better	3	1.03
Sad	4	0.82	Confident	3	1.03
Stable	4	0.82	Psychologically	3	1.03
Balanced	3	0.62	Self-confident	3	1.03
Currently	3	0.62	Strong	3	1.03
Feel	3	0.62			
Now	3	0.62			
Room	3	0.62			
Still	3	0.62			
Time	3	0.62			

[1]Shows what percentage of the total words the word represents. BD: Bipolar disorder; HC: Healthy controls.

disappeared. This finding suggests that believing processes reflect important aspects of life that are also represented by the questionnaire for psychological symptoms. This could be explained by an intrinsic *modulator function* that is accounted for by the credition model[1]. On the molecular level, the modulator function may be linked to the dopamine system which plays an important role in believing processes[54, 55] as well as for abnormal believing processes in psychiatric disorders[56-58].

The word clouds we created showed that the individuals with BD used words of emotion with negative connotations more often compared to the control group. Moreover, those with BD used more self-centered language than HC. We, therefore, assume that individuals with BD tend to consider the self in the focus of their believing processes more often than the HC. Interestingly, individuals with BD more frequently answered the two items "When I think of the coronavirus, I believe" and "When I think of what the future holds 6 mo from now, I believe" from an individual perspective using the word "I", whereas HC more often answered from a group perspective with "We". Perhaps individuals with BD depend more upon the self in the context of coping while healthy individuals are more likely to refer to social reasoning. Another explanation for this finding is that individuals with BD could be the disorder itself and the associated introspection processes and self-awareness, possibly learned in psychotherapy, as all patients were treated at the outpatient center for BD at the Medical University of Graz.

Table 4 Bipolar group: Bonferroni adjusted Spearman correlations between the parameters of the Believing Questionnaire and the psychiatric symptoms

	BSI-18	Somatization[2]	Depression[2]	Anxiety[2]	BDI-II	ASRM	PSQI
Positive propositions	**-0.66**[c]	-0.38[b]	**-0.72**[c]	**-0.56**[c]	**-0.56c**	0.20	**-0.51**[c]
Negative propositions	**0.54**[c]	0.38[b]	**-0.60**[c]	0.42[b]	**0.63c**	-0.21	**0.54**[c]
Indifferent propositions	0.28[a]	0.11	0.25	0.32[a]	-0.05	-0.02	0.06
Positive emotions	**-0.70**[c]	-0.47[b]	**-0.71**[c]	**-0.62**[c]	**-0.79**[c]	0.09	**-0.59**[c]
Negative emotions	**0.66**[c]	0.44[b]	**0.68**[c]	**0.58**[c]	**0.77**[c]	-0.14	**0.62**[c]
Indifferent emotions	0.07	-0.04	-0.04	0.19	-0.10	0.10	-0.22
Incongruence[1]	0.28[a]	0.18	0.31[a]	0.18	0.20	-0.16	0.17
Certainty	-0.20	-0.21	-0.17	-0.12	-0.17	0.03	-0.16
Mightiness	0.03	-0.05	0.08	0.07	0.09	0.05	0.08

[1]Incongruence between the propositions and the emotions.
[2]Subscales of the BSI-18.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
Bold letters: Bonferroni corrected significant correlations. BSI-18: Brief-Symptom Inventory-18; BDI-II: Beck Depression Inventory; ASRM: Altman Self-Rating Mania Scale; PSQI: Pittsburgh Sleep Quality Index.

Table 5 Bipolar group: Bonferroni adjusted Spearman correlations between the parameters of the Believing Questionnaire

	Pos. Pro.	Neg. Pro.	Ind. Pro.	Pos. Emo.	Neg. Emo.	Ind. Emo.	Incongruence[1]	Certainty	Mightiness
Pos. Pro.									
Neg. Pro.	**-0.78**[c]								
Ind. Pro.	-0.44[b]	-0.15							
Pos. Emo.	**0.67**[c]	**-0.61**[c]	-0.10						
Neg. Emo.	**-0.68**[c]	**0.63**[c]	0.10	**-0.96**[c]					
Ind. Emo.	0.00	-0.14	0.19	-0.09	-0.11				
Incongruence	-0.37[b]	0.04	**0.55**[c]	-0.31[a]	0.29[a]	0.11			
Certainty	0.23	-0.19	0.04	0.26	-0.26	-0.04	-0.07		
Mightiness	-0.05	0.12	0.01	-0.01	0.02	-0.18	-0.04	**0.66**[c]	

[1]Incongruence between the propositions and the emotions.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
Bold letters: Bonferroni corrected significant differences. Pos.: Positive; Neg.: Negative; Ind.: Indifferent; Pro.: Propositions; Emo.: Emotions.

Limitations

The present study had several limitations. Due to the lockdown in Austria at the time of study, testing was limited to online questionnaires precluding face-to-face interactions with study participants. Nevertheless, scores from self-report did allow us to capture and control for current symptoms. Another potential problem of this, as well as other online studies, is that of sampling bias. Only data from individuals who were motivated to participate in the survey were collected. Thus, results may not apply to the general population. Furthermore, believing processes themselves could not be studied, as only the verbalized expressions could be directly assessed. It may be inferred that believing processes were influenced by the introspective ability of the subjects; however, introspective ability was not measured in the present study. A further limitation of the current study is that the qualitative data of the BQ had to be transformed into positive, negative and indifferent categories, that is, the data were reduced profoundly and may thus miss some important information. Lastly, as this was a cross-sectional study, causality cannot be determined.

Table 6 Control group: Bonferroni adjusted Spearman correlations between the parameters of the Believing Questionnaire

	Pos. Pro.	Neg. Pro.	Ind. Pro.	Pos. Emo.	Neg. Emo.	Ind. Emo.	Incongruence[1]	Certainty	Mightiness
Pos. Pro.									
Neg. Pro.	**-0.74**[c]								
Ind. Pro.	**-0.77**[c]	0.16							
Pos. Emo.	**0.61**[c]	-0.40[b]	**-0.50**[c]						
Neg. Emo.	**-0.56**[c]	**0.52**[c]	0.35[a]	**-0.86**[c]					
Ind. Emo.	-0.20	-0.06	0.33[a]	**-0.51**[c]	0.11				
Incongruence	**-0.58**[c]	0.33[a]	**0.55**[c]	-0.34[a]	0.44[b]	0.01			
Certainty	0.11	0.01	-0.10	0.12	-0.13	-.12	-0.18		
Mightiness	0.26	-0.12	-0.22	0.26	-0.19	-0.15	-0.16	**0.60**[c]	

[1]Incongruence between the propositions and the emotions.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
Bold letters: Bonferroni corrected significant differences. Pos.: Positive; Neg.: Negative; Ind.: Indifferent; Pro.: Propositions; Emo.: Emotions.

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Figure 1 Word clouds showing the most frequently used words of individuals with bipolar disorder and healthy controls for items 2 and 3 concerning their beliefs during the first lockdown of the COVID-19 pandemic.

Practical Implications

Our findings offer practical implications for the treatment of individuals with BD. Because differences in believing parameters were no longer present after controlling for psychiatric symptoms, the credition model could contribute to a better understanding of negative or even positive dysfunctional schemata in psychiatric individuals, as well as be adopted into the psychotherapeutic context. Since humans tend to believe their perceptions to be true and beliefs can be updated by confirming or disproving new evidence[57], dysfunctional cognitive schemata could presumably be changed if they were revealed. It is hypothesized that belief evaluation is one approach to help with this and could be used as a tool for cognitive treatment approaches in psychotherapy.

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Figure 2 Word clouds showing the most frequently used words of individuals with bipolar disorder and healthy controls for items 1 and 4 concerning their beliefs during the first lockdown of the COVID-19 pandemic.

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Figure 3 Word clouds showing the most frequently used words of individuals with bipolar disorder and healthy controls for items 5 and 6 concerning their beliefs during the first lockdown of the COVID-19 pandemic.

CONCLUSION

The present study showed that the model of credition is applicable in the clinical context regarding the postulated believing processes. Individuals with BD differed in their believing processes regarding the COVID-19 pandemic from healthy persons. Thus, this study provides a deep insight into the attitudes and beliefs of particularly vulnerable people during a global crisis. Believing parameters should be examined in other clinical groups in future studies.

ARTICLE HIGHLIGHTS

Research background

Believing, or "credition," refers to psychological processes that integrate the cognitions and emotions influencing our behavior. Angel and Seitz created a model consisting of four credition parameters: proposition, certainty, emotion and mightiness. Believing processes are postulated to be influenced by external or environmental circumstances, such as the coronavirus disease 2019 (COVID-19) pandemic.

Research motivation

As empirical evidence about believing processes is lacking, studies examining this field of research are needed. Investigating credition during a crisis, such as the COVID-19 pandemic, will hopefully provide valuable insight into the mind of individuals with bipolar disorder (BD) and might be able to offer implications for treatment.

Research objectives

The purpose of this study was to explore credition in individuals with BD as well as healthy controls (HC) during the COVID-19 pandemic.

Research methods

Euthymic individuals with BD (n = 52) and age- and sex matched HC (n = 52) from Austria participated in an online survey taking place from April 9th to June 4th, 2020. The following questionnaires were completed: Brief Symptom Inventory-18, Beck Depression Inventory-II, Altman Self-Rating Mania Scale, Pittsburgh Sleep Quality Index and a Believing Questionnaire assessing four parameters of credition (proposition, certainty, emotion and mightiness). The MAXQDA software was used to analyze data about believing processes. Statistical analyses included analyses of variance, a multivariate analysis of variance and a multivariate analysis of co-variance.

Research results

Individuals with BD showed significantly more negative propositions and negative emotions, whereas HC reported significantly more positive propositions and emotions. Moreover, individuals with BD showed a higher incongruence between their propositions and emotions. Positive as well as negative emotions and propositions were associated with scores measuring symptoms of depression, anxiety and sleep quality.

Research conclusions

During the COVID-19 pandemic, believing parameters were associated with psychiatric symptoms in BD and differed from HC. Results demonstrate the sensitivity of believing processes to external influences in individuals with BD.

Research perspectives

Believing processes should be further examined in future studies, especially regarding cognitive treatment approaches in psychotherapy.

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FOOTNOTES

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study procedure; Wagner-Skacel J, Angel H-F, Ratzenhofer M, Fellendorf FT, Körner C, Reininghaus EZ, Seitz RJ and Dalkner N edited the manuscript and gave important intellectual input.

Institutional review board statement: The study was reviewed and approved by the local ethics committee in accordance with the current revision of the Declaration of Helsinki, ICH guideline for Good Clinical Practice and current regulations (Medical University of Graz, Austria; individuals with BD were from the BIPLONG study, EK-number: 25-335 ex 12/13; data was collected in the course of a new study, EK number: 32-363 ex 19/20).

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ORIGINAL ARTICLE

Observational Study

Treatment outcome, cognitive function, and psychopathology in methamphetamine users compared to other substance users

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Abstract

BACKGROUND

The rising number of people using methamphetamine leads to an increasing need for treatment options for this patient group. Evidence-based research on the efficacy of treatment programs for methamphetamine users is limited. Due to specific characteristics of methamphetamine users, the question arises whether established treatment methods for individuals using other substances can be effective for the treatment of methamphetamine dependence as well. We hypothesize that there are significant differences between the two groups that may affect the effectiveness of treatment and worsen the prognosis of treatment outcomes for methamphetamine users compared to consumers of other substances.

AIM

To investigate potential differences in cognitive functioning and psychopathology between methamphetamine users and other substance users and possible correlations with treatment outcomes.

METHODS
A total of 110 subjects were recruited for an observational, longitudinal study from a German inpatient addiction treatment center: 55 patients with methamphetamine dependence and 55 patients with dependence of other substances ("OS group"). Both groups were examined at beginning (baseline) and end of treatment (after 6 mo) with regard to treatment retention, craving, cognitive functioning, psychosocial resources, personality traits, depression, and other psychiatric symptoms. Instruments used were Raven's IQ test, Mannheimer craving scale, cognitrone cognitive test battery, NEO personality factors inventory, Hamilton depression scale, Becks depression inventory, and a symptom checklist. The statistical methods used were χ^2-test, *t*-test and multiple mixed ANOVAs.

RESULTS
A total drop-out rate of 40% (methamphetamine-group: 36.4%; OS-group: 43.6%) was observed without significant differences between groups. At baseline, methamphetamine-group subjects significantly differed from OS-group individuals in terms of a lower intelligence quotient, fewer years of education, slower working speed, and decreased working accuracy, as well as less cannabinoid and cocaine use. Methamphetamine-group subjects further showed a significantly lower score of conscientiousness, depressive, and psychiatric symptoms than subjects from the OS-group. In both groups, a reduction of craving and depressive symptoms and an improvement of working speed and working accuracy was noted after treatment.

CONCLUSION
There are differences between methamphetamine users and users of other drugs, but not with regard to the effectiveness of treatment in this inpatient setting. There are differences in cognitive function and psychopathology between methamphetamine and other drugs users. The existing treatment options seem to be an effective approach in treating methamphetamine dependence.

Key Words: Treatment outcome; Cognitive function; Psychopathology; Methamphetamine; Substance use; Comparison

Core Tip: There are differences between methamphetamine users and users of other drugs, but not with regard to the effectiveness of treatment in this inpatient setting. The existing treatment options seem to be an effective approach in treating methamphetamine dependence.

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INTRODUCTION

The United Nations estimated that about 27 million people worldwide regularly abuse amphetamine-type stimulants (ATS) in 2018[1]. The rising number of people using methamphetamine has been considered the "next addiction crisis"[2] and causes growing concern[1]. Accordingly, there is a growing need for evidence-based treatment options for methamphetamine users[2,3]. Evidence-based research on the efficacy of treatment programs for methamphetamine users is still limited[4], with no established pharmacotherapy available[2,5]. The question arises whether established treatment methods for individuals using other substances can be effective for the treatment of methamphetamine dependence as well. This question is important since – until a few years ago – methamphetamine use played a minor role in German substance treatment services, and therefore, most methamphetamine users are treated in institutions having a focus on other drugs of abuse, such as alcohol, opioids, amphetamine, or cocaine. However, representative studies comparing the characteristics of methamphetamine users to users of other substances are limited. A study based on expert interviews and focus groups on characteristics of methamphetamine consumers showed that they differ from users of other stimulants with respect to higher levels of dissocial behavioral (*e.g.*, aggressiveness, impuls-

iveness, egoism, or irritability), as well as emotional instability, unreliability, and other comorbidities [6]. The authors also reported that the therapy of methamphetamine users is substantially affected by their comorbidities and stated, that the provided rehabilitation for methamphetamine users in Germany is inadequate, resulting in a need to adapt the treatment concepts for this group[6]. Another study also showed that methamphetamine use seems to be associated with co-occurring substance use and mental illness[8]. This may be of relevance as reviewed comorbidities were frequently associated with worse treatment outcomes[9]. The available data demonstrate that the rise in methamphetamine use is intimately linked to the ongoing opioid crisis. The concurrent use of opioids and methamphetamines may decrease adherence to short-term residential treatment. Accordingly, effective strategies should be identified to retain individuals who use opioids and methamphetamines concurrently in treatment[10, 11]. In addition, there are also data suggesting methamphetamines cause neural damage and persistent forms of cognitive impairment, including deficits in attention, memory, and executive function[12]. These results are in line with other studies also indicating that methamphetamine users may differ from other substance users with respect to cognitive function[13,14]. This may be important in terms of treatment outcome, since for example Bernhardt *et al*[15] reported correlations between methamphetamine treatment outcome and the recovery of cognitive impairment.

Another study found an association between a low level of perceived social support and methamphetamine dependence[16]. However, the authors also found an association between moderately (and not distinct) pronounced personality factors (agreeableness, neuroticism, extraversion, conscientiousness, and openness) and methamphetamine use[16]. A systematic review of psychological treatments for methamphetamine use disorders states that focusing more on the helping-relationship categories is a key approach for increasing the efficacy of treatments for methamphetamine use[17].

These studies have been mostly of exploratory in nature and were exclusively investigating methamphetamine users without direct comparison to other drug users. In this study, we focus on factors such as cognition, personality traits, comorbidities, psychiatric symptoms, and psychosocial resources and their implication on treatment outcome. Based on limited previous research, one may assume that methamphetamine users have more neuropsychiatric symptoms compared to users of other substances. Specifically, a higher rate of comorbid psychiatric symptoms and disorders, a lower level of cognitive functioning, limited psychosocial resources and lower retention rates in treatment in methamphetamine users can be postulated. This exploratory study focuses on these possible differences in primary methamphetamine users compared to users of other substances. We hypothesize that there are significant differences between the two groups that may affect the effectiveness of treatment and worsen the prognosis of treatment outcomes for methamphetamine users compared to consumers of other substances.

MATERIALS AND METHODS

Participants and treatment program

All participants were inpatients at a hospital specialized for treatment of substance use disorders (MEDIAN Klinik Mecklenburg) and were recruited by psychologists and physicians during the first 2 wk to 4 wk after admission. Participation was voluntary. The treatment was set up for 6 mo and the interventions were applied as individual and group therapy, with the main focus on group sessions (five times per week). Table 1 shows details about the treatment concept. Main treatment goals were the analysis of triggers for craving and the development of new behavioral strategies for coping with craving and other substance related problems. The 2-wk initial phase aimed at completion of diagnostics, establishment of self-reflection and motivational support, and defining therapy goals. During the 22-wk core treatment phase, interventions such as psychoeducation, situation and trigger analyses, mindfulness strategies and assertiveness training were applied. The last 2 wk focused on relapse prevention and aftercare. For further details see also Soyka *et al*[18].

Inclusion criteria were a history of methamphetamine abuse or addiction (meeting the respective ICD-10 criteria) for the primary methamphetamine user group and a history of abuse or dependence of other substances for the other substances group ("OS group"). Because polydrug use is very common [19] methamphetamine-group participants were included when having a history of previous use of other substances, but methamphetamine had to be the primary drug of abuse and the main reason for admission to treatment. See Table 2 for information about the history of substance use in both groups.

Minimum age was 18 years. Exclusion criteria were acute psychotic symptoms, intoxication on test days, and insufficient comprehension of study materials or procedure. Informed written consent was obtained from all participants after a complete and extensive description of the study protocol. The study protocol was approved by the Ethics Committee of the Ludwig-Maximilians-University of Munich. All participants were financially reimbursed with 15 Euro after completion of assessments. Routine urine samples and breath alcohol tests were collected to verify substance use. These tests were part of the usual hospital practice and were conducted by the clinic staff on a sample basis and in case of suspected substance use.

Table 1 Phases of the therapeutic treatment concept

Therapy phase	Content and therapy frequency	Duration
Admission	Checking the entry requirements, *e.g.*, recent drug use	Admission day
Entry phase	Diagnostics, self-reflection, strengthen and increasing motivation, defining therapy goals, treatment planning	2 wk
Main phase	Change-, testing and stabilization phase: psychoeducation (2x/wk), mindfulness-based relapse prevention (1x/wk), trigger analysis (1x/wk), individual psychotherapy (50 min/wk), sports (1x/wk), further offers according to the results of diagnostics *e.g.*, nutrition counseling (1x/wk), body therapy (1x/wk), ergotherapy (1x/wk), assertiveness training (1x/wk)	22 wk
Discharge, planning aftercare	Follow-up plan, relapse prevention, arrangement of further care management *e.g.*, contact to job center and clarified housing situation	2 wk

Table 2 Substance use in both groups

Substance class	*n*		*P*
	MA-group	OS-group	
Alcohol	16	21	0.31
Cannabis	32	42	0.04
Cocaine	5	19	0.001
Hallucinogens	0	1	0.3
Opioids	3	7	0.18
Sedativa	2	3	0.65
Tobacco	49	42	0.07
Volatile solvents	1	0	0.3
Stimulants	55 (methamphetamine)	31 (amphetamine)	-

MA: Methamphetamine; OS: Other substances.

Study design

The observational longitudinal study was designed to capture within and between group differences at two time points: "T0" Baseline at the beginning of treatment and "T1" at the end of treatment, after approximately 24 wk. The T1 assessment took place during the last 3 wk before discharge, but the exact time point varied individually. Both surveys were conducted by trained staff. Data were collected between November 2016 and June 2018 for the Methamphetamine-group and between June 2018 and February 2019 for the OS-group. See Figure 1 for details.

Outcome measures and instruments

The main outcome of interest was the completion of treatment as scheduled (regular discharge). Individuals stopping treatment prematurely (at own request or as a disciplinary decision) were defined as dropouts. A positive urine test result was classified as a non-reported relapse, which led to a disciplinary dismissal.

Further outcomes of interest were differences between methamphetamine- and OS-group and between time points T0 and T1. These differences include craving, cognitive functioning, psychosocial resources, depression, and other psychiatric symptoms, as well as personality traits (only measured at baseline). Table 3 displays the used instruments at the respective assessment.

Statistical analyses

Continuous variables were summarized by their mean (m) and standard deviation (SD), categorical variables by absolute (n) and relative frequencies (%). Group comparisons were performed using χ^2-test (for categorial variables, or in case of small cell numbers, Fisher's exact test) and t-test (continuous variables). Multiple mixed ANOVAs were calculated to compare mean differences between substance groups taking into account both time points (T0 and T1). Since t-tests and ANOVAs are regarded as robust statistical procedures, both methods were also used for variables potentially deviating from the

Table 3 Study instruments

Instrument	Description	Assessment
Becks Depression Inventory-II (BDI-II) (Hautzinger *et al*[29], 2006)	21-question multiple-choice self-report inventory measuring the severity of depression. Raw scores were used for analyses	T0, T1
Cognitrone (Wagner and Karner[30], 2003)	Computer administered Test of cognitive working speed and working accuracy (comparisons of geometrical figures). Scores were standardized into *T*-values according to test norms	T0, T1
Documentation standards III for the evaluation of the treatment of dependent individuals (German Society for Addiction and Therapy [31], 2001)	Defined items to assess substance use and related factors (*e.g.*, years of substance use, age at use onset, number of withdrawals)	T0
Hamilton Depressive Rating Scale (HAMD)(Hamilton[32], 1960)	Clinician-administered depression assessment scale, containing 17 items of symptoms of depression. Time period: past week. Assessed as a semi structured interview. Raw scores were used for analyses	T0, T1
Inventory of personal psychosocial resources(Küfner *et al*[33], 2006)	Self-report questionnaire measuring psychosocial resources in the past and at present based on different scales, *e.g.*, relationship, friends, financial and work situation. A total raw score of all scales measuring the present situation was built and used for analyses	T0, T1
Mannheimer Craving Scale (Nakovics *et al*[34], 2009)	Self-report questionnaire with 12 multiple choice items and 4 additional items measuring Craving within the last 7 d. Raw scores from the main 12 items were used for analyses	T0, T1
NEO-Five-Factor-Inventory (NEO-FFI)(Borkenau and Ostendorf[35], 2008)	Self-report questionnaire with 60 items for the measurement of the so-called "big five" personality traits (neuroticism, extraversion, openness, agreeableness, consciousness). Scores were standardized into *T*-values according to test norms	T0
Raven's Standard Progressive Matrices(Raven *et al*[36], 2016)	Nonverbal intelligence test, Computer version. Scores were standardized into IQ values according to test norms	T0
Structured Clinical Interview for DSM-IV Axis I (Wittchen *et al*[37], 1997)	Diagnostic structured interview to determine the presence of DSM-IV Axis I disorders	T0
Symptom Checklist 90-R (SCL-90R) (Franke [38], 1995)	Self-report questionnaire assessing symptoms of psychopathology on different scales. For this study two scales were use: intensity of depressive symptoms scale and "Positive Symptom Distress Index" (PSDI), a measure of intensity of present symptoms. Scores of both scales were standardized into T-values according to test norms	T0, T1
Wender Utah Rating Scale -short Version (Wursk) (Retz-Junginger *et al*[39], 2002)	Short version (25 items including 4 control items) of a self-report questionnaire assessing retrogradely childhood symptoms of attention deficit hyperactivity disorder. Raw Scores were built from the 21 core items and used for analyses	T0

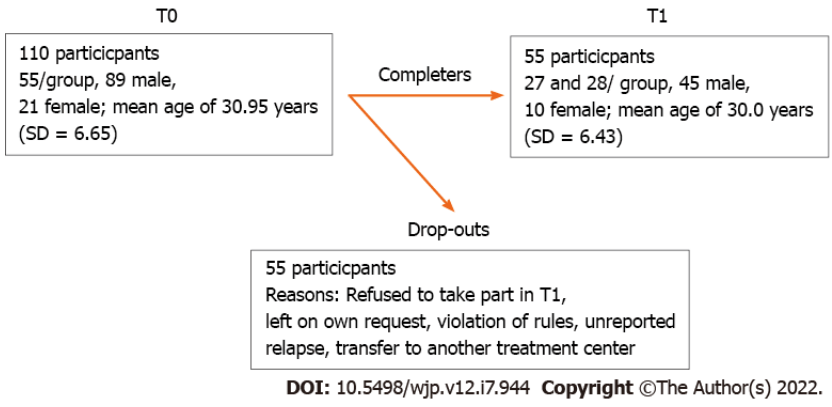

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Figure 1 Characteristics of participants at each time point (T0 and T1).

normality assumption. Univariable logistic regression models were applied to investigate the effect of independent factors on treatment drop-out. Odds ratios (OR) are reported together with their 95% confidence intervals (CI). The significance level was set at $P = 0.05$ and no P value adjustment for multiple testing was applied in this explorative study. All statistical analyses were conducted in SPSS version 24.

RESULTS

Participants' flow and treatment completion

A total of 110 participants (55 in each group, 89 men and 21 women) with a mean age of 30.95 years (SD = 6.65) were included in the first assessment at T0. There were no statistically significant differences in age (30.0 years *vs* 32.0 years, $P = 0.12$) or sex distribution (76.4% *vs* 85.5% males, $P = 0.23$) between methamphetamine- and OS-groups. Out of this original sample, 18 subjects refused to take part in further assessments after T0 and 55 subjects (27 from methamphetamine, 28 from OS-group) participated again in the second measurement T1 with a mean age of 30.0 years (SD = 6.43). Again, the majority of T1 subjects was male (45 men, 10 women) and there was no significant difference in sex distribution ($P = 0.50$).

From the baseline sample, 66 subjects (60%) completed the treatment while 44 individuals (40%) dropped-out of treatment. Comparison of the methamphetamine-group and the OS-group revealed no significant difference in drop-out rates (36.4% *vs* 43.6%, $P = 0.44$). In addition, there was neither a significant difference in age ($P = 0.19$) nor in sex distribution ($P = 0.84$) between drop-outs and completers.

The most common reason for treatment drop-out was at own request (42.2%), followed by violation of institution rules (26.7%), unreported relapse during treatment (24.4%), and transfer to another treatment center (6.7%). There was no significant association in the reasons for drop-out between methamphetamine and OS-group ($P = 0.21$).

Participants remained in treatment for a mean time of 147 d (SD = 68). There was a trend towards a longer treatment retention in the methamphetamine-group compared to OS-group, but this difference failed to reach statistical significance [159 (SD = 60) *vs* 135 d (SD = 73), $P = 0.07$]. The OS group attended a slightly higher mean number of group sessions [OS: 103 (SD = 57); methamphetamine: 87 (SD = 35), $P = 0.07$], while the methamphetamine-group had a slightly higher mean number of individual therapy sessions [methamphetamine: 27 (SD = 18); OS 22 (SD = 13), $P = 0.08$]. However, both differences were not statistically significant. A mean treatment duration of 93 d (SD = 57) was found among the patients dropping out of treatment.

Baseline comparisons of methamphetamine and OS-group characteristics

Methamphetamine-group subjects had fewer years of education than OS-group subjects ($P = 0.048$) and showed a significantly lower mean intelligent quotient (Raven`s IQ = 93.7) at baseline than the OS-individuals (IQ = 100.1, $P = 0.02$, see also Table 4). Methamphetamine-group participants also performed worse on both measures of the cognitive test battery Cognitrone, resulting in a significantly decreased working speed ($P = 0.002$) and working accuracy ($P = 0.03$) compared to OS-subjects. Methamphetamine- and OS- subjects showed no significant differences with respect to employment ($P = 0.19$) or partnership during the last 6 mo prior to admission ($P = 0.46$).

Participants from the methamphetamine-group showed a significantly lower score of the personality trait conscientiousness (measured by the NEO-Five-Factor-Inventory) compared with subjects from the OS-group ($P = 0.04$). No other personality traits differed significantly between both groups. The OS group showed significantly higher Hamilton Depressive Rating Scale (HAMD) ($P = 0.04$) and Symptom Checklist (SCL) depression ($P = 0.03$)but not Beck Depression Inventory-II (BDI- II) ($P = 0.17$) mean scores at T0 than the methamphetamine-group. The OS-group also had a higher mean score of the SCL "Positive Symptom Distress Index" (PSDI), a measure of intensity of present symptoms, compared to the methamphetamine-group ($P = 0.02$). There were no statistically significant differences in attention deficit hyperactivity disorder (ADHD) scores ($P = 0.56$), craving ($P = 0.87$), or psychosocial resources ($P = 0.69$) at baseline.

As explained, methamphetamine-group subjects may have had a history of other drug use, but methamphetamine had to be the prior substance. The majority of all subjects also used cannabinoids, but the number of cannabinoid users was significantly higher in the OS-group than in the methamphetamine-group ($P = 0.04$, see Table 2). The OS-group also included a significantly higher number of individuals that used cocaine ($P = 0.001$), while there were no differences in the use of other substances. There was no significant difference between groups concerning the number of previous substance abuse treatments ($P = 0.98$)

Regarding the number of comorbid psychiatric diagnoses (measured by ICD-10), a significantly higher rate of anxiety disorders ($P = 0.03$) and somatoform disorders ($P < 0.0001$) was found in methamphetamine-group patients, while there was a higher rate of other psychotic disorders in OS-group participants ($P = 0.04$, see Table 5).

Comparisons of groups over time

Mixed ANOVAs were used to compare the cognitive functioning over time and between groups. The working speed significantly improved from T0 to T1 in both groups ($P < 0.001$, see also Table 6) and there was a significant group effect for both measurements, showing a better performance in the OS- than in the methamphetamine group in working speed ($P < 0.001$, see Figure 2). There was no interaction effect ($P = 0.94$). Regarding working accuracy, there also was a significant improvement of

Table 4 Comparison between MA- and OS-group at baseline T0

	MA-group	OS-group	*P*
n	55	55	
Male	42 (76.4%)	47 (85.5%)	0.23
Age	30.0 (± 5.3)	32.0 (± 7.7)	0.12
Number of withdrawals (*n* = 48)	3.0 (± 4.1)	3.0 (± 4.1)	0.98
Raven's IQ (MA *n* = 50, OS *n* = 54)	93.7 (± 13.5)	100.1 (± 13.6)	0.02
Cognitrone working speed (MA *n* = 53, OS *n* = 54)	49.1 (± 8.0)	54.3 (± 9.0)	0.002
Cognitrone accuracy (MA *n* = 53, OS *n* = 54)	43.0 (± 8.9)	47.1 (± 9.8)	0.03
Personality factors	*n* = 37	*n* = 42	
Neuroticism	22.8 (± 6.7)	25.1 (± 9.7)	0.24
Extraversion	25.0 (± 6.0)	25.2 (± 7.5)	0.89
Openness	26.3 (± 5.6)	28.6 (± 6.7)	0.11
Agreeableness	26.6 (± 4.2)	27.9 (± 6.8)	0.33
Conscientiousness	29.0 (± 5.6)	31.9 (± 6.6)	0.04
BDI-II Score (MA *n* = 42, OS *n* = 54)	13.6 (± 10.8)	16.8 (± 11.3)	0.17
HAMD Score (MA *n* = 46, OS *n* = 42)	5.3 (± 4.8)	8.3 (± 7.9)	0.04
SCL-PSDI Score (MA *n* = 39, OS *n* = 40)	53.5 (± 11.1)	59.3 (± 10.1)	0.02
Wursk Score (MA *n* = 36, OS *n* = 40)	*n* = 3628.6 (± 16.7)	*n* = 4030.8 (± 15.1)	0.56
Craving (MA *n* = 39, OS *n* = 40)	13.9 (± 9.5)	14.2 (± 8.0)	0.87
Years of education	*n* = 52	*n* = 50	0.048
≤ 9 yr	35	24	
≥ 10 yr	17	26	
Employment	*n* = 51	*n* = 48	0.19
Unemployed	43	33	
Employed	4	7	
Other (*e.g.*, retiree)	4	8	
Ever injected	*n* = 49	*n* = 40	0.75
	7	4	

Data displays means ± standard deviation or number of participants (education and employment). Different *n* result from missing values. BDI-II: Becks Depression Inventory-II; HAMD: Hamilton Depressive Rating Scale; MA: Methamphetamine; OS: Other substances; SCL: Symptom Checklist; Wursk: Wender Utah Rating Scale-short Version.

performance over time in both groups ($P < 0.001$). The OS-group showed a higher working accuracy at both times, but this effect was not statistically significant ($P < 0.43$). Again, there was no interaction effect ($P < 0.79$, see Figure 2). Both groups showed a significant reduction of the intensity of psychiatric burden, as measured by the SCL-90-R PSDI score, over time ($P < 0.001$). The OS-group showed a greater decrease than the Methamphetamine-group (see Figure 3), but the interaction effect failed to reach statistical significance ($P = 0.07$). The groups no longer differed significantly in this regard over time ($P = 0.29$). SCL-90-R depression scores ($P < 0.001$) and HAMD depression scores ($P = 0.001$) were significantly decreased over time in both groups. However, taking baseline and T1 assessment together, the difference between the OS- and methamphetamine-groups was no longer significant (SCL depression score: $P = 0.09$; HAMD: $P = 0.09$). Again, no interaction effects were found (SCL depression score: $P = 0.97$; HAMD: $P = 0.66$, see Figure 4). Analyzing the BDI-II depression scores also revealed a significant reduction of depression scores over time ($P < 0.001$), but without interaction ($P = 0.81$) or group effect ($P = 0.56$). Similar results were seen regarding craving scores with a significant reduction over time ($P < 0.001$), without interaction ($P = 0.94$), and without group effect ($P = 0.86$). We found a significant increase of psychosocial resources over time ($P = 0.048$), but again, no significant differences between both groups ($P = 0.99$) and no interaction effect ($P = 0.71$).

Table 5 Number of comorbid diagnoses

	MA group, *n* = 54	OS group, *n* = 55	*P*
Depression	11	15	0.40
Anxiety disorder	5	0	0.03
Eating disorder	0	2	0.49
Obsessive-compulsive disorder	0	0	-
Posttraumatic stress disorder	15	12	0.47
Personality disorder	11	11	0.96
ADHD	6	7	0.80
Psychotic disorder	3	10	0.042
Somatoform disorder	18	0	< 0.001

Data displays number of participants diagnosed with the respective comorbidity. ADHD: Attention deficit and hyperactivity disorder; MA: Methamphetamine; OS: Other substances.

Table 6 Comparison over time and between groups (ANOVA results)

		MA-group	*n*	OS-group	*n*	*P*
BDI	T0	15.31 (± 11.55)	26	16.36 (± 12.39)	33	P_{time}[b]; P_{group} NS; $P_{time \times group}$ NS
	T1	7.27 (± 7.20)		8.97 (± 8.98)		
Cognitrone accuracy	T0	43.62 (± 7.84)	26	44.93 (± 9.85)	28	P_{time}[b]; P_{group} NS; $P_{time \times group}$ NS
	T1	50.50 (± 8.63)		52.54 (± 10.16)		
Cognitrone speed	T0	48.81 (± 7.68)	26	57.18 (± 9.05)	28	P_{time}[b]; P_{group}[b]; $P_{time \times group}$ NS
	T1	54.08 (± 10.04)		62.61 (± 10.88)		
HAMD	T0	6.52 (± 5.36)	25	9.59 (± 9.14)	27	P_{time}[b]; P_{group} NS; $P_{time \times group}$ NS
	T1	3.60 (± 4.77)		5.81 (± 5.98)		
IPR	T0	204.43 (± 36.47)	21	201.78 (± 33.84)	27	P_{time}[a]; P_{group} NS; $P_{time \times group}$ NS
	T1	215.48 (± 38.71)		217.78 (± 54.15)		
MaCS	T0	14.39 (± 9.81)	23	14.59 (± 6.69)	27	P_{time}[b]; P_{group} NS; $P_{time \times group}$ NS
	T1	8.57 (± 5.71)		8.96 (± 8.04)		
SCL 90R Depression Score	T0	58.14 (± 9.09)	21	62.70 (± 10.52)	27	P_{time}[b]; P_{group} NS; $P_{time \times group}$ NS
	T1	50.71 (± 8.19)		55.19 (± 11.55)		
SCL 90 R PSDI	T0	55.90 (± 10.51)	21	61.26 (± 11.40)	27	P_{time}[b]; P_{group} NS; $P_{time \times group}$ NS
	T1	51.71 (± 8.33)		52.61 (± 10.66)		

[a]$P < 0.05$.

[b]$P \leq 0.001$.

Data displays means and standard deviations. BDI: Becks Depression Inventory; BDI-II: Becks Depression Inventory-II; HAMD: Hamilton Depression Rating Scale; IPR: Inventory of personal resources; MaCS: Mannheimer Craving Scale; NS: Not significant; *P*group: Group effect; *P*time: Effect of time; *P* timexgroup: Interaction effect; SCL: Symptom Checklist.

Predictors of treatment drop-out

Neuroticism measured at baseline was a significant predictor for treatment drop-out in the whole sample, showing decreasing odds for drop-out with increasing neuroticism scores [OR = 0.93, 95%CI: (0.87, 0.99), $P = 0.03$]. No other baseline personality variables predicted treatment drop-out. Higher scores in Cognitrone working accuracy, measured at baseline, also significantly predicted a treatment drop-out [OR= 1.05, 95%CI: (1.0, 1.09), $P = 0.04$], while working speed was not a significant predictor ($P = 0.20$). Raven's IQ ($P = 0.90$), craving at baseline ($P = 0.99$), and SCL depressive scores ($P = 0.10$) were also not significant predictors of drop-out.

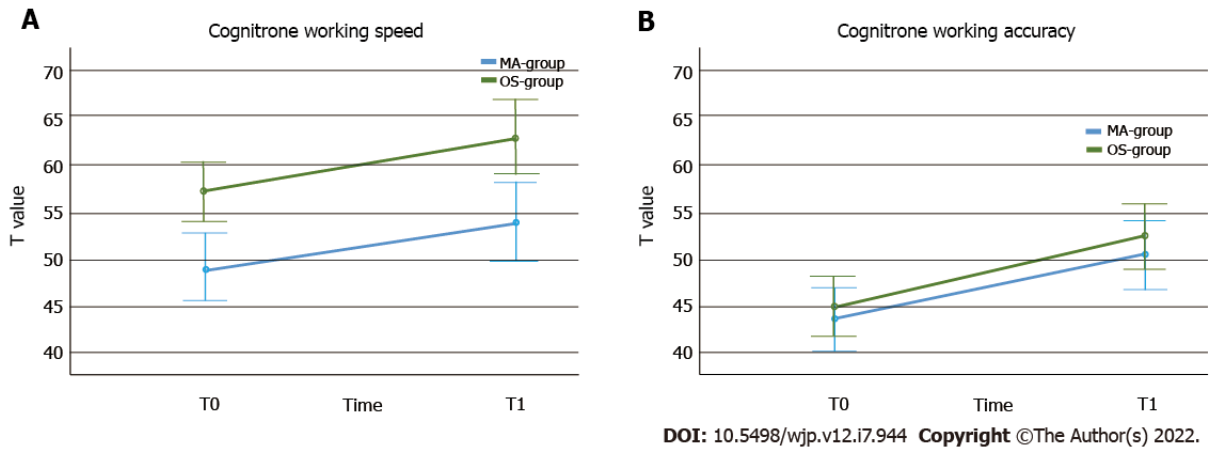

Figure 2 Working speed (A) over time and between groups (error bars represent 95% confidence interval) and working accuracy (B) over time and between groups (error bars represent 95% confidence interval). MA: Methamphetamine; OS: Other substances.

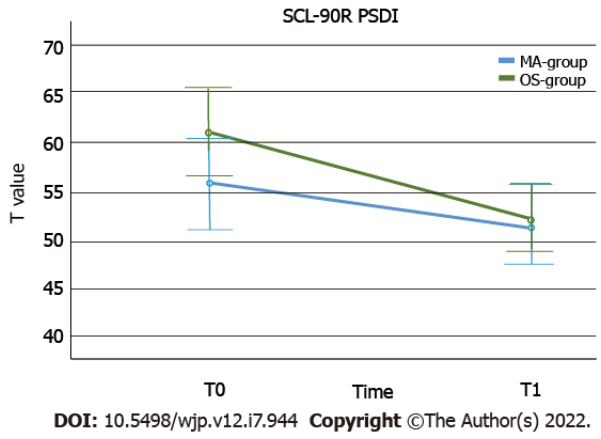

Figure 3 Positive Symptom Distress Index over time and between groups (error bars represent 95%CI). MA: Methamphetamine; OS: Other substances; SCL-90-R: Positive symptom distress index.

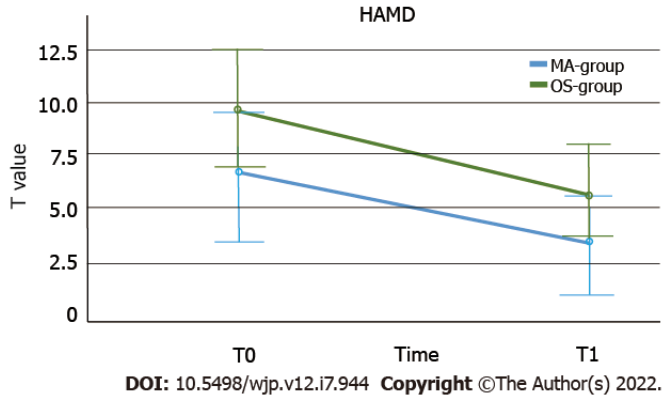

Figure 4 Hamilton Depressive Rating Scale scores over time and between groups (error bars represent 95% confidence interval). HAMD: Hamilton Depression Rating Scale; MA: Methamphetamine; OS: Other substances.

DISCUSSION

The present study found differences between methamphetamine and other drug users in terms of cognitive function, psychiatric comorbidities, and personality traits, but not regarding treatment outcome and retention. The latter finding suggests that despite the encountered differences between

methamphetamine users and other drug users, methamphetamine users do not perform worse than other drug users in currently provided treatments. This result raises the question if there is need for new and specialized treatment options for methamphetamine users. For example, patients may have reported methamphetamine related situations or consequences when reflecting their use patterns and for example possible relapse situations. Previously, in another longitudinal study, we compared the methamphetamine group from this study with another methamphetamine user group that received a more stimulant specific treatment[20]. We found no differences in treatment retention or long-term relapse rates between both groups, which supports the hypothesis that methamphetamine users may not benefit automatically from a more stimulant specific treatment. Study results reveal that a high number of methamphetamine users use other substances, too. These patients may benefit from existing treatments.

Interestingly, the present study revealed a trend (although not statistically significant) towards longer treatment duration of approximately 20 d in the methamphetamine group, which may indicate that methamphetamine users may have a greater benefit from the investigated treatment. However, with regards to all other treatment outcome measures, we did not find any relevant interaction, which suggests that both groups overall benefited from treatment. For example, both groups showed a reduction of craving, depression scores and overall psychiatric burden (measured by SCL-90R) and an improvement in working speed and working accuracy, as well as an increase of psychosocial resources at the end of the treatment compared to its initiation. Therefore, it can be concluded that a current "treatment as usual" inpatient addiction program is helpful for methamphetamine users and users of other substances, and that both user groups do not differ from each other in their response to the treatment.

Nevertheless, this study did reveal differences between methamphetamine users and other substance users; for example, differences were found between the two groups with respect to cognitive function. Neurotoxic effects of metamphetamine use are well established[2]. As we hypothesized, methamphetamine users had significantly lower baseline intelligence quotient, slower working speed, and decreased working accuracy compared to users of other drugs. This finding confirms results from other studies indicating that methamphetamine use can impair cognitive functions[13,14]. However, years of school education were fewer in the methamphetamine-group, raising the question of whether impaired cognitive function in the methamphetamine-group is a reason for, or rather a consequence of, methamphetamine use. Unfortunately, there are no longitudinal data to further explore this point. A previous study failed to show improvement of cognitive impulsivity deficits in metamphetamine users after short term abstinence of 6 wk[21]. Furthermore, the performance of the methamphetamine user group was still in the average range, when applying the test norms (*t*-values), and we had no matched control group without drug users to clarify the differences between both groups. Interestingly, and contrary to our hypothesis, higher scores in working accuracy at baseline were associated with a higher likelihood for treatment drop-out. Other studies that have examined ADHD patients have found lower accuracy scores as significant predictors of drop out and mild cognitive deficits, which is in contrast to the results of this study[22]. Furthermore, we did not find an effect of working speed and IQ on treatment retention, which makes it difficult to generalize the impact of cognitive performance on drop-out rates.

Again, as assumed, methamphetamine-patients had a higher rate of comorbid anxiety and somatoform disorders. But contrary to this result, OS- group participants showed a higher rate of psychotic disorders, and there were no differences between both groups in terms of other comorbidities. Therefore, different substance use patterns may be associated with different comorbidities, but not in this study.

Another unexpected result was the negative association between neuroticism and treatment drop-out which found that the higher the score for neuroticism, the lower the odds of treatment drop-out. Other studies conclude, contrary to our results, that emotional instability and high neuroticism scores are risk factors for relapse, at least in alcohol users[23]. Treatment dropouts in a program for cocaine addiction showed a higher score on histrionic and antisocial scales compared to completers[24]. Since it can be assumed that histrionic, as well as antisocial personality traits, tend to be associated with higher neuroticism, this result is also not consistent with our finding. We are not aware of any studies that specifically examined neuroticism as a predictor of addiction treatment dropout.

Our study has several limitations. For example, we did not correct the analyses for multiple testing, as this study was designed to generate hypotheses for future research on possible differences between methamphetamine- and OS patients.

Furthermore, in the group that used other substances, amphetamine use was not an exclusion criterion. Even though the two substances are very similar, it has been suggested that methamphetamine has a stronger effect on the dopamine transporter mediated cell physiology than methamphetamine; therefore, the latter has a higher addictive potential[25].

Beyond that, the reported treatment effects are limited to the sample of treatment completers. Regarding the therapeutic outcome of the drop-out patients, there were no available data for T1, and therefore, the treatment effects for the drop-out sample remain unclear. In particular, there is not enough information on patients who stopped treatment at their own request. The present study showed that the average time patients spend in treatment before they dropped out is still quite high (around 3

mo). It remains unclear why they did not continue the treatment. Future investigations covering the whole treatment process may help gaining further information on characteristics of later drop-outs with focus on craving, treatment satisfaction and value of therapeutic relationship[26-28].

CONCLUSION

There are differences between methamphetamine users and users of other drugs, but not with regard to the overall effectiveness of a 6-mo inpatient addiction treatment. Both groups showed a reduction in psychiatric symptoms over time and improved cognitive function after treatment. Methamphetamine users, therefore, seem to benefit from existing, stimulant nonspecific treatment options in a similar way than other drug users do.

ARTICLE HIGHLIGHTS

Research background

Over the last years the misuse of methamphetamine has risen, leading to an increased need for treatment options for this group of patients. To date, it remains elusive whether treatment programs for methamphetamine users are effective. One question arises whether established treatment methods for individuals using other substances can effectively target individuals with methamphetamine dependence.

Research motivation

The present study aims to investigate the potential differences in cognitive functioning and psychopathology between methamphetamine users and other substance users and possible correlations with treatment outcomes.

Research objectives

In order to provide effective therapy for the subgroup of methamphetamine users, differences to the group of other substance abusers need to be identified.

Research methods

For this observational longitudinal study from a German inpatient addiction treatment center a total of 110 subjects were recruited. Of those, 55 patients had methamphetamine dependence and 55 patients had dependence of other substances ("OS group"). Both groups were examined at beginning (baseline) and end of treatment (after 6 mo) with regard to treatment retention, craving, cognitive functioning, psychosocial resources, personality traits, depression, and other psychiatric symptoms. Instruments used were Raven's IQ test, Mannheimer craving scale, Cognitrone cognitive test battery, NEO personality factors inventory, Hamilton depression scale, Becks depression inventory and symptom checklist. The statistical methods used were χ^2-tests, *t*-tests, and multiple mixed ANOVAs.

Research results

Over the period of 6 mo, a total drop-out rate of 40% (methamphetamine-group: 36.4%; OS-group: 43.6%) was observed without significant differences between groups. At baseline, methamphetamine-group subjects significantly differed from OS-group individuals in terms of a lower intelligence quotient, fewer years of education, slower working speed and lower working accuracy as well as less cannabinoid and cocaine use. Methamphetamine-group subjects further showed a significantly lower score of conscientiousness, depressive, and psychiatric symptoms than subjects from the OS-group. In both groups a reduction of craving and depressive symptoms and an improvement of working speed and working accuracy were noted after treatment.

Research conclusions

The existing treatment options for substance abuse seem to be an effective approach in treating methamphetamine dependence.

Research perspectives

Future studies should investigate specific programs that aim to improve cognitive function and psychopathology in methamphetamine dependent patients.

FOOTNOTES

Author contributions: Koller G and Soyka M were responsible for the study concept and design; Behle N and Kamp F wrote the manuscript; Behle N, Kamp F, Proebstl L, Hager L, Riebschläger M, Schacht-Jablonowsky M, Hamdorf W, and Neumann S performed the research and data collection; Behle N, Kamp F and Manz K performed data analysis; Behle N, Kamp F, and Krause D interpreted the analyses outcomes; Koller G, Soyka M, Franke AG, and Krause D reviewed and edited the manuscript; All authors critically reviewed content and approved final version for publication.

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Clinical characteristics of pediatric patients with treatment-refractory Tourette syndrome: An evidence-based survey in a Chinese population

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Abstract

BACKGROUND

Tourette syndrome (TS) is a complex neurodevelopmental condition marked by tics, as well as a variety of psychiatric comorbidities, such as obsessive-compulsive disorders (OCDs), attention deficit hyperactivity disorder (ADHD), anxiety, and self-injurious behavior. TS might progress to treatment-refractory Tourette syndrome (TRTS) in some patients. However, there is no confirmed evidence in pediatric patients with TRTS.

AIM

To investigate the clinical characteristics of TRTS in a Chinese pediatric sample.

METHODS

A total of 126 pediatric patients aged 6-12 years with TS were identified, including 64 TRTS and 62 non-TRTS patients. The Yale Global Tic Severity Scale (YGTSS), Premonitory Urge for Tics Scale (PUTS), and Child Behavior Checklist (CBCL) were used to assess these two groups and compared the difference between the TRTS and non-TRTS patients.

RESULTS

When compared with the non-TRTS group, we found that the age of onset for TRTS was younger ($P < 0.001$), and the duration of illness was longer ($P < 0.001$). TRTS was more often caused by psychosocial ($P < 0.001$) than physiological factors, and coprolalia and inappropriate parenting style were more often present in the TRTS group ($P < 0.001$). The TRTS group showed a higher level of premonitory urge ($P < 0.001$), a lower intelligence quotient (IQ) ($P < 0.001$), and a higher percentage of family history of TS. The TRTS patients demonstrated more problems ($P < 0.01$) in the "Uncommunicative", "Obsessive-Compulsive", "Social-Withdrawal", "Hyperactive", "Aggressive", and "Delinquent" subscales in the boys group, and "Social-Withdrawal" ($P = 0.02$) subscale in the girls group.

CONCLUSION
Pediatric TRTS might show an earlier age of onset age, longer duration of illness, lower IQ, higher premonitory urge, and higher comorbidities with ADHD-related symptoms and OCD-related symptoms. We need to pay more attention to the social communication deficits of TRTS.

Key Words: Treatment-refractory Tourette syndrome; Yale Global Tic Severity Scale; Child Behavior Checklist; Premonitory Urge for Tics Scale; Social withdrawal; Obsessive-compulsive disorder

Core Tip: This study provides important evidence of treatment-refractory Tourette syndrome (TS) among Chinese patients due to the current shortage of studies based on Chinese samples. We found that the onset age of pediatric patients with treatment-refractory TS (TRTS) might be younger, and they might have a longer duration of illness, a lower intelligence quotient, and a higher premonitory urge, which often fluctuate due to psychosocial factors. Moreover, TRTS children might suffer more emotional and behavioral problems including social communication deficits (such as uncommunicative and social withdrawal), attention deficit hyperactivity disorder-related symptoms (hyperactive, aggressive, and delinquent), and obsessive-compulsive symptoms. These were the basic clinical characteristics of TRTS based on Chinese pediatric patients. Unravelling these clinical characteristics is beneficial for the early diagnosis and treatment of TRTS.

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INTRODUCTION

Tourette syndrome (TS) is a complex neurodevelopmental condition marked by tics, as well as a variety of psychiatric comorbidities, such as obsessive-compulsive disorders (OCDs), attention deficit hyperactivity disorder (ADHD), anxiety, and self-injurious behavior[1,2]. The worldwide prevalence of tic disorders (TDs) ranges from 0.4 to 1.5%[3]. In a recent report, the prevalence of TS in children and adolescents in China was 0.4%[4]. Some patients with TS fail to respond to traditional treatment, and this condition is referred to as "treatment-refractory Tourette syndrome" (TRTS)[5]. To the best of our knowledge, being refractory to "traditional treatments" (*i.e.*, medicine treatment or behavioral treatment) implies failure to respond to (or have severe side effects from) alpha-adrenergic agonists, typical and atypical antipsychotics, and benzodiazepine, as well as behavioral therapies (*i.e.*, habit-reversal training and exposure type therapy)[6]. It should be noted that one of the unresolved issues is the definition of what constitutes treatment-refractory TS; the most likely reason is the lack of the robust clinical features of TRTS, especially the features associated with the co-occurring other mental disorders [7].

However, different criteria are used to define TRTS in different countries[8]. The most commonly used criterion for TRTS was from the International Deep Brain Stimulation Registry and Database for Gilles de la Tourette Syndrome[9]. It recommended that TRTS should be the major source of disability, with a Yale Global Tic Severity Scale (YGTSS) score of 35/50, failure of conventional therapies (medications from 3 pharmacologic classes), and a trial of CBIT if feasible. European clinical guidelines for Tourette syndrome also reported the criteria of TRTS for European countries[10]. However, no Chinese version of the TRTS criteria has been described. The most likely reason is the lack of confirmed evidence related to TRTS, especially for Chinese patients. Moreover, the different criteria for TRTS were established mostly based on the clinical characteristics of adult patients with Tourette syndrome[8,9]. However, there is no evidence focusing on pediatric patients with TRTS.

Therefore, we need more confirmatory evidence about the clinical characteristics of TRTS. There are some reasons why we need to investigate the clinical characteristics of TRTS. First, TS is frequently encountered by both psychiatrists and neurologists, indicating that TS holds a unique status as a quintessentially neuropsychiatric condition at the interface between neurology (movement disorder) and psychiatry (behavioral condition)[11]. However, few studies have focused on the behavioral and emotional components of TRTS. Second, TS onset occurs between the ages of six and eight years; tics typically start simple and become more complex toward the teenage years[12,13]. Identifying the "indicators" of TRTS in the early stage may help in the treatment of these patients[14]. However, few studies have focused on these potential "indicators" of TRTS. For example, premonitory urge was

suggested as an indicator for the severity of tic symptoms[15-17], and confirmatory evidence is required to ascertain if it is also an important sign for TRTS. Third, OCD, ADHD, anxiety, and depression disorders were the top four comorbidities of TS[11], especially TRTS[18], but no evidence links these comorbidities to pediatric TRTS. Fourth, some authors suggested that there might be different subtypes of TS[19,20]. Whether TRTS is different from "pure TS" (only tic symptoms without comorbidities) is unknown. More evidence is needed to explore these differences, especially at the early stage of TRTS. Taken together, we might need more evidence about the clinical characteristics of TRTS, especially in pediatric patients.

In addition, the Child Behavior Checklist (CBCL) is one of the most important tools to identify the emotional and behavioral profiles of different mental disorders[21]. It has been suggested that the CBCL can be used to identify ADHD-related[22], obsessive-compulsive[23], anxiety[24], and depression symptoms[25]. It might provide different dimensions of clinical characteristics for TRTS, which can distinguish it from other types of TS.

Therefore, this study aimed to examine the clinical characteristics of TRTS in a Chinese pediatric population. We will compare the clinical characteristics (*i.e.*, the onset of tic age, duration of illness, intelligence quotient (IQ), and behavioral and emotional problems) of patients with TRTS and non-TRTS patients. Furthermore, the locations and the frequency of tic onset in TRTS will be reported. The CBCL will be used to present the different dimensions of mental problems between TRTS and non-TRTS. We hypothesized that TRTS patients might show more severe behavioral and emotional problems, especially in the dimensions of obsessive-compulsive, ADHD-related (*i.e.*, hyperactive, aggressive, and delinquent), and depression symptoms. This study will provide important information for a Chinese version of the TRTS criteria, especially for pediatric patients.

MATERIALS AND METHODS

Participants

All participants were recruited from the Department of Psychiatry, Beijing Children's Hospital, China from October 1, 2018 to January 1, 2021. Both inclusion and exclusion criteria for TS patients were developed. The inclusion criteria were as follows: (1) Aged from 6 to 12 years; and (2) Met the diagnostic criteria for Tourette syndrome according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)[26]. The exclusion criteria were as follows: (1) Epilepsy or any known comorbid brain medical conditions; (2) IQ less than 80; and (3) Serious physical illness.

The criteria for TRTS were as follows: (1) Nonresponsive to trials of medications from dopamine antagonists (typical and atypical) or other medications (*i.e.*, alpha-adrenergic or benzodiazepine) at adequate dosage for at least 6 mo; (2) YGTSS severity total score greater than 35; and (3) Failure following 12 sessions of habit reversal training (if the included TS patients did not meet the criteria for TRTS, they were identified as a non-TRTS group).

The ethics committee of the Beijing Children's Hospital of Capital Medical University approved this study, and we also obtained written informed consent from the parents or guardians of the enrolled children and adolescents.

Measures

Basic clinical information: A basic information list was used to identify the baseline clinical information, including age, sex, age of onset, duration of illness, factors associated with the fluctuation of tic symptoms (psychosocial factors, *i.e.*, negative emotion or stress; physiological factors, *i.e.*, respiratory tract infection or allergy symptoms), locations of onset of tic, coprolalia frequency, and inappropriate parenting style, among others.

Yale Global Tic Severity Scale: The YGTSS is a semi-structured scale rated by a clinician or trained interviewer. It was developed for assessing the tics observed within 1 wk before the assessment[27,28]. The five dimensions included in the YGTSS are the number, frequency, intensity, complexity, and interference. The total YGTSS score (range: 0-100) is derived by summing the tic severity ranging between 0 and 50 (motor tics range = 0-25 and vocal tics range = 0-25) and the impairment rating score (range = 0-50). The YGTSS is a widely used scale with excellent reliability and validity for assessing children and adolescents with TD[29].

Premonitory Urge for Tics Scale: The Premonitory Urge for Tics Scale (PUTS) is a nine-item self-report questionnaire measuring premonitory sensations in individuals with tics[30]. Each item is scored from 1 (not at all true) to 4 (very much true). The total score is computed by summing the nine items. Total scores range from 9 to 36, where higher scores represent greater severity of premonitory urges. The PUTS has demonstrated good internal consistency, test-retest reliability, and construct validity among adolescents between 11 and 16 years of age[31].

Child Behavior Checklist: The CBCL is a widely used questionnaire to assess behavioral and emotional problems. It is often used as a diagnostic screener. The Chinese version of the CBCL contains 118

specific behavioral and emotional problem items and two open-ended items. Each symptom question in the CBCL was scored 0 (not true, as far as you know), 1 (somewhat or sometimes true), or 2 (very true or often true). Liu completed a regional survey in Shandong and reported that the 2-wk test-retest reliability was 0.90 in 30 children, and the internal consistency as measured by Cronbach's α was 0.93 [32,33]. Cronbach's α was also calculated in the present study, and it was 0.87 for the total scale. The CBCL was completed by the parents or other caregivers for a given child or adolescent. In young patients, the CBCL included eight subscales in the boys' group (including the Schizoid, Depressed, Uncommunicative, Obsessive-Compulsive, Somatic Complaints, Social-Withdrawal, Hyperactive, Aggressive and Delinquent) and 9 subscales in girls' groups (including the Depressed, Social-Withdrawal, Somatic Complaints, Schizoid-Obsessive, Hyperactive, Sex Problem, Delinquent, Aggressive, and Cruel).

In addition, the Wechsler Intelligence Scale for Children-4th Edition (WISC-IV) was used to calculate the full IQ[34]. All the included participants were outpatients. The assessments were performed by child psychiatrists after diagnosis was completed.

Statistical analysis

We used the Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago, IL, United States, v25.0) to perform the statistical analyses. Descriptive statistics were performed to identify the basic clinical information, and *t* tests or χ^2 tests were used to compare the different variables of different TS groups. A *P*-value of 0.05 was set as the significance threshold.

RESULTS

Basic information of the whole sample

The total sample comprised 126 patients diagnosed with TS, with a male percentage of 73.02%. The mean age of the included patients was 9.24 ± 2.06 years (range, 6-12 years), and the mean duration of illness was 3.83 ± 2.52 years. A total of 64 patients with TS were identified as having TRTS, while 62 non-TRTS patients were also included (Figure 1).

Clinical characteristics of TRTS

After comparing the basic clinical characteristics of the TRTS group with those of the non-TRTS group, we found that in the TRTS group, the onset age was lower ($P < 0.001$), and the duration of illness was longer than those in the non-TRTS group ($P = 0.02$). Children in the TRTS group self-reported more fluctuations in conjunction with psychosocial rather than physiological factors ($P < 0.001$); coprolalia was more often present in the TRTS group than in the non-TRTS group ($P < 0.001$); and the TRTS group showed more severe functional impairment ($P < 0.001$). More patients with TRTS showed a positive family history of TS ($P = 0.02$). The TRTS group showed a lower level of premonitory urge ($P < 0.001$) and a higher level of tic symptoms ($P < 0.001$) than the non-TRTS group. Lower IQ was identified in the TRTS group ($P < 0.001$). In addition, the TRTS group showed more severe tic symptoms and premonitory urges ($P < 0.001$) (Table 1).

Locations of first-onset tic symptoms in TRTS group

We listed the locations of the first onset of tic symptoms, and the order was the face (48.44%), throat (18.75%), shoulder (12.50%), abdomen (10.93%), and upper/lower limbs (9.38%) (Figure 2).

Most frequent tic symptoms in TRTS group

We listed the top five motor and vocal tic symptoms that were frequently present in TRTS patients. The top five motor tic symptoms included head shaking/nodding, blinking, shrugging, hand moving, and mouth moving, while the vocal tic symptoms included clearing the throat, coprolalia, repetitive speech, imitating speech, and cough (Figure 3).

Emotional and behavioral profiles in TRTS group

We found that the total CBCL score was higher in the TRTS group ($P < 0.001$). We also found that the TRTS patients demonstrated more problems in the "Uncommunicative" ($P < 0.001$), "Obsessive-Compulsive" ($P = 0.001$), "Social-Withdrawal" ($P < 0.001$), "Hyperactive" ($P < 0.001$), "Aggressive" ($P = 0.002$), and "Delinquent" ($P < 0.001$) subscales of the CBCL in the boys group and "Social-Withdrawal" ($P = 0.02$) in the girls group (Tables 2 and 3).

Table 1 Basic clinical characteristics of patients with treatment-refractory Tourette syndrome and non-treatment-refractory Tourette syndrome patients

Related variable	TRTS (*n* = 64)	Non-TRTS (*n* = 62)	t/χ^2	*P* value
Sex (male percentage)	48 (75.0%)	44 (71.0%)	0.26	0.61
Age	9.64 ± 3.01	8.82 ± 2.63	1.63	0.11
Onset age	5.12 ± 2.81	7.29 ± 3.67	-3.73[c]	< 0.001
Duration of illness	4.39 ± 2.17	3.27 ± 2.93	2.43[a]	0.02
Caused by psychosocial factors	34 (53.1%)	16 (25.8%)	9.82[c]	< 0.001
Caused by physiological factors	32 (50.0%)	24 (38.7%)	1.63	0.20
Coprolalia	30 (46.9%)	10 (16.1%)	13.74[c]	< 0.001
Function impairment	46 (71.9%)	28 (45.2%)	9.27[c]	< 0.001
Family of TS history	16 (25%)	6 (9.7%)	5.13[a]	0.02
YGTSS total	66.35 ± 4.61	39.58 ± 3.97	34.88[c]	< 0.001
YGTSS severity total	40.41 ± 3.51	21.32 ± 2.78	33.77[c]	< 0.001
Impairment	25.94 ± 3.89	18.26 ± 2.21	13.57[c]	< 0.001
PUTS	26.23 ± 3.28	18.33 ± 2.76	14.61[c]	< 0.001
IQ	92.42 ± 7.63	101.05 ± 10.03	5.45[c]	< 0.001

[a]$P < 0.05$.
[c]$P < 0.001$.
TRTS: Treatment-refractory Tourette syndrome; YGTSS: Yale Global Tic Severity Scale; PUTS: Premonitory Urge for Tics Scale; IQ: Intelligence quotient.

Table 2 Behavioral and emotional characteristics of treatment-refractory Tourette syndrome and non-treatment-refractory Tourette syndrome in the boys group

Subscales of CBCL	TRTS (*n* = 48)	Non-TRTS (*n* = 44)	*t*	*P* value
Schizoid	3.75 ± 0.67	3.51 ± 0.84	1.52	0.13
Depressed	6.17 ±1.24	5.81 ± 0.93	1.56	0.12
Uncommunicative	3.52 ± 0.89	2.81 ± 0.73	4.75[c]	< 0.001
Obsessive-compulsive	7.69 ± 0.74	6.97 ±1.25	3.40[c]	0.001
Somatic complaints	3.24 ± 0.68	3.44 ± 0.71	-1.38	0.17
Social-withdrawal	3.78 ± 0.91	2.96 ± 0.54	5.20[c]	< 0.001
Hyperactive	6.59 ± 0.87	5.64 ± 1.13	4.54[c]	< 0.001
Aggressive	14.87 ± 2.01	13.55 ± 1.94	3.20[b]	0.002
Delinquent	3.49 ± 0.66	2.81 ± 1.02	3.83[c]	< 0.001
Total Score	50.72 ± 6.19	43.13 ± 7.16	5.45[c]	< 0.001

[b]$P < 0.01$.
[c]$P < 0.001$.
CBCL: Child Behavior Checklist; TRTS: Treatment-refractory Tourette syndrome.

DISCUSSION

In the present study, we found that pediatric patients always developed TRTS at an earlier age, had a longer duration of illness, had a lower IQ, and had a higher premonitory urge, which often fluctuated due to psychosocial factors. In addition, the incidence of coprolalia seemed higher in the TRTS group. The locations of tics often occur at the face, followed by the throat and shoulder in TRTS; the most common motor tics were nodding or shaking the head, blinking, or shoulder shrugging, while the vocal tics commonly included clearing the throat, coprolalia, and repeated speech. These were the basic

Table 3 Behavioral and emotional characteristics of treatment-refractory Tourette syndrome and non-treatment-refractory Tourette syndrome in the girls group

Subscale of CBCL	TRTS (*n* = 16)	Non-TRTS (*n* = 18)	*t*	*P* value
Depressed	8.75 ± 1.67	7.65 ± 1.84	1.82	0.08
Social-withdrawal	6.23 ± 1.17	5.24 ± 1.22	2.41[a]	0.02
Somatic complaints	3.22 ± 1.03	3.05 ± 0.93	0.51	0.62
Schizoid-obsessive	2.19 ± 0.44	2.07 ± 0.35	0.89	0.38
Hyperactive	6.29 ± 1.27	5.94 ± 1.13	0.85	0.40
Sex problem	0.59 ± 0.17	0.56 ± 0.21	0.45	0.65
Delinquent	2.79 ± 0.66	2.61 ± 0.72	0.76	0.46
Aggressive	8.17 ± 1.25	7.55 ± 1.04	1.58	0.12
Cruel	2.13 ± 0.67	2.07 ± 0.47	0.31	0.76
Total Score	41.06 ± 5.17	36.80 ± 4.65	2.53[a]	0.02

[a]$P < 0.05$.

CBCL: Child Behavior Checklist; TRTS: Treatment-refractory Tourette syndrome.

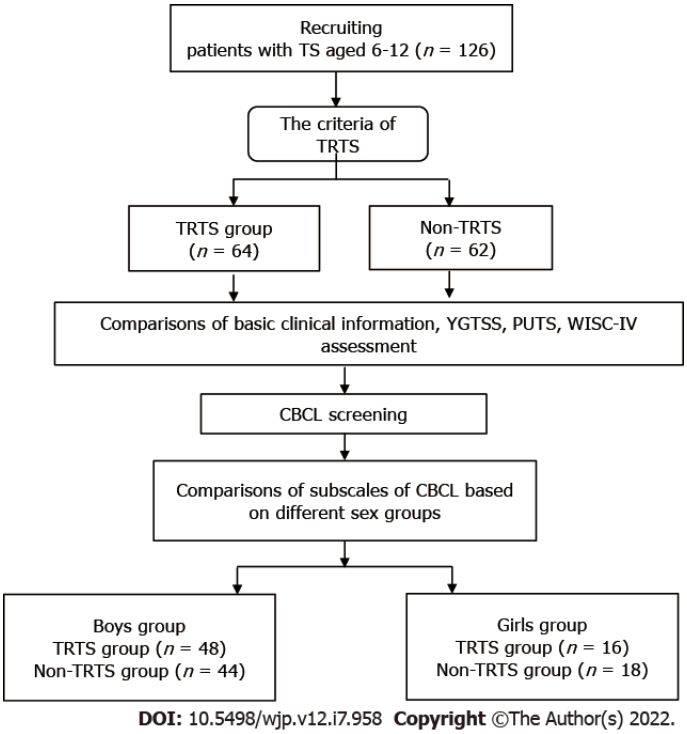

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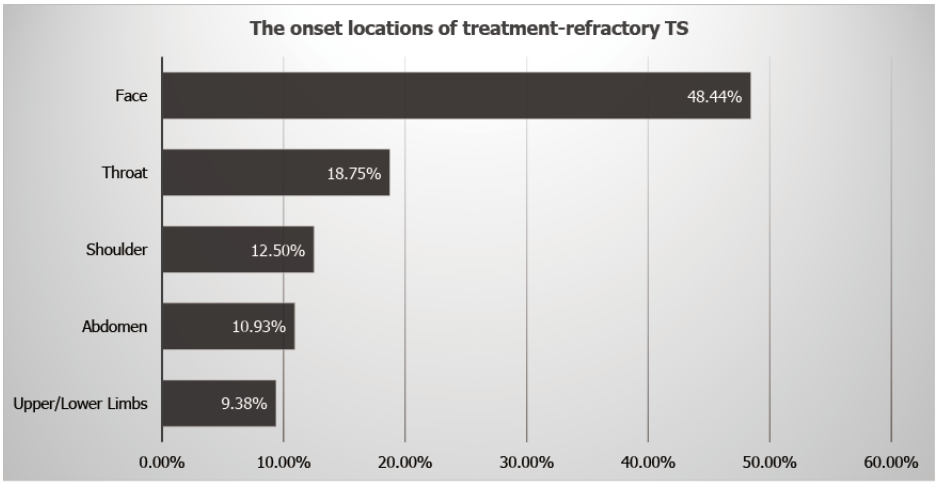
Figure 1 Flowchart of identification of included participants. TRTS: Treatment-refractory Tourette syndrome; YGTSS: Yale Global Tic Severity Scale; PUTS: Premonitory Urge for Tics Scale; WISC-IV: Wechsler Intelligence Scale for Children-4th Edition.

clinical characteristics of TRTS based on Chinese pediatric patients. Unraveling these clinical characteristics is beneficial for the early diagnosis and treatment of TRTS.

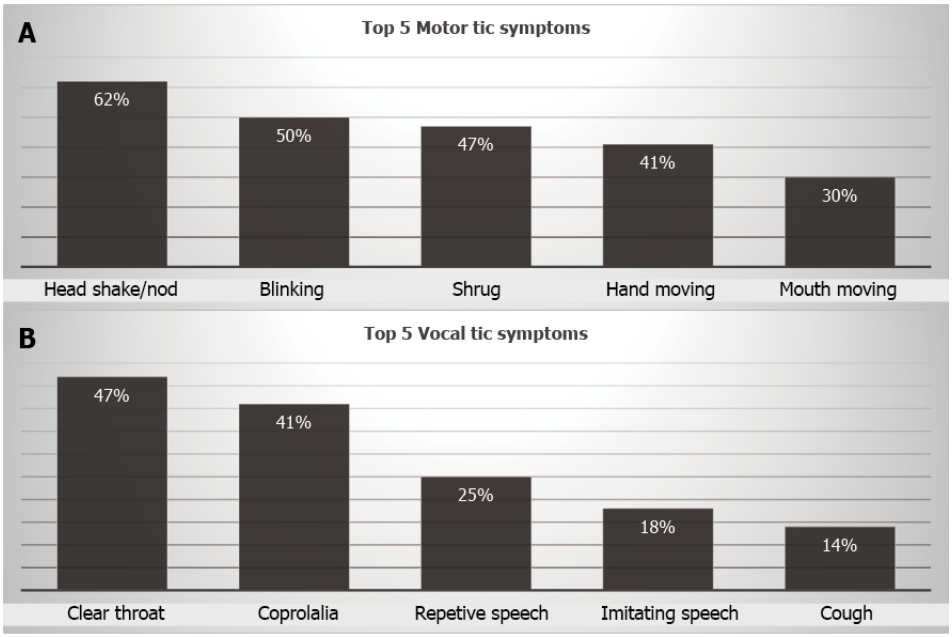
Based on the results of this study, psychiatric components might be robust features of TRTS. Cavanna *et al*[11] performed a review of the psychopathological spectrum of TS and reported that the psychiatric components of TS included OCD, ADHD, and affective disorders. A large cross-sectional survey including 1001 TSs found that 85.7% of TSs had at least one psychiatric disorder, and 57.7% had two or more psychiatric disorders[35]. It seems that the most common psychiatric disorders were ADHD and OCD[6].

In this study, we found that children diagnosed with TRTS might suffer more emotional and behavioral problems than non-TRTS children. These included social communication deficits (such as uncommunicative and social withdrawal), ADHD-related symptoms (hyperactive, aggressive, and



DOI: 10.5498/wjp.v12.i7.958

Figure 2 Percentage of onset locations of tic symptoms in treatment-refractory Tourette syndrome.



DOI: 10.5498/wjp.v12.i7.958

Figure 3 Percentage (top 5) of high frequency motor and vocal tic symptoms in treatment-refractory Tourette syndrome. A: Top 5 high frequency motor tic symptoms in treatment-refractory Tourette syndrome (TRTS); B: Top 5 high frequency vocal tic symptoms in TRTS.

delinquent), and obsessive-compulsive symptoms. The high levels of ADHD-related symptoms and obsessive-compulsive symptoms in TRTS suggest that the comorbid psychiatric conditions of ADHD and OCD seem to be the main clinical characteristics of TRTS. Comorbid ADHD might increase the risk of impulsive behavior (such as running the red light)[36], and these might develop into new psychosocial factors that can cause fluctuations in tic symptoms in TS. Comorbid ADHD might also result in the failure of psychotherapeutic interventions for TS[37]. Moreover, the severity of obsessive-compulsive symptoms in TS was one of the most important predictors of the severity of tic symptoms [38]. Taken together, the comorbid ADHD and OCD might make the traditional treatment of TS harder, which is the most likely reason for the treatment refractoriness of TS.

In addition, in the present study, we found that premonitory urge might be one of the indicators of TRTS. Indeed, obsessive-compulsive symptoms also showed an association with premonitory urge in TS [39]. It seemed that premonitory urge could predict the severity of tic symptoms[40]. This finding suggested that we need to pay attention to the assessment of premonitory urge at the early stage of treatment of TS, which might be an indicator of potential progression to TRTS.

However, we hypothesized that patients diagnosed with TRTS might have more depressive symptoms, but the opposite result was found. Notably, two aspects of social communication,

uncommunicative and social withdrawal, were prominent among children diagnosed with TRTS. Regarding the social communication deficits of TS, a recent study reported that TS showed significantly higher mean Social Communication Questionnaire (SCQ) scores than the general population[41]. These results suggested that more attention should be given to social communication deficits in TS.

Based on the clinical characteristics of TRTS, a younger onset age of tics, a longer duration of illness, comorbidities and social communication deficits may be indicators for TRTS. Up to 70% of the troubles caused by nontic-related functional impairment result from ADHD or OCD[42]. The functional impairment could be caused by both the tics and the comorbidities. Moreover, psychiatric comorbidities might lead to less effective medical treatment or psychotherapeutic treatment[6]. It is indicated that practitioners should pay more attention to early screening and properly treat the comorbidities of patients with TRTS. This could improve the global function and prognosis of TRTS patients with comorbidities. In addition to medicine and psychotherapeutic treatment, there are also some other treatment options. Repetitive transcranial magnetic stimulation can significantly relieve tic and obsessive-compulsive symptoms in TS patients in a meta-analysis[43]. Deep brain stimulation was carefully recommended to patients with TRTS for more consideration of its efficacy and tolerability[44].

In this study, we investigated the clinical characteristics of TRTS, which will provide conforming evidence to the definition of the Chinese version of the criteria for TRTS. According to our study, TRTS might be an important subtype of TS, which differs from "pure TS". The following aspects might be indicators of pediatric TRTS: An earlier age of onset, longer duration of illness, higher incidence rates of complicated tics such as coprolalia, higher premonitory urge, lower IQ, and more severe functional impairment than other "pure TSs". Moreover, TRTS is more frequently associated with ADHD-related symptoms, obsessive-compulsive symptoms, and social communication deficits. Cumulatively, these clinical characteristics provide important information for the definition of TRTS in China, especially for pediatric patients.

What may account for the social communication deficits in children diagnosed with TRTS? There might be the following three factors. First, both motor and vocal tic symptoms last longer and are more severe in TRTS than in other types of TS. For example, we found that the incidence rates of coprolalia were higher, which brought self-stigma pressure to the patients upon receipt of negative comments such as being called "freak" by peers. A study reported that stigma, social maladjustment, social exclusion, bullying, and discrimination are considered to be caused in large part by misperceptions of the disorder by teachers and peers[45]. Second, psychosocial factors have a huge impact on TRTS. The high comorbidity with ADHD makes children with TRTS suffer poorer test performance and rejections from peers or teachers at school[46]. Moreover, we found that children with TRTS might experience more negative parenting styles, indicating that they might suffer lower self-esteem and become socially withdrawn[47]. Third, it has been confirmed that social cognition deficits can also influence the social communication function of TS[48]. Overall, it indicated the importance of social communication deficit-related symptoms for TRTS.

However, in previous studies, we focused more on ADHD and obsessive-compulsive symptoms in TRTS, and social communication-related problems seemed to be neglected. It should be noted that social communication deficits are crucial signs of functional impairment[45], suggesting that we also need to assess social communication deficits during the assessment of function in TRTS. Therefore, we should pay more attention to social communication deficits in TRTS regardless of the assessment or the treatment.

Some of the following limitations existed in this study. First, the sample size should be larger to increase the effect size. Second, the evaluation tool was limited to the CBCL. Although the CBCL can assess the emotional and behavioral problems associated with TS, more specific tools should be included to evaluate TS comorbidities. Third, this study was a cross-sectional study, and a longitudinal follow-up study will provide more confirmatory evidence in the future.

CONCLUSION

Pediatric TRTS might show an earlier age of onset age, longer duration of illness, lower IQ, higher premonitory urge, and higher comorbidities with ADHD-related symptoms and OCD-related symptoms than 'pure TS'. Moreover, TRTS shows more social communication deficits that need to be covered in both the assessment and treatment of TRTS. TRTS might be one of the subtypes of TS. We need to develop a proper Chinese version definition of the TRTS in the future, especially for pediatric patients.

ARTICLE HIGHLIGHTS

Research background

Tourette syndrome (TS) is a complex neurodevelopmental condition marked by tics, as well as a variety

of psychiatric comorbidities, such as obsessive-compulsive disorders (OCDs), attention deficit hyperactivity disorder (ADHD), anxiety, and self-injurious behavior. However, no Chinese version of the TRTS criteria has been described. Moreover, the different criteria for TRTS were established mostly based on the clinical characteristics of adult patients with Tourette syndrome.

Research motivation

We need more confirmatory evidence about the clinical characteristics of TRTS. However, few studies have focused on the behavioral and emotional components of TRTS. Identifying the "indicators" of TRTS in the early stage may help in the treatment of these patients. Whether TRTS is different from "pure TS" (only tic symptoms without comorbidities) is unknown. More evidence is needed to explore these differences, especially at the early stage of TRTS.

Research objectives

This study aimed to examine the clinical characteristics of TRTS in a Chinese pediatric population, compare the clinical characteristics (*i.e.*, the onset of tic age, duration of illness, intelligence quotient (IQ), and behavioral and emotional problems) of patients with TRTS and non-TRTS patients, and report the locations and the frequency of tic onset in TRTS.

Research methods

A total of 126 pediatric patients aged 6-12 years with TS were identified, including 64 TRTS and 62 non-TRTS patients. The Yale Global Tic Severity Scale (YGTSS), Premonitory Urge for Tics Scale (PUTS), and Child Behavior Checklist (CBCL) were used to assess these two groups and compared the difference between the TRTS and non-TRTS groups. Descriptive statistics were performed to identify the basic clinical information, and t tests or χ^2 tests were used to compare the different variables of different TS groups.

Research results

When compared with the non-TRTS group, we found that the age of onset for TRTS was younger ($P < 0.001$), and the duration of illness was longer ($P < 0.001$). TRTS was more often caused by psychosocial ($P < 0.001$) than physiological factors, and coprolalia and inappropriate parenting style were more often present in the TRTS group ($P < 0.001$). The TRTS group showed a higher level of premonitory urge ($P < 0.001$), a lower intelligence quotient (IQ) ($P < 0.001$), and a higher percentage of family history of TS. The TRTS patients demonstrated more problems ($P < 0.01$) in the "Uncommunicative", "Obsessive-Compulsive", "Social-Withdrawal", "Hyperactive", "Aggressive", and "Delinquent" subscales in the boys group, and "Social-Withdrawal" ($P = 0.02$) subscale in the girls group.

Research conclusions

Pediatric TRTS might show an earlier age of onset age, longer duration of illness, lower IQ, higher premonitory urge, and higher comorbidities with ADHD-related symptoms and OCD-related symptoms than 'pure TS'. Moreover, TRTS shows more social communication deficits that need to be covered in both the assessment and treatment of TRTS. TRTS might be one of the subtypes of TS. We need to develop a proper Chinese version definition of the TRTS in the future, especially for pediatric patients.

Research perspectives

In previous studies, we focused more on ADHD and obsessive-compulsive symptoms in TRTS, and social communication-related problems seemed to be neglected. It should be noted that social communication deficits are crucial signs of functional impairment, suggesting that we also need to assess social communication deficits during the assessment of function in TRTS. Therefore, we should pay more attention to social communication deficits in TRTS regardless of the assessment or the treatment.

FOOTNOTES

Author contributions: Li Y and Yan JJ contribute equally to this study; Cui YH and Li Y took the initiative; Yan JJ participated in the data collection; Li Y performed the data analysis; Yan JJ finished the draft; all authors have read and approved the manuscript.

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Effect of distinct psychological interventions on changes in self-reported distress, depression and loneliness among older adults during COVID-19

Stav Shapira, Daphna Yeshua-Katz, Orly Sarid

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Abstract

BACKGROUND

Older adults have been considered a primary at-risk population during the coronavirus disease 2019 (COVID-19) pandemic, and many efforts have been and still are directed toward supporting them and enhancing their capacity to cope with the pandemic. Evidence shows that by enhancing proactive coping abilities through psychological interventions, in which cognitive-behavioral and mindfulness techniques are taught and practiced effectively, these interventions have supported older adults throughout the pandemic. However, the underlying mechanisms by which specific intervention components affect various mental states such as distress, depression and loneliness among older adults remain unclear and warrant investigation.

AIM

To determine the effect of an intervention using cognitive-behavioral and mindfulness techniques on changes in distress, depression and loneliness.

METHODS

We performed a secondary analysis on data from a previous study in which community-dwelling older adults attended a short-term, internet-based intervention during the first COVID-19 wave in Israel. The intervention included seven sessions during which various cognitive-behavioral and mindfulness techniques were learned and practiced. In-session changes in psychological distress were measured using the Subjective Units of Distress Scale (SUDS), which participants rated at the beginning and end of each session. Participants also filled out questionnaires that evaluated levels of depression [Patient Health Ques-

tionnaire (PHQ-9)] and loneliness (UCLA loneliness Scale) prior to and after the entire intervention process. The effect of in-session changes in the SUDS on changes in post-intervention depression and loneliness levels were assessed, as a proxy for distinct technique effectiveness.

RESULTS

The findings indicated in-session differences in terms of a decrease in psychological distress (SUDS). Sessions that included relaxation exercises and guided imagery, as well as sessions that included cognitive restructuring and mindfulness meditation, demonstrated the largest decreases in in-session psychological distress (≥ 35%). Two multivariate regression models, one for levels of post-intervention depression (PHQ-9 score) and the other for levels of post-intervention loneliness (UCLA loneliness score), were fitted. The results revealed two statistically significant explanatory variables for depression: The SUDS difference for sessions in which cognitive restructuring and mindfulness meditation were practiced, beta = -0.25, 95%CI: -1.23 to -0.1, and the pre-intervention level of depression, beta = 0.62, 95%CI: 0.37-0.75. The second model for loneliness revealed only one significant explanatory variable: The SUDS difference for sessions in which relaxation and guided imagery were practiced, beta = 0.41, 95%CI: 0.14-0.65.

CONCLUSION

Different psychological techniques seem to have different effects on distress, loneliness and depression. Understanding the pathways by which distinct techniques affect negative mental symptoms has implications for future intervention design.

Key Words: COVID-19; Depression; Loneliness; Aged; Cognitive behavioral therapy; Subjective Units of Distress Scale; Intervention studies

Core Tip: The present study explored how distinct cognitive, behavioral and mindfulness interventions affect depression and loneliness *via* changes in psychological distress among older adults. This study is, to the best of our knowledge, the first to explore underlying mechanisms of change in aspects of mental health against the unique backdrop of the coronavirus disease 2019 pandemic among older adults. The results provide both theoretical and clinical insights into future intervention design and in regard to ways of supporting older adults during times of change and uncertainty.

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INTRODUCTION

Ever since the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, a vast number of studies have investigated the effects of protective measures such as social distancing, quarantining and self-isolating on those individuals defined as comprising the primary at-risk population–older adults. Indeed, much evidence has pointed to elevated levels of psychological distress, depressive symptoms and loneliness among quarantined older adults, especially during the first 6 mo of the pandemic[1-4]. Conversely, later studies have suggested a much more nuanced picture with evidence indicating that the mental health of older adults remained roughly stable through the pandemic[5] and that, in fact, older adults have been more resilient to the negative mental health repercussions of the pandemic compared with younger individuals who have suffered greater economic losses[6] and struggled with managing childcare and work commitments[7]. In an effort to trace the protective factors that contributed to older adults' resilience during the pandemic, several studies have pointed to the importance of maintaining close and meaningful social connections[8], of implementing proactive coping[9] and of being able to use technology and function well in digital environments in these regards [10].

Digital environments and tools can be used not only as a means of staying connected with loved ones but also as powerful platforms to deliver designated psychological interventions to support older adults' mental health and well-being throughout the pandemic and promote proactive coping[11-13].

Indeed, remotely-delivered programs which have been developed during the pandemic have mainly focused on increasing social connectedness and combating the consequences of social isolation, as well as in augmenting coping skills[14]. One of the widespread and common therapeutic approaches used for adapting and enhancing coping abilities involves cognitive-behavioral tools (which include a wide range of techniques) in combination with other modalities such as mindfulness meditation. Previous evidence found that internet-based cognitive and behavioral interventions combined with peer support, such as interventions conducted in a group format, can effectively reduce depression[15] and loneliness [16].

Cognitive-behavioral interventions, as well as mindfulness interventions, are currently very much in use by therapists to help individuals combat depression[17] and loneliness[18]. Theoretically, these interventions focus on several mental pathways. Examples include: (1) Targeting the autonomic nervous system and sympathetic-parasympathetic responses[19,20]; by using techniques such as relaxation, breathing exercises, guided imagery and mindfulness meditation, which share key components of body-based exercises and mind-based practice, therapists aim to retrieve stressful autobiographical memories and alter those memories to be less alarming; and (2) focusing on high-order cognitive processes such as identifying maladaptive thinking patterns, altering them on a moment-to-moment basis and restructuring self-supportive talk[21]. These "bottom-up" and "top-down" processes, respectively, are of great relevance to different populations with whom therapists work. Although older adults are considered to have better regulatory emotional responses compared to younger people[22], it is important to understand which interventions are most effective in reducing distress, depression and loneliness among this cohort, as well as in different stressful situations.

We previously reported the results of a short-term, internet-based intervention which was found to alleviate symptoms of loneliness and depression among older adults during the initial COVID-19 outbreak and the first general lockdown in Israel[23-26]. Our intervention protocol aimed to provide participants with the skills to facilitate effective coping with the dire circumstances and uncertainty that typified that period-resulting from high infection and mortality rates, increasing economic pressures, along with reduced social connections and contact. Whereas we focused then on the effectiveness and acceptability of the intervention as a whole, we did not explore whether the mechanisms of change in psychological distress, loneliness and depression were related to the use of those specific techniques that constituted the full protocol. The process of developing the intervention protocol had been based on previous evidence that highlighted the importance of addressing older adults' own thoughts and emotions[27] and deficits in social cognition, as primary components of programs aiming to support older adults through times of change and uncertainty[28]. Furthermore, multifaceted interventions that incorporate a collection of therapeutic techniques, such as cognitive, behavioral and mindfulness techniques, as well as elements of social interaction and peer support through guided group discussions, have been found to be effective in assisting older adults' coping with various health conditions and stressful events[29-31]. The specific techniques that were incorporated into the intervention protocol were chosen on the basis of previous and solid evidence regarding their effectiveness in reducing depression, loneliness and distress. These included relaxation and guided imagery [32], cognitive restructuring[33,34] and mindfulness meditation[35]. Yet the specific mechanism of change for each of these techniques when delivered and practiced online has not previously been explored among older adults in the context of the pandemic.

We hypothesized that the above-mentioned online intervention would reduce psychological distress, depressive symptoms and loneliness among older adults during the initial COVID-19 outbreak. Furthermore, we explored the links between the different techniques that were learned in terms of changes in psychological distress during sessions, as well as the effect of these changes (in distress) on post-intervention depressive symptoms and loneliness.

MATERIALS AND METHODS

The analysis described here was performed on data obtained from a randomized controlled trial pilot study. The initial study aimed to evaluate the effectiveness of a short-term, internet-based group intervention to alleviate mental health difficulties among community-dwelling older adults during the pandemic's first lockdown in Israel. The intervention protocol and findings regarding its effectiveness were previously described elsewhere[24,26]. Briefly, the intervention included seven guided online sessions over 3.5 wk *via* the videoconferencing app Zoom, for small groups of up to seven participants. Each session lasted approximately 60-90 min. During the intervention, participants learned and practiced cognitive-behavioral and mindfulness techniques such as the use of repeated self-talk mantras, cognitive restructuring, breathing exercises, guided imagery and mindfulness meditation (Figure 1). The group moderators were clinical social workers trained to guide the intervention; additionally, they received ongoing supervision by a senior clinical social worker from the research team.

Study participants

Between March and June 2020, following approval by the institutional review board of Ben-Gurion

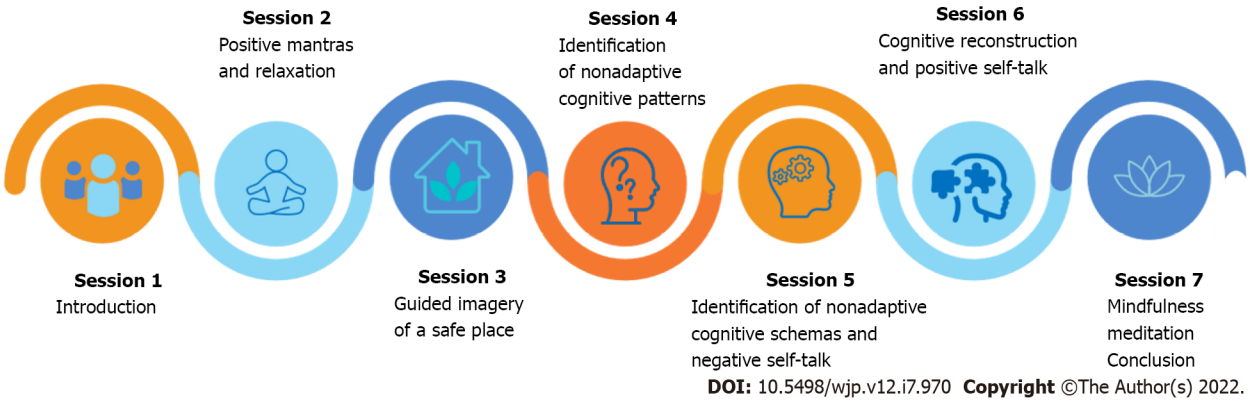

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Figure 1 Intervention protocol: Skills and techniques learned in each session.

University of the Negev, an online invitation to participate in the study was circulated to prospective participants. The invitation was distributed *via* WhatsApp groups of a local non-governmental organization that focuses on promoting digital literacy among seniors, as well as through welfare departments of several local municipalities in Israel. Eligible participants were community-dwelling older adults (aged 65+) who were: (1) Proficient in Hebrew; and (2) Could provide informed consent. Additional inclusion criteria were: (1) Having an active internet connection; (2) Possessing at least one device that enables online communication (*i.e.* a computer or smartphone); and (3) Having a minimal ability to operate this device (*i.e.* switching it on and off). A total of 124 applicants applied and were screened for eligibility: 37 applicants were excluded due to age (< 65) (21) or non-response (16), and one applicant withdrew from the study for personal reasons, leaving 86 eligible participants. The participants were then randomized *via* a 4:1 ratio into either the intervention or the waitlist control group. We used this allocation instead of an even ratio for ethical reasons; we wanted to provide mental support as quickly as possible to the greatest number of people who were, at the time (during the initial months of the pandemic), confined to their homes for an unknown period. The current analysis will focus on data obtained solely from the intervention group (n = 64). For detailed information on drop-out reasons and rates see Shapira *et al*[26] (2021).

Procedure

Participants filled out pre- and post-intervention online questionnaires (web-based survey, https://www.qualtrics.com) that had been sent to them by the group moderator *via* email or mobile phone in accordance with their preference. Additionally, at the beginning and immediately at the end of each session, all participants rated their level of subjective mental distress (see in detail in the section below); these data were collected *via* the use of Google Forms. At the end of the study, each participant provided two measurements (pre- and post-intervention) of the study questionnaire, in addition to 14 measurements of subjective distress (two measurements at the beginning and end of each of the seven sessions).

Measurement

Pre- and post-intervention questionnaire: Dependent variables: The dependent variables were depression and loneliness. Depression was assessed using a 9-item measure, which is part of the Patient Health Questionnaire (PHQ-9). The PHQ-9 is a commonly used self-administered measure of depression containing nine items that map each of The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria for major depression[36]. The items assess the frequency of depressive symptoms over the past 2 wk and are rated on a four-point Likert-type scale: 0 (not at all) to 3 (nearly every day). The responses were summed, with a range of 0–27. The PHQ-9 was previously translated into Hebrew and tested among the Israeli population with good reliability (α ranged between 0.88 to 0.93)[37]. Loneliness was assessed using the short 3-item version of the UCLA loneliness Scale [38]. The items in this scale are related to lack of companionship, social exclusion and social isolation. Participants rated their feeling of loneliness on a 3-point Likert-type scale: (1) Hardly ever; (2) Some of the time; and (3) Often. Scores for the three items were summed with a possible score of 3–9. Higher scores indicated greater loneliness. This scale was previously translated into Hebrew and used among the Israeli population with good reliability (α = 0.87)[39].

Independent variables: The independent variables included sociodemographic data and evaluation of subjective health. Sociodemographic data included age, sex, educational level (dichotomized: Tertiary education *vs* non-tertiary education) and household composition [dichotomized: Live alone *vs* live with other(s)]. *Subjective* Health was assessed *via* one item from Israel's Central Bureau of Statistics survey of health indicators[40]. The participants were asked to rate their perception of personal health on a 4-

point Likert-type scale: 1 (poor) to 4 (excellent). Higher scores indicated better self-rated health.

In-session evaluation of subjective mental distress: Psychological distress was assessed using The Subjective Units of Distress Scale (SUDS)[41], at the beginning and end of each session. The SUDS provides a quick and simple way to measure distress in a given moment. The respondents were asked to estimate the severity of their emotional distress by providing a numerical value ranging from 0 (no distress) to 10 (highest distress you ever felt). The SUDS is a common tool for measuring the effect of therapeutic interventions[42] and has been previously used among older individuals[43,44].

Statistical analysis

Data were analyzed in three steps. First, the differences between the SUDS start score and the SUDS end score for each session were calculated, resulting in seven new variables *per* participant that represented their changes in mental distress (SUDS) during each session (SUDS1 to SUDS7). Pearson's correlations were used to assess the intercorrelations between the seven SUDS differences. If the correlation coefficient between two values was higher than 0.65, a mean score was calculated for those values to avoid possible multicollinearity and potential bias in the following stages of analysis. The second analysis step included bivariate analyses to evaluate associations between the two dependent variables (post-intervention loneliness and depression levels), SUDS differences and other study variables using Pearson's correlations and Mann-Whitney U-test. Finally, two multivariate linear regression models were developed to identify significant associations between the explanatory variables that were found significant in the bivariate analyses and each outcome measure: Post-intervention depression and loneliness levels. A P value of ≤ 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS (version 26, SPSS Inc., Chicago, IL, United States).

RESULTS

Descriptive statistics

Out of the 86 participants who met the inclusion criteria, a total of 64 participants completed the intervention program and provided data for the current analysis. The baseline characteristics of those participants were as follows: sex, 52 female participants (81%) and 12 male participants (19%); age, M = 72.1 (SD = 5.3) years; household composition, 24 residing alone (37.5%) and 40 residing with other(s) (62.5%); education, 48 had a tertiary education (76%) and 16 had a non-tertiary education (24%). In terms of subjective health, 33% reported their health to be "very good" or "excellent," 44% reported their health to be "fair," and the rest (23%) reported their health as "not so good" or "poor." The PHQ-9 score (depression) was 6.6 (SD = 5.2) at baseline and decreased to 5.2 (SD = 4.7) post-intervention. The score on the UCLA loneliness scale was 5.4 (SD = 2) at baseline and decreased to 4.7 (SD = 1.6) post-intervention. For detailed information on study participants and changes in outcome measures, see previous publications[25,26].

Subjective mental distress

Subjective mental distress was evaluated by measuring the SUDS rating (on a scale from 0-10) at the beginning and end of each session. Figure 2 presents the mean values of the SUDS measure for each of the seven sessions in the program and the average percentage of change in each session.

The findings indicate that the sessions in which the average decrease in subjective mental distress was highest (≥ 35%) were sessions 2, 3, 6, and 7. Further analysis estimated the intercorrelations between the seven variables representing the delta differences in SUDS ratings. The results revealed a strong correlation (defined as $r > 0.6$) between the delta values of sessions 2 and 3 ($r = 0.65$, $P < 0.001$) and between the delta values of sessions 6 and 7 ($r = 0.69$, $P < 0.001$). Given these results, the variables were merged by calculating a mean value for each of the two pairs.

Bivariate analysis

The associations between levels of post-intervention depression and loneliness, and SUDS difference scores, were assessed. Significant associations were observed between levels of depression and the SUDS difference of sessions 2 + 3 ($r = -0.36$, $P = 0.003$) and of sessions 6 + 7 ($r = -0.4$, $P = 0.001$). Only one significant association was detected between levels of loneliness and the SUDS difference of sessions 2 + 3 ($r = -0.33$, $P = 0.009$). An additional association was found between levels of depression and age ($r = -0.3$, $P = 0.03$). Other personal characteristics did not reach statistical significance. Table 1 presents the intercorrelations between study variables.

Multivariate analysis

Two multivariate regression models were fitted to identify statistically significant associations between the study variables: (1) Levels of post-intervention depression (PHQ-9 score); and (2) Levels of post-intervention loneliness (UCLA loneliness score). The variables entered into each model were selected on the basis of the bivariate analysis results; in addition, we controlled for levels of pre-intervention

Table 1 Correlation matrix of study variables (*n* = 64)

	Loneliness	Depression	SUDS1	SUDS_2_3	SUDS4	SUDS5	SUDS_6_7	Age	Subjective health
Loneliness	1								
Depression	-0.01								
SUDS1	0.12	-0.18	1						
SUDS_2_3	-0.33[b]	-0.36[b]	0.57[b]	1					
SUDS4	0.21	-0.30	0.21	0.52[b]	1				
SUDS5	-0.02	-0.20	-0.09	0.24	0.31[a]	1			
SUDS_6_7	0.07	-.40[b]	0.26	0.48[b]	0.42[b]	0.50[b]	1		
Age	-0.16	-.27[a]	0.14	0.03	-0.13	-0.10	-0.08	1	
Subjective health	0.02	-0.13	0.27	0.20	0.14	0.07	0.10	-0.15	1

[a]$P < 0.05$.
[b]$P < 0.001$.
All Subjective Units of Distress Scale variables are delta differences.

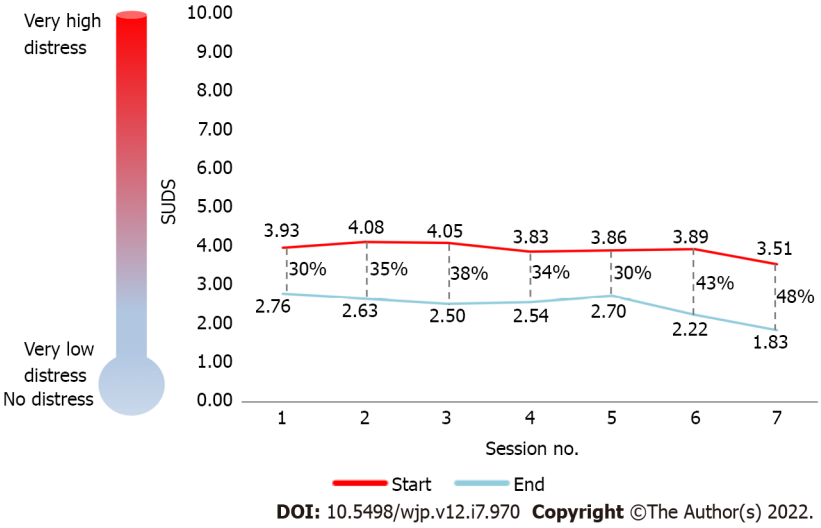

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Figure 2 Mean values for the Subjective Units of Distress Scale measure at the start and end of the intervention sessions for the entire study sample (*n* = 64). The dashed lines and accompanying values represent the mean percentage of change in Subjective Units of Distress Scale scores for each session. SUDS: Subjective Units of Distress Scale.

depression/loneliness. Both models employed a standard linear regression analysis. The results revealed two statistically significant explanatory variables for depression: The SUDS difference for sessions 6 + 7, beta = -0.25, 95%CI: -1.23 to -0.1, and the level of pre-intervention depression, beta = 0.62, 95%CI: 0.37-0.75. The second model for loneliness revealed only one significant explanatory variable: The SUDS difference for sessions 2 + 3, beta = 0.41, 95%CI: 0.14-0.65 (Tables 2 and 3).

DISCUSSION

This study examined the effectiveness of a short-term group intervention using cognitive-behavioral and mindfulness interventions for alleviating psychological distress, depression and loneliness among older adults during the first wave of the COVID-19 pandemic and a national lockdown in Israel. The findings indicated in-session differences in terms of decreases in psychological distress. Sessions during which the techniques of relaxation exercises and guided imagery were learned, and sessions during which cognitive restructuring and mindfulness meditation were learned, led to the highest reduction in distress and these reductions were related to significant changes in levels of post-intervention loneliness and depression, correspondingly. These results suggest that specific techniques may have different

Table 2 Multivariate regression (with post-intervention Patient Health Questionnaire-9 score as dependent variable)

	Unstandardized coefficients		Standardized coefficients		95% confidence interval for β		*P* value
	β	Std. Error	β	t	Lower bound	Upper bound	
(Constant)	8.248	7.321		1.127	-6.417	22.913	0.265
Age	-0.099	0.094	-0.110	-1.057	-0.287	0.089	0.295
Sex	-0.655	1.239	-0.055	-0.529	-3.136	1.826	0.599
SUDS_2_3	0.040	0.317	0.014	0.127	-0.594	0.675	0.899
SUDS_6_7	-0.666	0.281	-0.255	-2.367	-1.230	-0.102	0.021
PHQ_SUM_1	0.563	0.095	0.626	5.948	0.374	0.753	0.000

n = 62, adjusted r^2 = 52.2%, F = 14.138, P < 0.001.

Table 3 Multivariate regression (with post-intervention UCLA loneliness score as dependent variable)

	Unstandardized coefficients		Standardized coefficients		95% confidence interval for β		*P* value
	β	Std. Error	β	t	Lower bound	Upper bound	
(Constant)	7.805	3.237		2.411	1.323	14.287	0.019
Age	-0.045	0.041	-0.147	-1.100	-0.126	0.037	0.276
Sex	-0.071	0.540	-0.017	-0.132	-1.152	1.010	0.896
SUDS_2_3	-0.399	0.129	-0.416	3.092	-0.657	-0.140	0.003
Lonely_1	0.155	0.109	0.195	1.427	-0.063	0.373	0.159

n = 62, adjusted r^2 = 11%, F = 2.847, P = 0.03.

effects on the mental constructs that were examined (*i.e.* depression and loneliness). Possible explanations for these results are elaborated upon below.

First, the associations between psychological distress, measured by SUDS, and loneliness and depression, have been established previously[45,46]. Changes in SUDS scores have also previously been used to evaluate the effectiveness of psychological interventions and of specific intervention components[47]. The current findings strengthen the notion that changes in SUDS scores can be used as an indicator reflecting adjustments attained by a specific intervention component, and thus make an important methodological contribution to the design and evaluation of psychological interventions.

Furthermore, in relation to the specific effect of distinct cognitive-behavioral and mindfulness intervention components, the different mechanisms underlying the abovementioned therapeutic techniques and their impact on mental health outcomes should be discussed. The need to consider the underlying mechanisms involved in the effects of psychological interventions has been previously identified[28,48]. These mechanisms are not yet well understood, and some evidence suggests that observed positive changes are likely to occur *via* several pathways, such as changing maladaptive cognitive biases[18], improving emotion self-regulation[49] and shifting the sympathetic/parasympathetic balance[50]. The current findings which point to body-oriented, behavioral interventions such as relaxation through breathing and guided imagery as effective in decreasing distress (and consequently loneliness), but not in decreasing depression, contradict some previous findings but align with others. The same can be said for the finding which indicated that relatively more complex techniques such as cognitive restructuring and mindfulness meditation effectively reduced distress and depression but not loneliness. It should be noted that a meta-analysis study concluded that interventions that address maladaptive social cognitions present the greatest potential for reducing loneliness[28]. This notion was partially supported by the current results, in that the study's entire protocol was indeed found to reduce loneliness[25], although the specific techniques that addressed social cognitions (*e.g.*, cognitive restructuring) were not necessarily found to do so. It is therefore possible to assume that the latter techniques indeed contributed to reducing loneliness in the specific context of the current intervention (the first COVID-19 wave in Israel) and population (older adults isolated in their homes) but that their contribution was smaller compared to that of other techniques identified. Previous evidence has indicated the effectiveness of mindfulness-based[51] as well as cognitive restructuring techniques[52,53] in interventions treating depression. The current findings align with this evidence and highlight the importance of combining these two techniques together in

programs to treat depression, specifically among older individuals.

Finally, it is also worth mentioning once again the unique setting of the current group intervention–which was internet-based, short-term and guided–and discussing the abovementioned insights in this context. Indeed, the current program was not designed as a classic therapeutic intervention, but rather as a study program aimed to provide participants with a toolkit that would be available to them, and which would be at their disposal during a period marked by social isolation, lockdowns, and other dire circumstances. As such, the effect of learning and practicing new skills in a digital environment may also have contributed to the beneficial changes observed *via* empowering the participants, perhaps by increasing their self-efficacy[54] and enhancing social inclusion[55]. Future research should explore the effects of online learning as an independent mechanism that enhances older adults' coping capacity during periods of crisis and uncertainty.

The current study had several limitations. First, as the intervention was delivered in a group setting, thus enabling discussion between participants during sessions, we cannot rule out a possible effect of participants' interactions on the outcomes obtained. Second, the effectiveness of the techniques learned was evaluated through a proxy measure: Changes in levels of psychological distress. It is possible that this measure does not fully reflect the effect of the intervention on the participants as it was self-reported and subjected to potential bias. Future studies should incorporate objective measures, such as monitoring facial expressions, as part of online interventions[56,57]. Third, the present study examined the group effect of the techniques learned and did not focus on individual-level preferences. Fourth, the small sample size may also compromise the study's conclusions. Larger studies in the future would allow for subgroup analyses and enable the determination of effectiveness for different program elements in a more robust manner.

CONCLUSION

The current study examined in depth the mechanisms underlying the beneficial changes in mental health outcomes among older individuals who participated in an internet-based group intervention during the early part of the COVID-19 pandemic. Findings indicated that different intervention components had different effects on psychological distress, loneliness and depression, and that each component may enhance the proactive coping abilities of older individuals in different ways. From a theoretical perspective it is important to understand the specific pathways by which distinct techniques affect mental capacities[49]. The frameworks of cognitive-behavioral and mindfulness interventions need to be dissected into segments as a way to better understand the role of each interventional strategy. Doing so would support the design of more concise and efficient interventions tailored to the needs of different populations and mental states. From a clinical perspective, the findings shed light on potential paths by which different therapeutic techniques might affect mental health outcomes among older adults specifically, and thus have implications for future intervention design. These insights may help in the enhancement of older individuals' resilience during future outbreaks, as well as during other large public health emergencies.

ARTICLE HIGHLIGHTS

Research background

Older adults have been considered a primary at-risk population during the coronavirus disease 2019 (COVID-19) pandemic. Recent evidence has shown that enhancing proactive coping abilities through psychological interventions can support older adults throughout the pandemic. However, the underlying mechanisms by which specific intervention components affect various mental states among older adults remain unclear and warrant investigation.

Research motivation

We previously reported the results of a short-term, internet-based intervention which was found to alleviate symptoms of loneliness and depression among older adults during the initial COVID-19 outbreak and the first general lockdown in Israel. We focused then on the effectiveness and acceptability of the intervention as a whole, but did not explore whether the mechanisms of change in mental states were related to the use of those specific techniques that constituted the full protocol. We believe that a better understanding of the role of each interventional strategy can support the design of more concise and efficient interventions tailored to the needs of different populations and mental states.

Research objectives

To determine the effect of an intervention using cognitive-behavioral and mindfulness techniques on changes in distress, depression and loneliness. Furthermore, we explored the links between the different techniques that were learned in terms of changes in psychological distress during sessions, as well as the

effect of these changes (in distress) on post-intervention depressive symptoms and loneliness.

Research methods

We performed a secondary analysis on data from the original intervention described above. The intervention included seven sessions during which various cognitive-behavioral and mindfulness techniques were learned and practiced. In-session changes in psychological distress were measured using the Subjective Units of Distress Scale (SUDS) which participants rated at the beginning and end of each session. In addition, levels of depression (Patient Health Questionnaire) and loneliness (UCLA Loneliness Scale) were assessed prior to and after the entire intervention process. The effect of in-session changes in the SUDS on changes in post-intervention depression and loneliness levels were assessed as a proxy for distinct technique effectiveness.

Research results

The findings indicated in-session differences in terms of decreases in psychological distress. Sessions during which the techniques of relaxation exercises and guided imagery were learned, and sessions during which cognitive restructuring and mindfulness meditation were learned, led to the highest reduction in distress, and these reductions were related to significant changes in levels of post-intervention loneliness and depression, correspondingly.

Research conclusions

Different psychological techniques seem to have different effects on the specific mental states that were assessed in the current study. The findings shed light on potential paths by which different therapeutic interventions might affect mental health outcomes among older adults specifically, and thus have implications for future intervention design. These insights may help in the enhancement of older individuals' resilience during future outbreaks and other emergencies.

Research perspectives

Larger studies are needed to allow for subgroup analyses that would enable the determination of effectiveness for different program elements in a more robust manner.

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FOOTNOTES

Author contributions: Shapira S, Yeshua-Katz D and Sarid O designed and performed the research; Shapira S and Sarid O analyzed the data; Shapira S wrote the first draft of the manuscript; all authors have read and approved the final manuscript.

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Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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

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SCIENTOMETRICS

Mapping the landscape and structure of global research on binge eating disorder: Visualization and bibliometric analysis

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Abstract

BACKGROUND

Binge-eating disorder (BED) is a clinical syndrome and is considered the most common type of eating disorder. However, our understanding of the global performance and progress of BED research is limited.

AIM

To describe and perform a bibliometric analysis of the state of BED research.

METHODS

The term 'Binge eating' was searched in the title throughout the previous year's up to December 31, 2020. We searched the Scopus and Reference Citation Analysis for publications on Binge eating. The VOSviewer software version 1.6.17 was used to produce the network visualization map of the most frequent author, collaborative relationships between countries/regions, and to determine the hotspots related to binge eating research. In addition, conventional bibliometric indicators were generated.

RESULTS

The search strategy found 2713 total articles and an average of 62 articles *per* year. Among them, 'Article' represented 82.49% of the publications (n = 2238 articles) and was the most frequent type, followed by reviews (n = 243; 8.96%). The number of publications increased steadily during the last decade of the study period. One hundred and thirty-two countries contributed to binge eating research, with 1495 (55.11%) articles published in the United States, followed by Italy with 256 (9.44%), the United Kingdom with 183 (6.75%), and Germany with 182 (6.71%). Currently, the main hot topics related to BED are 'type of treatment and management and treatment provided to BED"; "processes and pathways to binge eating"; and 'diagnosis, signs and symptoms, comorbidities and prevalence and associated factors with BED'.

CONCLUSION

The number of publications has increased noticeably during the previous decade. There are indeed relatively few publications on BED from low-and middle-income nations, so much is to be learned from the experience of all countries. Studies on this topic are critical in all countries to discover risk factors and effective intervention measures. Although our findings are preliminary, they imply that the future prospects for interventions aimed at BED management are bright, focusing on complex models of care and long-term maintenance of therapeutic gains.

Key Words: Binge-eating disorder; Scopus; Bibliometric; VOSviewer; Eating disorders.

Core Tip: Over the last decade, research on binge eating disorder (BED) has focused on various issues. A review of the published literature would aid in determining the density and gaps of research. The number of publications related to BED has significantly increased over the last decade. Research on this topic is critical for identifying risk factors and developing effective intervention strategies in all countries. Although our findings are preliminary, they suggest that the future of BED management interventions is bright, emphasizing complex models of care and long-term maintenance of therapeutic gains.

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INTRODUCTION

Disordered eating is a common condition that is often comorbid, especially when associated with obesity. Patients may suffer from various forms of eating disorders, including anorexia nervosa, bulimia nervosa, and binge eating disorder (BED). In the general population, almost 1%–3% of individuals will develop BED during their lifetime, making this form the most common eating disorder[1-3]. Psychiatrist Albert Stunkard first identified BED in 1959[4]. Stunkard outlines an eating habit characterized by eating large amounts of food at irregular intervals in his study "*Eating Patterns and Obesity*"[4].

BED is characterized by recurrent episodes in which people eat larger amounts of food than most people could eat simultaneously and under similar circumstances while experiencing feelings of loss of control and the absence of compensatory behaviors such as vomiting. Individuals suffering from BED can experience rapid eating in the absence of hunger, uncomfortable fullness, and afterward feelings of disgust, guilt, or sadness[5-9].

Several studies reported that many factors could facilitate binge eating, including impulsivity, inability to control emotions, and negative mood conditions[10-13]. In 2015, a meta-analysis of 33 studies found that negative mood conditions increase food intake in patients with BED compared to

those who do not suffer from BED, suggesting a strong relationship between negative mood conditions and binge eating behaviors[14].

However, despite the significant physical and psychological impairment, a higher percentage of binge-eaters did not seek treatment or receive any treatment[15,16]. Therefore, current treatments for BED primarily focus on behavioral, psychological, and physical outcomes that include cognitive behavioral therapy (CBT) and behavioral weight loss therapy (BWLT)[15,17]. CBT is considered the most effective approach for BED episodes, while BWLT is more effective in weight loss[18].

Over the last decades, research on BED has focused on a variety of topics. An examination of the published literature would aid in determining the density of research and the gaps. We found some bibliometric publications related to certain nutritional subjects[19-22], but none related to BED; therefore, this article is a novelty in this field. This study investigates the global performance and progress of BED research and maps the research patterns and trends using a visualization tool to address this gap. A bibliometric study of previous publications could serve as a foundation for a comprehensive understanding of existing research on BED and highlight some future research topics.

MATERIALS AND METHODS

Data source

The Scopus database was used to perform a descriptive bibliometric evaluation of BED publications. The Scopus database has a wider coverage of health and biomedical disciplines than the Web of Science and PubMed and has a higher coverage of citation reports[23,24]. It is also simple to access various legitimate analytical tools, making it an ideal choice for our research[23,24]. Scopus has also been used and validated in bibliometric analyses published in the previous two years[25-29].

Search strategies

On October 1, 2021, the search and download procedure was completed in order to avoid significant mistakes caused by daily database changes. The data was immediately retrieved from the Scopus database and Reference Citation Analysis (RCA) (https://www.referencecitationanalysis.com/). "Binge eating" was used as a search term in the Scopus database for the whole preceding year, up to December 31, 2020. This search term included 'Binge eating', 'Binge-eating', 'Binge eating disorder', and 'Binge-eating disorder'. We used the keyword 'binge-eating' because we are concerned with binge-eating *per se* rather than related terminology. The search method for phrases relevant to binge-eating was confined to title alone to gain higher accuracy in the findings since when other search fields such as Abstract and Keywords were widened; numerous publications were found that were not connected to binge-eating (*i.e.*, false-positive data). According to the researchers' experience[30-32], including search elements in the title rather than a topic search (title, abstract, and keywords) substantially improves specificity with minimal loss of sensitivity.

Bibliometric indicators

Document types, yearly number of publications, author names, journal names, country names, institution names, funding agency names, and number of citations were included in the data exported from the Scopus. The impact index *per* article for the top ten most-cited publications based on RCA was calculated. RCA is an open, multidisciplinary citation analysis database owned by Baishideng Publishing Group Inc. (Pleasanton, CA 94566, United States)[33].

Network visualization maps

The VOSviewer 1.6.17 software produced the network visualization map of the most frequent author, collaborative relationships between countries/regions, and the hotspots related to binge-eating research. The size of the nodes on the network visualization map is proportional to the number of occurrences, while the distance between words reflects the strength of the relationship between countries, authors, and terms, with a closer distance suggesting a stronger relationship[34].

Ethical approval

Because all data were collected from previously published articles, there was no ethical approval requirement for this bibliometric study.

RESULTS

General description of the retrieved publications

The search strategy found 2713 total documents and an average of 62 documents *per* year. Among them, 'Article' represented 82.49% of the publications (n = 2238 articles) and was the most frequent type,

followed by reviews (*n* = 243; 8.96%). The remaining publication types were 232 documents (8.54%).

Annual growth of publications

The oldest paper was written by Wilson[35] in 1976 entitled 'Obesity, binge eating, and behavior therapy: Some clinical observations' in *Behavior Therapy*. After this, the number of publications grew slowly from 1976 to 1990, with little fluctuation. Figure 1 shows the publication trend related to BED from 1976 to 2020. Clearly, the number of relevant publications has increased sharply since 2011, while 2020 netted the largest amount of binge eating research (195 published documents).

Active countries

One hundred and thirty-two countries contributed to binge eating research, with 1,495 (55.11%) articles published in the United States, followed by Italy with 256 (9.44%), the United Kingdom with 183 (6.75%), and Germany with 182 (6.71%) (Table 1). Figure 2 shows the collaboration of the international network. Countries with a minimum contribution of ten articles (*n* = 26) were included in the network. The map is divided into eight clusters of varying colors, each representing one of eight different cross-country network collaborations. The United States and Canada had the strongest cross-country collaboration, as indicated by the thickness of the connecting line.

Active institutions

Table 2 lists the top ten core institutions publishing the most documents on the BED. The most active institutions in this field were those associated with American colleges. The top 10 active institutions contributed 835 articles (30.77%). Ten of the top active institutions were located in North America. *The Yale School of Medicine* came in first with 172 articles, followed by *Yale University* with 116, the *University of Minnesota Twin Cities* with 91, and the *Neuropsychiatric Research Institute, Fargo* with 85.

Contributions of funding agencies

Table 3 includes the top ten core funding agencies with the most documents in the BED. Among them, nine agencies were from the United States, and one agency was from the United Kingdom. The *National Institutes of Health* came first, with 562 studies that the *Department of Health* supported. The *US Department of Health and Human Services* came second (*n* = 537). In contrast, the *National Institute of Diabetes and Digestive and Kidney Diseases* came third (*n* = 319), and the *National Institute of Mental Health* came fourth (*n* = 289).

Active authors

The total number of authors who published on BED was 6223, of whom 40 (0.64%) published more than 20 documents for each author. Figure 3 shows the map of the co-authorship network of authors with at least ten publications. The authors with the largest node size contributed the most and included Grilo CM; Masheb RM; Mitchell JE; Crosby RD; White MA; McElroy SL; Crow SJ; Peterson CB; Wilfley DE; and Bulik CM.

Active journals

Table 4 shows the top ten active journals for the literature related to BED. The *International Journal of Eating Disorders* (*n* = 398, 14.57%) was first ranked, followed by Eating *Behaviors* (*n* = 139, 5.12%), *Appetite* (*n* = 94, 3.46%), and the *European Eating Disorders Review* (*n* = 85; 3.13%).

Citation analysis

According to citation analysis, the retrieved articles got 99491 citations, with an average of 36.7 *per* article and an h-index of 137. The number of citations ranged from 0 to 1454. Two hundred and fifty of the articles retrieved had zero citations, while 248 received 100 or more citations. The top 10 most-cited papers received 7126 citations in all. The total citations of these articles that quoted the research on BED research ranged from 458 to 1454 (Table 5). Furthermore, the ten most cited articles have an impact index *per* article of 0.7 to 64.4 (Table 5).

Research themes

Three clusters emerged from the mapping of terms in the titles and abstracts of the retrieved literature, reflecting three major research themes in this field (Figure 4). The first group (blue) signifies a research theme on the management and treatment provided for BED (psychotherapy, CBT, interpersonal psychotherapy, and pharmacotherapy). The second cluster (green) is a research theme that focuses on processes and pathways to binge eating (dietary restriction theory, cognitive models of binge eating, cognitive behavior model of BED, and emotional regulation theory). Finally, the third theme (red) is the largest topic and discusses diagnosis, signs and symptoms, comorbidities, and prevalence and associated factors with BED.

Table 1 List the top ten core countries publishing the most documents on binge-eating disorder

Ranking	Country	Number of documents	%
1st	United States	1495	55.11
2nd	Italy	256	9.44
3rd	United Kingdom	183	6.75
4th	Germany	182	6.71
5th	Canada	157	5.79
6th	Australia	127	4.68
7th	Brazil	101	3.72
8th	Spain	59	2.17
9th	Switzerland	58	2.14
10th	France	57	2.10

Table 2 List the top ten core institutions publishing the most documents on binge-eating disorder

Ranking	Institution	Country	*n*	%
1st	*Yale School of Medicine*	United States	172	6.34
2nd	*Yale University*	United States	116	4.28
3rd	*University of Minnesota Twin Cities*	United States	91	3.35
4th	*Neuropsychiatric Research Institute, Fargo*	United States	85	3.13
5th	*The University of North Carolina at Chapel Hill*	United States	70	2.58
6th	*Harvard Medical School*	United States	67	2.47
7th	*University of Cincinnati College of Medicine*	United States	65	2.40
8th	*Columbia University*	United States	60	2.21
9th	*University of North Dakota*	United States	56	2.06
10th	*Stanford University School of Medicine*	United States	53	1.95

Table 3 List the top ten core funding agencies that have the most documents on binge-eating disorder

Ranking	Funding agencies	Country	*n*	%
1st	*National Institutes of Health*	United States	562	20.72
2nd	*U.S. Department of Health and Human Services*	United States	537	19.79
3rd	*National Institute of Diabetes and Digestive and Kidney Diseases*	United States	319	11.76
4th	*National Institute of Mental Health*	United States	289	10.65
5th	*National Institute on Drug Abuse*	United States	71	2.62
6th	*Eunice Kennedy Shriver National Institute of Child Health and Human Development*	United States	39	1.44
7th	*National Institute of Alcohol Abuse and Alcoholism*	United States	36	1.33
8th	*Shire*	United Kingdom	32	1.18
9th	*National Center for Advancing Translational Sciences*	United States	31	1.14
9th	*National Institute of Heart, Lung, and Blood Institute*	United States	31	1.14

DISCUSSION

The present study used a bibliometric methodology to analyze global research publications on BED. In addition to reviewing current research on BED, this study identifies hot topics in this field and suggests future study options. The interest in global research in BED has increased significantly in recent years.

Table 4 List the top ten core journals that have the most documents on binge-eating disorder

Ranking	Journal	*n*	%	IF[1]
1st	*International Journal of Eating Disorders*	398	14.67	3.668
2nd	*Eating Behaviors*	139	5.12	2.156
3rd	*Appetite*	94	3.46	3.608
4th	*European Eating Disorders Review*	85	3.13	3.560
5th	*Eating and Weight Disorders*	67	2.47	3.634
6th	*Behaviour Research and Therapy*	48	1.77	4.500
7th	*Journal of Consulting and Clinical Psychology*	45	1.66	4.632
8th	*Obesity*	40	1.47	3.742
9th	*Comprehensive Psychiatry*	35	1.29	2.567
10th	*Eating Disorders*	33	1.22	2.013
10th	*Journal of Clinical Psychiatry*	33	1.22	4.204
10th	*Physiology and Behavior*	33	1.22	2.826
10th	*Psychiatry Research*	33	1.22	2.118

[1]Impact factor (IF) from 2020 Journal Citation Reports (Clarivate Analytics).

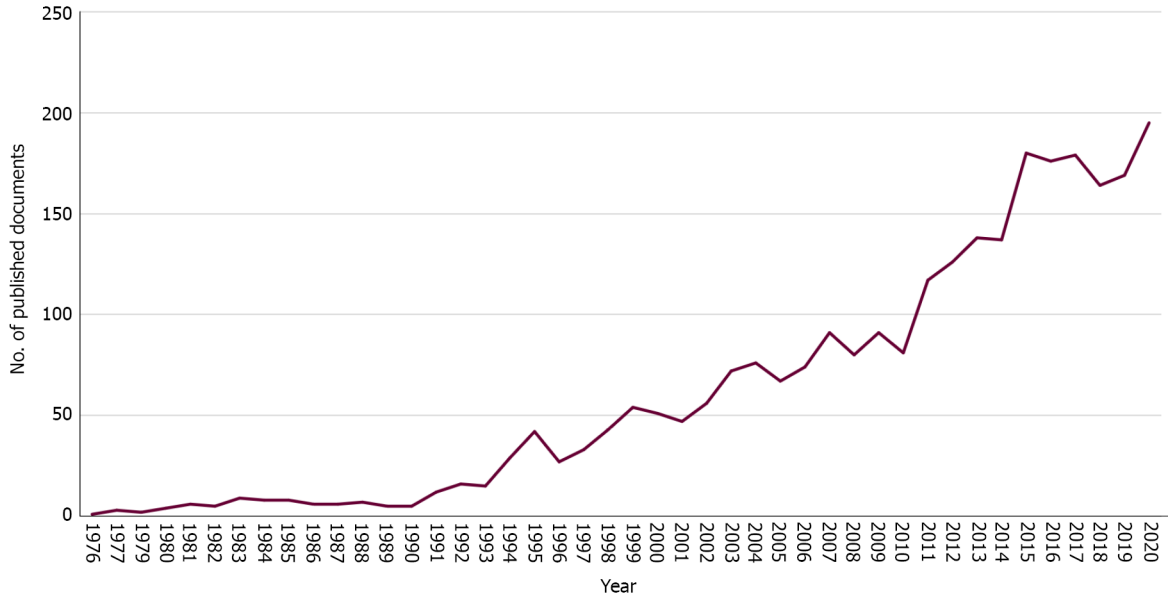
Table 5 List of the top 10 cited articles for studies related to binge-eating disorder

Ranking	Ref.	Year	Source title	Cited by	Impact index *per* article[1]
1st	Heatherton and Baumeister[6]	1991	*Psychological Bulletin*	1454	7.4
2nd	Gormally *et al*[6]	1982	*Addictive Behaviors*	1292	29.1
3rd	Spitzer *et al*[6]	1993	*International Journal of Eating Disorders*	686	17.2
4th	Spitzer *et al*[6]	1992	*International Journal of Eating Disorders*	659	17.3
5th	Kessler *et al*[1]	2013	*Biological Psychiatry*	602	64.4
6th	Stice *et al*[6]	2002	*Health Psychology*	531	23.3
7th	Stice *et al*[6]	2000	*Psychological Assessment*	506	0.7
8th	Telch *et al*[70]	2001	*Journal of Consulting and Clinical Psychology*	473	19.4
9th	Halmi *et al*[7]	1981	*Psychological Medicine*	465	34.2
10th	Fairburn *et al*[7]	2000	*Archives of General Psychiatry*	458	16.7

[1]The impact index *per* article is presented based on Reference Citation Analysis [Source: Baishideng Publishing Group Inc. (Pleasanton, CA 94566, United States)].

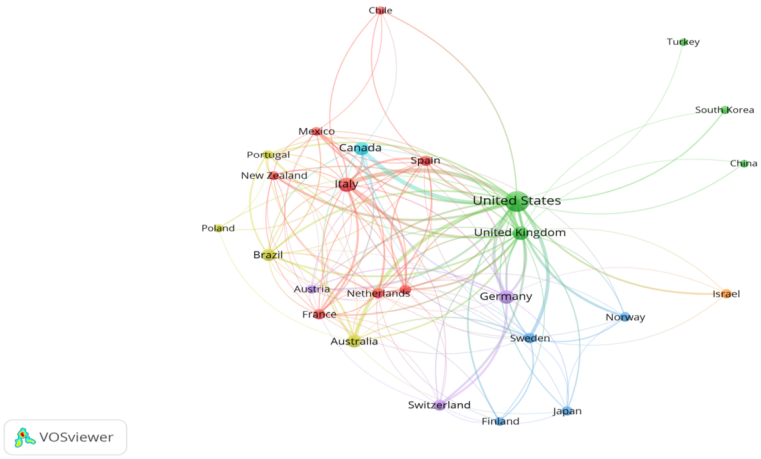
Furthermore, it is clear that the output in this field has risen steadily as the risk of BED has been better understood. In addition, there is a shift from surgical to preventative techniques for BED management, including lifestyle interventions such as physical therapy or pharmacological treatment[36-40].

The United States, Italy, the United Kingdom, Germany, and Canada had the most binge eating research published in the literature, accounting for 83.8% of all publications in the study. Although no bibliometric study on BED has been published on BED, some studies have been conducted on nutrition research productivity in various fields[41,42], as measured by publications, and found that the United States, the United Kingdom, and Europe countries were the top producers of binge eating publications during this time. Eating disorders are more common in western societies than in non-western societies, although the incidence appears to be increasing[43,44]. Furthermore, the burden of eating disorders is likely to increase in low- and middle-income countries as they grow and experience cultural change [44]. As a result, the rising prevalence of eating disorders among Western cultures or in low- and middle-income countries and the scarcity of research documents published in these areas point to an urgent need for more research on this subject.



DOI: 10.5498/wjp.v12.i7.982

Figure 1 Annual growth of publications in the field of binge-eating. The publication trend related to binge-eating disorder from 1976 to 2020. Clearly, the number of relevant publications has increased sharply since 2011, while 2020 netted the largest amount of binge eating research (195 published documents). There is zero publication in the year 1978.



DOI: 10.5498/wjp.v12.i7.982

Figure 2 Network visualization map of country collaboration in the field of binge-eating with a minimum contribution of 10 documents *per* the country was set as a threshold (*n* = 26).

Based on the analysis of terms and specific domains of research interest, three significant research themes were identified in binge-eating research. This study identified the terms most often used terms in the scientific literature and showed how they appeared in various publications. One of the main hot topics in the current study was the 'type of treatment and management provided for BED'. The most well-known psychotherapy treatment for BED is cognitive-behavioral therapy. In addition, interpersonal psychotherapy has been investigated as an alternative treatment for BED by targeting these individuals' social and interpersonal impairments[45]. BED's remission rates for the CBT and interpersonal psychotherapy have been higher than remission rates for anorexia nervosa and bulimia nervosa[46].

Other pharmacological treatment methods that are effective for BED include antidepressants, antiepileptic drugs, anti-obesity medications, and central nervous system stimulants. These treatments show modest short-term efficacy in reducing binge eating, and fewer eating compulsions without losing weight than patients experienced when using antidepressants, while topiramate showed a greater weight reduction[47]. However, the use of pharmacological treatment is limited due to potential adverse effects and harms, which are reported in 80% of studies and lead to higher rates of discontinuation[48].

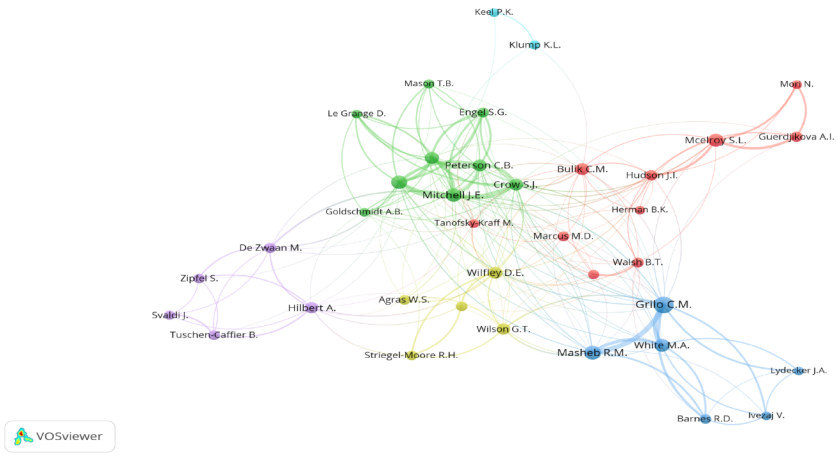


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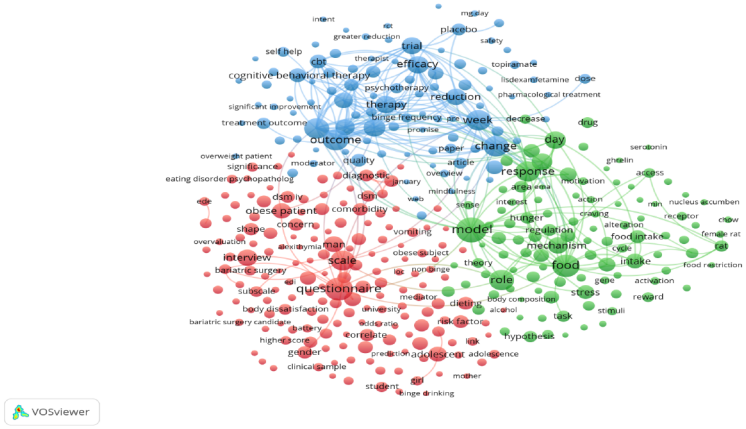
Figure 3 Network visualization map of authors in the field of binge-eating with a minimum contribution of 20 documents.



DOI: 10.5498/wjp.v12.i7.982

Figure 4 Network visualization map of terms related to the field of binge eating with minimum occurrence of 30 in the titles/abstracts of the retrieved publications.

In 2015, the United States Food and Drug Administration approved lisdexamfetamine dimesylate (LDX) as the first and only drug for BED. LDX was previously approved as a central nervous system stimulant for treating Attention Deficit Hyperactivity Disorder and is now considered the only currently approved drug for BED[49].

Another subject that has received much attention has focused on processes and pathways to binge eating, including concepts related to dietary restriction theory, cognitive models of binge eating, the cognitive-behavioral model of BED, and emotional regulation theory. Most research on cognitive models of binge eating has concentrated on limiting or dieting behavior, negative affect, emotional control and behavioral dysregulation, preoccupations with body, shape, and weight, and low self-esteem[50,51]. Dietary restriction and body image or weight worries may cause the development and/or maintenance of binge eating behavior in certain people. However, for others, highly processed meals may induce neuroplastic changes in the brain, resulting in an addictive process[52]. Some theoretical advances have focused on investigating the persistence of beliefs or schemas that can contribute to the high rate of post-treatment relapse found in the binge eating group[53,54].

Another hot topic is the diagnosis, signs and symptoms, comorbidities, prevalence, and associated factors with BED. Furthermore, BED has a major burden on psychiatric and physical health[55]. Almost 80% of individuals with BED have suffered from mood disorders, such as major depressive disorder, anxiety, suicidal tendency, and bipolar disorder, as well as physical comorbidities, such as hypertension, obesity, chronic types of pain, and chronic diabetes[1,55,56].

Several studies estimate the prevalence, incidence, and sex differences in BED in adolescents and children and found that the prevalence rates are the same as those of adults and count between 1 and 3%, with almost double the number of girls compared to boys, which are similar to the results in adults [57]. Late adolescence to early adulthood was the age of onset of BED and is also associated with physical and psychological impairments[58]. BED was found to be strongly associated with diabetes

and metabolic syndrome. Furthermore, those with obesity and BED have a higher risk of respiratory and gastrointestinal diseases than those without obesity and BED[59]. This makes people with BED suffer from a lower quality of life-related to health[60,61].

Citation analysis is one of the most important ways to evaluate the influence or importance of a specific publication for some time or determine its level of recognition. The most cited articles can determine which study topic has received the most attention from the scientific community[62,63]. The findings of our analysis show that the most widely cited articles on BED focused on a number of subtopics in cooccurring terms that are close to the study hotspots, including "type of treatment and management provided to BED"; "processes and pathways to binge eating"; and "diagnosis, signs and symptoms, comorbidities and prevalence and associated factors with BED".

The most cited article was by Heatherton and Baumeister[64] and published in the *Psychological Bulletin*. This study put a hypothesis for BED to break away from self-awareness. Specifically, binge eaters tend to avoid the surrounding stimuli and significant ideas that will result in disinhibition of eating. The second most cited article was by Gormally *et al*[65] and published in *Addictive Behaviors*. Using two tools to assess binge eating among obese individuals, the study found a varied degree of binge disorder. It should be noted that those with severe binge eating were more likely to plan rigorous eating habits that are difficult to follow and maintain. The third most cited article was Spitzer *et al*[66], published in the *International Journal of Eating Disorders*. This study discussed the deep associations of certain characteristics with binge eating problems, including, but not limited to, the frailty of social and working life, inappropriate feelings toward body weight, and having psychological problems or substance abuse. The fourth most cited article was by Spitzer *et al*[67] and was published in *International Journal of Eating Disorders*. The researchers in this article have tested the criteria for the diagnosis of binge disorder. They found that this problem is prevalent in women and people who follow hospital weight control programs, and it was correlated with the degree of obesity of individuals. The fifth most cited article was by Kessler *et al*[1] and published in *Biological Psychiatry*. A public survey reported a prevalence of binge eating problems, which is slightly closer to bulimia nervosa. The binger begins in late adolescence, and its risk increases in females. However, the study identified the clinical value of asking patients about eating abnormalities.

The sixth most cited article was undertaken in 2002 by Stice *et al*[68]. This publication concluded a list of biological and psychological variables that predict BED. For example, the need to be thin, modeling of eating disorder, exaggerated appearance, body shape umbrage, depression, body weight, and low self-confidence were potential risk factors for binge eating. The seventh most cited article was published in 2000 by Stice *et al*[69]. This study established a self-diagnostic tool for binge eating problems, tested for reliability and validity, and showed acceptable levels for both tests. Consequently, the researchers recommend that this instrument be used clinically and for research purposes.

The eighth article most cited was the study by Telch *et al*'s using dialectical behavioral treatment in women with BED[70]. It found a great improvement in binge eating measures, and most of them curbed this diet problem compared to the control group. However, factors related to changes in mood and weight were not found to be significant. The ninth most cited article was carried out in 1981 by Halmi *et al*[71]. This research was conducted to characterize BED among college students. It was found that 13% of students had main symptoms of eating disorder, with the main skewed toward the female gender. Additionally, people with a history of increased weight were associated with symptoms of eating disorders. Lastly, the tenth most cited article was published in 2000 by Fairburn *et al*[72]. This article explained the natural sequence of BED in young women (aged 16 to 35 years) for five years. In general, a great improvement was initially observed, and then the improvement gradually became gradual. The percentage with any form of the clinical eating problem was decreased to 18% at the end of the study. However, the weight increased in thirty-nine percent of this population.

Strengths and limitations

This is the first study to use bibliometrics to report and evaluate global trends in binge eating research. In addition, this study will assist researchers seeking to find hotspots and issues in need of investigation in this subject and those seeking to identify influential articles and the most prolific authors in this research niche. The present study has some limitations. Only one database (Scopus) was used to obtain bibliometric data; some binge-eating-related publications might have been missed. On the other hand, Scopus remains the finest accessible database for analyzing research activity and locating research hotspots on a certain topic. Another limitation is the possibility of errors in ranking institutions or authors due to differing spelling in various publications. Furthermore, publications that do not include the binge-eating term in the title might not be considered for our analysis. Despite these limitations, the findings of this investigation were sufficient to provide an accurate picture of the situation in binge-eating-related publications.

It's interesting and perhaps worthy of comment that there are few articles on the neurobiology or cognitive neuroscience of BED. This is truly a 'hot topic' in the field of eating disorders in general, and it is possible that less has been published on BED than on other eating disorders or that these types of articles are more often based on transdiagnostic dimensional features or underlying constructs (*i.e.*, RDoC) that do not map neatly onto diagnoses such as BED and would be detected by a methodology as that employed herein.

CONCLUSION

This timely bibliometric review examines the findings of the BED, which could help advance the discipline and establish the basis for future research. Over the last decade, the amount of global research output on BED has expanded substantially, accounting for most publications in relevant journals. The United States and the United Kingdom have made significant contributions to the number of publications. Furthermore, research institutions from the United States have contributed to the centrality of publications. There are indeed relatively few publications on BED from low-and middle-income nations, so there is much to be learned from the experience of all countries.

Studies on this topic are critical in all countries to discover risk factors and effective intervention measures. Currently, the main hot topics related to BED are "type of treatment and management provided to BED"; "processes and pathways to binge eating"; and "diagnosis, signs and symptoms, comorbidities and prevalence and associated factors with BED". Although our findings are preliminary, they imply the future prospects to identify some of the currently most important categories of studies, such as randomized clinical trials.

ARTICLE HIGHLIGHTS

Research background

Binge-eating disorder (BED) is associated with various psychological and non-psychological issues that impair daily life to varying degrees, with a few severe impairments. Diabetes, obesity, chronic pain, and hypertension are some of its comorbid conditions.

Research motivation

A growing body of evidence shows that the BED appears to impact human health significantly. We discovered some bibliometric publications on specific nutritional topics, but none on BED; thus, this article is novel in this field.

Research objectives

This study aims to analyze research publications on the BED and identify global hotspots on this topic.

Research methods

A comprehensive research technique was undertaken using the SciVerse Scopus database to meet the study's goal.

Research results

This is the first bibliometric analysis of trends in BED publications. The interest in global research in BED has increased significantly in recent years. It is clear that the output in this field has risen steadily as the risk of BED has been better understood.

Research conclusions

In conclusion, based on our timely examination and analysis of hotspots and research trends, we found that the main hot topics related to BED are "type of treatment and management provided to BED"; "processes and pathways to binge eating"; and "diagnosis, signs and symptoms, comorbidities and prevalence and associated factors with BED".

Research perspectives

This study explores the global performance and advancement of BED research and maps the research patterns and trends using a visualization tool to fill this knowledge gap. In addition, a bibliometric analysis of prior articles could lay the groundwork for a full understanding of existing research on BED and indicate some potential future research subjects.

FOOTNOTES

Author contributions: Zyoud SH conceptualized and designed the research project, took care of data management and analysis, generated figures, made significant contributions to the manuscript's existing literature search and interpretation of the manuscript, and drafted the manuscript; Shakhshir M, Abushanab AS, Al-Jabi SW, Jairoun AA, Shahwan M and Koni A were involved in the interpretation of the data, contributed to the manuscript writing, and made revisions to the initial draft; all authors provided a critical review and approved the final manuscript before submission.

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LETTER TO THE EDITOR

COVID-19 survivors: Multi-disciplinary efforts in psychiatry and medical humanities for long-term realignment

Henriette Löffler-Stastka, Monika Pietrzak-Franger

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Abstract

The coronavirus disease 2019 pandemic represents an enduring transformation in health care and education with the advancement of smart universities, telehealth, adaptive research protocols, personalized medicine, and self-controlled or artificial intelligence-controlled learning. These changes, of course, also cover mental health and long-term realignment of coronavirus disease 2019 survivors. Fatigue or anxiety, as the most prominent psychiatric "long coronavirus disease 2019" symptoms, need a theory-based and empirically-sound procedure that would help us grasp the complexity of the condition in research and treatment. Considering the systemic character of the condition, such strategies have to take the whole individual and their sociocultural context into consideration. Still, at the moment, attempts to build an integrative framework for providing meaning and understanding for the patients of how to cope with anxiety when they are confronted with empirically reduced parameters (*e.g.*, severe acute respiratory syndrome coronavirus type 2) or biomarkers (*e.g.*, the FK506 binding protein 5) are rare. In this context, multidisciplinary efforts are necessary. We therefore join in a plea for an establishment of 'translational medical humanities' that would allow a more straightforward intervention of humanities (*e.g.*, the importance of the therapist variable, continuity, the social environment, *etc*) into the disciplinary, medial, political, and popular cultural debates around health, health-care provision, research (*e.g.*, computer scientists for simulation studies), and wellbeing.

Key Words: Long COVID; Resilience; Multi-disciplinarity; Medical Humanities; Psychiatric sequelae

Core Tip: Recovery from coronavirus disease 2019 demands that multidisciplinary efforts be brought together to inquire, assess, and learn from various strategies of resilience we have witnessed in this context. Extant studies into individual, communal, and social-environmental aspects of (multisystemic) resilience can thus be expanded and validated; in effect, novel interventions may ensue.

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TO THE EDITOR

We read with interest the narrative review by Putri C *et al*[1], who presented various biological factors contributing to psychiatric sequelae of coronavirus disease 2019 (COVID-19). We agree with the authors' insights concerning both the screening and the prevention of the COVID-19 psychiatric sequelae. They suggested such measures as music therapy, strengthening of social support, and self-management to foster resilience in long-COVID-19 patients. As a complement to this perspective, we would propose (following Wolf and Erdos[2]), a multidisciplinary patient-oriented approach that is directed towards a better (e-Health) infrastructure (including a precise, reliable data-protection-conform privacy framework[3]), investment in (digital) media literacy, and an emphasis on transcultural competence in doctor-patient communication.

The COVID-19 pandemic represents an enduring transformation in health care and education with the advancement of smart universities, telehealth, adaptive research protocols, personalized medicine, self-controlled or artificial intelligence-controlled learning, and flexible approaches to achieve solutions. But attempts to build an integrative framework for providing meaning and understanding for the patient when he or she is confronted with empirically reduced parameters or biomarkers are rare and are lacking in Putri *et al*[1]. A parallel development has spotlighted the role of multidisciplinary efforts, such as Medical/Health Humanities, in the understanding, learning, and overcoming the (psychological) effects of the pandemic. Kirsten Ostherr[4] has called for the establishment of 'translational medical humanities' that would allow a more straightforward intervention of humanities scholars into the disciplinary, medial, political, and popular-cultural debates around health, health-care provision, and wellbeing.

Understanding the factors contributing to resilience is key when designing interventions to support the improvement or development of resilience. Meta-analyses have shown that in longitudinal studies investigating protective factors in children exposed to traumata, the most robust factors were self-regulation, self-efficacy, and socioenvironmental support (supportive communities, family, peers, school). Investigations on resilience vis-à-vis adversary events show that mutual support and sharing capacity are based on social capital as a buffer to deal with poverty and vulnerability. However, when shocks are systemic or last longer, these traditional coping mechanisms fail, especially in households with low incomes or human resources. On an individual level, features associated with personality functioning have been shown to be very relevant. In medical doctors the personality traits associated with better resilience and well-being are maturity, taking responsibility, optimism, perseveration, and cooperation[5,6]. Hartmann's theory of different boundary types gives a way of understanding individual differences in terms of thick or thin boundaries (boundaries between inner and outer experience, past and present, and so on). Boundaries are necessary for well-being; what is even more important is an efficient management of these boundaries (self-regulation, self-awareness) dependent on the context and situation (responsibility of setting, maintaining professional boundaries). Acceptance of boundaries relies on a contented, sound development and is linked to psychic maturity with the establishment of a supporting balanced and trusting super-ego function. Epistemic trust[7] is established in early childhood together with secure attachment; shared knowledge is valued as "trustable." However, in cases of early adversity, credulity and mistrust may develop, with associations of insecure attachment, deficits in mentalizing, affect-, and self-regulation, unstable relationships, and poor resilience.

In order to establish resilience, in the psychiatric-psychotherapeutic relationship, empathy and adequate management of this relationship including authentic acknowledgement of biographically important relationship experiences are important for the outcome on an individual and group level. Further, clinicians' therapeutic attitudes affect regulation capacities and socialization correlated with relationship factors and therefore with the effectiveness of treatment[8]. Resilience depends on affect regulation abilities; resilient individuals recover from negative experiences by buffering against stress and distressing triggers with positive emotions (positive reappraisal, giving positive meaning, problem-focused coping, and so on). The pandemic has led to a variety of foundational transformations in the

very definition of mental health and mental disorder with a significant shift towards more liberal understandings of values implicated under COVID 19 (*e.g.*, values comprising coherence and quality of life). Social and environmental conditions[5] have to be taken into consideration in order to inquire into an individual's resilience, recovery, and containment possibilities. Putting the subject(ive)[9] more into the forth in the form of public-patient-involvement research designs and in the interdependence with the mentioned surrounding is of particular importance in understanding (psycho)pathoplastic dynamics. An integration of intrapersonal, interpersonal, and person-environmental dimensions of resilience on a personal, communal, and social-environmental level will lead to a more systemic approach doing justice to the dynamics of interactions with the outer world[10].

Consequently, as a way of establishing epistemic trust, it is necessary to focus on training programs for individuals and their microsystems. Interventions will have to be directed to the exo- and macrosystem and to formal and informal structures containing or indirectly influencing the target group (*e.g.*, people with mental health problems). Psychiatry has a long tradition in this field[11]. Instruments with known social impact like education and culture (music, art, poetry) should be applied based on the existing knowledge concerning the processes and contexts of resilience and individual and communal adaptability.

Against this backdrop, it is of importance to include Medical/Health Humanities in the discussion on resilience. With their "interdisciplinary, inclusive, applied, democratizing, and activist approach … in informing and transforming health care, health, and well-being"[12], Medical/Health Humanities have gone far beyond the concern with training medical practitioners by using arts and humanities. Instead, their proponents have asserted the complicated and not always linear or one-directional (expert – public) models of such application and have stressed the importance of bringing "the public to therapeutic uses of the arts and humanities"[12]. With these goals in mind, Medical/Health Humanities strive to emphasize "co-design, co-creativity, and co-learning"[12]. In view of these developments and vis-à-vis recent trends in Humanities, current tendencies in Medical/Health Humanities encompass a series of thematic, theoretical, and methodological innovations, all of which have received even a greater impetus from the pandemic. In this context, extant research into pandemic narratives, blame allocation strategies, discriminatory discourse, and resultant exacerbation of inequalities is central to future interventions.

Combining such multi- and transdisciplinary efforts is also helpful in a critical rethinking both of the positive (and negative) sides of the resilience in its individual, communal, and social-environmental levels as well as in tracing their dependencies with suggesting practical interventions.

FOOTNOTES

Author contributions: Löffler-Stastka H conceived the idea; Löffler-Stastka H and Pietrzak-Franger M interactively discussed the content, performed research on this topic previously, and wrote and revised the letter.

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LETTER TO THE EDITOR

Underlying reasons for the decline in physical activity during COVID-19

Yang-Fen Zhang, Li-Ke Qiu, Zhi-Peng Li, Lian-Ping He, Ling-Ling Zhou

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Abstract

The article not only successfully evaluated regular physical activities can improve mental well-being during self-isolation and social distancing policies related to the coronavirus disease 2019 (COVID-19), but also concluded that the COVID-19 pandemic may lead to augmented levels of angiotensin-converting enzyme-2. By reading the article of Walid Kamal Abdelbasset, we have some questions and put forward some suggestions on the content of the article.

Key Words: Angiotensin-converting enzyme-2; COVID-19; Mental health; Physical activity

Core Tip: During the coronavirus disease 2019, physical activity declined. There are many reasons behind this phenomenon. And the surveys in the article don't attach survey area. Additionally, the mutually affected relationship between physical activity and mental health is not clearly elaborated. The above are the areas that need to be improved in the article, and we also put forward some suggestions for improvement.

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TO THE EDITOR

We were happy to read the ingenious article by Abdelbasset *et al*[1], in which they illustrated the effect of physical activity on mental well-being during the coronavirus

disease 2019 (COVID-19). The author not only elaborate the impact of physical activity on mental health through three sections: Mental health and community, neurological manifestations related to COVID-19, physical activity and mental health, but also conclude that the COVID-19 pandemic is correlated with angiotensin-converting enzyme-2, leading to related diseases. The article has had a significant impact on the current world that is still affected by the epidemic, but there are still some issues that need further consideration.

There are many reasons for the decline in physical activity from COVID-19. On the one hand, the COVID-19 itself can affect the body's metabolic process, directly causing musculoskeletal symptoms, such as muscle pain and numbness, and joint swelling and soreness[2]. On the other hand, the disease can affect the patient's respiratory system, digestive system and circulatory system and indirectly cause symptoms of physical decline. In the acute stage, patients often have respiratory symptoms such as dry cough and dyspnea, resulting in insufficient oxygen intake. At this time, patients often have fever symptoms. Fever will accelerate the body's metabolic process, thereby increasing oxygen consumption and further reducing blood oxygen content, and even acidosis may occur[3]. The patient is in such a state of oxygen imbalance that it is very easy for the patient to feel decreased physical strength or muscle weakness. Gastrointestinal symptoms can also occur in the acute phase, causing the patient to lose appetite. Studies have also shown that the COVID-19 may cause anosmia in patients[4]. In short, the effects of COVID-19 on patients with eating disorders will weaken the body's intake of food, thereby weakening the body's energy conversion. Without sufficient energy intake, patients often feel muscle soreness and weakness, because at this time the body has more the glycolysis pathway is used to generate adenosine-triphosphate, and the muscles use more creatine phosphate to maintain muscle activity[5]. The lactate and creatine phosphate metabolites produced by the glycolysis pathway take a longer time to complete metabolic consumption, so it accumulates in the muscles for a long time and causes muscle soreness. Therefore, we suggest that the authors supplement the reasons for the above-mentioned physical decline in order to make the theory of this review more complete and richer. What's more, not everyone's physical activity has decreased during the COVID-19 period, and some people are still able to maintain regular exercise as usual, which suggests that we need to think more deeply. During the period of the COVID-19, measures such as increasing people's ownership of sports equipment, developing interesting sports software or games, and converting ordinary sports into online sports competitions will greatly promote people's enthusiasm for physical exercise. This is something we should strive to do in the future.

In addition, the author detailed many surveys on the relationship between physical activity and mental health. However, the COVID-19 appeared in China and spread around the world, affecting populations worldwide and causing thousands of deaths[6,7]. If the survey area can be attached to the table, and if the survey areas are diverse and extensive, then it can highly increase the reliability of the results, as well as widen the applicability of the conclusions. Thus, we suggest that the author should include the survey area in the table, so that the results of each survey area can be clearly seen, and the conclusion that physical activity affects mental health can be more convincing and reliable.

One of the conclusions of the article is that exercise training for a long time does not indicate good mental well-being, but it may be a predictor of developing mood disorders[8]. But nothing is absolute, and so is the conclusion, which applies to people who are physically active for a long time, especially during lockdown periods when their need for exercise can not be met. The definition of prolonged exercise varies from person to person. Therefore, we suggest that the author should add a conditional supplement to this conclusion to increase the rigor of the article. It would be better if the author could give a general definition of exercise training for a long time in the article.

The terms exercise and physical activity are often used interchangeably, but by definition they are two different things. Physical activity is a process in which people use their skeletal muscles to consume energy to achieve human movement. Exercise is part of physical activity, and if someone runs once on a whim and then doesn't continue that activity, it's not exercise. Exercise is a subcategory of physical activity that is planned, structured, repetitive, and purposefully focused on improvement or maintenance of one or more components of physical fitness[9]. People who run in the park every morning, young people who play basketball two or three times a week, old women who dance in the square every evening, they have well integrated exercise into their lives. But not everyone can exercise consistently. Many people just do physical activity and call it exercise. This is the phenomenon of combining exercise and physical activity. Doing housework at home, walking, running and so on are just physical activities that are more common than exercise. In the future, provided that different levels of exercise are proposed to improve people's mental health, the distinction between physical activity and exercise should not be ignored.

Nevertheless, as the author wrote, anxiety and depression may lead to negative effects on various quality of life domains, such as being physically inactive[10]. This shows that not only does physical activity affect mental health, but mental health can also affect physical activity. In other words, physical activity and mental health are closely related and mutually affected.

FOOTNOTES

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