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Psychosomatic medicine in general hospitals: Cross-disorder and interdisciplinary collaboration

Edited by
Wenhao Jiang, Yonggui Yuan, Jessica A. Turner and Yuqun Zhang

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Psychosomatic medicine in general hospitals: Cross-disorder and interdisciplinary collaboration

Topic editors

Wenhao Jiang — Southeast University, China
Yonggui Yuan — Southeast University, China
Jessica A. Turner — The Ohio State University, United States
Yuqun Zhang — Nanjing University of Chinese Medicine, China

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Stephan Zipfel,
University of Tübingen, Germany

*CORRESPONDENCE
Yonggui Yuan
yygylh2000@sina.com

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Editorial: Psychosomatic medicine in general hospitals: Cross-Disorder and interdisciplinary collaboration

Wenhao Jiang[1], Yuqun Zhang[2], Jessica A. Turner[3] and Yonggui Yuan[1]*

[1]Department of Psychosomatics and Psychiatry, School of Medicine, ZhongDa Hospital, Southeast University, Nanjing, China, [2]School of Nursing, Nanjing University of Chinese Medicine, Nanjing, China, [3]Department of Psychiatry and Behavioral Health, Wexner Medical Center, The Ohio State University, Columbus, OH, United States

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Editorial on the Research Topic
Psychosomatic medicine in general hospitals: Cross-Disorder and interdisciplinary collaboration

Psychosomatic medicine focus on the etiology, diagnosis, treatment, and prevention of psychosomatic disorders (1). Although the definitions of psychosomatic medicine may vary, the burden of psychosomatic disorders has been well-recognized. During the past decades, increasing efforts have been made to improve our understanding of psychosomatic disorders and related risks. The management of these disorders is critical in general hospitals. Identifying psychosomatic disorders, accurate early diagnosis, treatment, and conducting clinical research have received increasing attention from physicians of all departments (2).

We initiated this special issue to encourage interdisciplinary studies in this field. This collection presented 23 manuscripts, including original research, reviews, and case reports worldwide. In addition, the Chinese Society of Psychosomatic Medicine (CSPM) has broadcasted this Research Topic to the local community. We covered papers introducing cross-cultural psychosomatic models and concepts, case reports, the development of assessment tools, related psychosomatic issues in psychiatric disorders, and psychosomatic problems in healthcare workers.

Cross cultural psychosomatic models and concepts

Psychosomatic medicine models, concepts, and current clinical practice vary in regions. A little more than half a century ago, European countries started to play

significant roles in this field. Sadlonova et al. introduced the development of multimodal psychosomatic treatment in Germany. They investigated treatment outcomes and long-term predictors among inpatients with such treatment programs. The authors discovered medium to considerable improvements in psychological and physical symptoms and the quality of life. They also found better quality of life improvement, and antidepressants during hospitalization might lead to a better prognosis. This finding emphasized the significance and effectiveness of multimodal psychosomatic treatment for inpatients.

Zerbinati et al. discuss a multicenter study focusing Consultation-Liaison Psychiatry (CLP) practice in Italian general hospitals. The authors compared CLP visits data of 3,943 patients from 10 Italian hospitals during 2018 with 4,183 participants and their data in 1998. Over 20 years, an increased CLP proportion was detected in surgical and onco-hematologic departments. Depressive disorders remained the most frequent diagnosis. The author stated that the significantly increased CLP workload required better organization and autonomy in Italian CLP services.

Bai et al. researched the history of depression as a concept in China. They analyzed materials, including newspaper stories, medication advertisements, and medical texts. They believed that the depression evolved from a hazy and ambiguous concept into a specific disease in the late Qing Dynasty and early Republican. This progress might parallel western medicine entering the Chinese pharmaceutical market in the 1920s. In addition, the authors explored the stereotypes related to depression during the early days. Bai's et al. paper is an exciting exploration of the history of psychosomatic medicine in China.

Psychosomatic symptom assessments in general hospitals

The assessment tools of psychosomatic symptoms, risk factor analysis, and interaction between them are essential in collecting clinical information for further investigations. Zhang J. et al. investigated sex, age, depression, insomnia, psychological stress, resilience, and perceived social support among patients with medically unexplained symptoms (MUS) in a general hospital's psychological clinic. They suggested middle-aged female patients were at high risk of presenting MUS and thus needed a comprehensive evaluation and timely intervention.

Cao et al. explored the accuracy of several assessment tools in detecting DSM-5 somatic symptom disorder in a general hospital. They found that Somatic Symptom Disorder—B Criteria Scale 12 or Whiteley-8 alone might show a better ability for detecting somatic symptom disorder. Li et al. validated the Chinese version of the Somatic Symptom Scale-8 (SSS-8) in outpatients. The authors found that this might be a reliable tool for assessing somatic symptoms in research and clinics.

A network approach was used by Wan et al. to explore the association between depressive symptoms in type 2 diabetes mellitus. The authors collected information from the electronic health record of 52,139 patients through deep learning. Their study's learning model and network alterations could effectively identify depressive symptoms.

Guo et al. explored the relationship between personality traits, alexithymia, and microbiome in patients with functional gastroenteropathy and generalized anxiety disorder. The authors found that the comorbidity related to the abundance of Fusobacterium. Functional gastroenteropathy alone might be related to the abundance of Haemophilus. Specific traits such as affective recognition and expression disorder, neuroticism, and negative cognition might be related to the abundance of Fusobacterium and Megamonas.

Psychosomatic issues in psychiatric disorders

This collection also included diverse research regarding psychosomatic issues in psychiatric disorders. In anxiety disorders, Hong et al. examined the interaction between rs2071345 and alcohol dependence behavior on anxiety symptoms of male problem drinkers. The authors suggested that rs2071345 was playing a role in this specific group. On the other hand, Chu et al. examined the BDNF Val66Met polymorphism, Plasma BDNF level, and anxiety traits in panic disorder. They found that Met/Met genotype might be more likely to exhibit risky anxiety traits. Yang et al. studied the association between subclinical hypothyroidism and anxiety in depressive patients. This was the first episodic and drug-naïve group, and the authors found that serum thyroid stimulating hormone level may be a promising biomarker of anxiety symptoms among them. The research by Shen et al. also focused on biomarkers for anxiety. Serum S100B and cytokines (IL-1β, IL-2, IL-4, and IL-10) were examined in untreated generalized anxiety disorder cases and healthy controls. They found that the combination of S100B and cytokines had a better diagnosis value with high accuracy.

Major depressive disorder (MDD) and related issues also received much attention. Zhou H. et al. studied the negative emotional bias in depressive patients. The anterior cingulate cortex and right insula were found to mediate the interoception dysfunction and negative emotional bias of MDD. The study from Zhou Y. et al. also focused on the brain function of MDD. However, they studied non-suicidal self-injury behaviors, the amplitude of low-frequency fluctuation, and regional homogeneity. The authors suggested that the default mode network and visual network might be related to such behavior. Wu et al. reviewed clinical studies of MDD using the Delphi method, and they suggested this method can be helpful both in clinical and research settings.

Bipolar disorder and schizophrenia were also covered. Wang et al. studied the effectiveness of hypomania checklist-32 in screening bipolar disorder while considering personality traits' influence. They believed that higher typical extraversion and neuroticism might lead to higher hypomania checklist-32 score. Clinicians should pay attention to these false positives while using this tool. Cheng et al. focused on the relationship between suicidal risk and childhood maltreatment in schizophrenia patients. Among all the risks, they found that schizophrenia with more positive symptoms relapses had more childhood trauma, stress, and suicidal risk.

Chen et al. investigated the impulsive personality traits and negative mood states in bulimia. The study included 146 female bulimia patients and identified three linked clusters ("ED-specific symptoms," "impulsivity," "anxiety," and "depression"). The authors showed that the cognition of "shape dissatisfaction" played a key role, and impulsivity and emotional symptoms contributed to the development of this eating disorder.

Care for healthcare workers

Two studies focused on psychosomatic health in healthcare workers, especially nurses. Huang et al. investigated a specific group of the nurse in the neonatal department. They explored the lifestyle and social factors contributing to mood disorders and functional dyspepsia. Nearly half of the participants exhibited mood symptoms such as depression and anxiety. Most neonatal nurses suffering from mood disorders also presented functional dyspepsia. Poor sleep and smoking might be risk factors among them. Yin et al. investigated nurses from psychiatric departments. They studied the relationship between coping style, sleep, and burnout. The authors suggested that coping style mediated between sleep quality and burnout. They called for developing coping skills to balance work and life in this group.

Case reports

Finally, several case reports were presented in the collection, and these cases described how physicians recognized and treated patients exhibiting psychosomatic symptoms. Lipkes et al. described a woman diagnosed with Hashimoto's thyroiditis. She was brought to the psychiatric emergency department with auditory hallucinations and persecutory delusions for the first time. The patient was treated effectively with IV thyroid replacement and antipsychotics. The authors emphasized the importance of a thorough medical workup for new-onset psychosis and called for future consensus in treatment choice.

Zhang Y. et al. described a woman who suffered from an unhealed sore and ulcer of a surgical wound after 10 years diagnosed with breast cancer. Combined with her mood symptoms, the patient's condition was identified as Qi (or vitality) deficiency in the view of Chinese traditional medicine. Herb medicine and a regimen based on Internal Vitality were given to her. The authors observed healed sore and ulcers over 6 months.

Dong et al. reported that a woman suffered from significant limb edema for 2 months. She was previously diagnosed with pituitary adenoma and received treatments. The authors believed the edema was caused by tumor recurrence, but all examinations provided negative results. Her existing severe mood problems then came into sight, and she was diagnosed with major depressive disorder after CLP. The patient's limb edema dramatically subsided after Deanxit and Tandospirone treatment.

To sum up, we expect that this special issue will expand knowledge in psychosomatic medicine and collaborative research. These studies will help reveal cross-cultural issues and underrepresented populations worldwide. In addition, the CSPM will continuously push forward domestic psychosomatic research and international collaborations. Finally, we hope the research achievement in biopsychosocial mechanisms will contribute to clinical practice.

Author contributions

WJ has prepared the first draft of this editorial. YZ, JT, and YY have revised the first draft and contributed to the final version of the manuscript. All authors approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CASE REPORT
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First Episode Psychosis and Pituitary Hyperplasia in a Patient With Untreated Hashimoto's Thyroiditis: A Case Report

Celeste Lipkes[1,2†], Shanzay Haider[3†], Ali Rashid[1], Gustavo A. Angarita[1,4] and Sarah Riley[1]

[1] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, United States, [2] Department of Mental Health, Charles George Veterans Affairs Medical Center, Asheville, NC, United States, [3] Department of Endocrinology, Yale University School of Medicine, New Haven, CT, United States, [4] Clinical Neuroscience Research Unit, Connecticut Mental Health Center, New Haven CT, United States

This case report describes a woman with no psychiatric history and previously diagnosed Hashimoto's thyroiditis who presented to the psychiatric emergency department with a first episode of psychosis. The initial workup for organic causes of psychosis revealed an astronomically high thyroid stimulating hormone (TSH) (> 1,000 μIU/mL) out of proportion to the patient's minimal physical symptoms of hypothyroidism. Additionally the patient's head imaging showed an enlarged pituitary, a rare, but reversible, presentation of chronically untreated primary hypothyroidism. The patient was transferred to a medical unit to receive IV thyroid hormone replacement as well as an adjunctive antipsychotic to assist with remission of her distressing auditory hallucinations and persecutory delusions. This case highlights the importance of a thorough medical workup for causes of new onset psychosis and the need for further consensus in the literature regarding choice of antipsychotic and duration of treatment for psychosis secondary to hypothyroidism.

Keywords: first episode psychosis, hypothyroidism, Hashimoto's thyroiditis, myxedema madness, pituitary hyperplasia

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Pooja Patnaik Kuppili, Sri Venkateshwaraa Medical College Hospital and Research Centre (SVMCH & RC), India
Silvia Martina Ferrari, University of Pisa, Italy

***Correspondence:**
Celeste Lipkes
celeste.lipkes@va.gov

† These authors have contributed equally to this work and share first authorship

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HIGHLIGHTS

- All patients with new onset psychosis should receive thyroid screening.
- Pituitary hyperplasia is a rare and reversible presentation of severe hypothyroidism.
- Treating patients with psychiatric symptoms secondary to thyroid illness will benefit from a multi-specialty approach, including teams from psychiatry, endocrinology, and in rare cases ophthalmology.
- Many patients with psychotic symptoms secondary to hypothyroid illness will benefit from taking short-term antipsychotics, however, there is no clear consensus on the preferred agent or length of treatment.

INTRODUCTION

Alterations in the levels of thyroid hormones thyroxine (T4) and triiodothyronine (T3) can lead to multi-system effects, including neuropsychiatric disturbances such as psychosis. Though the underlying mechanism is not completely clear, both T4 and T3 are critical to maintaining adequate neuronal conduction and cerebral blood flow (1, 2) and low T4 or T3 have been associated

with reduced glucose uptake in areas of the brain such as the amygdala and hippocampus (2). Psychosis is present in 5–15% of hypothyroid patients and was first described as early as 1888 by the Committee of the Clinical Society of London (3). In 1949, Dr. Richard Asher coined the term "myxedema madness" to describe psychosis secondary to hypothyroidism and described a wide range of mental changes that could accompany it (4). Psychotic symptoms in hypothyroid patients typically follow months to years of physical symptoms (5) and can include visual and auditory hallucinations, paranoia, (6) delusions such as Capgras syndrome (believing that a close family member has been replaced by an identical-looking imposter), (7) and disordered thought process, including perseveration and loose associations. A recent systematic review of case studies identified the median age of presentation of myxedema psychosis as 42 years, with the most common presenting feature being the presence of delusions (91%), the majority (84%) of which were paranoid or persecutory in nature. Approximately half of these patients did not have a hypothyroidism diagnosis at presentation, and 37% of patients presented without physical symptoms. The maximum thyroid stimulating hormone (TSH) level identified was 139 μIU/mL, with a median of 93. Notably, 89% of patients had normal head imaging (8).

CASE DESCRIPTION

Our patient is a 29-year-old female with hypothyroidism and no psychiatric history who was sent to the Emergency Department by Urgent Care for one week of new-onset psychotic symptoms.

Upon initial presentation to the urgent care clinic, the patient endorsed auditory hallucinations ("I'm hearing other people's conversations and they are not saying anything to comfort me!"). Her vital signs and physical examination were normal. She was diagnosed with "acute paranoia" and sent to Yale New Haven Hospital for evaluation, where she was directly triaged to the psychiatric emergency department.

Upon evaluation by a psychiatrist, the patient endorsed a one-week history of hearing people speaking negatively about her and resultant worsening anxiety. She denied command auditory hallucinations, suicidality, and homicidality. She denied any mood symptoms or changes in sleep or appetite. She made several odd statements about being followed that she was unable to explain. She endorsed sporadic THC use, last used over two months ago, and denied all other substance use. She denied any prior personal or familial history of psychosis. She had fair insight into her family's concern and gave consent for the team to contact collateral sources of information. Her boyfriend and her sister reported that for the prior few days the patient had skipped work because she believed people were talking about her. They also noted that the patient seemed suspicious and would ask them repeatedly, "did you hear that?" in an otherwise silent room. On physical exam, her cranial nerves were intact with normal testing of her visual fields. She endorsed mild fatigue and cold intolerance and denied other symptoms of hypothyroidism. On mental status exam, she was pleasant, anxious-appearing, paranoid, and fully oriented.

DIAGNOSTIC ASSESSMENT AND INTERVENTION

Initial workup for our patient included a urine toxicology screen (including negative THC), urine pregnancy test, and COVID swab, which were unremarkable. Prior to the patient's CBC, BMP, TSH, and T4 resulting, a head CT was completed showing "enlargement of the pituitary gland (measuring 1.3 cm craniocaudally) with suprasellar component encroaching upon the optic chiasm." Neurosurgery was consulted and recommended an MRI brain with pituitary protocol as well as endocrine and ophthalmology consults. Meanwhile, the patient became increasingly paranoid, anxious, and tearful, stating she had "revealed too much, and her life was ruined." The initial laboratory results then returned significant for a normal morning cortisol, prolactin of 114 ng/mL, TSH of >1,000 μIU/mL, and a low free thyroxine (FT4) of 0.25 ng/dL. Upon further questioning, the patient confirmed a history of Hashimoto's thyroiditis diagnosed at age 18. Pre-electronic medical records corroborated a history of elevated thyroid peroxidase antibodies, confirming this diagnosis.

On examination by the endocrine team, her extraordinarily elevated TSH was out of proportion to both her reported hypothyroid symptoms and physical exam, which revealed only mild puffiness of the face, pale color, and a delayed relaxation phase in her deep tendon reflexes. The MRI with pituitary protocol returned, showing "a 2.3 cm enhancing intrasellar mass with extension into bilateral cavernous sinuses and suprasellar compartment contacting the optic chiasm, likely to represent a pituitary macroadenoma" (see **Figure 1**). The endocrine team determined the enlargement of the patient's pituitary seen on imaging was physiologic in the setting of primary hypothyroidism and neurosurgical intervention was not required. Chart review and discussion with the patient revealed she was diagnosed with Hashimoto's thyroiditis in 2017 and self-discontinued her levothyroxine a year later without follow-up. The patient stated that prior to arrival to the emergency department she had taken several of her levothyroxine pills to see if it would make her feel better. The endocrinology team felt her profound hypothyroidism was the cause of her new onset psychotic symptoms, and she was medically admitted for IV levothyroxine treatment.

During the patient's eight-day admission, she was followed by endocrinology, ophthalmology, and psychiatry consult services. She received three days of 100mcg IV levothyroxine before transitioning to her home dose of 150mcg levothyroxine daily. The ophthalmology team completed formal testing of the patient's visual fields, which were normal. On evaluation by psychiatry, the patient initially endorsed a decrease in her auditory hallucinations but reported ongoing paranoid thoughts (doctors were listening to her on the phone, her food had

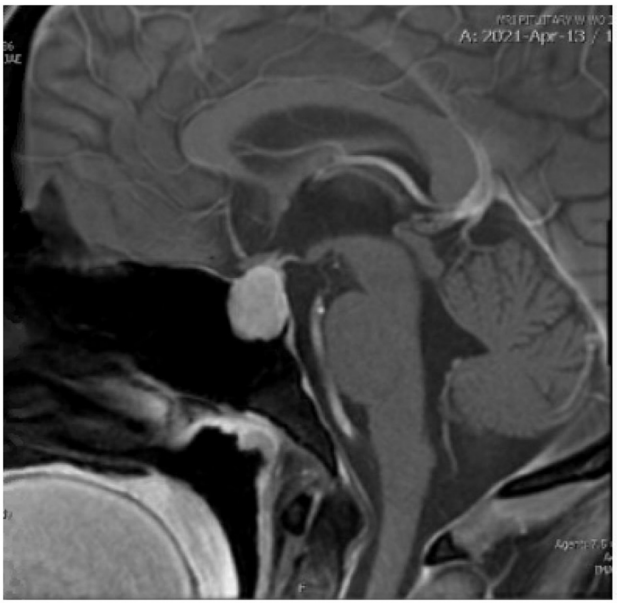

FIGURE 1 | The patient's initial MRI with pituitary protocol.

been laced with laxatives in the emergency department, etc.). Despite these delusions about her care team, the patient was amenable to workup and treatment by all her providers, including our team's recommendation that she trial an antipsychotic. The patient took aripiprazole, titrated to 5 mg, for two days without significant improvement in her paranoia. She was then switched to risperidone 1 mg BID; after two days on this regimen, she denied all paranoid thoughts. When asked if people were speaking ill of her or trying to poison her food, she stated "I have no idea how I could have thought that." She showed good insight into her prior delusions and the need for ongoing hypothyroid treatment. She was referred to outpatient psychiatric care and was scheduled for endocrine labs and follow-up post discharge.

One month after discharge, the patient was found to have normal TSH (4.070 μIU/L). Given an elevated FT4 (1.76 ng/dL), her levothyroxine was reduced to 125 mcg daily.

Two months after discharge, she followed up in the endocrinology clinic and reported compliance to both levothyroxine and risperidone. She endorsed hearing only rare voices, though felt this was because she was "overthinking things" rather than experiencing true auditory hallucinations. She denied paranoia and had returned to work full time.

The patient was lost to formal psychiatric follow-up; however four months after discharge, she was contacted by a member of our team, which she had previously consented to. At this time, she endorsed stopping risperidone about two months after discharge, around when her auditory hallucinations completely resolved. She denied any symptoms of psychosis, was compliant with daily thyroid replacement, and was pleased to relay the results of her follow-up MRI: her pituitary measured 7mm in height and the hyperplasia had fully resolved.

DISCUSSION

Thyroid Hormone and Neuropsychological Conditions

Our patient's presentation was suspicious for an organic psychosis, given her lack of prodromal symptoms, no history of familial psychotic illness, and history of thyroid dysfunction. A thyroid panel should be included in every standard workup for new-onset psychosis; our patient's initial labs revealed an astronomically high TSH—the highest ever seen by Yale endocrinology and significantly higher than levels seen in similar case reports. When a TSH is noted to be elevated, assessment of T4 levels is the next step in assessing the hypothalamic-pituitary-thyroid axis. In our patient, her T4 was 0.25 ng/dL, which was likely detectable only because of the levothyroxine the patient had taken before arrival to the hospital.

The sequelae of hypothyroidism exist on a spectrum ranging from minimal symptoms to florid myxedema coma. It is important to recognize myxedema coma early, as mortality rates can be as high as 50% (9). The magnitude in altered TSH and T4 levels are poorly correlated with severity of symptoms. Notably, the diagnosis of myxedema encephalopathy, or coma, is based solely on clinical evaluation. Clinical features which raise concern for myxedema and warrant a higher level of care include altered mental status, presence of hypothermia, and preceding events like infection, which can unmask underlying severe hypothyroidism (9). A scoring system for myxedema is present in the literature and can be useful in aiding whether myxedema coma is likely (10). However, this scoring system has not been repeatedly validated within the literature.

Thyroid hormone has several roles within the central and peripheral nervous systems, which can explain the varying degrees of neurological symptoms associated with hypothyroidism, such as depression, delayed reflexes, etc. (1). There is speculation about whether antibodies present in autoimmune thyroid disease, specifically Hashimoto's thyroiditis, may have a role in altered neurological function independent of thyroid hormone levels (11). However, current literature is conflicting and has not shown a clear causative effect. Irrespective of the cause, long-standing untreated hypothyroidism seems to be most consistently associated with neurological symptoms.

Hypothyroidism and Pituitary Hyperplasia

Another unique feature of this case is the presence of pituitary hyperplasia on imaging, which is a known but rare presentation of chronically untreated primary hypothyroidism. It is typically seen in patients with Hashimoto's disease when there is underproduction of thyroid hormone from the thyroid gland. This deficiency signals the hypothalamus to produce thyrotropin releasing hormone (TRH) to stimulate the thyrotropes within the pituitary gland to produce TSH. Normally TSH would then bind to its receptor on the thyroid gland and produce both T4 and T3, which suppresses further release of TRH. However in primary hypothyroidism, the thyroid gland does not produce thyroid hormone in

response to TSH. In chronic primary hypothyroidism, there is a loss of T4-mediated suppression of TRH which leads to tonic stimulation of the pituitary gland and subsequent hypertrophy. Of note, TRH also stimulates the lactotrophe cells within the pituitary gland which produce prolactin (PRL). As noted in this case, patients can often have a mild elevation in PRL. With appropriate treatment, there should be normalization of both TSH and PRL as well as resolution of the pituitary hypertrophy—as seen in our patient in follow up imaging.

Treatment of Hypothyroidism and Controversies in Psychosis Management

Under the guidance of the endocrinology team, the patient was initially treated with intravenous (IV) levothyroxine and transitioned to a weight-based dose of oral levothyroxine on discharge. The use of IV levothyroxine is typically reserved for treatment of severe hypothyroidism or myxedema coma. However, IV levothyroxine also has a role in individuals who cannot tolerate oral levothyroxine for prolonged periods of time while hospitalized. Once clinically improved, patients can be transitioned to oral levothyroxine. It is typically recommended to start an oral dose of 1.6 mcg/kg in an otherwise healthy, young individual. Clinicians should consider a reduced dose of levothyroxine in those patients who are elderly or have underlying cardiac conditions, as levothyroxine can be arrhythmogenic (1). Other therapies such a liothyronine and steroids are typically reserved for those who are critically ill requiring step-down or intensive care. Therapies such as myoinositol and selenium are not typically prescribed in the acute setting and are not standard of care by endocrine society guidelines. Thyroidectomy is not recommended in acute treatment of hypothyroidism, as it has little clinical impact on disease.

While intravenous levothyroxine was clearly indicated for the patient's severe hypothyroidism, it was less obvious how best to manage her psychotic sequelae. A majority of similar case reports of patients with delusions and hallucinations secondary to hypothyroidism describe the use of short-term antipsychotics to minimize psychotic symptoms. Antipsychotic augmentation of thyroid replacement may be especially helpful in elderly patients—whose neuropsychiatric symptoms often take longer to resolve and can even become permanent—and patients like ours whose psychotic symptoms are distressing, disabling, or likely would interfere with their ability to comply with a daily thyroid medication (12).

There is no clear standard of care in the literature for preferred antipsychotic agent or length of treatment; in several reports both low dose typical (haloperidol) and atypical (risperidone, olanzapine) antipsychotic medications were administered over a period of weeks. Initially, the team selected low dose aripiprazole for our patient due to concern over exacerbating her elevated prolactin (114). Some guidelines suggest that when antipsychotic-induced elevated prolactin levels are >50 or there are clinical symptoms, medication such as aripiprazole should be added to reduce prolactin levels; although this case was not antipsychotic-induced, initial agent selection was based upon this principle (13). After multiple days receiving low dose aripiprazole without reduction in her psychotic symptoms, she was switched to risperidone, given several case studies suggesting clinical improvement within two weeks' duration on this regimen (12). So long as a patient is not experiencing symptoms such as infertility from elevated prolactin, medications with a higher risk of prolactin elevation can be safely used. However, upon review, given the patient's female gender, pituitary hyperplasia, and prolactin levels <100, lengthier trial of aripiprazole instead of switching to risperidone may have been warranted. Guidance on initial antipsychotic selection and criteria for switching in psychotic patients with hyperprolactinemia secondary to hypothyroidism are needed, as highlighted by this case.

It was clear that after several days taking risperidone, the patient's positive symptoms, particularly her paranoia, had significantly improved. Unfortunately, because the patient was lost to formal psychiatric follow-up, it is unclear exactly when her psychotic symptoms fully resolved, though she estimated that her auditory hallucinations completely remitted two months after her initial presentation, at which time she self-discontinued her risperidone.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

CL, SR, GA, and AR contributed to initial psychiatric care and workup of the patient in the Crisis Intervention Unit, conceptualization of the case report, and writing and editing it. SH contributed to the medical care of the patient, conceptualization of the case report, and writing and editing it. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Management of Long-Term Sores and Ulcers of Breast Cancer Survivors With Chinese Herbal Medicines: A Case Report

Yuanfeng Zhang[1,2], *Bing Zhang*[1]*, *Weilong Zhou*[1] and *Tao Lu*[3]

[1] School of Chinese Materia Medica, Beijing University of Chinese Medicine, Beijing, China, [2] China Traditional Chinese Medicine Science and Technology Development Center (Talent Exchance Center of National Administration of Traditional Chinese Medicine), Beijing, China, [3] School of Life Sciences, Beijing University of Chinese Medicine, Beijing, China

Background: The treatment of long-term sores and ulcers of breast cancer metastatic recurrence is a serious challenge with successful cases rarely being documented. Herein we reported a successful case using the internal vitality supporting method of Chinese herbal medicine (CHM).

Case Summary: A 59-year-old female Chinese patient, 10 years after breast cancer surgery, developed metastatic lesions in the lung. Thereafter she received radiofrequency ablation and adjuvant treatments for 1 year with severe sequelae, a right unhealed sore and ulcer. She became frustrated and depressive. And subsequently sought exclusive treatment under the guidance of a Traditional Chinese Medicine (TCM) physician. The patient's condition was categorized as a *Qi* (or vitality) deficiency-related sore and ulcer. In the next six months, the patient still follows a traditional Chinese medicine therapeutic regimen based on the internal vitality supporting method of Chinese herbs.

Conclusion: The sore and ulcer from the surgical wound were healed. Up to now, the tumor markers have remained stable. TCM personalized survivorship treatment and psychosocial support can help patients improve their quality of life after acute treatment and in the long-term for cancer survivors.

Keywords: Chinese herbal medicine, sore and ulcer, cancer metastatic recurrence, psychosocial support, post-radiofrequency ablation wound, breast cancer survivors

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Edited by:
Wenhao Jiang,
Southeast University, China

Reviewed by:
Chenglong Li,
Peking University Clinical Research Institute, China
Xianbin Zhang,
Shenzhen University, China

***Correspondence:**
Bing Zhang
zhangb@bucm.edu.cn

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INTRODUCTION

Breast cancer is the most common cancer diagnosed in women worldwide, and it alone accounts for 30% of cancer in women (1). Death rates for female breast cancers were estimated to be 6.9% in 2020 (2).

Surgery represents the only potentially curative therapeutic intervention for breast cancer patients, and postmastectomy locoregional recurrences (LRRs) were found in 5–25% (3). The sites of LRRs were usually confined to the chest wall (68%) and supraclavicular nodes (41%) (3, 4). The lung, bone, and liver were the most common metastatic sites for breast cancer. A total of 60–70% of metastatic breast cancer patients who eventually died were diagnosed with lung metastasis (5). Unique signal transduction pathways were found for breast tumors to metastasize to the lung, and nine genes have been defined as specific for lung-specific metastasis (6–8). Surgery is the first

line choice of treatment. Other treatments (e.g., cryoablation, intraoperative radiotherapy, high-intensity focused therapy, and ultrasound) are used in the experimental/investigational phase, if applicable (3). Radiofrequency ablation (RFA) is a popularity intervention for its advantages of reduction in tumor mass and intraprocedural pain (9). However, adverse events are common with RFA, such as vascular injury (10), atrio-esophageal fistula (11), and deep esophageal ulcers and abscesses (12–15), which seriously affect patients' quality of life. At present, post-RFA wound management is a serious challenge, as the wound is difficult to heal and has to be kept clean by rising with saline water, which is the main conservative approach for wound management. According to traditional Chinese medicine (TCM) theory, *Yang* and *Qi* are the driving forces of biological activities in the human body. Deficiencies in *Yang* and *Qi* are common in cancer patients (16). Chinese herbal medicine (CHM) has been utilized as a supplementary treatment (17, 18) for breast cancer patients who received a surgical operation (19–21). We report herein the case of a 59-year-old women who had a surgical operation in the year of 2007. The patient was diagnosed with lung metastasis by CT, for which RFA treatment was then performed. Unfortunately, the cancer recurred and the chest ulcer failed to be controlled following interventional therapy. In the absence of further treatment options, the surgeon decided to offer only palliative treatment. The patient developed anxiety and depressed mood. Without further improvement, the patient turned to CHM for help, and she witnessed a stable improvement in her condition, with the sore and ulcer healed.

Ethical Approval

This case report was a retrospective study; hence it did not belong to the Ethical committee's scope of review, which means that ethical approval was not necessary.

Patient Consent

Written informed consent was obtained from the patient before and after every procedure.

CASE PRESENTATION

Chief Complaints

The patient was a 59-year-old woman diagnosed with right breast cancer who underwent a right mastectomy in 2007. The patient complained of persistent chest pain and ulcers for 1 year, and she had low quality of life.

History of Present Illness

The patient was sent to Guoyitang TCM Clinic, Beijing University of Chinese medicine on 29 June 2017. She reported having developed an ulcer on the right side of her chest 1 year prior, after receiving RFA treatment in Guangdong hospital. The patient reported coughing with a lot of white sputum. She reported that she had persistent pain on the right side of her chest and there was secretion at the scar, and she had poor mental status. We observed that her tongue was pale-white-with tenderness and the tongue coating was white with exfoliative tongue fur. The patient's pulse was deep.

Abbreviations: TCM, Traditional Chinese medicine; LRRs, Locoregional recurrences; RFA, Radiofrequency ablation; CT, Computed tomography; CHM, Chinese herbal medicine.

History of Past Illness and Family History

In October 2007, the patient had an invasive ductal carcinoma that was diagnosed by puncture. Grade II was confirmed in the right breast tissue and lymph node via microscopy, with metastases involving the axillary lymph node (7) 4/7 and lymph node (9) 5/9 depicted in the surgical pathology report. Immunohistochemical analyses revealed the following: ER (+ + +), PR (+ + +), C-erbB-2 (-), VEGF (++), P53 (+ + +), and Ki-67 (+ + +). Having received postoperative radiotherapy, the patient continued taking toremifene as a means of endocrine therapy for 5 years.

In May 2016, a CT scan demonstrated a recurrence of right breast cancer and aroused suspicions of lung metastasis, after which ultrasound and CT-guided right recurrent breast lesions and radiofrequency ablation of the lung metastases were conducted. Following radiofrequency ablation of the lesions within the lung and right chest wall, the wound did not heal completely, and a chest wall sinus was formed. Next, the patient started taking tegafur gimeracil oteracil potassium capsules (20 mg per day) until January 2020. And is currently being administered fulvestrant injections.

In March 2017, the patient received a secondary radiofrequency ablation for the metastasized lesion in her left lung. Unfortunately, the patient complained of persistent chest pain and ulcers; a chest CT revealed a mass measuring 12 mm at its thickest point, suggesting the presence of recurrence and that the lesion was inoperable. The wound was covered with dressing, and the surgeon recommended the patient use a saline cleaner for the wound 1∼2 times daily. However, in the patient's perspective, she said there has been almost no improvement. She felt that the condition gradually worsened. This clearly devastated the patient and seriously affected her quality of life.

Regarding her psychosomatic symptoms, the patient had suffered chronically from dysthymia after cancer diagnosis. Depressive symptoms increased with cancer diagnosis and multiple RFA therapy regimes. And her psychiatric profile became worse when the wound was still unhealed after 1 year. The timeline for medical history and treatment is shown in **Figure 1**.

Diagnostic Assessment and Treatment

According to TCM syndrome differentiation, the patient was diagnosed with *Yang (spleen and kidney)* deficiency and *Qi* deficiency. Professor Dr. Zhang's (Doctor of CHM) main treatment goal was to relieve the patient's pain. She used the internal vitality supporting method (22) to strengthen the patient's anti-pathogenic ability. A treatment course lasted for 7 days. The composition formula is displayed in the **Supplementary Table.** First, the patient was instructed to take the herbal decoction once a day for 7 days. At the second visit, the patient appeared cheerful and lively. The improvement elicited during the treatment was highly significant (**Figure 2**).

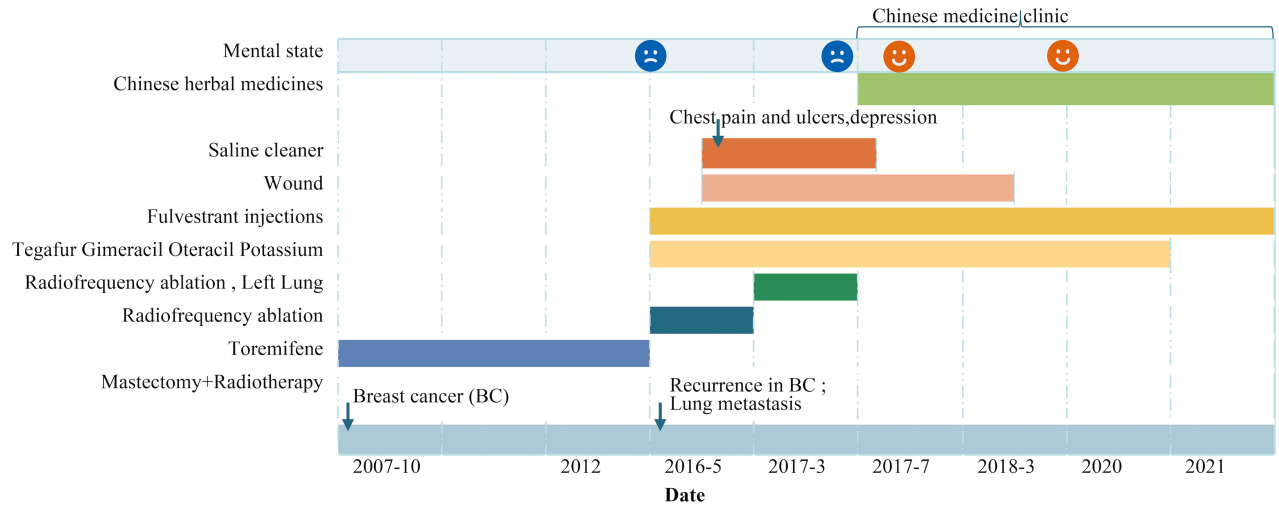

FIGURE 1 | The timeline for medical history and treatment.

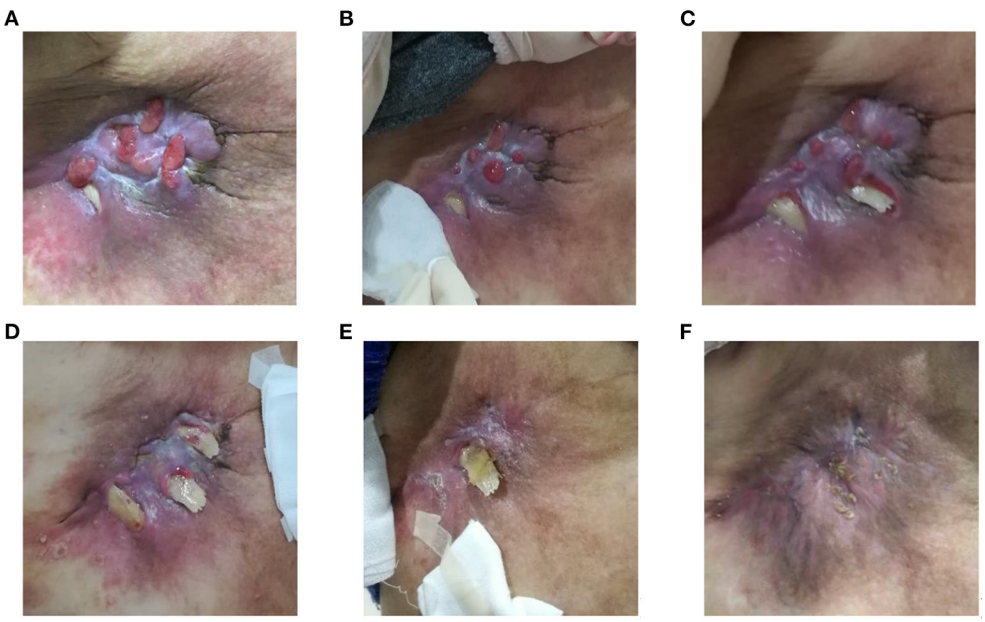

FIGURE 2 | Sore and ulcers. **(A)** Severe sore at the first visit (with eight ulcers on right chest). **(B–E)** By the second and fifth visits, the sore and ulcers were significantly improved. **(F)** At the sixth visit, the ulcers had already healed.

Currently, the patient continues to take Chinese herbs after completing five treatment courses. Over the last 6 months, the wound has healed and the overall situation has remained stable with a slight cough. "I was very surprised at my change because I could hang out easily at home with my family with a comfortable mind", the patient said.

Outcome and Follow-Up

In March 2018, the CT report pointed out that the lesion in the right chest wall with its thickest part measuring 9 mm, was smaller in size than previously reported (12 mm) in June 2017. The tumor marker test was sustained within the normal range (**Table 1**).

DISCUSSION

There are three stages in the wound healing process: inflammation, proliferation, and remodeling, which depend on the host's ability to repair tissue (23). It was proposed that

TABLE 1 | Tumor marker test.

Test item	Prior treatment with CHM	Post-treatment with CHM	Reference	Units
CA15-3	14.17	13.11	0.00∼25.00	U/ml
CA125	7.12	6.97	0.00∼35.00	U/ml
CEA	1.42	2.02	0.00∼5.00	ng/ml
CA19-9	–	21.43	0.00∼35.00	U/ml

CA15-3, carbohydrate antigen 153; CA125, carbohydrate antigen 153; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 199.

there was an aspect of surgical tumor resection that triggered the outgrowth of otherwise-dormant metastases, leading to the synchronous pattern of relapse during the postoperative period. In general, 10∼41% of breast cancer patients experience recurrences, and 10% develop overt metastases relatively soon after tumor eradication (3, 24). There is compelling evidence of an increased risk of anxiety, depression, and suicide, and neurocognitive and sexual dysfunctions in breast cancer survivors compared with women with no prior cancer (25). Clinically relevant symptoms of stress and depression are common shortly after diagnosis and metastatic recurrence, because women feel uncertainty about the future and their cancer may be perceived as life-threatening. The patient mentioned in this case report who suffered from long-term sores and ulcers of breast cancer metastatic recurrence had low quality of life. From the surgeons' perspective, ulcers of breast cancer metastatic recurrence are local inflammation, and they only recommend washing the ulcer with normal saline, but in this case, the ulcer failed to heal for 1 year. This case was complex and difficult to treat. Seeking the help of a doctor was spiritually necessary for the patient. So when the surgeon was helpless or the treatment plan was not ideal, this led to despair in the patient.

The holistic concept is an essential philosophy of TCM. The mind and body together are a dynamic battlefield, in which all the organs and mind are interconnected and bound to each other, and should be considered and treated as a whole, rather than an isolated pathology. In TCM theory, individual health is formed by *Yin-Yang*; an imbalance between *Yin* and *Yang* in the body can render an individual more prone to certain disease (26). This theoretical advantage simplifies the complexity. TCM uses different methodologies to diagnose mental and body disorders. The four diagnostic methods (inspection, listening/smelling, inquiry, and palpation) are the means to obtain patient information. This information is then analyzed using diagnostic models, such as yin/yang, interior/exterior, excess/deficiency, and hot/cold to differentiate the pattern and form a diagnosis. Zhang suggested that the patient's long-term sore and ulcer were due to *Qi* deficiency; the psychiatric symptoms of the long-term sore and ulcer resulted in emotional upset and stagnation of *Qi*. These were associated with the impairment of spleen and kidney (*Spleen-Yang* and *Kidney-Yang*). *Yang*-deficiency (e.g., *spleen*, *kidney*) may not only be related to hypothalamic-pituitary-adrenal (HPA) axis and hypothalamic-pituitary-thyroid (HPT) axis dysfunction, but also to functional disorders of the cyclic nucleotide and immune systems (27). These factors are involved in depression. The patient's mind and body were affected by the sore and ulcer. Zhang's main treatment goal was to relieve the patient's pain, which could improve the patient's quality of life.

After the malignant lesions had been removed by surgical excision, there was a persistent poor growth of granulation tissue, following delayed wound healing. The patient exhibited middle-staged boils and sores, and the pus was not completely discharged after breaking the ulceration. The patient had a compromised immune function; thus a tonic was used for reinforcing the primordial *Qi* in order to treat suppurative infection in this situation. This method was named the internal vitality supporting method according to the theory of TCM (22). This therapeutic regimen aimed at strengthening the host's anti-pathogenic ability and removing pathogenic factors via herbs to achieve the goal of canceling the tumefaction and shrinking its base to avoid ulceration.

The ulcer was effectively healed by Chinese herbs via boosting the primordial *Qi*, conditioning the internal vitality of key viscera to circulate *Qi*, activating the energy supply, and dispersing the inflammatory blockage. HuangQi (*Radix astragali seu Hedysari*), DangShen (*Radix codonopsis pilosulae*), Baizhu (*Rhizoma Atractylodis Macrocephalae*), Danggui (*Radix Angelicae Sinensis*), Baizhi (*Radix Angelicae Dahuricae*), etc., have been documented to modulate the immune response. These were used in inhibiting cancer cell proliferation, arresting the cell cycle, inducing apoptosis, inhibiting epithelial-mesenchymal transition, regulating immune function (28), and exerting antioxidative and anti-inflammatory effects (29) in cells and animal studies. Compared to local treatment therapies for chronic inflammatory skin disease, this herb intervention altered the gut microbiome, taking advantage of the gut-skin axis to control different skin conditions (30). As these herbs encompass a group of substances that produce a therapeutic effect, multiple pathways and receptors were targeted, plenty of compounds were involved, which acted synergistically to improve cancer-related symptoms, enhance vital energy, and boost immunity. What is more, herbs used in traditional medicine can be significantly effective in reducing depression, depressive symptoms, and improving patients' performance via regulating the HPA axis (31). So as the patient witnessed her wound healing, she became more optimistic.

This case was the first description of management of a long-term sore and ulcer of breast cancer metastatic recurrence with the internal vitality supporting method of Chinese herbal medicine. The patient was effectively cured due to cross-disorder and interdisciplinary collaboration**.** The holistic concept of TCM provided a novel therapeutic strategy for mind–body medicine.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the relevant individual(s) for the publication of any potentially identifiable images or data included in this article. Written consent and

accompanying photos were obtained from the patient and her husband for publication.

AUTHOR CONTRIBUTIONS

YZ drafted the manuscript. BZ treated the patient and provided the case analysis. WZ and YZ provided the critical analysis in preparing this article. TL revised the manuscript. All the authors approved the final version.

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SUPPLEMENTARY MATERIAL

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ORIGINAL RESEARCH
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Interoception Dysfunction Contributes to the Negative Emotional Bias in Major Depressive Disorder

Hongliang Zhou[1], Haowen Zou[2], Zhongpeng Dai[3], Shuai Zhao[1], Lingling Hua[2], Yi Xia[1], Yingling Han[2], Rui Yan[2], Hao Tang[1], Yinghong Huang[2], Yishan Du[1], Xiaoqin Wang[1], Zhijian Yao[1,2] and Qing Lu[3,4]**

[1] Department of Psychiatry, The Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China, [2] Nanjing Brain Hospital, Medical School of Nanjing University, Nanjing, China, [3] School of Biological Sciences and Medical Engineering, Southeast University, Nanjing, China, [4] Key Laboratory of Child Development and Learning Science of Ministry of Education, Nanjing, China

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Edited by:
Wenhao Jiang,
Southeast University, China

Reviewed by:
Shen Li,
Tianjin Medical University, China
Yansong Liu,
Suzhou Guangji Hospital, China

***Correspondence:**
Zhijian Yao
zjyao@njmu.edu.cn
Qing Lu
luq@seu.edu.cn

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Background: Previous research studies have demonstrated that impaired interoception is involved in emotional information processing in major depressive disorder (MDD). Heartbeat-evoked potential (HEP) amplitudes, an index for interoception, could be manipulated by emotional faces in healthy people. Considering negative emotional bias is the core characteristic in MDD, we hypothesized that interoception dysfunction was associated with the negative emotional bias in MDD.

Methods: An electroencephalogram (EEG) study under an emotional faces task was applied to explore the relationship between interoception and emotional bias. HEPs before emotional faces stimuli were used to predict the late positive potential (LPP) amplitudes and it worked as an index of emotional bias. Twenty-seven patients with MDD and 27 healthy controls (HCs) participated in this study. Source analysis gave an auxiliary description for results in sensory level.

Results: Major depressive disorders (MDDs) had poor performance in the heartbeat count task (HCT) and attenuate HEP average amplitudes (455–550 ms). Compared with HCs, cluster-based permutation *t*-tests revealed that MDDs had attenuated LPP amplitudes (300–1,000 ms) over centroparietal regions and enhanced LPP amplitudes over frontocentral regions. Furthermore, abnormal attenuated HEPs could predict aberrant LPPs under sad face stimuli in MDDs, which could be associated with the dysfunction of the anterior cingulate cortex (ACC) and right insula.

Conclusion: Mediated by ACC and insula, interoception dysfunction contributes to the negative emotional bias of MDD, highlighting the importance of interoception in the disorder.

Keywords: major depressive disorders, negative emotional bias, interoception, predictive coding, HEP (heartbeat evoked potential)

INTRODUCTION

Major depressive disorder (MDD) is a common affective psychiatric disorder and has been the leading cause of burden worldwide (1). Emotion dysregulation is the core characteristic of MDD and efforts to elaborate potential mechanisms of emotion are particularly pressing for the development of effective prevention and therapy in MDD (2). Previous works have reported that depressive patients are characterized by the negative emotional bias (3), concretely showing in abnormal negative faces processing (4). It was reported that depressive patients showed abnormal event-related potential (ERP) amplitude resulting from aberrant neuron discharge evoked by emotional faces stimuli (5). Compared with healthy controls (HCs), negative emotion stimuli evoked more aberrant ERPs than positive emotion stimuli and neutral emotion stimuli tended to evoke negative similar ERPs (6, 7) in depressive patients, which was mediated by the abnormal activity patterns within common networks of brain regions that include the amygdala, basal ganglia, insula, anterior cingulate cortex (ACC), and several regions of the prefrontal cortex (8–10). Late positive potential (LPP), which occurs between 300 and 1,000 ms after stimuli and maximum over centroparietal regions, is a late emotion-related ERP component specially related to negative emotional bias (11, 12). LPPs were thought to reflect emotion arousal and motivated attention for their synchronism with the arousal of the autonomic nervous system (13, 14). The attenuated mean amplitude of LPPs in MDD was associated with low dopamine levels (15).

The theory of embodied cognition indicates that not only cognitive processes are influenced by the body but also cognition exists in the service of action (16). Interoception is the core of the theory of embodied cognition, and embodied cognition supports the extension to other brain regions of the principles of organization of cerebral cortical connections (17, 18). Further investigating the relationship between interoception and depression would be helpful in understanding the neural mechanism of MDD. In psychology, predictive coding is applied to study the brain function, especially in electrophysiological investigations (19). Unlike the traditional experimental model, which recognized the brain as a "stimulus-response" organ, in the predictive coding model, the brain actively applies learned predictions to infer the causes of incoming sensory information, namely, brain could predict the following state by previous experiences in a probability-driven way (20). By integrating the neuroanatomical model, Barrett provided the Embodied Predictive Interoception Coding (EPIC) model to explain the potential pathological mechanism for MDD (21). The model speculates that the imbalance of allostasis detected by interoception dysfunction leads to diverse clinical features (such as emotion dysregulation) that result from the disabled internal-and-external information processing. ACC, insula, primary interoceptive cortex, and somatosensory regions could be the neural basis mediated by dopamine and acetylcholine (21). The neural network in this model had been proved with a large healthy sample of MRI study and macaque monkeys study, which put a new perspective to understand the emotion dysfunction in MDD (22, 23).

Up to now, many studies had revealed the correlation between peripheral system dysfunction and MDD (24–26), highlighting the important role of allostasis in MDD. It is conceived that the interoception dysfunction leads to an imbalance of allostasis in MDDs by the abnormal integration of internal and external information (27), which would affect emotion information processing ulteriorly. ERPs, with the advantages of the high temporal resolution, are beneficial to studying high informative power on neural alterations in MDD (28). Cardiac interoception working as a robust internal signal (29) is a majority way to investigate interoception because of heartbeats' large effect and easy availability (30). By time-locking to the electrocardiogram (ECG) R-peak of the heartbeat, cardiac interoception is quantified with the heartbeat-evoked potential (HEP) (31, 32). It was reported that depressive individuals had decreased heartbeat perception accuracy and reduced HEP amplitudes (33, 34). Further evidence of an impaired association between HEP amplitudes and heartbeat perception accuracy in depressive patients suggested the imbalance of allostasis in MDD (34). In addition, many researchers had reported the relationship between emotional information processing and interoception in psychiatric disorders, such as anxiety (35), alcohol use disorder (36), and functional neurological symptom disorder (37). However, previous research studies on interoception mainly focused on somatic symptoms in MDD (27, 38). Recently, some studies have shown that HEP amplitude could be manipulated by negative emotional face stimuli in healthy people (39), which provided the clue to explore the relationship between interoception and the negative emotional bias in MDD.

The current study was aimed to study the negative emotional bias in MDD from the aspect of internal-external information integration. We supposed that there is an association between impaired interoception and negative emotional bias in MDD. We further speculate that aberrant HEPs before emotional faces stimuli could predict abnormal LPPs in MDD.

MATERIALS AND METHODS

Ethics Statement

Procedures were approved by the ethics committee of the Affiliated Nanjing Brain Hospital of Nanjing Medical University in accordance with the Declaration of Helsinki, and all participants provided written informed consent. The data were collected from 01 March 2021 to 30 October 2021.

Participants and Procedures

Participants included 30 MDDs and 30 healthy volunteers who matched for age, sex, and body mass index (BMI). The education of parents was also matched in that this information contained intelligence and economic level at the same time. MDDs fulfilled the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) diagnosis of MDD as verified with the Chinese version of the Mini-International Neuropsychiatric Interview (MINI) interview to further study inclusion. Beck Depression Inventory-II (BDI-II) (40) and the State-Trait Anxiety Inventory (STAI) (41) were applied to assess the depressive level and anxiety

state. General exclusion criteria comprised (a) neurological disorders; (b) alcohol dependence, nicotine dependence, or other psychoactive substance abuse; (c) comorbidity or diagnosis of other psychiatric disorders; (d) severe medical illness, such as cardiac dysregulations; (e) received medicine therapy in 2 weeks; and (f) received Electroconvulsive Therapy (ECT) or modified ECT within last 6 months. After data processing, a total of 54 participants remained (shown in **Figure 1B**).

After evaluating the depressive level and anxiety state, participants have a 10-min rest and completed a standard HCT (42). They were instructed to report their heartbeats numbers in a calm state during five time periods (25, 35, 45, 55, and 60 s), which were presented in random order. Guessing the number of heartbeats was forbidden. The task was performed twice and participants with large differences in reports were asked to attend the experiment another day. Heartbeat tracking score was calculated using the following formula:

$$\frac{1}{5}\sum (1 - [(\text{recorded heartbeats} - \text{counted heartbeats}) \div \text{recorded heartbeats}])$$

Then, participants finished a revised emotional face visual paradigm.

Produces and Task Design

An emotional face visual paradigm was used to produce emotional stimuli edited by E-prime 3.0 (Psychology Software Tools Inc.). In total, 300 gray-scale photographs of different Chinese individuals without hair posing one of three different facial expressions (100 sad faces, 100 happy faces, and 100 neutral faces, half male and half female faces in each condition) were selected from the revised version of the Chinese Facial Affective Picture System (43). All faces with white fixation crosses at the point of the nose were resized to present centrally on a computer screen at a viewing distance of 80 cm.

In the task, we set a cue stimulus with a black fixation dot ranged from 1,500 to 2,500 ms randomly in order to capture HEP before an emotional stimulus. Then, 2,500 ms emotional faces would be followed. A cue stimulus and an emotional face stimulus constituted a trial, and trials were separated by a 2,500–3,500 ms interval to avoid residual emotion effect that affected the next pre-stimulate HEP. To avoid potential confusion, we set 20% capture trials to assess participants' attention. The capture trials contained a red arrow replacing white fixation cross randomly in the emotional faces, which need participants to make a response by pressing "A" (right) or "L" (left) as soon as possible. The participants who failed to press the button were excluded from later analyses (as shown in **Figure 1A**). The task was divided into three blocks. The training session contained 10 trials and the duration of each block was about 15–20 min.

Electroencephalogram Data Acquisition

Electroencephalogram (EEG) signal was acquired from a 64-channel active electrode system with Compumedics Neuvo at a sampling rate of 1,000 Hertz (Hz), referenced to a common average reference. The electrode cap was Quik-Cap HydroCell Array made in Australia. Two additional ECG electrodes were put on the participants' wrist and ankle on the same side. The continuous EEG signal was filtered with a 30 Hz low filter and a 0.3 Hz high filter. Considering the volume-conduction effects, the electrodes, which neared the orbital cavity, were excluded. Finally, 47 EEG channels were included in the following analysis. Independent component analysis (ICA) as implemented in EEGLAB (EEGLAB 9.0.3, University of San Diego, San Diego, CA, United States) was conducted to remove eye movements, blinks, and the cardiac field artifact (CFA) (44). The removing ICA components in every data were no more than 4. LPPs and HEPs were calculated by averaging across trials in different conditions.

Late Positive Potential and Heartbeat-Evoked Potential Analyses

For the LPP, the segment set was put from − 200 to 1,000 ms relative to the presentation of the segment set the facial stimulus. Every participant completed 100 trials per condition and at least 70 trials (70–93 trials, average 90.47) leaving after artifact correction. The LPP in this study was defined as the mean voltage from 300 to 1,000 ms.

For the HEP, the R-peak was marked by HEPLAB [HEPLAB: a MATLAB graphical interface for the preprocessing of the HEP (Version v1.0.0)]. EEG data were segmented into 1,000–2,500 ms periods relative to the ERP stimulus' markers to reduce the overlap from vision-evoked potential. Although in a recent study, authors were asked to segment heartbeat period with −100 to 700 ms based on the R-peak marker in the healthy population, the heartbeats of the most MDDs in our study were above average 86/per min during the task, which was in line with the authenticated phenomenon that MDDs had faster heartbeats than healthy human (45–47). It would fail to show disease attributes with segmentation standard by −100 to 700 ms. Therefore, epochs were further segmented into periods ranging from −100 to 600 ms according to the R-peak marker in our study (48–50). In HEP analysis, CFA was considered as the most important confounding factor for its same event time-locked characteristics with HEP (42). The strong electrical signal of CFA would influence results by spatio-temporal overlap with the HEP. ICA has been accepted as one of the most effective methods to excluded CFA; however, it is hard to completely remove the CFA with ICA. In our study, we had chosen the mean voltage from 455 to 595 ms after the ECG R wave as HEP index in that it was reported that CFA in this time window is less than 1% (51–54). Furthermore, the ECG mean amplitude in 455–595 ms was also compared between the two groups to avoid confounding cardiac effects (39).

Heartbeat-evoked potentials before emotion stimuli were used to predict LPPs that were induced by emotional faces.

Source Localization of the Scalp-Domain Electrophysiological Activity

In this study, the different scalp-domain electrophysiological activity was further explored by source localization analysis, which was conducted by free standardized low-resolution

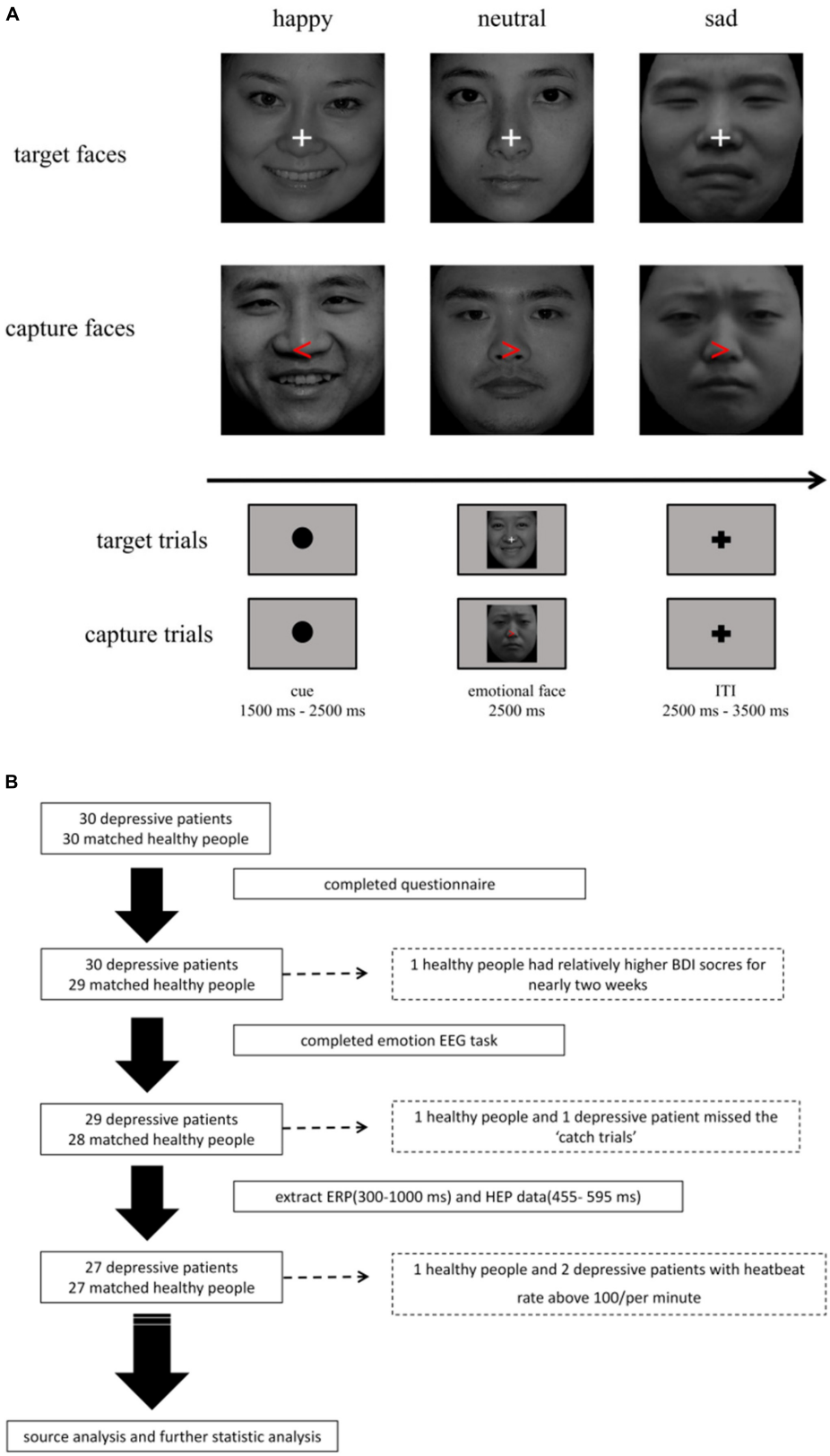

FIGURE 1 | (A) Emotional facial stimuli task. The task was divided into two parts (target trials: 80%; capture trials: 20%). **(B)** The flowchart for the study. After processing of data, 27 major depressive disorders (MDDs) and 27 healthy controls (HCs) were involved in the task.

brain electromagnetic tomography (sLORETA) software.[1] The sLORETA estimates brain neural activity by solving the EEG inverse problem, which has been widely applied in the EEG source localization analysis. The time windows were set according to significant scalp-domain electrophysiological activity, and mean amplitude analysis was used to figure out the different source activation between HCs and MDDs for HEPs (455–595 ms) and LPPs (300–1,000 ms).

Statistical Analyses

Independent *t*-tests and chi-square test were performed to compare the differences between the MDD group and HC group in demography characteristics (age, BMI, parents' education, disease course, ECG data, and gender) and questionnaires (BDI-II, STAI) with IBM Statistical Product and Service Solution (SPSS) Statistics for Windows, version 17 (IBM Corp., Armonk, NY, United States). Non-parametric cluster-based permutation tests were performed in both sensor and source levels with a value of p was set for < 0.05. Partial correlation analysis was applied to examine the relationship between the significant electrodes of HEPs and LPPs, with age, BMI, gender, education of parents, disease course, BDI-II, SAI, and TAI as control variables. To eliminate the effect of dimension, data were normalized and a stepwise regression analysis was used to establish a predictive mode with the significant clusters of LPPs as the dependent variables and the significant clusters of HEPs as the independent variables. The value of p was set for < 0.05. The best model was selected to explain the relationship between LPP and HEP.

RESULTS

Demographic and Clinical Characteristics

As shown in **Table 1**, there are no differences in age, BMI, gender, and the education of parents between the MDD group and HC group. However, the differences were found in heartbeat interoception, the scores of BDI-II, SAI, and TAI between the two groups.

Heartbeat-Evoked Potentials Component

As shown in **Figure 2**, HEPs during the prediction stage (predict-HEPs) are significantly attenuated in MDDs vs. HCs ($p < 0.005$, marked by the red pot in **Figure 2**). While there were no significant differences in ECG during the same stage, which indicated that the significant differences of HEP amplitudes were not evoked by ECG (ECG during prediction stage: $t = -1.291$, $p = 0.203$).

Late Positive Potentials Component

As shown in **Figure 3**, LPPs in MDDs over right centroparietal sites are significantly attenuated in all emotional face trials while LPPs over left frontocentral sites are significantly increased in sad and neutral faces than HCs ($p < 0.005$).

[1]http://www.uzh.ch/keyinst/loretaOldy.htm

Source Reconstruction of Event-Related Potential Components

Source localization analysis was applied to find the underlying responsible generators of HEPs during the prediction stage and LPPs in sad face trials. Non-parametric voxel-wise tests with $p < 0.01$ were used to compare sources between HCs and MDDs, separately for HEPs and LPPs.

The Different Source Localization of Heartbeat-Evoked Potentials in Major Depressive Disorder Group vs. Healthy Control Group

As shown in **Figure 4**, the sLORETA analysis suggests that there are 963 voxels different in two groups, mainly located in the frontal lobe [middle frontal gyrus (BA6) (maximal activity at montreal neurological institute (MNI) coordinates 30, 15, and 60), superior frontal gyrus (BA8) (maximal activity at MNI coordinates 25, 20, and 55)], and limbic lobe [cingulate gyrus (BA32) (maximal activity at MNI coordinates − 5, 20, and 45)]. These significant voxels showed a higher source activation in the HC group than the MDD group.

The Different Source Localization of Sad-Late Positive Potentials in Major Depressive Disorder vs. Healthy Control

As shown in **Figure 5**, the significant differences of sad-LPPs are mainly located in the right hemisphere. The sLORETA analysis showed that the source activation of the HC group was significantly higher in limbic lobe than the MDD group, especially in the anterior cingulate (BA32) (maximal activity at MNI coordinates 5, 30, and 25). While in the parietal lobe, such as the postcentral gyrus (BA2, BA40) (maximal activity at MNI coordinates 60, −30, and 20), inferior parietal lobe (BA40) (maximal activity at MNI coordinates 65, −45, 25), the source activation is higher in MDDs than HCs. In addition, the right insula (BA13) (maximal activity at MNI coordinates 55, −35, and 20) is also salient in MDDs.

Regression Model Analysis

As shown in **Figure 6**, only under sad face stimuli, significant differences in HEPs are correlated with LPPs cluster in the MDD group. In the MDD group, HEP electrode sites have a significantly positive correlation with LPP electrode sites in three clusters as shown in **Figure 4**. These results showed that the all significant HEP electrode sites could positively predict LPPs in left frontocentral sites (F5, F3, FC5, FC3, and FC1) ($r = 0.586$, $p = 0.008$). HEPs in right frontocentral sites (FC2, FC4, and FC6) were negatively correlated with LPPs in centroparietal sites (C4, CP4, and CP6) ($r = -0.545$, $p = 0.016$), while HEPs in right frontal sites (F2, F4, and F6) were negatively correlated with LPPs in parieto-occipital sites (PO4, PO8, and O2) ($r = -0.470$, $p = 0.042$). However, the correlation did not appear in the HC group.

In addition, the item-20 in BDI-II ("evaluation of own health") correlated with HEPs in right frontocentral sites positively in

TABLE 1 | Demographic information for the major depressive disorder (MDD) group and healthy control (HC) group.

Variables	MDD	HC	Test statistic
Gender ratio (M/F)	27 (16/11)	27 (15/12)	$\chi^2 = 0.076$, $p = 0.783$
Mean age (SD)	27.0 (6.7)	25.3 (3.8)	$t = -1.150$, $p = 0.257$
BMI	21.6 (2.8)	21. 6(2.9)	$t = -0.059$, $p = 0.953$
Education (SD)	13. 6 (3.9)	14.0 (3.2)	$t = 0.497$, $p = 0.653$
Education of parents (SD)	14.7 (1.8)	15.3 (1.8)	$t = 1.29$, $p = 0.20$
Total duration of depressive episode (month, SD)	54.2 (57.8)	–	–
Number of depressive episode onset (SD)	5.1 (3.2)	–	–
BDI-II (SD)	27.9 (9.3)	2.7 (3.3)	$t = -13.247$, $p = 0.000$
SAI (SD)	54.7 (11.2)	30.3 (5.5)	$t = -10.161$, $p = 0.000$
TAI (SD)	57.7 (9.3)	30.7 (7.2)	$t = -11.909$, $p = 0.000$
HCT	0.3 (0.2)	0.5(0.2)	$t = 2.077$, $p = 0.043$
HR	70.4 (8.8)	69.9 (7.6)	$t = -0.216$, $p = 0.830$
Hit rate for catch trails	0.993(0.023)	0.994(0.016)	$t = 0.345$, $p = 0.731$

MDD, major depressive disorder group; HC, healthy control group; F, female, M, male; SD, standard deviation; BDI-II, Beck Depression Inventory-II; SAI, State Anxiety Inventory; TAI, Trait Anxiety Inventory; HCT, heartbeat count task; HR. heartbeat rate.

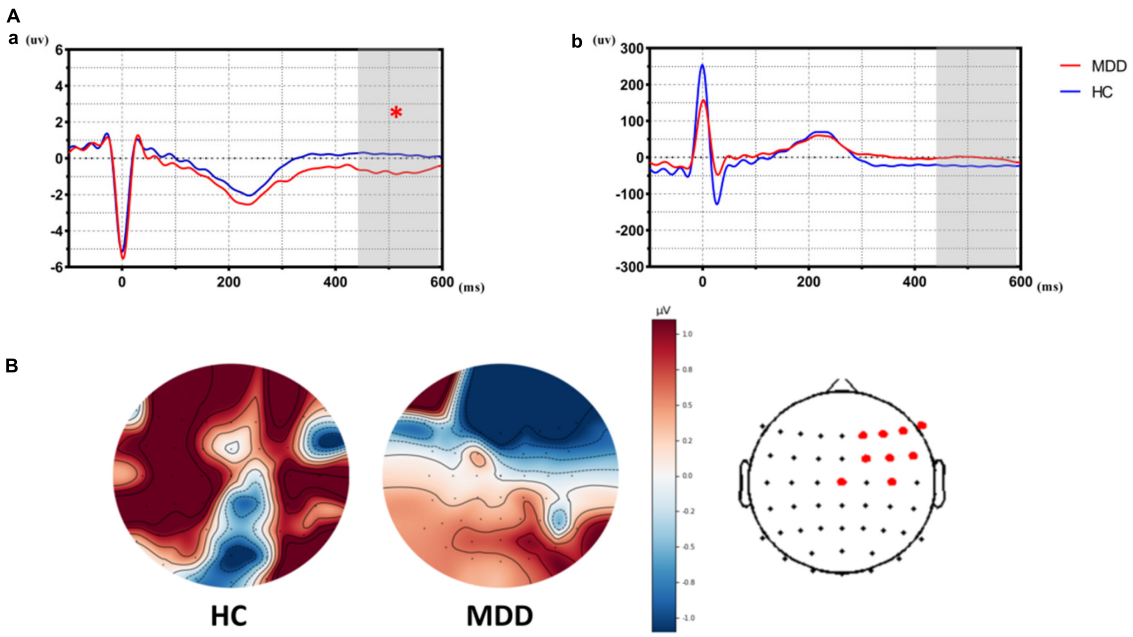

FIGURE 2 | The differences of heartbeat-evoked potentials (HEPs) in the stage of affective prediction between the major depressive disorder (MDD) group and the healthy control (HC) group. **(A**a**)** Showed significant differences in HEPs during the prediction stage between the MDD group and the HC group. **(A**b**)** Suggested that significant differences did not exist in ECG during the prediction stage between the MDD group and the HC group, which indicated significant differences in HEPs did not result from the effect of cardiac field artifact (CFA). **(B)** Topological graph of HEP in both groups. Electrodes marked with red color indicate a significant group-difference.

MDDs ($r = 0.538$, $p = 0.010$), while the scores of HCT were negative correlated with the scores of TAI ($r = -0.468$, $p = 0.028$) in HCs. LPPs in right centroparietal sites (C4, CP4, and CP6) were negatively correlated with a cognitive factor of BDI-II ($r = -0.464$, $p = 0.034$) in MDD. With stepwise regression analysis, two optimally predictive models were created. The equation is shown below:

$$\begin{aligned} \text{LPP(F5F3FC5FC3FC1)} &= 0.091 + 0.540 \\ &\times \text{HEP(F2F4F6FC2FC4FC6)} \\ &+ 0.178 \times \text{gender} \end{aligned}$$

$$R^2 = 0.409;\ F = 8.317 \qquad (1)$$

Where the adjusted R^2 statistic was 0.360 and the p of the model was 0.002. The values of p for included variables in (1) are shown in **Table 2**.

$$\begin{aligned} \text{LPP (C4CP4CP6)} &= 1.142 - 0.431 \times \text{HEP(FC2FC4FC6)} \\ &- 0.178 \times \text{gender} \\ &- 0.226 \times \text{cognitive factor} \end{aligned}$$

$$R^2 = 0.531;\ F = 8.696 \qquad (2)$$

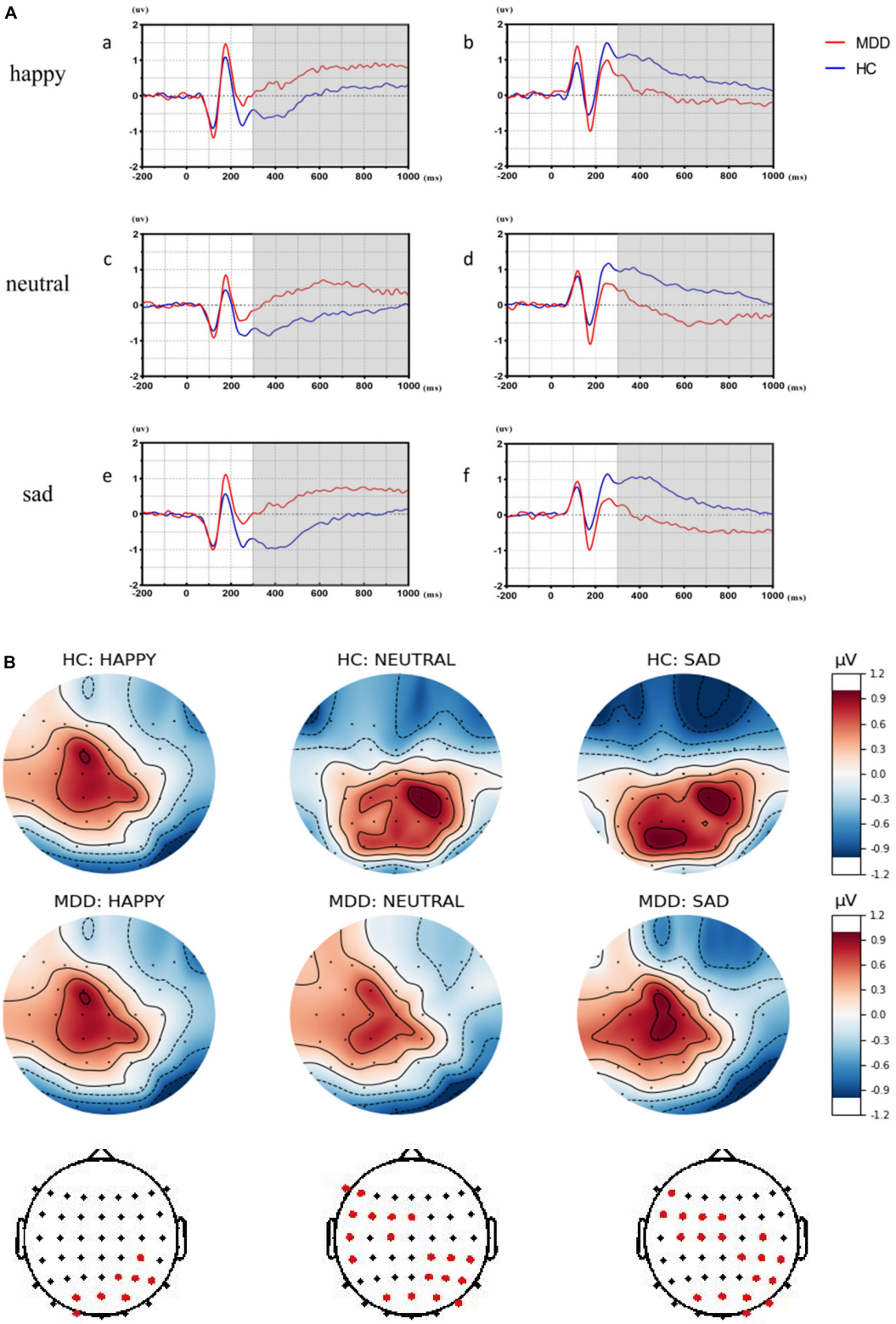

FIGURE 3 | The significant differences of late positive potentials (LPPs) in different affective faces trials between major depressive disorder (MDD) group and healthy control (HC) group. **(A**a,c,e**)** Showed the significant differences over left frontocentral sites between the MDD group and the HC group by averaging significant differences in electrodes in different affective face trials. **(A**b,d,f**)** Showed the significant differences over right centroparietal sites between MDD group and HC group by averaging significant differences in electrodes in different affective face trials. **(B)** Was the top plots with significant differences for LPPs.

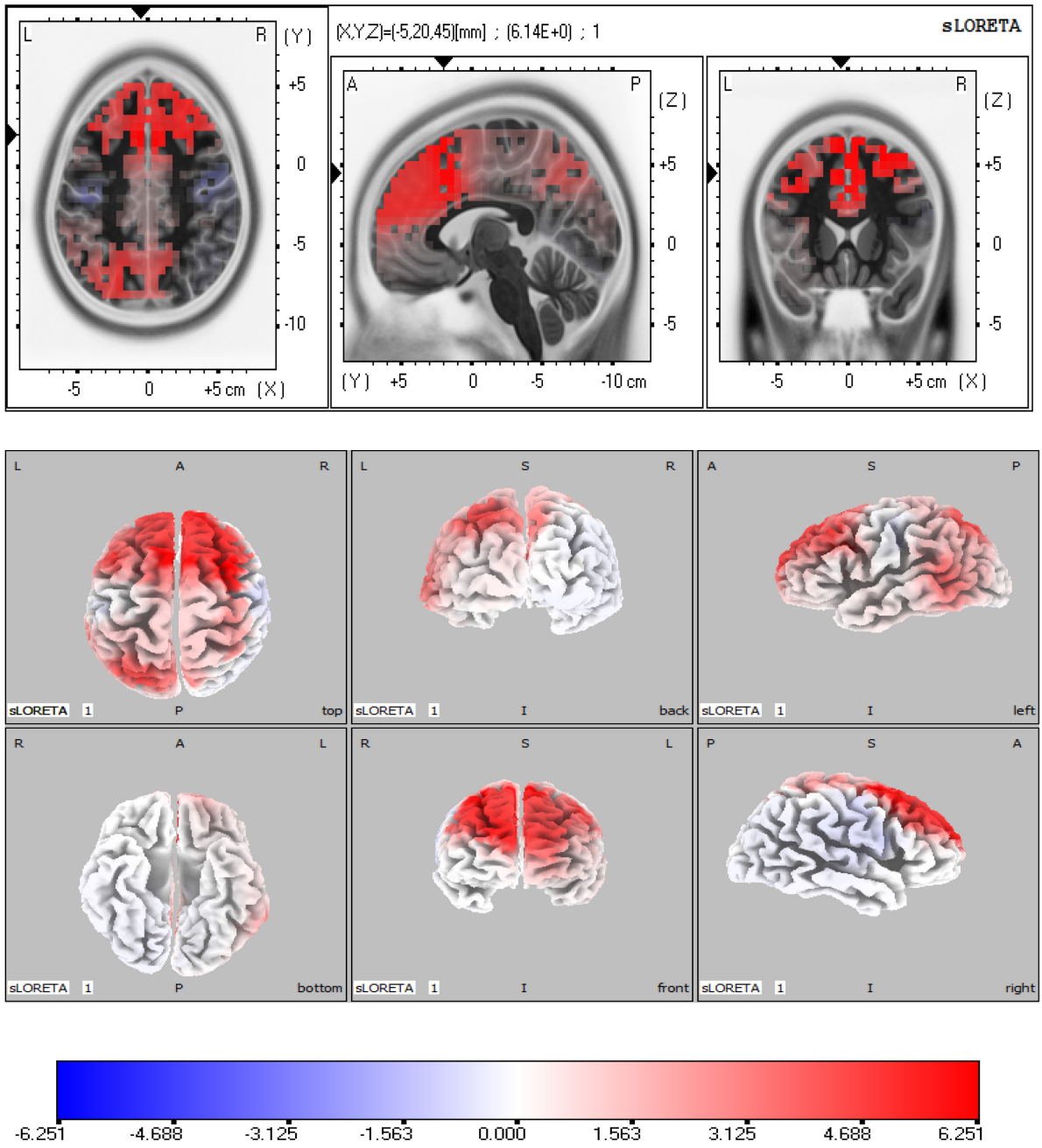

FIGURE 4 | Source analysis showed the attenuated Heartbeat-evoked potentials (HEPs) in major depressive disorder (MDD) mainly resulted from the frontal lobe (BA6, BA8) and limbic lobe (BA32). The marked site was anterior cingulate cortex (ACC) (BA32).

Where the adjusted R^2 statistic was 0.470 and the p of the model was 0.000. The values of p for included variables in (2) are shown in **Table 3**.

DISCUSSION

To our knowledge, this study was the first to investigate the negative emotional bias in MDD from the aspect of internal-external information integration by interoception. With converging evidence reporting the intimate connections between the peripheral nervous system and emotion in MDD (55, 56), the role of allostasis in depression pathological mechanism could not be ignored anymore. In the current study, we found that abnormal HEPs could predict aberrant LPP clusters in sad face trials only in the MDD group, indicating the possibility that aberrant interoception dysfunction has led to abnormal processing of sad faces in MDDs. Furthermore, by combing with

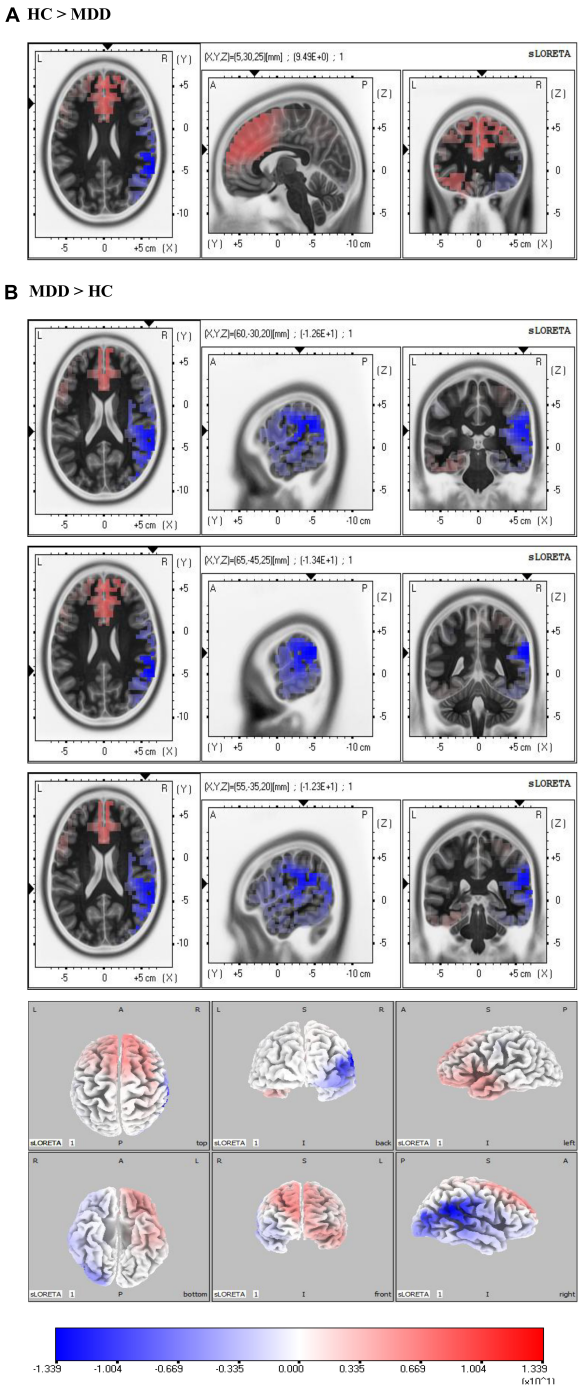

FIGURE 5 | Source analysis in the time window of sad-late positive potentials (LPPs). **(A)** Revealed the activity of anterior cingulate cortex (ACC) in the healthy control (HC) group was higher than major depressive disorder (MDD) group. In **(B)**, the MDD group showed higher activity in the right parietal lobe. Especially, the right insula showed higher activity in the MDD group than the HC group.

source location analysis and previous research studies (29, 57), we cautiously provided the initial evidence that low activity of ACC might be the primary source of attenuated HEPs and predicted the overactivity of the right insula in sad face processing in MDD. These results revealed that an abnormal internal-external interactive way could be the reason for impairment of emotion processing in MDD and provide valuable clew to extend the understanding of pathological mechanism of depression.

Many studies had reported that depressive patients had abnormal interoception that is reflected by poor performance in HCT and attenuated average HEP amplitudes (27, 58). Our study had similar findings. HEP, which is generated from the cardiac signal and processed by the brain, has been proved to be a valid index for interoception (59). Previous studies focused on the relationship between HEPs and early visual evoked potentials have suggested that HEPs could predict the threshold of the visual sad faces in healthy people (60). Here, considering the relatively slow conduction of interoceptive information by weakly myelinated neurons (61), we focused on the relationship between HEPs and LPPs (62, 63). We found blunt HEPs over frontocentral regions before emotion stimulation could predict abnormal LPPs over right centroparietal sites and left frontocentral regions under emotion stimulation. More importantly, aberrant HEPs contribute to abnormal LPPs under sad emotion processing merely existed in MDD. Although limited studies in this field have been conducted in MDD, recently research studies that focused on the association between HEPs and psychiatric disorders have dramatically increased, such as social anxiety, nightmare disorder, and borderline personality disorder (57, 64–66), and revealed that interoception fluctuation contributed to perception dysfunction. Negative emotional bias seems to indicate that patients with MDD had affective perception dysfunction. Our results validated this point and further elucidated the potential neuroimaging mechanism that negative emotional bias in MDD would have resulted from the dysfunction of interoception. In our study, attenuated HEPs predicted more health-like sad-LPPs in MDD, suggesting that the HEP worked as a self-compensation to recruit more cognition resources for negative emotion processing (67–69).

Combined with source analysis, the present results showed that abnormal interoception contributed to aberrant emotion processing in two different ways in MDD. One of them was controlled by frontal electrodes. In this way, predict-HEPs could predict LPP amplitude over left frontocentral sites under sad face context, which was implicated in low activity ACC. ACC was one of the major sources of HEPs and was famous for its autonomic function (39). Generally, ACC received wide nerve projections from the frontal lobe and took part in negative emotion-related information processing (70–73). In major depression, it was reported that the connectivity between ACC and orbitofrontal cortex (OFC) was decreased with increasing depressive symptoms (29, 74) and electrical stimulation in ACC could relieve depression (75). In our study, hypoactive ACC performed its limited ability in a time frame of both predict-HEPs and sad-LPPs. Considering the crucial role of ACC in viscera signal processing and emotion processing, it was easy to understand that the low activity ACC contributed to abnormal HEPs and emotion-related LPPs, which was in consonance with the fact that HEP was correlated with LPPs over left frontocentral

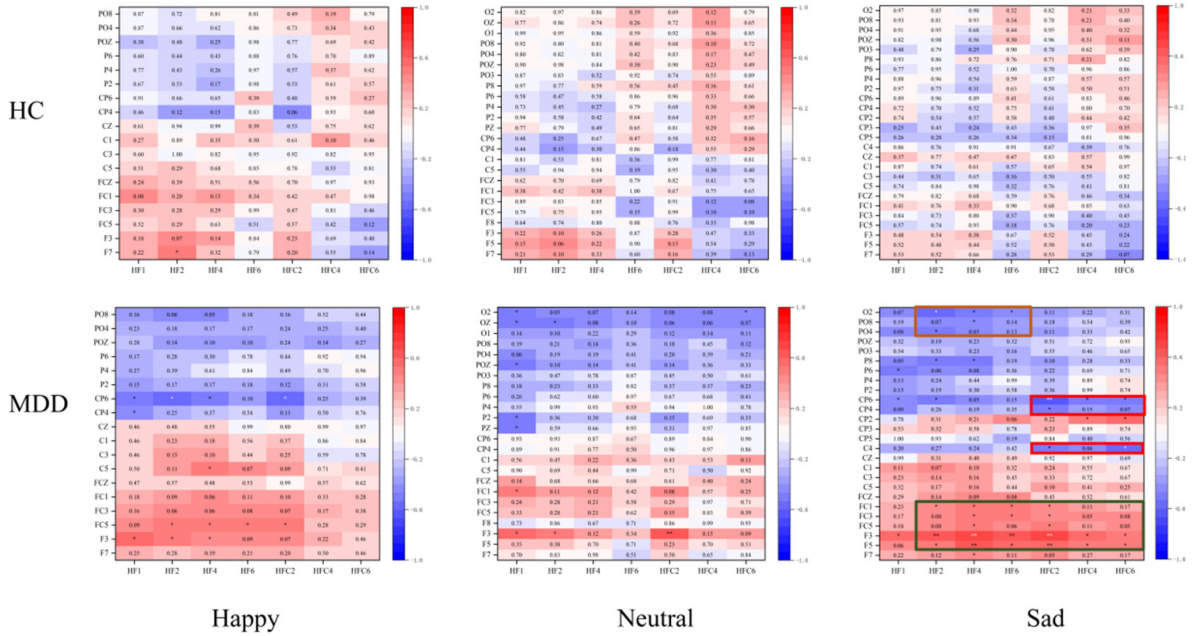

FIGURE 6 | The correlation between predict-heartbeat-evoked potentials (HEPs) and sad-late positive potentials (LPPs) in major depressive disorder (MDD) and healthy control (HC) groups. The significantly correlated clusters were only found in the MDD group.

TABLE 2 | The results of the predictive model (1).

Included variables	Unstandardized coefficients (B)	Unstandardized coefficients (Std. Error)	*p*	Standardized coefficients (Beta)
HEPs (F2, F4, F6, FC2, FC4, FC6)	0.540	0.138	0.001	0.645
Gender	0.178	0.075	0.026	0.393

TABLE 3 | The results of the predictive model (2).

Included variables	Unstandardized coefficients (B)	Unstandardized coefficients (Std. Error)	*p*	Standardized coefficients (beta)
HEPs (FC2, FC4, FC6)	−0.431	0.121	0.002	−0.534
Gender	−0.178	0.054	0.003	−0.509
Cognitive factor	−0.226	0.110	0.052	−0.301

sites positively. The other of them was a cognition-related way that is mainly controlled by right centroparietal sites under sad content. Sad-LPPs over centroparietal sites were reported to have intimate connections with emotional motivation and were correlated with the cognition scores in BDI-II in our work. The hyperactivity of the right insula (BA40) might be the source of abnormal sad-LPPs. The right insula was famous for its high response in negative emotion processing (70, 76) and was provided to have a connection with depression's negative emotional bias (77). Notably, the hyperactivity right insula in sadness could be predicted by hypoactive ACC, which validated the insight that interoception constitutes the emotion context by the interaction between limbic sensory (right insula) and limbic motor (ACC).

In our study, we suggested that the self-compensation of cognition source function is mediated by the information flow from ACC to the right insula. When processing sad face information, hypoactive ACC led to low emotional motivation which led to the potential negative effects, and to protect oneself, the right insula had to over-activated trying to arousing activation of ACC. This also could explain the result that blunt average amplitudes of predict-HEPs would arouse better sad-LPPs over right centroparietal sites.

In conclusion, the abnormal HEPs predict aberrant LPP amplitudes in MDD, which may result from the ACC and right insula. This study highlighted the importance of interoception for depressive patients and indicated the underlying mechanism of interoception dysfunction in emotional information processing. The study highlights interoception in MDD not only contributes to somatic symptoms but also affects emotion processing. The role of interoception in MDD is seriously undervalued. What is more, the therapy for MDD without considering homeostasis,

especially at the cost of disturbing autonomic function, should be seriously reconsidered.

LIMITATIONS

The major limitation in this study is a relatively small sample size, therefore, the results must be considered as preliminary. The cardiac rates of depressive patients were easy to increase during the task. To keep the accuracy of HEPs, we had to choose the segmentation from − 100 to 600 ms and excluded people whose heartbeats were above 86/min. In addition, considering the heartbeat is constantly changing, it is difficult and inappropriate to study the direction of information flow in our study by effective connectivity and other methods. We could only infer the process by time sequence. Future studies with larger sample sizes and optimized parameters are warranted to further verify these findings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Affiliated Nanjing Brain Hospital of Nanjing Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HLZ: data curation, formal analysis, methodology, writing-original draft, and writing-review and editing. HWZ: data curation. ZPD, SZ, LLH, YX, YLH, RY, HT, YHH, YSD, and XQW: methodology. QL and ZJY: data curation, formal analysis, methodology, and writing-review and editing. All authors contributed to the article and approved the submitted version.

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The Interaction Between *POMC* rs2071345 Polymorphism and Alcohol Dependence in Anxiety Symptoms Among Chinese Male Problem Drinkers

Liuzhi Hong[1†], *Lutong Wen*[2†], *Michelle Niculescu*[3†], *Fan Zhou*[1], *Yang Zou*[1], *Guanghui Shen*[1], *Wei Wang*[1,4], *Yanlong Liu*[1,4], *Yu-Hsin Chen*[5*], *Fan Wang*[6,7*] and *Li Chen*[1,4*]

[1] School of Mental Health, Wenzhou Medical University, Wenzhou, China, [2] Department of Neurosurgery, Affiliated Cixi Hospital, Wenzhou Medical University, Ningbo, China, [3] Department of Social Sciences, Chatham University, Pittsburgh, PA, United States, [4] The Affiliated Kangning Hospital, Wenzhou Medical University, Wenzhou, China, [5] Department of Psychology, College of Liberal Arts, Wenzhou-Kean University, Wenzhou, China, [6] Beijing Hui-Long-Guan Hospital, Peking University, Beijing, China, [7] Xinjiang Key Laboratory of Neurological Disorder Research, The Second Affiliated Hospital of Xinjiang Medical University, Urumqi, China

Objective: Alcohol dependence can increase the level of anxiety. A growing body of research has identified a link between anxiety symptoms of problem drinkers and their genetic or environment factors, respectively. However, to date few studies have directly examined gene-environment (G × E) interaction on their anxiety symptoms during the acute alcohol withdrawal. The present study aims to examine the interaction between the proopiomelanocortin (*POMC*) rs2071345 polymorphism and alcohol dependence on anxiety symptoms of male problem drinkers, and further test the exact form of interaction on two competing models: the diathesis-stress model vs. the differential susceptibility model.

Methods: A total of 440 male problem drinkers (M_{age} = 44.5 years, SD = 9.45) were recruited from nine main psychiatric hospitals of northern China during acute alcohol withdrawal. Blood samples were collected for genotyping, self-reported anxiety symptoms, and levels of alcohol dependence were assessed.

Results: Results indicated that the *POMC* rs2071345 polymorphism significantly moderated anxiety symptoms associated with alcohol dependence. A region of significance (RoS) test showed that male problem drinkers with T allele were more likely to experience more anxiety symptoms than those with CC homozygote when the standardized score of concurrent alcohol dependence was above 0.31. Confirmatory model evaluation indicated that the interaction effect involving *POMC* gene polymorphism conformed to the diathesis-stress model rather than differential-susceptibility model of person × environment interaction.

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Minglong Shao,
Second Affiliated Hospital of Xinxiang Medical University, China

***Correspondence:**
Li Chen
psychologychenli@163.com
Fan Wang
FanWang@bjmu.edu.cn
Yu-Hsin Chen
yuhchen@kean.edu

[†]*These authors have contributed equally to this work*

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Conclusions: This study suggested that the SNP in *POMC* rs2071345 was associated with alcohol dependence in anxiety symptoms of male problem drinkers and further provided evidence in support of the diathesis-stress hypothesis of alcohol dependence in terms of anxiety symptoms.

Keywords: alcohol dependence, *POMC* gene polymorphism, rs2071345, anxiety, diathesis-stress model

INTRODUCTION

Alcohol dependence is a chronic, relapsing neuropsychiatric disorder that results from a variety of genetic, psychosocial, and environmental factors, causing physical and mental diseases such as anxiety and depression (1). A global prevalence of alcohol dependence among 2.4 billion alcohol drinkers was up to 39.60%, which represents a considerable public health burden (2). Moreover, alcohol dependence shares a high co-morbidity with anxiety-related disorders (3, 4). Furthermore, those with comorbid anxiety and alcohol dependence typically have a poorer psychosocial functioning, physical health, and ultimately cause serious consequences including divorce, crime, self-harm, and suicide tendency, especially in the context of alcohol withdrawal (5, 6). Therefore, it is an urgent issue to investigate the association between alcohol dependence and anxiety in the context of alcohol withdrawal among problem drinkers.

However, the presence and extent of anxiety under the context of alcohol withdrawal, varies greatly among problem drinkers, which points out that these external stressors are neither a necessary nor a sufficient cause for psychopathology. A meta-analysis of twin studies demonstrated that the genetic influences could explain 0.32–0.43 of the variance in anxiety (7). Thus, genetic vulnerability that may influence the environmental contributors on anxiety has attracted more attention. A previous study has demonstrated that participants with FKBP5 polymorphism were more likely to exhibit anxiety when exposed to childhood trauma (8). Moreover, another study had found that SLC1A1, GSTZ1, and CALCRL gene polymorphisms, in association with harsh punitive parenting, may contribute to social anxiety in adolescence (9). Furthermore, existing G × E research has largely focused on the modulator role of gene in negative emotions caused by early stressful experiences (i.e., childhood abuse, ignoring and maltreatment) (10–13), whereas few studies have examined the interaction of gene and current stressful experiences (acute alcohol withdrawal). These findings highlight that the interaction between genetic vulnerability and adverse environmental factors (G × E) is increasingly emphasized as an important mechanism in understanding the link between alcohol dependence and anxiety.

Proopiomelanocortin (*POMC*), a gene that located in the arcuate nucleus, responds to metabolic stress, such as food deprivation and glucoprivation (14, 15), and psychological stress (16), which appears to be a strong candidate for this interaction. The *POMC* processes many functionally different peptides, and among these biologically active peptides, ACTH and β-endorphin (β-END) are two principal components of the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is known as the major brain circuitry that regulates the neuroendocrine response to stress (17). β-END is a member of opioid peptides that are widely and differentially distributed throughout the nervous system, which has been implicated in a variety of behaviors including the regulation of pain and reward, as well as processes associated with stress, fear, or anxiety (18). In the central nervous system, β-END contributes to the positive reinforcement and motivational properties of drugs of abuse. In addition, there is an evidence that lowered plasma β-END during alcohol withdrawal may contribute to their experienced anxiety (19, 20). Moreover, it is reported that the *POMC* gene expression is associated with anxiety-like behavior in those that experienced maternal deprivation (21). Another study found that *POMC* gene polymorphisms related to alcohol dependence (22). In addition, Chang et al. (23) investigated the role of gene–environment interaction between *POMC* rs2071345 polymorphism and stressful life events and found that *POMC* rs2071345 polymorphism, via an interaction with stressful life events, are associated with antidepressant treatment outcomes in major depressive disorder patients.

To date, few studies have examined the exact form of the interaction between the environment and *POMC* gene polymorphisms. There are two models can explain the potential role of genetic factors in G × E interactions: the diathesis-stress model and the differential susceptibility model. In the diathesis-stress model, carriers of 'risk' genotype variants when exposed to adverse environmental experiences would be more likely to develop the negative outcome (24, 25). While the differential susceptibility model suggests that 'risk' genotypes would be better considered 'plasticity' or 'susceptibility' genotypes, and that carriers would be susceptible to both adverse and enriched environments, for better and for worse (24, 26, 27).

Therefore, this study aimed to examine the moderating role of *POMC* rs2071345 polymorphism on the association of alcohol dependence and anxiety among problem drinkers, and further explored the nature of *POMC* rs2071345 × alcohol dependence by testing two competing models: diathesis-stress vs. differential susceptibility model.

METHODS

Participants and Procedure

Participants were 440 male problem drinkers (18 years and above) recruited from Psychiatric Hospitals in northern China. All the male problem drinkers were hospitalized for alcohol dependence, meeting the criteria according to the DSM-IV. Moreover, general mental assessments including anxiety

symptoms were carried out by the admitting physician before recruiting into hospital. Among the participants, no outstanding anxiety symptoms were initially found. All participants were of Chinese Han ethnicity. The mean age of the participants was 44.15 years (SD = 9.45, range = 20–67 years). Most of the participants (65.45%) had earned a junior high school education level, and the average time in schooling was 10.64 years (SD = 2.87, range = 5–17 years).

Exclusion criteria for participants included a history of other substance use disorders beyond nicotine, which was allowed, presence of serious liver or kidney disease, history of serious neuropsychic diseases illness, or lacking a clear understanding of informed consent.

All study procedures were approved by the Ethics Committee of Peking University Health Science Center. First, participants were provided with a detailed description of the study procedures by the trained research investigators. Second, written informed consent from participants was obtained prior to data collection (98.89% agreed to participate in our study). Then, participants were asked to complete a series of questionnaires in a quiet ward. Finally, participants provided a blood sample for DNA extraction, checked one by one on location by research investigators. Genomic DNA was extracted from peripheral blood.

Measures

Assessment of Alcohol Dependence

A modified Chinese version of the Michigan Alcoholism Screening Test (MAST) (28) was used to measure the severity of symptoms associated with disordered alcohol use. Each of 24 items on the MAST is rated on a 4-point scale ranging from "not at all" (value = 0) to "extremely" (value = 4). The sum of the response scores can range from 0 to 96. Higher scores indicate more severe alcohol dependence. The Cronbach's alpha for the whole scale was 0.90 (29).

Assessment of Anxiety

The 20-item Self-Rating Anxiety Scale (SAS) (30) was used to assess the severity of depression anxiety. In this scale, participants are asked to respond how often he has experienced each symptom on a 4-point scale ranging from 1 (none or a little of the time) to 4 (most or all the time). The total sum of all the items was used in the analyses; higher scores indicate greater severity of anxiety. The SAS has high internal-consistency reliability, with alpha values of 0.82 (31).

Genotyping

Genomic DNA was extracted from 5 ml of peripheral blood of each participant using the salting-out method. The *POMC* rs2071345 were conducted using the Taqman SNP genotyping assay (ABI: Applied Biosystems Inc., Foster City, CA, USA). The primers and probes of SNPs were analyzed from ABI assay on demand kit. Reactions were carried out according to the manufacturer's protocol. All laboratory procedures were carried out in a manner blind to case-control status. The conditions of PCR were as follows: 50°C for 2 min, 95°C for 10 min, followed by 50 cycles of 95°C for 15 s and 60°C for 1 min. Ten percent of the DNA samples were duplicated randomly and tested, and no-fault genotyping was found.

Statistical Analysis

Firstly, we tested the genotype distributions of *POMC* rs2071345 genotyping for Hardy-Weinberg equilibrium (HWE) proportions by using the χ^2 test (32) and Pearson correlation analyses were conducted to examine correlations between *POMC* rs2071345, age, educational years, alcohol dependence and anxiety. Consistent with other research, CT and TT genotypes was collapsed into T-allele group and coded as 1, CC genotype was coded as 0.

Secondly, we conducted the traditional linear regression to examine the interactive effect between the *POMC* rs2071345 polymorphism and alcohol dependence on male problem drinkers' anxiety. When significant interactions were found, *post-hoc* probing of significant interactions is conducted using regions of significance (RoS) analysis (33). RoS analysis provides the lower and higher bound where the association between *POMC* rs2071345 and alcohol dependence is significant for estimating the forms of G×E interaction. Thirdly, re-parameterized regression model, a newly developed approach proposed by Widaman et al. (34), was conducted to examine the nature of G×E interaction. The models were as follows:

$$Y \begin{cases} \text{Group}: \text{D} = 1 \quad B_0 + B_2(\text{X} - \text{C}) + B_3X_2 + B_4X_3 + E \\ \text{Group}: \text{D} = 0 \quad B_0 + B_1(\text{X} - \text{C}) + B_3X_2 + B_4X_3 + E \end{cases}$$

Here Y is the dependent variable of anxiety, X represents alcohol dependence, X_2 and X_3 are controlled variables: age and educational years, group is the different allelic group; C is the crossover point where the slopes of two genotype groups cross. The crossover point C estimate and confidence interval estimate can be determined whether the interaction between the *POMC* rs2071345 polymorphism and alcohol dependence is consistent with the differential susceptibility model or the diathesis-stress model. If the point estimation and 95% confidential interval of C fall at the maximum value of alcohol dependence, the interaction is consistent with diathesis stress model. In contrast, if the estimate of C is within the range of alcohol dependence, the form of interaction is consistent with differential susceptibility model. As diathesis-stress model and differential susceptibility model can be further subdivided into "strong" and "weak" version. Strong versions assume that only individuals with "risk/plasticity allele" are affected by environment, while the weak versions assume that both allele carriers are affected by environment but "non-risk/non-plasticity allele" carriers are less affected by environment than "risk/plasticity allele" carriers (35). These models are nested within each other. Thus, we used an F test to examine whether one model explained significantly more variance than another one. In addition, for non-nested models, Akaike information criterion (AIC) and Bayesian information criterion (BIC) was used to evaluate which model fits better. Lower scores indicated better fitting.

TABLE 1 | Descriptive statistics and correlations between the variables.

	rs2071345	Age	Educational years	Alcohol dependence	Anxiety
rs2071345	1				
Age	0.02 (0.02)	1			
Educational years	−0.08 (−0.09)	−0.39***	1		
Alcohol dependence	0.04 (0.02)	0.17***	−0.18***	1	
Anxiety	0.01 (0.01)	0.03	−0.13**	0.46***	1
M	(–)	44.15	10.64	9.43	34.19
SD	(–)	9.45	2.87	5.38	9.41

$^{**}p < 0.01$, $^{***}p < 0.001$.

TABLE 2 | Interaction between POMC rs2071345 and alcohol dependence on anxiety.

Variables	Anxiety					
	ΔR^2	*B(SE)*	*B*	*t*	*p*	95%CI
Age	0.02	0.01 (0.01)	0.02	0.04	0.66	[−0.01, 0.01]
Educational years		0.05 (0.02)	0.14	2.68	0.01	[0.01, 0.08]
Alcohol dependence	0.20	0.46 (0.04)	0.46	10.56	<0.001	[0.37, 0.54]
rs2071345		0.03 (0.09)	0.02	0.40	0.69	[−0.13, 0.20]
Alcohol dependence × rs2071345	0.01	0.19 (0.09)	0.15	2.11	0.03	[0.01, 0.36]

RESULTS

Descriptive Statistics

Of the 440 male problem drinkers, 202 (45.91 %) were CC homozygotes, 186 (42.27%) were CT heterozygotes, and 52 (11.82 %) were TT homozygotes. Genotype distribution for *POMC* rs2071345 was consistent with Hardy–Weinberg equilibrium ($\chi^2 = 0.83$, $p > 0.05$). We conducted a series of *t*-tests to examine whether male problem drinkers differed by genotype between alcohol dependence and anxiety symptoms. Results indicated that no significant differences were found (alcohol dependence: $t = 0.85$; anxiety: $t = 0.14$, $p(s) > 0.05$).

The descriptive statistics of research variables are shown in **Table 1**. Anxiety ($r = 0.46$, $p < 0.01$) was positively correlated with alcohol dependence, while the education year ($r = -0.18$, $p < 0.01$) was negatively correlated with alcohol dependence. Besides, there were no significant relationships between the polymorphism *POMC* rs2071345 and all the other variables.

Interactions Between *POMC* rs2071345 Genotype, Alcohol Dependence, and Anxiety

We conducted traditional hierarchical regression analysis to identify the interaction between the *POMC* rs2071345 genotype and alcohol dependence on anxiety. There was a main effect of alcohol dependence on anxiety ($p < 0.001$), such that more alcohol dependence was associated with higher levels of anxiety. There were no significant main effects of *POMC* rs2071345 genotype on anxiety ($p > 0.05$). The interaction between the *POMC* rs2071345 genotype and alcohol dependence was significant ($p = 0.03$).

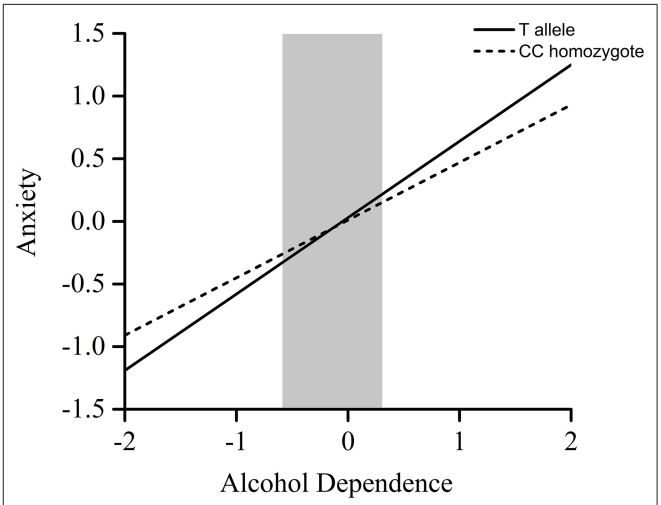

FIGURE 1 | RoS test on anxiety from alcohol dependence in *POMC* rs2071345 allelic groups. *Gray shaded* area represents 95% CI of the crossover point *C* of the interaction on the alcohol dependence axis. Ninety-five percent CI of *C* ranged from −0.59 to 0.31.

Furthermore, the RoS test was conducted to interpret the interaction effect. The slopes for alcohol-dependence on anxiety were as follows: T allele carriers, $\beta = 0.61$, $t = 13.01$, $p < 0.001$; CC homozygote carriers, $\beta = 0.46$, $t = 14.55$, $p < 0.001$ (**Table 2**). The lower and upper bounds of regions of significance were −0.59 and 0.31. That is, subjects with T allele were more likely to experience more anxiety symptoms than subjects with CC homozygote when the standardized score of concurrent alcohol dependence was above 0.31 (see **Figure 1**).

TABLE 3 | Re-parameterized regression analyses for participants.

Parameter	Differential susceptibility		Diathesis-stress	
	Strong: model A	Weak: model B	Strong: model C	Weak: model D
B_0	−0.60 (0.34)	−0.71 (0.40)	−0.31 (0.35)	0.07 (0.33)
B_1	0.00 (–)	0.34 (0.07)***	0.00 (–)	0.47 (0.05)***
C	−0.03 (0.17)	−0.17 (0.47)	1.57 (–)	1.57 (–)
95%CI of C	[−0.36, 0.30]	[−1.09, 0.75]	(–)	(–)
B_2	0.52 (0.06)***	0.53 (0.05)***	0.25 (0.04)***	0.43 (0.05)***
B_3	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)
B_4	0.03 (0.02)	0.03 (0.02)	0.03 (0.02)	0.03 (0.02)
R^2	0.18	0.23	0.10	0.22
F(df)	24.20*** (4,435)	31.68*** (5,434)	15.50*** (3,436)	30.40*** (4,435)
F vs. A(df)	(–)	24.44*** (1,434)	45.54*** (1,434)	(–)
F vs. B(df)	24.44*** (1,434)	(–)	36.22*** (2,434)	4.01* (1,434)
AIC	1171.26	1149.16	1213.07	1151.21
BIC	1195.78	1177.77	1233.51	1175.73

****p < 0.001.*

Re-parameterized Regression Analysis

In order to test the specific form of G × E, re-parameterized regression analysis was conducted by using the regression models adapted from Belsky et al. (36). Results involving rs2071345 × environment (severity of alcohol dependence) interaction (see **Table 3**) showed that the weak differential susceptibility model (model B) had strong fit to data ($R^2 = 0.23$, $p < 0.001$), in which the slopes for severity of alcohol dependence in CC homozygote group ($B_1 = 0.34$, $SE = 0.07$, $p < 0.001$) and T allele group (B_2=0.53, $SE = 0.05$, $p < 0.001$) were significant. The estimated point and 95% CI of crossover point C both fell within the range of alcohol dependence C = −0.17 (SE = 0.47), 95%CI = [−1.09, 0.75]. Furthermore, the weak differential susceptibility model could explain more variance ($\Delta R^2 = 0.05$, $p < 0.001$) by adding one more parameter than the strong differential susceptibility model, explaining more variance ($\Delta R^2 = 0.13$, $p < 0.001$) by adding two more parameters than the strong diathesis-stress model, explaining more variance ($\Delta R^2 = 0.01$, $p < 0.05$) by adding one more parameter than the weak diathesis-stress model, which demonstrated that CC homozygote were non-plasticity homozygote and T allele was plasticity allele in anxiety.

DISCUSSION

We examined the interactions between *POMC* rs2071345 polymorphism with alcohol dependence on anxiety symptoms during acute alcohol withdrawal, and further explored the nature of *POMC* rs2071345 × alcohol dependence by testing two competing models: diathesis-stress vs. differential susceptibility.

First, as expected, significant concurrent associations were found between alcohol dependence severity and anxiety symptoms during acute alcohol withdrawal, and further analysis revealed that the severity of alcohol dependence increased the risk of anxiety symptoms. It is in alignment with previous studies (37–40). Further, we found that the *POMC* rs2071345 is unexpectedly associated with the severity of anxiety symptoms during acute alcohol withdrawal, which previously has not been reported. Considering the location of the variant in the genomic structure of the *POMC* gene, rs2071345 may be involved in the regulation of transcription factor binding, which would need to be confirmed by further molecular biological experiments.

Next, in the anxiety model, *POMC* rs2071345 polymorphism significantly moderates the association between severity of alcohol dependence and anxiety symptoms during acute alcohol withdrawal, confirming the hypothesis we proposed and supporting the diathesis-stress theory. Furthermore, all the indexes in the re-parameterized regressions indicated that the *POMC* rs2071345 polymorphism × environment (alcohol problem severity) interactions were consistent with the weak diathesis-stress model among male problem drinkers with anxiety symptoms. Specifically, compared to adults with CC homozygote of *POMC* rs2071345, those with the T allele reported more anxiety symptoms when experiencing more severe alcohol withdrawal as measured by alcohol problem severity. That is, T allele of POMC rs2071345 may be a genetic risk gene, affecting the stability of transcribed mRNA which is one of the main mechanisms of adaptation to stress (41). The findings suggest that CC homozygote of *POMC* rs2071345 may buffer the effects of alcohol dependence, such that carriers of the CC homozygote of *POMC* rs2071345 may be better equipped to handle problematic situations and challenges that arise from a higher level of alcohol dependence or other stressors. Alternatively, carriers of the CC homozygote of *POMC* rs2071345 may not need to rely on lower level of alcohol dependence or be as sensitive to lower level of alcohol dependence as those with T allele of *POMC* rs2071345, suggesting higher level of alcohol dependence may not confer the same level of risk among carriers of the CC homozygote of *POMC* rs2071345. These findings together suggest that the stress from different sources may interact with different vulnerability genes, even belonging to the same functional group. As such, our study provides new evidence for the moderating function of the *POMC* polymorphism in the association between current stress as measured by the severity of alcohol dependence during withdrawal and anxiety symptoms.

The current study contributes to the existing literature by providing valuable information about the underlying etiology of alcohol dependence and anxiety during acute alcohol withdrawal and has several notable strengths. First, to our knowledge, this study is the first to examine the G × E interactions on this *POMC* polymorphism, alcohol dependence severity and anxiety during acute alcohol withdrawal, providing preliminary evidence for the distinct G × E interactions on alcohol dependence and anxiety. Further, with the newly developed approach of regions of significance (RoS) analysis, the present study explored whether the G × E interactions would be consistent with the diathesis-stress model or the differential susceptibility model and determined the range of values of the environment where the environment-predicting-outcome regression lines significantly differ from each other (42). Finally, by focusing on the re-parameterized regression analysis, the present study is likely to maximize the statistical power by aligning analyses with hypotheses of interest and can directly compare and evaluate different G × E hypotheses (36).

There are several limitations in the present study. First, only males were investigated. Previous work has demonstrated differences between men and women in regard of OXTR polymorphisms (43–45), which highlights the importance of further studies of sex differences concerning differential diathesis. Second, our data on the associations between genes, alcohol dependence severity, and anxiety were cross-sectional, which did not allow for cross-lagged relationships between alcohol dependence severity and anxiety across different genotypes to be tested. Therefore, future research with longitudinal design will be needed to explore the G × E interaction across different genotypes. Third, an additional uncontrolled factor is the possibility that various withdrawal symptoms may contribute to anxiety, which could be explored in further research. Fourth, the current study only estimated the interactions between the *POMC* rs2071345 polymorphism with alcohol problem severity on anxiety symptoms, which is another limitation. Previous work demonstrated that β-END differentially affected anxiety and depression (46), highlighting the importance of further studies of the interactions between depression, *POMC* rs2071345 polymorphisms, and alcohol dependence.

CONCLUSION

The present study provides preliminary evidence for distinct G × E interactions such that the *POMC* rs2071345 polymorphism interacted with alcohol dependence on male problem drinkers' anxiety during acute alcohol withdraw. These findings contribute to a more comprehensive view of the complex genetic etiology of problem drinkers' negative emotions during alcohol withdrawal.

With regard to the nature of G × E interactions on anxiety observed in the present study, our findings were in accordance with the diathesis-stress hypothesis. These empirical findings have important implications for interpreting genetic moderation of alcohol problem severity on individual differences of adults' negative emotion during alcohol withdrawal. The findings might also encourage more work at the molecular level on the role of the underlying mechanisms in response to environment and in modulating anxiety, especially in relation to functional studies of neural systems.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Peking University Health Science Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LC, FW, and Y-HC designed the study. LH, LW, YL, and FW contributed to data acquisition. LH, LW, MN, and WW drafted the manuscript. LH, LW, MN, FZ, YZ, and GS participated in data analysis and interpretation. All authors read and approved the final manuscript.

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Lifestyle and Social Factors Exacerbated on the Prevalence of Mood Disorders and Functional Dyspepsia Among Neonatal Nurses in China

Zhen-peng Huang[1†], Fang Huang[2,1†], Mei-jun Wang[2], Chuan-zhuang Tang[2], Jiang-ping Huang[3], Juan Ling[4], Shan-e Li[5], Su-qiao Wei[5], Hai-hua Lei[6], Jing-jing Li[7] and Xiu Lan[2]*

[1] Faculty of Nursing, Guangxi University of Chinese Medicine, Nanning, China, [2] Department of Neonatology, Nanning Maternal and Child Health Hospital, Nanning, China, [3] Department of Community, Nanning Maternal and Child Health Hospital, Nanning, China, [4] Department of Neonatology, Guangxi Zhuang Autonomous Region Maternal and Child Health Hospital, Nanning, China, [5] Department of Neonatology, The Second Nanning People's Hospital, Nanning, China, [6] Department of Neonatology, Guangxi International Zhuang Medicine Hospital, Nanning, China, [7] Department of Neonatology, The First People's Hospital of Nanning, Nanning, China

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***Correspondence:**
Zhen-peng Huang
huang_zhenpeng@126.com

†These authors have contributed equally to this work

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Background: Nursing is a high-stress occupation that can have an impact on mental health, particularly for neonatal nurses. Job-related stress factors and work-related behaviors have played a critical role in nurses' mental health. This study aimed to explore the prevalence of mood disorders and the impact of social factors, lifestyle on mood disorders among neonatal nurses.

Methods: A total of 260 participants comprising neonatal nurses and nurses who work in neonatal intensive care units (NICU) were recruited. Data were collected using a validated generalized anxiety disorder questionnaire, patient health questionnaire-9, Pittsburgh sleep quality index, and social factors and lifestyle assessments.

Results: In total, 49.23% of neonatal nurses exhibited mood disorders, particularly a combination of depression and anxiety. Female, poor interpersonal relationships and unhappy marital status, preference for smoking, alcohol, irregular diet, and poor sleep were common in neonatology nurses who exhibited mood disorders; preference for coffee and tea were lower in neonatology nurses without mood disorders (all $P < 0.05$). Interpersonal relationships, marital status, irregular diet, and poor sleep were independent factors associated with mood disorders among neonatal nurses (all $P < 0.05$). Mood disorders presented as functional dyspepsia (FD) among 50.78% of the participants ($P < 0.05$). Poor sleep and preference for smoking were common among neonatal nurses who had FD with mood disorders (all $P < 0.05$). Furthermore, the preference for sugary beverages was lower in participants with FD and mood disorders ($P < 0.05$). Poor sleep was independently associated with FD with mood disorders in neonatology nurses ($P < 0.05$).

Conclusion: Prevalence of anxiety and depression was higher among neonatal nurses. Furthermore, most cases of mood disorders presented as FD. Thus, social factors and lifestyle have an impact on mood disorders which can manifest through somatic symptoms.

Keywords: neonatal nurses, anxiety, depression, functional dyspepsia, social factors, lifestyles

INTRODUCTION

Nurses play an important role in the healthcare workforce. In addition to providing health care, nurses also assist patients during rehabilitation and impart health education to patients (1). Nursing is a high-stress occupation involving night-shift work schedules, addressing different patient needs, and irregular lifestyles that can have a severe impact on nurses' mental health (2, 3). Newborn patients are often susceptible to experiencing respiratory, nutrition, feeding, and neurologic injury problems. Furthermore, the parents also face an increased risk of perinatal mood and anxiety disorders (4, 5). Particularly, the challenges faced by nurses who work in the neonatal department and neonatal intensive care unit (NICU) are more severe and stressful, thereby significantly effecting their mental health.

Psychosomatic diseases can result from the interaction of biological, psychological, and social factors (6). Anxiety and depression are the most prevalent mood disorders associated with psychosomatic diseases (7). Psychological indicators for distress include, but are not limited to, disturbances in sleep and appetite. Furthermore, physical effects experienced by nurses may include the increased risk of functional dyspepsia (FD) (8, 9). Moreover, chronic stress may lead to or exacerbate maladaptive behaviors such as smoking, alcohol consumption, and irregular diet (10, 11). Additionally, job-related stress factors, work-related behaviors, and past experiences also play a critical role in nurses' mental health (12, 13).

Recent studies revealed a high prevalence of mood disorders, including anxiety and depression, among nurses worldwide (14, 15). Approximately 41.1% and 35.88% of nurses in China experienced anxiety and depression, respectively. (16, 17). However, the prevalence of anxiety and depression among neonatal department nurses and NICU nurses is still unknown. Furthermore, the effects of social factors and lifestyles on anxiety and depression among neonatal nurses remain unknown. Thus, this study aimed to explore the prevalence of anxiety and depression among neonatal nurses. Furthermore, this study analyzed the impact of social factors and lifestyle on mood disorders among neonatal nurses.

MATERIALS AND METHODS

Study Design and Participants

This cross-sectional study was conducted using several questionnaires. The snowball sampling strategy was used to recruit the participants. The inclusion criteria were nurses who have no previous history of psychiatric diseases and who worked in the Department of Neonatology and the NICU of 12 general hospitals and 2 specialized hospitals affiliated to universities in Nanning city, Guangxi province, China. The questionnaire surveys were administered either by head nurses or neonatal nurses from January 1, 2022, to February 28, 2022. During this period, the participants could answer the anonymous questionnaire survey at any time; however, they could take the questionnaire survey only once and were required to answer all questions within 30 min. Written informed consent was provided by all participants before participating in the study; the study was approved by the Institutional Ethical Committee of Guangxi University of Chinese Medicine.

Questionnaires

A validated Chinese version of a 7-item generalized anxiety disorder questionnaire (GAD-7) was administered to all the participants to identify the participants with generalized anxiety disorder, as defined by the DSM-5 (18). Researchers calculated each item score based on the following scale: a total score above five points can be identified as anxiety; namely, five–nine points indicated mild anxiety, 10–14 points indicated moderate anxiety, and scores higher than 15 points indicated severe anxiety.

The Chinese version of the Patient Health questionnaire-9 (PHQ-9) was used to screen the participants for depression, as defined by the DSM-5 (19). Researchers calculated each item score of the PHQ-9 based on the following scale: a total score above five points can be identified as depression. Specifically, five–nine points indicated mild depression, 10–14 points indicated moderate depression, 15–19 points indicated severe depression, whereas scores >20 points indicated severe anxiety.

The Chinese version of the Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep quality. Sleep quality can be analyzed by measuring seven components over a period of 1 month, namely, subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Researchers calculated each item score of the PSQI, as well as an overall sum of at least five indicators of poor sleep (20). Participants were excluded if they experienced any additional diseases according to the results of various tests, namely, electrocardiogram, abdominal ultrasound, X-ray, and blood tests from physical examinations conducted during annual check-ups. The endoscopy and diagnoses procedures were performed by a gastroenterologist.

The Rome IV diagnostic questionnaire for adult's functional gastrointestinal disorders identifies FD gastrointestinal symptoms among participants. Rome IV diagnostic questionnaire for measure postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS), including postprandial fullness, early satiation, epigastric pain occurred in the last 3 months, and course of disease at least 6 months (21).

Social factors dates were self-reported by all participants as observed in their responses to the 11 items included in the questionnaires. These items comprise educational level (high school, or junior college, or undergraduate, or postgraduate), technical title (junior, or intermediate, or senior), years of working (1 year below, 1–5 years, 6–10 years, 10 years above), continuation of education (yes or no), head nurses (yes or no), interpersonal relationships (dissatisfaction, on average or satisfaction), previous work experience in the field of emerging infectious diseases (yes or no), marital status (single, married or divorced), spouse occupation (health care profession or non-healthcare profession), fertility status (nullipara, first births, second births or third births or above) and support from parents (yes or no).

Lifestyle dates were self-reported by all participants and the four items included in the questionnaire were preference for smoking (yes or no), alcoholism (yes or no), diet preference (coffee, tea, sugary beverages, chocolate, spicy, raw, deep-fried, hot, dairy products), and irregular diet (yes or no).

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics version 25.0 to assess the study dates. Continuous variables such as age are presented as mean ± standard deviation. Categorical variables such as gender, diet preference and so on are expressed as proportions and percentages. The associations between relevant factors and study outcomes are presented as odds ratios (OR) and 95% confidence intervals (95% CI). Continuous variables were compared using Student's *t-test*. Categorical variables used x^2 test, Fisher's exact test, or the *Ridit* test, as appropriate. Multivariable logistic regression analyses were used to identify the independent social and lifestyle factors associated with mood disorders. A two-sided *P*-value less than 0.05 was regarded as statistically significant.

RESULTS

Prevalence of Mood Disorders Among Neonatal Nurses

A total of 260 nurses who had worked in the Department of Neonatology or the NICU of hospitals affiliated to universities participated in this study, including 8 (3.08%) males and 252 (96.92%) females, with ages varying between 20–48 years (30.0885 ± 5.43156).

Neonatal nurses' susceptibility to suffering from mood disorders, such as anxiety and depression has increased. In this study, 128 (49.23%) participants were affected by mood disorders, including anxiety or depression, with most nurses in neonatal suffering from mood disorders. Furthermore, 17 (13.28%) nurses had anxiety, whereas 29 (22.66%) nurses had depression, with 82 (64.06%) nurses exhibiting both anxiety and depression. Moreover, most participants with mood disorders exhibited mild anxiety and depression (**Table 1**).

TABLE 1 | Prevalence of mood disorders among neonatal nurses (%).

Degree	Anxiety	Depression
Mild	74 (28.46)	77 (29.62)
Moderate	16 (6.15)	23 (8.85)
Moderate-severe	–	6 (2.31)
Severe	9 (5.45)	5 (1.92)
Total	99 (29.09)	111 (42.69)

Effect of Social Factors on Neonatal Nurses With Mood Disorders

Various social factors have an impact on the mental health of neonatal nurses. This study confirmed that most of the nurses with mood disorders were female and had poor interpersonal relationships and an unhappy marital status. The prevalence was significantly higher than that of neonatal nurses without mood disorders (all $P < 0.05$) (**Table 2**).

Effect of Different Lifestyles on Neonatal Nurses With Mood Disorders

This study also confirmed that different lifestyles can affect the mental health of neonatal nurses. Specifically, smoking, alcohol consumption, and irregular diet were common among participants with mood disorders. Preference for both coffee and tea were lower among participants with mood disorders as opposed to the participants without (all $P < 0.05$) (**Table 2**).

Poor sleep has contributed toward mood disorders, as well as subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, daytime dysfunction, and total PSQI scores among neonatal nurses with mood disorders, which were all higher than those without mood disorders. The differences in subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, daytime dysfunction, and total PSQI scores (all $P < 0.05$) were statistically significant (**Table 3** and **Figure 1**).

Multivariable Logistic Regression Analysis on Independent Factors for Mood Disorders

Interpersonal relationships (OR = 0.530, 95%CI 0.326–0.860), marital status (OR = 1.849, 95%CI 1.763–1.940), irregular diet (OR = 1.972, 95%CI 1.880–2.069) and poor sleep (OR = 7.295, 95%CI 6.850–7.770) were selected as independent factors associated with mood disorders among neonatal nurses (all $P < 0.05$) (**Table 4**). These results suggest that good interpersonal relationships are an independent protective factor for mood disorders in neonatal nurses. Unhappy marriage or divorce, irregular diet, and poor sleep are independent risk factors for mood disorders in neonatal nurses.

TABLE 2 | Demographic and social factors among neonatal nurses in mood disorders.

Variables	Category	Nurses in mood disorders (%)	Nurses without mood disorders (%)	
Gender	Male	1 (0.78)	7 (5.30)	
	Female	127 (99.22)	125 (94.70)	$x^2 = 105.679$, $P = 0.0000$
Age		30.6484 ± 5.02997	29.5455 ± 5.76163	$t = 1.646$, $P = 0.101$
Educational level	High school	1 (0.78)	3 (2.27)	
	Junior college	20 (15.63)	20 (15.15)	
	Undergraduate	106 (82.81)	108 (81.82)	
	Postgraduate	1 (0.78)	1 (0.76)	$x^2 = 0.9574$, $P = 0.8116$
Technical level	Junior	85 (66.41)	92 (69.70)	
	Intermediate	42 (32.81)	36 (27.27)	
	Senior	1 (0.78)	4 (3.03)	$x^2 = 2.4774$, $P = 0.2898$
Years of working	1 year below	5 (3.91)	10 (7.56)	
	1–5 years	42 (32.81)	47 (35.61)	
	6–10 years	42 (32.81)	41 (31.06)	
	10 years above	39 (30.47)	34 (25.77)	$x^2 = 2.2411$, $P = 0.5239$
Taking continuing education		47 (36.72)	54 (40.91)	$x2 = 0.3201$, $P = 0.5715$
Head nurse		3 (2.34)	6 (4.55)	$x^2 = 0.3989$, $P = 0.5276$
Interpersonal relationship	Dissatisfaction	4 (3.13)	1 (0.76)	
	On average	56 (43.75)	40 (30.30)	
	Satisfaction	68 (53.12)	91 (68.94)	$x^2 = 7.7340$, $P = 0.0209$
Previous work experience in anti-COVID-19		52 (40.63)	46 (34.85)	$x^2 = 0.6937$, $P = 0.4049$
Marital status	Single	43 (33.59)	66 (50)	
	Married	82 (64.06)	66 (50)	
	Divorced	3 (2.34)	0 (0)	$x^2 = 5.2409$, $P = 0.0221$
Spouse occupation	Health Care Profession	30 (35.29)	30 (45.45)	
	Non-health Care Profession	55 (64.71)	36 (54.56)	$x^2 = 1.2055$, $P = 0.2722$
Fertility status	Nullipara	63 (49.21)	74 (56.06)	
	First births	36 (28.13)	30 (22.73)	
	Second births	28 (21.88)	27 (20.45)	$x^2 = 1.3856$, $P = 0.7089$
	Third births or above	1 (0.78)	1 (0.76)	
Support parents		98 (76.56)	94 (71.21)	$x^2 = 0.9632$, $P = 0.3264$

TABLE 3 | Lifestyles among neonatal nurses in mood disorders.

Variables	Nurses in mood disorders (%)	Nurses without mood disorders (%)	
Smoking	3 (2.34)	0 (0)	$x^2 = 123.0080$, $P = 0.0000$
Alcohol	7 (5.47)	3 (2.27)	$x^2 = 110.3952$, $P = 0.0000$
Diet preference			
Coffee	34 (26.56)	42 (31.82)	$x^2 = 19.1250$, $P = 0.0000$
Tea	29 (21.97)	32 (24.24)	$x^2 = 33.2519$, $P = 0.0000$
Sugary beverages	71 (55.47)	88 (66.67)	$x^2 = 3.4302$, $P = 0.0640$
Chocolate	45 (55.47)	88 (66.67)	$x^2 = 0.0029$, $P = 0.9570$
Irregular diet	85 (66.41)	62 (46.70)	$x^2 = 9.2155$, P=0.0024
Poor sleep	113 (88.28)	75(56.82)	$x^2 = 30.5748$, $P = 0.0000$

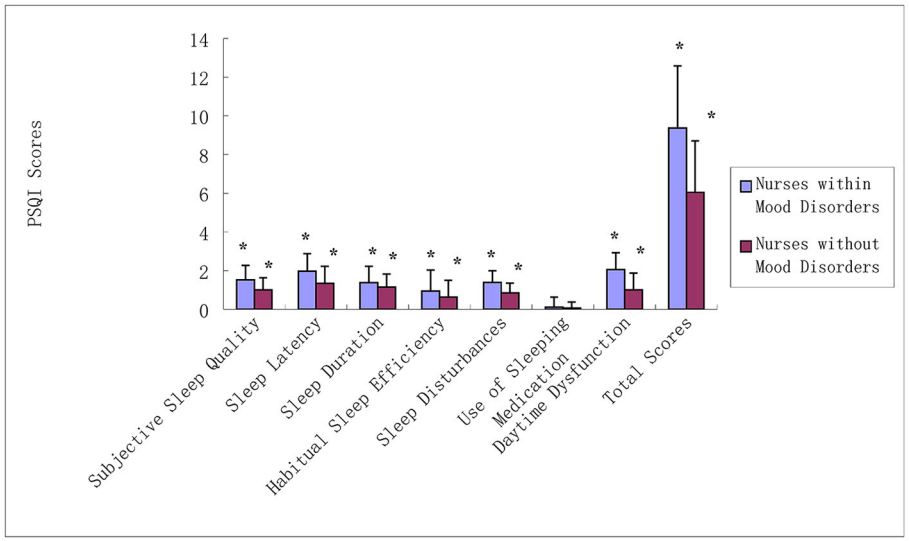


FIGURE 1 | PSQI scores between neonatal nurses and mood disorders. All part of total PSQI scores and total PSQI scores among neonatal nurses with mood disorders were all higher than those without mood disorders. The differences in subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, daytime dysfunction, and total PSQI scores (all $P < 0.05$).

TABLE 4 | Multivariate logistic regression analyses on selected factors associated with mood disorders.

Selected factors	Mood disorders		
	OR	95%CI	*P*-value
Gender	3.936	(3.337, 4.643)	0.373
Interpersonal relationship	0.530	(0.326, 0.860)	0.044
Marital status	1.849	(1.763, 1.940)	0.009
Alcohol	2.028	(1.770, 2.324)	0.375
Coffee	0.757	(0.719, 0.798)	0.253
Tea	1.054	(0.995, 1.116)	0.838
Irregular diet	1.972	(1.880, 2.069)	0.025
Poor sleep	7.295	(6.850, 7.770)	0.000

TABLE 5 | Prevalence of FD in mood disorders among neonatal nurses (%).

Variables	Nurses in mood disorders	Nurses without mood disorders
FD*	65 (50.78)	14 (11.48)
EPS#	17 (26.15)	1 (7.14)
PDS#	35 (53.85)	11 (78.57)
Both EPS and PDS#	13 (20)	2 (14.29)

**Prevalence of FD between nurses within and without mood disorders: $x^2 = 42.8479$, $P = 0.000$; #Prevalence of FD subtypes between nurses within and without mood disorders: $x^2 = 3.2347$, $P = 0.1984$.*

Prevalence of FD-Associated Mood Disorders Among Neonatal Nurses

Among 128 nurses with mood disorders, 65 (50.78%) presented FD symptoms, which was higher than those without mood disorders (50.78% vs. 11.48%; $P < 0.05$). Most of them (53.85%) had PDS, but there was no difference ($x^2 = 3.2347$, $P = 0.1984$) (**Table 5**).

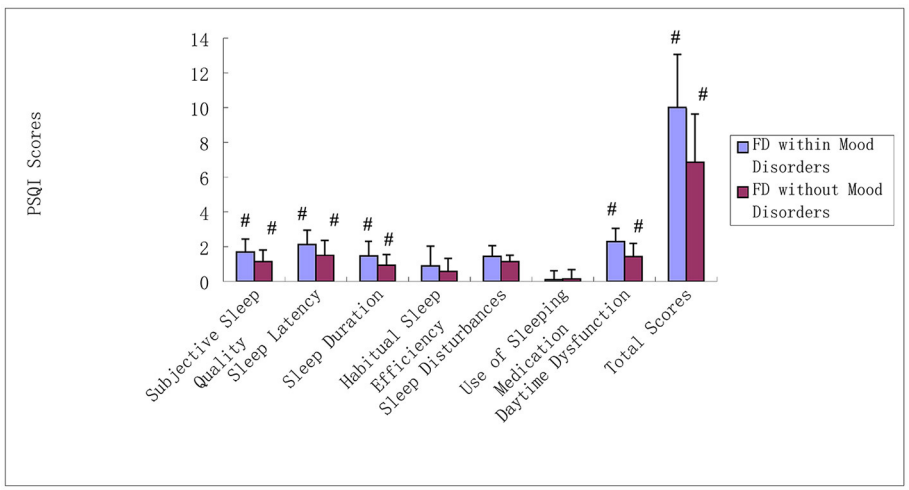
Lifestyle Impact on FD-Associated Mood Disorders

This study showed that different lifestyles exhibit varying impacts on mood disorders associated with FD. The prevalence of smoking and poor sleep was significantly higher in patients with FD and mood disorders than in those without mood disorders (all $P < 0.05$). However, the prevalence of preference for sugary beverages was lower in participants with mood disorders associated with FD ($P < 0.05$) (**Table 6**).

Poor sleep also displayed effects on FD-associated mood disorders. The scores of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, daytime dysfunction, and total PSQI scores among neonatal nurses with FD-associated mood disorders were all higher than those exhibiting FD without mood disorders. There was a statistically significant difference among the subjective sleep quality, sleep latency, sleep duration, daytime dysfunction, and total PSQI scores (all $P < 0.05$) (**Table 6** and **Figure 2**).

TABLE 6 | Lifestyles among neonatal nurses in FD with mood disorders.

Variables	FD within mood disorders (%)	FD without mood disorders (%)	
Smoking	1 (1.54)	0 (0)	$x^2 = 0.7237$, $P = 0.03949$
Alcohol	2 (3.08)	0 (0)	$x^2 = 0.0746$, $P = 0.7848$
Diet preference			
Coffee	14 (21.54)	5 (35.71)	$x^2 = 0.6100$, $P = 0.4348$
Tea	15 (23.08)	5 (35.71)	$x^2 = 0.4194$, $P = 0.5173$
Sugary beverages	14 (21.54)	10 (71.43)	$x^2 = 11.2995$, $P = 0.0008$
Chocolate	21 (32.31)	7 (50)	$x^2 = 0.8974$, $P = 0.3435$
Spicy food	38 (58.46)	6 (42.86)	$x^2 = 0.5923$, $P = 0.4415$
Row food	17 (26.15)	2 (14.29)	$x^2 = 0.3573$, $P = 0.5500$
Deep-fried food	18 (27.69)	4 (28.57)	$x^2 = 0.80687$, $P = 0.7933$
Hot food	15 (23.08)	3 (21.43)	$x^2 = 0.0475$, $P = 0.8275$
Dairy products	18 (27.69)	3 (21.43)	$x^2 = 0.80218$, $P = 0.8825$
Irregular diet	51 (78.46)	8 (57.14)	$x^2 = 1.7561$, $P = 0.1851$
Poor sleep	61 (93.85)	10 (71.43)	$x^2 = 4.1359$, $P = 0.0420$



# P<0.05

FIGURE 2 | PSQI scores between neonatal nurses in FD and mood disorders. The scores of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, daytime dysfunction, and total PSQI scores among neonatal nurses with FD-associated mood disorders were all higher than those exhibiting FD without mood disorders; the subjective sleep quality, sleep latency, sleep duration, daytime dysfunction, and total PSQI scores were statistically significant difference (all $P < 0.05$).

Multivariable Logistic Regression Analysis on Independent Factors for Mood Disorders With FD

A multivariable logistic regression model was performed to identify the association between lifestyle factors and FD-associated mood disorders. Consequently, poor sleep (OR = 6.10, 95%CI 1.309–28.419, $P < 0.05$) was identified as an independent risk factor associated with FD among neonatal nurses (**Table 7**).

DISCUSSION

Nurses are one of the frontline health workers for patient care, especially newborn infants. Newborn infants have decreased habituation and dishabituation capabilities, resulting in increased environmental vulnerability. Thus, patient care is more critical among newborn infants (22). However, neonatal nurses are often overworked and stressed by the heavy workload pressures associated with clinical care. As a result, nurses are more likely

TABLE 7 | Multivariate logistic regression analyses on selected factors associated with FD and mood disorders.

Selected factors	Mood disorders		
	OR	95%CI	*P*-value
Sugary beverages	0.503	(0.160, 1.985)	0.179
Poor sleep	6.10	(1.309, 28.419)	0.013

to experience mood disorders such as anxiety and depression (1). Furthermore, several studies have confirmed a high prevalence of mood disorders such as anxiety and depression among nurses; in China, approximately 35% of the nurses experienced depression, while 32–43% have anxiety (23–25). In a recent study, 49.23% of neonatal nurses experienced mood disorders, including anxiety and depression. From this sample, 31.54% experienced both anxiety and depression, which was relatively higher than other departmental nurses as well as the general population (26).

Previous studies confirm that social and lifestyle factors can impact mood disorders, such as anxiety and depression (24–27). This study found that poor interpersonal relationships, unhappy marital status, high levels of smoking and alcohol consumption, irregular diet, and poor sleep increased the susceptibility of experiencing anxiety and depression among neonatal nurses. In contrast, coffee and tea were identified as having a protective effect against mood disorders. Following the multivariable logistic regression analysis, good interpersonal relationships were identified as an independent protective factor associated with mood disorders in neonatal nurses. Whereas unhappy marital status, irregular diet, and poor sleep were all identified as independent risk factors associated with mood disorders in neonatal nurses.

Individuals with depression tended to interact with others in ways that elicit rejection, typically characterized by poor interpersonal relationships; furthermore, these nurses have been associated with an increased occurrence of negative interpersonal dependent events, which, in turn, increase the risk of future depression and anxiety (28, 29). Moreover, anxiety and depression were also independently associated with irregular diet and sleep (30–33). Sleep disorders, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction, have all been found to affect mood disorders (34). Night-shift work is common among neonatal nurses which often affects nurses' sleep rhythm and sleep quality. As a result, neonatal nurses experience poor sleep which may have an impact on anxiety and depression.

Recent findings have also confirmed that smoking is regarded as a false safety behavior that has led to anxiety and depression. Consequently, mood disorders further exacerbate smoking behavior (35, 36). Furthermore, alcohol can influence the severity of moods experienced. While negative mood symptoms can disappear in a short period, mood disorders can result in alcohol misuse. Moreover, family factors, poor family interpersonal relationships, or unhappy marital status can all impact alcohol misuse and the occurrence of mood disorders (37–39). In contrast, coffee and tea have potential protective effects against depression. Caffeine, chlorogenic acid, and 5-hydroxytryptamides in coffee and tea can increase calcium signaling and dopamine release, thus, forming protection against mood disorders (40–42).

Gastrointestinal sensory mechanisms play a key role in transferring sensory information from enteric reflex circuits to the central nervous system (CNS) via the vagal and spinal nervous systems. Furthermore, CNS has a significant effect on the gastrointestinal tract. Functional gastrointestinal disorder is a psychosomatic disorder. FD is one of the most common physical symptoms of psychosomatic disorders (43–45) and is divided into two subtypes according to abdominal symptoms: postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS).

In this study, 50.78% of neonatal nurses experienced anxiety and depression presented through FD. Most of them had PDS (53.85%), followed by EPS (26.51%). Whereas a few of these nurses had both PDS and EPS (20%). There was a statistically significant difference between the prevalence of FD with and without mood disorders. However, no difference was observed between the two subtypes of FD, with and without mood disorders. Another study confirmed that the prevalence of anxiety and depression in patients with FD was higher than in the healthy population (46). Psychiatric comorbidity was common among the patients who presented with FD referred to the Department of Gastroenterology. Further, psychiatric comorbidity increased the number, frequency, and severity of gastrointestinal symptoms associated with functional gastrointestinal disorders (FGIDs) (47).

Lifestyle factors also play an important role in FD-associated mood disorders among neonatal nurses. This study found that neonatal nurses who preferred smoking and poor sleep were more likely to suffer from FD associated with anxiety and depression. Based on the multivariable logistic regression analysis, poor sleep was identified as an independent risk factor associated with FD and mood disorders among neonatal nurses. Furthermore, other studies have suggested that sugar-sweetened beverage consumption is one of the modestly high-risk factors underlying depression. The current study did not note any differences; thus, further studies are required to confirm otherwise (48).

This study had several limitations. First, this was a cross-sectional study to explore the effects of social and lifestyle factors on mood disorders and FD solely among neonatal nurses, thus, limited information was available. Second, the self-report questionnaire used in this study may have caused some deviation in the results or the information could be false. Finally, most of participants were female in this study, it may cause deviation in the result of gender factor.

To conclude, this study confirmed that the prevalence of anxiety and depression among neonatal nurses is significantly high, as opposed to other departments' nurses and the

public. Furthermore, most of the psychiatric comorbidities in participants commonly presented as FD. Thus, social and lifestyle factors play a key role in mood disorders among neonatal nurses. Moreover, social and lifestyle factors have a significant impact on FD, anxiety, and depression in neonatal nurses.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Ethical Committee of Guangxi University of Chinese Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Z-pH and FH designed the study. Z-pH, FH, M-jW, C-zT, J-pH, JL, S-eL, S-qW, H-hL, J-jL, and XL performed the experiments. Z-pH acquired and analyzed the data and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Network Analysis of Eating Disorders Symptoms Co-occurring With Impulsive Personality Traits and Negative Mood States in Patients With Bulimia Nervosa

Yan Chen[1†], Lei Guo[1†], Mengting Wu[1], Lei Zhang[1], Qianqian He[1], Yuchen Zheng[1], Lin Wu[2], Hui Zheng[3] and Jue Chen[1*]*

[1] Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2] Military Medical Psychology School, Air Force Medical University, Xi'an, China, [3] Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

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Wenhao Jiang,
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Paolo Meneguzzo,
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ASL Napoli 3 Sud, Italy

***Correspondence:**
Jue Chen
chenjue2088@163.com
Hui Zheng
zh.dmtr@gmail.com

[†] These authors have contributed equally to this work

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Background: Bulimia nervosa (BN) is characterized by recurrent episodes of eating large amounts of food without control. Studies have found positive correlations of BN symptoms with impulsive traits and negative affect. However, the network relationship supporting BN symptoms is unclear.

Methods: The study participants included female BN patients (146) and healthy controls (HCs, 146). The participants were matched for age. All participants completed the Eating Disorder Examination Questionnaire 6.0, Barratt Impulsiveness Scale-11, Beck Anxiety Inventory, and Beck Depression Inventory. We characterized the centrality parameters of BN, impulsiveness, and anxiety and depression symptoms of BN patients compared with HCs.

Results: Among all symptoms in the constructed BN group network, Shape dissatisfaction had the highest strength. In the BN group network, three clusters of symptoms ("ED-specific symptoms," "impulsivity," and "anxiety and depression") were linked to each other by several symptoms. Compared to the HC network, impulsiveness was strongly associated with Concerns about Others Seeing One Eat in the BN network.

Conclusion: This study shows that ED-specific symptoms, i.e., Shape dissatisfaction, play a key role in BN. The cognition of "shape dissatisfaction" is a basis, and impulsivity and emotional symptoms are maintaining factors that may lead to BN development.

Keywords: bulimia nervosa, anxiety, depression, impulsivity, network analysis

INTRODUCTION

Bulimia nervosa (BN) (1) is a severe and complex eating disorder (ED). BN is mainly characterized by fear of weight gain, excessive preoccupation with body weight and shape, recurrent binge eating and subsequent purging behaviors, which are common in adolescents and young women (2). Clinically, 90–95% of BN patients are female (3). Lifetime estimates of BN diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) are between 4 and 6.7% (4).

Patients with BN often show impaired inhibitory control. Previous studies have demonstrated that individuals with BN have high trait impulsivity (5, 6). Patients with BN act on impulse and without planning. In addition, impulsive traits are related to suicide attempts and non-suicidal self-injury (NSSI) in BN patients (7). Thus, impulsive traits may be a risk factor related to BN. Patients with BN are frequently comorbid with depression and anxiety (1). Under stress, patients with BN easily generate negative affect (such as anger and sadness), and they may engage in impulsive action (i.e., binge eating, NSSI) to alleviate negative emotions (8). Therefore, emotional state may be another risk factor for BN (9). Impulsivity and depression/anxiety may have different roles in the development and maintenance of BN. Understanding how specific facets of impulsive traits and negative affect may relate ED-specific symptoms could provide insight into this complex disease.

Network analysis is a means for understanding the complex interactions that occur in diseases. It has been applied to clinical psychology in recent years, with an advantage in that it can provide insight into the roles of various symptoms in mental disorders (10). An important goal of the network analysis technique is to identify the central symptoms in the network, which are thought to be highly influential symptoms. Because high-centrality symptoms can be activated by other symptoms in the network, they have strong associations with other symptoms (11). In general, identifying high-centrality symptoms may help identify targets for clinical intervention (12–14).

In recent years, several network analyses have been carried out in patients with BN (15–18). Previous studies have focused more specifically on ED symptoms; for example, Overvaluation of Weight and Shape (15), Shape and Weight Preoccupation (16), Fear of Weight Gain (17), Desiring Weight Loss, Restraint and Worries that the feeling will get out of control, and Guilt after overeating (18) were the most important ED symptoms. Previous network analyses studies focused more attention on cognitive bias in weight and shape. Although a previous network study with a large sample of BN patients focused on emotional states and personal traits, it did not focus on impulsivity (19). Nevertheless, impulsivity and anxiety/depression also play key roles in BN development and progression. However, little is known about how ED-specific symptoms, impulsive traits and mood states interact with each other in this complex system. It is necessary to focus on personality traits, emotional states and the relationship between impulsive traits/emotional states and the ED-specific symptoms of BN. This will be helpful to BN patients in developing new treatments and promoting recovery.

The main aim of the present study was to utilize a network analysis approach to identify the central symptoms of BN. We compared networks of individuals with BN and healthy controls (HCs) and analyzed the differences between the two networks to understand the relationships between ED symptoms, impulsivity, anxiety and depression. We hope to provide a theoretical basis for novel therapeutic interventions by identifying the relationship between ED symptoms and the abovementioned risk and perpetuating factors. The hypotheses of the study were as follows: (a) ED-specific symptoms, i.e., Shape/weight dissatisfaction, Fear of Weight Gain and Desire to lose weight, are more central to the BN network; and (b) the ED-specific symptoms, impulsivity and emotional symptoms influence one another, which contribute to the development and maintenance of this disease.

MATERIALS AND METHODS

Participants

This study was a retrospective and cross-sectional observational study. We included BN patients who were recruited from the outpatient and clinical psychological wards of Shanghai Mental Health Center from January 2019 to December 2020. All patients were diagnosed by certified psychiatrists using the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Patient information (including age, BMI, years of education, etc.) is provided in **Table 1**. The exclusion criteria were as follows: (1) subjects with other psychiatric comorbidities (e.g., substance dependence in the last 3 months, schizophrenia, bipolar I disorder, current significant suicidal ideation or behaviors); (2) subjects with cognitive impairment or a history of brain trauma or brain disease; and (3) the researchers considered participation in this study inappropriate for other reasons (e.g., patients who could not understand the content of the questionnaire, patients unable to comply with the requirements of the tests). The HCs were recruited by advertising. The HC subjects did not currently or previously meet any psychiatric diagnosis criterion. The HC participants were matched to the BN patients according to various characteristics. This study complies with ethical standards, and it was approved by the Ethics Committee of Shanghai Metal Health Center (Ethical Approval No. 2020–14).

TABLE 1 | Sample demographics and symptom descriptions.

	BN (n = 146) (Mean ± SD)	HC (n = 146) (Mean ± SD)	t-value	p-value
Age	20.84 ± 2.70	20.93 ± 2.62	−0.29	***0.775***
Education year	14.25 ± 2.39	14.08 ± 2.86	0.58	***0.564***
BMI	20.78 ± 5.44	21.45 ± 6.19	−0.99	***0.323***
EDE-Q†				
Restriction	3.11 ± 1.89	0.69 ± 0.93	13.87	***<0.001***
Eating concern	3.43 ± 1.37	0.39 ± 0.63	24.37	***<0.001***
Shape concern	4.33 ± 1.48	1.47 ± 1.31	17.51	***<0.001***
Weight concern	3.95 ± 1.51	1.29 ± 1.25	16.37	***<0.001***
Total score	3.71 ± 1.33	0.96 ± 0.91	20.63	***<0.001***
BIS-11†				
Attention impulsiveness	14.49 ± 3.63	5.80 ± 6.45	14.19	***<0.001***
Motor impulsiveness	19.51 ± 5.03	8.44 ± 9.38	12.57	***<0.001***
Unplanned impulsiveness	24.56 ± 5.99	10.71 ± 12.05	12.44	***<0.001***
Total score	58.56 ± 12.17	24.95 ± 27.60	13.46	***<0.001***
BDI†				
Total score	27.45 ± 12.09	2.64 ± 4.51	23.23	***<0.001***
BAI†				
Total score	15.43 ± 10.95	1.16 ± 2.68	15.30	***<0.001***

†*EDE-Q, The Eating Disorders Examination Questionnaire, Chinese version; BIS-11, The Barratt Impulsiveness Scale (version 11, BIS-11); BDI, Beck Depression Inventory; The bold values are BAI, Beck Anxiety Inventory. n, number of samples; t, t-value; p, p-value.*

Informed consent was obtained from all participants before any study procedure was conducted.

Measures

Eating Disorder Examination Questionnaire 6.0

The EDE-Q 6.0 is a widely used 28-item self-report questionnaire that assesses the main behavioral and psychological characteristics of eating disorders over the previous 4 weeks (20, 21) using a 7-point Likert-type scale (0: never; 6: every day). The Chinese version had excellent internal consistency (Cronbach's $\alpha = 0.95$) (22). The EDE-Q includes four subscale scores, namely, Restriction, Eating concern, Shape concern and Weight concern. The EDE-Q generates two types of data. First, 22 items (items 1–12 and 19–28) reflect the severity of ED symptoms. Second, 6 items (items 13–18) provide data on the six main behavioral characteristics of ED in terms of presence/absence and frequency with which the behavior occurred and loss of control. The scores of the subscales are obtained by calculating the average of the items of each subscale, and the global score (EDE-Q 6.0) is the average of scores of the four subscales.

Barratt Impulsiveness Scale (Version 11)

The BIS-11 is one of the most widely used self-report measurements of impulsivity (23). It consists of 30 items measured on a 4-point Likert scale (1 = rarely/never, 2 = occasionally, 3 = often, 4 = almost always/always), with 11 items reverse scored. The BIS-11 is divided into three dimensions: attentional impulsiveness (AI), motor impulsiveness (MI), and nonplanning impulsiveness (NPI). The scale has been translated into Chinese, and the internal consistency of the 30-item scale and the three 10-item subscales are excellent (Cronbach's $\alpha = 0.77$-0.89) (24). The total score for the BIS-11 ranges from 30 to 120. The higher the score is, the higher the impulsiveness.

Beck Depression Inventory II

Depression symptoms were assessed with the BDI-II (25, 26), a 21-item self-report measure of depression. Each item is scored on a 4-point Likert scale, indicating the intensity level of symptoms. The higher the score is, the higher the depression. Studies have shown that the Chinese version of the BDI-II scale has good internal consistency (Cronbach's $\alpha = 0.94$) (27).

Beck Anxiety Inventory

The BAI is a 21-item self-report scale for assessing symptoms of anxiety (28, 29). Each symptom is scored on a 4-point scale rating severity from "not at all" to "severely, it bothered me a lot." The Chinese version of the BAI has been verified to have excellent internal consistency (Cronbach's $\alpha = 0.95$) (30).

Statistical Analyses

To ensure data quality, records were screened for inappropriate responses and a lack of response variation to open-ended questions. The descriptive analysis of demographic information and scale measures was performed with SPSS version 26.0 software. The scores of the above scales were compared by using

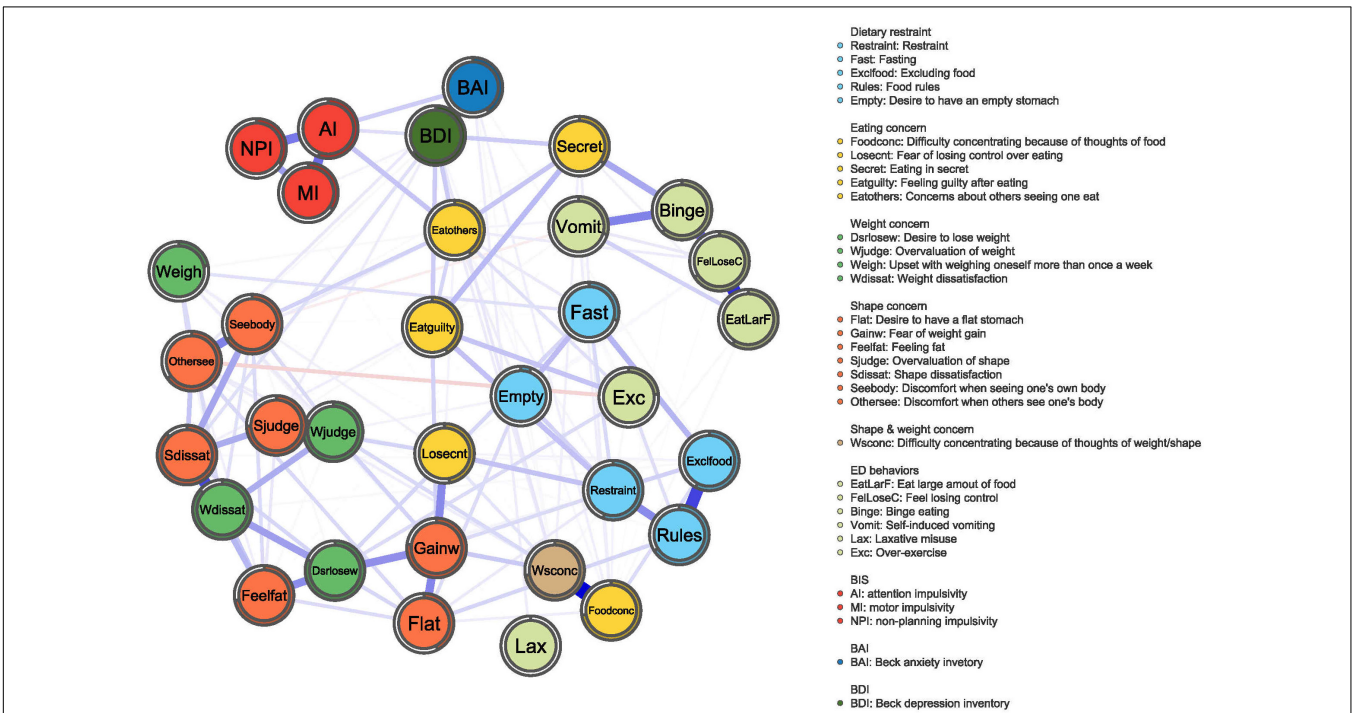

FIGURE 1 | BN network. The network graph shows associations and predictability estimates between ED symptoms (i.e., fear of weight gain, Shape dissatisfaction, Weight dissatisfaction, and Restraint), depression symptoms, anxiety symptoms, and impulsivity (i.e., attention impulsiveness, motor impulsiveness, and unplanning impulsiveness) in BN. The edges represent the strength of association between nodes. The colors of the node indicate the different subscales.

two-tailed independent *t*-tests between the BN and HC groups, with the significance level set as 0.05.

Network Estimation

Network models were constructed and analyzed with R software (version 4.05) using the qgraph package (31, 32).

The partial correlation network method was used to estimate all symptom networks, and the edges of the network can be understood as correlations between symptoms after adjusting all other edges. The procedure for estimating each partial correlation network was as follows. First, we used a Gaussian graph model to estimate the pairwise correlation parameters between nodes (33). As parameter estimation of all edges can lead to type I error, we controlled this by using a least absolute shrinkage and selection operator (LASSO) (34) to create a more parsimonious network by reducing small correlations to exactly zero (34, 35). This step was embedded in a best model selection procedure, in which the extended Bayesian information criteria (EBIC) were minimized.

In this network, a circle represents an individual symptom (one item from the symptom measures) from the EDE-Q 6.0, three subscales of BIS-11 or BDI and the BAI total score. The associations between nodes are represented with lines (or "edges"). "Edges" are lines between nodes representing regularized partial correlations. The existence of edges represents dependencies between variables; blue edges indicate positive associations, and red edges indicate negative associations. The wider the edge is, the stronger the association. Abbreviations were used to designate each of the 28 EDE-Q 6.0 items and the three subscales of the BIS-11 in the study (see **Supplementary Table 1**). These abbreviations are used in figures depicting the centrality values of nodes.

Network Centrality Estimation

We employed the three common measures of centrality measures, i.e., "strength," "closeness," and "betweenness," to quantify the features of the nodes (36). "Strength" represents the total weights of connections from other nodes to a specific node. "Closeness" is defined as the inverse of the sum of the shortest distances from a particular node to all other nodes in the network, whereby the shortest distance is the minimal number of edges traversed from one node to the next. High closeness indicates that the average distance between a given node and all other nodes in the network is short. "Betweenness" is the number of times that the shortest path between any two symptoms passes

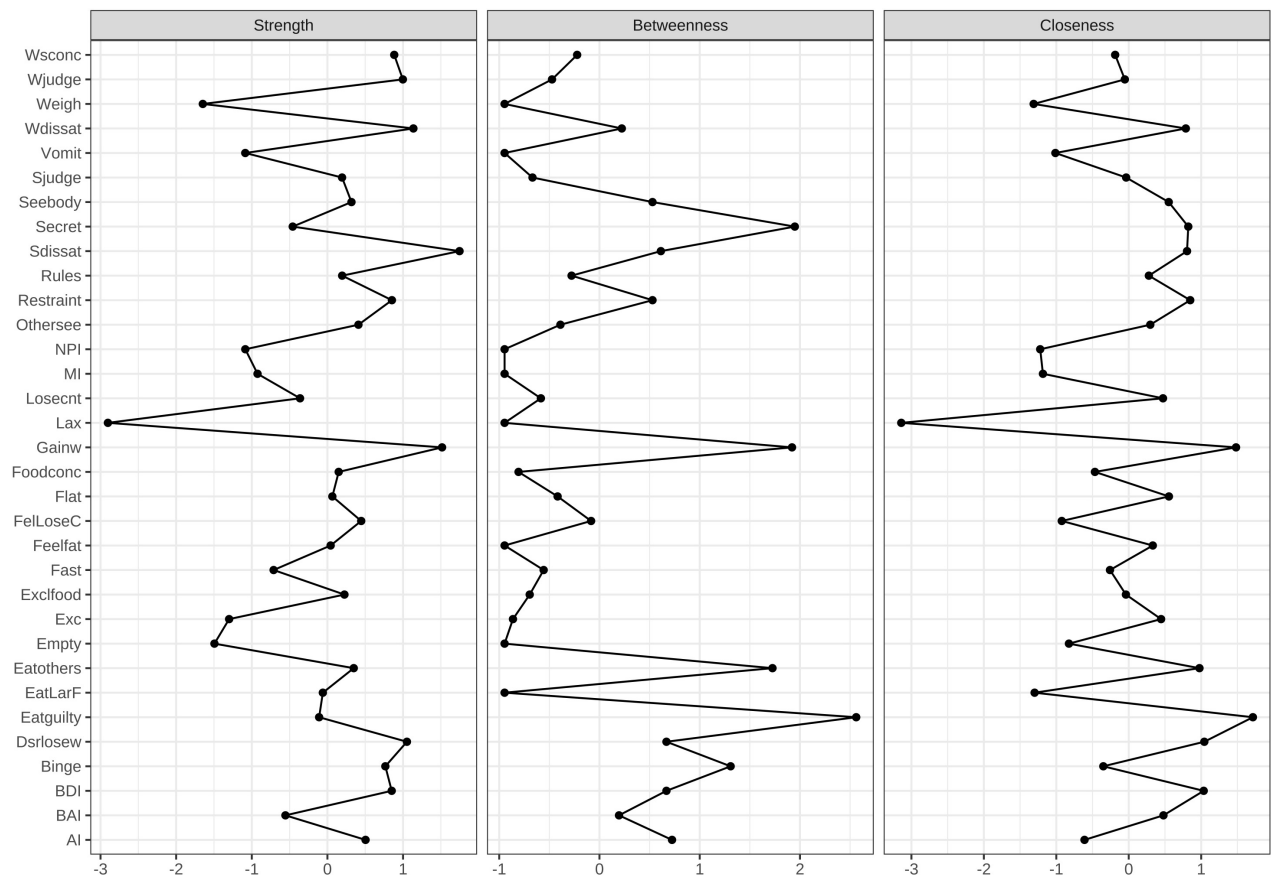

FIGURE 2 | Centrality measures for the BN network representing the strength, closeness, and betweenness of each node. Higher numbers indicate that the item is more central to the network.

through another. A node high in "betweenness" can be regarded as a "bridge" that connects other symptoms; that is, if a high node is removed, the distances among other nodes will generally increase (37).

Network Accuracy and Stability Estimation

The accuracy of edges and stability estimates for the network were calculated using a bootstrapping procedure with 1000 iterations (32). First, we estimated the accuracy of the edge through the 95% confidence interval (CI) of the bootstrap edge weight, with a narrower edge weight CI denoting higher accuracy. Second, we tested the stability of the centrality by subset bootstrapping. We estimated the centrality stability coefficient (CS-coefficient) as a reference index. For the CS-coefficient, values below 0.25 indicate unstable strength, and values greater than or equal to 0.5 are recommended (32).

Network Comparison

To explore the possible difference in global connectivity and to examine the differences in network structure between the BN and HC groups, we compared the partial correlation network for the BN and HC samples using the NetworkComparisonTest package in R (38). Comparing networks for unequally sized groups is problematic because network analysis methods penalize/shrink edges based on sample size. A workaround for this issue is to balance group sizes using a bootstrapping/subsampling method.

RESULTS

Clinical Characteristics

In this study, 250 questionnaires were distributed, and 209 were completed, with a response rate of 83.6% in the BN group; 484 questionnaires were distributed, and 479 questionnaires were effectively returned from the HC group, for a response rate of 99.0%. All questionnaires were administered online. Propensity score matching was used to match BN patients and HCs based on age. Ultimately, 146 BN patients and 146 HCs were selected for final analysis. The descriptive statistics for the sample are shown in **Table 1**. The EDE-Q total and four subscale scores, BIS total scores and three subscale scores, BDI total scores, and BAI total scores were significantly higher in the BN group than in the HC group. However, there was no significant difference in age, education years, or BMI between the BN group and HC group.

Characteristics of the Symptom Networks

The network structure of the EDE-Q, three subscales of BIS-11, BDI, and BAI total scores in different groups, as well as a comparative plot centrality index of the two groups are depicted in **Figures 1–4**, respectively.

The Core Symptoms of Bulimia Nervosa Psychopathology

Figure 1 shows the constructed symptom network of BN. As illustrated in **Figure 2**, the highest strengths included (top 3):

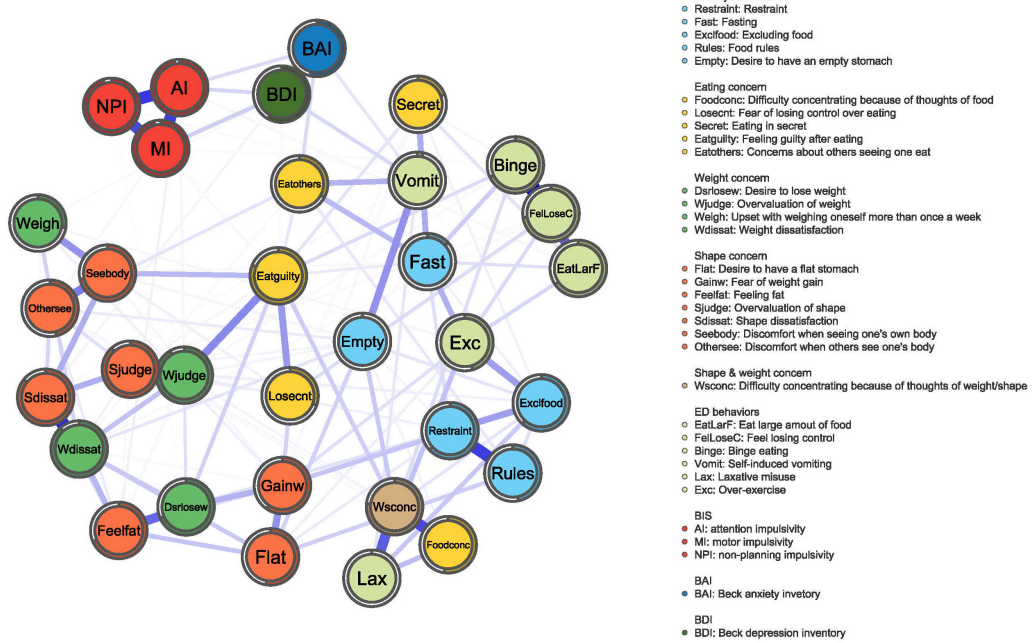

FIGURE 3 | HC network. The network graph shows associations and predictability estimates between ED symptoms (i.e., feel losing control, Shape dissatisfaction, Weight dissatisfaction, Difficulty concentrating because of thoughts of weight/shape), depression symptoms, anxiety symptoms, and impulsivity (i.e., attention impulsiveness, motor impulsiveness, and unplanning impulsiveness) in HC. The edges represent the strength of association between nodes. The different colors of the node indicate the different subscales.

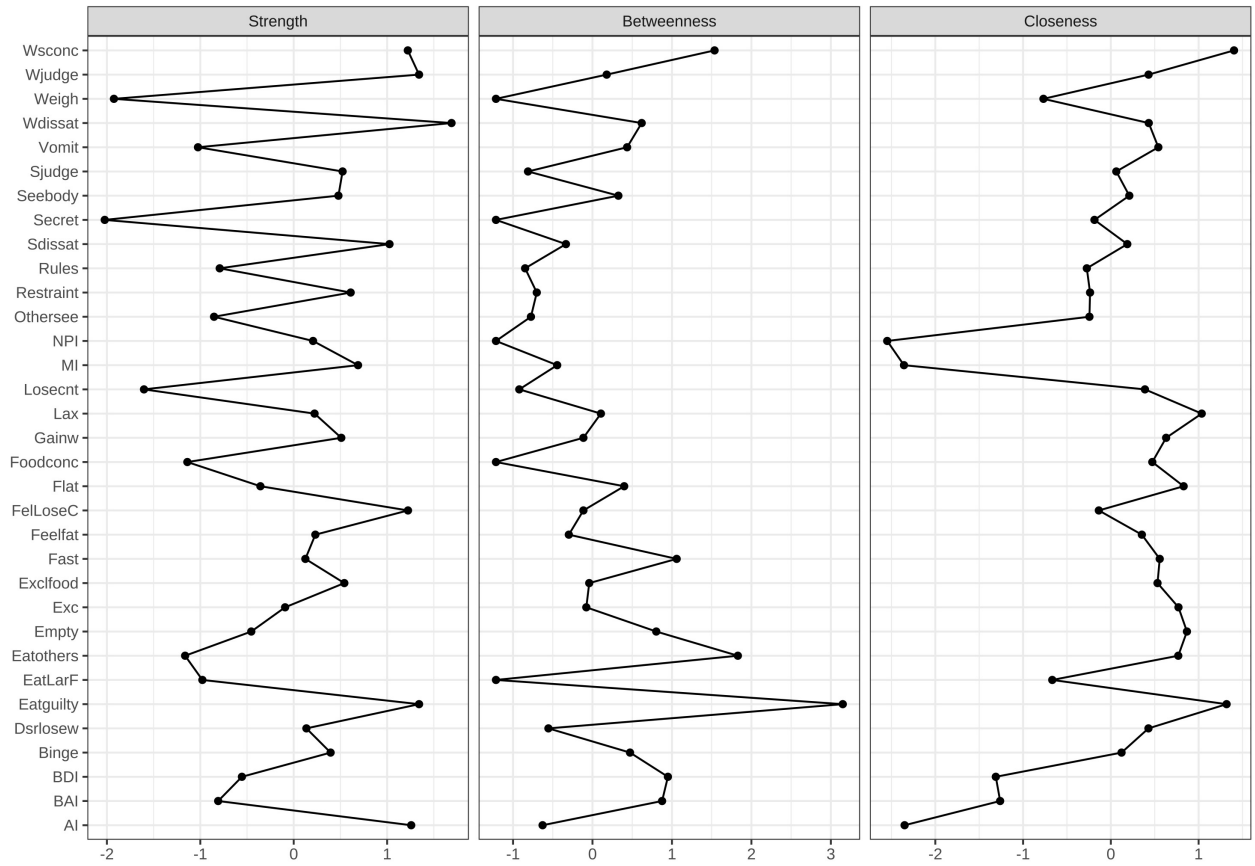

FIGURE 4 | Centrality measures for the HC network representing the strength, closeness, and betweenness of each node. Higher numbers indicate that the item is more central to the network.

Shape dissatisfaction (strength = 1.31), Fear of weight gain (strength = 1.25), and Weight dissatisfaction (strength = 1.11). It is worth noting that several nodes have the highest value for "strength" measures, suggesting that these symptoms are of particular importance in the network (i.e., Shape dissatisfaction, Fear of weight gain, and Weight dissatisfaction). Shape dissatisfaction had significantly higher strength values than all other symptoms. Regarding node predictability, the mean node predictability was 53.2%; thus, on average, 53.2% of the variance in each node was explained by neighboring nodes.

Three clusters of symptoms ("ED-specific symptoms," "impulsivity," and "anxiety and depression") are linked to each other by several symptoms in **Figure 1**. As shown, the ED-specific symptom that is closest to "impulsivity" is "Concerns about others seeing one eat." Those closest to "anxiety and depression" symptoms are as follows: Feeling guilty after eating, Concerns about others seeing one eat, and Eating in secret.

Core Symptoms of Healthy Controls

Figure 3 displays the constructed network for the HCs. As indicated in **Figure 4**, the highest strengths include (top 3): Weight dissatisfaction (strength = 1.27), Feeling guilty after eating (strength = 1.19), and Overvaluation of weight (strength = 1.19). Weight dissatisfaction had significantly higher strength values than all other symptoms. The mean predictability of the nodes was 58.6%, which was similar to the mean node predictability of the BN group.

Eating disorder-specific symptoms had a weak correlation with both impulsivity and mood states (anxiety and depression) in the network analysis of HCs.

Accuracy and Stability Analysis

Figure 5 shows the nodes used to determine centrality estimate stability (edge weight bootstrapping accuracy in the BN and HC networks, see **Supplementary Figures 1**, **2**, respectively). The CS-coefficient indexes of the BN and HC groups were 0.28 and 0.36, respectively, and the results from the stability analyses showed that the network models were relatively stable.

Network Comparison Analysis

We used the NetworkComparisonTest package to compare differences in edge weights between the BN and HC networks, and the edge weight was false discovery rate (FDR)-adjusted. Significant positive and negative correlations are shown in **Figure 6**. The global strength difference between the BN network (global strength = 13.75) and HC network (global strength = 14.49) was significant ($p = 0.01$).

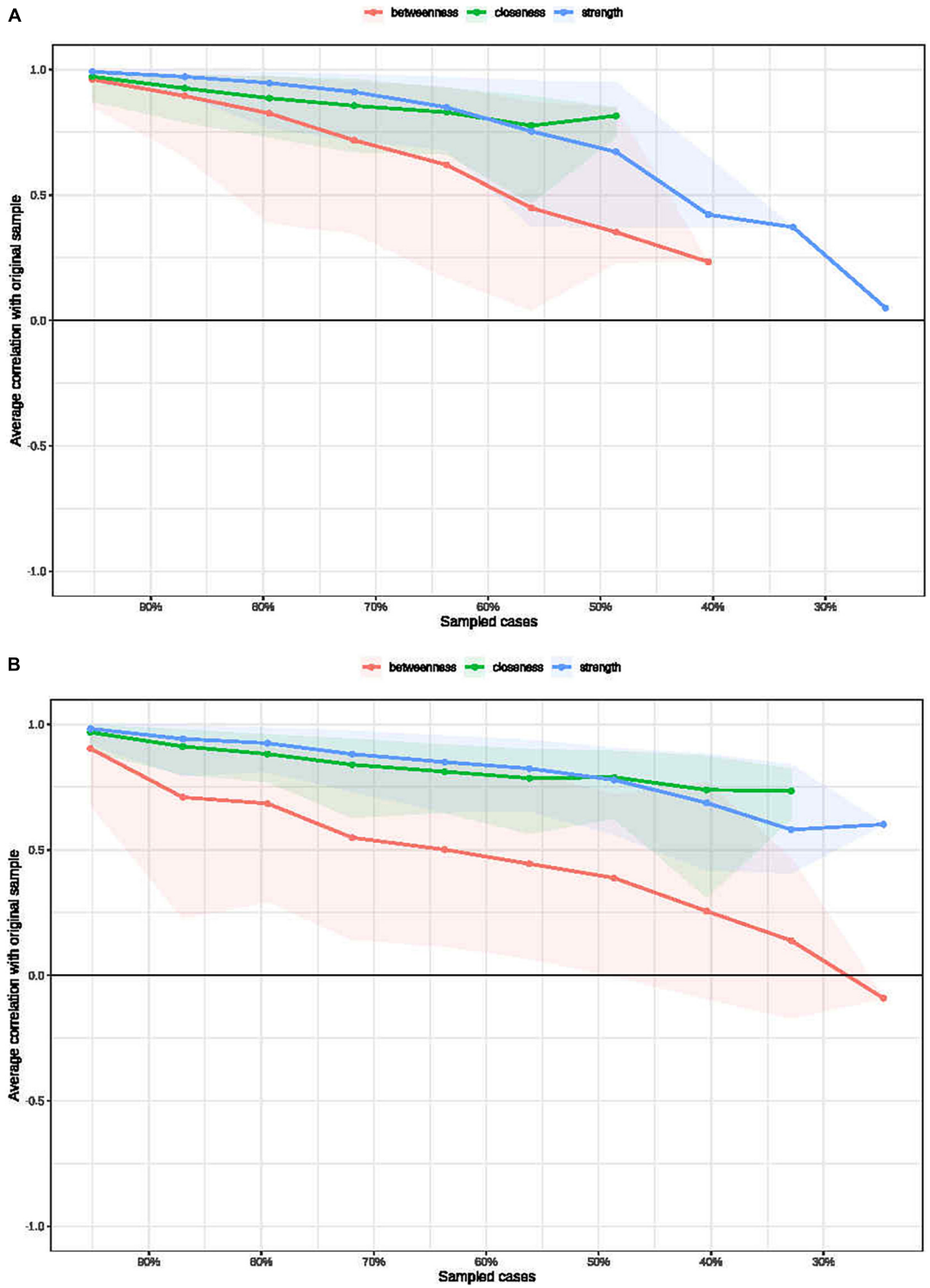

FIGURE 5 | Bootstrapped stability for the BN **(A)** and HC **(B)** graphical least absolute shrinkage and selection operator networks. The *x*-axis indicates the included portion of cases, and the *y*-axis indicates the average correlations with the original samples.

Compared to HCs, attentional impulsiveness on the BIS-11 was more strongly connected with Concerns about others seeing one eat (mean difference = 0.13, p = 0.000) on the EDE-Q (**Figure 6A**). In contrast, the symptom of Feeling guilty after eating showed weak connections with Overvaluation of weight (mean difference = −0.27, p = 0.000) and Fear of

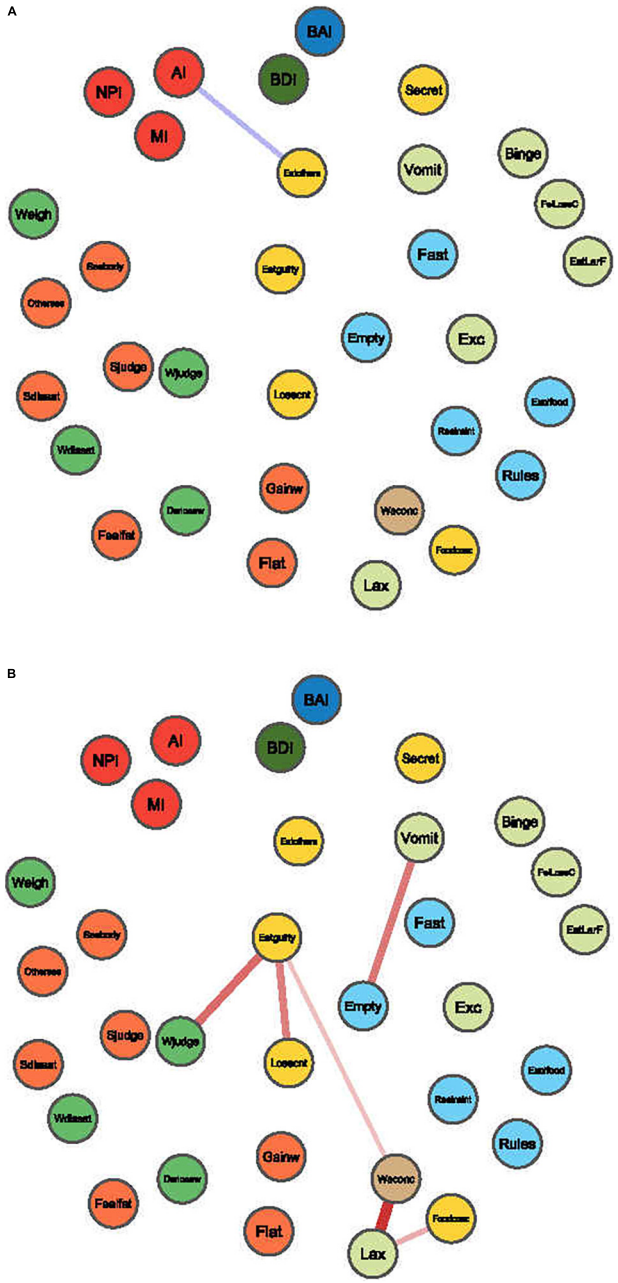

FIGURE 6 | Edges exhibiting significant differences between BN and HC. The blue edges denote the increased correlations between items in the BN compared with those in the HC network **(A)**, and red edges denote the decreased correlations **(B)**.

losing control over eating (mean difference = −0.24, p = 0.04) on the EDE-Q. Similarly, Self-induced vomiting had a weak connection with Desire to have an empty stomach (mean difference = −0.25, p = 0.000). Laxative misuse weakened the connectivity of Difficulty concentrating because of thoughts of weight/shape and Difficulty concentrating because of thoughts of food (mean difference = −0.38, −0.15, and −0.12; p = 0.000, 0.000, respectively) on the EDE-Q (**Figure 6B**).

DISCUSSION

This study identified the core ED symptoms and the relationships among ED symptoms, impulsive traits, anxiety and depression in BN patients in mainland China. First, Shape Dissatisfaction, Fear of Weight Gain and Weight Dissatisfaction had the highest strength in the BN symptom network. Second, three clusters of symptoms ("ED-specific symptoms," "impulsivity," and "anxiety and depression") were linked to each other by several symptoms. Overall, generating a complex network based on the relationship between symptoms may help better understand the disease.

First, our results showed that Shape dissatisfaction, Fear of Weight Gain and Weight dissatisfaction had the highest strength in the BN network, with Shape dissatisfaction having the highest strength value. Shape dissatisfaction and Fear of Weight Gain are part of the "Shape concern" subscale, and Weight dissatisfaction is part of the "Weight concern" subscale. Shape concern and Weight concern involve dissatisfaction with one's own body shape and weight, desire to control weight, and preoccupation with shape and weight. These symptoms are core ED-specific symptoms in patients with BN. Previous cross-sectional studies also found similar results in patients with BN (15–17, 19, 39). These findings show that Shape dissatisfaction, Fear of Weight Gain and Weight dissatisfaction are central to BN psychopathology, and ED thinking rather than ED behaviors plays a central role in BN (4).

Second, the results also showed that some symptoms on the EDE-Q were connected to anxiety/depression symptoms and impulsivity in the BN group. Patients with BN are often described as being in a "vicious cycle": BN patients are concerned about weight, shape and strict dietary restrictions. Then, they experience physical and psychological cravings for food, break dietary rules, think that they have failed and feel out of control and guilty. Finally, they compensate by binge-fasting, purging, and exercise and are more focused on weight and shape (4). Hence, in this state, they often experience anxiety and depression. Moreover, BN patients are associated with emotional regulation problems. During the COVID-19 lockdown, BN patients experienced exacerbated binge eating because of difficulties in emotional regulation (40). When they are in a bad mood, they are unable to adopt positive methods to deal with their emotions instead of using impulsive behaviors, such as episodic binge eating, to relieve their emotions, which aggravates their emotional problems (41). Solmi et al. suggested that core ED symptoms, depression and anxiety symptoms play an important role in BN (19). However, their studies did not focus on impulsivity traits. Our results were consistent with those of a previous study showing that ED-specific symptoms and emotional state occupied a major position. In addition, our study suggests that impulsivity traits may be another key factor. In short, ED-specific symptoms, i.e., Concern about weight and shape and Fear of gain weight are the foundation of BN. Impulsive traits and negative mood are maintenance factors of BN. These factors influence each other in the BN network. However, this study missed information on comorbidities. Anxiety and depression are co-occurring diseases of BN needing treatment. These issues require more attention in future research.

Third, our study indicated that the total score and three subscale scores of the BIS-11 were increased in the BN group compared with the HC group. Our study also found that in the BN network, attentional impulsiveness had a stronger connection with Concerns about others seeing one eat on the EDE-Q than that in the HC network. These findings suggest that the greater impulsiveness in BN patients is extensive and non-specific. Attentional impulsiveness includes two factors: attention and cognitive instability. Attentional impulsiveness is correlated with both proactive and reactive control (42). Dorsolateral prefrontal cortex (DLPFC) areas are associated with impulsivity (43). Interestingly, the DLPFC also plays an important role in emotion regulation (44). In recent years, dialectical behavioral therapy (DBT) has become a good treatment for emotional eating in BN (45). DBT is a behavioral treatment that draws its principles from behavioral science, dialectic philosophy, and Zen practice, including mindfulness and distress tolerance (46). Furthermore, some studies have shown that novel non-invasive neuromodulation therapy, such as transcranial magnetic stimulation (TMS), can improve impulsiveness (43). It is directed at modulating activity in brain regions (i.e., the DLPFC) and may also be used as an alternative intervention for BN in the future.

Several limitations should also be considered. First, the current study involved cross-sectional data without longitudinal follow-up; a cross-sectional study cannot distinguish symptoms that change over time or infer the directionality of relationships between ED-specific symptoms, impulsiveness and emotional symptoms. Future research should focus on properly designed prospective cohort studies, and longitudinal designs will elucidate treatment-based symptom changes in BN networks. Second, a previous study showed that patients with binge eating disorder (BED) have regular binge eating behaviors. BED is regarded as multifactorial, with a special focus on several neurocognitive deficits in executive functioning, such as inhibitory control and attentional bias. The present study did not explore the effect of these intriguing variables, which requires further investigation in future studies. Finally, information on relevant comorbidities was missing. These covariates may have influenced the analyzed outcome variables.

CONCLUSION

This network analysis assessed ED-specific symptoms, impulsive personality traits, anxiety and depression in a sample of patients with BN in mainland China. This study was matched by age, which reduces possible confounding by these factors. In addition, we included some potentially important risk factors, such as impulsivity and emotion-related variables (BDI and BAI). The study found that Shape Dissatisfaction, Fear of Weight Gain, and Weight Dissatisfaction are the core symptoms in the BN network. There was a relationship between impulsiveness, anxiety/depression symptoms and ED-specific symptoms. Thus, the results will provide a potential theoretical basis for new intervention measures, such as DBT and TMS, in the future.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Shanghai Metal Health Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JC and HZ contributed to the study concept and design. YC assisted with data analysis and wrote the manuscript. LG conducted statistical analysis and interpretation. YC, LG, MW, LZ, and QH contributed to the acquisition of the data and clinical assessment. JC, HZ, LW, and YZ contributed to a critical revision of the manuscript for important intellectual content. All authors reviewed the manuscript and approved the final version.

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SUPPLEMENTARY MATERIAL

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The History of the Introduction of the Concept of Depression Into China

Jike Bai[1,2]*, *Jun Li*[2] *and Daqing Zhang*[2]*

[1] *Global Health and Social Medicine, Harvard Medical School, Boston, MA, United States,* [2] *School of Medical Humanities, Peking University, Beijing, China*

This is a thematic historical study on the historical construction of the concept of depression in early modern China. Using an external historical research method, through the analysis of newspaper stories, drug advertisements, and medical texts (textbooks and reference books), it presents the sociocultural context of depression in the late Qing Dynasty and early Republican period and depicts the germination and evolution of the depression from a hazy and ambiguous concept in the late Qing Dynasty to a clear and complete disease entity of Western medicine, at least in the Chinese pharmaceutical market in the 1920s. This article examines the three internal logical clues in the localization of depression in China, namely, (1) the transformation of the disease from a symptom (the symptom of a disease) to a disease (an independent disease entity); (2) the pathological mechanism of depression was first made from the perspective of Traditional Chinese Medicine—"caused by stagnation of liver qi," which was joined later by the pathological mechanism of Western medicine—"caused by brain dysfunction"; (3) the introduction of the knowledge of "depression" presents a pattern of "cross-fertilization" between the West and the East. This study also examines the cultural imagery of depression during its early introduction to China and finds the three stereotypes of the manifestation of depression among the then Chinese public, namely, a feminized disease, a disease that afflicted the intellectual youth who were worried about the country, and the association between the disease and the morbid and distorted state of life of the upper-class literary youth.

Keywords: depression, early stage, input, introduction, public cognition

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Yongsheng Tong,
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Yue Wang,
Peking University, China
Yifang Wang,
Peking University, China
Cheng Yu,
Sun Yat-sen University, China

***Correspondence:**
Jike Bai
jike_bai@hms.harvard.edu
Daqing Zhang
zhangdq@bjmu.edu.cn

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THE EMERGENCE OF THE CONCEPT OF DEPRESSION

The concept of depression spread to China in the late Qing Dynasty. Actually, it was the concept of melancholia, not depression, that was introduced into China, and it was often translated as *Youyu Zheng (in Pinyin) or 忧郁症 (in Chinese characters)*. Its debut was in the *North China Herald & Supreme Court and Consular Gazette* on 26 May 1893, entitled *Victim of Panama* (1), a short story about a man in London, Charles, sent to hospital due to severe depression.

As early as the beginning of the Republic of China, advertisements for antidepressants appeared in newspapers. The advertisement for *Zhongjiang Tang (中将汤)*, a drug for melancholia sold by the East Asia Company Pharmacy located on Henan Road in Shanghai, first appeared on page 11 of *Ta Kung Pao (大公报)*, a newspaper published in the northern city of Tianjin, in 1911 (2), and later in the healthcare columns of the *Shibao 时报 (or Times)* on 1 April 1913 (page 11, **Figure 1A**) (3); 4 April 1913 (page 14) (4); and 13 August 1913 (page 4); and in page 16 of *Shen Bao 申报 (or Shanghai News)* (5) on 15 April 1914 (6). Analysis of the content and the frequency of the advertisements proves that this drug had been manufactured and sold by a pharmaceutical company in China

at that time and that there was a market for antidepressants. We could infer that the concept of depression had appeared in China then.

In the 1920s, Western medicines for depression began to appear in the Chinese market. The explanation of the pathological mechanism of depression was one of traditional Chinese Medicine (TCM)—"stagnation of *Qi* due to the depression of the liver" in the beginning, and was replaced by "neuropsychiatric disorder and brain function depletion." In other words, there was a transition of explanation of the mechanism from an inward perspective of TCM to an integrated perspective of TCM and Western medicine. The advertisements for the Red Qingdao Pill, a drug made by Dr. Williams' Pharmacy for anger and melancholy, were published in the *Industrial and Commercial News (Gong Shang Xinwen, 工商新闻)* on 10 (7), 17 (8), and 31 January (page 12) (9), *the Shibao 时报 (or Times)* on 29 March (page edition) (10) and 31 March (page 8) (11), *the News (Xinwen Bao, 新闻报)* on 29 March (page 6) (12), and 24 December (page 16) (13), and *the National News, Guomin Bao 国民报* (14, 15) on 31 March in 1925 (**Figure 1B**). The advertisement reads, "Have you ever suffered from anger and melancholia? If you have, please regulate your liver meridian, as they are often caused by the imbalance of the liver meridian." The beginning sentence of the advertisement implies that it is a drug for the disease of bad emotions, which equals melancholia, together with anger, as a disease. In traditional Chinese culture, emotion was rarely considered a disease. At most, it was considered as a sign. Therefore, when the mechanism of this Western medicine was explained, the TCM rhetoric "liver meridian disorder, and rising of liver Yang" was cited. Such an approach of grafting Western drugs on TCM reflects the penetration of depression, a disease in Western medicine in TCM in the early days of the Republic of China. It was probably a cleverly devised marketing means to make the medicine more acceptable as well.

In the late period of the Republic of China, the explanation of the pathology of melancholia gradually showed the integration of TCM and modern medicine. The TCM pathological perspective of "the liver meridian damaged by melancholia" and the modern medical knowledge, such as nervous system disorder, the physiological function of brain, psychopathy, were put together to explain the pathology of depression. An advertisement of the Sino-French Pharmacy published on the third page of *the News* on 29 November 1940, which was entitled the *Ailuo Brain Tonic: The Only Time-tested Tonic for the Neurological System*, wrote:

> It is said that anger hurts Qi and melancholia the liver. The cause of anger and melancholia is excess thinking affecting the nervous system, resulting in mental exhaustion and psychopathy. It is like mental frictions that generate heat, extremely hot and dry, that stagnates the functioning of the mind. Self-willed men and sentimental women often suffer from these two diseases. If they could take the drug, they could enhance their brain power and harmonize their emotions. Those who are overexcited can suppress over-excitement, and those who are weak in their mind can strengthen it. They could become neither arrogant, nor humble in their demeanor, well-organized, tranquil, and tolerant. They could restore their physical health, and socialize with others properly (16) (**Figure 1C**).

It could be seen that the Ailuo Brain Tonic mentioned in the advertisement was a drug for anger and depression. The advertisement also pointed out that depression was a disease of the neuropsychiatric system caused by overthinking, and the people susceptible to it were self-willing, paranoid men and sentimental women.

EARLY INPUT OF THE CONCEPT OF DEPRESSION FROM ABROAD

Most early introductions to depression in China appeared in English-language newspapers, with *The Shanghai Times*, *The China Press*, and *The North-China Herald* as the top three. There were three categories of depression-related information in these newspapers, namely, stories on depression care or suicide due to depression; information about relevant films and books; and information about professional knowledge. Among them, the latter two categories dominate, mainly published in the culture and life columns of the newspapers. Examples of each category are described below.

News on Depression Care or Suicide Due to Depression

On 26 September 1911, *The China Press* reported the case of a young German living in Kobe, who had just turned 26, cut his throat and wrist due to depression and eventually died from excessive blood loss (17). On 13 May 1914, *The China Press* reported the news that Mr. Warner, consul of the United States Consulate in Harbin, committed suicide with a pistol in the hospital and pointed out that he was suffering from depression, a mental illness, for a long time (18). The 1937 report of *The North-China Herald* explains to readers the serious consequences of depression through the case of suicide of a female patient suffering from mild depression and nervousness, and conveys to readers that depression is a hereditary but often progressive disease through the words of the patient's doctor (19). The news of suicide or hospitalization due to depression at least taught the Chinese readers that depression was a mental illness and could have serious consequences like suicide.

Information on Films and Books

The North-China Herald's culture and life column reported in 1929 on a new, academic, and artistic interpretation of Dürer's famous painting *Melencolia I* (20), and in 1933 on Dr. Norman's academic discovery that people with Melancholia would lose their sense of pain, with the several cases Norman received as the evidence (21). In February 1914, *The China Press* introduced and highly praised Burton's *The Anatomy of Melancholy*, which was also the first introduction to the book in China (22). On 4 August 1937, the black-humor comedy "Oh Doctor!" based on the 1923 novel of the same name by Harry Leon Wilson, a depression-themed thriller, was shown at the Shanghai Theater. The film tells the story of a patient with depression who lived in remorse

FIGURE 1 | (A) Advertisement of *Zhongjiang Tang*. Source: *Times* (时报), 1 April 1913. **(B)** Advertisement of the Red Qingdao pill. Source: *Republic of China Daily* (国民报), 31 March 1925. **(C)** Advertisement of Ailuo Brain Tonic. Source: *The News* (新闻报), 29 November 1940.

for bargaining before recovering his inheritance and losing his inherent rights due to excessive intake of pills. *The China Press* reported the showing of the film on the same day (23). A short story of the newspaper on 11 October 1938, reported that Pokers were invented in 1390, with its original purpose to amuse King Charles VI of France, who suffered from melancholia (24). On 15 November 1938, the newspaper reported that the Kawasaki Song and Dance House in Tokyo, Japan, opened in 1932, would close at the end of the year due to the impact of the Sino-Japanese War and the depression of business and that the girls working in the house, who used to live a life of singing and dancing, had to face a bleak future—to work in factories or marry and thus got depressed and suffered from melancholia (25).

Professional Knowledge

Medical information and research advances related to depression, mostly written by doctors. *The Shanghai Times*' published in its 15 January 1930, column, *Your Health and Your Brain*, a story entitled *Melancholia*, written by Dr. Leland B. Alford (26). The author emphasizes the importance of mental health for assessing a person's overall health in clinical practice. The author also points out that individuals with melancholia often complain of physical discomfort. However, the physician could not detect any physical illness that could cause such complaints despite the assertion of the patient for the existence of serious diseases underlying such discomforts. On the contrary, patients with serious physical disorders rarely have similar complaints. The author continues to emphasize, "To be sure, the symptoms of melancholia are due to mental disorders. The patient's mind becomes so sensitive that it converts many normal physical feelings into unpleasant ones. The fear of disease is further amplified by excessive attention to their physical health." The author also points out that this painful feeling, although real and profound, may be imagined and caused by the disruption of the balance of mental activity. An accurate description of the process of depression can be obscure and vague, but the author believes that the pain it causes can be simply imagined. Therefore, it may be extremely difficult to distinguish between depression and physical disease by simply relying on the typical symptoms caused by "imbalance." Alford uses "hypochondria" to refer to depression in this article, but with the author's mentioning of the symptoms of fear, hypochondria, imagination in the article, the disease he discusses is likely to encompass today's hypochondria disorder. *The Shanghai Times* clarified the relationship between melancholia and depression in an article written by Dr. Lago Galdston published in the *Daily Health Talk* column on 22 November 1934. He believes that the ancient name melancholia suggests that depression was thought to be caused by black bile

and was considered an excessive state. Furthermore, the black bile explanation implies that he believes the mental state of depression is caused by aberrations of chemicals and anatomy, or dysfunction of the body, rather than subtle, uncertain psychological causes. In other words, depression was thought to be a complex mental disorder caused by physiological disorders in ancient times. He also believes that depression is not a special mental disorder, but a mental symptom of many mental diseases that occur in both sexes, although likely to be more common in women and that people are prone to suffer it in their 40s and 50s and women would have an earlier onset than men. He states that patients with depression would complain of neurological symptoms, show a loss of interest, a significant loss of memory and attention, cry frequently, have unwarranted worry and fear, and some patients would develop delusions (27). It can be seen that his understanding of depression is very similar to that of contemporary people, both in terms of demographic factors and in the interpretation of clinical manifestations. In the next day's newspaper, Dr. Galdston continued to introduce the latest research on climacteric melancholia, which used a new treatment of estrogen in a controlled experiment to overturn the previous theory that climacteric depression was caused by typical personality characteristics, such as seriousness, rigidity, lack of humor, and over-cautiousness and lifestyle factors (28). In the news of 19 August 1939, *The Shanghai Times* reported that Dr. F. T. Thorpe of West Knight Hospital had discovered a new type of depression called senile depression and published his discovery in the *British Medical Journal* (29).

There were few psychiatry books available in modern China. Most of them were translated from Japanese or European works, and the works of local psychiatrists were also influenced by Japanese, European, and American scholars.

The works of Japanese psychiatrists were introduced into China. Examples include *The Essentials of Psychiatry* 精神病学集要 written by Ying Shuzo 吴秀三 published in 1916 (30), *Diagnosis and Treatment of Psychiatric Diseases* 精神病诊断及治疗学 by Miyake Koichi 三宅矿一 and Takaburo Matsumoto 松本高三郎 in 1921 (31), *Outlines of Psychiatry* 精神病学精要 by Miyake Koichi in 1934 (32) (and reprinted in 1940) (33), and *Summary of Psychiatry* 精神病学馀沥 by the same author in 1935 (34), Minor Psychiatry 小精神病学 by Sugita Naoyuki/Naoki Sugda 杉田直树 in 1933 (35), and *Lecture Notes on Psychiatry* 精神病学讲义 by Kijuro Uematsu in 1942 (36). Miyake Koichi mentions in his works that depression is associated with narcolepsy encephalitis, suggesting that encephalitis may lead to depression. Moreover, he believes that depression may be inheritable in families, and there is a linear regression relationship between typical depression and early-onset dementia. The process of diagnosis and treatment of patients with depression described by him in *Tongren Medicine* in 1931 includes cerebrospinal fluid as an examination item (37).

The authors of the article also found that cerebrospinal fluid examination was a routine examination item in the medical records of patients with depression treated in modern China in Nanjing Brain Hospital (for details, see another article by the authors). It can be seen that the theories of Japanese scholars have had an impact on the diagnosis and treatment of depression in modern China. The contents related to depression, such as bipolar disorder, and depressive state in the *Psychiatric Lecture Notes of Peiping Medical College* were deeply influenced by Japanese psychiatric works.

FIGURE 2 | Advertisement of *Treasure of the Women's World*. Source: *The News* (新闻报), 13 April 1930.

China's first monograph on psychiatry *A Brief Introduction to Mental Illness* (38), co-translated by P. B. Cousland and M. J. Chu from the *Insanity in Everyday Practice* by E. G. Younger, a British M. D., was published by the China Medical Missionary Association; the first edition in 1912 and the second edition in 1929. As a famous missionary doctor engaged in medical education in China in the early days, Cousland is an extremely important figure in the translation of Western medical books in modern Chinese history. He once served as the president of China Medical Missionary Association, the first national medical society in China, and was also a founder of the Compilation and Translation Department of China Medical Missionary Association. The medical books translated by him became authoritative in the early dissemination of Western medicine in China (39). Cousland wrote in the preface of *A Brief Introduction to Mental Illness* that "there is no medical book of insanity (madness) in China, and I would like to choose a book to render a simplified translated version for introduction. The book *Sanity in Everyday Practice* by Younger, designed for the diagnosis and treatment of mental illness by general practitioners, is concise but clear, comprehensive, coherent, and practical. I

therefore chose it for my translation. As for those who specialize in the study of mental illness, this book is not enough." In China, psychiatry developed later than other medical disciplines. Besides *A Brief Introduction to Mental Illness*, there were only four other monographs on psychiatry in the *Bibliography of the Republic of China 1911–1949: Natural Science: Medicine and Health* (40). The other four monographs are Huaying Ma's *Lecture Notes on General Psychiatry* published in 1919 (41); Han'en Zhao's *Psychiatry*, published by Commercial Press in Shanghai on 18 October 1929 (42); and Chi-liang Kwei's *Modern Psychiatry* published in August 1932 in Shanghai and Beiping, with its copyright belonging to Crescent Moon Bookstore (43).

Chi-liang Kwei (1900–1956) was the first female psychiatrist in China, the first child psychiatrist, and one of the first generation of mental health experts who contributed to the development of modern psychiatry in China. She was funded by the Boxer Indemnity in 1922 to study at Wesleyan College in the United States. In 1925, she transferred to Hopkins University to specialize in psychiatry and obtained her M.D. in 1929. After returning to China in 1931, she successively worked with the Graduate School of Beijing Daoji Hospital (now the Sixth Hospital of Peking University), Hujiang University (now Shanghai University of Technology), and the Second Military Medical University, among others (44).

Hongqi Yao's *Psychiatry* is actually an internal Lecture Notes for the fourth grade of the Medical College of Peiping University. There are four volumes of the Lecture Notes, namely, The Lecture Notes of the 20th Year (of the Republic of China) (1931) (45), the 21st Year (1932) (46), the 22nd Year (1933) (47), and the 23rd Year (1934) (48).

Han'en Zhao's *Psychiatry* and Chi-liang Kwei's *Modern Psychiatry*, written by the two local scholars, are the earliest professional works of psychiatry issued in modern China.

In terms of publication years, these four books are all later than *A Brief Introduction to Mental Illness*. Besides, Cousland, an authoritative figure who translated Western medical books in the early days, called the book "the first monograph on Psychiatry." Therefore, it is quite credible that *A Brief Introduction to Mental Illness*, published in 1912, is the first monograph on psychiatry in China.

Depression was introduced as one of the six mental disorders (the other five are mania, paranoia, psychotic paralysis, dementia, and cretinism) and considered to be the most common and treatable of all mental illnesses, with a cure rate of about 70% in *A Brief Introduction to Mental Illness*. The book also states that any kind of depression would always have a gradual onset and degenerative, prodromal symptoms. It can be seen that this is quite different from the understanding of the pathology of depression today.

PUBLIC UNDERSTANDING OF DEPRESSION IN EARLY DAYS

In the previous section, we examined how depression was introduced and constructed in early modern China and found that the public cognition of depression was influenced and shaped by the mass media at that time, such as magazines, newspapers, and books, further leading to different forms of "rational oppression of irrational," and formed the public stereotype about depression. The focus of this section is on the cultural images of depression in China in its early stages.

After the Meiji Restoration, Japan, on the one hand, "Westernized" and translated many depression-related texts from European and American psychiatric literature, and, on the other hand, integrated such knowledge into the psychological soil of East Asian society and culture. Obviously, localized knowledge borrowed from Japan was applied to China's interpretation of the meaning of "depression" with a distinctive "polyphony" character. In this period in China, both among the nascent Chinese academic community of psychiatry and the general public, in medical texts, and literary and artistic works, depression was perceived and interpreted from both Western and Eastern perspectives. Thus, a new cognitive paradigm was created for the construction of localized psychiatry in China, where culture served both as a background and as a vehicle for the development of depression in neuropsychiatry. Unlike somatic diseases, mental disorders have relatively few specific objective indications; instead, they have a relatively rich narrative of wandering, experiential subjective sufferings. In early modern China, the pathology of depression was characterized by the psychological projection of suffering of the public, and the manifestation of the complexity of social context and uncertainties in life as a disease, and these characteristics also bring entanglement and confusion to the scientific construction of depression.

Modern Chinese people often associate melancholia with femininity, and depression was often regarded as a feminine disease. "Melancholia is the cause of women's illness. If a woman is unhappy, she will be depressed. It must be pointed out that her excessive *Qi* in the chest hurts her liver meridian. The liver is the instrument for clearing blood, and if the liver meridian is out of control, then both *Qi* and blood will be blocked. If the condition persists, the menstrual period would be disrupted, and she would fall sick!" reads the advertisement sponsored by the Five Continent Dispensary in the healthcare column of the *News* published on 13 April 1930 (49), and in the advertisement entitled *Treasure of the Women's World*, published consecutively in the *Times* on 20–24 April 1930 (50–54) (**Figure 2**). It was pointed out that women's anger and depression are the causes of gynecological diseases. This case shows that people had already understood the relationship between emotional state and physical diseases at that time, and knew that psychological problems could lead to physiological problems, which could be regarded as the predecessor of the concept of psychosomatic diseases.

The depression in modern China is often regarded as a symbol of the intellectual youth, who were worried about the country and the people, and it is the label of this special group of youth. Under the background of national crisis and internal and external troubles, an individual's depression is linked to the fate of the country. With social unrest and turmoil, young people encountered challenges in their education and employment, and their melancholia became a serious social problem, which raised concerns among scholars, who wrote articles to express their

worries. In *Unwanted Melancholia: One of the Treatments for Youth' Disease*, the author wrote:

> I think most Chinese youths born in this era are afflicted by melancholia. Although they shout the slogan of progress, claim that they had god-gifted energy, and are forced by reality to move forward, they seem to always be bedridden of self-doubt, and could never struggle out of the types of sentimental young lords and ladies. Some are severely ill, walking slowly and sitting with unrest (55).

Due to depression, many young people look at everything in the world with an unhappy face as if everything were in shade or they were crushed by a rock on their chest. Sadness, anger, and other unnecessary emotions dominate their lives. They are wary of this world, although do not hate it, and live their lives as if they were in another realm. Some scholars got upset and criticized these young people's depression as a disease-free moan and pointed out that they might spread depression to their peers by the influence of their demeanor. They believed that young people at that time would naturally become depressed because they lived in a restless era, encountered setbacks in their personal growth, had witnessed many cases of others' failure, and heard the melancholy groans of their predecessors. They warned that when the depression of one person or some people was assimilated into many people, an "epidemic of the times" would break out, not only destroy the bright future of young people who make unnecessary sacrifices for nothing, but also, more importantly, undermines the future of the nation.

Clearly depression in young people was associated with worry about the strength of the nation and the endurance of the nation. Scholars warned that young people's depression had threatened the development of the national economy and hindered the process of social evolution and that, in light of the consequences for the nation and society, attention must be paid to their malaise and to stop the deterioration of the situation. The depression of young people was even linked with the survival of the nation, and it was believed that the depression of young people is not only their great misfortune but also that of the nation.

It was emphasized that young people should take responsibility for their depression. As for the way to overcome depression, the following proposals were made, namely, keep fit in body and mind; be discernible but do not get obsessed with things; be optimistic; work hard without caring for reward; no worry about failure, maintain curiosity, and be forward-looking; and make use of leisure life to avoid loneliness and the subsequent sadness.

In his article *On the Melancholia of Young People*, Ping Jiang argues that the reason young people got confused and suffered from depression was that the complex and treacherous social environment in China at that time made it difficult for young people who were not deeply involved in the world yet, to make choice. This shows his sympathy for the young people. He wrote that "the opinions in China have not yet been consistent. Some people advocate prioritizing efforts on survival and competing with the enemy; some people believe in mutual assistance, tolerance, and accommodation with external forces. Take the way to save the nation as an example. There are a range of propositions, advocating saving it by conscience, learning and study, science and technology, entertainment, or reading and chanting Buddhist sutra. It is confusing even for sophisticated, older people to see the true face from behind the masks, let alone a young man/woman!" (56).

The author gives his prescription to fight depression. He calls the young to believe that human beings are evolving and the youth should understand their responsibilities in evolution so that they will not regard their lives as worthless. The author believes that at the same time, young people, although should be ambitious and think about how to save the nation, should talk, laugh, jump, and sing in their daily life, instead of reading books all day long.

Hypochondria was often translated as *忧郁症 Youyuzheng* in early literary works. The word hypochondria, as is known to well-educated people, reflects preoccupation with imagined problems with health. For example, *The Hypochondria*, a collection of dozens of short essays published in the *London Journal* between 1777 and 1783, written by James Boswell, was translated into *The Melancholy Patient* when it was introduced to China (57). Dr. Beili, professor of literature at Stanford University, has verified the authorship of this collection. In addition, Dafu Yu, a famous author at that time, also wrote in the preface of his novel *Sinking* that "this work describes the psychology or hypochondria of sick youth, revealing the depression of modern people, caused by the (unsatisfied) sexual desire and conflict between body and soul" (58). The characters described in the novel are often literati with lung disease and depression, suffering from self-blame, sorrow, melancholy, nothingness, and imagination of sexual intercourse caused by unsatisfied sexual desire. In *Paratypical Melancholia* in *Novel: Shanghai 1934* (59) published in 1935, a tragic character, *Fengzi*, is such an image. *Fengzi* is depicted as a pale-face, thin-cheeked, and dry-eye intellectual suffering from depression and tuberculosis.

The depression was also regarded as a popular symbol of modern urban life. Depression in literary and artistic works is often accompanied by mental overwork, entangled romantic relationships, debauchery, lust, weakness, loneliness, pain and sufferings of separated lovers, addiction to the pleasures of music, women, hunting, and racing. For example, melancholia was taken as the theme in the article *One of the Sketches of Modern Urban Life: Epidemic Melancholia* published on 23 November 1934, in *Min Pao Daily 民报* (60), the novel *Women, Coffee, and Melancholia* published in *the Spring* magazine in 1935 (61), and the poem *Melancholia* published in the *Shilin Bimonthly* in 1936 (62). Obviously, in the Republic of China period, people had already known about this disease. In poems, novels, and essays, melancholia is often accompanied by love, coffee, jazz, beer, and wine, the elements of modern life at that time, alongside the representation of resentment, boredom, restraint, sadness, laziness, laziness, and loneliness. Melancholia has become a special form of sadness that possesses superiority unique to the rich and idle upper class. Through the shaping of these literary and artistic works, in the public impression at that time, depression was not so much a disease, but a morbid and distorted "gray" state of life common in "literary youth" and the upper class.

The expression of disease does not exist in a vacuum irrelevant to the social environment. So are mental diseases. In the early period of the introduction of depression into Chinese society, the pattern of depression presentation also had the characteristics of the times. In 1934, an article published on page 23 of *Shen Bao* 申报 posits that mental disorders such as suicide, melancholia, women's hysteria, neurasthenia, and madness were prevalent in society at that time and that in the modern, civilized world, almost everyone had the possibility of suffering from mental illness. In the then-Chinese society, under panic induced by economic depression and prevalent employment difficulties, ill-health of mind had become common. Melancholia, suicide, madness, and other behaviors are the ways used by the unemployed to express their protests against the tragic social context and their pathetic failure (63). We have found that at that time people around 30 years old have a high risk of melancholia. If one wants to recover from melancholia, he/she needs to absorb more nutrients and reduce labor, especially mental work. However, for those who did not have enough food and clothing despite daily work that exceeds more than 10 h, it was simply impossible.

NOTES

Advertisements for antidepressants and descriptions of depression began to appear in Chinese and English newspapers and in journals in the late period of the Qing Dynasty (1616–1911) and the Republic of China (1911–1949), as well as in early psychiatric books. Such advertisements and descriptions reached their peak in the 1930s, in the time frame of early modern China. The Western concept of depression was quietly implanted in the country through the abovementioned media and, to a certain extent, shaped the public cognition of depression in China. This study adopts a text analysis method, which uses first-hand historical documents as a carrier, and finds the results as follows.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

JB: conception and design of study, conductor of the study, acquisition of materials, analysis and interpretation of materials, and drafting the manuscript. JL: help translate. DZ: approval of the version of the manuscript to be published. All authors contributed to the article and approved the submitted version.

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A Resting State Functional Magnetic Resonance Imaging Study of Unmedicated Adolescents With Non-suicidal Self-Injury Behaviors: Evidence From the Amplitude of Low-Frequency Fluctuation and Regional Homogeneity Indicator

*Yi Zhou[1], Renqiang Yu[2], Ming Ai[1], Jun Cao[1], Xiao Li[1], Su Hong[1], Qian Huang[1], Linqi Dai[1], LiXia Wang[1], Lin Zhao[1], Qi Zhang[1], Lei Shi[1] and Li Kuang[1]**

[1] Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China, [2] Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

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Edited by:
Yuqun Zhang,
Nanjing University of Chinese Medicine, China

Reviewed by:
Huawei Tan,
Renmin Hospital of Wuhan University, China
Chao-Gan Yan,
Chinese Academy of Sciences (CAS), China

***Correspondence:**
Li Kuang
201388@hospital.cqmu.edu.cn

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Background: Non-suicidal self-injury (NSSI) behaviors are common in adolescents with major depressive disorder (MDD). Brain studies specifically targeting adolescents with MDD and NSSI may provide new insights into suicide warnings in adolescents with MDD.

Methods: This study examined the whole-brain neural activity in adolescents aged between 12–17 years, 50 unmedicated MDD patients with (nsMDDs) or without NSSI (nnsMDDs), and 25 healthy controls (HCs) participated in this study, and analyzed the correlation between the values of amplitude of low-frequency fluctuation (ALFF), fractional amplitude of low-frequency fluctuation (fALFF) and regional homogeneity (ReHo) in significantly different brain regions and the scores of the relevant clinical psychological scale.

Results: Compared with nnsMDDs, nsMDDs had enhanced ALFF values in left middle occipital gyrus and left median cingulate and paracingulate gyri; the fALFF values of the right caudate nucleus was weakened in the nsMDDs; the ReHo values of right middle occipital gyrus and right middle temporal gyrus weakened and the ReHo values of right medial cingulate gyrus enhanced in nsMDDs. And all of differences were statistically significant. In nsMDDs, the value of ALFF in the left calcarine fissure and surrounding cortex was negatively correlated with the score of Children's depression Inventory (CDI); the value of fALFF in the right caudate nucleus was positively correlated with the score of Beck Scale for Suicidal Ideations (BSSI); the value of ReHo in the right middle temporal gyrus was positively correlated with the score of Multidimensional Anxiety Scale for Children (MASC); and the value of ReHo in the right median cingulate and paracingulate gyri was negatively correlated with the score of BSSI.

Conclusions: We found that in ALFF, fALFF and ReHo, the significant differences between nsMDDs and nnsMDDs are mainly located in default mode network (DMN) and visual network (VN), and there may be brain regions related to NSSI in DMN and VN. The significant differences brain regions in ALFF, fALFF and ReHo between nsMDDs and nnsMDDs were related to the total score of the relevant clinical psychological scale, and may be related to NSSI.

Keywords: major depressive disorder (MDD), non-suicidal self-injury (NSSI), resting-state functional magnetic resonance imaging (rs-fMRI), adolescents, amplitude of low-frequency fluctuation (ALFF), fractional amplitude of low-frequency fluctuation (fALFF), regional homogeneity (ReHo)

INTRODUCTION

Major depressive disorder (MDD) is a mental disorder characterized by a persistent depressive mood and loss of well-being, loss of interest or pleasure in all activities, and a feeling that life is worthless (1). Between 2005 and 2015, the number of people suffering from MDD increased by 18.4% worldwide. The global rate of MDD is estimated at 322 million people, or 4.4% of the world's population. It has been reported that MDD was the major reason for global non-fatal health loss in 2015, and MDD is predicted to become the greatest burden worldwide by 2030 (2). In recent years, MDD has shown a trend toward a gradual decline with age. The incidence of MDD has gradually increased in the adolescent population, and their prevalence is 20% among all adolescents (3). MDD can have serious consequences, such as self-injury and suicide (4).

Non-suicidal self-injury (NSSI) refers to repetitive behaviors that are not accepted or recognized by the society in which an individual who does not intend to commit suicide causes varying degrees of damage to his or her body (5, 6). A large number of studies have shown that NSSIs are common among adolescents (7–9). Under certain conditions, NSSIs can further aggravate diseases and can even result in suicide (10–12). NSSIs should be recognized a as specific predictor of suicide and a non-specific predictor of psycho-pathological development (13). Self-injury and suicide are major public health problems among adolescents. Self-injury rates are very high among adolescents, and suicide is the second most common cause of death among young people worldwide (14). NSSI is one of the strongest predictors of future suicidal behaviors and has become a public health problem of universal concern (15–17).

In recent years, functional magnetic resonance imaging (fMRI), which has the advantages of non-invasive and non-radiation, plays a more and more important role in the research of mental illness. Many brain area signal abnormalities related to adolescent depression have been found in the study of adolescent depression, but such studies are still lacking, and most of them are based on tasking-state functional magnetic resonance imaging (ts-fMRI). The results may be affected by the differences between the experimental design and the task itself (18). Resting-state functional magnetic resonance imaging (rs-fMRI) provides a non-invasive and non-task method to eliminate some performance-related effects, and provides a reliable method for measuring "baselines" and connections of brain activity (19). Amplitude of low frequency fluctuation (ALFF) is one of the most important indicator in resting state functional magnetic resonance imaging and it is an indicator for measuring resting blood oxygenation level dependent (BOLD) signal changes, which reflects the synchronous cyclic modulation of total cortical excitability and long-distance neurons, and can objectively reflect the brain physiological state of its subjects (20, 21). Although previous studies have certain scientific research value and clinical significance, there is still a lack of research on the abnormality of brain function in adolescent depression from the resting state, in order to more comprehensively understand the brain function activity of adolescent patients with depression. Therefore, this study provides another perspective to explore the abnormal brain activity in adolescent depression with or without NSSI by resting fMRI.

There were few previous studies on MDD adolescents with NSSI, and some brain activity abnormalities related to NSSI were found. Compared with MDD adolescents without NSSI, there were significant abnormalities in amygdala, parahippocampal gyrus, fusiform gyrus, anterior cingulate gyrus and orbital part of frontal gyrus (22, 23). Several other studies found that there were significant differences in amygdala, cingulate gyrus, orbital part of frontal gyrus, precuneus, putamen and striatum in MDD adolescents with NSSI compared those in the with healthy controls (22–26). In a study, compared to healthy control participants, the NSSI group showed decreased amygdala and increased cingulate cortex and orbitofrontal cortex activation to NSSI and negative images (26). In our previous study of depression in MDD adolescents with NSSI, we found that MDD adolescents with NSSI showed significant activation of ALFF signals in the right median cingulate and paracingulate gyri and right fusiform gyrus compared with MDD adolescents without NSSI (27).

The above studies found that the brain regions in default mode network (DMN) are mainly related to NSSI. Most previous studies are based on the exploration of ALFF, with a lack of the analysis of fALFF and ReHo (28). In order to more comprehensively explore the brain abnormalities of adolescent depression patients with NSSI, these two indicators should be added to the data analysis to better explore the differences of local non-parametric consistency in a certain region of the brain and complement each other with ALFF. Thus, this study focuses on the changes of ALFF, fALFF and ReHo in DMN.

The purpose of this study is to explore the brain signal abnormalities of MDD adolescent patients with depression

with or without NSSI from the multiple indicators of ALFF, fALFF and ReHo. According to the previous studies and the research results of our research group, the following hypotheses are put forward: (I) Compared with healthy subjects, MDD adolescent patients with or without NSSI show significant differences in ALFF, fALFF and ReHo, and the differences are significant in the brain regions of DMN. (II) Compared with MDD adolescent patients without NSSI, MDD adolescent patients with NSSI show significant differences in ALFF, fALFF and ReHo.

METHODS

A total of 50 right-handed Han adolescents with MDD who were treated at the outpatient clinic of the Department of Psychiatry, the First Affiliated Hospital of Chongqing Medical University, China, were recruited. Their ages were between 12 and 17 years. Twenty five patients (nsMDD group) exhibited NSSI, and 25 patients (nnsMDD group) had no more than 3 NSSI in their lifetime and had no NSSI in the last month. These patients did not take any antidepressants and had not received any psychological or physical therapy before participating in this study.

All of the patients were evaluated by two experienced psychiatrists using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-kid) (29), a screening and evaluation tool that conforms to the standards for diagnosing MDD described in the Diagnostic and Statistical Manual of Mental Disorders, the fourth edition (DSM-IV). According to the diagnostic standard for NSSI presented in the Diagnostic and Statistical Manual of Mental Disorders, the fifth edition (DSM-V), only patients who had reported NSSI events lasting 5 days or longer in the past 12 months and at least 1 NSSI in the past month were included in the analysis. The exclusion criteria included a lifetime history of psychiatric illness other than MDD, a history of severe head trauma or neurological illness, a history of any drug or alcohol abuse/dependence at any time, a history of mental illness or suicide in first-degree relatives, other clinically relevant abnormalities in the medical history or laboratory tests and any contraindication for MRI.

In addition, 25 right-handed HC subjects were recruited through advertisements. They were screened with the patient group through the MINI-kid semi-structured clinical interview screening and assessment tool to ensure that subjects with MDD and other mental diseases were excluded from the control group. Exclusion criteria included a history of nervous system illness; severe traumatic brain injury; heart, liver or kidney disease or other serious physical illness; contraindications for any type of MRI scan; substance dependence or abuse; and a history of mental disorders or suicidal behavior among first-degree relatives. All participants underwent additional psychometric testing.

After the completion of this research, all participants received a proper research participation reward.

Before entering the experiment, all the subjects were fully aware of the complete experimental process and their related rights and interests and signed the informed consent form, and all the subjects and their guardians jointly signed the informed consent form. This experiment was approved by the Medical Ethics Committee of The First Affiliated Hospital of Chongqing Medical University (No. 2017–157), and carried out in strict accordance with the experimental procedure.

Clinical Assessment

The diagnosis of MDD was further confirmed by two senior psychiatrists using the MINI-kid, and the presence of diseases other than MDD, including mania and schizophrenia, was excluded. The Children's depression Inventory (CDI) (30), which has high reliability and validity, was used to evaluate the severity of MDD. Furthermore, all MDD patients underwent an NSSI-related clinical interview. This clinical interview was based on the diagnostic standard recommended by the DSM-V and was used to subjectively and objectively determine whether patients had NSSI, no matter whether they or their parents had reported NSSI or not. To capture the patients' NSSI in as many ways as possible, we asked each recruited patient to complete the Ottawa Self-Injury Inventory (OSI) assessment (31). In addition, the Multidimensional anxiety scale for children (MASC) (32) was used to evaluate the degree of anxiety of patients. The Beck Scale for Suicidal Ideations (BSSI) (33) was used to evaluate patients' self-injury suicidal ideation. The Barratt Impulsiveness Scale (BIS-11) (34), the Connor-Davidson Resilience Scale (CD-RISC) (35) and the Emotion Regulation Questionnaire (ERQ) (36) were used to evaluate the emotion regulation style and behaviors of patients. The Chinese version of the above scale has good reliability and validity in teenagers. And the self-assessments of the adolescents with MDD and the entire clinical assessment process were conducted with the participation of experienced psychiatrists to ensure that the self-assessment data were relatively objective, timely, accurate and complete.

Acquisition of rs-fMRI Data

All of the recruited adolescents underwent a head MRI examination within 36 hours of the clinical assessment. The majority of the recruited adolescents had never received a head MRI examination; therefore, they were asked to rest for at least 30 minutes between the clinical assessment and the MRI examination. In addition, they were asked to arrive at the waiting area of the examination room 30 minutes in advance to adapt to the environment in order to minimize the first-test effect. During this period, they were asked not to deliberately engage in any activity that involved excessive physical and mental effort. MRI images were acquired through a 3T GE Signa HDxt MRI scanner (General Electric Healthcare, Chicago, Illinois, USA) and an 8-channel head coil. The subjects were asked to remain relaxed, close their eyes, keep their minds clear and avoid thinking as much as possible. None of the participants reported falling asleep during the scan. Appropriate foam pads were used to secure the head to minimize head movement, and comfortable earplugs were used to reduce machine noise and minimize the impact of noise on the examination. The pulse sequence parameters were as follows: repetition time (TR) 2000 ms, echo time (TE) 40 ms, field of view (FOV) 240×240 mm^2, matrix 64×64, flip angle 90°, number of slices 33, slice thickness/interval 4/0 mm,

scan time 8 min, and volume 240 min. Three-dimensional T1-weighted MRI images were used for rs-fMRI joint registration. The following parameters were recorded: TR 24 ms, TE 9 ms, FOV 240×240 mm^2, matrix 256×256, flip angle 90°, and slice thickness/interval 1.0/0 mm.

Preprocessing of rs-fMRI Data

The quality of the original data is controlled by two experienced imaging professionals to ensure that there is no excessive head movement or abnormal signals in each image, and then classify and sort out the scanned data for pre-processing.

After the classified image data is stored in the form of DPABI software based on MATLAB2018b platform and SPM12 (http://www.fil.ion.ucl.ac.uk/spm) toolkit (DPABI_V5.1 version of https://rfmri.org/dpabi) recognizable data, the data pre-processing goes through the following processes: (1) the original data of structural and functional images are converted into NII and NIFTI formats. (2) the first 10 time points are removed to ensure that all images are not affected by the initial instability of the magnetic field and the first measurement effect of the subjects. (3) the difference method is used to correct the scanning time difference by using the 33rd layer as the reference layer. (4) use Friston-24 model to regress various covariates such as white matter, cerebrospinal fluid and head movement parameters to minimize the impact of physiological noise on data analysis (37). (5) use DARTEL method to register all subjects on the brain template in standard space, and then use its algorithm to transform and resample each subject's brain image to a spatial resolution of 3 × 3 × 3 (mm ^{3}). (6) spatial de-smoothing, the parameters are set to 4 × 4 × 4 (mm^3) half width and height to remove the influence of individual extreme signals. (7) use de-linear drift to regress the influence of signals related to the time series of BOLD signals. (8) filter the frequency signals other than 0.01–0.1 Hz to eliminate the signals that may accompany ALFF from the heartbeat, respiratory signals and the noise of the scanner itself, so that the fMRI signals belonging to the subjects' brain can be better analyzed later. (9) check the head motion parameter file. The data of head movement rotation $\leq 3°$ and translation $\leq$ 3 mm in three directions (x, y, z) were retained for subsequent data analysis. After the above steps, the data of 75 subjects met the requirements of preprocessing and were included in the follow-up analysis.

ALFF, fALFF and ReHo Analysis

In the preprocessing step, the eighth filter is removed, and then the operation is carried out based on the ALFF/fALFF module included in the DPABI software. In order to ensure that the signal of the image is based on the signal of the original brain, the results of ALFF and fALFF data are used for analysis. ALFF/fALFF is a commonly used indicator in fMRI, which is based on the fast Fourier transform of each voxel signal of the time series in the whole brain image and converted into the square root of the frequency domain power spectrum. In this study, ALFF represents the average value of each voxel in the frequency range from 0.01–0.1 Hz, while fALFF is based on the ratio of 0.01–0.1 hZ in the full frequency range retained by this study. fALFF is regarded as one of the ways to regress some of the horizontal signals of the whole brain (38). The calculation of ReHo indicator is based on the removal of the sixth de-smoothing in the preprocessing steps, and after the calculation of ReHo indicator, the mean and spatial de-smoothing is carried out to return to a very small number of individual extremes, so as to reduce the false positive signal of a single voxel. ReHo calculation indicator can reflect the synchronization of neurons in the local area, which is widely used in fMRI research, and is more representative (39). Therefore, the calculation of this indicator is included in this study in order to better reflect the brain functional activity of MDD adolescent patients with NSSI.

Statistical Analysis

In IBM SPSS22.0, Chi-square test was used for the gender data of all subjects included in the study. One-way analysis of variance (ANOVA) was used for age, years of education, age of first episode, total course of disease and clinical scale scores (CDI, MASC, BSSI, CD-RISC, BIS-11 and ERQ). *Post-hoc* Bonferroni tests were performed for each scale score. The significance threshold was set to $p < 0.05$.

In this study, ANOVA was used to evaluate the differences of ALFF, fALFF and ReHo in the brains of the three groups of subjects. If there were statistical differences, two-sample t-test was performed afterwards. The ANOVA was corrected by Gaussian random field theory (gaussian random field, GRF) when calculating the differences between the three groups of ALFF and ReHo. The threshold of voxel was set to 0.05 and the threshold of cluster was set to 0.05 and the one-tail test was used to form the mask brain region after correction. This brain region was used as a restricted statistical analysis area for post-test. When two-sample t-test was performed afterwards, GRF correction was limited to the area of Mask in the previous step (voxel < 0.001, cluster < 0.05, two-tails). Sex, age and mean head movement parameters (mean_FDjenkinson) were taken as covariates when calculating ALFF and ReHo, excluding the possible false results caused by sex, age and head movement.

In addition, we skipped ANOVA and directly used DPABI's own analysis method for *post-hoc* test (Tukey-Kramer) (40). The results showed that DPBAI's own analysis method was more significant in ALFF than in the three groups of brain regions that did not skip ANOVA (cluster contained more voxels), and there was no significant difference between fALFF and ReHo (see the attachment). In this study, we chose not to skip the ANOVA analysis method.

RESULTS

Demographic Data and Clinical Characteristics

There was no significant difference between nsMDD, nnsMDD and HC groups in terms of gender ($p = 0.927$), age ($p = 0.444$), education years ($p = 0.738$), ERQ ($p = 0.129$) and cephalomotor parameters [average cephalomotor parameters meanFD-jenkinson (41), $p = 0.241$]. Compared with HC group, nsMDD and nnsMDD groups had higher scores in CDI, MASC and BSSI, and there was no significant difference between the two groups, but in CD-RISC, compared with HC group, nsMDD group and nnsMDD group, the scores were significantly lower, and there was no significant difference between the two groups.

TABLE 1 | Demographic and clinical characteristics and head-motion.

	nsMDD *N* = 25	nnsMDD *N* = 25	HC N = 25	T/F	p	*Post hocs*
Gender (male/female)	5/20	6/19	6/19	0.152	0.927[a]	-
Age (year)	14.48 ± 1.36	14.96 ± 1.43	14.96 ± 1.77	0.822	0.444[b]	-
Education (year)	8.72 ± 1.65	9.08 ± 1.55	8.96 ± 1.77	0.306	0.738[b]	-
First onset age (year)	12.72 ± 2.48	14.28 ± 1.49	-	0.184	0.010[c]	-
Course (month)	20.08 ± 26.01	8.21 ± 6.19	-	2.176	0.039[c]	-
CDI	34.29 ± 6.71	30.40 ± 4.21	8.10 ± 6.52	76.630	<0.0001[b]	nsMDD>HC, nnsMDD>HC
MASC	76.01 ± 12.31	71.65 ± 11.96	24.10 ± 22.27	50.311	<0.0001[b]	nsMDD>HC, nnsMDD>HC
BSSI	39.64 ± 13.93	30.81 ± 14.47	1.20 ± 2.15	31.676	<0.0001[b]	nsMDD>HC, nnsMDD>HC
CD-RISC	27.67 ± 20.66	32.15 ± 9.62	63.00 ± 10.00	18.908	<0.0001[b]	nsMDD<HC, nnsMDD<HC
BIS-11	100.12 ± 20.08	83.23 ± 15.31	74.70 ± 20.37	8.645	<0.001[b]	nsMDD>nnsMDD, nsMDD>HC
ERQ	39.72 ± 11.20	34.68 ± 11.42	42.60 ± 9.94	2.128	0.129[b]	-
Head motion	0.06 ± 0.03	0.05 ± 0.02	0.06 ± 0.02	1.450	0.241[b]	-

nsMDD, the depressed adolescent group with non-suicidal self-injury; nnsMDD, the depressed adolescent group without non-suicidal self-injury; HC, the healthy control group. All statistical descriptive parameters are mean ± standard deviation; a, passes chi-square test; b, one-way ANOVA; c, two-samples T-test; pos-hoc, the post-test of one-way ANOVA.

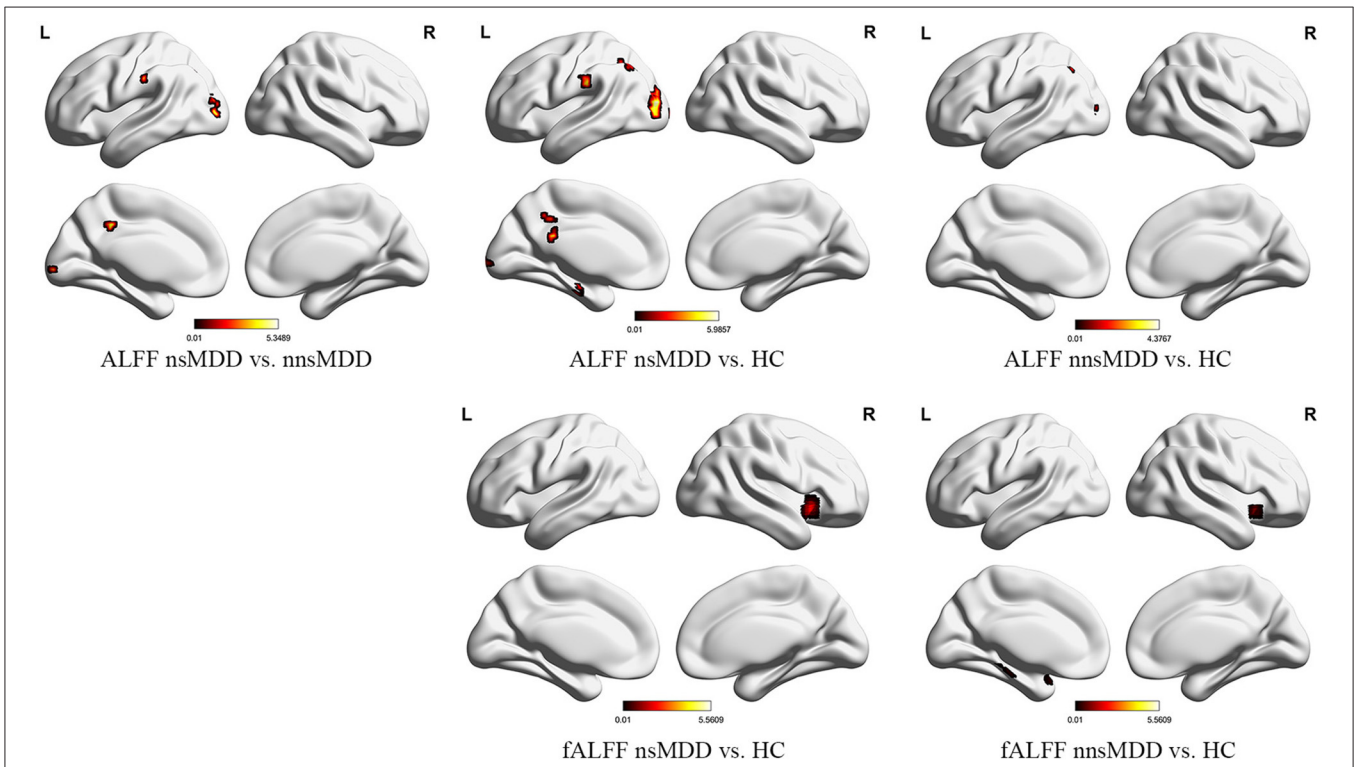

FIGURE 1 | The significant differential brain areas with increased ALFF and fALFF in nsMDD, nnsMDD and HC groups. The figures tool: (https://www.nitrc.org/projects/bnv/).

It is worth noting that the score of BIS-11 in nsMDD group was significantly higher than that in nnsMDD group and HC group, and there was significant statistical difference, but there was no significant statistical difference between nnsMDD group and HC group. The age of first episode in nsMDD group was earlier than that in nnsMDD group, and the total course of disease in nsMDD group was significantly higher than that in nnsMDD group. The statistical data of the three groups are shown in **Table 1**.

ALFF, fALFF and ReHo Results

Compared with nnsMDD group, nsMDD group had enhanced ALFF values in left middle occipital gyrus and left median cingulate and paracingulate gyri. Compared with HC group, nsMDD group had enhanced ALFF values in left middle occipital gyrus, left inferior occipital gyrus, left angular gyrus, left calcarine fissure and surrounding cortex and left parahippocampal gyrus. Compared with HC group, nnsMDD group had enhanced ALFF

values in left middle occipital gyrus and left angular gyrus (**Figure 1**, **Table 2**).

Compared with the nnsMDD group, the fALFF values of the right caudate nucleus was weakened in the nsMDD group. Compared with the HC group, the nsMDD group had enhanced the fALFF values of the right insula. Compared with the HC group, the nnsMDD group had enhanced the fALFF values of the right insula (**Figure 2**, **Table 3**).

Compared with nnsMDD group, the ReHo values of right middle occipital gyrus and right middle temporal gyrus weakened and the ReHo values of right medial cingulate gyrus enhanced in nsMDD group. Compared with the HC group, the ReHo values in the left middle occipital gyrus was enhanced and the ReHo values in the right medial superior frontal gyrus and left middle frontal gyrus weakened in the nsMDD group. Compared with the HC group, the ReHo values of the right middle occipital gyrus was enhanced and the ReHo values of the left precuneus was weakened in the nnsMDD group. And all of differences were statistically significant (**Figure 3**, **Table 4**).

Correlation of ALFF, fALFF and ReHo With Clinical Scale Scores

In nsMDD group, the value of ALFF in brain region 4 (the left calcarine fissure and surrounding cortex), which was significantly different from that of nnsMDD group, was negatively correlated with the total score of Children's depression Inventory (CDI);

TABLE 2 | Areas with increased or decreased ALFF in groups.

Region (peak)	AAL	X	Y	Z	t	Voxel
nsMDD vs. nnsMDD						
Occipital_Mid_L	51	−33	−87	3	5.15971	19
Cingulum_Mid_L	33/67/35	−9	−42	39	5.34890	18
Occipital_Mid_L	51	−24	−87	15	3.81805	4
Calcarine_L	43	−9	−96	0	3.69098	2
SupraMarginal_L	63	−60	−24	33	3.76369	2
Occipital_Mid_L	51/61	−36	−69	39	4.20263	2
nsMDD vs. HC						
Occipital_Mid_L	51/49	−33	−90	12	5.98572	80
SupraMarginal_L	53/57	−60	−27	27	4.77878	29
Angular_L	65/61/51	−42	−63	42	5.79640	22
Calcarine_L	43/51/47/49	−15	−93	0	4.46443	18
Hippocampus_L	39/37/55	−24	−12	−21	4.08006	11
Cingulum_Post_L	35	−3	−39	24	4.53527	7
Precuneus_L	67/33	−6	−42	39	4.72634	7
Precuneus_L	67	0	−57	51	4.41656	7
nnsMDD vs. HC						
Occipital_Mid_L	51	−36	−93	6	4.37670	6
Angular_L	65	−42	−63	42	4.01027	3

AAL, Automated anatomical labeling; X Y Z, montreal neurological institute (MNI); Sup, superior; Inf, Inferior; Mid, middle; Post, posterior; L, left; R, right.

TABLE 3 | Areas with increased or decreased fALFF in groups.

Region (peak)	AAL	X	Y	Z	t	Voxel
nsMDD vs. nnsMDD						
Caudate_R	72	12	−3	18	−3.63883	3
nsMDD vs. HC						
Insula_R	30	36	15	−9	5.56086	18
Temporal_Sup_R	82	45	0	−9	3.65109	1
Insula_R	30	45	−3	3	3.56323	1
Hippocampus_L	37	−24	−36	6	3.95574	1
nnsMDD vs. HC						
Insula_R	30	36	15	−9	4.00475	8
Thalamus_R	78	9	−15	12	3.75248	3
ParaHippocampal_L	39	−15	0	−24	3.96507	2
Temporal_Pole_Sup_L	83	−36	9	−24	3.90666	2
ParaHippocampal_L	39	−21	−27	−18	3.91029	2
ParaHippocampal_L	39	−15	−6	−24	3.69830	1
Fusiform_L	55	−18	−36	−15	3.67418	1
Temporal_Sup_R	82	48	−12	3	3.63470	1
Caudate_R	72	15	−12	21	3.60546	1

AAL, Automated anatomical labeling; X Y Z, montreal neurological institute (MNI); Sup, superior; Inf, Inferior; Mid, middle; Post, posterior; L, left; R, right.

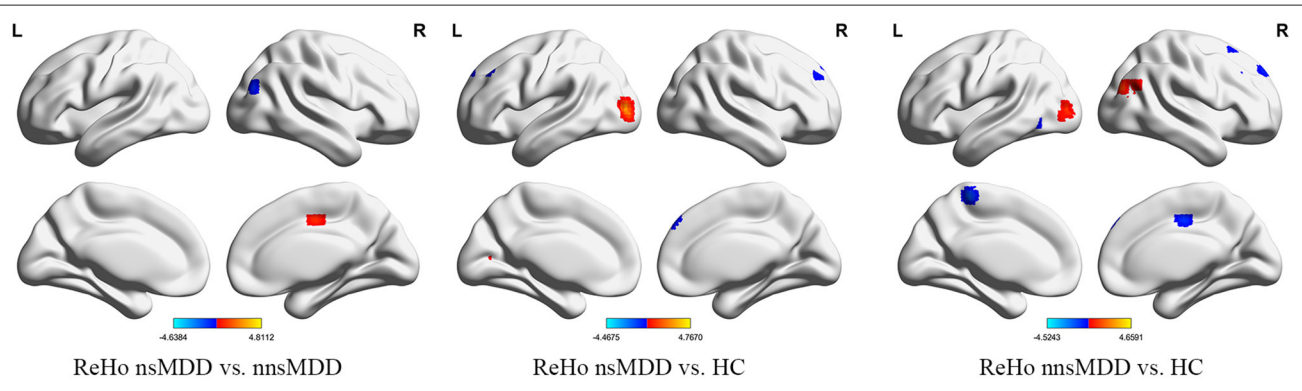

FIGURE 2 | The significant differential brain areas with increased or decreased ReHo in nsMDD, nnsMDD and HC groups. The figures tool: https://www.nitrc.org/projects/bnv/.

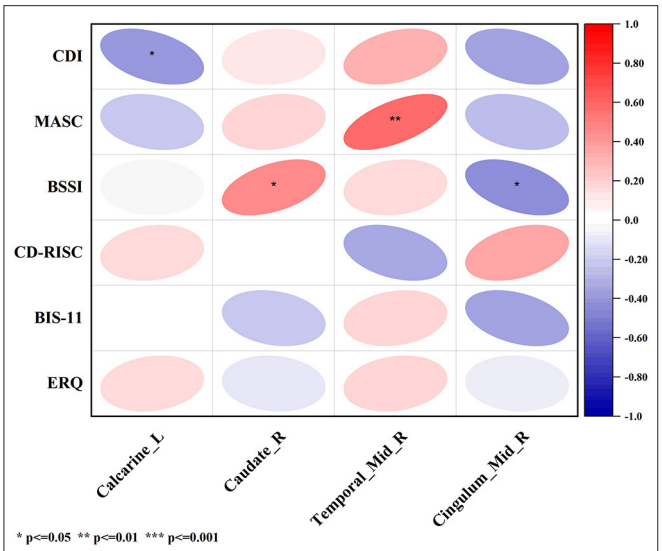

FIGURE 3 | The correlation between ALFF, fALFF and ReHo in the altered brain regions in nsMDD group compared with nnsMDD group and clinical characteristics. The figure tool: www.OriginLab.com. OriginPro Learning Edition (2019110152@stu.cqmu.edu.cn).

the value of fALFF in brain region 1 (the right caudate nucleus), which was significantly different from that of nnsMDD group, was positively correlated with the total score of Beck Scale for Suicidal Ideations (BSSI); the value of ReHo in brain region 1 (the right middle temporal gyrus), which was significantly different from that of nnsMDD group, was positively correlated with the total score of Multidimensional Anxiety Scale for Children (MASC); and the value of ReHo in brain region 3 (the right median cingulate and paracingulate gyri), which was significantly different from that of nnsMDD group, was negatively correlated with the total score of BSSI (**Figure 3**, **Tables 5**, **6**).

DISCUSSION

In this study, it was found that the differences between nsMDD and nnsMDD in ALFF, fALFF and ReHo were located in DMN and visual network (VN) as well as a small number of salience network (SN) and sensorimotor network (SMN). There may be brain regions closely related to NSSI in DMN, VN, SN and SMN brain networks. Compared with the HC group, there were significant differences in the brain regions of nsMDD in DMN, VN and a small amount of central executive network, which confirms with previous studies (22–27).

There was a significant difference in the total score of the BIS-11 between the nsMDD group and the nnsMDD group. The score of the nsMDD group was significantly higher than that of the nnsMDD group. The higher the score of the BIS-11 was, the more impulsive and impulsive the subjects would be to deal with things. The score of the BIS-11 of MDD adolescents with NSSI was significantly higher than that of MDD adolescents without NSSI, which is consistent with previous studies. The related BOLD signals on fMRI were significantly different. The ALFF was significantly enhanced in the left middle occipital gyrus and medial lateral cingulate gyrus, while the ReHo was significantly weakened in the right middle temporal gyrus, middle occipital gyrus and medial lateral cingulate gyrus. This indicates that the signal abnormalities in these brain regions may be closely related to NSSI. Some scholars have pointed out

TABLE 4 | Areas with increased or decreased ReHo in groups.

Region (peak)	AAL	X	Y	Z	t	Voxel
nsMDD vs. nnsMDD						
Temporal_Mid_R	86	60	−66	21	−3.68597	7
Occipital_Mid_R	52	42	−81	27	−3.62894	6
Cingulum_Mid_R	34	12	−12	42	4.81121	5
nsMDD vs. HC						
Occipital_Mid_L	51	−33	−87	9	4.76701	32
Frontal_Sup_Medial_R	24/23	6	48	45	−3.53581	23
Frontal_Mid_L	7	−33	45	39	−3.52675	12
Calcarine_L	43	−18	−75	12	4.01667	3
Frontal_Sup_R	4	24	45	42	−3.53249	3
Frontal_Sup_L	3	−15	54	39	3.53905	1
Frontal_Sup_R	4	24	39	54	−3.53939	1
nnsMDD vs. HC						
Occipital_Mid_R	52/86	48	−78	24	4.65908	30
Paracentral_Lobule_L	67/69	−9	−36	66	−3.55170	12
Occipital_Mid_L	51	−36	−90	6	4.03762	9
Cingulum_Mid_R	34	12	−9	42	−3.59837	6
Frontal_Sup_R	24/4	15	48	39	−3.58942	4
Frontal_Mid_R	8	45	33	42	−3.72898	4
Occipital_Mid_L	51	−45	−87	0	4.16002	2
Temporal_Mid_R	86	60	−66	21	3.73527	2
Frontal_Sup_Medial_L	23	0	54	42	−3.59599	2
Frontal_Sup_R	4	24	21	63	−3.52180	2
Temporal_Inf_L	89	−45	−60	−6	−3.61300	1

AAL, Automated anatomical labeling; X Y Z, montreal neurological institute (MNI); Sup, superior; Inf, Inferior; Mid, middle; Post, posterior; L, left; R, right.

TABLE 5 | The brain regions of interest for correlation analysis with clinical characteristics.

Indicator	ROI	Region (peak)	AAL	X	Y	Z	t	Voxel
nsMDD vs. nnsMDD								
ALFF	N0.1	Occipital_Mid_L	51	−33	−87	3	5.15971	19
ALFF	N0.2	Cingulum_Mid_L	33/67/35	−9	−42	39	5.34890	18
ALFF	N0.3	Occipital_Mid_L	51	−24	−87	15	3.81805	4
ALFF	N0.4	Calcarine_L	43	−9	−96	0	3.69098	2
ALFF	N0.5	SupraMarginal_L	63	−60	−24	33	3.76369	2
ALFF	N0.6	Occipital_Mid_L	51/61	−36	−69	39	4.20263	2
fALFF	N0.1	Caudate_R	72	12	−3	18	−3.63883	3
ReHo	N0.1	Temporal_Mid_R	86	60	−66	21	−3.68597	7
ReHo	N0.2	Occipital_Mid_R	52	42	−81	27	−3.62894	6
ReHo	N0.3	Cingulum_Mid_R	34	12	−12	42	4.81121	5

ROI, region of interest; AAL, Automated anatomical labeling; X Y Z, montreal neurological institute (MNI); Sup, superior; Inf, Inferior; Mid, middle; Post, posterior; L, left; R, right.

TABLE 6 | Pearson's correlations between ALFF, fALFF and ReHo in the altered brain regions in nsMDD group compared with nnsMDD group and clinical characteristics.

Indicators	ROI		CDI	MASC	BSSI	CD–RISC	BIS−11	ERQ
ALFF	Calcarine_L (NO.4)	r	−0.412*	−0.223	−0.042	0.164	0.021	0.176
		p	0.045	0.295	0.845	0.444	0.922	0.409
fALFF	Caudate_R (No. 1)	r	0.133	0.186	0.463*	0.033	−0.223	−0.112
		p	0.536	0.383	0.023	0.877	0.296	0.601
ReHo	Temporal_Mid_R(No. 1)	r	0.330	0.600**	0.162	−0.356	0.191	0.188
		p	0.115	0.002	0.449	0.088	0.370	0.380
ReHo	Cingulum_Mid_R(No. 3)	r	−0.372	−0.280	−0.456*	0.365	−0.380	−0.085
		p	0.073	0.185	0.025	0.079	0.067	0.693

*$p <= 0.05$ **$p <= 0.01$ ***$p < =0.001$; ROI, region of interest; Sup, superior; Inf, Inferior; Mid, middle; Post, posterior; L, left; R, right.*

that the level of impulsive behavior can be used as a predictor of NSSI in MDD adolescents with NSSI (42). In the future, the score of BIS-11 and bilateral middle occipital gyrus and medial lateral cingulate gyrus may be used as focus on brain areas to further explore the situation of MDD adolescents with NSSI before and after treatment, in order to further discover the pathophysiological mechanism closely related to NSSI. In this study, obvious abnormalities were only found in ALFF and ReHo between the two patient groups, and the differences in ALFF and ReHo in this study were also found to be fewer voxels. Although corrected by multiple comparisons, a larger sample size is still needed to further verify in the future, and then further explore the abnormal areas of the brain that may be related to NSSI.

Due to the limited number of cases collected and because the age of the first episode and the total course of disease could not be easily controlled, subjects were thus not more carefully grouped to explore the abnormal BOLD signal of the brain of MDD adolescents with or without NSSI. Although no obvious abnormality of brain BOLD signal was found in MDD adolescents with or without NSSI in this study, there were still significant differences in ALFF, fALFF and ReHo between these two patient groups and HC group, which is consistent with the previous research in our group (43–45), which further confirms that the brain network closely related to MDD may be related to DMN and SN. Some related studies have shown that there is a close relationship between DMN and SNs and cognition, while the NSSI of MDD adolescents with NSSI may be closely related to the level of self-awareness. We can thus infer that NSSI may be closely related to DMN and SN. In the future, we can combine a variety of data analysis methods (such as graph theory combined with data-driven independent component analysis) to further explore the abnormal activity of DMN and SN in the brain functional network of MDD adolescents in NSSI.

The difference between this study and other studies lies in that, in the correlation analysis with the multiple clinical psychological scales, each cluster was analyzed separately with the total score of the scale in order to further clarify the specific clusters related to the differential brain regions and the total score of the scale. In this study, it was found that ALFF, fALFF and ReHo signals in different brain regions of nsMDD and nnsMDD groups were correlated with the total scores of CDI, MASC and BSSI. There was a negative correlation between the fourth area of interest in ALFF (mainly in the left calcarine fissure and surrounding cortex, belonging to the VN) and the total score of CDI (**Figure 3**, **Tables 5**, **6**). Although there were only two voxels, it could still reflect to some extent that the brain of MDD adolescents may be closely associated with depression-related symptoms in the VN. The lower the ALFF signal in the left calcarine fissure and surrounding cortex may indicate more severe depressive symptoms in MDD adolescents. So far, few studies have found that there is a correlation between VN brain area and MDD and NSSI in adolescents. In the future, we can further explore whether there is a significant correlation between VN brain area and NSSI. In the different brain regions of the fALFF indicators of the two patients, it was found that there was a positive correlation between the brain region of interest No 1 (mainly in the right caudate nucleus, belonging to the SN) and the total score of BSSI (**Figure 3**, **Tables 5**, **6**). There were only 3 voxels, but it can be inferred from this correlation analysis that the fALFF signal value in the brain region of the SN, especially in the right caudate nucleus, was positively correlated with suicidal ideation (post-test). There was no significant difference in the total score of BSSI between nsMDD group and nnsMDD group, but the average score of nsMDD group was higher than that of nnsMDD group. We can speculate that in MDD adolescents, the higher the fALFF signal in the right caudate nucleus is, the more likely it is to have NSSI. In addition, in the ReHo indicator, there was a significant correlation between the differential brain regions between nsMDD and nnsMDD groups and the total scores of MASC and BSSI scales. The signal value of the first region of interest (right middle temporal gyrus, belonging to SMN) in the differential brain regions of ReHo was positively correlated with the total score of MASC (**Figure 3**, **Tables 5**, **6**), and in the third brain area of ReHo differential brain regions (right medial cingulate gyrus). There was a negative correlation between the signal value of SMN and the total score of BSSI (**Figure 3**, **Tables 5**, **6**). It can be inferred that the higher the ReHo signal value of the right middle temporal gyrus in the SMN of the brain is, the severer their anxiety symptoms are, and the lower the ReHo signal value of the right medial cingulate gyrus in the SMN of the brain indicates that their suicidal ideation is more obvious and NSSI is more likely to occur. It is worth noting that there was no significant correlation between the differential brain regions of ALFF, fALFF and ReHo and the total score of clinical

psychological scale between the two case groups and the healthy control group, respectively. It is possible that in the resting state functional magnetic resonance imaging, MDD adolescents with or without NSSI have no specific brain regions related to the total score of each clinical psychological scale in this study, and may not be found to be true positive because of the small sample size (46).

CONCLUSION

In this study, it was found that in the indicators of ALFF, fALFF and ReHo, MDD adolescents with or without NSSI may be closely related to DMN and SN compared with adolescents with physical and mental health. In the correlation analysis with the clinical psychological scale, the differences of the local indicators of ALFF, fALFF and ReHo in the resting state fMRI of the nsMDD, nnsMDD and HC groups were compared with the clinical psychological scale. The correlation analysis between the brain regions and the clinical psychological scale showed that the ALFF signal value in the brain area of the VN (especially in the left calcarine fissure and surrounding cortex) of MDD adolescents was significantly lower than that of normal adolescents, which may indicate that they have more serious depressive symptoms. NSSI is more likely to occur. The significant increase of fALFF signal value in the brain region of SN (especially the right caudate nucleus) may indicate that it is more likely to have NSSI and have stronger suicidal ideation, while the significant abnormality of ReHo signal value in the brain region of SMN (especially in the right middle temporal gyrus and right medial cingulate gyrus) indicates that NSSI, severer anxiety symptoms and stronger suicidal ideation are more likely to exist.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the First Affiliations Hospital of Chongqing Medical University (No. 2017-157). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minors' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YZ designed the research, collected samples, analyzed data, and wrote the original of manuscript. RY collected samples, supervised, and conducted quality control. MA, JC, XL, and SH supervised data and conducted quality control. QH, LD, and LW collected samples and gave some advice. LZ supervised the research, gave some advice, and revised the manuscript. QZ and LS collected samples and gave some advice. LK supervised the research, provided funding, and gave some advice. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.925672/full#supplementary-material

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Combining S100B and Cytokines as Neuro-Inflammatory Biomarkers for Diagnosing Generalized Anxiety Disorder: A Proof-of-Concept Study Based on Machine Learning

Zhongxia Shen[1,2], *Lijun Cui*[1], *Shaoqi Mou*[3], *Lie Ren*[1], *Yonggui Yuan*[4]*, *Xinhua Shen*[2]* and *Gang Li*[5,6]

[1] School of Medicine, Southeast University, Nanjing, China, [2] Department of Neurosis and Psychosomatic Diseases, Huzhou Third Municipal Hospital, The Affiliated Hospital of Huzhou University, Huzhou, China, [3] Department of Psychiatry, Wenzhou Medical University, Wenzhou, China, [4] Department of Psychiatry, Affiliated ZhongDa Hospital of Southeast University, Nanjing, China, [5] College of Engineering, Zhejiang Normal University, Zhejiang, China, [6] Key Laboratory for Biomedical Engineering of Ministry of Education, Department of Biomedical Engineering, Zhejiang University, Zhejiang, China

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Rafael Christophe Freire, Queen's University, Canada

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***Correspondence:**
Yonggui Yuan
yygylh2000@sina.com
Xinhua Shen
shenxinhuasun@sina.com

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Introduction: S100 calcium-binding protein B (S100B) is a neurotrophic factor that regulates neuronal growth and plasticity by activating astrocytes and microglia through the production of cytokines involved in Generalized Anxiety Disorder (GAD). However, few studies have combined S100B and cytokines to explore their role as neuro-inflammatory biomarkers in GAD.

Methods: Serum S100B and cytokines (IL-1β, IL-2, IL-4, and IL-10) of 108 untreated GAD cases and 123 healthy controls (HC) were determined by enzyme-linked immunosorbent assay (ELISA), while Hamilton Anxiety Rating Scale (HAMA) scores and Hamilton Depression Rating Scale (HAMD) scores were measured to evaluate anxiety and depression severity. This was used to help physicians identify persons having GAD. Machine learning techniques were applied for feature ordering of cytokines and S100B and the classification of persons with GAD and HC.

Results: The serum S100B, IL-1β, and IL-2 levels of GAD cases were significantly lower than HC ($P < 0.001$), and the IL-4 level in persons with GAD was significantly higher than HC ($P < 0.001$). At the same time, IL-10 had no significant difference between the two groups ($P = 0.215$). The feature ranking distinguishing GAD from HC using machine learning ranked the features in the following order: IL-2, IL-1β, IL-4, S100B, and IL-10. The accuracy of S100B combined with IL-1β, IL-2, IL-4, and IL-10 in distinguishing persons with GAD from HC was 94.47 ± 2.06% using an integrated back propagation neural network based on a bagging algorithm (BPNN-Bagging).

Conclusion: The serum S-100B, IL-1β, and IL-2 levels in persons with GAD were down-regulated while IL-4 was up-regulated. The combination of S100B and cytokines had a good diagnosis value in determining GAD with an accuracy of 94.47%. Machine learning was a very effective method to study neuro-inflammatory biomarkers interacting with each other and mediated by plenty of factors.

Keywords: neuro-inflammatory biomarkers, S100B, cytokines, Generalized Anxiety Disorder (GAD), machine learning

INTRODUCTION

Generalized Anxiety Disorder (GAD) is a chronic psychiatric disease characterized by persistent, excessive worry, which seriously impairs the social and cognitive function of patients, with a lifetime prevalence of up to 6.2% in the United States (1) and 5.3% in urban China (2). Unfortunately, the diagnosis of GAD mainly depends on the syndrome, including excessive, uncontrollable worry or a disproportionate sensation of potential risk (3), all of which provide a low diagnostic accuracy. This partly resulted in the lifetime prevalence of GAD varying from 0.1% in Nigeria to 6.2% in New Zealand (4). And even within China, it varies from 0.3% (5) to 4.1–4.6% (6). Thus, far, no specific laboratory test, brain scan, or bio-marker is available to distinguish GAD from other mental disorders and healthy populations (7, 8).

Previous studies have attempted to explore the biomarkers of GAD. Genetic (7) and neurobiological biomarkers (8) failed to be applied as trait biomarkers in anxiety disorders because anxiety disorders may have different subtypes with distinctive etiopathogenesis (9). However, chronic inflammation induced by the dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis in response to stressors has been identified as one of the etiologies of anxiety (10, 11). Neuro-inflammatory responses initiated by inflammatory cytokines and the subsequent neuronal dysfunction can lead to further glial activation and continued overexpression of inflammatory cytokines, which eventually cause mental disorders such as anxiety and depression (12, 13). Inflammatory biomarkers such as C reactive protein (CRP) and cytokines have been studied to identify GAD from healthy controls (HC). In their study, Tang et al. (14) reported increased CRP in GAD and a positive correlation with the severity of anxiety syndromes. Hou et al. (15) reported increased TNF-α in GAD patients compared to HC, but Vogelzangs et al. (16) found no difference between GAD and HC as well as other anxiety disorders.

Cytokines consist of pro-inflammatory cytokines such as IL-1β, IL-2, and IL-6 and anti-inflammatory cytokines such as IL-4 and IL-10 (17). Despite the fact that they are still poorly studied, the effects of these cytokines on GAD remain controversial (17). Additionally, just a limited number of studies have combined pro-inflammatory cytokines with anti-inflammatory cytokines in their research.

Peripheral cytokines are mediated by cortisol and other factors such as S100 calcium-binding protein B (S100B) and interact with each other through complex mechanisms. S100B is secreted by astrocytes in gray matter and expressed by oligodendrocytes in white matter, which modulates the proliferation and differentiation of neurons and glial cells (18). S100B is a neurotrophic factor and neuronal survival protein secreted in response to stress; S100B is always up-regulated in acute stress environments (19). A meta-analysis by Schroeter et al. (20) revealed that S100B serum levels were consistently increased in patients with depression [major depressive disorder (MDD)] and decreased after antidepressant treatment. Brown et al. (21) estimated the lifetime comorbidity of MDD and GAD as up to 90%, suggesting GAD and depression may share specific etiology and pathogenesis mechanisms. Meryem (22) reported decreased S100B levels in the hippocampus and prefrontal cortex in anxious diabetic rats, which were revised by anti-anxiety therapy. Compared to the studies on S100B levels in depression, the research on S100B as a biomarker in anxiety, especially in GAD, is limited. As a glia-originated protein, S100B activates IL-1β production through mitogen-activated protein kinase (MAPK) pathways (23). Studies have evaluated the ability of IL-8 and IL-10 combined with S100B as risk factors in alcohol use groups (24). But whether the interactions of S100B with different cytokines induce different affective diseases is still a question (25).

The neuro-inflammatory responses in GAD involve many cytokines and other factors, and cytokines are regulated by many factors and interact with each other. So, a combination of different cytokines and upstream regulators such as S100B is more likely to reveal the neuro-inflammatory responses in GAD. Existing evidence suggests that GAD patients may have abnormal serum S100B and cytokines levels, but the specific change of S100B and cytokines in GAD is still a question, and the roles of cytokines in predicting the diagnosis of GAD deserve further study. To address these lacunae, machine learning techniques for big data may help handle the multiple and asymmetrically distributed variables (26). Machine learning techniques create a paradigm shift in the prediction of diagnosis using complex computational algorithms fed by large data sets (27, 28). Recent studies have shown good prediction abilities in distinguishing patients with bipolar disorder from HC with serum biomarkers (28). We, therefore, conducted this study using machine learning algorithms to determine the roles of S100B and cytokines as neuro-inflammatory biomarkers in GAD.

MATERIALS AND METHODS

Subjects

Patients who met the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for GAD were recruited from Huzhou Third Municipal Hospital between June 2018 and June 2019. Inclusion criteria: (1) Han nationality; (2) age range 18–65 years; (3) Hamilton Rating Scale for Anxiety (HAMA) scores $\geq$ 17 and 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) $\leq$14; (4) free of major psychotropic drugs or psychotherapy for at least 4 weeks before inclusion. Exclusion criteria: (1) any mental illness requiring medical intervention such as dementia, schizophrenia, bipolar disorder, major depressive disorder, and so on; (2) substance abuse disorders; (3) inability to complete examination and questionnaires; (4) with severe physical diseases (including epilepsy, severe cardiopulmonary, malignant tumor or hematopathy, and autoimmune diseases); (5) taking immunomodulatory drugs, such as glucocorticoids, immunomodulators, antipyretic and analgesic drugs in the preceding 6 months; and (6) pregnant women. Healthy controls recruited from the local community were assessed by a psychiatrist using the Structural Clinical Interview for DSM-IV Disorders (SCID). The HAMA scores of all control subjects were $\leq$7. Those with a history of any psychiatric disorder were excluded. The protocol was approved

by the Ethics Committee of Huzhou Third Municipal Hospital. Written informed consent was obtained from all participants before enrolling. Based on our pilot study, a sample size of 120 was calculated using PASS11.0 with $\alpha = 0.05$ and $\beta = 0.10$. About 146 GAD patients who matched the criteria were enrolled, of which 26 refused blood tests, and blood samples from 12 patients failed to detect cytokines and S100B. According to the match ratio of 1:1, 120 HC were required, and 123 HC cases were actually enrolled.

Rating Symptoms

The severity of the GAD symptoms was rated using HAMA, which was administered by a single trained evaluator. The HAMA entails assessing 14 items and measuring them on a 5-point scale: 0 (symptoms not present), 1 (mild symptoms), 2 (moderate symptoms), 3 (severe symptoms), and 4 (very severe symptoms). The total score is then calculated by summing the scores of the 14 items. The evaluator and laboratory staff were blind to the purpose of the study. In addition, the evaluator was blind to the laboratory data, and the HAMA scores were not disclosed to the laboratory staff. To maintain blindness, a trained research coordinator managed all data and schedules.

Determination of Serum S100B and Cytokines

From the GAD patients, 10 ml blood samples were collected from June 2018 to June 2019 in two sterile tubes between 7 and 8 a.m. using a standard sterile preparation before treatment. Blood samples were also taken from the HC at the same time and centrifuged for 15 min at 2,500 rpm. The cell-free serum was pipetted and aliquoted in 2 ml standard freezer vials, which were then stored within 2 h at −80°C to determine the serum S100B and cytokine levels. The inflammatory cytokines, including IL-1β, IL-2, IL-4, and IL-10, were measured by ELISA. The ELISA kits were manufactured by Shanghai Yaoyun Biotechnology Limited Company. And S100B ELISA kit was manufactured by Wuhan USCN Business Co., Ltd. The sensitivity of this assay for detecting S100B, IL-1β, IL-2, IL-4, and IL-10 was 1.0 pg/L. To minimize inter-assay variations, S100B and cytokines were determined after all samples were collected.

For S100B, the inter- and intra-assay coefficients of variation were 5 and 6.5%, respectively. For cytokines, the inter- and intra-assay coefficients of variation were <10%.

Feature Ranking and Classification

Feature ranking is of great significance in the clinical diagnosis of GAD, and important features can be extracted to assist doctors in clinical diagnosis. A feature ranking method with correlation bias reduction (RFE-CBR) based on a support vector machine (SVM) was applied to calculate the weight of all features (S100B, IL-1β, IL-2, IL-4, and IL-10). The feature with the least effect on the SVM performance was removed. The rest of the features performed the same procedure to remove the least effect feature until all the features were removed. Feature ranking was determined based on the removal order (i.e., the last deleted feature was the most important). In this study, 100 repetitions of cross-validation were performed on the training set (90% samples for the training) with the SVM-RFE-CBR method, resulting in a 100 × 5 matrix (where 5 denotes the number of features). The final ranked feature order was obtained from the 100 × 5 matrix according to the feature emerging frequency (e.g., the first important feature is the most common feature in the first column of the 100 × 5 matrix; the second important feature is the two most common features in the first two columns, and so on).

Machine Learning Model

In this study, three popular machine learning models, SVM, random forest (RF), and integrated back propagation neural network based on bagging algorithm (BPNN-Bagging), were utilized with 10-fold cross-validation (80% for the training set and 20% samples for the testing set, respectively) (Zhang et al., 2017). Specifically, the radial basis function was applied as the kernel function for the SVM, and a decision tree number was set to 500 in the RF. As for BPNN-Bagging, 80% of features and training samples were implemented for feature perturbation and sample perturbation, and 100 BPNNs with 6 hidden layers and 100 neuron cells were used as the base learners. Then a voting method was performed on the outputs of 100 base learners to gain the final result.

Statistical Analysis

SPSS 19.0 for Windows was used to analyze the data. Data were generally reported as mean ± SD. A Chi-square test and the independent *t*-test were performed to compare demographic data and the serum S100B/cytokines levels between GAD patients and HC. The distributions of all variables were checked by the Kolmogorov–Smirnov test, and all showed equal or nearly equal distribution. A receiver operating characteristic (ROC) curve was applied to compare the predicting value of baseline S100B and cytokines levels in GAD, Relationships between S100B/cytokines and clinical variables (age, HAMA scores, and illness duration) were evaluated using Pearson correlations.

RESULTS

Demographic Information of GAD and HC

Demographic information of 108 GAD cases and 123 HC were compared, and, as shown in **Table 1**, there was no significant difference in the male/female ratio, age, and BMI (Body Mass Index) between the two groups. The scores of HAMA and HAMD in GAD were 22.5 ± 3.1 and 9.6 ± 2.9, respectively. The mean illness duration of GAD was 24.4 ± 37.5 months.

The ROC Value of S100B, IL-1β, IL-2, IL-4, and IL-10 in GAD

The ROC area of S100B, IL-1β, IL-2, and IL-4 in the diagnosis of GAD (shown in **Figures 1**, **2**) was 0.740 ± 0.032, 0.900 ± 0.021, 0.920 ± 0.018, and 0.696 ± 0.037 respectively, and all of them suggested a good predicting value of $P < 0.001$. The ROC area of IL-10 was 0.544 ± 0.038, with a predicting value of $P = 0.251$.

TABLE 1 | Demographic information of GAD and HC.

Characteristics	GAD ($n = 108$)	HC ($n = 123$)	χ^2/t	*P*-value
Sex (male/female)	30/78	40/83	0.612	0.434
Age (years)	49.62 ± 11.28	47.54 ± 8.41	1.567	0.119
BMI (kg/m^2)	21.90 ± 3.39	21.64 ± 2.99	0.620	0.536
HAMA score	22.52 ±2.99	NA		NA
HAMD score	9.63 ± 2.91	NA		NA
Illness duration (month)	24.42 ± 37.47	NA		NA

GAD, (people with) generalized anxiety disorder; HC, healthy controls; BMI, Body Mass Index; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; NA means the value is null.

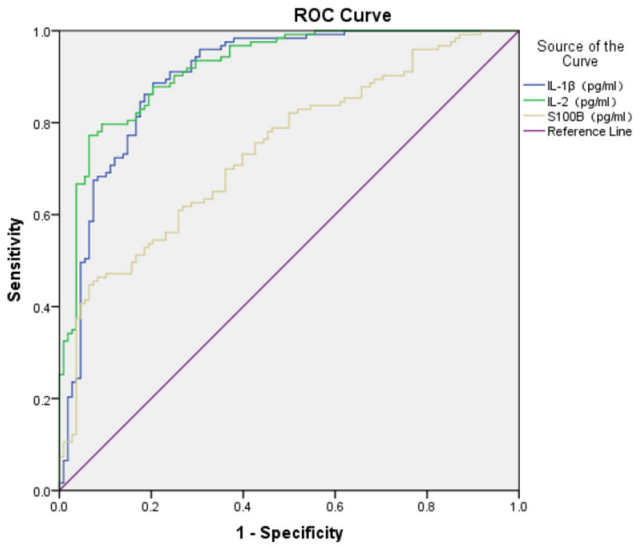

FIGURE 1 | ROC of S100B, IL-1β, IL-2 in diagnosis of GAD.

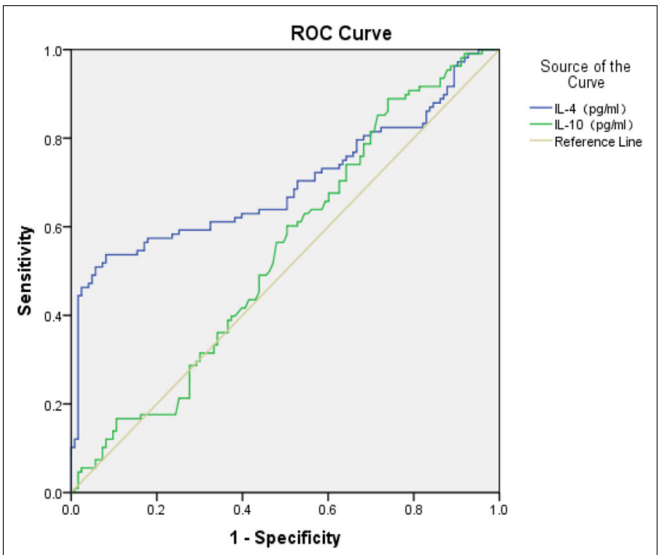

FIGURE 2 | ROC of IL-4, IL-10 in diagnosis of GAD.

Clinical Characteristics Ranking and Statistics

The clinical characteristics ranking in the differential diagnosis of GAD and HC using the SVM-RFE-CBR method resulted in the following ranking order: IL-2, IL-1β, IL-4, S100B, and IL-10. As shown in **Figure 3** and **Table 2**, the baseline serum S100B, IL-1β, and IL-2 levels of GAD cases were significantly lower than HC ($P < 0.001$), the IL-4 levels were higher than HC ($P < 0.001$), and there was no significant difference in IL-10 between the two groups ($P = 0.215$).

The Diagnosis of GAD Based on Machine Learning

The accuracy of S100B combined with IL-1β, IL-2, IL-4, and IL-10 in classifying GAD and HC was 91.06 ± 2.42% using SVM, 92.73 ± 3.82% using RF, and 94.47 ± 2.06% using BPNN-Bagging (**Table 3**).

Relationship Among GAD Influence Factors

The correlation of serum S100B and IL-1β, IL-2, IL-4, and IL-10 levels in GAD cases with age was $r = -0.065$, $P = 0.505$, $r = -0.147$, $P = 0.128$, $r = -0.056$, $P = 0.568$, $r = 0.013$, $P = 0.893$, and $r = -0.113$, $P = 0.244$, respectively. The correlation between serum S100B and IL-1β, IL-2, IL-4, and IL-10 was $r = 0.175$, $P = 0.070$, $r = 0.237$, $P = 0.014$, $r = 0.261$, $P = 0.006$, and $r = 0.055$, $P = 0.589$, respectively. The correlation between serum S100B and HAMA score, and illness duration was $r = -0.386$, $P < 0.001$ and $r = 0.080$, $P = 0.410$, respectively.

DISCUSSION

This study, to our knowledge, is the first to combine general statistical methods and machine learning to explore the characteristics of S100B and cytokines (IL-1β, IL-2, IL-4, and IL-10) in GAD patients and their role in diagnosing GAD. Currently, the exact pathology of GAD has not been well-established and is still a controversial subject. Many studies have concentrated on the neuro-inflammation pathogenesis of GAD based on the changes in cytokines as cytokines play a key role in the neuro-inflammation pathway (29, 30). Cytokines, including pro-inflammatory IL-1β, IL-2, and IL-6, and anti-inflammatory IL-4 and IL-10, are mediated by many factors such as S100B (30). S100B is mainly expressed in glial cells and plays its biological roles depending on its concentrations (19, 31–33). It acts as a growth and protection factor for neurons and astrocytes in nanomolar concentrations, and assumes neurotoxic roles, and induces the apoptosis of neurons and astrocytes in micromolar concentrations (34). The results of this study indicate that serum S100B level is significantly down-regulated in GAD patients compared to healthy controls. Few researchers have reported controversial results of S100B on anxiety. Bergh et al.

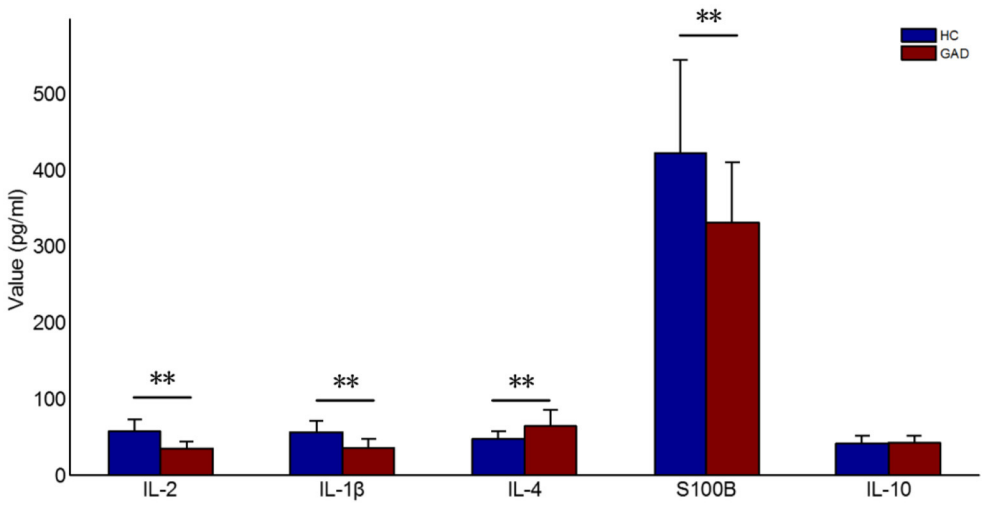

FIGURE 3 | Feature ranking results of S100B, IL-1β, IL-2, IL-4, IL-10. $^{**}p < 0.001$.

(35) reported that patients with elevated S100B suffered more anxiety 3–6 years after cardiac surgery. Tomas et al. (36) found no correlation between cerebrospinal fluid S100B levels and anxiety symptoms. Another study found that S100B-positive cells and anxiety levels were markedly increased after treatment (37). But our study found that serum S100B was negatively correlated with anxiety syndromes. Buschert et al. (16) reported that elevated S100B levels increased behavioral and neural plasticity in response to acute environmental stimuli, but chronic mild stress decreased S100B in hippocampal and cerebrospinal fluid and can be revised by fluoxetine (18). S100B may be a protective factor in the acute stage of anxiety when individuals face stress. But with the development of the disease, the down-regulation of S100B may be a result of decompensation, which is closely related to the chronic pathological genesis of GAD, and the illness duration of GAD always lasts more than 6 months (chronic anxiety). S100B is mainly expressed in astrocytes and oligodendrocytes in the white matter (19), and in nanomolar concentrations, it stimulates neurite growth and increases neuronal maturation and glial cell proliferation. Reduced volumes of white matter in the dorsolateral prefrontal cortex, anterior limb of the internal capsule, and midbrain were observed in GAD patients (38). The reduced white matter volumes may help explain the down-regulation of S100B levels in GAD patients, but the interaction between the two factors needs further study.

Both central and peripheral immune dysregulation has been researched as an etiology of anxiety disorders. The results of our study reveal that GAD patients have lower serum and pro-inflammatory IL-1β and IL-2 cytokines and higher IL-4 anti-inflammatory cytokines with no dysregulated IL-10. Given the consistent hyper activation of inflammatory cytokines in depression, the results in anxiety are always controversial. Zhen Tang (14) found that serum levels of CRP, IL-1α, IL-2, IL-6, IL-8, IL-12, IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF) were significantly higher in the GAD group compared to the control group, while Vogelzangs found (31) no associations with IL-6 or TNF-a in anxiety disorders including GAD. Among people with alcohol use disorder, IL-10 was negatively associated with anxiety score (39). Labaka Ainitze et al. (40) reported chronic social instability stress induced anxiety-like behavior and decreased IL-10 expression in the hippocampus of the female mice, while no differences in pro-inflammatory cytokines such as IL-1β and IL-6 were observed. Our study found decreased pro-inflammatory cytokines of IL-1β and IL-2 as well as increased anti-inflammatory cytokines IL-4, while IL-10 showed no obvious difference between GAD and control. Both cytokines and serum S100B showed a promising diagnosis value in GAD based machine learning. The classifying accuracy was 94.47 ± 2.06%. Considering the complex interaction of inflammatory mediators, cytokines in depression and other mental disorders are usually defined as networks. A single specific cytokine extends very limited influence on the whole net, but

TABLE 2 | Clinical characteristics of GAD and HC.

Characteristics	GAD ($n = 108$)	HC ($n = 123$)	*P*-value
S100B (pg/ml)	330.28 ± 79.86	421.82 ± 122.99	<0.001
IL-1β (pg/ml)	35.52 ± 11.30	56.11 ± 14.96	<0.001
IL-2 (pg/ml)	34.68 ± 8.72	57.02 ± 16.28	<0.001
IL-4 (pg/ml)	63.71 ± 21.44	46.73 ± 10.57	<0.001
IL-10 (pg/ml)	42.65 ± 9.36	41.00 ± 10.62	0.215

TABLE 3 | Clinical characteristics of GAD and HC.

Model	SVM	RF	BPNN-bagging
Accuracy (%)	91.06 ± 2.42	92.73 ± 3.82	94.47 ± 2.06

certain key cytokines may have a huge impact on a specific disorder [45]. With the help of machine learning methods, we found the feature ranking in the differential diagnosis of GAD and HC to be IL-2, IL-1β, IL-4, and IL-10. From the ranking, we can infer that IL-2 and IL-1β were key plots in the neuro-inflammation pathogenesis of GAD compared to IL-4 and IL-10, which deserve more attention in future studies.

In addition, inflammatory cytokines are influenced by many factors in anxiety disorder (30). The relation between age and cytokines has no positive connections. But it was found that serum S100B was positively correlated with IL-2 and IL-4, while it had no correlation with IL-1β and IL-10. Evidence suggests that S100B stimulates mitogen-activated protein kinase (MAPK) pathways and then induces an increase in microglial IL-1β production, and each MAPK to IL-1β production depended on the activating stimulus (23). This implies that different glial activators use distinct sets of signaling pathways to induce different inflammatory cytokines changes, which develop into different central nervous system diseases in microglia. Preliminary studies also show that S100B upregulates IL-1β and TNF-αexpression in microglia *via* the receptor for advanced glycation end products and later induces upregulation of COX-2, which eventually causes brain damage (30). Compared to IL-1β, S100B had a closer association with IL-2 in GAD in our study, though no direct evidence had been found between S100B and IL-2. Based on the results of our study, it can be inferred that the roles of S100B in the neuro-inflammation pathway of GAD may be mainly *via* the activating of IL-2 upregulation, so the downregulation of S100B coordinated with IL-2 in our work may be interpreted from this point.

There are a few limitations to our study. (1) The sample size is too small to prove that S100B's value in the neuro-inflammation pathway of GAD. (2) It would have been better to analyze the results in subgroups (sex and age), but the impact would be decreased. Samples well-matched in age and sex would be ideal for subsequent studies. (3) Although we tried to eliminate the effects of depression syndromes, GAD has high comorbidity with MDD, and stricter inclusion criteria could be helpful in future studies. (4) If we can acquire more dynamic changes in S100B and cytokines levels during the treatment (we did not collect blood samples post-intervention), the dynamic role of S100B and cytokines in the neuro-inflammation pathway of GAD will be clearer. (5) There are so many cytokines, and their inflammatory status is affected by many factors. Therefore, whether the results in this study can be duplicated in subsequent trials with other cytokines is still a question.

CONCLUSION

In conclusion, our study adds to the literature by showing that serum S-100B, IL-1β, and IL-2 levels were down-regulated while IL-4 was up-regulated in persons with GAD. A combination of S100B and cytokines had a better diagnostic value with an accuracy of 94.47% than any single factor. S100B, IL-1β, IL-2, and IL-4 are very effective neuro-inflammatory biomarkers of GAD according to the clinical characteristics ranking and statistical results. There are many cytokines and regulatory factors in the neuro-inflammation pathway of GAD, and it is difficult to conclude that any specific cytokine or relevant indicator can be applied as a standard biomarker to monitor the pathological process of GAD, though limited factors were investigated in this study. Machine learning methods have been demonstrated to be very effective in studying neuro-inflammatory biomarkers interacting with each other and mediated by plenty of factors. Therefore, there are good reasons to believe that machine learning methods will play a more effective role in studying the pathological inflammatory process of GAD, which may be a network in the future compared to general statistical methods.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Huzhou Third Municipal Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

Conception and design: YY and XS. Administrative support: ZS. Provision of study materials or patients: ZS and LR. Collection and assembly of data: ZS, SM, and GL. Data analysis and interpretation: LC. Manuscript writing and final approval of manuscript: All authors.

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The Relationship Among BDNF Val66Met Polymorphism, Plasma BDNF Level, and Trait Anxiety in Chinese Patients With Panic Disorder

Lijun Chu, Xia Sun, Xiaoju Jia, Dazhi Li, Ping Gao, Yong Zhang and Jie Li**

Laboratory of Biological Psychiatry, Institute of Mental Health, Tianjin Anding Hospital, Mental Health Center of Tianjin Medical University, Tianjin, China

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Edited by:
Yuqun Zhang,
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***Correspondence:**
Yong Zhang
zhyzhangyong003@163.com
Jie Li
jieli@tjmhc.com

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Background: Brain-derived neurotrophic factor (BDNF) is a candidate for susceptibility locus of Panic disorder (PD). However, the findings about the role of the BDNF Val66Met variant in PD were not consistent. Till now, the relationship between BDNF Val66Met polymorphism and anxiety-related traits in PD patients has been rarely explored. This study aimed to explore the relationship among BDNF Val66Met polymorphism, plasma BDNF level and anxiety-related trait in Chinese PD patients.

Method: This multi-center study included 116 PD patients and 99 health controls. We detected single-nucleotide polymorphism (SNP) of BDNF rs6265 (Val66Met) and BDNF plasma level in the two groups. In addition, PD patients were administered the State-Trait Anxiety Inventory (STAI), Panic Disorder Severity Scale-Chinese Version (PDSS-CV) and Hamilton Anxiety Rating Scale (HAMA-14). Quantitative comparison of the differences of BDNF concentration among subjects with different genotypes and association between BDNF Val66Met genotype and trait anxiety were performed.

Results: There were no significant differences in the genotype frequency ($p = 0.79$) or allele frequency ($p = 0.88$) between PD patients and health controls. BDNF plasma levels of PD patients were significantly lower than those in control group ($p = 0.003$). BDNF plasma levels of the Met/Met genotype were significantly lower than those of Val/Met genotype in PD patients ($p = 0.033$). PD patients carried Met/Met genotype showed significantly higher scores in STAI trait compared to those carried Val/Val genotype ($p = 0.045$) and Val/Met genotype ($p = 0.018$). STAI trait scores of PD patients with agoraphobia were significantly higher than those of patients without agoraphobia ($p < 0.05$). The ANCOVA showed that the dependent variable STAI trait score was significantly affected by factor "genotype" (Val/Val, Val/Met, Met/Met, $p = 0.029$), and covariate "agoraphobia" ($p = 0.008$). In this model, 11.5% of the variance of the STAI trait score was explained by the BDNF genotype. Contrast analysis showed STAI trait scores of Met/Met subjects were significantly higher than those of Val/Met ($p = 0.018$) and Val/Val individuals ($p = 0.045$).

Conclusion: We found that anxiety trait was associated with the BDNF polymorphism in PD patients. BDNF Met/Met genotype may decrease plasma BDNF level and increase trait anxiety in panic disorder.

Keywords: panic disorder, BDNF (brain derived neurotrophic factor), gene polymorphism, BDNF plasma level, trait anxiety

INTRODUCTION

Panic disorder (PD) is characterized by recurrent and unexpected panic attacks, persistent concerns about future attacks and significant changes in behavior to avoid attacks. Panic attacks are defined as an abrupt episode of severe fear reaching a peak within several minutes, accompanied by a range of additional physiological or cognitive symptoms (1), which makes PD different from other anxiety disorders. Panic disorder is one of the most prevalent and disabling psychiatric disorders with a lifetime prevalence of 2–4% (2), while in primary care settings, the prevalence of panic syndromes is around 10% (3). The 12-month prevalence of PD is higher among women, with the female-to-male ratio as high as 2.8 (4). About 25% PD patients are comorbidity of agoraphobia, which increases severity and impairment compared with those without agoraphobia (5). Various lines of evidence suggest that both genetic and environmental factors could play important roles in contributing to PD. Family and twin studies estimate 43% of heritability for PD (6), with a relative risk of PD in proband's first-degree relatives being 8 times higher than that of healthy controls in a large-scale investigation (7). However, the genetic pathogenesis of PD remains unknown.

Brain-derived neurotrophic factor (BDNF), a neurotrophin hypothesized to limit or repair the damage caused by stress, is considered to be one plausible relevant genetic factor. BDNF plays a key role in functions and development of brain. BDNF conditional mutant mice absent of central BDNF were found to be hyperactive after exposure to stress, and had higher level of anxiety when evaluated in the light/dark exploration test (8), indicating serotonergic dysfunction might be involved in this behavioral abnormality in mutant mice. Another animal study reported that chronic administration of antidepressants promoted expression of BDNF mRNA in the rat cerebral cortex (9). Likewise, major depressed patients could display lower serum BDNF levels (10, 11), but after antidepressant treatment, the concentration of serum BDNF was higher than before (11). BDNF gene may be implicated in the putative common pathophysiology of depression and anxiety. One frequent, non-conservative polymorphism in the human BDNF gene (single nucleotide polymorphism database [dbSNP] number rs6265) has been identified, which produces a valine (Val)-to-methionine (Met) substitution at codon 66 (Val66Met). Several studies have suggested that the Met allele is related to decreased hippocampal volume and abnormal hippocampal activation in human subjects (12–14), and the hippocampus were implicated in regulating the state of mood. It could be expected that BDNF Val66Met polymorphism might influence behavior and anxiety.

The proportion of Met allele carriers of BDNF gene is significantly higher in Asians (41%) than that in Caucasians (approximately 18%), indicating an ethnic difference in the frequencies of the SNP (Val66Met) of the BDNF gene (15). Therefore, the results of BDNF Val66Met should be interpreted by racial stratification. A meta-analysis of population-based, case-control studies on BDNF Val66Met, which considered the dominant ethnicity Caucasian or Asian, suggested that the 66Met allele acted as a protective effect for substance-related disorders and exerted a risk factor for eating disorders and schizophrenia (16). Unfortunately, recent findings on relationship between the functional BDNF Val66Met and psychopathology in PD have yielded inconsistent outcomes. Some findings (17–19) reported that the BDNF gene polymorphisms are not associated with PD in neither Chinese nor Japanese population, while a meta-analysis revealed a significant association between the BDNF Val66Met and panic disorder, suggesting the Val66Met polymorphism of BDNF gene be a susceptibility factor for PD (20). The discrepancy might due to different methodologies in different studies.

According to Cloninger's theory, temperaments, including trait anxiety, are dominantly vulnerable to genetic factors. In healthy subjects, two findings showed that Met allele was associated with anxiety-related personality (21, 22), while other study evidenced that Val/Val genotype obviously dominated on anxiety trait compared to Val/Met and Met/Met genotypes (23). Another finding even reported it is BDNF serum level, not BDNF Val66Met genotype, that was correlated with anxiety personality traits in healthy people (24). In a relatively large community sample, it was found that plasma BDNF concentration was associated with depression-related personality traits in men, but not in women (25). Still in healthy participants, plasma BDNF levels were confirmed to be significantly correlated with harm avoidance, a well-known anxiety-related personality trait (26). To date, researches on the relationship between BDNF variation and trait anxiety were mostly conducted in healthy subjects. Only one study focused on the association of BDNF variation with trait anxiety in PD patients (27), however, it did not consider the factor of peripheral BDNF concentration. The changes in plasma BDNF levels could reflect variation in the release of BDNF from the brain (28). In addition, it is reported that serum and cortical BDNF levels are positively correlated (29), suggesting that it can reflect the BDNF level in the brain as well. Considering that serum BDNF is predominantly derived from clotted peripheral platelets, plasma BDNF might represent a more reliable and sensitive marker of BDNF in the brain compared to serum BDNF (30).

TABLE 1 | Demographic characteristics and plasma BDNF levels between PD group and HC group.

	PD ($n = 116$)	HC ($n = 99$)	χ^2/F	P
Gender (male/female)	49/67	42/57	0.24	0.62
Age (year)	47.62 ± 10.56	49.95 ± 10.43	−1.52	0.13
Marriage (married/single)	101/15	82/17	2.04	0.15
Education (L/M/H)	28/53/35	20/52/27	4.68	0.09
Occupation (labour/staff)	52/64	43/56	0.02	0.89
Plasma BDNF (ng/ml)	1.72 ± 1.02	2.11 ± 0.85	9.21	**0.003***

H, an education level of junior college or above; L, an education level lower than junior high school; M, an education level of junior high school or above but lower than junior college. PD, Panic disorder; HC, Healthy control. Bold values are significant at P < 0.05.

To the best of our knowledge, there is a lack of study on the association among BDNF Val66Met polymorphism, plasma BDNF concentration and anxiety-related personality traits in PD. We first carried out such innovative research. In this study, we examined the association between BDNF gene polymorphism and pathogenesis of panic disorder, and explored whether anxiety trait is associated with plasma BDNF level and BDNF Val66Met genotype in PD patients.

MATERIALS AND METHODS

Participants and Study Design

Patients with PD were recruited from outpatient or inpatient department in 3 general hospitals (First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin Academy of Traditional Chinese Medicine Affiliated Hospital, and Tianjin Chest Hospital) and 1 psychiatric hospital (Tianjin Anding Hospital) in Tianjin, China.

We recruited patients based on the following inclusion criteria: (a) aged from 18 to 60 years; (b) diagnosis of PD was conducted according to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental fifth edition (DSM-5) (SCID) criteria through a psychiatric interview; (c) total score of Hamilton Anxiety Scale (HAMA-14) ≥14; (d) total score of Panic Disorder Severity Scale–Chinese Version (PDSS-CV) ≥10. Exclusion criteria of participants included: (a) neurological diseases, severe physical diseases, comorbid other psychiatric disorder except agoraphobia. (b) use of antidepressant treatments in the past 4 weeks; (c) any physical therapy history (such as MECT and rTMS) in the past three months. Healthy controls (HCs) matched in gender, age and education levels were recruited from the local community by advertisement. The SCID was also applied to exclude lifetime prevalence of current diagnosis of both PD and other psychiatric disorders. The study protocol was approved by the Ethics Committees of the four hospitals mentioned above, and written informed consents were obtained from all participants.

Measurements

We obtained all subjects' demographic information by a self-designed questionnaire (gender, age, marital status, education level, occupation type, past medical history, family history). PD patients were also noted their illness duration, current episode duration and whether comorbid agoraphobia.

Before study began, total two raters in Tianjin Anding Hospital who were responsible for all assessments received training program on the use of questionnaires and clinical scales. After training, repeated assessment showed that the inter-rater correlation coefficient (ICC) on the total scores of PDSS-CV and HAMA-14 were greater than 0.8. We evaluate the severity of panic symptoms and whole anxiety through the Panic Disorder Severity Scale-Chinese Version (PDSS-CV) and Hamilton Anxiety Rating Scale (HAMA-14), respectively. PDSS-CV includes seven items: panic attack frequency, distress during panic attacks, anticipatory anxiety, agoraphobic fear and avoidance, interoceptive fear and avoidance, social impairment and occupational impairment. Each item is rated on a 5-point from 0 to 4. The total score ranges from 0 to 28. The cut-off scores of this scale for severity are as follows: score 8–10 is slight; 11–13 is moderate; 14–16 is marked, and 17 and above is the most severe. The PDSS-CV has been shown excellent reliability and validity in measuring the severity of panic symptoms in Chinese patients with PD (31). HAMA-14 is one of the most widely used rating scales for the severity of anxious symptoms with good reliability and validity (32). Besides, HAMA-14 comprised 14 items, and each item is scaled by a five-point Likert ranging from 0 (absent) to 4 (severe). The total score of HAMA-14 ≥14 means definite anxiety symptoms. The Chinese version of the HAMA-14 has been demonstrated to have good reliability and validity (33). State-Trait Anxiety Inventory is a self-report assessment of state anxiety and trait anxiety, including two subscales, State-Trait Anxiety Inventory-State (STAI-S) and State-Trait Anxiety Inventory-Trait (STAI-T) (34). STAI-S and STAI-T are used for assessment the temporary condition of state anxiety and the more general and long-standing quality of trait anxiety, respectively. Each subscale consists of 20 items. The STAI-S scale is rated on 4-point likert scale (1 = not at all, 2 = somewhat, 3 = moderately and 4 = very much). Each STAI-T item is rated on a 4-point Likert scale as well (1 = rarely, 2 = sometimes, 3 = often and 4 = almost always). STAI has been shown to have good internal consistency and test-retest reliability (35).

Genotyping and Detection of BDNF Levels

In the early morning, we took 5 mL of fasting venous blood from each patient, then spilt and stored at −80°C until later detection of BDNF plasma level and BDNF genotypes (rs6265, Val66Met). A dedicated experimental technician measured plasma concentrations of BDNF by enzyme-linked immunosorbent assay (ELISA) kit (DG10522H, Lvyuan Biotechnology) and a standard microplate reader (EL10A, BIOBASE). Two experimental technicians conducted all genotyping based on the standard procedures. The BDNF rs6265 SNP was performed via polymerase chain reaction (PCR). (The primers used for the PCR: forward 5′-ACT CTG GAG AGC GTG METT-3′ and reverse 5′-ATA CTG TCA CAC ACG CTC−3′). These samples were tested in 11 plates. The inter-and intra-assay coefficients of variation were <15%.

Statistical Analysis

All BDNF SNPs in the present study were tested for a chi-square test-based Hardy-Weinberg equilibrium (HWE) program. First, the chi-square tests and analysis of variance (ANOVA) were used to compare demographic characteristics and plasma BDNF levels between PD group and HC group. Then, the chi-square tests were used to compare genotype distributions and allele frequency between PD patients and healthy controls. Further, the chi-square tests and ANOVA were used to compare the demographic information, clinical variables and plasma BDNF levels among three BDNF genotype subgroups. Last, we used the *t* test and ANOVA to test related variables on STAI state scores and trait scores. The effects of genotype, gender, and agoraphobia on anxiety trait and anxiety state were computed with ANCOVA. Multiple tests were adjusted using Bonferroni corrections. All tests were performed with a two-tailed type-I error rate of $p < 0.05$. Statistical calculations were carried out using SPSS 20.0.

RESULTS

Demographic Characteristics and Plasma BDNF Levels Between PD Group and HC Group

As shown in **Table 1**, there were no significant differences in gender, age, marriage, education level, occupation between PD patients and healthy controls. For the PD patients, the duration of illness was 37.8 ± 59.6 months, and the current duration was 4.6 ± 14.1 months. Twenty (17.24%) PD patients had family history, thirty-four (29.31%) patients were first-episode patients, and thirty-three (28.45%) patients were comorbid with agoraphobia. BDNF plasma level of PD patients were significantly lower than that of healthy controls ($F = 9.21$, $p = 0.003$). In addition, a negative correlation between plasma BDNF level with age ($r = -0.28$, $p = 0.003$) was found in PD group, indicating that older PD patients had lower plasma BDNF concentrations. Zero-order correlations indicate that the other covariates including gender were not associated with plasma BDNF levels ($p > 0.05$).

Genotype and Allele Frequencies of BDNF Val66Met for all Participants

The genotype distributions of the G196A SNP (rs6265) were in agreement with the Hardy–Weinberg equilibrium in both panic disorder patients ($\chi^2 = 2.84$, $p = 0.09$) and healthy control group ($\chi^2 = 0.44$, $p = 0.51$). The genotype frequency of Val/Val ($n = 42$), Val/Met ($n = 48$), Met/Met ($n = 26$) in panic disorder group was 36.2, 41.4, and 22.4% respectively. The frequency of the alleles in panic disorder group was Val= 56.9% and Met= 43.1%. No significant differences were observed in the allele frequency or genotype frequency between PD patients and healthy controls (allele Met, $p = 0.88$, OR 1.05, 95% CI 0.72–1.54; $p = 0.79$; **Table 2**).

Demographic Characteristics and Clinical Variables Among Different BDNF Genotype Subgroups

There were no significant differences in gender, age, marriage, education level, occupation type among BDNF genotype subgroups, neither in attack frequency, family history, comorbid agoraphobia, illness duration, current duration and STAI-S score, HAMA-14 score and PDSS-CV score (all $p > 0.05$). BDNF plasma levels and STAI-T scores among three BDNF genotype subgroups were found significantly different ($p < 0.05$). Furthermore, *post-hoc* Bonferroni comparisons showed that the BDNF plasma levels of PD patients with Met/Met genotype were significantly lower than those of Val/Met genotype ($p = 0.033$); STAI-T scores of PD patients with the Met/Met genotype were significantly higher than those of both Val/Met genotype ($p = 0.018$) and Val/Val genotype ($p = 0.045$) (**Table 3**).

Associations Between BDNF Plasma Level, BDNF Genotypes, and Anxiety Trait

There were no significant differences in gender, marriage, education level, occupation, attack frequency, family history, comorbid agoraphobia on STAI state scores (all $p > 0.05$). The same results were observed on STAI trait scores except comorbid agoraphobia. STAI trait scores of PD patients with agoraphobia were significantly higher than those of patients without agoraphobia (57.19 ± 9.422/50.68 ± 11.565, $p < 0.05$). Age was not correlated with neither STAI state ($r = 0.066$, $p = 0.481$) nor STAI trait ($r = 0.132$ $p = 0.158$). Neither STAI state ($r = 0.023$, $p = 0.806$) nor STAI trait ($r = -0.178$, $p = 0.055$) was correlated with BDNF plasma level.

The ANCOVA showed that the dependent variable STAI trait score was significantly affected by factor "genotype" (Val/Val, Val/Met, Met/Met: $F = 3.667$, $df = 2$, $p = 0.029$), and covariate "agoraphobia" ($F = 7.411$, $df = 1$, $p = 0.008$), but not by the factor "gender" ($F = 1.967$, $df = 1$, $p = 0.164$) or "gender × genotype" interaction ($F = 0.871$, $df = 2$, $p = 0.421$). In this model, 11.5% of the variance of the STAI trait score was explained by the BDNF genotype. Contrast analysis revealed that the STAI trait scores were higher in Met/Met subjects compared to those in Val/Met ($p = 0.018$) and Val/Val individuals ($p = 0.045$). With respect to the STAI state score, ANCOVA showed no significant effects of the factor "genotype" ($F = 0.104$, $df = 2$, $p = 0.902$), "gender" ($F = 0.686$, df = 1, $p = 0.409$), or "gender × genotype" interaction ($F = 0.169$, $df = 2$, $p = 0.845$).

DISCUSSION

Our main findings in this current study included: (a) BDNF plasma levels of PD patients were significantly lower than those of healthy controls, and BDNF plasma levels of Met/Met genotype were significantly lower than those of Val/Met genotype in PD patients; (b) Trait anxiety in PD patients was associated with BDNF Val66Met polymorphism and comorbid agoraphobia, but not with BDNF plasma concentration; (c) No significant differences were found in BDNF allele frequencies and the

TABLE 2 | Genotype distributions and allele frequency between PD patients and healthy controls.

		Genotype			p^a	Allele		p^b
	n	Val/Val	Val/Met	Met/Met		Val	Met	
PD	116	42 (36.2%)	48 (41.4%)	26 (22.4%)	0.79	132 (56.9%)	100 (43.1%)	0.88
HC	99	35 (35.4%)	45 (45.5%)	19 (19.2%)		115 (58.1%)	83 (41.9%)	

[a] $\chi^2 = 0.48$, $df = 2$.
[b] $\chi^2 = 0.02$, $df = 1$.
PD, Panic disorder; HC, Healthy control.

BDNF genotype distributions between PD patients and health control subjects.

Association of BDNF Plasma Level With BDNF Val66Met Polymorphism in PD

This current study revealed that there was a significant difference in plasma BDNF level between PD patients and healthy control subjects, which is consistent with previous research (36). Compared with BDNF Val carriers, the plasma BDNF levels of individuals with Met/Met genotype were the lowest in all of the PD patients. Some clinical researches also evidenced this association between the BDNF Met carrier and lower BDNF levels in the patients with major depressive disorder (37), schizophrenia, and bipolar disorder (38) respectively, suggesting the Met allele may play a key role in regulating BDNF protein expression (39). However, the results of researches in this area are inconsistent. For example, plasma BDNF concentration in Han Chinese heroin-dependent patients were not associated with BDNFVal66Met gene variants (40). And a finding with a relatively large community sample could not verify this association of plasma concentration of BDNF with Val66Met variant (25). Moreover, another study revealed significantly higher BDNF serum levels in Met carriers, compared with the Val/Val homozygotes in healthy subjects (24). The conflicting conclusions might result from different means of BDNF detection and the heterogeneity of diseases. Several technical issues influence serum or plasma BDNF levels such as clotting time, bioassays, temperature, and a second centrifugation to correct plasma levels, among others (41–43). Little data were collected on BDNF plasma concentration of different BDNF genotype subgroups in PD, more researches should be conducted.

Association Between BDNF Val66Met Polymorphism and Anxiety Trait in PD

We found PD carriers of BDNF Met/Met were more sensitive to anxiety. This study displayed BDNF Val66Met genotype was associated with anxiety trait in PD patients, in line with a previous study (27). Yoshiaki found that the STAI trait score was highest in the Met/Met group in patients with early-onset PD, whereas the STAI trait score of the Val/Val group tended to be higher for healthy subjects. Similarly, a meta-analysis found that healthy individuals with both Met/Met and Val/Met showed a statistically significant lower neuroticism score compared to healthy people with Val/Val (44). It seemed that BDNF Met allele might be protective factor for healthy controls but a risk for PD patients on anxiety or depression personality. Some researchers believed Met/Met subgroup was more sensitive to stress, and BDNF Met-early life stress interaction predicted elevated neuroticism, higher depression and anxiety levels in PD patients (27). Another study suggested that BDNF rs6265 had a significant interaction effect with Catechol-O-methyltransferase gene (COMT) polymorphism to neuroticism and anxiety trait in PD patients, instead of healthy control subjects (45). Furthermore, a neuroimaging study has found BDNF Val66Met polymorphism is associated with white matter connectivity of the body and splenium of the corpus callosum in PD, which involved in visual memory-related processing and cognitive and affective functions (46). And these functions may be major components of PD patients with higher anxiety sensitivity (47). A recent study revealed that depending on the BDNF Val66Met polymorphism, there was an interactive genetic association between 5-HTTLPR and anxiety, and the effect of 5-HTTLPR genotype on anxiety was fully mediated by functional connectivity between the left amygdala and the right dorsolateral prefrontal cortex (48). Taken together, genetic variety could play a crucial role in trait anxiety of panic disorder. It is reported that in a sample of sixty-four healthy participants, there are differential associations between the trait anxiety measure of harm avoidance (HA) and resting regional Cerebral Blood Flow (rCBF) in BDNF Val/Val and Met carriers in several regions relevant to stress regulation brain (49). However, at the behavioral level, the relationship between BDNF Val66Met polymorphism and HA is not confirmed, thus suggesting that its effect size may be relatively small, if there is a reliable genotype–HA relationship. The effects of BDNF Val66Met polymorphism on trait anxiety in PD and the underlying mechanisms awaits further research.

Other Findings on Trait Anxiety in PD

Considering that PD is as much as 2 times more prevalent in women than in men, a sex-specific vulnerability is involved in the etiology and/or maintenance of this disorder (50). However, we did not find sex difference on trait anxiety or state anxiety in PD. Possibly most women were during perimenopause period with average age of 46 years old. Only one study found women manifest greater trait anxiety than men did in agoraphobia patients with panic attacks (51), but other studies did not replicate this finding in panic disorder patients with agoraphobia (52, 53). It is suggested that the sex differences detected in

TABLE 3 | Demographic characteristics and clinical variables for PD patients separated by BDNF genotype.

	Val/Val ($n = 42$)	Val/Met ($n = 48$)	Met/Met ($n = 26$)	χ^2/F	*P*
Gender (male/female)	17/25	21/27	11/15	0.098	0.952
Age (year)	47.87 ± 10.00	45.02 ± 11.03	44.46 ± 11.04	1.164	0.316
Marriage (married/single)	38/4	40/8	23/3	1.073	0.585
Education (L/M/H)	12/17/13	12/23/13	4/13/9	1.920	0.750
Occupation (labour/staff)	18/24	23/25	11/15	0.318	0.853
Attack frequency (first-episode/recurrence)	11/31	17/31	6/20	1.549	0.461
Family history (yes/no)	7/35	9/39	4/22	0.149	0.928
Comorbid agoraphobia (yes/no)	10/32	13/35	10/16	1.769	0.413
Illness duration (month)	37.95 ± 69.24	34.49 ± 56.01	38.71 ± 46.52	0.055	0.946
Current duration (month)	4.16 ± 7.22	2.84 ± 3.66	3.14 ± 4.40	0.686	0.506
BDNF plasma level (ng/ml)	1.63 ± 0.96	2.02 ± 1.19	1.39 ± 0.65	3.623	**0.030***
STAI-T	51.53 ± 11.41	50.58 ± 12.01	58.07 ± 8.28	4.400	**0.014***
STAI-S	53.16 ± 12.88	53.05 ± 12.41	54.39 ± 12.36	0.104	0.902
HAMA-14	24.21 ± 8.86	20.81 ± 6.78	23.04 ± 8.04	1.786	0.172
PDSS-CV	15.71 ± 3.99	15.16 ± 3.30	14.71 ± 3.84	0.644	0.527

H, an education level of junior college or above; L, an education level lower than junior high school; M, an education level of junior high school or above but lower than junior college. STAI-T, State-trait Anxiety Inventory-Trait; STAI-S, State-trait Anxiety Inventory-State; HAMA-14, Hamilton Anxiety Rating Scale-14; PDSS-CV, Panic Disorder Severity Scale-Chinese Version. Bold values are significant at P < 0.05.

the former study (51) may have been statistically but not clinically significant.

In addition, we found that comorbid agoraphobia is associated with anxiety trait in PD. The relationship between agoraphobia and panic disorder remains unclear. PD patients with comorbid agoraphobia were more likely to emerge serious anxiety symptom and avoidance behavior, and agoraphobia was considered to result from recurrent panic attacks (54). A recent study also showed that patients with PDA (panic disorder with agoraphobia) had severer anxiety symptom and higher anxiety trait than those with PD alone (55). PDA patients were reported greater self-criticism and fatalism (56) and higher severity of fear of bodily sensation (57) than those with PD alone. Here, we highlight the importance of recognizing comorbid agoraphobia with PD.

Association Between BDNF Val66Met Polymorphism and Panic Disorder

Our findings found no association between BDNF Val66Met polymorphism and panic disorder, which was consistent with previous findings in Japanese and Chinese PD patients (17, 19, 27). This result indicated that BDNF rs6265 may not contribute to PD susceptibility. Reasons for the lack of association reported in various studies might partly be explained by the role of BDNF in conjunction with other "hypothetical" genes (58, 59). In addition, PD patients with the G-C haplotype for 196G/A (rs6265) and 11757G/C (rs16917204) may be more susceptible in the development of PD (60). Therefore, more researches with high-quality design, large samples are needed to explore the association between BDNF Val66Met variant and panic disorder.

LIMITATION

The limitations of our study come as follows. First, STAI score of healthy controls in different BDNF Val66Met genotypes were not evaluated. Hence, we cannot distinguish the levels of anxiety between PD patients and healthy controls. The lack of relevant data collection is a methodological limitation in this study. Second, the sample size was relatively small. Therefore, the effect of gender on anxiety trait in PD may be underestimated. Third, we only used STAI to test individual's anxiety trait, more anxiety-related traits could be evaluated by other scales such as the Harm Avoidance (HA) scale of Tridimensional Personality Questionnaire (TPQ), which may enhance credibility of the study. Moreover, the measure of trait anxiety, using self-administered questionnaires, may be susceptible to reporting bias. Fourth, this is a cross-sectional design, long-term psychopathology may not be reflected by a single point assessment. Last but not least, the interaction of gene plus gene should be considered, such as BDNF gene and COMT gene. And haplotype for the three SNPs (rs6265-rs16917204-rs56164415) in gene BDNF should be taken into consideration to explore BDNF gene polymorphism and anxiety trait.

CONCLUSIONS

In summary, we first explored the relationship among BDNF Val66Met polymorphism, plasma BDNF level and anxiety trait in PD patients. We found that BDNF Val66Met genotype is associated with anxiety trait in PD patients. BDNF Met/Met genotype may decrease plasma BDNF level and increase trait anxiety in panic disorder. However, due to the small sample and other limitations, these results should be replicated in a larger sample of high-quality study design.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committees of Tianjin Anding Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LC, JL, and YZ designed the study and obtained the data. XS undertook the analysis supervised by JL. LC and XS wrote the manuscript. XJ, DL, and PG performed the survey. All authors read the final manuscript and agreed with the text.

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The Mediating Role of Coping Style in the Relationship Between Sleep Quality and Burnout: A Cross-Sectional Study Among Psychiatric Nurses

Ming Yin[1†], Weiqin Li[1†], Qun Yang[2†], Yan Yue[1,3†], Xiaojia Fang[1,4], Zhong Yang[5], Xinda Wang[6], Qin Liu[1], Fanzhen Kong[1], Caifang Ji[1], Xiaoli Lv[1], Hao Wang[1], Nian Yuan[1], Zhe Li[1], Caiyi Zhang[4], Kan Li[7], Yang Yang[8] and Xiangdong Du[1]**

[1] Suzhou Guangji Hospital, The Affiliated Guangji Hospital of Soochow University, Suzhou, China, [2] Nanchong Psychosomatic Hospital, Nanchong, China, [3] Medical College of Soochow University, Suzhou, China, [4] Affiliated Hospital of Xuzhou Medical University, Xuzhou, China, [5] The Third People's Hospital of Changshu, Suzhou, China, [6] Taicang Third People's Hospital, Suzhou, China, [7] Jiangxi Mental Hospital, Nanchang, China, [8] Mental Hospital of Yunnan Province, Kunming, China

Background: Although sleep quality is clearly associated with job burnout as shown in the existing research, the mechanism underpinning such relationship remains undefined. This work, thus, aimed to assess the current situation of sleep quality and burnout in Chinese psychiatric nurses, and to analyze the relationships between sleep quality, burnout and coping style, in order to provide possible targets to enhance mental health and wellbeing among psychiatric nurses.

Method: This cross-sectional study was carried out in seven rehabilitation centers located in four different regions of China. The Pittsburgh Sleep Quality Index, the Epworth Sleeping Scale, the Maslach Burnout Inventory General Survey, and the Coping Style Questionnaire were distributed to 853 nurses in various mental hospitals, with a total of 664 participants being recruited in the final research.

Results: The results of this current study showed a high prevalence of sleep disorders and burnout in Chinese psychiatric nurses. Moreover, emotional exhaustion ($r = 0.456$), cynicism ($r = 0.323$) and negative coping style ($r = 0.191$) in nurses were all positively correlated with total Pittsburgh Sleep Quality Index (PSQI) score, while professional efficacy ($r = -0.079$) and positive coping style ($r = -0.140$) were negatively correlated with total PSQI score. More interestingly, of all negative coping strategies, we found that self-blame had the most significant effect ($\beta = 0.156$).

Conclusions: The above results showed that coping style mediates the association of poor sleep quality with job burnout in Chinese psychiatric nurses. This study claimed that there is an urgent need to development the coping skills to sustain a healthy work life for nurses.

Keywords: nurses, mental health, sleep quality, coping styles, job burnout

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Adriano Friganovic,
University Hospital Centre Zagreb, Croatia
Piotr Jerzy Gurowiec,
Państwowa Wyzsza Szkoła Zawodowa w Głogowie, Poland
Giulia Avvenuti,
IMT School for Advanced Studies Lucca, Italy

***Correspondence:**
Yang Yang
787052308@qq.com
Xiangdong Du
xiangdong-du@163.com

[†]These authors have contributed equally to this work and share first authorship

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INTRODUCTION

Burnout is reflected by physical and mental exhaustion, which refers to prolonged stress response to lasting workplace-related emotional and interpersonal stressors (1). There are three dimensions of burnout, including emotional exhaustion, cynicism and decreased professional performance. Emotional exhaustion is the excessive emotional consumption of individuals, leading to depleted individual resources, which represents the stressful dimension of burnout. Cynicism is a negative, cold or extremely disconnected response to the patient populations served. Decreased performance is an overall sense of one's inefficiency at the workplace, as well as a lack of professional achievement, which represents the dimension of self-evaluation. Compared with other occupations, nursing represents a high-risk of burnout, being admittedly stressful and emotionally demanding (2, 3). The nurse-to-population ratio in China is 1:1,750, far lower than the 1:140 to 1:320 reported in developed countries (4). In the micro level, because of inability to effectively cooperate with the nurse for treatment, suicide risk, self-injury, impulse and violent behavior in mental illness patients, psychiatric nurses are in more risk of serious mental health problems (5–7). On the other hand, the invigorated nursing plays an important role in psychiatric treatment considering the quality of nursing directly affects the mental state of hospitalized psychiatric patients, the degree of treatment cooperation, and even the final outcome (8–10). In this sense, exploring the mediating factors that are possibly related with nurses' job burnout has important implications not only for enhancing the mental health and wellbeing among psychiatric nurses, but also the entire treatment system.

One possible reason for nurses' job burnout can be the poor sleep quality. Nurses cannot be able to get enough sleep because of intense work and frequent shifts. Studies have shown that nurses sleep worse significantly than professionals of other occupations (11, 12). Other reports have identified that psychiatric nurses have poorer sleep even than general hospital nurses (13). Deficient sleep quality can indeed bring with many serious problems, such as irritability, anxiety, fatigue and memory loss (14). These negative emotional issues could decline work enthusiasm, efficiency, and eventually, affecting the nursing performance. Although both sleep problems and job burnout have been paid attention to in the field of public health, the mechanism by which sleep quality affects job burnout in psychiatric nurses has not been explored in previous studies.

Another possible reason is coping style. Coping is the continuous effort of a given individual to change cognition and behavior to cope with demands considered to be stressful and beyond the reach of personal resources (15, 16). Previous evidence suggested that coping styles act a critical mediating role in psychological stress (17). Individual coping style can both affect the properties and strength of response to stress, as well as further regulate the relationship between stress and its results. According to the coping effect, coping style can be divided into positive and negative coping (15, 18). Burnout represents a progressive condition caused by inefficient coping strategies (19). As illustrated in the previous studies, positive coping is negatively associated with and could predict burnout (20, 21). Conversely, negative coping has a positive association with burnout as well (22–25). In addition, coping style, as an individual susceptibility factor, mediates the relationship between stress and sleep quality (26). A report revealed that it is not stress itself that causes sleep disorders, but the evaluation of and response to it (27). Although job burnout and coping style are overtly associated, as well as sleep quality and coping style, the mechanism underpinning such relationships remains undefined this far, which will be investigated directly by this current study.

Admittedly, multiple parameters can affect burnout, but the present work focused on sleep quality and coping style only. This study aimed to (1) understand the current situation of sleep quality and burnout in Chinese psychiatric nurses; (2) evaluate the relation between sleep quality and burnout; and (3) analyze whether coping style mediates the impact of sleep quality on burnout.

METHODS

Participants

This trial included 853 psychiatric nurses from Jiangsu Province, Jiangxi Province, Sichuan Province, and Yunnan Province in China. The trial was approved by the ethics committee of Suzhou Guangji Hospital. Investigators were psychologists qualified for human studies. The questionnaires were distributed, alongside the explained study aims. Questionnaire filling was anonymous. Individuals agreeing to take part in this trial were required to read the questionnaires and provide answers to all questions at the workplace. The data were collected in Aug. and Sep. 2017.

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) is a self-assessment scale that subjectively evaluates sleep quality in seven areas, including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep abnormalities, hypnotic drug utilization and daily quality of life. Final scores were calculated based on the seven dimensions and it ranged between 0 (best sleep) and 21 (worst sleep), with a score above 7 indicating a sleep abnormality (Cronbach's alpha was 0.83) (28).

The Epworth Sleeping Scale

The Epworth Sleeping Scale (ESS) subjectively assesses daytime sleepiness, based on eight items (29). The participants are required to fill in a 4-point Likert scale from 0 (never) to 3 (elevated odds) for self-assessment of the odds of "dozing off or falling asleep" in eight situations. Overall scores ranged between 0 (no sleepiness) and 24 (constant sleepiness). Scores of 0–4, 5–10, 11–16, and >16 reflected no, mild, moderate and severe sleepiness, respectively. Internal consistency among these 8 items is high (Cronbach's of 0.73–0.88) (30).

Maslach Burnout Inventory General Survey (MBI-GS)

The MBI-GS constitutes a 15-item self-reported assessment tool for job burnout, including three dimensions (emotional

exhaustion, cynicism and professional efficacy) (1). A Likert scale from 0 (never) to 6 (daily) was utilized for scoring. The broadly utilized Chinese version of the MBI-GS has satisfactory reliability and validity (31). Here, Cronbach's α values in the three dimensions were 0.896, 0.747, and 0.825, respectively.

Coping Style Questionnaire

The Coping Style Questionnaire has been applied to measure coping style in some existing Chinese studies to assess psychological health of participants. The questionnaire was developed on the basis of Folkman's interactive theory (32), and was adapted from the COPE Scale (33), and the Ways of Coping Questionnaire (34). It aims to evaluate the manner by which a participant dealt with a very stressful event/situation in the last month. Positive coping style, negative coping style and rationalization were measured with 62 items on a 4-point scale (0, never; 1, seldom; 2, sometimes; 3, often). The sub-subscales had a strong reliability of 0.70.

Statistical Analysis

All data were expressed as mean ± SD. Independent samples *t*-test was carried out for comparisons. Statistical significance was reflected by $P < 0.05$. Pearson correlation was carried out to assess the associations of sleep quality, burnout and coping style. The Baron and Kenny's method was applied for assessing the impact of coping style on the association of sleep quality with burnout (35). SPSS 20.0 was utilized for data analysis.

RESULTS

Demographic and Occupational Characteristics

By conducting the initial analysis, 189 questionnaires were excluded due to the missing data, and the final sample consisted of 664 psychiatric nurses, including 138 men (20.78%) and 526 women (79.22%). A total of 210 (31.60%) participants were aged below 25 years, 254 (38.30%) were 26∼31 years old, 182 (27.4%) were 32∼46 years old, and 18 (2.70%) were 47∼52 years old. In relation to marital status, 454 (68.40%) were married, 194 (29.20%) were unmarried, and 16 (2.40%) were divorced. Regarding the level of education, four (0.60%) had only completed lower vocational or lower secondary education, 216 (17.50%) had completed intermediate vocational or intermediate/higher secondary education, and 544 (81.90%) had a college degree or above. With respect to job title, 156 (23.50%) were junior nurses, 241 (36.30%) were intermediate nurses, 210 (31.60%) were senior nurses, and 57 (8.60%) were head nurses. The participants' years of working experience ranged from 0 to 43. In the past one month, 427 nurses (64.30%) had night shifts and 237 (35.70%) had no night shifts.

Sleep Quality of Nurses

The average PSQI score were 6.87 ± 3.59, i.e., statistically significant difference ($P < 0.05$) compared with the Chinese norm (3.88 ± 2.52). A total of 411 (61.90%) nurses reported that they had good sleep quality, while 255 (38.10%) had poor ones. The total ESS scores in the 664 participants were 9.86 ± 5.07, which also showed statistical significance compared with Chinese control values ($P < 0.05$). There were 107 (16.10%) nurses with normal sleep, 262 (33.39%) with mild sleepiness, 198 (29.82%) with moderate sleepiness, and 97 (14.61%) with severe sleepiness. Total ESS scores in nurses with night shifts in the last month were significantly higher than those of counterparts without night shifts ($t = 2.90$, $P = 0.004$). Similarly, total PSQI scores in nurses with night shifts in the last month were significantly higher than those of individuals without night shifts ($t = 3.31$, $P = 0.001$). Total ESS scores significantly differed by marital status ($F = 5.60$, $P = 0.004$). As shown in the least significant difference (LSD) test, married nurses had the highest ESS scores.

Job Burnout and Coping Style of Nurses

In this study, the total burnout scores of the 664 participants were 1.96 ± 1.01. Taking the average score of 4 (7-point Likert scale), 265 nurses had a high level of burnout. Job burnout significantly differed by age ($F = 5.33$, $P = 0.001$). After post-hoc LSD test, the burnout scores of nurses aged 32 to 46 and 26 to 31 were significantly higher than those of counterparts under 25 ($P = 0.000$, $P = 0.007$ by LSD test). Total burnout scores also significantly differed by marital status ($F = 3.78$, $P = 0.023$). The burnout scores of divorced nurses were significantly higher than those of unmarried and married colleagues ($P = 0.009$, $P = 0.029$ by LSD test). The level of job burnout was significantly different based on job title ($F = 2.68$, $P = 0.046$). The burnout scores of intermediate and senior nurses were significantly higher than those of junior nurses ($P = 0.024$, $P = 0.047$ by LSD test). Nurses' coping styles for burnout ranged from high to low in frequency: problem-solving, help-seeking, escape-avoidance, rationalization, wishful thinking, and self-blame. There was a significant difference in positive coping style based on age ($F = 4.83$, $P = 0.002$). Nurses younger than 25 years had higher odds of utilizing positive coping style than the other age groups ($P = 0.004$, $P = 0.000$, $P = 0.030$ by LSD test). The negative coping styles were significantly different based on marital status ($F = 3.20$, $P = 0.042$). Divorced nurses used significantly more negative coping styles than unmarried and married colleagues ($P = 0.016$, $P = 0.044$ by LSD test). The use of positive coping styles significantly differed by marital status ($F = 6.15$, $P = 0.002$). Positive coping style scores in unmarried nurses were significantly elevated compared with those of divorced and married nurses ($P = 0.009$, $P = 0.004$ by LSD test). The use of positive coping styles significantly differed by job title ($F = 6.84$, $P = 0.000$). Positive coping style scores in junior nurses were significantly elevated in comparison with those of intermediate and senior nurses ($P = 0.002$, $P = 0.000$ by LSD test).

Associations of Sleep Quality, Coping Style and Burnout

Table 1 summarizes the results from Pearson correlation analysis. Emotional exhaustion, cynicism, job burnout and negative coping style had significant positive relationships with total ESS score ($P < 0.01$). Emotional exhaustion, cynicism, job burnout and negative coping style had significant positive associations with total PSQI score ($P < 0.01$). Professional efficacy and positive coping style had significant negative relationships with

TABLE 1 | Means, standard deviations and zero-order correlations (Pearson r) among various parameters.

Variables	Mean	SD	1	2	3	4	5	6	7	8
ESS	9.86	5.07	1							
PSQI	6.87	3.59	0.286**	1						
Emotional exhaustion	1.77	1.20	0.268**	0.456**	1					
Cynicism	1.37	1.24	0.255**	0.323**	0.763**	1				
Professional efficacy	3.47	1.58	0.019	−0.079*	−0.126**	−0.217**	1			
Job burnout	1.97	1.01	0.178**	0.335**	0.724**	0.764**	−0.745**	1		
Negative coping styles	0.35	0.19	0.116**	0.191**	0.275**	0.278**	−0.177**	0.310**	1	
Positive coping styles	0.71	0.18	−0.056	−0.140**	−0.323**	−0.389**	0.212**	−0.387**	0.116**	1

*$P < 0.05$.
**$P < 0.01$ (two-tailed).

total PSQI score ($P < 0.01$). Job burnout had a significant positive correlation with negative coping style ($P < 0.01$) and a significant positive correlation with negative coping style ($P < 0.01$).

Factors Associated With Job Burnout Amongst Nurses

Job burnout amongst Chinese psychiatric nurses were evaluated by additional dummy-variable regression analyses as presented in **Table 2**. The dependent variable was job burnout, and independent variables were demographic indexes for which significant differences were found in group comparison analyses, as well as the total ESS score, the total PSQI score, and coping style. At the model 1 level, the coefficient of determination R^2 was 0.02. We next included age, marital status and job title as control variables in the regression analysis, and the adjusted R^2 was 0.34. The results showed that total ESS score, total PSQI score, and escape-avoidance were significant positive predictors of job burnout. Problem-solving constituted a significant negative predictive factor of job burnout, accounting for 34% of its variance.

TABLE 2 | Multivariable linear regression analysis of sleep quality, coping style, and job burnout in Chinese psychiatric nurses.

Variables	Job burnout	
	Model 1	Model 2
	β	β
Independent variables		
≤25	−0.126	−0.086
32∼46	0.102	0.097
47∼52	0.001	0.016*
Unmarried	0.031	0.056
Divorced	0.074	0.037
Intermediate nurses	0.009	−0.010
Senior nurses	−0.050	−0.108
Head nurses	−0.068	−0.021
ESS		0.054***
PSQI		0.200**
Self-blame		0.156
Wishful thinking		−0.016
Escape-avoidance		0.168**
Rationalization		0.071
Problem-solving		−0.349***
Help-seeking		−0.078
R^2	0.04	0.36
ΔR^2	0.02	0.34
ΔF		22.67***

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Mediating Effects of Coping Style on Sleep Quality and Burnout

Analysis was performed with the Process software (PROCESS-Model#4) (36). The results showed that total PSQI score represented a significant positive predictive factor of self-blame ($\beta = 0.014$, $P < 0.001$; **Figure 1**). Meanwhile, self-blame constituted a significant positive predictive factor of job burnout ($\beta = 1.211$, $P < 0.001$; **Figure 1**). The 95% confidence intervals for the mean did not include zero; therefore, there was a significant mediating effect of self-blame on job burnout (**Table 3**).

Mediating Effects of Wishful Thinking on Sleep Quality and Burnout

Analysis was performed with Process (PROCESS-Model#4) (36). The results showed that total PSQI score constituted a significant positive predictive factor of wishful thinking ($\beta = 0.009$, $P < 0.01$; **Figure 2**). Meanwhile, wishful thinking was a significant positive predictive factor of job burnout ($\beta = 0.753$, $P < 0.001$; **Figure 2**). The 95% confidence intervals for the mean did not include zero; therefore, there was a significant mediating effect of wishful thinking on job burnout.

Mediating Effects of Escape-Avoidance on Sleep Quality and Burnout

Analysis was performed with Process (PROCESS-Model#4) (36). The results showed that total PSQI score was a significant positive predictive factor of escape-avoidance ($\beta = 0.010$, $P < 0.001$; **Figure 3**). Meanwhile, escape-avoidance was a significant positive predictive factor of job burnout ($\beta = 1.108$, $P < 0.001$; **Figure 3**). The 95% confidence intervals for the mean did not

include zero; therefore, there was a significant mediating effect of escape-avoidance on job burnout.

Mediating Effects of Rationalization on Sleep Quality and Burnout

Analysis was carried out with Process (PROCESS-Model#4) (36). The results showed that total PSQI score was a significant positive predictive factor of rationalization ($\beta = 0.007$, $P < 0.001$; **Figure 4**). Meanwhile, rationalization was a significant positive predictive factor of job burnout ($\beta = 0.903$, $P < 0.001$; **Figure 4**). The 95% confidence intervals for the mean did not include zero; therefore, there was a significant mediating effect of rationalization on job burnout.

Mediating Effects of Problem-Solving on Sleep Quality and Burnout

Analysis was performed with Process (PROCESS-Model#4) (36). The results showed that total PSQI score was a significant negative predictive factor of problem-solving ($\beta = -0.007$, $P < 0.001$; **Figure 5**). Meanwhile, problem-solving was a significant negative predictive factor of job burnout ($\beta = -1.584$, $P < 0.001$; **Figure 5**). The 95% confidence intervals for the mean did not include zero; therefore, there was a significant mediating effect of problem-solving on job burnout.

Mediating Effects of Help-Seeking on Sleep Quality and Burnout

Analysis was performed with Process (PROCESS-Model#4) (36). The results showed that total PSQI score was a significant negative predictive factor of help-seeking ($\beta = -0.008$, $P < 0.01$; **Figure 6**). Meanwhile, help-seeking was a significant negative predictive factor of job burnout ($\beta = -1.180$, $P < 0.001$; **Figure 6**). The 95% confidence intervals for the mean did not include zero; therefore, there was a significant mediating effect of help-seeking on job burnout.

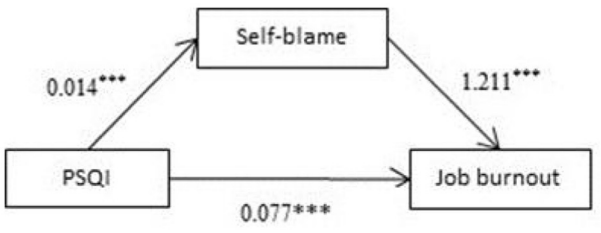

FIGURE 1 | Mediating effects of self-blame on sleep quality and burnout. ***$p < 0.001$.

DISCUSSION

The results of this current study showed a high prevalence of sleep disorders and burnout in Chinese psychiatric nurses. Moreover, the present trial assessed the associations of sleep quality, burnout and coping style in Chinese psychiatric nurses, revealing that coping style might have both direct and indirect effects on burnout. In addition to sleep promotion, improving coping skills as an approach to ameliorate mental health in nurses is critical. Therefore, coping strategies should be developed for burnout prevention in nurses.

The results of this survey showed a high prevalence of sleep disorders in Chinese psychiatric nurses, which was higher than that of general nurses shown in the previous research (37). This suggested that the sleep quality of psychiatric nurses is more seriously altered than that of general nurses due to their special occupation, with night shift psychiatric nurses having more problems with sleep quality and sleepiness in particular as further shown in this study. In addition to the working patterns, the problem was also sensitive to marriage status that married nurses reported a worse sleeping. This survey generally showed that 39.9% of nurses' job burnout was at a high level, and this figure is larger than the 34% reported by Aiken LH in American (38). One possible reason for this difference is that psychiatric nurses in China are applying support for more severe mental illnesses. Among the three sub-domains of job burnout, low professional efficacy is one of the most serious problems. This may be due to the psychiatric nurses need to deal with patients who do not cooperate with treatment. It appears that older and higher professional title nurses experienced increased burnout compared with younger counterparts, which is inconsistent with previous studies (37, 39). This may be explained by the fact that older, higher professional title nurses take on heavy responsibilities, undertake heavier nursing workload, face critical patients and emergencies, and supervise nurses with less seniority, which costs more energy. Meanwhile, they might face much more complex pressures from family and daily life, including marriage, child care and education, lacking free time for leisure and relaxation. This can also explain the results that that young, unmarried and low-professional title nurses used more positive coping methods, as they are less likely being challenged by the lower family and financial issues. Interestingly, divorced nurses preferred to use negative coping styles and experienced elevated burnout. Based on these descriptive findings, hospital administrators should be attentive to the burnout problems of psychiatric nurses, and particularly prioritizing the older, divorced, and high-job title nurses, in order to help them cultivate positive coping strategies.

According to Folkman and Lazarus's model of cognitive interaction, coping style can be divided into positive coping

TABLE 3 | Mediating effect analysis.

	Direct effect	Standard error	*T*	*P*-Value	*LLCI*	*ULCI*
Direct effect	0.095	0.010	9.145	0.000	0.074	0.115

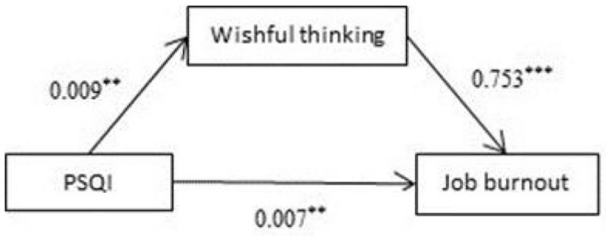

FIGURE 2 | Mediating effects of wishful thinking on sleep quality and burnout. $^{**}p < 0.01$, $^{***}p < 0.001$.

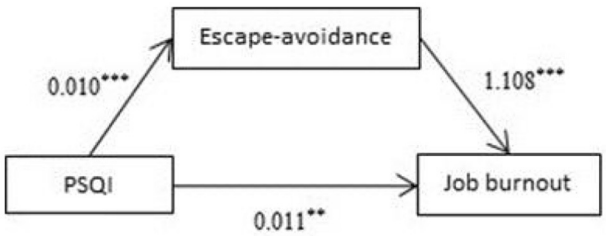

FIGURE 3 | Mediating effects of escape-avoidance on sleep quality and burnout. $^{**}p < 0.01$, $^{***}p < 0.001$.

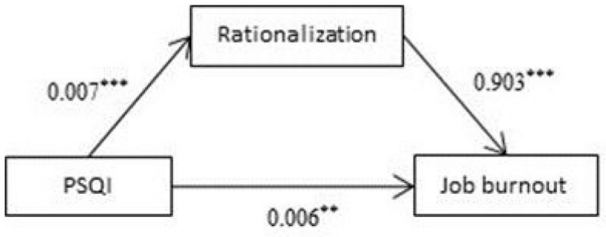

FIGURE 4 | Mediating effects of rationalization on sleep quality and burnout. $^{**}p < 0.01$, $^{***}p < 0.001$.

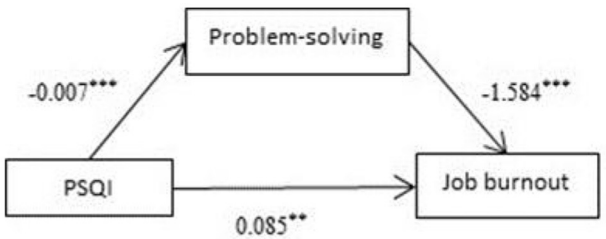

FIGURE 5 | Mediating effects of problem-solving on sleep quality and burnout. $^{**}p < 0.01$, $^{***}p < 0.001$.

(problem-solving and/or help-seeking), negative coping (self-blame, wishful thinking and/or escape-avoidance), and rationalization (15). In this study, we found that emotional exhaustion, cynicism and negative coping style in nurses were positively correlated with total ESS and PSQI scores. Meanwhile, both the professional efficacy and positive coping style had

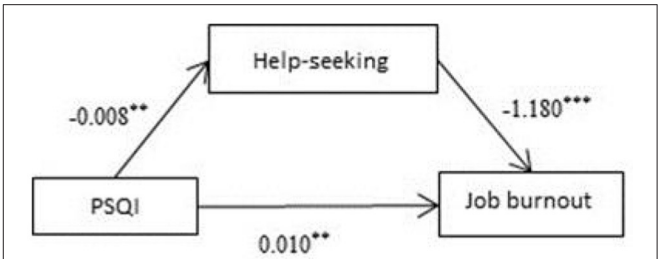

FIGURE 6 | Mediating effects of help-seeking on sleep quality and burnout. $^{**}p < 0.01$, $^{***}p < 0.001$.

significant negative correlation with total PSQI score. This is consistent with previous studies. Early studies assessing the association of stress with sleep quality indicated that stressful life events could predict sleep disorders in individuals. However, recent studies showed that the cause of sleep disorders is not stress itself, but the evaluation of and coping with stress (40, 41). Positive coping makes people more skilled in coping with pressure in life and work, which can reduce stress response in patients, and thus improve the quality of sleep (42). Negative coping people cannot deal with stress correctly, and tend to indulge in stressful situations and not be resolved, aggravating stress, thereby reducing their sleep quality (43). The results in this study further support coping style represented a potential predictive factor of job burnout in earlier studies (31, 44). These data suggested that negative and positive coping aggravates and alleviates burnout in nurses, respectively.

Sleep disturbance is an important risk factor for emotional and physical exhaustion (45). On the other hand, sleep disorders are also the most common symptoms of job burnout. We demonstrated that coping style had a mediating impact on the association of sleep quality with burnout in nurses. Sleep problems may elicit coping patterns, which in turn cause job burnout. In addition to dealing with sleep problems, improving coping skills is critical to reducing burnout among nurses. Studies by Spataro et al. (46) have shown that an increase in self-blame coping style can lead to job burnout in female medicine residents (47). In consistent with the predecessor's research, of all negative coping strategies, we found that self-blame had the most significant effect. The results showed that total PSQI score represented a significant positive predictive factor of self-blame, which in turn significantly predicted job burnout. Overgeneralized self-blame, which leads to uselessness and hopelessness, is a core symptom of major depressive disorder and a predictor of relapse (48). Increased utilization of self-blame as a coping mechanism could remarkably exacerbate burnout and sleep problems in psychiatric nurses. This suggested that observation of self-blame among nurses may help impede burnout. On the other hand, Chinese culture is considered more collectivist than individualist, and therefore might use a more self-blame coping style (49). Training programs should work toward raising self-compassion and decreasing self-blame (50), especially in nurses with poor sleep quality. More interestingly, of all positive coping strategies, we found that problem-solving

had the most significant effect. Prior studies have shown that problem-solving coping style was associated with less sickness absence among female nurses working in hospital care (51). Our study further supports this view. Training programs should work toward raising acknowledging various thoughts concerning the problem, undertaking efforts to understand the situation, predicting the course of events, choosing the most appropriate solutions, planning to solve the problem and implementing this plan as well as taking consistent action to solve the problem.

Limitations and Strengths

This work had many strengths, including its large sample and a high response rate. We selected hospitals in different regions of China to make the sample representative, and different regions where the hospitals are located reflect different levels of economic development in China. The present findings call for increasing nurses' competency and designing active interventional methods. However, the results and findings reported in this study shall be interpreted with caution as well. Firstly, this research was designed as a cross-sectional trial, from which the causal relationships could not be definitely inferred. In this sense, further longitudinal studies are warranted to further examine these initial findings. Secondly, because all the participants were recruited only from seven rehabilitation centers located in four different regions, these findings have limited generalizability and are difficult to be extrapolated to all the Chinese nurses. At the same time, the sample size was not sufficiently large to analyze possible differences across the regions. This calls for the following researchers who are interested in the nationwide trials in this field. Thirdly, considering this current study only concerned the sleep quality and coping style, some other possible mediating factors, such as mood (e.g., depression and anxiety (52)) can be explored in the future studies. Fourthly, the findings of this research can be deconstructed, for example, specific workplace and individual stressors could be assessed with regard to coping and emotion regulation approaches. Finally, burnout should be examined across multiple facilities and work shifts to provide further data describing the impacts of contextual variables.

IMPLICATIONS

Poor sleep and mental health in nurses might substantially affect their overall health as well as those of patients. Consequently, nurses should be provided adequate sleep knowledge and information regarding the association of sleep with mental health. We suggest that nursing education should include opportunities dealing with healthy sleep, coping approaches, and mental health promotion, to prevent burnout in nurses. The training about the etiology and signs/symptoms of burnout may help nursing students detect symptoms in themselves and timely seek help. The accurate analysis and determination of a person's coping strategy can help identify the effectiveness of the coping strategy used and provide guidance for studying coping skills and developing therapeutic interventions. To change their PSQI scores, hospitals might provide training nurses on problem-solving skills, which could help develop and apply positive coping styles to mitigate workplace stress (53). Such training should comprise approaches for managing negative affectivity and decreasing disconnected response, e.g., by cognitive reframing (54) and mindfulness-related methods (55, 56), as well as organizational actions addressing burnout by increasing job resources (57). This would ameliorate health and wellbeing in nurses, reducing professional burnout and improving healthcare.

RELEVANCE STATEMENT

Poor sleep and mental health in nurses might substantially affect their overall health as well as those of patients. High prevalence rates of sleep disorders and burnout were found in Chinese psychiatric nurses. This cross-sectional study demonstrated the mediating effects of coping style on the association of poor sleep quality with burnout symptoms in Chinese psychiatric nurses. Specifically, self-blame coping plays a critical mediating role in this association. In addition to sleep promotion, improving coping skills as an approach to ameliorate mental health in nurses is critical. It is therefore important to improve coping skills to sustain a healthy work life for nurses.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Suzhou Guangji Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XD: study conception and design, WL, QY, XF, ZY, XW, QL, FK, CJ, XL, HW, NY, ZL, YYu, CZ, KL, YYa, MY, and XD: experiments, MY: data analysis and manuscript writing. All authors contributed to the article and approved the submitted version.

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Association of Subclinical Hypothyroidism With Anxiety Symptom in Young First-Episode and Drug-Naïve Patients With Major Depressive Disorder

Ruchang Yang[1,2†], Xiangdong Du[2†], Zhe Li[2], Xueli Zhao[2], Xiaoli Lyu[2], Gang Ye[2], Xinchuan Lu[2], Guangya Zhang[2], Chuanwei Li[2], Yan Yue[1,2], Yuxuan Wu[1,2], Ruijie Peng[1,2], Yue Zhou[2,3], Haitao Wang[4], Siqi Wu[2,4], Pallavi B. Ganapathi[5], Hanjing Emily Wu[5] and Xiangyang Zhang[6*]*

[1] Suzhou Medical College of Soochow University, Suzhou, China, [2] Suzhou Guangji Hospital, The Affiliated Guangji Hospital of Soochow University, Suzhou, China, [3] Xuzhou Medical University, Xuzhou, China, [4] School Psychology and Mental Health, North China University of Science and Technology, Tangshan, China, [5] Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, Houston, TX, United States, [6] CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China

Backgrounds: Subclinical hypothyroidism (SCH) was reported to be associated with depression; however, its role in coexisting anxiety symptom in young patients with major depressive disorder (MDD) remains unclear. The objective of this study was to explore the relationship between SCH and anxiety symptom in young first-episode and drug-naïve (FEDN) MDD patients.

Methods: A total of 520 outpatients diagnosed as FEDN MDD with SCH were recruited in this study. Their socio-demographic, clinical data and thyroid function parameters were collected. The Hamilton Anxiety Rating Scale (HAMA) and the Hamilton Depression Rating Scale (HAMD) were employed to measure the severity of anxiety symptom and depressive symptom, respectively. Based on the HAMA scores, patients who scored $\geq$ 25 were defined as anxious major depressive disorder (A-MDD) while others as non-anxious major depressive disorder (NA-MDD).

Results: The prevalence rate of A-MDD was 15.8% in young FEDN MDD patients with comorbid SCH. Moreover, serum thyroid stimulating hormone (TSH) levels were significantly higher in patients with A-MDD compared with those with NA-MDD ($p < 0.001$). Multivariate binary logistic regression analysis indicated that A-MDD was associated with serum TSH levels with an odds ratio (OR) of 1.602. Serum TSH level of 6.17 mIU/L was the critical value to distinguish A-MDD and NA-MDD, with sensitivity of 0.805 and specificity of 0.539. There were no statistically significant differences between NA-MDD and A-MDD patients in terms of socio-demographic variables, serum free triiodothyronine (FT3), free thyroxine (FT4), thyroid peroxidases antibody (TPOAb) and anti-thyroglobulin (TgAb) levels.

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Wenhao Jiang,
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Fengchun Wu,
The Affiliated Brain Hospital of Guangzhou Medical University, China
Wei Deng,
Affiliated Mental Health Center and Hangzhou Seventh People's Hospital, China

***Correspondence:**
Xiangdong Du
xiangdong-du@163.com
Xiangyang Zhang
zhangxy@psych.ac.cn

†These authors have contributed equally to this work and share first authorship

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Conclusions: A-MDD patients presented higher serum TSH level. It is suggested that serum TSH level may be a potential biomarker for predicting moderate and severe anxiety symptoms in young FEDN MDD patients with SCH.

Keywords: subclinical hypothyroidism, anxiety symptom, young, major depressive disorder, first-episode and drug-naïve

INTRODUCTION

Major depressive disorder (MDD) is the most prevalent mood disorder in China, with a lifetime prevalence of 3.4% and 12-month prevalence of 2.1% (1). MDD is a common reason for years lived with disability with a high incidence rate, causing great burden to individuals and society (2, 3). Previous studies suggest young adults are at serious risk of MDD. A multinational study showed 12-month prevalence estimates of MDD between 8.3 and 12.4% among people aged 18–33 (4), while the overall 12-month prevalence of MDD is approximately 6% (5). A large sample study in Singapore reported a higher risk for adults aged 18–34 than other age groups to suffer from MDD (6).

Anxiety is one of the most commonly seen comorbidities in MDD patients, with a prevalence of 45–67% (7). Patients with anxious depression, which has been characterized as MDD with high levels of anxiety symptoms, were more likely to experience serious psychiatric symptoms, more severe depression, and a greater risk of suicide (8). In addition to psychological impairments, physical comorbidities such as pain, hypertension and diabetes mellitus are particularly elevated among patients with co-occurring depressive and anxiety disorders (9).

There is a considerably strong correlation between mood disorders and thyroid function (10, 11). Thyroid hormones (TH) are critical not only for brain development, but also for lifelong central nervous system (CNS) function (11–13). Numerous studies have demonstrated that TH affect depression and anxiety through multiple mechanisms. For example, Buras et al. noted that TH act via the thyroid hormone receptor (TR) α and β isoforms. Both isoforms are expressed in the limbic system, which plays an important role in mood regulation (14). Yu et al. demonstrated that by modulating hippocampal brain-derived neurotrophic factor (BDNF) level, thyroid dysfunction has bidirectional effects on anxiety- and depression-like behaviors (15). TH may also modulate the brain serotonergic system (16), further influencing anxiety and depression.

Anxiety and depression are highly prevalent among patients with hypothyroidism (11). Multiple studies have focused on the role of thyroid function in depression and anxiety, but no consistent conclusion has been reached. Erensoy recommended serum thyroid stimulating hormone (TSH) as a useful biochemical marker for more efficient depression management (17), while a systematic review on hypothalamic-pituitary-thyroid (HPT) axis function in anxiety disorders implicated a negative relationship between self-reported anxiety and TSH levels (18). This may result from different inclusion criteria such as age, gender, also suggesting further investigation. Yet Yu and colleagues suggested a bidirectional effect of thyroid function toward anxiety and depression (15). A retrospective study in China suggested thyroid hormones can reflect the clinical outcome of depression and normal-range free thyroxine (FT4) values are associated with the severity of anxiety and depression (12). Ittermann et al. found serum thyroid peroxidases antibody (TPOAb) levels to share no apparent correlation with depression and anxiety (19), while van de Van and colleagues suggested TPOAb to be a predictive biomarker for the vulnerability of depression (20).

With the increasingly precise testing and widespread screening during routine physical examination, subtle degrees of thyroid dysfunction can be discovered at the subclinical stage and diagnosed in young and middle-aged people at a higher frequency than ever before. Subclinical thyroid disease (SCTD) is defined as normal serum FT4 and free triiodothyronine (FT3) levels in the presence of abnormal serum TSH levels (44), high and low abnormality for subclinical hyperthyroidism and subclinical hypothyroidism (SCH), respectively (44). However, there are insufficient studies on the association between SCH and anxiety and depression, and no unanimous consensus has been reached. A systematic review suggested a higher risk of depression and anxiety in SCH patients (21), implying the significant role thyroid may play in regulating mood disorders. Zhao et al. found that recurrent and high body mass index (BMI) female depressed inpatients to be at increased risk of developing SCH. Stress likely plays a crucial role here, as depressed females are more vulnerable to stressors, leading to increased TSH level, thyroid dysfunction, psychological problems, and overeating (22). However, Bensenor et al. found SCH was negatively associated with anxiety disorder, but the result lost statistical significance after adjustment for multiple comparisons (23). A large sample study in China suggested depression and anxiety symptoms are correlated with severe SCH and elevated TSH levels (24).

Association between thyroid function and depression and anxiety can differ significantly for age, races and different disease episodes. A cross-sectional study in Europe suggested hypothyroidism is relevant with the severity of depression and its psychopathologic features in older people of Caucasian origin (2). Similarly, a Western Pomerania population-based study concluded that diagnosed untreated hypothyroidism is associated with depression and anxiety (19). Apart from races, the endocrine system changes in different life periods. For instance, there is a drastic difference before and after climacteric, typically in middle-aged people. It should be noted that endogenous depression or menopause-relative psychological manifestation may affect the assessment of psychiatric disorders (11). Moreover, it is considered that the titer of antibodies, such as TPOAb may vary with the development of disease (25). All these factors above may render inconsistent results of

TABLE 1 | Socio-demographical and clinical characteristics of the participants.

Variable	Young FEDN MDD patients with SCH		$\chi^2/z/F$	*P*
	NA-MDD (*N* = 438)	A-MDD (*N* = 82)		
Socio-demographic and clinical characteristics				
Age, mean ± SD, y	24.81 ± 5.36	24.49 ± 5.26	0.245	0.621
Illness duration, mean ± SD, m	5.37 ± 3.46	5.28 ± 3.38	0.044	0.834
Age at onset, mean ± SD, y	24.70 ± 5.28	24.40 ± 5.26	0.214	0.644
Gender			1.531	0.222
Male, *N* (%)	171 (39.0%)	38 (46.3%)		
Female, *N* (%)	267 (61.0%)	44 (53.7%)		
Education level			1.804	0.187
Middle school, *N* (%)	233 (53.2%)	37 (45.1%)		
College degree or above, *N* (%)	205 (46.8%)	45 (54.9%)		
Marital status			0.016	0.905
Married, *N* (%)	205 (46.8%)	39 (47.6%)		
Unmarried, *N* (%)	233 (53.2%)	43 (52.4%)		
BMI, mean ± SD, kg/m^2	24.58 ± 2.11	24.74 ± 2.18	0.370	0.543
Scale assessment				
HAMD, mean ± SD	31.22 ± 2.68	31.32 ± 2.81	0.083	0.774
HAMA, median [IQR]	20 (18–22)	27 (26–28)	−14.439	<0.001***
Biological indicators				
TSH, median [IQR], mIU/L	5.98 (4.96–7.35)	7.33 (6.26–9.41)	−6.364	<0.001***
TgAb, median [IQR], IU/L	22.14 (14.35–73.50)	23.21 (17.19–119.05)	−1.495	0.135
TPOAb, median [IQR], IU/L	19.78 (12.44–47.66)	22.35 (13.20–93.34)	−1.273	0.203
FT3, median [IQR], pmol/L	5.07 (4.39–5.54)	5.12 (4.33–5.47)	−0.405	0.686
FT4, median [IQR], pmol/L	16.33 (14.21–18.71)	16.81 (14.70–18.94)	−1.430	0.153

*SD, standard deviation; IQR, interquartile range; FEDN MDD, first episode and drug naïve major depressive disorder; A-MDD, anxious major depressive disorder; NA-MDD, non-anxious major depressive disorder; BMI, body mass index; HAMD, Hamilton Depression Rating Scale; TSH, thyroid stimulating hormone; TgAb, anti-thyroglobulin; TPOAb, thyroid peroxidases antibody; FT3, free triiodothyronine; FT4, free thyroxine; ***p < 0.001.*

TABLE 2 | Multivariate binary logistic regression for factors associated with anxiety symptom in young FEDN MDD patients with SCH.

Variable	*β*	Odds ratio	95% Confidence interval		*P*
			Lower	Upper	
Age	−0.330	0.719	0.286	1.810	0.484
Illness duration	0.009	1.009	0.910	1.118	0.868
Age at onset	0.277	1.319	0.523	3.327	0.557
Gender	−0.218	0.804	0.480	1.347	0.407
Education level	0.258	1.294	0.765	2.190	0.336
Marital status	0.494	1.640	0.739	3.636	0.224
BMI	0.055	1.057	0.941	1.186	0.349
HAMD	0.049	1.050	0.956	1.152	0.307
TSH	0.471	1.602	1.388	1.849	<0.001***
TgAb	−0.001	0.999	0.998	1.000	0.121
TPOAb	0.000	1.000	0.999	1.001	1.000
FT3	−0.054	0.948	0.663	1.354	0.768
FT4	0.041	1.042	0.958	1.132	0.338

****p < 0.001.*

thyroid function in depression and anxiety, particularly because participants' age, race and physical status are not preserved across different studies.

Though many previous studies have demonstrated the relevant association between hypothyroidism and anxiety and depression, few studies focused on the potential association

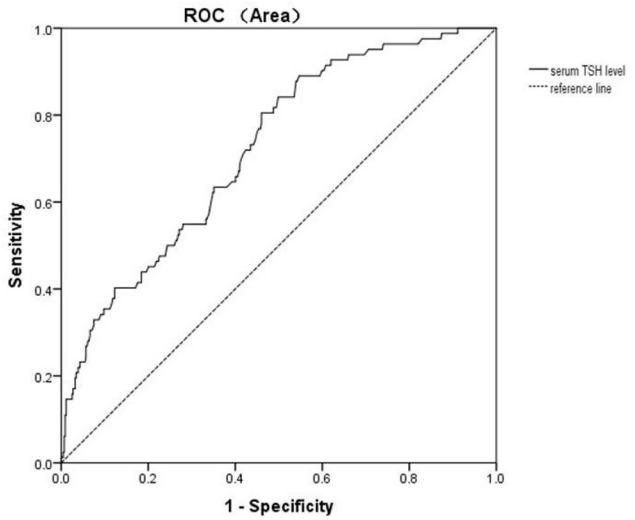

FIGURE 1 | Diagnostic accuracy of serum TSH level for A-MDD in young FEDN MDD patients with SCH. The area under the ROC curve is 0.721 on serum TSH level.

between SCH and anxiety and depression. By exploring at the subclinical stage, we can further understand the role of the thyroid and HPT axis in the occurrence and development of A-MDD. This may contribute to greater comprehension regarding pathogeny and early intervention. Moreover, with the introduction of TH therapy to depression treatment in recent years (26, 27), it may also provide evidence and bolster support for clinical practice. SCH has a different diagnostic standard and hormone level than clinical hypothyroidism; thus, results drawn from clinical hypothyroidism patients should be extended to SCH with caution. Even within SCH patients, ordinary thyroid indicators such as TSH and TPOAb may vary with age and race. Medication (15) or other antidepressant treatments (28) could also affect physical hormone levels. Therefore, our study recruited 520 Chinese Han population with first-episode and drug-naïve major depressive disorder (FEDN MDD), where the influence of antidepressant treatment on thyroid relevant indicators can be ignored, to explore the associations of SCH with anxiety. To minimize disturbances caused by aging, all the participants are in the age group of 18–35. To our best knowledge, no prior study has focused on this specific population to explore the association between SCH and anxiety symptom. The purposes of this study were to: (1) examine the relationship between SCH and anxiety in young FEDN MDD patients; (2) identify contributors that are significantly associated with anxiety symptom in young FEDN MDD with SCH.

METHODS

Subjects

From 2015 to 2017 this cross-sectional study included 520 outpatients from a psychiatric clinic at a tertiary general hospital in China.

The study inclusion criteria were: (1) Han nationality; (2) age between 18 and 35 years; (3) a diagnosis of MDD according to DSM-IV; (4) first episode patients with no previous medication history; (5) course of illness $\leq$24 months; (6) a score of $\geq$24 on the 17-item Hamilton Rating Scale for Depression (HAMD-17); (7) serum TSH level>4.20 mIU/L (upper limit of normal value), serum FT3 and FT4 level within their respective reference ranges; (8) no previous thyroxine therapy, or any specific medications. Exclusion criteria were: (1) having a serious physical disease; (2) pregnancy or lactation; (3) alcohol or substance dependence or abuse except for tobacco smoking.

All participants were voluntarily recruited and signed a written informed consent before enrollment. The medical ethics committee in First Hospital of Shanxi Medical University approved this study.

Socio-Demographic Characteristics

Socio-demographic characteristics including age, gender, age at onset, illness duration, marital status, education level and BMI were collected by well-trained researchers.

Clinical Measures

In this study, the severity of depression was assessed by the 17-item Hamilton Depression Scale (HAMD) (29). The 14-item Hamilton Anxiety Rating Scale (HAMA) was employed to measure anxiety severity (30). Each item in HAMA was scored on a scale of 0–4, with a total score of 56 points. Participants who scored 0–17 were considered as having no anxiety, 18–24 as mild anxiety, 25–29 as moderate anxiety, and $\geq$ 30 as severe anxiety (31). Based on the HAMA scores, we defined patients who scored $\geq$ 25 as anxious major depressive disorder (A-MDD) while others as non-anxious major depressive disorder (NA-MDD) (32). They were distributed to A-MDD and NA-MDD subgroup, respectively, and compared socio-demographic and clinical data between two groups.

The information above was collected by two qualified psychiatrists with no prior knowledge of participants' clinical conditions. After repetitive evaluation, the inter observer correlation coefficients of the HAMD and HAMA total score were both >0.8.

Blood Sample

Participants' blood samples were taken between 6:00 and 8:00 a.m. after an overnight fast, and sent for testing before 11 a.m. The laboratory center of the hospital was responsible for the measurement of serum levels of FT3, FT4, TSH, anti-thyroglobulin (TgAb), and TPOAb, with Roche C6000 Electrochemiluminescence Immunoassay Analyzer (Roche Diagnostics, Indianapolis, IN, USA). The normal range was 0.27–4.20 mIU/L for TSH, 3.10–6.80 pmol/L for FT3, 10–23 pmol/L for FT4, 0–115 IU/L for TgAb and 0–34 IU/L for TPOAb.

Statistical Analysis

The Kolmogorov-Smirnov test was used to assess the normality of all variables. For those variables that were normally distributed, they were expressed as mean $\pm$ standard deviation (SD), and parametric tests were performed and analysis of variance

(ANOVA) was used for group comparisons. For those variables that were not normally distributed, they were expressed as median [interquartile range, IQR] and a non-parametric Mann-Whitney U test was performed to compare differences between groups. For those categorical variables, they were expressed as absolute numbers (percentages) and a chi-square test was performed to compare group difference. A univariate binary logistic regression was performed, in which A-MDD was used as dependent variable and serum TSH level was used as independent variable. After controlling for demographic and clinical characteristics, a multivariate binary logistic regression analysis was performed, in which A-MDD was used as dependent variable and age, illness duration, age at onset, gender, educational level, marital status, BMI, HAMD, TSH, TgAb, TPOAb, FT3, and FT4 were used as independent variables, to assess the factors associated with A-MDD. Receiver-operating characteristic (ROC) curve was constructed to assess the diagnostic accuracy of serum TSH level. Statistical analysis was computed using SPSS 23 with two-tailed p-values of 0.05.

RESULTS

Socio-Demographic and Clinical Characteristics

As shown in **Table 1**, a total of 520 participants met the inclusion criteria. Among them 82 (15.8%) met the criteria for A-MDD and 438 (84.2%) were NA-MDD. Compared with NA-MDD, there were no significant differences in age, illness duration, age at onset, gender, HAMD score, serum TgAb, TPOAb, FT3, and FT4 levels and BMI. The only significant difference between the groups was in serum TSH level ($p < 0.001$), with the A-MDD subgroup displaying a higher level than the NA-MDD subgroup.

Factors Associated With A-MDD in Young FEDN MDD With SCH

Univariate binary logistic regression showed that serum TSH levels (OR = 1.515; 95% CI: 1.336–1.717) were associated with A-MDD. Multivariate binary logistic regression showed that serum TSH levels (OR = 1.602; 95%CI: 1.388–1.849) were associated with A-MDD (**Table 2**). The performance of serum TSH level was evaluated according to the ROC curve. The area under the ROC curve of serum TSH level was 0.721 ($p < 0.001$; 95%CI: 0.664–0.778), and its optimal cut-off value was ≥6.17 mIU/L (**Figure 1**). The sensitivity and specificity of the cut-off point for serum TSH levels were 0.805 (95% CI: 0.703–0.884) and 0.539 (95% CI: 0.491–0.586), respectively.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the association between SCH and anxiety symptom in young FEDN MDD patients. Our study revealed that the A-MDD rate among young FEDN MDD patients with SCH was 15.8%. We did not find significant socio-demographical differences between A-MDD and NA-MDD. As for blood samples, serum TSH level in A-MDD was higher than in NA-MDD. Further logistic regression analysis showed that higher serum TSH level was associated with A-MDD, suggesting it a predictive biomarker for A-MDD patients. The cut-off serum TSH level for distinguishing A-MDD was 6.17 mIU/L.

According to previous studies in Germany and the United States, A-MDD accounted for approximately half of MDD patients (33, 34). However, in our study, the prevalence of A-MDD among young FEDN MDD patients with SCH was 15.8%, appearing an obvious decrease. Although the lifetime prevalence of depression is significantly higher in patients with SCH (35), a cross-sectional study with a large sample size suggested that SCH is negatively associated with anxiety disorder (23), which may be a leading reason for the decrease found in our study. It is also of note that patients in our study were recruited from outpatient clinics, with illness duration of no more than 24 months and at the first stage of MDD, which may imply less and milder comorbidity, thus leading to the significant decrease of A-MDD rate. Moreover, Belov and Pshuk found that the severity of anxiety would increase with aging (36), with Lin and colleagues also suggesting that patients with A-MDD were likely to be older (8). Since patients in our study were of a younger population under the age of 36, this further suggests that age was a potential influencing factor contributing to the lower prevalence of A-MDD in this study. In addition, previous studies assessed anxiety using scale systems such as HAM-D anxiety-somatization factor (ASF), which may inflate false positive diagnosis of A-MDD (32). In contrast, our study employed the HAMA, recognized as the gold standard of anxiety severity assessment (32), indicating greater credibility.

One of the critical findings in our current study is that high serum TSH level is associated with A-MDD in young FEDN MDD with SCH. TH play essential roles in the adult brain, and depression and anxiety are commonly observed in hypothyroidism patients (11), demonstrating the importance of TH in regulating mood. The HPT axis works via negative feedback regulation. Absolute or relative TH deficit may lead to the secretion of thyrotropin-releasing hormone (TRH) and TSH. Though SCH patients displayed a normal range of serum FT3 and FT4 levels, the elevated serum TSH level was a potential indication of relative TH deficit, which may cause by decreased receptor sensitivity. Our study is consistent with many previous studies. Andrade and colleagues found a higher risk of anxiety and depression in SCH, and recommended TSH screening for symptom assessment (37). A community-based population study in Brazil suggested a positive relationship between high TSH levels and anxiety and depression in patients with T4 treatment (38). Teixeira Pde et al. reported positive relationships between the severity of depression, anxiety and TSH level (39). An Indian study revealed that after receiving treatment, the severity of anxious and depressive symptoms was decreased in depression patients with SCH. Besides, they also observed a serum TSH level decrease (28), suggesting parallel relationship with anxiety severity in depressive patients with SCH. However, a systematic review reported a negative relationship between anxiety severity and TSH in people without thyroid diseases when looking at patients in two large sample studies (18, 38, 40). Ittermann et al. observed an association between hypothyroidism and anxiety,

depression, but no significant correlation between the symptoms and serum TSH level (19). Several reasons may account for the discrepancy. Firstly, some results were derived from secondary analysis and failed to adjust these for relevant confounders (18). Secondly, participants in our study are SCH, whose HPT axis may function abnormally, rendering different TSH secretion in SCH with other population groups. Thirdly, patients recruited in our study received no previous antidepressant treatment, which may influence TSH level (15, 28), while the previous studies may have had different inclusion criteria. Fourthly, participants in various studies included widely varying age groups. The endocrine system is volatile during climacteric. Furthermore, endogenous depression or menopause-relative psychological manifestations may affect the results (11). Since our study included young patients under the age of 36, it is possible to reach different conclusion than with studies comprising of older age groups.

In our study, serum FT3, FT4, TgAb, and TPOAb levels have no significant differences between A-MDD and NA-MDD. Hitherto, no consensus has been reached among previous studies. Wu et al. suggested FT4 as an independent biomarker related to anxiety and depression in AID patients (41). An animal experiment with male mice demonstrated T3 and T4 supplement effective anxiety regulators (14), while Yu et al. observed decreased anxiety and depression in mice with lower FT3 and FT4 levels (15). A study targeting Chinese females saw no significant correlation between hair T3 or T4 levels and the HAMA and HAMD scores, as well as hair TH level changes in different episodes of depression (42). Yang and colleagues' research targeted a similar population, revealing a negative correlation of hair T3 levels with anxiety and depression severity in first-episode patients with major depressive disorder (F-MDD) (43). A recent study found FT4 values within the normal range were associated with the severity of depression and anxiety (12). Though untreated diagnosed hypothyroidism was positively related to depressive symptoms and anxiety, it appeared no significant link existed between these two symptomologies and TPOAb (19). The possible reasons for these variable conclusions may be the inconsistent study design in our and previous studies. Samples from different body parts or collecting time may lead to different results. Subjects within different disease episodes can also partly explain the discrepancy among the studies (25, 42).

No significant demographical differences were found between A-MDD and NA-MDD in this study. Previous studies have reached variable conclusions. A cross-sectional study in India suggested no significant gender difference existed in HAMA score in hypothyroidism patients (11). A Korean review indicated that patients with anxious depression are more likely to be female gender, non-single and less educated (7). Another study conducted in the USA revealed a higher risk of anxious depression among those who were unemployed, with less education and once married or married (34). A German randomized controlled trial (RCT) listed older age, lower education levels and longer duration of the current episode as risk factors of anxious depression (33). Belov and Pshuk postulated that the severity of anxiety is associated with older age and female gender in depressive disorder (36), though this study included a mixed population with bipolar affective disorder (current episode of depression), depressive episode and recurrent depressive disorder. However, no prior studies have been conducted in young FEDN MDD patients with SCH to explore demographical features between A-MDD and NA-MDD.

To the best of our knowledge, our study is the first to explore associations between SCH and anxiety symptom in young FENN MDD patients. Hormones in the HPT axis have long been considered significant regulators of anxiety and depression (18, 38, 40). As the endocrine system is easily influenced by age, race, endocrine disease states, episodes of psychiatric disorders and medical treatment, our study focused on young FEDN MDD with SCH in the Chinese Han population to minimize these disturbances. Therefore, our results might be more accurate in clinical practice toward this particular group. It may contribute to predicting the severity of anxiety symptom in young FEDN MDD with SCH patients, thus appropriate evidence-based clinical prevention or intervention can be imposed. Compared with previous studies, this study employed HAMA, which is considered as the gold standard for anxiety assessment, rather than ASF to distinguish A-MDD patients, indicating a more concrete result. Moreover, given both SCH (44) and MDD (4, 6, 45) are more frequently diagnosed in young adults, our study appears to have more profound practicality.

Several limitations should be noted in our study. Firstly, as a cross-sectional study, its effectiveness in explaining the causal relationship between SCH and anxiety symptom in young FEDN MDD patients is limited. Further longitudinal studies are indispensable to investigate their causal relationship. Secondly, the medication history was obtained by interviewing patients and their family members instead of medical records. Thirdly, several confounding factors critical to the study, such as family income, diet and serum TSH level before the onset of MDD, which should be remedied in future studies by doing a prospective study. Fourthly, all MDD patients were recruited from the outpatient department of a regional general hospital. Therefore, our findings should be extended with caution to inpatients, community patients, and outpatients from other regions or racial groups. Fifthly, in this study, the recruitment of FEDN patients was used to avoid potential influence by medication and disease episodes. However, this led to the limitation of its extension to the entire MDD patient populations. Future research should involve MDD patients in different phases. Moreover, although all patients received a second diagnosis in the following 3–6 months and only patients with consistent MDD diagnosis were enrolled, it is possible to include diseases other than MDD. For instance, bipolar disorder and schizophrenia can manifest as depression in certain disease stages. As a sixth consideration, pregnant or lactating women were excluded from this study, given their drastic endocrine differences. Therefore, future research targeting this group is certainly needed. Seventhly, we only collected a blood sample one time. Repeated thyroid hormone tests within at least 3 months apart were recommended for a determined SCH diagnosis (46). Future study should impose repetitive examinations of TSH, T4 and T3 levels for a

more accurate assessment of SCH. Total thyroxine (TT4) and total triiodothyronine (TT3) should also be included as the complete profile of thyroid hormones. Eighthly, our research results should be considered preliminary due to a lack of healthy control group, expecting future studies to confirm and replicate. Finally, serum TSH level was recommended as a potential predictive biomarker for A-MDD and a cut-off value of serum TSH level for distinguishing A-MDD was given. However, the critical value was low in specificity. Further studies are needed for a more accurate critical value with high specificity and sensitivity.

CONCLUSION

In conclusion, this study suggested that the A-MDD rate among young FEDN MDD patients with SCH was 15.8%. There is no significant age, gender, age at onset, illness duration, marital status, education level and BMI difference between A-MDD and NA-MDD among young FEDN MDD patients with SCH. Serum TSH level may serve as a potential biomarker for A-MDD, which is equivalent to MDD with moderate to severe anxiety symptoms, in young FEDN MDD patients with SCH. While serum TSH level was over 6.17 mIU/L, patients were more likely to experience moderate to severe anxiety symptoms. We recommend that young FEDN MDD patients with SCH have their serum TSH levels checked to better assess the severity of anxiety symptom.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee in First Hospital of Shanxi Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RY: conceptualization, methodology, software, investigation, formal analysis, and writing—original draft. ZL, XZ, XLy, GY, XLu, GZ, and CL: data curation, visualization, and investigation. YY, YW, and RP: resources, supervision, and software. YZ, HW, and SW: software and validation. PG and HEW: visualization and writing—review and editing. XD and XZ: conceptualization, funding acquisition, resources, supervision, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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REVIEW
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Application of the Delphi Method in the Study of Depressive Disorder

Hengjin Wu[1,2†], Linjie Xu[2,3†], Yu Zheng[1], Lei Shi[1], Liangfan Zhai[1] and FengQuan Xu[1]*

[1] Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [2] Graduate School of Beijing University of Traditional Chinese Medicine, Beijing, China, [3] Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Depressive disorder is a common mental disorder that has a high prevalence and low visiting rate, which caused patients years lived with disability. Due to the complexity of the depressive disorder, the Delphi method is a better choice compared with other commonly used methods, which provides a new perspective for the prevention and treatment of depression. This article will summarize the clinical studies of depressive disorders using the Delphi method from four perspectives, and summarize the advantages and disadvantages of the Delphi method in depressive disorders research, arguing that the Delphi method can cross the gap between clinical research and clinical practice, and is a highly practical part of the research process.

Keywords: depressive disorder, Delphi study, clinical research, indigenous, treatment

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Medical University of Bialystok, Poland

***Correspondence:**
FengQuan Xu
xufengquan@gamyy.cn

†These authors share first authorship

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INTRODUCTION

Depressive disorder is a common mental disorder manifested with depressed mood, loss of interest, insomnia or drowsiness, fatigue, psychomotor retardation, poor concentration, and memory loss as the main manifestations (1). A study indicates that in countries around the world, the prevalence of depressive disorder ranged from 6% (Shenzhen, China) to 21% (France), and a close look at WHO World Mental Health (WMH) results shows that on average about half of the respondents have positive symptoms of depression (2). Among them, major depression is the top three causes of years lived with disability (YLDs) in 136 countries (3), but only 16.5% of patients with major depression have received adequate treatment (4). As the modern population still harbors misconceptions and fears about mental disorders, a study showed that more than 80% of people agree that professional help should be sought for mental illness, but less than 40% are likely to take action (5). Regarding psychiatric medications, the same is true that with 57% of respondents agreeing that medications should be taken regularly, more than 60% believed that they would be harmful. Depressive disorders are heterogeneous with complex etiology (6), and their regression and prognosis are also influenced by biological, psychological, and social factors of the patient, and there is some disagreement in clinical treatment (7).

There are many commonly used methods to study depressive disorder, such as observational research and experimental research. In observational studies, inferences are usually drawn from a sample, so the representativeness of the sample directly affects whether the inference is correct or not. In contrast to observational studies, experimental studies need to strictly follow the three principles of statistical "replication, control, and randomization," including setting up a certain number of replicate observation samples, establishing a control group, and adopting randomized grouping or random sampling to ensure the balance between groups. They have a higher level of evidence than Delphi studies, but the findings are not compatible with the complex clinical environment and may be difficult to apply practically. The Delphi Study is a reliable prediction

and evaluation method combined with quantitative and qualitative, which uses an anonymous survey of expert opinions, and after several rounds of feedback, communication, and discussion, the expert opinions eventually converge to produce an expert consensus on the study objectives (8). A comparison of the advantages and disadvantages of the three can be seen in **Table 1**. Patients with depressive disorders have poorer adherence and greater individual differences than other disorders, making observational and experimental research more difficult to perform and more difficult to obtain valid conclusions. Using the Delphi method to conduct research at this time can help bridge the gap between theory and reality and lead to more realistic conclusions. Other commonly used clinical research methods may be difficult to handle due to the complex and varied clinical characteristics of depressive disorder and its various personalized characteristics. However, the Delphi method is a structured group communication process that can make decisions through collective subjective judgment and then deal with expert consensus by statistically aggregating opinions. It can also be compared with other research methods to exclude subjective factors and draw more accurate conclusions. In recent years, more and more scholars have started to use the Delphi method to conduct multi-faceted research on depressive disorders, and this article intends to summarize and organize the relevant studies, so as to provide references and inspiration for clinical research.

METHODS

We conducted a search using PubMed and Embase with the keywords Delphi study, Delphi technique, depressive disorder, and depression. Papers on the above keywords were then screened and selected According to our inclusion criteria and exclusion criteria, papers should use the Delphi method, or use research methods that include the Delphi method, and papers should study depressive disorder or study subjects that include or are related to depressive disorder. Any article that was not related to the Delphi method or did not study depressive disorders should be excluded.

RESULTS

Using the above criteria, we screened 72 papers. We did not find reviews of Delphi studies on depressive disorders. In terms of specific research content, 6 papers (8% of studies) produced clinical guidelines, consensus, or quality indicators for different types of depressive disorders, 3 papers (4% of studies) made recommendations for the prevention of depressive disorders, 5 papers (7% of studies) improved and validated relevant diagnostic scales, 5 papers (7% of studies) provided consensus on the care needs of patients with depressive disorders, and 5 papers (7% of studies) 5 papers (7% of studies) provided a consensus on the care needs of patients with depressive disorders, 5 papers (7% of studies) provided references on emergency care for different types and severity of depressive disorders, 2 papers (3% of studies) told patients with depressive disorders how to help themselves, 8 papers (11% of studies) developed an expert consensus on the use of multiple medications, Four papers (5% of studies) examined other therapies and tools that have been helpful in depressive disorders, Sixteen papers (22% of studies) focused on the co-morbidity of depressive disorders with other disorders and made recommendations, and 18 papers (25% of studies) analyzed and explored depressive disorders in different populations, including adolescents, the elderly, pregnant parents, and physician (medical student) groups. Findings from our review were summarized by indigenous studies of depressive disorders, diagnosis and differential diagnosis of depressive disorders, treatment process for depressive disorders, and prevention and prognosis of depression disorder.

Localization of Depressive Disorders by Delphi Method

Currently, the more recognized definition and diagnostic criteria for depressive disorders are based on the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) compiled by the American Psychiatric Association, and most of the scales used in clinical practice are developed based on the DSM-5. However, the occurrence and development of depressive disorders are complex, and different social backgrounds, economic levels, and cultural folklore can have an impact on their clinical manifestations and prognosis, so indigenous studies of depressive disorders are significant (9–12). In contrast, indigenous studies are mostly difficult to quantify due to the low level of evidence of the conventional studies (7). Comparatively, the expert experience and consensus obtained from disease studies based on original assessment modalities through Delphi studies provide a novel exploration for clinical study and are helpful for indigenous studies of depressive disorders.

Psychological scales are the most important means of assessing depressive disorders (13), but their reliability and validity, and applicability to a certain population still need corresponding localization studies. At this point, Delphi studies can facilitate the process of localization of psychological scales. Loneliness is closely related to depressive disorders and is a risk factor for depressive disorders that can be intervened, affecting the development, progression, and prognosis of depressive disorders (13–16), which in turn affects the physical and mental health of older adults. However, the lack of a valid instrument to evaluate loneliness has hindered the prevention of depressive disorders in older adults to some extent. Instead of designing a new instrument, it would be better to have a common instrument in English and Chinese, such as a localized translation of the 6-item De Jong Gierveld Loneliness Scale, which would help to integrate data from different centers around the world for cross-cultural analysis. To develop and validate a Chinese version of the 6-item De Jong Gierveld Loneliness Scale to better assess the risk of depression among the elderly in China, Leung et al. (17) issued a Chinese version of the De Jong Gierveld Loneliness Scale to 103 Hong Kong elderly people aged 60 years or older to conduct a statistical analysis of the reliability and

TABLE 1 | Advantages and disadvantages of the three methods.

Name	Observational research	Experimental researches	Delphi study
Sample size	A large patient sample size is required to exclude error, but large individual differences in clinical patients can also introduce error and bias.		A smaller number of experts (around 15) can also lead to valuable conclusions, and ultimately to a statistical unification of expert opinion.
Compliance with study subjects	Patients may have low adherence and may easily disengage.		Compliance of specialists is usually high.
Problems of medical theology	Certain theoretical problems create problems for research.		No theoretical problems.
Factors affecting results	More quantity	High quantity and complexity	Low quantity
The difficulty of research implementation	A little difficult	Difficult	Not very difficult
Evidence level	High	Higher	low
Matching with the real world	Not very high	Not very high	Higher

validity of the scale, while the Delphi group later determined the validity of the scale content. The results showed that the total loneliness score was significantly and positively correlated with the direct measure of loneliness (rpb = 0.71; $p < 0.001$), which is considered the gold standard for assessing loneliness, indicating that the Chinese version of the De Jong Gierveld Loneliness Scale has good reliability and validity The application of this scale will be beneficial for better prevention of depressive disorders in the elderly.

A new, culturally adapted scale could also be developed through a Delphi study. Xie et al. (18) concluded that depression among older adults in China is not given enough attention, so they used the Delphi method to develop a culturally appropriate scale to screen for depression in older adults in a non-psychiatric context, and tested it for diagnostic reliability and validity, both with high levels. Their results showed that for the Chinese society, the presence of appetite or weight changes, sleep disturbances, and somatic complaints were the top three most valuable symptoms for the diagnosis of depression in older adults.

The Delphi study may also assist in localizing treatment tools. For example, Hart et al. (19) developed a series of local culture-based guidelines through the Delphi study in order to maintain indigenous mental health in Australia. The findings suggest that physicians must be aware of relevant cultural factors in mental illness, such as cultural behaviors that may mimic symptoms of mental illness, the important role of family and community, and the need to facilitate supporting relationships. For example, concerning cultural factors, where patients may mimic cultural behaviors that are symptomatic of mental illness. These findings are consistent with other works of literature related to culturally based care for depressive disorders.

Using Delphi Research to Clarify the Diagnosis and Differential Diagnosis of Depressive Disorder

The clinical manifestations of depression are varied, but in clinical diagnosis and treatment, patients' poor insight into their disease may mislead doctors, making it difficult for doctors to make a quick and accurate diagnosis (20–22). Traditional scales, such as Minnesota Multiphasic Personality Inventory (MMPI) have some defects, such as the large number of questions and long time-consuming, while simple scales, such as SDS, are difficult to assess accurately the severity of depression (23), it is difficult for patients with a depressive disorder to obtain psychological scale efficiently and comprehensively. There are many scales used in the clinical diagnosis of depressive disorder, and the reliability and efficiency of different scales are also difficult to choose. Nabbe (24) conducted a Delphi study on the selection of clinical scales and concluded that the Hospital Anxiety and Depression Scale and the Hopkins Symptoms Checklist-25 (HSCL-25) are sufficiently valid and reliable clinical options.

There is also a clinical dilemma that is difficult to identify with bipolar disorder type 1. To assess the value of Bipolar Spectrum Diagnostic Scale(BSDS) in the differential diagnosis of unipolar and bipolar depression, Juan Pablo et al. used BSDS to evaluate patients with a depressive episode, and then patients are reassessed using the Structured Clinical Interview for DSM-IV Axis I Disorders. The SCID-I diagnosis was compared with the BSDS screening results to analyze the accuracy, sensitivity, and specificity of BSDS screening for bipolar disorders. Studies have shown that in patients with depressive episodes in Mexican, a cut-off value of 12 reached the most stable sensitivity and specificity, with predictive powers higher than 0.80, which is basically consistent with foreign studies (25–27). This result suggests that BSDS screening for patients with bipolar disorder in depressive episodes has a certain degree of accuracy and specificity, but its sensitivity is not ideal (28).

Corresponding, McIntyre et al. (29) have used the Delphi method to create a rapid mood screening tool to identify both unipolar and bipolar disorder, which can screen for not only manic symptoms but also bipolar disorder, it also includes risk factors for bipolar disorder 1 (for example, the age of onset of depression) to help clinicians reduce the risk of misdiagnosing bipolar disorder 1 as a depressive disorder. The sensitivity and specificity of the tool were 0.88 and 0.80, respectively. The positive and negative predictive values were 0.80 and 0.88, respectively. The accuracy of the tool was higher than that of the other mood disorders questionnaire, at the same time, the questionnaire options were reduced by more than 50%. The use of this tool effectively addresses the need for a more comprehensive assessment of bipolar disorder 1, helping to reduce misdiagnosis and improve treatment regimens.

There is a lack of consensus on certain subtypes of depressive disorders, which can hinder evaluation, testing, and treatment, and the Delphi method can be used to guide clinical practice.

Freitas et al. (30) conducted a Delphi study aimed at reaching an expert consensus on the defining factors of paternal depression during pregnancy and postpartum. They believe that perinatal paternal depression is "depression that starts during pregnancy or a year after birth." Many for "depressed mood, negative thinking, physical symptoms (weight loss, sleep problems), as well as pregnancy or postpartum about a year 'masked male depression symptoms." Found several symptoms specific to this group, including confusion about fatherhood/concern about fatherhood and reduced involvement in caregiving activities, experiencing "conflict between who you should be and who you really are," feeling trapped in life, and grieving over the loss of your old life and relationships; Experts also point out that there is a lack of appropriate tools for assessing perinatal paternal depression in response to these symptoms, even with male-specific depression tools such as the Gotland Male Depression Scale, there is no consensus on its use in this particular population, which may be due to the unique experiences of the father during the pregnancy of the partner or after the birth of the child.

Use the Delphi Method to Evaluate and Improve the Treatment Process for Depressive Disorders

The clinical use of antidepressants needs extra caution, its side effects are various (31). Antidepressants bring pain to patients, but they may also reduce patients' compliance to medication, induce patients' sense of shame and increase patients' anxiety (32), and it takes some time for antidepressants to take effect, dosage selection also needs to be considered, after taking a certain degree of addiction, the withdrawal will also have a considerable degree of withdrawal reaction (31, 33, 34). Antidepressants tend to be expensive, and discretionary use can put a financial strain on the health care system and on patients, which can ultimately translate into emotional stress (35–37). In response to these dilemmas, several researchers have evaluated the clinical use and health economics of antidepressants and other therapies, providing detailed expert advice on clinical drug selection.

Delphi study provides expert advice on clinical drug use, for example, Lee et al. (38) conducted a Delphi study to build local consensus and guide doctors to use bupropion for different mental illnesses. The study ultimately yielded 11 consensuses, covers indications, contraindications, side effects, etc. It provides a valuable reference for clinical medication and also puts forward a more detailed application consensus. Besides treatment for major depressive disorder, bupropion is also indicated for seasonal affective disorder and is particularly useful for patients with anhedonia, reduced motivation, weight concern, and sexual dysfunction; Off-label uses of bupropion include smoking cessation, attention deficit hyperactivity disorder (ADHD), bipolar disorder, Parkinson's disease, depression, and occasionally for some anxiety disorders. Similarly, Simonetti et al. (39) reached an expert consensus on the importance of mood stabilizers represented by lithium-ion preparations combined with antidepressants in the treatment of chronic bipolar disorder and suggested that for the manic/mixed phase, whether used alone or in combination with mood stabilizers, second-generation antidepressants may be effective in the short to medium term. In addition to advising on the clinical application of a drug, there are also experts comparing multiple drugs through the Delphi study. To select the most suitable antidepressant drugs for the elderly, Agüera-Ortiz (40) led an expert group to select 21 common antidepressant drugs and evaluate the operation of different strategies in terms of efficacy and safety in dealing with drug-resistant cases. Considering drug therapy, agomelatine is the most widely mentioned drug in terms of safety in comorbid conditions. In general, venlafaxine, sertraline, and vortioxetine are the most commonly recommended antidepressants.

However, even if a patient is fully on-target for a drug, there is still a chance that the drug will not work well (41, 42). Selective serotonin reuptake inhibitors (SSRIs) are often recommended as the antidepressant of choice (43), but 30–40% of patients do not respond adequately to the first prescribed antidepressant (44), this may be due to the patient's genotype insensitive to SSRIs. Oestergaard et al. (45) conducted a Delphi study on whether 5-HTTLPR polymorphism screening should be used in clinical problems of depression, expert opinion pointed out the impact of 5-HTTLPR pre-detection on clinical outcomes, the introduction of 5-HTTLPR genotyping will lead to 33.8, 48.2, 57.8, and 65.1% of patients reaching remission at 1, 2, 3, and 6 months, respectively. It is determined that, in some special situations the test could be combined with 5-HTTLPR to better predict patient characteristics of depressive responses resistance.

While using the medicine, in addition to considering whether the drug is suitable for the patient, it is also necessary to consider the cost that the patient needs to bear. At this time, the Delphi method is also often used for pharmacoeconomic evaluation and drug cost-effectiveness research. Wade et al. (46) used the Delphi method to study the cost and benefit of escitalopram and citalopram in the treatment of major depressive disorder in the United Kingdom. Escitalopram had a higher overall response rate and first-line success rate, and the average treatment cost was 15.7% lower than citalopram. This conclusion is also supported by a study by Nuijten et al. (47) in the Netherlands, where the favorable clinical benefit of escitalopram resulted in positive health economic benefits. In addition, Le Pen et al. (48) evaluated the potential economic benefits of fluoxetine versus tricyclic antidepressants (TCAs) in the treatment of mild to moderate depression, and Lenox-Smith et al. (49) assessed the cost-effectiveness ratio of venlafaxine versus fluoxetine and amitriptyline for the treatment of major depressive disorder in the United Kingdom. Both studies have shown that although the development of new drugs is expensive, better efficacy can bring higher social value and more economic savings, so slightly higher treatment costs should not be a hindrance to the first-line choice for new drugs to treat depressive disorders.

In addition to antidepressants, adjuvant therapy with other medications can also help with depressive disorders. The International Society for Research in Nutritional Psychiatry (ISNPR) developed the first practice guidelines for the use of n-3 polyunsaturated fatty acids (PUFAs) in the treatment of major depressive disorder in 2019 (50), but there is a gap between evidence and consensus. To strengthen these

guidelines and improve their clinical applicability, Guu et al. (51) synthesized the evidence and clinical experience previously obtained through the Delphi methodology, and based on the support of a large body of evidence, ultimately "N-3 PUFAs are one of the potential adjunctive therapies for MDD in adults" reached the highest consensus. In addition to drug treatment, adjuvant therapy such as exercise therapy and mindfulness therapy can also help patients with depressive disorders. And in the information age, it is also possible to use information and communication technology (ICT) to improve depression. Gros et al. (52) have used the Delphi method to explore ways to help patients with depressive disorders through ICT, such as improving patients' mood through games, and online psychological counseling through VR. These methods are very positive for the improvement of patients' conditions.

Consensus Study on Improvement of Prevention and Prognosis of Depression Disorder

It is difficult to predict the prognosis of patients with depression (53, 54), as most patients often relapse within a few years or require lifelong maintenance medication if they relapse more than once (55). So how to determine and improve the prognosis of patients is also of great concern to researchers. Based on patients with insights on the disease (including the understanding of disease, symptoms, the demand for treatment, and social consequences of mental illness) is related to the prognosis of mood disorders (20–22), Olaya et al. (56) through the Delphi study design and apply a scale of insight for depression patients. They found a correlation between patients' poorer insight and a higher number of previous hospitalizations, but not with patients' demographic characteristics, including gender, age, or education.

Similarly, patients leaving the hospital do not mean the end of the diagnosis and treatment process. Compared with other diseases, patients with depression disorder need spiritual care, and it is also an important part of daily care and follow-up of patients during the diagnosis and treatment process. A Delphi study by Koekkoek et al. (57) concerned many difficulties in the care of chronic depressive disorders, such as the risk of relapse, dependence on treatment, and the sense of hopelessness caused by recurrent episodes. With another Delphi study undertaken, Palmer (58) agreed on 5 points about how primary care settings serve depressive disorders and related conditions: including listening, understanding, compassion, providing thorough and competent diagnosis and management, regularly following and monitoring patients' condition, facilitating patient visits, and providing comprehensive treatment and tailored care according to individual needs.

The rehabilitation of patients with depressive disorder not only needs the efforts of medical staff and caregivers, but also patients' efforts play a significant role. Several experts have conducted Delphi studies, offering patients a range of steps that they can take to improve their situation, such as recognizing and acknowledging depression, how to avoid self-harm and suicide attempts, how to seek help from the outside world, and separating advice on how to deal with psychological crises (59–62). Shin et al. (63) tested the effect of self-help intervention on depressive symptoms and sub-threshold depression by Delphi, which showed that lifestyle change and psychological methods were the best choices for depression patients, while health care products were the least effective. They also found that psychiatrists (82.6%) and the general population (67.2%) were more likely to prefer self-help methods than depressed patients (28.4%), perhaps because of patients' pessimism that they would not benefit from self-help strategies. In terms of specific operations, Morgan et al. (64) proposed a series of sub-threshold depression self-help strategies, aim to help reduce the sub-threshold depression degree, improve the quality of life of the people, thus preventing depression, the concreting content includes regular sleep and exercise, do like things, avoiding excessively overworked, learning relaxation techniques, associating with positive people, etc.

DISCUSSION

Due to the diversity of social background of the patients with depressive disorder, the disunity of the evaluation scale, the difficulty of clinical diagnosis and differential diagnosis, and the uncertainty of prognosis, the Delphi method is regarded as a better research method. A combination of the Delphi method was applied to study the localization of depressive disorder, diagnosis and differential diagnosis, treatment, and prognosis of the status, we found that in different regions, different cultural backgrounds, different economic characteristics of the social system, the application of each kind of different depression scale for assessment of all need to take into account the application of the reliability and validity. Given the clinical confusion that it is difficult to distinguish single depression from bidirectional depression, the establishment of an evaluation scale with high reliability and efficiency is an urgent problem to be solved in the clinic. The selection of clinical antidepressants is characterized by the contention of a hundred schools of thought and is affected by the lack of development of biomarkers for depression. Years of network meta-analysis established Sertraline Hydrochloride in the treatment of depressive disorder status, but the different social backgrounds, economic, the age of the onset of depressive disorder lead to the treatment of depressive disorder need accuracy, so the Delphi method research can be integrated clinical expert clinical experience, improve the accuracy of clinical treatment; The recurrence and prognosis of depression are difficult to be solved clinically, and the choice of different treatment schemes also leads to the difficulty in estimating drug withdrawal and disease recurrence. Delphi method can gather the clinical experience of experts in the clinical field and make clinical treatment more grounded, which is difficult to be achieved by other research methods.

As an anonymous expert investigation method, the Delphi method has obvious advantages and disadvantages. Though it is difficult to measure the reliability and validity of Delphi method, and it is requires a long research period, obtains a low level of evidence, and difficult to reach an accurate consensus in the face of controversial content, Delphi research avoids the shortcoming of low credibility of general questionnaire survey through

several rounds of expert consultation and makes comprehensive statistical analysis of the conclusions, and finally transforms the personal experience of experts into expert consensus on a certain aspect. Due to the complexity of depression, it is difficult for traditional research methods to obtain high-level evidence, and the research conclusions do not match the complex clinical environment, so it is difficult to apply to clinical practice. Delphi research can combine the existing research results with the rich experience of experts, which is a shortcut to the clinical application of research results. At the same time, in the process of continuous feedback and communication with experts, Delphi research is better at discovering the shortcomings of the current research, which can point out the direction of the next research. When we use the Delphi method in a suitable environment and time for research, it may bring more help to our research.

AUTHOR CONTRIBUTIONS

FX was responsible for the conception of the thesis. HW was responsible for writing the thesis. LX, YZ, LS, and LZ were responsible for thesis revision. All authors contributed to the article and approved the submitted version.

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EDITED BY
Yuqun Zhang,
Nanjing University of Chinese Medicine, China

REVIEWED BY
Yingying Yue,
Southeast University, China
Jennifer Geske,
Mayo Clinic, United States

*CORRESPONDENCE
Peng Zhao
zpw1979@163.com

†These authors have contributed equally to this work and share first authorship

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Personality traits influence the effectiveness of hypomania checklist-32 in screening for bipolar disorder

Qiang Wang[1†], Aiping Sui[2†], Lin Gong[3], Mohammad Ridwan Chattun[4], Ruichen Han[5], Qiuyun Cao[1], Diwen Shen[1], Yuzhe Zhang[1] and Peng Zhao[1*]

[1]Department of Medical Psychology, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China, [2]Jinling Institute of Technology, Nanjing, China, [3]Department of Psychology, The Air Force Hospital from Eastern Theater of People's Liberation Army (PLA), Nanjing, China, [4]Department of Psychiatry, The Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China, [5]Nanjing Drum Tower Hospital, Clinical College of Jiangsu University, Nanjing, China

Background: It is clinically challenging to distinguish bipolar disorder (BD) from major depressive disorder (MDD) in the early stages. While the hypomania checklist-32 (HCL-32) is a proper auxiliary tool that is useful to differentiate between BD and MDD, there is currently no standard cut-off value. The variations in HCL-32 cut-off values could potentially be influenced by personality traits. Therefore, the aim of this study is to explore the effect of personality traits on the screening performance of HCL-32.

Methods: In this retrospective cross-sectional study, 168 patients with BD or MDD were evaluated with the Eysenck Personality Questionnaire (EPQ) and HCL-32. The associations between demographic data, diagnosis and clinical rating scales were analyzed.

Results: Diagnosis was not associated with extraversion but was related to neuroticism. HCL-32 scores in typical extraverted patients were higher in contrast to atypical extraverted patients. The best cut-off value for BD recognition of typical and atypical extraversion groups were 15 and 12.5, respectively. In patients with MDD, HCL-32 score of typical neuroticism was higher than the atypical type, but there was no difference in patients with BD. In typical neuroticism, there was no difference in HCL-32 scores between patients with MDD and BD. But among atypical neurotic patients, HCL-32 scores of BD were higher compared to MDD, with a cut-off value of 14.5.

Limitations: This study had a small sample size.

Conclusion: HCL-32 scores were affected by personality traits, with higher scores for typical extraversion and neuroticism. Clinicians should also consider the patients' personality traits when referring to HCL-32 scores, so as to increase the recognition rate of BD and eliminate false positives.

KEYWORDS

bipolar disorder, major depressive disorder, personality traits, Eysenck Personality Questionnaire, hypomania checklist-32

Introduction

While major depressive disorder (MDD) and bipolar disorder (BD) are both mood disorders, they are clinically distinct psychiatric illnesses (1). Since BD patients usually suffer from depressive episodes in the initial course of the disease, it is clinically difficult to distinguish BD from MDD (2). A nationwide study in China reported that approximately 20% of patients with BD are initially misdiagnosed with MDD (3). A misdiagnosis will delay the appropriate treatment and hence prolong the suffering of the patient and worsen the prognosis (4).

The hypomania checklist-32 (HCL-32) is a scale that screens for hypomanic symptoms and is useful to discriminate between BD and MDD (5), but its optimal cut-off value, sensitivity and specificity are still not completely homogenous. A study based in primary health care showed that 15 is the best cut-off value for distinguishing BD and MDD (6). Other studies have demonstrated that 14 is the ideal cut-off value, but there are variations in its sensitivity and specificity, for instance, in Europe (sensitivity 0.8, specificity 0.51) (7), Taiwan (sensitivity 0.82, specificity 0.67) (8) and China Mainland (sensitivity 0.69, specificity 0.98) (9). Another study validated that an optimal cut-off value of 13 could distinguish patients with BD-II from MDD, with a sensitivity of 0.77 and a specificity of 0.62 (1). Not only has the cut-off value of HCL-32 been found to be inconsistent in previous studies but, in clinical practice, some BD patients have low HCL-32 scores while MDD patients have high scores. The inconsistencies in the cut-off values of HCL-32 could potentially be explained by different personality traits.

Personality refers to the characteristic sets of behaviors, cognitions, and emotional patterns that are acquired through learning and habits (10). It is widely accepted that "The Big Five Personality Traits" comprise of extraversion, neuroticism, openness, agreeableness and conscientiousness (11). However, according to Hans Eysenck, the three major dimensions of personality that account for most of the variance in personality are extraversion, neuroticism, psychoticism (12). Both the "three-factor model" and "the five-factor model" are widely accepted approaches which extensively make use of self-report questionnaires to investigate personality (13). In personality theory, neuroticism is characterized by the disposition to experience negative emotional states (14). Extraversion is described as being talkative, outgoing and having a positive affect with very high levels of arousal (15). Psychoticism is not only associated with the liability to have a psychotic episode but also with aggressivity, impulsivity and sensation-seeking (16). To date, the most widely studied core personality traits that associated with BD and MDD are neuroticism and extraversion (17).

A study that investigated whether personality traits could predict the onset of depressive or manic episode found that both of the two episodes were associated with neuroticism and extraversion (18). Another study which explored the levels of neuroticism or extraversion between BD and MDD patients revealed that a high neuroticism might indicate a vulnerability to both BD and MDD patients (19). Personality traits in BD were characterized by high neuroticism as well as low extraversion (20). Compared to patients with BD I, BD II patients had higher neuroticism and lower extraversion (21). For depression, it was previously reported that extroversion was a protective factor while neuroticism was a risk factor (22). These findings suggest that the two traits of neuroticism and extraversion in personality traits have a strong influence on the course and outcome of both MDD and BD.

The aim of this study is to explore the effect of the two traits of neuroticism and extraversion in personality on the HCL-32 score in patients with MDD and BD. We hypothesized that personality traits might interfere with the screening performance of HCL-32. The importance of the current study is to improve the early clinical recognition of BD and reduce the misdiagnosis rate with MDD.

Materials and methods

Participants

In this retrospective cross-sectional study, 168 patients were recruited from Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School from December 2020 to October 2021. The participants were evaluated and diagnosed by one consultant psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, fifth Edition (DSM-V) criteria. This study was approved by the Research Ethics Board of the Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School. This study is retrospective, and the risk to the subjects is not greater than the minimum risk, so informed consent was abandoned.

All patients met the following inclusion criteria: (1) MDD or BD; (2) 16 years old and above; (2) Han Chinese; (3) the ability to understand the meaning of each section of the rating scale. Patients who were diagnosed with other psychotic disorders including schizophrenia were excepted. Subjects who presented with comorbid psychiatric illnesses, alcohol or substance use disorders, were pregnant or had severe somatic diseases were also excluded.

Psychological rating scales

The clinical data and two psychological scales data were retrospectively collected from electronic medical records. The demographic information included age, gender, education, clinical diagnosis.

In the current study, the Eysenck Personality Questionnaire (EPQ) was administered to both MDD and BD patients in order to examine personality traits (23). Only the two personality traits of extraversion and neuroticism were calculated. Extraversion scores higher than 61.5 was defined as typical extraversion, otherwise it was atypical extraversion. Among the atypical extraversion group, scores higher than 38.5 was defined as extraversion-intermediate, otherwise it was typical introversion. Similarly, if the neuroticism score was higher than 61.5, it was defined as typical neuroticism (24). Else, the scores were recognized as atypical neuroticism.

All participants were assessed with the self-administered HCL-32 questionnaire. Afterward, patients were divided into two groups according to their HCL-32 score. A score $\geq$14 was considered as a HCL positive group and a score <14 was regarded as a HCL negative group.

TABLE 1 Demographic characteristics and psychological scale results of patients.

Clinical characteristics	HCL positive (N = 104)	HCL negative (N = 64)	*P*-value
Age	23.8 ± 5.6	25.0 ± 6.9	0.26[a]
Female	71 (68.3%)	44 (68.6%)	0.95[b]
Education	87.3	79.9	0.29[c]
HCL-32	21.0 ± 4.2	7.81 ± 3.1	
Extraversion	57.7 ± 6.7	54.0 ± 6.7	0.001[a]
Neuroticism	58.0 ± 6.4	53.8 ± 7.2	<0.001[a]
Diagnosis			<0.001[b]
MDD	37 (35.6%)	49 (76.6%)	
BD	67 (64.4%)	15 (23.4%)	

HCL-32, the 32-item hypomania checklist; EPQ, the Eysenck Personality Questionnaire; MDD, major depressive disorder; BD, bipolar disorder.
[a]Two-sample *t*-test. [b]Chi-square test. [c]Rank sum test.

TABLE 2 Number of subjects with different personality traits.

Personality traits	Diagnosis		
	All patients (168)	MDD (86)	BD (82)
Extraversion			
Typical introversion	6	5	1
Extraversion-intermediate	124	73	51
Typical extraversion	38	8	30
Neuroticism			
Atypical neuroticism	132	74	58
Typical neuroticism	36	12	24

TABLE 3 Hypomania checklist score of each group.

Personality traits	Diagnosis		
	All patients	MDD	BD
Extraversion			
Typical introversion	14.0 ± 6.9	14.8 ± 7.4	10 ± 0
Extraversion-intermediate	14.3 ± 6.9	11.9 ± 6.6	17.7 ± 5.8
Typical extraversion	21.8 ± 6.4	15.3 ± 8.3	23.6 ± 4.6
Neuroticism			
Atypical neuroticism	14.9 ± 7.3	11.5 ± 6.3	19.3 ± 5.9
Typical neuroticism	19.7 ± 6.9	17.8 ± 7.3	20.6 ± 6.7

Statistical analysis

Continuous data are presented as mean ± standard deviation and categorical data are presented as percentage (%). Independent two-sample *t*-test was used for age and each personality trait score of EPQ while rank sum test was utilized for education, and Chi-square test or Fisher's exact test was employed for gender and diagnosis. Two-factor analysis of variance was used to explore the impact of diagnosis and personality traits on HCL-32 scores. ROC curve analysis was computed to find the best HCL-32 cut-off value under different personality traits. The HCL-32 score corresponding to the maximum value of "sensitivity + specificity −1" was used as the cutoff value. All statistical analyses were conducted using SPSS 21.0 software. All statistical tests were two-tailed, and $p < 0.05$ was considered statistically significant. As for multiple comparisons, Bonferroni correction were applied, the *p*-value output by the SPSS software was the calculated probability *p* multiplied by the number of comparisons, so that as long as the *p*-value was less than 0.05, the correction was passed.

Results

Description of the study sample

There were 168 patients included in the study. All subjects were divided into HCL positive (N = 104) and HCL negative (N = 64) groups. The demographic and clinical characteristics of the subjects are summarized in **Tables 1**, **2**. In addition, see **Table 3** for HCL-32 scores of subjects with different personality traits and diagnoses.

Comparisons between hypomania checklist positive and hypomania checklist negative groups

There were statistically significant between-group differences in diagnosis (χ^2 = 26.636, $p < 0.001$), extraversion (t = 3.456, p = 0.001), and neuroticism (t = 4.001, $p < 0.001$). The differences in age (t = 1.128, p = 0.261), education (z = 1.067,

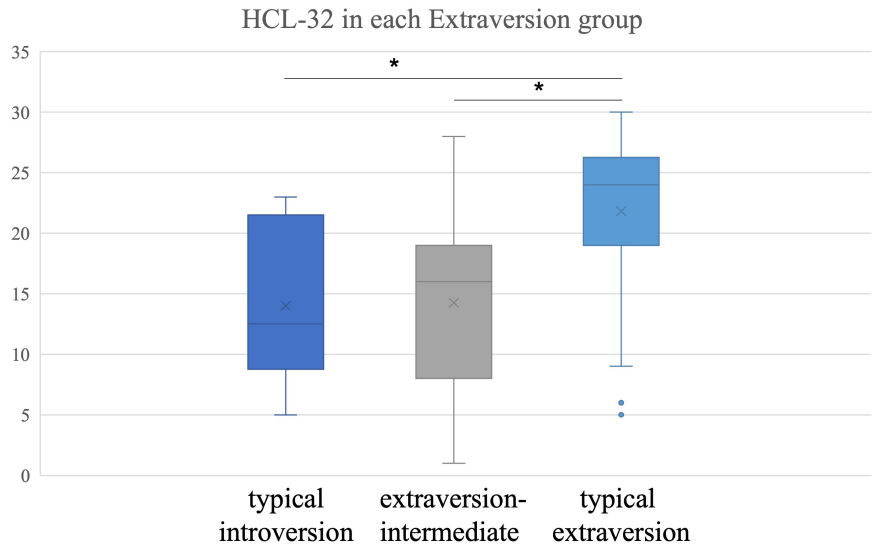

FIGURE 1
Hypomania checklist-32 score in each Extraversion group. *$p < 0.05$ Bonferroni correction.

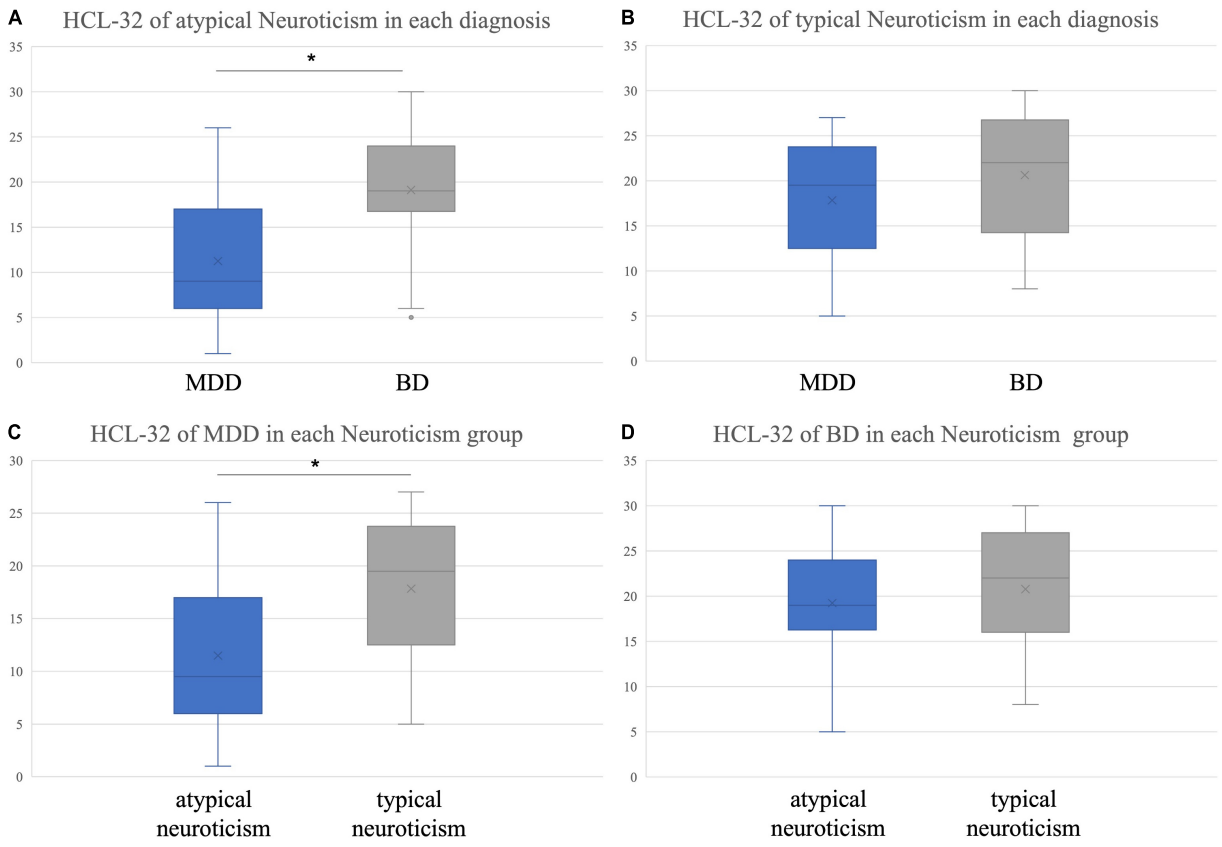

FIGURE 2
Hypomania checklist-32 score of different personality traits in each diagnosis. **(A)** Differences in HCL-32 scores between BD and MDD patients in the atypical neuroticism group; **(B)** Differences in HCL-32 scores between BD and MDD patients in the typical neuroticism group; **(C)** Differences in HCL-32 scores between atypical and typical neuroticism in MDD patients; **(D)** Differences in HCL-32 scores between atypical and typical neuroticism in BD patients. *$p < 0.05$ Bonferroni correction.

p = 0.29), and gender (χ^2 = 0.004, p = 0.948) between the two groups were not statistically significant. See Table 1.

Two-factor analysis of variance

Extraversion and diagnosis

There was no interaction between extraversion and diagnosis on the HCL-32 score (F = 1.764, p = 0.175, partial η^2 = 0.021). An increase in extraversion score led to higher overall HCL-32 scores. Patients exhibiting typical extraversion scored 7.56 ± 1.1 points higher than the extraversion-intermediate group (p < 0.001, Bonferroni correction) and 7.82 ± 2.7 points higher than the typical introversion group (p = 0.013, Bonferroni correction) (Figure 1), but there were no differences between the extraversion-intermediate and typical introversion groups.

Neuroticism and diagnosis

There was an interaction between neuroticism and diagnosis on the impact of HCL-32 score (F = 4.144, p = 0.043, partial η^2 = 0.025). When neuroticism was atypical, HCL-32 scores of distinct diagnosis were different (F = 50.484, p < 0.001); BD score was 7.86 ± 1.1 higher than MDD score (p < 0.001, Bonferroni correction) (Figure 2A). Conversely, when neuroticism was typical, there was no statistically significant difference in the HCL-32 scores of the two diagnoses (Figure 2B).

In patients with MDD, the difference in HCL-32 scores between the two types of neuroticism was statistically significant

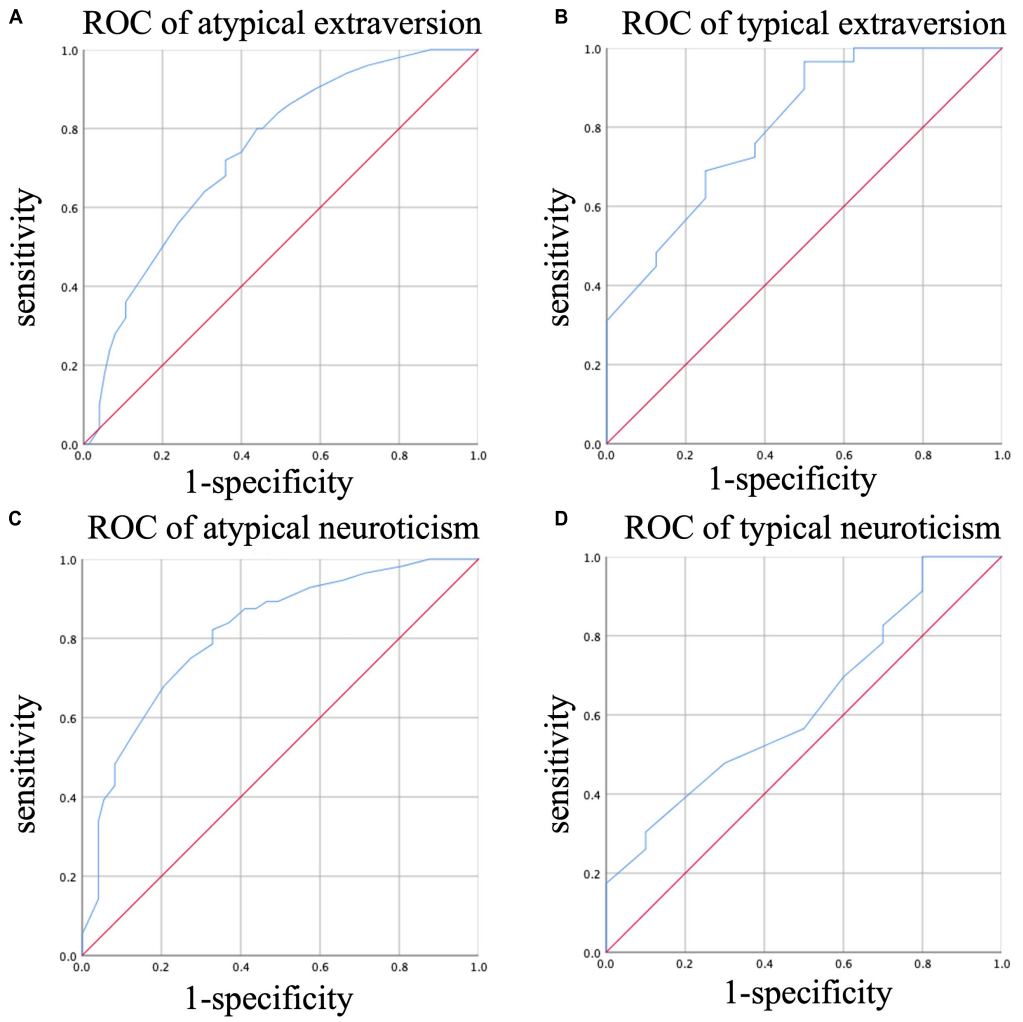

FIGURE 3
ROC of HCL-32 for different diagnosis in different personality traits. **(A)** ROC analysis of the ability of HCL-32 to discriminate between MDD and BD in atypical extraversion group; **(B)** ROC analysis of the ability of HCL-32 to discriminate between MDD and BD in typical extraversion group; **(C)** ROC analysis of the ability of HCL-32 to discriminate between MDD and BD in atypical neuroticism group; **(D)** ROC analysis of the ability of HCL-32 to discriminate between MDD and BD in typical neuroticism group.

TABLE 4 ROC index of each group.

Group	AUC	*P*-value	Sensitivity (%)	Specificity (%)	Cut-off value
Atypical extraversion	0.80	0.009	0.97	0.5	15
Typical extraversion	0.74	<0.001	0.8	0.56	12.5
Atypical neuroticism	0.81	<0.001	0.82	0.67	14.5
Typical neuroticism	0.63	0.248	–	–	–

(F = 10.458, p = 0.001), and the typical neuroticism score was 6.35 ± 2.0 higher than the atypical type score (p = 0.001, Bonferroni correction) (Figure 2C). However, in patients with BD, the difference in HCL-32 scores between the two types was not statistically significant (F = 0.699, p = 0.404) (Figure 2D).

ROC analysis

According to extraversion, patients were divided into typical extraversion and atypical extraversion groups. The best cut-off value of HCL-32 in the atypical extraversion group for identifying BD was 12.5 (AUC = 0.74, $p < 0.001$, sensitivity = 0.8, specificity = 0.56) (Figure 3A), and the best cut-off value of HCL-32 in the typical extraversion group was 15 (AUC = 0.80, p = 0.009, sensitivity = 0.97, specificity = 0.5) (Figure 3B).

When neuroticism was atypical, the best cut-off value of HCL-32 for identifying BD was 14.5 (AUC = 0.81, $p < 0.001$, sensitivity = 0.82, specificity = 0.67) (Figure 3C). However, when neuroticism was typical, ROC curve analysis showed no positive results (AUC = 0.63, p = 0.248) (Figure 3D). The above results were also shown in Table 4.

Discussion

In the present study, HCL-32 scores were related to different personality traits reflected in the EPQ scale. While there was no association between extraversion and diagnosis, extraversion had an impact on HCL-32 scores. A higher extraversion score contributed to higher overall HCL-32 scores. In addition, the HCL-32 score of typical extroverted patients was significantly higher compared to intermediate and typical introverted patients. Moreover, diagnosis was associated with neuroticism. When neuroticism was typical, there was no difference in HCL-32 scores between patients with MDD and BD. Although there was no difference in the HCL-32 scores of BD patients with different neurotic types, the scores of typical neurotic patients were higher than those of atypical neurotic patients in MDD patients.

Previous studies have shown that HCL-32 is related to personality which is consistent with the results of the current study. However, these studies only provided qualitative results. A study which investigated the temperament and bipolar features in depressed patients found that elevated neuroticism resulted in an increase in Beck Depression Index (BDI) score which was positively correlated with HCL-32 score (25). This finding suggested that neuroticism is associated with a high HCL-32 score. A previous study which assessed the association between symptoms of mood disorders and personality traits *via* the Big Five Personality Questionnaire revealed that extraversion was the most reliable predictor of hypomania symptoms assessed by HCL-16 and neuroticism was positively correlated with the hypomanic symptoms of the Mood Disorder Questionnaire (MDQ) scale (26). Another study that examined personality traits in patients with postpartum hypomania reported that extraversion on the EPQ scale was significantly associated with an increased risk of hypomanic symptoms as assessed by HCL-32 scale (27). The abovementioned findings are in line with the results of the current study which illustrated that HCL-32 scores are affected by distinct personality traits.

In our study, diagnosis was not associated with extraversion but was linked to neuroticism. Previous studies on personality traits differences in BD, MDD and the general population revealed that patients with MDD and BD have higher levels of neuroticism but lower extraversion compared with the general population (19, 22). Since patients with BD and MDD usually experience negative emotional states, it is not surprising that these patients have neuroticism traits. On the other hand, the HCL-32 score of typical extraverted patients was higher than those of typical introverted and extraversion-intermediate patients. When ROC analysis was performed, increasing the HCL-32 score of typical extraverted patients to 15 points was more beneficial in eliminating false positives while reducing the HCL-32 score of atypical extraverted patients to 12.5 points was beneficial in enhancing BD recognition rate. When neuroticism was typical, there was no difference in HCL-32 scores between MDD and BD, suggesting that the HCL-32 discrimination ability was not suitable for patients with this type of personality. When neuroticism was atypical, the HCL-32 score of MDD patients was lower than that of BD patients, and the recommended cut-off value was 14.5 points.

To the best of our knowledge, this is the first research to explore the interaction of personality traits *via* EPQ scale and HCL-32 scores, and quantify the results to provide clinicians with specific reference values to distinguish between BD and MDD. The results showed that HCL-32 needs to be combined with the assessment of patients' personality traits.

Conclusion and limitations

In summary, the results of this study could provide clinicians with more practical and numerical reference indicators of HCL-32 scale, which are conducive to early clinical identification of BD patients. In the future, clinicians should also consider the patients' personality traits when

referring to HCL-32 scores, so as to increase the recognition rate and eliminate false positives as much as possible. The main limitation of this study is that sample size is small. A larger and more representative sample is needed for validation of our results. Moreover, a post-morbid change of personality in patients with BD and MDD has not been thoroughly assessed and cannot be completely excluded. Since all the scales used in the current study are self-rating scales, there is the possibility of a bias.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Board of the Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

QW and AS: conceptualization, data curation, formal analysis, and writing original draft. LG, RH, DS, and YZ: data curation. MC: writing original draft. PZ and QC: conceptualization. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Wenhao Jiang,
Southeast University, China

REVIEWED BY
Haitham Jahrami,
Arabian Gulf University, Bahrain
Darpan Kaur,
Mahatma Gandhi Missions Medical College and Hospital, India

*CORRESPONDENCE
Shuping Tan
shupingtan@126.com
Ronghuan Jiang
jiangrh55@126.com

†These authors have contributed equally to this work

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Differences of medically unexplained symptoms among patients of different ages and sexes in the psychological clinic of a general hospital and the influencing factors of MUS: A cross-sectional study

Jie Zhang[1†], Yu Pan[2†], Jiangyue Hong[1], Hong Guo[2], Mengyu Wang[2], Xiaolei Liu[2], Yanbin Dong[2], Dejun Wang[2], Lu Liu[2], Shuping Tan[1*] and Ronghuan Jiang[2*]

[1]Beijing HuiLongGuan Hospital, Peking University HuiLongGuan Clinical Medical School, Beijing, China, [2]Department of Psychological Medicine, The First Medical Center, Chinese PLA (People's Liberation Army) General Hospital, Beijing, China

Objective: To analyse differences in sex, age, depression, insomnia, psychological stress, resilience, and perceived social support among patients with medically unexplained symptoms (MUS) in a psychological clinic of a general hospital, and to explore the influencing factors of MUS.

Methods: This is a cross-sectional study. Seven hundred forty-six first-time patients were assessed with the integrated psychosomatic comprehensive evaluation system (IPS) to evaluate their MUS, depression, insomnia, psychological stress, resilience, and perceived social support. The psychological characteristics were compared with regard to sex and age group (<25 years, low age group; 26–44 years, middle age group; >45 years, high age group). The relationships between age and MUS were explored, and how psychological stress affects MUS was analyzed using the mediator effect model.

Results: Different age groups had significant differences in sex, MUS, depression, psychological stress, resilience, and perceived social support. In further pairwise comparison, no significant difference existed in depression, psychological stress, resilience and perceived social support in the middle and low age groups, depression and psychological stress were higher than those in the high age group, resilience and perceived social support were lower than those of the high age group. MUS were higher in the middle age group than in the low age group. No significant difference existed between the two groups and the high age group. Age, severity of MUS, and perceived social support were significantly different between the sexes. Differences in MUS between men and women in different age groups were analyzed using two-factor analysis of variance. It revealed no interaction between sex and different age groups on MUS. The main effect analysis showed that the effects

of different age groups on MUS were statistically significant. Based on pairwise comparative analysis, the MUS score in the low age group was lower than that in the middle age group. To clarify a nonlinear relationship between age and MUS, threshold effect analysis was conducted. The results indicated that the piecewise linear regression model could better depict the relationship between age and MUS. The inflection point was at the age of 60 years. Before the age of 60 years, MUS increased with age. No significant correlation existed between age and MUS after the age of 60 years. To understand the influencing factors of MUS, the intermediary effect model was analyzed using MUS as the dependent variable, psychological stress as the independent variable, resilience as mediator variable M1, perceived social support as mediator variable M2, and depression as mediator variable M3. Resilience, perceived social support, and depression had significant mediator effects on the effects of psychological stress on MUS with a total indirect effect of 69.81%.

Conclusion: The middle age group had greater MUS than the low age group. Before the age of 60 years, MUS increased with increasing age. Women had more severe MUS than men. Resilience, perceived social support, and depression had significant mediating effects on the effects of perceived stress on MUS. These findings suggest that clinicians should make more comprehensive and detailed evaluations and timely intervention for middle-aged and female patients. Improving psychological resilience and social support can reduce the impact of psychological stress on MUS. Therefore, psychotherapy and multidisciplinary comprehensive treatment are very important for patients is very important for patients.

KEYWORDS

depression, medically unexplained symptoms, stress, psychological, resilience, social support

Introduction

Medically unexplained symptoms (MUS) is one of the most common problems encountered by clinical departments, which was first proposed by Slavney and Teitelbaum (1). The meaning of MUS is the somatic symptoms that cannot be reasonably explained by the pathological structural changes and pathophysiological abnormalities of biomedicine (2). Clinical workers are also used to calling MUS as nonspecific symptom, functional somatic symptom or neurosis.Based on findings of a survey conducted in certain developed countries (3), approximately one-third of patients in the outpatient department of general hospitals have MUS. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and the 10th edition of the International Classification of Diseases (ICD-10) classify MUS as a "somatoform disorder." In actual clinical diagnosis and treatment, doctors and patients are often dissatisfied (4). The DSM-5 replaced somatoform disorder with "somatic symptoms and related disorders." This classification no longer emphasizes that somatic symptoms cannot be explained medically, but highlights poor adaptation to somatic symptoms (5). ICD-11 issued by the World Health Organization also replaced somatoform disorder with "Disorders of bodily distress or bodily experience" (6) in order to integrate the previous diagnostic system. Therefore, for patients with somatic symptoms in outpatient departments of general hospitals, compared with the previous dualism-based view, their symptoms are not considered a medical problem or a psychological problem (7), but the psychosomatic diseases in which the two interact are considered. The patient health questionnaire physical symptoms scale (PHQ-15) is a widely used physical symptoms evaluation scale with good reliability and validity (8, 9), and has been translated into many languages.

Abbreviations: ANOVA, analysis of variance; MUS, medically unexplained symptoms; CD-RISC, Connor–Davidson Resilience Scale; ISI, Insomnia Severity Index; PHQ-9, Patient Health Questionnaire-9; PHQ-15, Patient Health Questionnaire-15; PSS-10, Perceived Stress Scale-10; PSSS, Perceived Social Support.

Psychosomatic diseases can be divided into three stages: psychosomatic reactions, psychosomatic disorders (with functional lesions), and psychosomatic diseases (with somatic organic lesions) (10). Epidemiological data on psychosomatic diseases in China and globally show that the incidence rate of psychosomatic diseases is approximately 22–35%. Early intervention in psychosomatic diseases is very important, especially during the stage of a psychosomatic reaction and psychosomatic disorder so as to avoid further aggravation of psychosomatic diseases. Patients for whom a physical examination cannot partially or fully explain their symptoms often have depression, anxiety, and other problems, which complicates the disease. A study (11) showed that 50% of patients with depression have a variety of MUS, and 35% of patients with MUS have depression. The physical symptoms of psychosomatic patients and psychological stress are linked. For people who are susceptible to stress, even mild to moderate stress may lead to psychosomatic diseases (12). Psychological resilience and social support provide a type of protection for psychosomatic patients. Psychological resilience is defined by the American Psychological Association as a good adaptation process for individuals to face adversity, trauma, tragedy, threat, or other major pressures (i.e., the ability to rebound from difficult experiences). Psychological resilience has multidimensional characteristics, which changes with background, time, age, sex, culture, and different living environments (13). Social support is the object or resource that an individual can turn to when facing pressure, including help from family, friends, and society. Compared to objective social support, the social support that individuals subjectively experience is more related to emotional support and inner satisfaction (i.e., perceived social support). Some studies have shown that perceived social support is more important to patients than objective social support (14). The more a person experiences being respected, supported, and understood emotionally, the higher the person's inner satisfaction is, and the stronger their ability to resist pressure.

A cross-cultural study (15) conducted by the World Health Organization on the primary health care sector in 14 countries revealed that individuals aged ≥45 years tended to have a higher risk of somatisation than patients aged 31–44 years. Sex-specific somatic symptoms have been reported (16, 17); in general, women usually report more intense and frequent somatic symptoms. The present study aimed to understand whether age and sex are risk factors for MUS. Patients with MUS should be comprehensively evaluated as soon as possible after presentation to understand the possible influencing factors and to ensure timely intervention, especially in the psychosomatic reaction and psychosomatic disorder stages, so as to avoid further aggravation of psychosomatic diseases.

Method

Participants

This is a cross-sectional study. Convenient sampling was used to investigate outpatients in the Medical Psychology Department of Chinese PLA (People's Liberation Army) General Hospital (<city>Beijing</city>, China) from April 1, 2021 to August 9, 2021. The participants were non-military civilians. The inclusion criteria were (1) age ≥18 years; (2) visiting the Department of Medical Psychology for the first time; and (3) the presence of somatic symptoms (Patient Health Questionnaire-15 [PHQ-15]≥1). The exclusion criteria were (1) the presence of psychotic symptoms, (2) patients with no insight and self-evaluation ability; and (3) somatic symptoms caused by physical diseases. All participants provided written informed consent. The protocol was approved by Chinese PLA General Hospital Ethics Committee.

Design

An exploratory observational study design was employed. The doctors in the psychological clinic are qualified as psychiatrists and are responsible for consultation and mental examination. Patients were recruited into the study after meeting the inclusion criteria.The enrolled patients provided general information and completed the self-assessment scale in the integrated psychosomatic comprehensive assessment system (IPS) on their mobile phone. Technical problems and questionnaire questions in this process were addressed by psychometrists who had been systematically trained; all information provided was kept confidential.Psychometrists have professional background in psychology and are skilled in various psychological measurement tools.

Measures

Patient health questionnaire-15

Körber et al. (18) demonstrated that the PHQ-15 has good reliability and validity and is suitable for screening for and evaluating the severity of MUS. It contains 15 items, which primarily measure the patients' MUS in the preceding 4 weeks before presentation. Symptom severity is divided into three grades: 0 (no distress), 1 (some distress), and 2 (a lot of distress). The total score range is 0–30 points, in which 0–4 indicates no MUS; 5–9 mild MUS; 10–14 moderate MUS; and ≥15 points severe MUS. When used to predict the diagnosis of somatisation disorder, the 10-point threshold of the PHQ-15 was determined to be the best value with a sensitivity of 80.2% and a specificity of 58.5%.

Patient health questionnaire-9

The PHQ-9 scale (19) is used to screen and evaluate depressive symptoms. It contains nine items, each with a score of 0 (not at all) to 3 (nearly every day). The total score range is 0–27 points, where 0–4 points indicates no depression; 5–9 points mild depression; 10–14 points moderate depression; 15–19 points moderate to severe depression; and 20–27 points severe depression.

Insomnia severity index

The Insomnia Severity Index (ISI) (20) is a reliable and effective tool for screening insomnia and evaluating its degree; it includes seven items. It contains five grades from 0 to 4. The higher the score, the more serious the symptoms of insomnia; 0–7 points indicates insomnia without clinical significance; 8–14 points subclinical insomnia; 15–21 points moderate clinical insomnia; and 22–28 points severe clinical insomnia.

Perceived stress scale-10

The Perceived Stress Scale-10 (PSS-10) is the most widely used stress perception assessment tool. The scale is a self-assessment tool compiled by Cohen et al. in 1983 (21). The 10-item version of the PSS-10 has been proven to have good consistency in large-scale community research in China (22). The PSS-10 is used to evaluate the uncontrollable, unpredictable, or overloaded situations in an individual's own life. Each item is graded from 0 (never) to 4 (very common). The scale is divided into 0–40 points for the total score of each item. The higher the score, the higher the perceived stress level.

Perceived social support

The Perceived Social Support (PSSS) (23) contains 12 items that can be carefully evaluated from three dimensions: family support, friend support, and other support. Each item adopts the 1–7 level scoring method. The higher the total score, the higher an individual's social support. A total score of 12–36 is considered low support, 37–60 medium, and 61–84 high.

Connor–davidson resilience scale

The Connor–Davidson Resilience Scale (CD-RISC) scale (24) contains 25 items, each of which is evaluated on a 5-point scale. The scores 0 to 4 indicate "not at all," "rarely," "sometimes," "often," and "almost always," respectively. The total score of the scale is 0–100. The higher the score, the higher is the psychological resilience.

Statistics

The data were statistically analyzed using SPSS 22.0 (IBM Corp., Armonk, NY, USA). The continuous variables are presented as the mean ± the standard deviation. Classification variables are expressed as the count and percentage. The differences between different age groups and different sexes were evaluated using the chi-squared test, one-way analysis of variance (ANOVA), and the independent samples *t*-test. Two-factor ANOVA was used to analyse differences in MUS between men and women in different age groups. The nonlinear relationship between age and MUS was visualized using a smoothed curve fitting (25). After visualizing the nonlinear relationship between age and MUS with a smoothed curve, for those with a potential nonlinear relationship, the piecewise regression model was used for fitting and the log likelihood ratio test was used to determine whether the nonlinear relationship was significant and whether a significant inflection point existed. The inflection point of the connecting line segment was determined based on the maximum likelihood value given by the piecewise regression model. In the piece-wise linear regression model, the turning point was determined using the trial-and-error method: firstly, selecting turning points according to a pre-defined interval and then choosing the turning point that gave the maximum model likelihood. In addition, a log-likelihood ratio test was conducted to compare the one-line linear regression model with the two-piecewise linear model. A 2-tailed $P < 0.05$ was considered to be statistically significant in analyses.The influencing factors of MUS were analyzed using the chain-mediated effect model in SPSS 22.0 (Process 3.4). Bootstrapping was used to test the significance of mediating effects.

Results

Seven hundred forty-six patients completed the integrated psychosomatic assessment of the IPS and included 467 (62.6%) men and 279 (37.4%) women. The youngest patient was 18 years old and the oldest patient was 79 years old. The average age was 33.21 ± 11.55 years. The patients were divided into three age groups: 18–25 years old (low age group), 26–44 years old (middle age group), and >45 years old (high age group). The PHQ-15 score used to measure MUS was <10 (i.e. mild physical symptoms) in 230 (30.8%) patients and ≥10 (i.e. moderate and severe physical symptoms) in 516 (69.2%) patients.

Differences in sex and scale scores among the different age groups are shown in Table 1. The sex ratios of the three groups were significantly different. There were significant differences in PHQ-9, PSS-10, PSSS and CD-RISC among different age groups.No significant difference existed in PHQ-9, PSS-10, PSSS and CD-RISC scores in the middle and low age groups, PHQ-9 and PSS-10 scores were higher than those in the high age group,

TABLE 1 Comparison of different age groups.

	18–25 (n = 224)	26–44 (n = 390)	45 (n = 132)	F/χ^2	p-value
Sex				33.819	**
Male	164 (73.21%)	247 (63.33%)	56 (42.42%)		
Female	60 (26.79%)	143 (36.67%)	76 (57.58%)		
PHQ-15	11.95 ± 6.284	13.63 ± 6.778	13.42 ± 6.614	4.818	**
PHQ-15	12.071 ± 0.498	13.695 ± 0.347	13.307 ± 0.582	3.601	0.028
Unweighted marginal mean*	95%CI	95%CI	95%CI		
	(11.092–13.049)	(13.013–14.376)	(12.165–14.449)		
PHQ-15				1.21	0.546
<10	75 (33.48%)	114 (29.23%)	41 (31.06%)		
≥10	149 (66.52%)	276 (70.77%)	91 (68.94%)		
PHQ-9	14.51 ± 6.758	13.90 ± 6.635	11.89 ± 6.781	6.612	**
ISI	13.86 ± 6.816	14.80 ± 7.060	14.40 ± 7.057	1.282	0.278
PSS-10	23.46 ± 3.899	23.91 ± 3.958	22.01 ± 4.973	16.537	**
PSSS	45.42 ± 17.680	47.27 ± 16.062	53.03 ± 15.702	9.15	**
CD-RISC	38.19 ± 16.525	39.88 ± 16.514	47.39 ± 15.393	14.222	**

PHQ-15, Patient Health Questionnaire-15; PHQ-9, Patient Health Questionnaire-9; ISI, Insomnia Severity Index; PSS-10, Perceived Stress Scale-10; PSSS, Perceived Social Support; CD-RISC, Connor–Davidson Resilience Scale.
**p < 0.01.

TABLE 2 Comparison of different sexes.

	Male patients (n = 467)	Female patients (n = 279)	T/χ^2	p-value
Age	30.97 ± 9.88	36.97 ± 13.08	−6.616	**
PHQ-15	12.76 ± 6.87	13.63 ± 6.20	−1.785	0.075
PHQ-15			6.889	**
<10	160 (34.26%)	70 (25.09%)		
≥10	307 (65.74%)	209 (74.91%)		
PHQ-9	13.59 ± 6.85	13.96 ± 6.58	−0.721	0.471
ISI	14.79 ± 7.18	13.86 ± 6.65	1.772	0.077
PSS-10	23.56 ± 4.05	23.24 ± 4.42	1.021	0.308
PSSS	39.43 ± 16.82	42.83 ± 16.07	−2.715	**
CD-RISC	48.59 ± 17.37	46.30 ± 15.38	1.878	0.061

PHQ-15, Patient Health Questionnaire-15; PHQ-9, Patient Health Questionnaire-9; ISI, Insomnia Severity Index; PSS-10, Perceived Stress Scale-10; PSSS, Perceived Social Support; CD-RISC, Connor–Davidson Resilience Scale.
**p < 0.01.

CD-RISC and PSSS scores were lower than those of the high age group in further pairwise comparison. PHQ-15 scores were higher in the middle age group than in the low age group. No significant difference existed between the two groups and the high age group.

Sex differences in age and scales are shown in Table 2. The average age and PSSS score of female patients were higher than those of male patients, but more female patients had moderate and severe physical symptoms.

The results revealed no interaction between sex and the different age groups (F[2, 740] = 0.321, p = 0.726, partial η^2 = 0.001). The main effect analysis revealed that the effects of different age groups on PHQ-15 scores were statistically significant (F[2, 740] = 3.601, p = 0.028, partial η^2 = 0.01). The main effect results of different age groups were analyzed using a pairwise comparison. The PHQ-15 score of the low age group was lower than that of the middle age group (95% CI, 0.35–3.01; $p < 0.01$) (Table 1).

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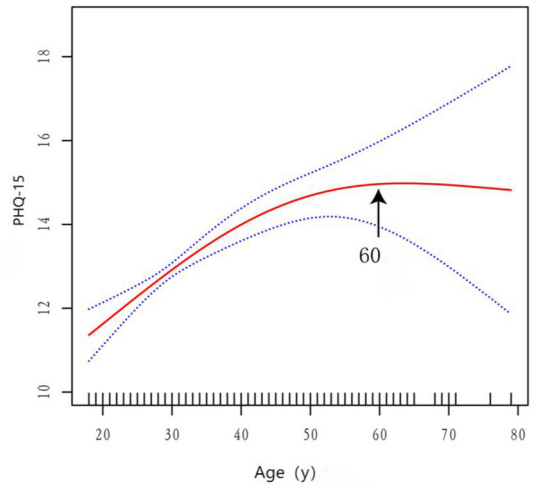

FIGURE 1
Multivariable adjusted smoothed spline curve of age and MUS.

TABLE 3 Threshold effect analysis of age and MUS.

Outcome variable	MUS	
	β (95%CI)	*p*-value
Model 1: Linear regression	0.09 (0.06, 0.12)	<0.001
Model 2: Piecewise linear regression		
Inflection point K	60	
<K	0.10 (0.07, 0.14)	<0.001
≥K	−0.21 (−0.50, 0.08)	0.158
Effect difference at both ends	−0.31 (−0.61, −0.01)	0.042
Predicted value of the equation at the inflection point	14.64 (13.32, 15.96)	
Log likelihood ratio tests	0.041	

To explore whether a nonlinear relationship existed between age and MUS, smoothed curve fitting analysis was conducted for visualization (Figure 1). The slope of the smoothed curve between age and MUS changed, which suggested the presence of an inflection point. To determine whether a significant inflection point in the smoothed curve existed between age and MUS, threshold effect analysis was conducted, as shown in Table 3. The results demonstrated that the piecewise linear regression model could better describe the relationship between age and MUS. The inflection point was at 60 years of age: before 60 years of age, MUS increased with increasing age; after 60 years old, the correlation between age and MUS was not statistically significant. The arrows in Figure 1 indicate significant inflection points.

To understand the factors influencing MUS, we conducted a mediation effect model analysis. MUS was the dependent variable, and psychological stress was the independent variable. Psychological resilience was mediation variable M1, perceived social support was mediation variable M2, and depression was mediation variable M3. Regression analysis revealed that psychological resilience, perceived social support, and depression had significant mediating effects on the effects of psychological stress on MUS (Table 4). The total indirect effect was 69.81% (Table 5). Figure 2 presents the path diagram of the impact of perceived stress on somatic symptoms.

Discussion

This cross-sectional study had several findings: (1) most patients had moderate and severe MUS and a high proportion of patients had severe MUS; (2) MUS was higher in the middle age group than in the low age group; (3) before the age of 60 years, MUS increased with increasing age; (4) more male patients than female patients were young to middle aged, whereas more female patients were in the high age group; (5) women had more severe MUS than men; and (6) psychological resilience, perceived social support, and depression had significant mediating effects on the effects of psychological stress on MUS.

Our study demonstrated that MUS in the middle age group was higher than in the low age group, and no significant difference existed between these two groups and the high age group. These findings differ from the findings of a World Health Organization study (15) conducted in 14 countries, which indicated that the risk of somatisation is higher in people >45 years of age. A possible reason for this difference is that we chose patients from the psychological clinic of a tertiary level A hospital in Beijing, China. In China's first-tier cities, 18- to 25-year-old individuals are facing the pressure of entering school and employment, and 26- to 44-year-old individuals have increased family, career, and social and psychological pressures, whereas, in most first-tier cities, individuals >45 years old have successful careers and happy families. Our research also confirmed this. Depression and psychological stress in the low and middle age groups were higher than those in the high age group, whereas psychological resilience and perceived social support were lower than those of the high age group. The threshold effect analysis of the relationship between age and MUS revealed that MUS increased with age until 60 years, but no significant correlation existed between MUS and age after 60 years.

The analysis of different sexes revealed significant differences in the severity of MUS between men and women. More women than men experienced moderate and severe MUS. Consistent with the present study, sex-specific somatic symptoms have been reported. In general, women usually report more intense and frequent somatic symptoms. The severity of MUS also predicted the level of mental health (26). As in the present study, the middle and low age groups contained more men than women, whereas the high age group contained more women. A study (27) conducted in the outpatient department of Guangzhou General Hospital in China also showed that female

TABLE 4 Regression analysis between variables.

	Regression equation		Overall fitting index		Significance of the regression coefficient	
Result variable	**Predictive variable**	***R***	***R*²**	***F***	β	***t***
Psychological resilience	Psychological stress	0.285	0.081	65.543	−1.133	−8.096**
Perceived social support	Psychological stress	0.565	0.319	174.026	−0.660	−5.272**
	Psychological resilience				0.492	15.656**
Depression	Psychological stress	0.712	0.507	254.259	0.440	9.977**
	Psychological resilience				−0.190	−15.175**
	Perceived social support				−0.066	−5.236**
MUS	Psychological stress	0.646	0.417	132.441	0.185	3.684**
	Psychological resilience				−0.013	−0.833
	Perceived social support				−0.037	−2.676**
	Depression				0.501	12.738**

**$p < 0.01$.

TABLE 5 Mediation effects of psychological resilience, perceived social support, and depression on the relationship between psychological stress and MUS.

	Effect value	Boot standard error	BootCI low limit	BootCI upper limit	Relative mediating effect
Total indirect effect	0.428	0.040	0.352	0.5109	69.81%
Indirect effect 1	0.015	0.018	−0.023	0.0504	2.36%
Indirect effect 2	0.024	0.010	0.007	0.0467	3.98%
Indirect effect 3	0.220	0.032	0.162	0.2867	35.91%
Indirect effect 4	0.021	0.009	0.005	0.0398	3.36%
Indirect effect 4	0.108	0.018	0.074	0.1455	17.59%
Indirect effect 6	0.022	0.006	0.011	0.0359	3.59%
Indirect effect 7	0.019	0.005	0.010	0.0293	3.02%

Indirect effect 1: X→ M1→ Y; Indirect effect 2: X→ M2→ Y; Indirect effect 3: X→ M3→ Y; Indirect effect 4: X→ M1→ M2→ Y; Indirect effect 5: X→ M1→ M3→ Y; Indirect effect 6: X→ M2→ M3→ Y; and Indirect effect 7: X→ M1→ M2→ M3→ Y.

sex, depression, and anxiety were the main risk factors of serious physical symptoms. Research has also shown opposing findings in terms of sex; the findings of one study (28) in adolescents showed that male individuals had more psychosomatic symptoms. Another study (29) on the correlation between sex, age, and physical symptoms also demonstrated that men had greater severity of physical symptoms. Findings in one study (30) revealed sex differences in somatic symptoms; fewer women than men went to a hospital for physical examination and diagnosis. The reasons for the inconsistencies in these studies may be that the applied somatic symptom measurement scale differed, the items of somatic symptoms are different between men and women, women are more sensitive to pain, and women are more likely to report gastrointestinal discomfort than men.

Some studies (18, 31) demonstrated that a correlation exists between the number and severity of MUS, negative psychological symptoms, and functional characteristics. The present study supports this finding in the further analysis of the influencing factors of somatic symptoms. Many studies indicated that psychological stress can lead to depression and MUS. A study (32) of 604 patients in a psychosomatic clinic showed that the number of MUS is associated with psychological stress and the severity of depression. Investigators from different medical disciplines believe that somatic symptoms are associated with changes in hypothalamic pituitary adrenal function, an imbalance in vagus sympathetic tone and the upregulation of immune and inflammatory function, and an enhanced response to threatening stimuli so as to promote the subjective experience of somatic symptoms (33). Somatic symptoms reflect

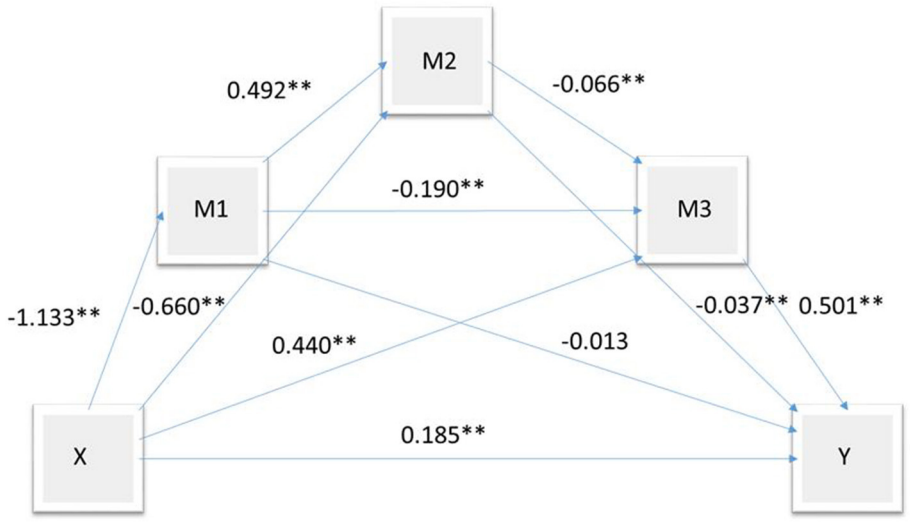

FIGURE 2
Path map of psychological stress on MUS; Y indicates MUS; X, psychological stress; M1, resilience; M2, perceived social support; M3, depression. $^{**}p < 0.01$.

disorders of the stress system. Psychological stress affects the pathogenesis of physical diseases through negative emotions such as depression or anxiety. Exposure to chronic stress is considered the most harmful because it is most likely to lead to long-term or permanent changes in emotional, physiological, and behavioral responses, thus affecting susceptibility and the course of physical diseases (34, 35). The analysis of the mediating effect model of physical symptoms caused by psychological stress revealed that psychological resilience, perceived social support, and depression all have mediating effects on MUS caused by psychological stress and that psychological resilience and perceived social support have a protective role in the occurrence of physical symptoms. A study (36) on resilience and mental health showed that psychological resilience depends on an individual's thoughts, emotions, and behaviors and depends on available and obtained cultural resources, such as the social environment. The intervention in multiple systems and fields of psychological resilience is more likely to establish psychological resilience to properly deal with serious or long-term adversity. One study (37) on the role of perceived social support in depression and somatic symptoms among college students showed that the ability to obtain emotional support could predict depression and physical symptoms.

Studies have confirmed that the outpatient and inpatient costs of patients with MUS are high (38) and that direct and indirect expenditures are increased, especially for patients with severe MUS (31). The present study and a previous study (39) demonstrated that MUS were closely associated with psychosocial factors. For the treatment of MUS, research emphasizes the effectiveness of psychosocial therapy (especially cognitive behavioral therapy) and the importance of multidisciplinary management (40). Therefore, comprehensive psychological evaluation can provide support for a patient's psychotherapy.

There are a few limitations. First, at present, there are still great differences on the clinical definition, diagnostic classification, pathological mechanism and clinical treatment of MUS. Our study included participant with MUS as long as there was one or more somatic discomfort symptoms that could not be explained by physical diseases. Secondly, we did not evaluate the duration of MUS, its impact on patients' daily life and the distress it brought to patients, so we did not make a clear diagnosis for the participants according to the ICD or DSM diagnostic system. We made a cross-sectional evaluation and did not continue to follow up.

The findings of the present study suggest that clinicians should make a more comprehensive and detailed evaluation and timely intervention for middle-aged and female patients. Our study has identified for the first time that MUS increased with age until 60 years, but no significant correlation existed between MUS and age after 60 years. Improving psychological resilience and social support can reduce the impact of psychological stress on physical symptoms. Therefore, psychotherapy is very important for patients. CBT (Cognitive Behavioral Therapy) and MBCT (Mindfulness Based Cognitive Therapy) have been proved feasible and effective intervention methods by many studies (41, 42). In terms of drug treatment, as patients with MUS are often accompanied by symptoms such as anxiety and depression, antidepressant drugs are usually given to patients to help them relieve pain and restore social function. Before visiting the psychological clinic, patients with MUS often repeatedly visit other outpatient clinics in

general hospitals, so multidisciplinary consultation and liaison is beneficial.

Subsequent studies can follow up these patients, including the definite diagnosis, treatment and prognosis. The clinical effects of different treatment methods and the clinical outcomes of patients of different sex and age were compared.

Data availability statement

The datasets presented in this article are available on request to the authors. Requests toaccess the datasets should be directed to xiaojie8706@163.com.

Ethics statement

The studies involving human participants were reviewed and the protocol was approved by Chinese PLA General Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Wenhao Jiang,
Southeast University, China

REVIEWED BY
Laura Polloni,
University Hospital of Padua, Italy
Wenbin Guo,
Central South University, China

*CORRESPONDENCE
Tao Zou
zoutaozou@tom.com
Weixiong Cai
tsaise@163.com

†These authors have contributed equally to this work

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Gut microbiome characteristics of comorbid generalized anxiety disorder and functional gastrointestinal disease: Correlation with alexithymia and personality traits

Xunyi Guo[1,2†], Feng Lin[1,2†], Fengjiao Yang[3], Jing Chen[1], Weixiong Cai[4*] and Tao Zou[1*]

[1]Department of Psychiatry, The Affiliated Hospital of Guizhou Medical University, Guiyang, China, [2]Department of Clinical Medicine, Guizhou Medical University, Guiyang, China, [3]Department of Psychiatry, The Second Affiliated Hospital of Xinxiang Medical University, Xinxiang, China, [4]Shanghai Key Lab of Forensic Medicine, Key Lab of Forensic Science, Ministry of Justice, Shanghai Forensic Service Platform, Academy of Forensic Science, Shanghai, China

Objective: The aim of this study was to investigate the characteristics of intestinal flora in patients with functional gastroenteropathy and generalized anxiety disorder (GAD) and the relationship between intestinal flora and psychological factors.

Materials and methods: From March 2020 to December 2020, a total of 35 patients with functional gastroenteropathy and generalized anxiety disorder, 30 healthy controls, 16 patients with functional gastroenteropathy, and 44 patients with generalized anxiety disorder were selected from the Affiliated Hospital of Guizhou Medical University. Fecal samples were collected from each group, and the related psychophysiological factors scales (Hamilton Anxiety Scale, Hamilton Depression Scale, Neurotic Personality Questionnaire, concept of illness questionnaire, Toronto Alexithymia Scale, Severity of Physical Symptoms Scale, and Cognitive Emotion Regulation Questionnaire) were improved. 16S rRNA high-pass sequencing was used to determine the correlation between intestinal flora changes and functional gastroenteropathy with generalized anxiety disorder. Then, the scale and gut microbiota results were analyzed for correlation to determine the correlation between personality traits and gut microbiota.

Results: We found similar intestinal microbiota in patients with functional gastroenterology, generalized anxiety disorder, and functional gastroenteropathy with generalized anxiety disorder. But the relative abundance of Clostridium was significantly increased in patients with functional gastrointestinal disease (FGID) and generalized anxiety. The relative abundance of *Haemophilus influenzae* was significantly increased in patients with functional gastrointestinal disease without a generalized anxiety disorder.

The intestinal microecological composition was significantly correlated with personality traits.

Conclusion: Functional gastrointestinal disease comorbidity GAD may be related to an increase in the relative abundance of *Fusobacterium*. FGID non-comorbidity GAD may be related to the increased relative abundance of *Hemophilus*. The increased relative abundance of *Fusobacterium* and *Megamonas* is associated with personality traits such as difficulty describing feelings and difficulty identifying feelings, neuroticism, and negative cognition of disease.

KEYWORDS

gut microbiome, functional gastrointestinal disorders (FGIDs), general anxiety disorders (GAD), 16S rRNA, comorbidity

Introduction

Generalized anxiety disorder (GAD) is characterized by persistent and significant tension and restlessness, accompanied by autonomic nervous function excitation and hypervigilance that persists for most of at least 6 months. The prevalence of generalized anxiety disorder was 13.6%, with a significantly higher prevalence in women than in men (1). It is also prolonged, prone to recurrence, and has a significant impact on the physiological and psychological functioning of the individual.

Functional gastrointestinal disease (FGID) is a clinically common gastrointestinal dysfunctional disorder that affects approximately one-third of the world's population (2). FGIDs are characterized by a variety of chronic, recurrent clusters of gastrointestinal symptoms, and the corresponding organic lesions cannot be detected by various medical examinations. FGID mainly includes functional dyspepsia (FD), irritable bowel syndrome (IBS), functional constipation (FC), functional bloating (FB), and so on. FGID is characterized by chronic or recurrent gastrointestinal symptoms, and these symptoms cannot be explained by known pathophysiological mechanisms (3). The pathogenesis of FGID is still unclear and is thought to be due to a combination of multiple factors. Psychosocial factors are thought to play a key role in its pathogenesis (4, 5).

Studies have shown that mood disorders can predict the development of functional gastrointestinal disorders (FGIDs), which in turn predict the development of mood disorders (6). The prevalence of comorbid anxiety disorders in patients with FGID is estimated to be more than 40% (7, 8). A recent meta-analysis similarly showed that the prevalence of anxiety symptoms in patients with FGIDs was 39.1% (9). Studies have shown a significant positive correlation between the degree of anxiety and depression and the grading of gastrointestinal symptoms in patients with FD, IBS, and FC (10). The prevalence of anxiety and depression increases progressively with the number of coexisting FGID disorders and the frequency and severity of gastrointestinal symptoms (11). Cognitive behavioral therapy and mood-improving medications may help alleviate gastrointestinal symptoms in patients with FGID (12). Anxiety was shown to be an independent predictor of first-episode FGIDs in a 12-year prospective study, and patients diagnosed with FGIDs also had higher anxiety during follow-up (13). These studies suggest that anxiety disorders and FGIDs often have comorbidities, but the pathophysiological mechanism of comorbidities is still unclear and needs to be further explored.

With the concept of the microbial-gut-brain axis, the role of the gut microbiome in gastrointestinal and psychiatric diseases has received increasing attention from scholars. The gut microbiome regulates the brain function and behavior of the host through the microbial-gut-brain axis, and the changes in the gut microbiome also affect the development and function of the central nervous system (CNS) through the microbial-gut-brain axis (14). In animal experiments, feces from chronically unpredictable mildly stressed mice were transplanted to control mice, and the recipient mice showed anxiety-like and depression-like behaviors similar to those of the donor mice (15). Studies have shown that the gut flora of patients with a generalized anxiety disorder has reduced alpha diversity compared to healthy populations and that there is a positive correlation between anthropoid genera and *Escherichia coli*-Shigella and anxiety severity (16). In patients with FGID, studies have shown that dysbiosis of small intestinal flora may be the basis of symptoms of functional gastroenteropathy (17). In addition, diarrhea, IBS, and depression patients have similar intestinal flora (18). Transplanting feces from a healthy person to FGID patients with anxiety or depression improves mood and gastrointestinal

symptoms (19). These findings suggest that the gut microbiome may play a key role in the physiological mechanism of comorbid GAD and FGID. However, few reports have been reported on the differences in gut microbiomes in FGID, GAD, and their comorbidities. In addition, personality plays a key role in mental health, and studies have shown genetic and biological links between mental health and personality (20). In addition, there are significant differences in pain duration, severity, and dysfunction of IBS disease in patients with different personalities (21). People with negative perceptions of the disease and a lack of expression of their own emotions are often more likely to develop functional gastroenteropathy disorders (8). Understanding the role of personality on gut microbiota can help us understand the role of mental health on gut microbiota.

This study was conducted to investigate the relationship between the diversity of intestinal flora and psychological factors in patients with functional gastrointestinal disease and generalized anxiety disorder, based on the intestinal flora-gut-brain axis, and to find the key bacteria associated between them. We further analyzed the correlation between intestinal flora and psycho-behavior as well as personality in order to provide a theoretical basis and a new target for intervention in the treatment and prognosis evaluation of functional gastrointestinal disease with generalized anxiety disorder.

Materials and methods

Participants

Written consent has been obtained from all patients before specimen collection. The study was reviewed and approved by the Medical Ethics Committee of the Affiliated Hospital of Guizhou Medical University and was in accordance with the Declaration of Helsinki. Patients with FGID and GAD in the psychiatric and gastroenterology inpatient department of the Affiliated Hospital of Guizhou Medical University were selected. The inclusion criteria were as follows: ① no history of other psychiatric disorders and psychoactive substance abuse; ② no serious organic disease; ③ ages 18–65. The exclusion criteria were as follows: ① previous history of psychoactive substance abuse; ② combined with serious organic diseases; and ③ pregnant or lactating women. Subsequently, according to the diagnostic criteria of functional gastroenteropathy (Rome IV), the diagnostic criteria of a generalized anxiety disorder (ICD-11), and the Hamilton anxiety scale score, they were divided into generalized anxiety disorder group (ADD), functional gastroenteropathy group (FGID), and functional gastroenteropathy with generalized anxiety disorder group (FAD). The inclusion criteria of the control group (CG) were ① family members living in the same area as the experimental group; ② age 18–65 years; ③ no previous history of psychiatric and gastrointestinal diseases; ④ laboratory routine examination (blood, urine, stool routine, liver function, and blood lipid) was normal. The exclusion criteria were the same as those for the experimental group.

Sample collection

After completing the questionnaire test, fresh feces from patients and volunteers were collected, and feces from 30 healthy controls, 16 patients with functional gastroenteropathy, 44 patients with generalized anxiety disorder, and 35 patients with comorbid GAD and FGID were collected in 50 ml sterile disposable tubules. The feces were numbered, packed in ice boxes, and transferred to the laboratory refrigerator at -80°C for standby.

Screening tool

(1) Hamilton Anxiety Scale (HAMA-14) (22): It was developed by Hamilton in 1959, and it is the most common scale used in the clinical assessment of anxiety. The reliability coefficient of this scale was 0.9, and the validity coefficient of the scale was 0.36, respectively. It included 14 items on a 5-point scale from 0 to 4: (0) asymptomatic, (1) mild, (2) moderate, (3) severe, and (4) extremely severe.

(2) Five Factors Inventory-Neuroticism Subscale (FFI-N) (23): The scale adopts the neuroticism dimension of the Big Five personality; it has 12 items in the questionnaire and is rated on a 5-point scale from 1 to 5: (0) completely disagree, (1) disagree, (2) have no opinion, (3) agree, and (4) completely agree. The scale is widely used in China, and higher total scores indicate the more obvious neuroticism characteristics. The internal consistency coefficient of the FFI-N in this study was Cronbach's alpha = 0.921.

(3) The Chinese version of Illness Perception Questionnaire Revised (IPQ-R): This scale was developed by Weinman et al. (24). In 2002, it was revised and formed IPQ-R through Moss-Morris et al. This study adopts the Chinese version translated by Xiong et al. (25). The questionnaire consisted of three subscales, and the second subscale was used in this study. There were 38 items in the questionnaire, including seven dimensions of the course of disease (acute and chronic), consequences, personal control, treatment control, disease consistency, disease periodicity, and emotional statement. It is rated on a 5-point scale from 1 to 5: (0) totally disagree, (1) disagree, (2) have no opinion, (3) agree, and (4) strongly agree. Among them, the course of disease (acute and chronic), consequences, disease periodicity, and emotional statements belong to negative sexiness knowledge. The higher the score is, the greater the negative sexiness knowledge is. Personal control, treatment

TABLE 1 Clinical parameters and demographic information of subjects.

	CG (n = 30)	FGIDS (n = 16)	ADD (n = 44)	FAD (n = 35)	合计 (n = 125)	F	P
Age	40.2 ± 6.4	37.6 ± 11.8	35.3 ± 9.5	34.4 ± 10.2	36.5 ± 9.6	2.435	0.068
Sex (female%)	73	50	77	54	67	2.468	0.065
BMI	23.1 ± 2.3	21.4 ± 3.4	21.4 ± 3.0	21.4 ± 3.5	21.8 ± 3.1	2.403	0.068
Race (%)						0.478	0.698
Han	60	75	66	71	67		
Others	40	25	34	29	33		
Smoking (%)	13	13	14	23	16	0.560	0.642
Drinking (%)	37	18	27	31	30	0.587	0.625
Residence (%)						0.654	0.582
Urban	57	38	43	49	47		
Rural	43	62	57	51	53		
Family history (%)	0	0	9	11	6	1.735	0.163
Formerly medical history (%)	3	19	14	11	11	1.008	0.392

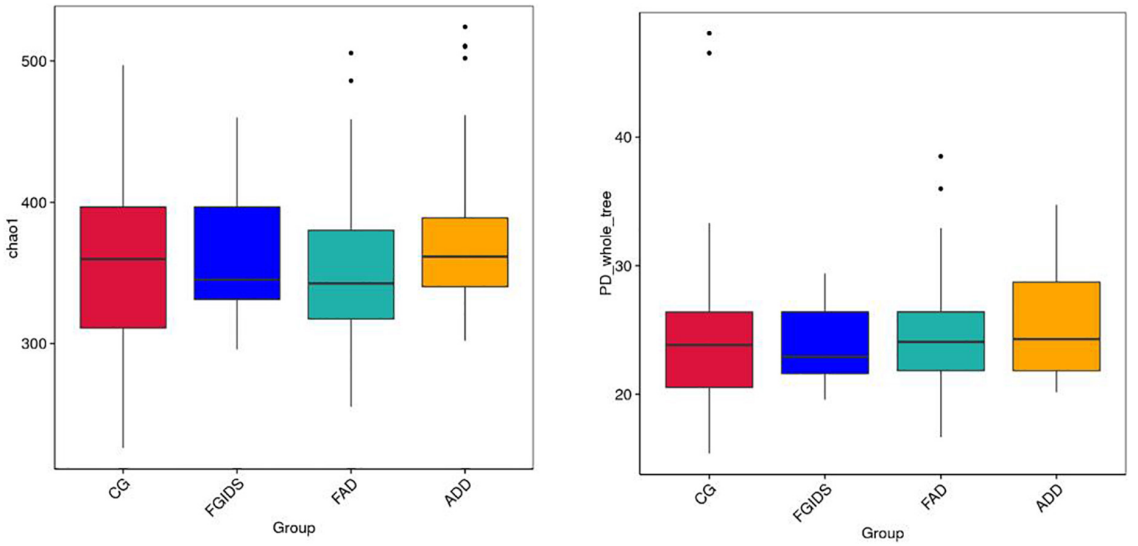

FIGURE 1
Analysis chart of α diversity of intestinal flora among different groups.

control, and disease consistency are positive perceptions, and the higher the score, the stronger the positive perceptions.

(4) The Twenty-Item Toronto Alexithymia Scale (TAS-20): This scale was developed by Bagby et al. (26). This study adopted the revised version by Yi et al. (27), which includes 20 items in total. It contains three dimensions, namely, difficulty describing feelings, difficulty identifying the feeling, and externally oriented thinking. The difficulty describing feeling subscale is used to measure difficulty describing emotions (five items); the difficulty identifying feeling subscale is used to measure difficulty identifying emotions (seven items); and the externally oriented thinking subscale is used to measure the tendency of individuals to focus their attention externally (eight items). The scale was rated on a 5-point scale from 1 to 5: (0) completely disagree, (1) disagree, (2) have no opinion, (3) agree, and (4) completely agree. The retest reliability of the scale was 0.87.

(5) Patient Health Questionnaire-15 (PHQ-15) (28): This scale consists of the 15 most common somatic symptoms and is used to assess the severity of somatic symptoms in the last month, using a 3-grade scoring method of 0–2, with a total score ranging from 0 to 30 points, in which ∼4 points represented no somatic symptoms, 5–9 points represented mild somatic symptoms, 10–14 points represented moderate somatic symptoms, and ≥15 points represented severe somatic symptoms. The internal consistency reliability coefficient was 0.73, and the retest reliability coefficient was 0.75.

(6) Cognitive Emotion Regulation Questionnaire-Chinese Version, CERQ (29): This scale is used to assess the

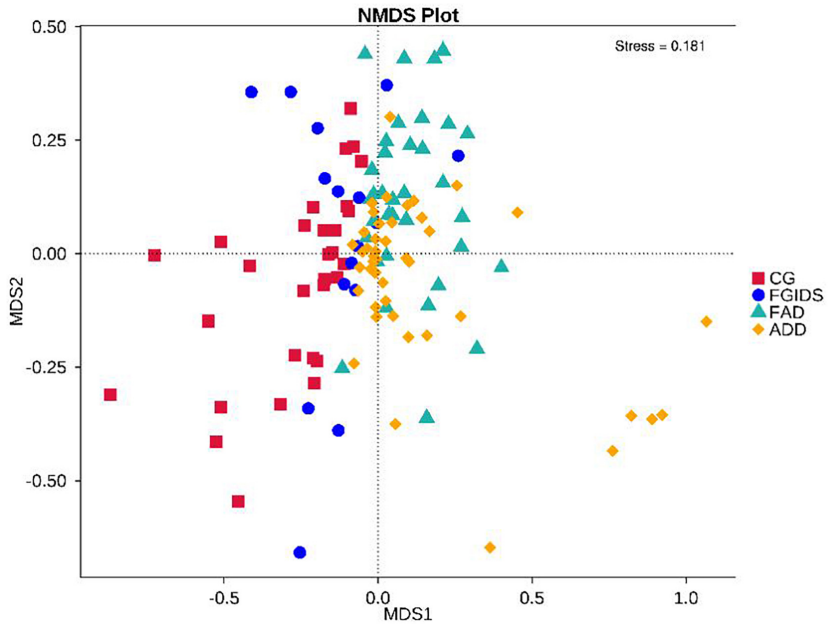

FIGURE 2
Analysis chart of β diversity of intestinal flora among different groups.

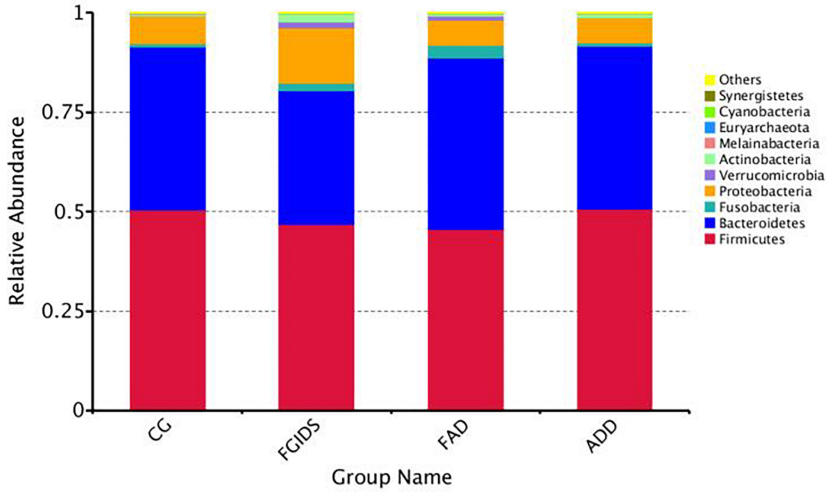

FIGURE 3
Phylum level species stack map.

cognitive strategies used by individuals in coping with negative events. The scale contains 36 entries, including acceptance, positive attention, plan of attention, positive reappraisal, rational analysis, self-blame, self-reflection, catastrophizing, and blaming others in nine dimensions using a 5-level scoring method. The higher the total score on the scale is, the lower the individual's cognitive emotion regulation level is. The Cronbach's α coefficient of the CERQ-C scale was 0.8 L, and the retest reliability of the full scale was 0.56.

Sequencing of 16srDNA amplicons

DNA was extracted from stool samples using the PowerSoil R®DNA isolation kit (Qiagen, Hilden, Germany) according to the manufacturer's recommended protocol. Primers 515F (5'-ACTCCT ACGGGAGgCAGCAGG-3') and 806R (5'-GGactachVGGGTWTCtaat-3') were used for PCR amplification of the v3-V4 variable region of bacterial 16S rRNA gene, and the PCR products were quality controlled with

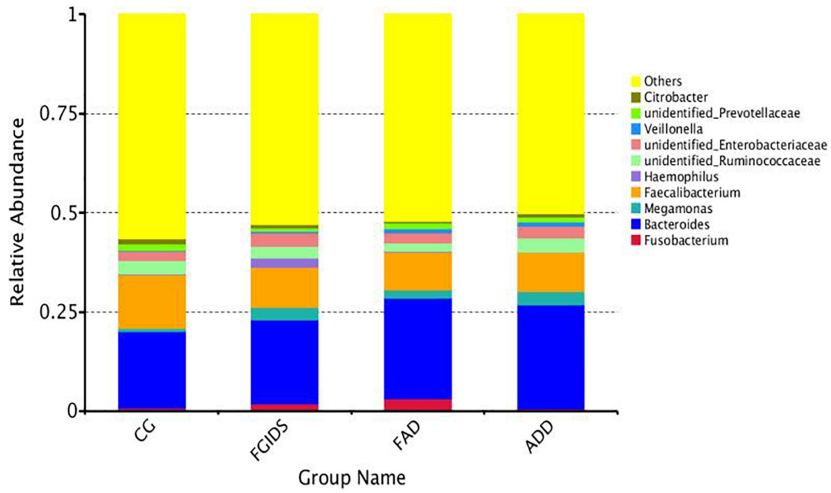

FIGURE 4
Stack diagram of horizontal species distribution of genus.

a 2% concentration agarose gel; NovaSeq PE250 (Illumina) was used for up-sequencing.

Bioinformatics processing

The original sequences obtained from Illumina NovaSeq were assembled, screened, and chimeras constructed according to the Qiime (V.1.9.1) quality control process. OTUs clustering of valid data with 97% consistency (Identity) was performed using the Uparse software (version 7.0.1001). The SILVA database (V123) was used as a reference for species annotation of OUT sequences with species using classifiers. Shannon, Simpson, Chao1, ACE, Goods_Coverage, PD_whole_tree, and other analysis indexes were used to evaluate α diversity. Weighted Unifrac and unweighted Unifrac were used to calculate β diversity. Weighted Unifrac distance and Unweighted Unifrac distance were used for PCoA analysis. To overcome the shortcomings of linear models (including PCA and PCoA), NMDS analysis was conducted based on Bray-Curtis distance to explore the differences in community structure among different samples or groups.

Statistical methods

The *SPSS 19.0* software was used for statistical analysis of the study data. Quantitative data were expressed as $-x \pm s$, grade data were expressed as frequency (%), and an independent *t*-test and one-way ANOVA were used for comparison between groups. The differences in intestinal flora between groups were analyzed by alpha diversity index and LDA Effect Size (LEfSe), and the scatter plot was based on a non-metric multidimensional scale (NMDS). Spearman correlation was used to analyze the correlation between intestinal microflora and psychological factors. $P < 0.05$ indicated that the difference was statistically significant.

Results

Demographic characteristics

A total of 125 subjects were recruited for this study, including 30 healthy subjects (CG), 16 in functional gastroenteropathy (FGID), 44 in generalized anxiety disorder group (ADD), and 35 in functional gastroenteropathy with a generalized anxiety disorder (FAD). The proportion of women in the ADD group (77%) was higher than in other groups. The proportion of Han nationality in the FGID group (75%) was higher than in the other groups. The proportion of smoking in the functional gastroenteropathy with generalized anxiety disorder group (23%) was higher than that in other groups. The proportion of drinking and city in the CG group (37 and 57%) was higher than that in other groups, but there was no statistical difference (Table 1).

Characteristics of intestinal flora

To explore the intestinal microbiota associated with GAD and FGID, the α diversity index of the total sample was analyzed. According to the chao1 index and PD whole_tree index analysis, there was no significant difference in species richness among groups [all *P*-values > 0.05 (Figure 1)]. NMDS analysis of β diversity based on Bray-Curtis distance revealed

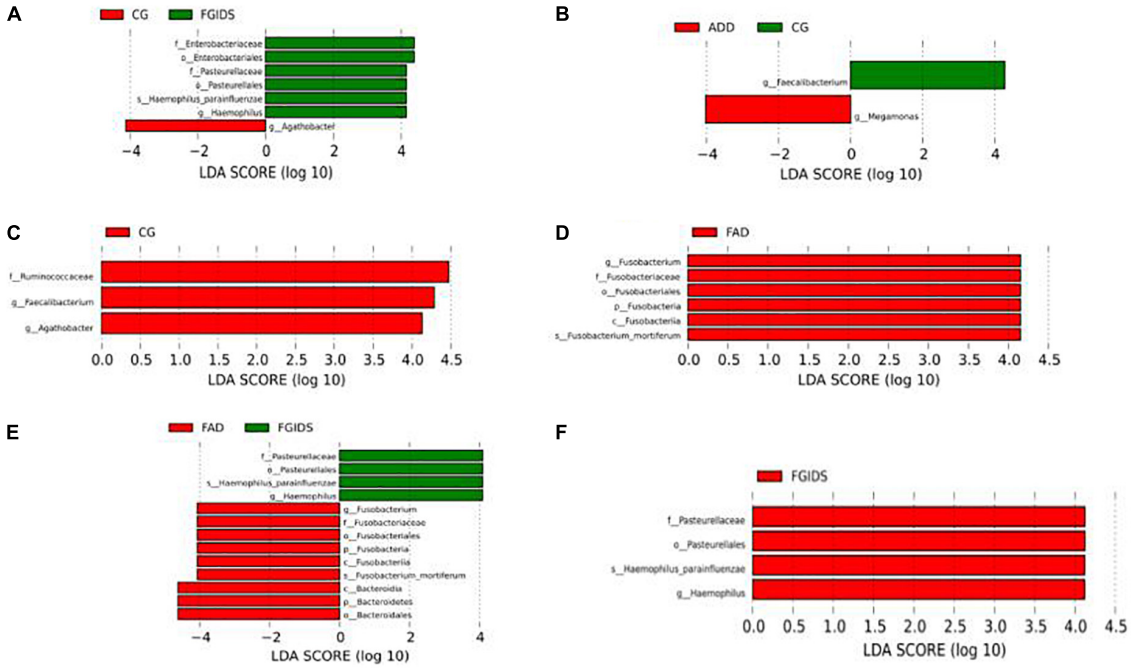

FIGURE 5
Analysis of significant difference flora among different group. **(A)** CG-FGIDS. **(B)** ADD-CG. **(C)** FAD-CG. **(D)** ADD-FAD. **(E)** ADD-FGIDS. **(F)** FAD-FGIDS.

TABLE 2 Comparison of scale scores among groups ($-x \pm s$).

项目	CG组 ($n = 30$)	FGIDS组 ($n = 16$)	ADD组 ($n = 44$)	FAD组 ($n = 35$)	F
TAS	27.53 ± 2.67	52.25 ± 8.01[a]	57.75 ± 7.45[ab]	61.14 ± 10.54[ab]	121.79
PHQ	2.33 ± 0.55	9.19 ± 4.43[a]	13.59 ± 4.77[ab]	17.11 ± 4.81[abc]	76.04
IPQ (负性)	22.50 ± 0.68	65.13 ± 6.54[a]	71.52 ± 8.96[ab]	72.86 ± 8.54[ab]	331.76
IPQ (正性)	16.17 ± 0.38	50.06 ± 4.17[a]	51.18 ± 5.13[a]	50.09 ± 4.63[a]	512.35
FFIN	12.10 ± 0.31	32.44 ± 5.11[a]	36.77 ± 4.62[ab]	37.57 ± 4.77[ab]	264.74
HAMA	4.93 ± 0.87	17.56 ± 2.06[a]	38.66 ± 9.28[ab]	39.80 ± 10.13[ab]	152.738
CERQ	37.33 ± 2.36	106.81 ± 16.56[a]	109.52 ± 13.11[a]	109.71 ± 17.66[a]	212.42

Compared to the CG group, [a]$P < 0.05$; Compared to the FGID group, [b]$P < 0.05$; Compared to the ADD group, [c]$P < 0.05$.

TABLE 3 Correlation analysis of psychosocial factors and intestinal flora (The Rs values).

Type	TAS	PHQ	FFIN	HAMA	CERQ	IPQ	IPQ (正性)	IPQ (负性)
Fusobacterium	0.345**	0.336**	0.304**	0.314**	0.209*	0.340**	0.218*	0.299**
Bacteroides	0.185*	0.161	0.180*	0.187*	0.068	0.114	0.112	0.046
Megamonas	0.284**	0.175	0.326**	0.312**	0.233**	0.324**	0.259**	0.381**
Faecalibacterium	-0.148	-0.236**	-0.214*	-0.251**	-0.140	-0.259**	-0.231**	0.196*
Haemophilus	-0.032	-0.070	-0.019	-0.161	-0.055	0.019	-0.062	0.058
Unidentified_Ruminococcaceae	-0.184*	-0.233**	-0.140	-0.228*	-0.013	-0.226*	-0.101	-0.159
Unidentified_Enterobacteriaceae	0.058	0.208*	0.301**	0.185*	0.156	0.202*	0.182*	0.188*
Veillonella	0.243**	0.242**	0.279**	0.251**	0.163	0.315**	0.298**	0.316**

**$P < 0.01$; *$P < 0.05$.

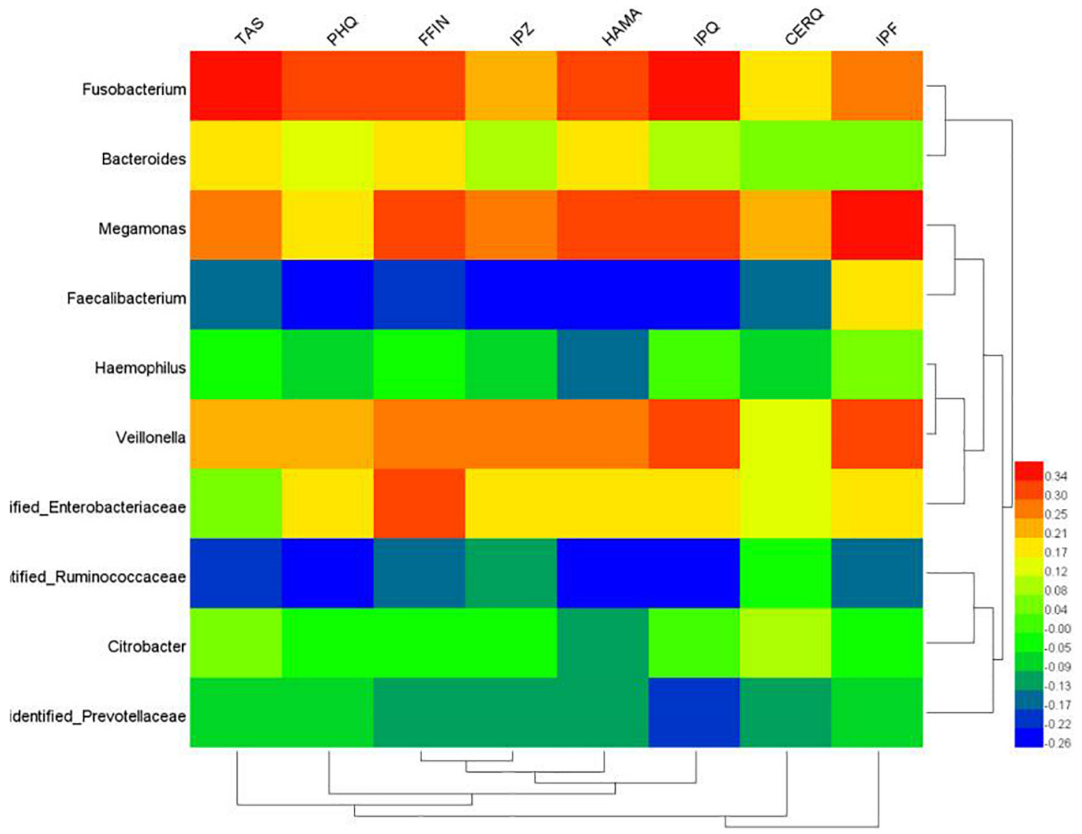

FIGURE 6
Heat map of correlation analysis between psychosocial factors and intestinal flora.

differences in the composition of intestinal flora between the four groups (Figure 2).

At the phylum level, the dominant bacteria attached to CG, FGID, FAD, and ADD groups were basically the same. Firmicutes, Bacteroidetes, Fusobacteria, and Proteobacteria occupy almost 98% of the intestinal flora. In the CG group, the proportion was 50.48, 40.79, 0.8, and 0.69%; in the ADD group, the proportion was 50.69, 41.04, 0.7, and 6.3%. In the FGID group, the proportion was 46.97, 33.57, 1.9, and 13.77%. In the FAD group, the proportion was 45.57, 43.16, 3.13, and 6.3%. We found that the abundance of Fusobacteria in the CG and ADD groups was relatively lower than in the FGID and FAD groups (0.8% CG and 0.7% ADD, 46.97% FGID, and 45.57% FAD) (Figure 3). At the genus level, *Fusobacterium*, *Bacteroides*, *Megamonas*, *Faecalibacterium*, *Haemophilus*, and Unidentified Ruminococcaceae were the dominant bacteria. In the CG group, the proportion was 0.8, 19.28, 0.8, 13.61, 0.2, and 3.3%; in the ADD group, the proportion was 0.7, 26.19, 3.2, 10, 0.8, and 3.6%; in the FGID group, the proportion was 1.9, 21.20, 3.1, 10.1, 2.42, and 3%. In the CG group, the proportion was 3.13, 25.38, 2.1, 9.54, 0.1, and 2.3%. We found that the abundance of Fusobacterium in the CG and ADD groups was significantly lower than that in the FGID and FAD groups (0.8% CG, 0.7% ADD, 1.9% FGID, and 3.13% FAD), and the abundance of Fusobacterium in the FGID group was also significantly lower than in the FAD group (Figure 4).

The LEfSe method further confirmed the difference in intestinal flora structure among groups. Ruminococcaceae, *Faecelibacterium*, and *Agathobacter* in the FAD group decreased significantly compared with the CG group, while Fusobacterium in the FAD group increased significantly compared with the ADD group. Fusobacterium and Bacteroid in the FAD group were significantly increased compared with the FGID group, while *Pasteurella*, *Hemophilus*, Parainfluenzae, and *Hemophilus* in the FAD group were significantly decreased compared with the FGID group. *Pasteurella*, *Hemophilus*, Parainfluenzae, and *Hemophilus* were significantly increased in the FGID group compared with the ADD group. *Enterobacterium*, *Pasteurella*, *Haemophilus*, Parainfluenzae, and *Haemophilus* in the FGID group were significantly increased compared with the CG group, while *Aathobacter* was significantly decreased compared with the CG group. Faecalibacterium in the ADD group decreased significantly compared with the CG group, while Megamonas increased significantly compared with the CG group (Figure 5).

Correlation analysis of psychogenic factors and intestinal microflora

The study showed that the scores of TAS, PHQ, IPQ (negative), FFIN, and HAMA in the FAD group were significantly higher than those in the FGID group. The PHQ score in the FAD group was significantly higher than that in the ADD group. The scores of TAS, PHQ, IPQ (negative), FFIN, and HAMA in the ADD group were significantly higher than those in the FGID group (**Table 2**). A Spearman correlation analysis was used to analyze the relationship between scale scores of TAS and the abundance of bacteria. The results showed that TAS scores were significantly positively correlated with *Fusobacterium*, *Megamonas*, and *Veillonella* ($P < 0.01$). PHQ scores were positively correlated with *Fusobacterium* and *Veillonella* ($P < 0.01$) and were significantly negatively correlated with *Faecalibacterium* and Ruminococcaceae ($P < 0.01$). FFI-N scores were significantly positively correlated with *Fusobacterium*, *Megamonas*, *Veillonella*, and Enterobacteriaceae ($P < 0.01$) and were negatively correlated with *Faecalibacterium* ($P < 0.01$). HAMA scores were significantly positively correlated with *Fusobacterium*, *Veillonella*, and *Megamonas* ($P < 0.01$), and *Bacteroides* and Enterobacteriaceae ($P < 0.05$). HAMA scores were significantly negatively correlated with *Faecalibacterium* ($P < 0.01$) and Ruminococcaceae ($P < 0.05$). The CERQ scores were significantly positively correlated with *Megamonas* ($P < 0.01$). The IPQ-R scores were significantly positively correlated with *Fusobacterium*, *Megamonas*, and *Veillonella* ($P < 0.01$) were significantly negatively correlated with *Faecalibacterium* and Ruminococcaceae ($P < 0.01$) (**Table 3**).

The heat map shows that *Fusobacterium*>*Megamonas*>*Veillonella* were closely related to anxiety. *Fusobacterium*>*Veillonella* was closely correlated with somatic symptoms. *Megamonas* was closely related to the negative perception of the disease, and *Veillonella* was closely related to the positive knowledge of the disease (**Figure 6**).

Discussion

Functional gastrointestinal disease is a common and multifaceted disease of the digestive system with symptoms as the main diagnostic basis and is influenced by multiple factors. The results of current studies have found that psychological factors play a key role in the pathogenesis of FGID. Currently, psychological factors have been found to play a key role in the pathogenesis of FGID, but the changes in intestinal flora in patients with FGID and GAD comorbidities have been less studied.

The results of this study showed that the abundance of *Fusobacterium* in the FAD and FGID groups was relatively higher than that in the ADD and CG groups. Furthermore, LEfSe analysis revealed that the relative abundance of *Fusobacterium* in the ADD and FAD groups was significantly lower in the FGID group. *Fusobacterium* is considered as a pathogen because of its invasive and inflammatory nature, its ability to enter the bloodstream and cause intestinal barrier dysfunction, and its role in immune activation of GAD. To the best of our knowledge, this is the first report of *Clostridium perfringens* alterations in patients with functional gastrointestinal disease comorbidities and generalized anxiety. However, it was found that the relative abundance of Fusobacterium and Bacteroid in patients with GAD was higher than that in healthy people (30). Compared with healthy people, the relative abundance of *Fusobacterium* in the intestinal flora of patients with IBS increased (31). Also, this study showed that *Fusobacterium* and *Veillonella* were significantly and positively correlated with the severity of somatic symptoms ($P < 0.01$), and the correlation coefficients were ($R = 0.336$, 0.242), respectively. It indicates that the higher the percentage in the intestinal tract, the more severe the patient's physical symptoms, aggravating the patient's disease. *Fusobacterium*, *Megamonas*, and *Veillonella* were significantly positively correlated with anxiety scores ($P < 0.01$). The correlation coefficients were 0.314, 0.312, and 0.251, respectively. Therefore, we suggested that the increase in the relative abundance of Fusobacterium in intestinal flora might be related to comorbid GAD and FGID.

The results of LEfSe analysis in this study showed that the relative abundance of Hemophilus in the CG, ADD, and FAD groups was significantly lower in the FGID group. Previous studies have shown that the relative abundance of Hemophilus is elevated in patients with functional gastroenterology compared with healthy people (32). Therefore, we speculated that the elevated relative abundance of Hemophilus in the intestinal flora might be related to the pathogenesis of FGID without GAD. Hemophilus is considered to be one of the main pathogens responsible for chronic inflammation. Somatic inflammatory reaction is believed to be the cause of FGID (33), but no relevant study has reported the correlation between the increased relative abundance of Hemophilus and FGID without GAD, which is worthy of further exploration.

Studies have shown that psychosocial factors are associated with disease awareness, difficulty describing feelings, symptom severity, and outcome in patients with FGIDs (8). Patients with different personalities have significant differences in the duration, severity, and functional impairment of their IBS disorders (21). Neuroticism and covert aggression are the most likely markers of FGID susceptibility (34). This study further revealed that the scores of TAS, PHQ, IPQ (negative), FFIN, and HAMA in the FAD group were significantly higher than those in the FGID group through correlation analysis of different groups and scales. The results showed that the severity of physical symptoms and the negative cognitive characteristics of the disease were prominent, the level of anxiety and depression was high, the neuroticism was more obvious,

and the difficulty describing feelings and difficulty identifying feelings were more likely. The results of a recent meta-analysis suggest that the mental health of inflammatory bowel disease patients is associated with inflammatory bowel disease outcomes (35). Functional gastroenterology patients with alexithymia tend to have more severe somatic symptoms (36). Enhanced perception of visceral stimulation is considered to be one of the key features of IBS. Alexithymia may enhance visceral hypersensitivity in IBS (3). People with severe alexithymia tend to amplify somatosensation (37). These findings support a significant association between FGID and psychological factors, but the role of gut microbiota remains to be explored. The Spearman correlation analysis showed that TAS scores were significantly positively correlated with *Fusobacterium*, *Megamonas*, and *Veillonella* ($P < 0.01$). The FFI-N score was significantly positively correlated with *Fusobacterium* and *Megamonas* ($P < 0.01$). The CERQ score was positively correlated with *Megamonas* ($P < 0.01$). The IPQ-R scores were significantly positively correlated with *Fusobacterium*, *Megamonas*, and *Veillonella* ($P < 0.01$). The composition of intestinal microecology is correlated with personality traits (38). People with high neuroticism had significantly lower gut microbiome β diversity than those with low neuroticism (39). Therefore, we believe that the increased relative abundance of *Fusobacterium* and *Megamonas* is associated with personality traits such as difficulty describing feelings and difficulty identifying feelings, neuroticism, and negative cognition of disease and that the comorbidity of GAD and FGID is more likely to occur.

The shortcomings of this study are the small sample size and the single detection method (only 16S high-throughput sequencing). To compensate for the above deficiencies, on the one hand, this study will expand the sample size, further explore whether the intestinal flora is specific for psychological effects, establish FGID with GAD and GAD population cohort, and further group FGID with GAD with or without antipsychotic drugs, in order to analyze the effects of antipsychotic drugs on the intestinal flora. On the other hand, metabolomic analysis was performed on the samples to screen for significantly different metabolites as potential biomarkers for FGID and GAD and to establish a link between intestinal peptide-mental disorders. Meanwhile, the role of probiotics in patients with comorbid GAD and FGID will also be explored, so as to elucidate the mechanism of the "intestinal microbiome-gut-brain" axis.

Conclusion

Functional gastrointestinal disease comorbidity GAD may be associated with an elevated relative abundance of Fusobacterium. FGID non-comorbidity GAD may be related to the increased relative abundance of Hemophilus. The increased relative abundance of *Fusobacterium* and *Megamonas* is associated with personality traits such as affective difficulty describing feelings and difficulty identifying feelings, neuroticism, and negative cognition of disease.

Data availability statement

The data presented in the study are deposited in the SAR repository, accession number PRJNA 863752.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the Affiliated Hospital of Guizhou Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XG drafted the manuscript for submission. XG and FL were responsible for data collection, the study's topic and scope, and research of evidence as well as analysis and interpretation of data. JC and FY were involved in data collection, coding of data, and provided intellectual input into the manuscript. TZ and WC supervised the study and provided intellectual input into the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Wenhao Jiang,
Zhongda Hospital, Southeast University, China

REVIEWED BY
Imad Maatouk,
University of Würzburg, Germany
Heribert Christian Sattel,
Technical University of Munich, Germany

*CORRESPONDENCE
Monika Sadlonova
msadlonova@mgh.harvard.edu

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Changes in treatment outcomes in patients undergoing an integrated psychosomatic inpatient treatment: Results from a cohort study

Monika Sadlonova[1,2,3,4,5]*, Julia Katharina Löser[6], Christopher M. Celano[4,5], Christina Kleiber[7], Daniel Broschmann[1] and Christoph Herrmann-Lingen[1,3]

[1]Department of Psychosomatic Medicine and Psychotherapy, University of Göttingen Medical Center, Göttingen, Germany, [2]Department of Cardiovascular and Thoracic Surgery, University of Göttingen Medical Center, Göttingen, Germany, [3]German Center for Cardiovascular Research, Göttingen, Germany, [4]Department of Psychiatry, Massachusetts General Hospital, Boston, MA, United States, [5]Department of Psychiatry, Harvard Medical School, Boston, MA, United States, [6]Department of Geriatrics and Early Rehabilitation, St. Joseph-Stift Hospital, Bremen, Germany, [7]Department of Psychosomatic Medicine and Psychotherapy, Medical Center Kassel, Kassel, Germany

Objective: In Germany, multimodal psychosomatic inpatient treatment can be initiated for patients with substantial mental disorders (e.g., depression, anxiety, somatoform disorders) and comorbid physical disease. However, studies investigating changes in psychological and functional treatment outcomes, and predictors of long-term treatment effects in patients undergoing psychosomatic inpatient treatment are needed.

Methods: This cohort study analyzed 160 patients aged ≥18 who were treated on an integrated psychosomatic inpatient unit at the University of Göttingen Medical Center. Its aim was to analyze changes in psychological and functional outcomes, and to identify predictors of long-term improvements in health-related quality of life (HRQoL) in patients with comorbid mental and physical illness who were undergoing integrated inpatient psychosomatic treatment. Assessments were completed at admission, discharge, and 12- or 24-month follow-up. Outcomes included physical complaints [Giessen Subjective Complaints List (GBB-24)], psychological symptoms [Brief Symptom Inventory (BSI)], and HRQoL [European Quality of Life Questionnaire (EQ-5D)].

Results: One-hundred sixty inpatients were included (mean age = 53.1 ± 12.6; 53.8% female). There were significant, medium- to large-sized improvements in psychological symptoms (BSI-Global Severity Index; $d = -0.83$, $p < 0.001$), physical symptom burden ($d = -0.94$, $p < 0.001$), and HRQoL ($d = 0.65$, $p < 0.001$) from admission to discharge, and significant, small- to medium-sized greater improvements in all psychological outcomes from admission to follow-up (BSI-GSI: $d = -0.54$, p < 0.001; GBB-24 total symptom burden: $d = -0.39$, $p < 0.001$; EQ-5D: $d = 0.52$, $p < 0.001$). Furthermore,

better improvement in HRQoL during hospitalization (partial $\eta^2 = 0.386$; $p < 0.001$) was associated with higher HRQoL at follow-up. Finally, intake of antidepressant at discharge was associated with impaired HRQoL at follow-up ($\eta^2 = 0.053$; $p = 0.03$).

Conclusion: There were significant short- and long-term improvements in psychological symptoms, physical complaints, and HRQoL after treatment on an integrated psychosomatic inpatient unit in patients with mental disorders and a comorbid physical disease.

KEYWORDS

psycho-cardiology, inpatient psychotherapy, psychosomatic medicine, cardiovascular disease, HRQoL

Introduction

Among individuals with chronic physical diseases, mental disorders are highly prevalent (1–4) and are associated with impaired quality of life (QoL) (3, 5–7), high disability burden (3, 4, 7, 8), medical complications (7), high healthcare utilization and costs (3, 9), and premature mortality (3, 10). Specifically, mental disorders have been linked to adverse cardiovascular outcomes (e.g., major adverse cardiac events or mortality in coronary heart disease patients) (11, 12), and patients with cardiovascular diseases require complex emotional-cognitive adaptations (11). Despite these relationships, mental disorders are underdiagnosed and undertreated in primary care settings (13), with previous studies demonstrating that over 50% of patients with mental disorders do not receive guideline-concordant treatment that can impact both psychological (e.g., QoL, psychological distress) and medical outcomes (e.g., hospitalizations, disease-related complications, mortality) (7, 14–19). Furthermore, existing treatments rarely utilize a holistic approach that targets both mental and physical symptoms and is guided by psychosomatic principles (20).

One potential treatment option for more severely ill patients with mental disorders (e.g., depression, anxiety, somatoform disorders) and comorbid physical illness is multimodal care in an inpatient psychosomatic medicine setting (21–23). Inpatient psychosomatic care involves inpatient hospitalization for a period of 4–6 weeks, during which patients engage in a variety of therapeutic interventions, including psychotherapy, patient-centered nursing, creative therapies, body-oriented and physical therapy, and pharmacotherapy (22). In Germany, psychosomatic medicine is not a subspecialty of psychiatry but represents a specialized medical discipline, and its clinical core competency is an integrated care approach that focuses specifically on patients with comorbid mental and concomitant physical disease (e.g., psycho-cardiology) (22, 24). As integrative patient-centered care concepts (e.g., psycho-cardiology) are increasingly recommended (24), the present study describes a unique, inpatient psychosomatic setting mainly focused on patients with mental disorders and comorbid cardiovascular diseases (e.g., coronary heart disease, malignant cardiac arrhythmias, heart failure). This setting allows the integration of psychological treatments, including psychological, creative, body-oriented, and specialized cardiac-based treatments, into an Academic Heart Center.

In addition, physical diseases (e.g., diabetes, inflammatory bowel disease, migraine) with pronounced psychological components are treated. A meta-analysis of randomized controlled trials (RCTs) evaluating these types of psychotherapy-focused hospital treatments (25) found that these interventions led to a medium within-group effect size (Hedges' $g = 0.72$) improvement in symptoms from admission to discharge, with a small reduction of the effect to follow-up ($g = 0.61$). However, fewer than 50% of patients in the reviewed studies had comorbid physical diseases and most were under 50 years of age. Therefore, additional research studies investigating short- and long-term treatment effects of multimodal psychosomatic inpatient care in older patients with both mental and physical illnesses are necessary. This would improve the scientific evidence for treatment effects of integrated psychosomatic units in medical centers (e.g., heart centers or internal medicine departments).

Additionally, identifying predictors of response to psychosomatic treatment may be beneficial. To date, both sociodemographic and treatment characteristics have been linked to treatment response, though the existing literature has been mixed. For example, while one cohort study found younger age to be associated with subjective change three months after psychosomatic hospitalization (26), a second observational study ($N = 1829$) found age not be associated with changes in psychological outcomes at admission, discharge, and 1-year follow-up (27). Similarly, though a RCT ($N = 298$) of standardized five-week multimodal cognitive-behavioral therapy (CBT) demonstrated that women with depressive disorders and chronic pain syndromes benefit significantly

more than men from the program (28), white men responded more robustly to a CBT intervention than other subgroups in a different study ($N = 2481$) investigating a treatment effects of CBT in patients with minor or major depression after myocardial infarction (29). Furthermore, comorbid physical diseases, lower self-efficacy, and the number of mental disorders were found to be predictors of treatment outcomes (e.g., subjective complaints and negative mood) assessed at 1-year follow-up after inpatient psychosomatic treatment (27). Finally, participation in a targeted outpatient aftercare intervention led to increased long-term effectiveness of inpatient psychosomatic treatment (30). Given the paucity of data, better understanding of predictors for short- and long-term treatment outcomes (e.g., psychological and functional symptom complaints, HRQoL) of integrated inpatient psychosomatic treatments (e.g., psycho-cardiology or psychosomatic internal medicine) in patients with mental disorders and comorbid physical disease is necessary.

To address the above-mentioned gaps, we performed a cohort study to examine changes in psychological and functional outcomes in patients undergoing an integrated, multimodal inpatient psychosomatic treatment program in an academic Heart Center, as well as to identify predictors of HRQoL at follow-up. Given previous scientific findings, we hypothesized that (1) the multimodal, inpatient psychosomatic treatment would lead to significant improvements in psychological and functional outcomes at discharge and 12- or 24-month follow-up compared to admission. Furthermore, we expected that (2) female sex, higher age, and the presence of comorbid cardiovascular disease would moderate these effects; and that (3) both sociodemographic and treatment-related variables (e.g., outpatient psychotherapy, intake of antidepressants) would be associated with HRQoL in this population.

Materials and methods

Study design

The primary aim of this single-center cohort study was to assess changes in psychological and functional outcomes from admission to discharge and 12- or 24-month follow-up in patients with mental disorders and a comorbid physical disease undergoing an integrated, inpatient psychosomatic treatment program. The secondary aims were to investigate whether (i) age, sex, and the presence of comorbid cardiovascular disease act as moderators of changes in treatment outcomes; and whether (ii) there are influencing factors on HRQoL at follow-up in patients with indication for an inpatient psychosomatic care with a comorbid physical disease. Ethical approval for this study protocol was obtained from the Ethics Committee of the University of Göttingen Medical Center (#1/10/11) on January 31, 2012.

Study setting and participants

In total, 160 patients aged 18 years or older who were treated on the multimodal inpatient psychosomatic unit of the Department of Psychosomatic Medicine and Psychotherapy located in the Heart Center of the University Medical Center in Göttingen, Germany, between February 2010 and January 2012 were included. The inclusion criteria were as follows: (a) completed inpatient treatment for at least three weeks; (b) age 18 years or more; and (c) sufficient cognitive skills and ability to speak, read and understand German; The exclusion criteria were severe cognitive impairment, communicative difficulties (e.g., aphasia), or inability to provide informed consent.

Data at baseline and discharge were obtained during routine diagnostics and quality assurance and were extracted from participant records retrospectively. They included detailed medical history data obtained during hospitalization, as well as a set of psychological and functional questionnaires completed upon admission and before discharge. For the prospective follow-up assessment at 12- or 24-month post-discharge (depending on the year of hospitalization), informed consent was obtained from all participants after providing detailed study information. Follow-up data were prospectively collected by mailing the study participants a set of the same questionnaires that had been used during hospitalization and a number of tailored items related to events and treatments that occurred after initial hospital discharge.

Inpatient psychosomatic treatment

The inpatient psychosomatic unit is run by the Department of Psychosomatic Medicine and Psychotherapy in collaboration with the Department of Cardiology of the University Medical Center Göttingen, Germany, and focuses on treating patients with mental disorders and comorbid cardiovascular or other physical diseases. The unit is integrated into the Göttingen Heart Center and has a treatment capacity for 18 inpatients.

Admission is electively planned after a detailed outpatient interview. The minimum age for admission is 18 years. A maximum age is not defined, but the patients should be physically and psychologically able to participate as much as possible in the treatment setting. Furthermore, common admission criteria for an inpatient stay are the simultaneous occurrence of a mental disorder (e.g., depression, anxiety or somatoform disorder), and a physical disease (e.g., cardiac disease) or severe functional somatic symptoms attributed to a putative underlying medical illness.

The treatment concept of the inpatient unit is based on a bio-psycho-social model (22). The four- to six-week psychosomatic inpatient care is a multimodal treatment combining individual and group psychotherapy (based on psychodynamic psychotherapy and CBT), psychoeducation, art therapy, relaxation training (e.g., progressive muscle relaxation), and body-oriented and physical therapy, including exercise training. Interpersonal and psychosocial problems can be addressed through inclusion of partners or family, as well as through the use of psychosocial skills training. Furthermore, patients receive daily medical visits (e.g., with medical workup or specialized consultations if indicated). If necessary, drug treatment for physical and mental conditions is initiated or adjusted. Each patient receives weekly therapy plans for the duration of their inpatient stay, which determines the daily structure and therapeutic program. In particular, cardiovascular diseases such as coronary heart disease, malignant cardiac arrhythmias, heart failure, and arterial hypertension are treated on the unit, if these are essentially caused by psychological and behavioral factors (including non-adherence) or if they are accompanied by depression, anxiety disorders or post-traumatic stress disorder. In addition, physical diseases (e.g., diabetes, inflammatory bowel disease, migraine) with pronounced psychological components are treated. Finally, specific behavioral treatment components are available for the management of a spectrum of eating disorders (from anorexia nervosa with body mass index <15 kg/m^2 to severe obesity).

Study assessments

Participants' health records were reviewed to obtain sociodemographic and clinical data, including primary admission diagnoses and healthcare utilization. Psychological and functional outcomes were assessed using valid and reliable questionnaires (31–34).

The Giessen Subjective Complaints List (GBB-24) is a 24-item questionnaire for the assessment of physical complaints. For each item there are possible answers from 0 = "not at all" up to 4 = "very much" (31). The individual complaints can be aggregated on four subscales: exhaustion, gastrointestinal complaints, musculoskeletal complaints, cardiovascular complaints. Total symptom burden ranges from 0 to 96.

The Brief Symptom Inventory (BSI) (32) assesses psychopathological and psychological symptoms. The questionnaire consists of 53 items, which are answered using a 5-point Likert scale from 0 = "not at all" to 4 = "very much". It covers nine symptom dimensions: somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. A global index of distress called Global Severity Index (GSI) can be created and ranges from 0 to 4.

The EQ-5D (European Quality of Life Questionnaire) is a short instrument, consisting of 5 items, which is used to record health-related quality of life (HRQoL). The 5 items represent the dimensions of mobility, self-care, usual activities, pain/physical complaints and fear/depression (33, 35). Individual item values were transformed into an index score on a scale from 0 to 100, with higher scores indicating better HRQoL.

Self-efficacy was assessed using a short form of the General Self-Efficacy Scale (GSE-6) (34). In the 6-item version, participants are asked to rate the degree to which items applies to them on a scale ranging from 1 "does not apply at all" and the value 4 means "applies completely". The mean value is created by dividing the sum of all 6 items by the number of items.

Statistical analysis

Clinical and psychological data are shown as means (M) and standard deviations (SD) of continuous variables or frequencies and percentages of categorical variables. To analyze relationships between physical and psychological variables at all three timepoints and the comorbid physical disorders, Mann-Whitney U tests were performed. To assess differences between the individuals who did or did not complete all three measurements, we performed one-way analyses of variance (ANOVAs) for continuous variables and Fisher's exact tests for categorical variables.

To examine changes in treatment outcomes of integrated inpatient psychosomatic care, the mean values of the psychological outcomes at admission, discharge, and 12- or 24-month follow-up were compared using ANOVA with repeated measurements. As there were no differences between the subgroups followed for 12 vs. 24 months, both groups were combined for further analyses. The effect sizes were determined either as Cohen's d ($d \geq 0.2$ as small effect; $d \geq 0.5$ medium effect; $d \geq 0.8$ as large effect) or in the form of the partial eta square (η^2): Concretely, $\eta^2 \geq 0.01$ assumes a small effect, $\eta^2 \geq 0.06$ a medium effect, and $\eta^2 \geq 0.14$ a large effect (36). Medium effect sizes are considered to be clinically relevant. To evaluate the analysis of variance, sphericity was first tested using the Mauchly test. If this could not be accepted, the Greenhouse-Geisser correction was used for the interpretation (37). The intra-subject effects of the two-stage time factor were tested.

To test influencing factors on the change in psychological and functional outcomes over the course of time between admission and discharge, multi-factorial ANOVA with repeated measurements were used. The time of assessment (discharge vs. admission) was defined as the intra-subject factor, and the influencing variable to be analyzed was the between-subject factor. Significant between-subject effects and within-subject contrasts were examined for their effect size using the η^2. We focused on the evaluation of the interaction term (time*between-subject factor) in order to test the influence of

the between-subject factor on the temporal development of the individual psychometric findings.

Finally, we used Spearman's correlation analysis to examine bivariate relationships between HRQoL at follow-up and HRQoL at admission and discharge, as well as intake of antidepressants at discharge, referral for outpatient psychotherapy post-discharge, and self-efficacy at admission and discharge. Afterward, a multi-factorial ANOVA with repeated measurements was performed to analyze factors associated with change in HRQoL over the course of time between follow-up and admission. The time of assessment (follow-up vs. admission) was defined as the intra-subject factor, and the influencing variable to be analyzed was the between-subject factor. Significant between-subject effects and within-subject contrasts were examined for their effect size using η^2. To compare mean scores in psychological and functional variables between patients with and without intake of antidepressants, a paired t-test was performed.

All analyses were performed using SPSS software, version 27 (SPSS Inc., Chicago, IL, United States). A p value of <0.05 was considered statistically significant.

Results

Recruitment and baseline characteristics

We identified 245 eligible patients who underwent inpatient psychosomatic treatment between February 2010 and January 2012. Of these, 160 patients (mean age in years = 53.1, SD = 12.6; 53.8% female) completed both the admission and discharge questionnaires and were enrolled in the study. Of these, 92 patients (mean age = 55.6, SD = 12.4; 52.2% female) completed the 12- or 24-month follow-up questionnaires (Figure 1). The clinical and psychological baseline characteristics of the total sample are shown in Table 1. In the total sample, the most prevalent mental disorders were affective disorders (38.1%), followed by somatoform disorders (30%), and anxiety and obsessive-compulsive disorders (19.4%). The most common physical comorbidities were hypertension (50%), ischemic coronary heart disease (20.6%), diabetes (10.6%), and atrial fibrillation/flutter (8.1%). In Whitney–Mann U tests, there were no associations between the comorbid physical diseases and the physical or psychological outcomes at any of the three timepoints.

Patients lost from discharge to follow-up ($N = 68$) were comparable to completers of all measurements in all variables at follow-up ($N = 92$), aside from having lower age (completers: mean age = 55.6, SD = 12.4; dropout: mean age = 49.7, SD = 12.1; $p = 0.003$), and higher psychological distress (BSI-GSI; completers: 1.0 ± 0.6; dropout: 1.2 ± 0.6; $p = 0.004$).

Changes in psychological and functional treatment outcomes

Regarding psychological and functional outcomes (Table 2), there were significant, large-sized improvements in psychological symptoms (BSI-GSI: paired t-test: M = −0.45; SD = 0.54; effect size: $d = -0.83$; 95% CI −0.53, −0.36; $p < 0.001$) and physical complaints (GBB total symptom

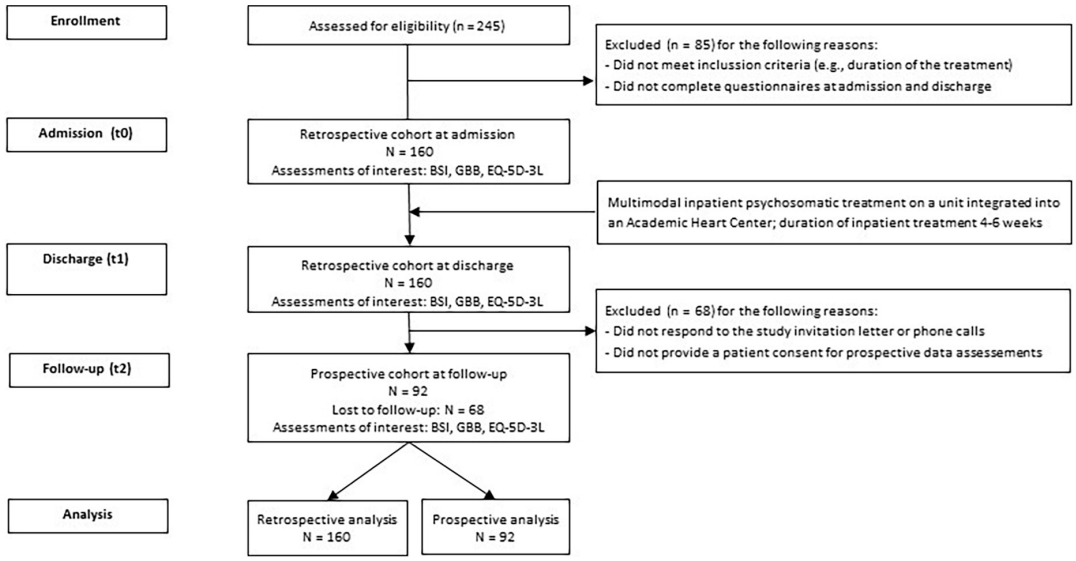

FIGURE 1
Flow chart of the study.

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TABLE 1 Characteristics of clinical and psychological variables.

Variables (range)	Total sample (N = 160) Mean ± SD or %
Women	53.8%
Age (years) (range 22–83)	53.1 ± 12.6
Main diagnosis	
F30-39 Affective disorders	38.1%
F40-42 Anxiety and OCD	19.4%
F43 PTSD and ASD	3.1%
F45 Somatoform disorders	30.0%
F50 Eating disorders	3.1%
F54 Psychological and behavioral factors associated with disorders or diseases	3.1%
Others	3.1%
Comorbid physical diseases	
Hypertension	50.0%
Coronary heart disease	20.6%
Hyperlipidemia	20.0%
Diabetes mellitus	10.6%
Atrial fibrillation/flutter	8.1%
Other cardiac diseases	18.3%
History of stroke	3.1%
Hypothyroidism	6.25%
Psoriasis	3.8%
Migraine	3.1%
Number of comorbid mental disorders (range 0–4)	2.0 ± 1.1
Number of comorbid physical diagnoses (range 0–10)	2.1 ± 2.1
BSI-GSI (range 0–4*)	1.1 ± 0.6
GBB total symptom burden (range 0–96*)	37.3 ± 15.0
GSE-6 (range 1–4*)	1.6 ± 0.7
EQ-5D index (range 0–100*)	53.9 ± 16.4
Duration of inpatient treatment (days; range 23–59 days)	40.9 ± 5.6

ASD, acute stress disorder; BSI, Brief Symptom Inventory; EQ, European Quality of Life Questionnaire; GBB, Giessen Subjective Complaints List; GSI, Global Severity Index; GSE, General Self-Efficacy Scale; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; SD, standard deviation. *Range of the assessment.

burden: M = −11.74; SD = 12.44; $d = -0.94$, 95% CI −13.68, −9.80; $p < 0.001$), and significant medium-sized improvements in HRQoL (EQ-5D: M = 10.77, SD = 16.70; $d = 0.65$, 95% CI 8.10, 13.45, $p < 0.001$), from admission to discharge in patients undergoing integrated inpatient psychosomatic treatment. The adjusted general linear models (**Supplementary Files 1, 2**) found no significant moderating effects of age, sex, and comorbid cardiovascular diagnosis on changes in physical and psychological symptoms from admission to discharge. Changes in HRQoL at discharge compared to admission were not significant after full adjustment for sex, age, and cardiac diagnosis, and the included variables did not show a significant moderating effect on HRQoL.

At follow-up (**Table 3** and **Figure 2**), patients still showed significant, small- to medium-sized improvements in psychological symptoms (BSI-GSI: M difference [FU - admission] = −0.283, 95% CI −0.40, −0.16; $d = -0.54$; $p < 0.001$), physical symptoms (GBB total symptom burden: M difference = −5.705, 95% CI −8.97, −2.44; $d = -0.39$; $p < 0.001$), and HRQoL (EQ-5D: M difference = 8.441, 95% CI 4.61,12.28; $d = 0.52$; $p < 0.001$) compared to admission. Between discharge and follow-up there was only a small and non-significant increase in psychological symptoms and only minimal decrease in HRQoL. Physical symptoms increased again at follow-up compared to discharge (M difference [FU - discharge] = 6.031, 95% CI 2.584, 9.477; $d = 0.40$; $p < 0.001$) but remained significantly lower than on admission. Changes in physical and psychological symptoms as well as HRQoL, were unrelated to the timing of follow-up assessment at 12 vs. 24 months.

In univariate correlation analysis, there was a significant association between EQ-5D-3L at follow-up and EQ-5D-3L at admission (Spearman's rho = 0.541, $p < 0.001$) and discharge ($r = 0.648$, $p < 0.001$), and a significant negative association between EQ-5D-3L at follow-up and intake of antidepressant at discharge ($r = -0.067$, $p = 0.021$). There were no significant associations between HRQoL at 12- or 24-month follow-up with referral of outpatient psychotherapy after discharge ($r = -0.067$, $p = 0.529$), self-efficacy at admission ($r = 0.156$, $p = 0.144$), or self-efficacy at discharge ($r = 0.112$, $p = 0.299$). In multi-factorial ANOVA with repeated measurements, improvement in HRQoL during hospitalization (partial $\eta^2 = 0.386$, $p < 0.001$) was associated with better HRQoL at follow-up. Furthermore, intake of antidepressant at discharge was associated with impaired HRQoL at follow-up (partial $\eta^2 = 0.053$, $p = 0.03$); there was no significant effect of follow-up assessment performed at 12 vs. 24 months on HRQoL at follow-up (all $p > 0.05$, **Table 4**). Finally, we performed a paired t-test to compare patients with and without intake of antidepressants. Patients with intake of antidepressant showed higher psychological distress ($p < 0.01$) as well as symptom burden ($p = 0.02$) at admission but not at discharge ($p = 0.06$; $p = 0.23$, respectively) compared with patients without a treatment with antidepressant. The HRQoL was only insignificantly worse in patients receiving antidepressants at admission and discharge while a significant difference emerged during follow-up (**Supplementary File 2**).

Discussion

This single-center cohort study demonstrates significant medium- to large-sized improvements in psychological and physical outcomes (BSI, GBB), and HRQoL (EQ-5D) in patients with mental disorders and physical comorbidity treated on an

TABLE 2 Changes in psychological scale scores at discharge compared to admission (paired *t*-tests, $N = 160$).

Outcome variables	Admission	Discharge	Mean difference (discharge-admission) ($N = 160$)						
	M (SD)	*M* (SD)	*M*	SD	95 CI%	T	df	*P*	*d**
BSI-GSI	1.08 (0.60)	0.63 (0.48)	−0.45	0.54	−0.53, −0.36	10.43	159	<0.001	−0.83
GBB total symptom burden	37.30 (0.48)	25.56 (15.24)	−11.74	12.44	−13.68, −9.80	11.94	159	<0.001	−0.94
EQ-5D-3L score	54.07 (16.37)	64.84 (16.97)	10.77	16.70	8.10, 13.45	−7.96	151	<0.001	0.65

BSI, Brief Symptom Inventory; df, degree of freedom; EQ, European Quality of Life Questionnaire; GBB, Giessen Subjective Complaints List; GSI, Global Severity Index; M, mean; SD, standard deviation; *P*, significance level. *P* value of <0.05 was considered statistically significant; *d = Cohen's d ($d \geq 0.2$ as small effect; $d \geq 0.5$ medium effect; $d \geq 0.8$ as large effect).

TABLE 3 Changes of psychological outcomes at follow-up compared to admission and discharge ($N = 92$).

Outcomes variables	Admission	Discharge	Follow-up	Mean difference (follow-up - admission)					Mean difference (follow-up - discharge)				
	M (SE)	*M* (SE)	*M* (SE)	*M* dif.	SE	95% CI	*P*	*d**	*M* dif.	SE	95% CI	*P*	*d**
BSI-GSI	0.97 (0.06)	0.59 (0.05)	0.69 (0.05)	−0.28	0.05	−0.40, −0.16	<0.001	−0.54	0.10	0.05	−0.01, 0.01	0.11	0.20
GBB-24 total symptom burden	36.66 (1.59)	24.92 (1.64)	30.95 (1.54)	−5.71	1.34	−8.97, −2.44	<0.001	−0.39	6.03	1.41	2.58, 9.48	<0.001	0.40
EQ-5D-3L score	56.24 (1.88)	66.12 (17)	64.68 (1.81)	8.44	1.57	4.61, 12.28	<0.001	0.52	−1.44	1.38	−4.82, 1.93	0.90	−0.08

BSI, Brief Symptom Inventory; EQ, European Quality of Life Questionnaire; GBB, Giessen Subjective Complaints List; GSI, Global Severity Index; *M*, mean; M dif., mean difference; SE, standard error; *P*, significance level. *P* value of <0.05 was considered statistically significant; *d = Cohen's d ($d \geq 0.2$ as small effect; $d \geq 0.5$ medium effect; $d \geq 0.8$ as large effect).

integrated inpatient psychosomatic unit in an academic Heart Center. These improvements were independent of age and sex and for most variables also of cardiovascular comorbidity. Small- to medium-sized improvements in all outcomes were still found at 12- or 24-month follow-up compared to admission. Better improvement of HRQoL during hospitalization was associated with substantially higher HRQoL at follow-up. Continued psychotherapy after discharge or self-efficacy at admission or discharge did not show significant associations with HRQoL at 12- or 24-month follow-up, while antidepressant medication at discharge was independently associated with poorer HRQoL at follow-up.

Inpatient psychosomatic treatment provides a protective environment with a variety of therapeutic interventions (e.g., individual and group psychotherapy, art therapy, body-oriented and physical therapy, pharmacotherapy), and can focus specifically on patients with a comorbid physical disease (e.g., with a cardiac diagnosis) (22). A meta-analysis of RCTs evaluating psychotherapeutic hospital treatments in Germany (25) demonstrated a medium within-group effect size for symptom change at discharge with a small reduction to follow-up, but most patients in this analysis were younger and did not have a significant physical comorbidity. The current analysis extends these findings by demonstrating significant medium- to large-sized improvements in psychological and functional outcomes specifically in patients with a mental disorder and a comorbid physical disease undergoing an integrated inpatient psychosomatic treatment in an academic Heart Center. Furthermore, these treatment effects largely persisted at follow-up, as small- to medium-sized improvements in all outcomes were still found at 12- or 24-month follow-up compared to admission. These findings are of high clinical relevance, as mental disorders are associated with the highest disability burden of all larger disease categories (8), and as the health goals have been shifted to decreasing disability burden rather than only to increasing life expectancy (38).

However, the present study did not compare the changes in mental health outcomes between integrated inpatient psychosomatic treatment with multimodal components (e.g., individual and group psychotherapy, art therapy, relaxation training, body-oriented and physical therapy, and specialized medical care) to an active comparator (e.g., outpatient or inpatient psychotherapy or psychiatric treatment) in patients with physical comorbidities. Future studies are necessary to provide more information on the following aspects in patients with mental health disorder and a comorbid physical disease: (a) effective duration of inpatient treatment (e.g., the presented integrated unit provides treatment for 4–6 weeks); (b) effectiveness of the treatment domains; and (c) cost-effectiveness of integrated multimodal inpatient units with specialized care of physical comorbidities (e.g., psycho-cardiological or psycho-diabetological units) compared to general psychosomatic/psychiatric units. Given the trend of sub-specialization in medicine, it might be of clinical importance that psychosomatic (and psychiatric) inpatient units focus on prevalent physical comorbidities in patients with mental health disorders with further expertise in areas such as psycho-cardiology, psycho-diabetology, or psycho-oncology. However,

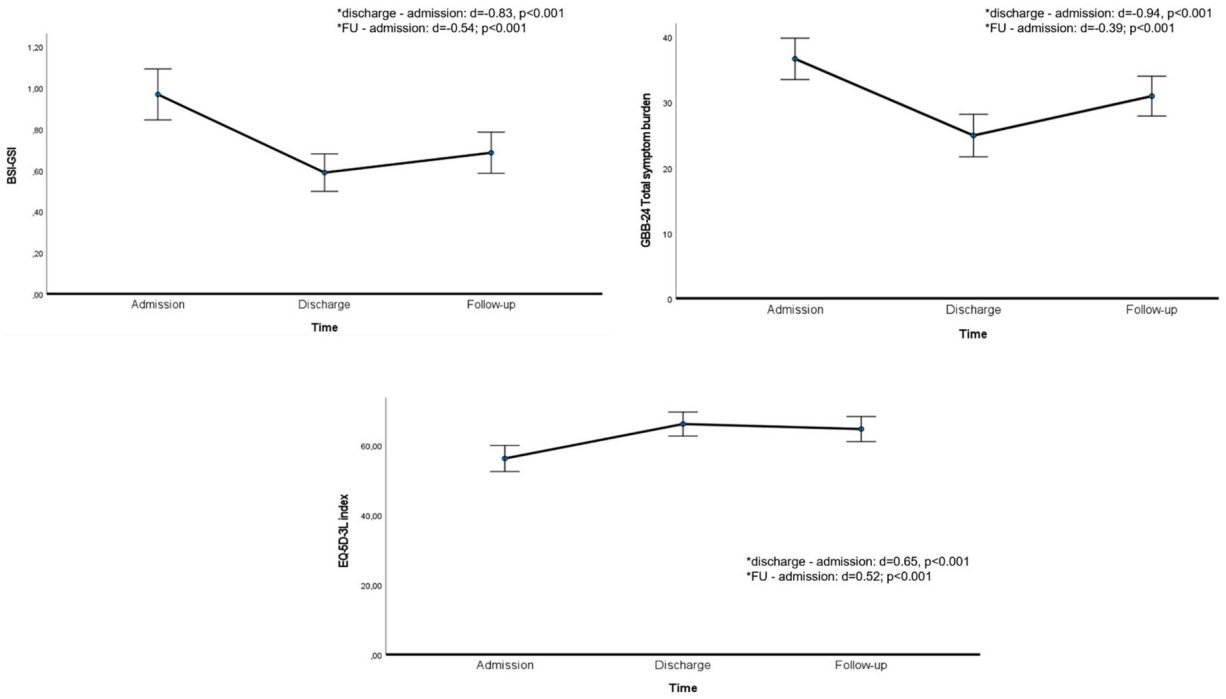

FIGURE 2
Time course of BSI-GSI, GBB-24, and EQ-5D variables. BSI, Brief Symptom Inventory; CI, confidence interval; EQ, European Quality of Life Questionnaire; FU, follow-up; GBB, Giessen Subjective Complaints List; GSI, Global Severity Index. Asterisks (*) indicate significant differences between adjacent time points. Error bars indicate 95% CIs.

TABLE 4 Multi-factorial ANOVA with repeated measures showing factors associated with change in HRQoL between follow-up and admission.

	Type III sum of squares	df	Mean square	*F*	*P*	Partial η^{2}*
EQ-5D-3L (follow-up–admission)						
Time	224.62	1	224.62	3.46	0.06	0.041
Follow-up assessment at 12- or 24-month	49.71	1	49.71	0.12	0.73	0.001
Change in EQ-5D-3L during hospitalization	2867.66	1	2867.66	6.79	0.01	0.077
Intake of antidepressant at discharge	2562.2	1	2562.2	6.07	0.02	0.07
Time*follow-up assessment at 12- or 24-month	3.6	1	3.6	0.06	0.81	0.001
Time*change in EQ-5D-3L during hospitalization	3304.01	1	3304.01	50.85	< 0.001	0.386
Time*intake of antidepressant at discharge	296.17	1	296.17	4.56	0.03	0.053
Error(time)	5263.33	81	64.98	–	–	–

ANOVA, analysis of variance; df, degree of freedom; EQ, European Quality of Life Questionnaire; *P*, significance level. *P* value of <0.05 was considered statistically significant; *η^2 = Eta ($\eta^2 \geq 0.01$ assumes a small effect, $\eta^2 \geq 0.06$ a medium effect, and $\eta^2 \geq 0.14$ a large effect).

better scientific evidence is necessary to implement more sub-specialized inpatients units not only in the German health system but also worldwide.

Furthermore, the finding that higher age and a comorbid cardiovascular diagnosis did not impair the improvements observed during and after inpatient treatment highlights the impact of an integrated inpatient psychosomatic care on psychological and functional outcomes in patients with cardiovascular comorbidity (e.g., coronary heart disease, atrial fibrillation/flutter or hypertension) who are typically older than those studies in the previous meta-analysis (25). This is of clinical relevance as mental disorders have been linked to adverse cardiovascular outcomes (e.g., major adverse cardiac events or mortality in coronary heart disease patients) (11, 12), and patients with cardiovascular diseases require complex emotional-cognitive adaptations (11). For example, a study ($N = 93$) comparing an integrated concept of psycho-cardiac rehabilitation vs. monodisciplinary cardiac or psychosomatic rehabilitation showed that cardiac patients benefit more from an integrated psycho-cardiac treatment concept (39). In line with

these results and ours, integrative patient-centered care concepts (e.g., psycho-cardiology) are increasingly recommended for treatment of patient with mental disorders and concomitant physical disease (24).

Finally, in the present study, intake of antidepressants at discharge was independently associated with poorer HRQoL at follow-up. There might be several explanations for this finding. First, patients on antidepressants showed higher symptom burden and psychological stress at admission compared with patients without intake of antidepressants. Therefore, higher initial symptom severity of major depressive disorder (MDD) may have been a reason for antidepressant prescription, which would suggest that it is the initial severity of depression rather that the medication itself that impaired follow-up HRQoL scores in patients taking antidepressants. However, our model controlled for baseline HRQoL, making such inverse causation less likely. Previous studies in patients with MDD undergoing inpatient treatment or day hospital treatment (40, 41) showed that intake of antidepressants was significantly related to more severe depression at admission and discharge that can lead to complex treatment situation (e.g., high number of antidepressants, switch in medication) (41). Second, antidepressants might have greater effects on depressive symptoms than on HRQoL. For example, a study investigating relationship between depressive symptoms and HRQoL in inpatients with MDD before and after 6-week treatment with fluoxetine demonstrated that antidepressant treatment was associated with a greater extent of change in depressive symptoms than in HRQoL (42). In our study, however, also the psychological symptoms remained significantly higher in the medicated vs. unmedicated group. Finally, the effect of antidepressants on HRQoL might not be as sustained at 12- or 24-month follow-up. Consistent to this explanation, a recent study in patients with MDD comparing a cohort with and without intake of antidepressants (43) showed that the real-world effect of antidepressant intake does not continue to improve patients' HRQoL over time, and the effect of antidepressants on improvements of HRQoL was limited to the initial 2–3 months of treatment. However, the HRQoL scores did not sufficiently improve in long-term compared to the general population (44, 45). Longer-term follow-up of randomized, controlled trials of antidepressant treatment efficacy would help to clarify the long-term effects of these medications on both depressive symptoms and HRQoL.

In summary, this cohort study provides further scientific support for significant improvement in patient-reported outcomes after integrated psychosomatic inpatient care and for factors influencing long-term improvements in HRQoL in patients with mental disorder and a concomitant physical disease (e.g., cardiac disease). The strengths of our study are the longitudinal approach with various psychological and functional outcomes at three time points. However, our study has several limitations. Firstly, this is a single-center cohort study without randomization or an active comparator. Secondly, we excluded 68 patients, as they did not complete all the study assessments. Finally, the German system with established departments for psychosomatic medicine and psychotherapy with inpatient treatments of 4–6 weeks duration and more represents a unique treatment system worldwide which impedes generalizability of our results to other health care systems.

Conclusion

Multimodal, integrated inpatient psychosomatic treatment was associated with significant medium- to large-sized improvements in physical and psychological symptoms, and HRQoL in inpatients with mental disorders and a comorbid physical disease. These results indicate that integrative patient-centered care concepts (e.g., psycho-cardiology) are useful for treatment of patient with somatic-mental comorbidity. Finally, improvement in HRQoL from admission to discharge seems to remain mostly stable over 1–2 years. Large, randomized-controlled, multi-center clinical trials investigating the effectiveness of integrated, specialized (e.g., psycho-cardiology, psycho-diabetology) psychosomatic inpatient treatments compared to an active comparator are needed to confirm their impact on psychological, functional, and medical outcomes. Furthermore, cost-effectiveness analyses should be provided. However, for the multimorbid patients treated on the unit studied here, inpatient treatment is often the last resort after unsuccessful outpatient therapies. Both, ethical considerations and clear patient preferences for an established and probably effective treatment make randomized trials hard to conduct in this setting, as long as no equally attractive treatment of proven efficacy can be offered as a comparator.

Data availability statement

The dataset generated and/or analyzed for the present article is not available for sharing as the informed consent form did not include information about data sharing policy. Requests to access the datasets should be directed to MS, msadlonova@mgh.harvard.edu.

Ethics statement

Ethical approval for this study protocol was obtained from the Ethics Committee of the University of Göttingen Medical Center (#1/10/11) on January 31, 2012. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MS and CH-L: conceptualization, methodology, statistical analyzes, and writing—original draft. JKL and CK: conceptualization, investigation, project administration, and data curation. JKL, CK, CC, DB, and CH-L: writing—review and editing. CC and CH-L: supervision. MS: data curation and writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

CC has received salary support from BioXcel Pharmaceuticals and honoraria for talks to Sunovion Pharmaceuticals on topics unrelated to this research. CC has received stipends from Elsevier for editorial work for General Hospital Psychiatry. CH-L reports that he is receiving royalties from Hogrefe Huber Publishers for the German version of the Hospital Anxiety and Depression Scale and research support from the German Research Foundation, the German Ministry of Education and Research, and the European Commission. During the last three years he has received a lecture honorarium from Pfizer.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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EDITED BY
Wenhao Jiang,
Southeast University, China

REVIEWED BY
Yegang Hu,
Shanghai Jiao Tong University, China
Ruipeng Wu,
Sun Yat-sen University, China
Yuqun Zhang,
Nanjing University of Chinese Medicine, China

*CORRESPONDENCE
Cuizhen Zhu
zhucuizhen88@126.com
Xulai Zhang
Xulaizhang@ahmhcentre.com

†These authors have contributed equally to this work and share first authorship

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Childhood maltreatment increases the suicidal risk in Chinese schizophrenia patients

Peng Cheng[1,2,3†], Peijun Ju[4,5†], Qingrong Xia[1,2,3†], Yuanyuan Chen[1], Jingwei Li[1], Jianliang Gao[1,2,3], Loufeng Zhang[1,2,3], Fanfan Yan[1,2,3], Xialong Cheng[1,2,3], Wenzhi Pei[1,2,3], Long Chen[1,2,3], Cuizhen Zhu[1,2,3*] and Xulai Zhang[1,2,3*]

[1]Department of Science and Education, Affiliated Psychological Hospital of Anhui Medical University, Hefei, China, [2]Anhui Clinical Center for Mental and Psychological Diseases, Hefei Fourth People's Hospital, Hefei, China, [3]Anhui Clinical Research Center for Mental Disorders, Anhui Mental Health Center, Hefei, China, [4]Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [5]Shanghai Key Laboratory of Psychotic Disorders, Shanghai, China

Objectives: Childhood trauma might be a modifiable risk factor among adults with serious mental illness. However, the correlation of child trauma and suicide is unclear, which were cited most frequently as the biggest challenge to schizophrenia (SCZ) patients in China. We aim to study relationships between child trauma and suicide in SCZ patients of different disease stages.

Methods: Ninety-one participants were included and divided into two groups, namely, first-episode group ($n = 46$), relapsed group ($n = 45$). The Positive and Negative Syndrome Scale was used to evaluate the severity of psychotic symptoms. The Beck's Suicide Intent Scale and The Nurses' Global Assessment of Suicide Risk were conducted by patient self-report to assess suicide symptom. The childhood trauma questionnaire was used to estimate severity of traumatic stress experienced during childhood.

Results: Childhood trauma and different dimensions of suicide were significantly higher in the relapsed group than first-episode group ($P < 0.01$, respectively). BMI has a significant positive relationship with recent psychosocial stress ($\beta = 0.473$, $t = 3.521$, $P < 0.001$) in first-episode group. As in relapsed group, BMI has a positive effect between severe mental illness and suicide ideation ($\beta = 0.672$, $t = 5.949$, $P < 0.001$; $\beta = 0.909$, $t = 2.463$, $P < 0.001$), Furthermore, emotional neglect presented positively related to the suicide risk and proneness to suicidal behavior ($\beta = 0.618$, $t = 5.518$, $P < 0.001$; $\beta = 0.809$, $t = 5.356$, $P < 0.001$).

Conclusion: Relapsed group of patients had significantly more severe childhood trauma, recent psychosocial stress, suicidal risk and proneness to suicidal behavior. BMI and emotional neglect are unique predictors for different dimensions of suicide.

KEYWORDS

suicide risk, suicide ideation, suicide behavior, schizophrenia, child trauma

Introduction

Schizophrenia (SCZ) is a complex dysfunction of genetic, heterogeneous behavioral and cognitive syndrome that is prevalent in ∼1% of the general population around the world, whose origins etiology appear to lie in genetic and/or environmental disruption of brain development (1). Life expectancy for people with SCZ is probably 10–25 years shorter than that for the general people (2, 3). It has long been recognized that individuals with traumatic experiences among persons are at increased risk of subsequently developing poor outcomes, including substance abuse (4), cognitive deficits (5), sexual dysfunction (6), personality disorders (7) and dissociative disorders (8). In recent years, abundant evidence has identified that traumatic events play a causal role in serious mental illnesses, including depression (8), anxiety disorders (9) and eating disorders (10), as well as SCZ (11), these findings has accumulated revealing that trauma/stressful events in childhood/adolescence have potential etiological relationship between the psychotic disorders (12), and these child traumatic events as a socio-environmental risk factor promote the psychotic symptoms evolving (13). A recent review and meta-analysis recommended that childhood traumatic events had relationship with offending behavior in SCZ. A dose-response-relationship was assumed that the treatment outcomes to be poorer in SCZ when there was a history of childhood maltreatment. Therefore, more efforts should be devoted on this research aspect (14).

Over recent decades, studies have consistently documented markedly elevated worldwide mortality in mental illnesses, notably, suicide accounted for major reason of unnatural deaths (15) especially in persons with SCZ (16). Sukanta Saha explored that the risk of suicide was approximately 13 times higher for persons with SCZ compared with the general population (17). It has been proposed among SCZ patients that the lifelong risk of suicide is around 5% (18), the rate of population-attributable risk of suicide is 8.9% (19), the rate of suicide attempt is 25–50% (20), and the rate of suicidal ideation at least once is 43–79% (21). It has been estimated up to 50% of those suffering from SCZ might experience suicidal ideation, with or without suicidal attempt, at some time during the course of the illness, usually 4.9% commit suicide from first admission or near illness onset (18). As well as, studies have also observed that 38% had at least 1 episode of self-harm in a 2–12-year follow-up period (22, 23). Furthermor, recurrent relapses, impairments of societal and occupational functioning, severity of the disease and realistic understanding of the harmful influence of disorder are regarded as schizophrenia-specific suicide risk factors (23). The higher risk of suicide among SCZ patients reveals that it is necessary to evaluate the disease-related factors and sociocultural factors for the improved identification of risky individuals and development of preventive interventions. It is worth noting the fact that most patients with SCZ experience relapses, and only less than one quarter of patients achieved complete recovery in long-term follow-up study. Hence, the different stages of disease is related to heterogenous psychotic symptoms of patients, with potentially distinct risk to suicide, Therefore, it is crucial to understand the different pattern of disease and its possible predictors for suicidal risks in this vulnerable population (24).

The existing studies have tried to identified several factors predicting the risk of suicide in individuals with SCZ, which include younger age, male gender, lack of social support, unemployment, being unmarried, being well-educated, being intelligent (21), a family history of psychiatric disorder, having poor work functioning, higher number of hospitalizations (25), presence of a previous suicide attempt, poor adherence to treatment, history of suicidal behavior (20), having had recent (i.e., within past 3 months) life events (26), having access to lethal means, and seriousness of psychiatric pathology (21), comorbid affective disorder and the strong stigma of mental illness in rural areas (16). Furthermore, some studies have also reported that a combination of genetic markers and early traumatic life events might indeed be used to identify patients at risk for suicide attempt in SCZ. Nevertheless, unique patterns of the early stressful events seem difficult to say that these factors are useful in predicting and preventing suicide in the SCZ, moreover, the existing researches are predominantly conducted in the Western countries (e.g., the USA, UK and Sweden) and many trends may not be generalizable to non-Western countries, thus the predictors for the suicide of persons with SCZ in China are unknown.

There are few studies that investigates the relationship between childhood maltreatment and their potentially distinct effects on suicide of SCZ patients in China. We hypothesized that childhood trauma events such as abuse, physical neglect and emotional neglect play vital effect during the onset or relapse course of the illness in the patients suffering from SCZ. In light of this information, we aimed to evaluated the relationship between early stress life events and clinical features of SCZ, and explore the risk factors which contribute to increasing knowledge relating to suicidal suicide attitude and suicide attempts behavior in SCZ patients.

Materials and methods

Ethics statement

Medical Ethics Committee of the Anhui Mental Health Center (AMHC) approved this study, all participants provided written consent prior to study participation in accordance with the principles of the Declaration of Helsinki. The trial clinical registration number was ChiCTR2100045240.

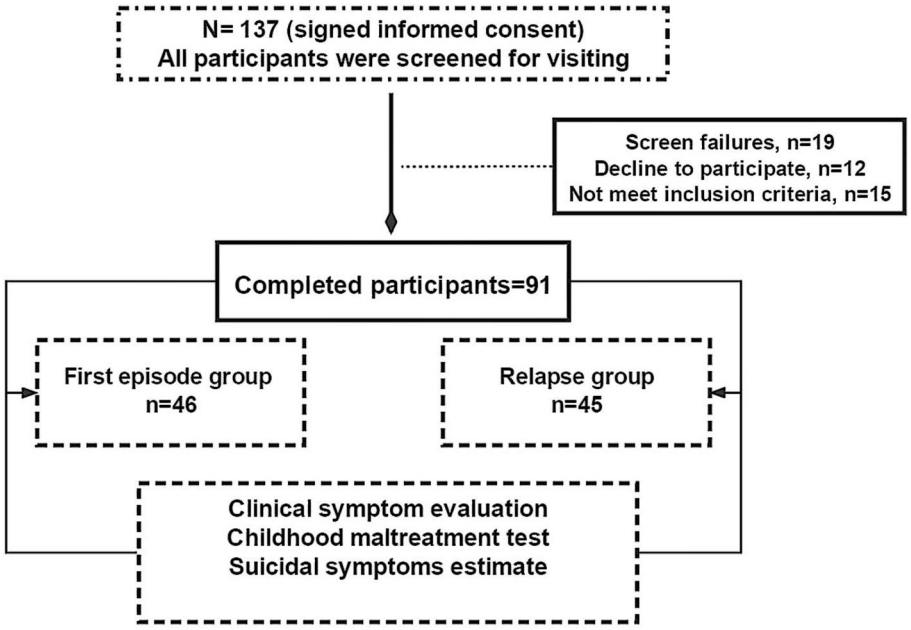

FIGURE 1
Study procedure.

Procedure

This pilot study explored the relationship about the childhood traumatic stress related suicidal symptoms in SCZ patients. A total of 137 participants were initially selected. Of these, 15 participants did not meet the inclusion criteria, 19 individuals could not complete the clinical estimate, and 12 individuals refused to sing informed consent. Hence, total of 45 subjects who did not meet the experimental criteria were excluded from present study. Ultimately, the remaining 91 participants were included in this study and divided them into two groups according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (27)–first episode group (SCZ patients of first episode, $n = 46$), relapsed group (relapsed SCZ patients, $n = 45$). All patients were hospitalized at the AMHC between February 2018 and August 2021 (Figure 1).

All participants were assessed by the two professional psychiatrists through the Mini-International Neuropsychiatric Interview (MINI) 6.0.0. According to the trial standards, patients of first episode group and relapsed group diagnosed with SCZ met the criteria of the DSM-5. The inclusion criteria for the patients in the first episode group were as follows: ① age = 18–60 years, ② fulfillment of the DSM-5 criteria for SCZ, ③ first-episode state SCZ. The inclusion criteria for the patients in the recurrent patient group were as follows: ①fulfillment of the first and second third criteria of first episode group. ② patients was treated with second generation anti-psychotic drugs, drug treatment matching between the two groups. The exclusion criteria were as follows: ① people with serious physical diseases and substance abuse, ② a history of craniocerebral trauma, organic cerebral diseases, or other mental disorders, ③ had received electroconvulsive therapy or transcranial magnetic stimulation within 6 months, ④ pregnant or lactating women. All subjects received two trained professional psychiatrists to assess basic sociodemographic data, clinical symptom.

Clinical assessments

Mini-international neuropsychiatric interview 6.0.0

The preliminary clinical diagnosis was verified by MINI 6.0.0. It is a concise diagnostic interview for psychiatric disorders exploited jointly by psychiatrists in the United States and Europe. All patients underwent the MINI 6.0.0 to confirm the clinical diagnosis SCZ (28).

The positive and negative syndrome scale

PANSS was used worldwide to estimate psychiatric symptoms for decades. Versions of the five-factor model have been used in diverse SCZ research areas including positive symptom, negative symptom, cognitive defect, hostility/excitement symptom and anxiety/depression symptom (26).

The beck's suicide intent scale

BSIS is one of the most commonly used clinician-rated measurements of suicidal symptoms in studies. It has 19 items and is divided into suicidal ideation and suicidal tendency. The higher scores are, the higher levels of suicidal ideation and suicidal tendency is (29).

The nurses' global assessment of suicide risk

NGASR is one of the most commonly used clinician-rated measurements of suicidal symptoms in studies as well (30). It has been proven to have good reliability and validity, with a Cronbach's alpha coefficient of 0.88 and an intra-class coefficient of 0.9 (30, 31). The higher scores are, the more severe the symptoms are.

The childhood trauma questionnaire

CTQ is a widely used instrument for measuring the severity of traumatic stress experienced during their childhood. It has been utilized for the assessment of emotional abuse, physical abuse, abuse, sexual abuse, emotional neglect, physical neglect, as shown in Table 2. A Mandarin version of a five-subscale model of the CTQ has been proven to have good reliability and validity (32).

Statistical analysis

The *t*-tests and chi-squared test were performed to compare the differences in either continuous or categorical parameters between the first episode patient group and relapsed patient group. We used spearman correlation coefficients with false discovery rate (FDR) judgment in each group to constructed the relationship between possible correlation factors and scales of PANSS, NGASR, BSIS and CTQ. Stepwise linear regression analysis was used to conducted the relationship and interaction among predicted risk factors, childhood trauma and different dimensions of suicide in the first-episode group and relapse group. All statistical tests were two-tailed tests, and statistical significance was set as $\alpha < 0.05$. All analyses were conducted using the SPSS version 22.0 (IBM Corp).

Results

Results of demographic background, psychotic symptom, suicidal symptom and childhood trauma between in the two groups

Overall, there was no significant difference in demographic background such as age, gender, BMI and years of education between two groups ($P \geq 0.05$). Moreover, we also found there was no significant difference in clinical symptoms between the first-episode group and relapse group, either in the total scores of the PANSS scale or in the subscale scores of positive symptoms, subscale scores of negative symptoms, subscale scores of hostility/excitement symptoms, subscale scores of anxiety/depression symptoms and subscale scores of disorganized thoughts ($P \geq 0.05$). Results was shown in Table 1. Furthermore, we investigated the occurrence of childhood trauma, suicide risk, suicide ideation and suicide behavior between the first-episode group and recurrence group, the results showed that the patients of recurrence group had more severe suicide risk than patients of first episode group ($p = 0.02$). Importantly, the results revealed the patients of recurrence group had more severe mental illness, more severe recent psychosocial stress and more likely proneness to suicidal behavior than the patients of first episode group ($P < 0.01$, respectively). Meanwhile, we also found that the level of childhood trauma in the relapse group was significantly serious than that in the first episode group. That is to say, they were more likely to face emotional abuse, emotional neglect and physical neglect ($P < 0.01$, respectively). Results was shown in Table 2.

The correlation between childhood trauma and suicide risk, suicide ideation and suicidal behavior

Tables 3, 4 presents the results of the spearman correlation analysis to compare the correlation about the child trauma and different dimensions of proneness to suicidal behavior in the first-episode group and relapse group. The results shown physical abuse and sexual abuse had positive related to recent psychosocial stress in the patients of first-episode group ($r = 0.312$, $P < 0.05$; $r = 0.334$, $P < 0.05$). Meanwhile, we found sexual abuse had the positive related to suicidal ideation ($r = 0.428$, $P < 0.001$), especially, the findings showed that emotional neglect had positive correlation to recent psychosocial stress, severe mental illness, suicide risk, suicidal ideation and proneness to suicidal behavior ($r = 0.451$, $P < 0.001$; $r = 0.657$, $P < 0.001$; $r = 0.681$, $P < 0.001$; $r = 0.848$, $P < 0.001$; $r = 0.566$, $P < 0.001$; respectively) in the patients of relapse group. Interestingly, we found index of BMI appeared the positive interrelated to the recent psychosocial stress, suicide risk, suicidal ideation and proneness to suicidal behavior ($r = 0.473$, $P < 0.001$; $r = 0.597$, $P < 0.001$; $r = 0.791$, $P < 0.001$; $r = 0.524$, $P < 0.001$; respectively) in the patients of relapse group. As well as, the results revealed the years of education had positive interrelated to mental illness ($r = 0.672$, $P < 0.001$) in the patients of relapse group. Moreover, results explored only suicide risk had positive relationship with the psychotic symptom in the patients with first-episode ($r = 0.331$, $P = 0.035$), while, both of suicide risk, suicidal ideation, suicide mood, severe mental illness, proneness to suicidal behavior and recent psychosocial stress have positive correlation ($r = 0.390$, $P = 0.0008$; $r = 0.434$, $P = 0.0003$; r

TABLE 1 Demographic information and psychotic symptom, suicidal symptom of participants.

Items and subscales	FEP($n = 46$)	RP($n = 45$)	t	P
Age	28.39 ± 9.10	31.00 ± 7.78	−1.47	0.15
BMI	22.99 ± 3.64	21.73 ± 3.50	1.68	0.10
Male (percentage%)	23(50.00%)	21(51.20%)	−1.15	0.25
Years of education	9.93 ± 4.46	11.24 ± 3.73	−1.52	0.13
PANSS				
Positive symptoms	22.59 ± 6.24	21.84 ± 5.86	0.59	0.56
Negative symptoms	17.89 ± 5.85	19.00 ± 6.05	−0.89	0.38
Hostility/excitement symptoms	9.54 ± 4.00	9.47 ± 3.53	0.97	0.92
Anxiety/depression symptoms	10.74 ± 3.42	11.67 ± 3.52	−1.28	0.21
Disorganized thoughts	7.78 ± 2.49	8.04 ± 2.02	−0.55	0.58
Total score	79.90 ± 18.60	80.00 ± 17.42	−0.29	0.77

FEP, first episode patient; RP, relapsed patient; BMI, body mass index; PANSS, positive and negative syndrome scale; P < 0.05: statistically significant.

TABLE 2 Comparisons in CTQ, suicidal symptoms and psychotic symptoms.

Scale	FEP($n = 46$)	RP($n = 45$)	t	p
BSIS				
Suicide risk	12.46 ± 4.10	24.07 ± 23.65	154.75	0.02
Suicide ideation	14.35 ± 14.11	12.62 ± 3.51	451.44	0.43
NGASR				
Suicide mood	1.98 ± 1.02	1.60 ± 1.39	12.50	0.142
Severe mental illness	0.74 ± 0.65	1.62 ± 1.03	10.72	<0.01
Proneness to suicidal behavior	0.80 ± 0.72	1.51 ± 1.44	24.32	<0.01
Recent psychosocial stress	0.33 ± 0.56	0.67 ± 0.48	0.22	<0.01
CTQ				
C1(emotional abuse)	7.57 ± 1.80	11.71 ± 3.58	12.98	<0.01
C2 (physical abuse)	9.17 ± 3.36	9.13 ± 4.43	1.32	0.96
C3 (sexual abuse)	6.65 ± 2.88	7.96 ± 3.77	4.42	0.68
C4(emotional neglect)	8.15 ± 2.35	10.98 ± 4.47	15.77	<0.01
C5(physical neglect)	7.78 ± 2.16	10.38 ± 3.39	9.58	<0.01

FEP, first episode patient; RP, relapsed patient; BSIS, Beck's suicidal ideation scale; NGASR, The Nurses' Global Assessment of Suicide Risk scale; CTQ, childhood trauma questionnaire. P < 0.05: statistically significant.

= 0.545, $P < 0.001$; $r = 0.540$, $P < 0.001$; $r = 0.358$, $P = 0.0016$; $r = 0.380$, $P = 0.010$) with psychotic symptom in the replace group, especially, the emotional neglect also presented the positive relation to the psychotic symptom in the replace group, these results may be seen in the Table 5.

Prediction risk factors of child trauma for recent psychosocial stress and suicide dimensions

Stepwise regression analysis of sociodemographic characteristics and child trauma factors were performed to predict recent psychosocial stress and different dimensions of suicide. In the first episode group of the final model from forward regression indicated that the index of BMI accounted for 22.4% of the variance recent psychosocial stress, A significant positive relationship was found between index of BMI and recent psychosocial stress ($\beta = 0.473$, $t = 3.521$, $P < 0.001$). As in the relapse group, the final model from forward regression indicated that the index of BMI accounted for 45.1% of the variance severe mental illness, meanwhile, emotional neglect of accounted for 45.1 and 41.4% of the variance about suicide risk and proneness to suicidal behavior, respectively. We found the variables of BMI and emotional neglect accounted for 75.5% of the variance in suicide ideation. A positive effect was explored between BMI and severe mental illness ($\beta = 0.672$, $t = 5.949$, $P < 0.001$). Furthermore, emotional neglect presented

TABLE 3 Correlation between demographic and childhood trauma risks with suicide factors in the relapse group.

Factors	Suicide risk		Suicidal ideation		Recent psychosocial stress		Severe mental illness		proneness to suicidal behavior		Suicide mood	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Gender	−0.133	0.385	−0.039	0.802	−0.127	0.405	0.161	0.618	0.013	0.935	0.012	0.935
Age	−0.156	0.271	0.171	0.891	0.184	0.218	0.618	0.837	0.144	0.253	0.191	0.209
BMI	0.597**	<0.001	0.791**	<0.001	0.473**	<0.001	0.057	<0.001	0.524**	<0.001	−0.034	0.826
YE	0.019	0.903	0.190	0.188	−0.043	0.719	0.672**	0.001	0.175	0.411	0.930	0.290
CTQ												
C1	0.217	0.290	0.029	0.435	−0.098	0.466	−0.067	0.561	−0.217	0.323	0.088	0.567
C2	0.032	0.462	0.183	0.069	0.043	0.990	0.136	0.189	0.064	0.260	0.338	0.239
C3	0.242	0.159	0.428**	<0.001	0.029	0.912	0.230	0.305	0.075	0.444	0.402	0.069
C4	0.618**	<0.001	0.848**	<0.001	0.451**	<0.001	0.657**	<0.001	0.566**	<0.001	0.931	0.055
C5	0.124	0.541	0.231	0.244	0.052	0.042	0.075	0.635	−0.120	0.435	0.204	0.189

Correlation between demographic and childhood trauma risks with suicide factors in the relapse group. RP, relapsed patient; CTQ, childhood trauma questionnaire, C1 (emotional abuse), C2 (physical abuse), C3 (sexual abuse), C4 (emotional neglect), C5 (physical neglect). The false discovery rate (FDR) method is used to adjust the p-value. *$p \leq 0.05$; **$p \leq 0.001$.

TABLE 4 Correlation between demographic and childhood trauma risks with suicide factors in the first episode group.

Factors	Suicide risk		Suicidal ideation		Recent psychosocial stress		Severe mental illness		Proneness to suicidal behavior		Suicide mood	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Gender	−0.020	0.894	−0.137	0.362	0.008	0.956	−0.183	0.223	−0.050	0.742	0.009	0.953
Age	0.226	0.131	0.193	0.198	0.031	0.841	0.230	0.124	−0.076	0.618	−0.052	0.731
BMI	0.002	0.990	0.116	0.443	−0.206	0.108	−0.108	0.474	0.042	0.779	−0.236	0.114
YE	0.195	0.195	0.060	0.691	−0.009	0.892	0.024	0.875	−0.005	0.972	0.029	0.847
CTQ												
C1	0.044	0.770	−0.040	0.791	0.188	0.707	0.009	0.951	−0.155	0.303	−0.099	0.511
C2	0.105	0.488	0.124	0.410	0.312*	0.007	0.188	0.211	0.065	0.666	0.017	0.908
C3	−0.020	0.893	−0.062	0.684	0.334*	0.008	0.114	0.451	0.193	0.199	0.033	0.826
C4	0.014	0.926	0.028	0.853	0.232	0.327	0.198	0.188	0.141	0.349	0.061	0.688
C5	0.081	0.592	0.038	0.805	0.262	0.136	0.192	0.201	0.157	0.297	0.190	0.205

RP, relapsed patient; CTQ, childhood trauma questionnaire, C1 (emotional abuse), C2(physical abuse), C3 (sexual abuse), C4(emotional neglect), C5 (physical neglect). The false discovery rate (FDR) method is used to adjust the p-value. *$P \leq 0.05$; **$P \leq 0.001$.

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TABLE 5 Correlation analysis between PANSS about suicide-related risks and childhood trauma.

Factors	PANSS total score			
	FEPs		RPs	
	r	*p*	*r*	*p*
Suicide risk	0.311*	0.035	−0.390**	0.008
Suicidal ideation	0.047	0.758	−0.434**	0.003
Suicide mood	−0.081	0.592	−0.545**	<0.001
Severe mental illness	−0.060	0.691	−0.540**	<0.001
Proneness to suicidal behavior	0.225	0.133	−0.358*	0.016
Recent psychosocial stress	0.054	0.721	−0.380*	0.010
CTQ				
C1	−0.028	0.856	−0.232	0.125
C2	−0.174	0.247	0.047	0.760
C3	−0.020	0.895	0.056	0.714
C4	0.052	0.733	−0.464**	0.001
C5	0.076	0.616	−0.243	0.108

Correlation analysis between PANSS about suicide-related risks and childhood trauma. FRP_S, first episode group; RP, relapsed patient; PANSS, positive and negative syndrome scale; CTQ, childhood trauma questionnaire, C1 (emotional abuse), C2 (physical abuse), C3 (sexual abuse), C4 (emotional neglect), C5 (physical neglect). The false discovery rate (FDR) method is used to adjust the p-value. *$p < 0.05$; **$p < 0.001$.

the positive related to the suicide risk and proneness to suicidal behavior ($\beta = 0.618$, $t = 5.518$, $P < 0.001$; $\beta = 0.809$, $t = 5.356$, $P < 0.001$), in addition, index of BMI and emotional neglect had positive correlation to the suicide ideation ($\beta = 0.909$, $t = 2.463$, $P = 0.018$), these results indicate that the index of BMI and emotional neglect in prone to be a predictive risk factor for the recent psychosocial stress and suicide risk, suicide ideation and suicide behavior. Results was shown in Table 6.

Discussion

The results of this study are summarized as follows: firstly, compared to the patients of first episode group, patients of relapse group had significantly more severe child trauma, recent psychosocial stress, suicidal risk and proneness to suicidal behavior. Secondly, physical abuse and sexual abuse had positive related to recent psychosocial stress in the patients of first-episode group. Meanwhile, in the patients of relapse group, sexual abuse had the positive related to suicidal ideation, especially, emotional neglect had positive correlation to recent psychosocial stress, severe mental illness, suicide risk, suicidal ideation and proneness to suicidal behavior. Moreover, index of BMI appeared the positive interrelated to the recent psychosocial stress, suicide risk, suicidal ideation and proneness to suicidal behavior. Thirdly, index of BMI was a unique predictor of severe mental illness and suicidal ideation. Fourthly, emotional neglect was a unique predictor of suicidal risk, suicidal ideation and proneness to suicidal behavior, whereas results shown no unique risk factor for the different dimensions of suicide in the patients of first episode group, suggesting that child emotional neglect are unique predictor for the relapsed SCZ patients.

In the present study, patients of relapsed group had higher current of child trauma and severe mental illness than those patients of first episode. According to the World health Organization (WHO), each year, about one million people die by suicide across the world. Scholars also found that all ages are at risk for suicide. Suicidal ideation and behavior are relatively common in healthy, It is worth noting that more than 90% of victims of suicide have a psychiatric disorder (23), in addition, a history of child trauma may lead to increased risk for psychiatric symptoms (29) and suicidal attempt in the SCZ (33). However, more recent research explored the heterogeneity in the relationship between child trauma and psychotic symptoms, a study of large population-based sample discovered intention to harm is the key factor linking child trauma and general psychopathology symptoms of hallucinations and delusions, rather than specific psychotic symptoms in isolation, these finding are consistent with present study, furthermore, no evidence supported that the specific type of child trauma had associations between with particular psychotic symptoms (30). Meanwhile, our finding observed that the patients of relapsed group had higher current of recent psychosocial stress, suicide risk, and proneness to suicidal behavior than those patients of first episode. Evidence of risk factors related to symptomatology shown that in an early part of the course of illness and not using antipsychotic drugs are associated with greater suicide risk in patients with SCZ (30), uniquely, excess mortality is seen mostly in patients lack of adherence to antipsychotic drugs treatment (34), specifically, recurrent relapses are regarded as SCZ-unique suicide risk factors (23), these outcome are unanimous with the results of present study, these results reminded us that recurrent relapses may contribute to limited suicidal ideation quickly intensify to a suicide attempt during early stages of SCZ.

There is abundant evidence indicating that anomalous psychosocial characteristics were consistently associated with elevated risk of suicide, and chronic psychosocial stress may be a potential predictor for suicide (35). Weight gain in SCZ patients due to the use of antipsychotic drugs is a leading cause of non-compliance, which is risk leading to increased relapse (36). Moreover, overweight is also linked to greater morbidity, mortality and lower quality of life, being obese can affect psychological wellbeing and form chronic psychological stress (35). Earlier studies investigated the association of BMI with suicidality among adolescents, they found that adolescent overweight increased the risk for suicide ideation up to 1.30 fold, interestingly, the author found if adolescents' perceived weight was entered into the analyses, the risk for suicide ideation became non-significant, these results suggest that perceived weight may be a mediator in the association of BMI with proneness to suicidal behavior (37). Although there is some circumstantial evidence for weight gain as a psychosocial stress,

TABLE 6 Prediction of risk factors for the different dimension of suicide.

Groups	dependent variables	independent variables	B	SE	Beta (β)	*t*	*P*	R^2
FEPs	Recent psychosocial stress	BMI	0.064	0.018	0.473	3.521	<0.001	0.224
RPs	Severe mental illness	BMI	0.198	0.033	0.672	5.949	<0.001	0.451
	Suicide risk	C4	3.268	0.634	0.618	5.158	<0.001	0.382
	proneness to suicidal behavior	C4	0.260	0.049	0.809	5.356	<0.001	0.414
	Suicide ideation	BMI	0.911	0.370	0.909	2.463	0.018	0.755
		C4	1.361	0.289	1.737	4.709	<0.001	

Gender, age, BMI, years of education and factors of childhood maltreatment were included in stepwise regression analysis to predict the risk factors of suicide between the two groups. FEP, first episode patient; RP, recurrent patient; BMI, body mass index. C4 (emotional neglect). Significant level at $p < 0.05$. B, unstandardized coefficient; SE, Standard error, Beta: standardized coefficient; R^2, R square.

in view of the paucity of adults studies means, it is not possible to draw a clear conclusion on role of obese in the being risk indices for suicide (35). In the present study, the increase of BMI index was not only related to psychological stress, but also closely related to suicide risk, suicidal ideation and proneness to suicidal behavior in the patients of relapsed group. These results reminded us the obese may be the predictive risk factor for the development of psychosocial stress and that we should take into account an action on the suicidal impulsive behavior in advance.

It is well-documented that individuals experienced the physical abuse, sexual abuse and emotional neglect of childhood adversities, have been related to the development of adult onset psychosis and SCZ (38). Specifically, SCZ patients who have a history of physical and/or sexual abuse have also been found the increased rates of hallucinations, delusions, or thought disorder (38), as well as the number and severity of childhood maltreatment may elevate symptoms of hallucinations and delusions, such findings highlight childhood maltreatment could be as meaningful factors in the development of later psychotic symptomatology (39). Which is similar to findings of this present study shown that the physical abuse and sexual abuse had positive correlation with chronic psychosocial stress of first episode group and suicide ideation of relapsed group. Although there are some mixed discoveries in these contexts, such Laura P et al. in his systematic review and meta-analysis explored no statistically significant correlation between a history of sexual abuse and a lifetime diagnosis of SCZ, but the author demonstrated the association between sexual abuse and psychiatric disorders persisted regardless of sex of the abuse survivor or age at which abuse occurred (40). In addition, in the nearly, evidence of scientific highlighted the early traumatic life events may have a substantial impact on essential brain structure and functions, which may persist throughout adulthood (41), the interaction between the brain and the external environment can be mediated by epigenetic alterations in gene expression, the specific molecular mechanisms leaves long-lasting marks that cause subsequent pathology and physiology. On the other hand, it is well-known that the lack of exposure to adequate stimuli (as is the case with emotional neglect) can also have profound effects on neurodevelopment (42). Typically, these finding might be similar with our results that effects of emotional neglect had positive related to the chronic psychosocial stress, severe mental illness, suicide risk, suicidal ideation and proneness to suicidal behavior, moreover, emotional neglect is expected as a more predictive risk factor, linking maltreatment exposure to suicide in the patients of relapsed group. It is essential comprehensive to understand these vulnerability risk factors to suicide as a promising future treatment and prevention measures in the field.

Limitations

Despite we gain some insight between the child trauma and suicide through studies discussed above, the present study had some limitations, Firstly, this study used relatively small sample sizes, thus decreasing statistical power to detect. Secondly, the study is a cross-sectional design and without longitudinal data, which pose explanation mainly focusing on temporary effects, and is difficult to clarify determining causality. Thirdly, Identifying the child trauma is based on the self-reports of patients, some subjects may be willing to recalling negative events, thus recall biases are thought to play a role (43). In consideration of the above-mentioned facts, further research is necessary to make lager scale and long-term investigated research, so as to getting better understand the relationship about the victims of child trauma and suicide in the patients of schizophrenia.

Conclusion

In conclusion, Child trauma are commonly encountered in SCZ patients, especially, in the relapsed SCZ patients. BMI and emotional neglect may be a specific detective factors for the suicide risk, suicidal ideation and proneness to suicidal behavior in the relapsed SCZ patients. With some of comprehensive understanding in the this filed and that will likely be essential for therapeutic developments and prevention measures.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethics Committee of the Anhui Mental Health Center. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CZ and XZ were responsible for study design and manuscript editing. PC was responsible for statistical analyses and manuscript writing. LC, YC, JL, and QX were responsible for literature searches, statistical analyses, and manuscript writing. JG, LZ, FY, XC, and WP were responsible for clinical-scale assessment data collection. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer YH declared a shared affiliation with the author PJ to the handling editor at the time of review.

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EDITED BY
Wenhao Jiang,
Southeast University, China

REVIEWED BY
Sowmya Kamath S,
National Institute of Technology Karnataka, India
Jungchan Park,
Sungkyunkwan University, South Korea
Venkatesh Avula,
Geisinger Health System, United States

*CORRESPONDENCE
Yun Liu
liuyun@njmu.edu.cn

†These authors have contributed equally to this work

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Association between depressive symptoms and diagnosis of diabetes and its complications: A network analysis in electronic health records

Cheng Wan[1†], Wei Feng[1†], Renyi Ma[1], Hui Ma[2], Junjie Wang[1], Ruochen Huang[1], Xin Zhang[1,3], Mang Jing[3], Hao Yang[2], Haoran Yu[2] and Yun Liu[1,3*]

[1]Department of Medical Informatics, School of Biomedical Engineering and Informatics, Nanjing Medical University, Nanjing, China, [2]Department of Medical Psychology, Nanjing Brain Hospital, Nanjing Medical University, Nanjing, China, [3]Department of Information, The First Affiliated Hospital, Nanjing Medical University, Nanjing, China

Objectives: Diabetes and its complications are commonly associated with depressive symptoms, and few studies have investigated the diagnosis effect of depressive symptoms in patients with diabetes. The present study used a network-based approach to explore the association between depressive symptoms, which are annotated from electronic health record (EHR) notes by a deep learning model, and the diagnosis of type 2 diabetes mellitus (T2DM) and its complications.

Methods: In this study, we used anonymous admission notes of 52,139 inpatients diagnosed with T2DM at the first affiliated hospital of Nanjing Medical University from 2008 to 2016 as input for a symptom annotation model named T5-depression based on transformer architecture which helps to annotate depressive symptoms from present illness. We measured the performance of the model by using the F1 score and the area under the receiver operating characteristic curve (AUROC). We constructed networks of depressive symptoms to examine the connectivity of these networks in patients diagnosed with T2DM, including those with certain complications.

Results: The T5-depression model achieved the best performance with an F1-score of 91.71 and an AUROC of 96.25 compared with the benchmark models. The connectivity of depressive symptoms in patients diagnosed with T2DM (p = 0.025) and hypertension (p = 0.013) showed a statistically significant increase 2 years after the diagnosis, which is consistent with the number of patients diagnosed with depression.

Conclusion: The T5-depression model proposed in this study can effectively annotate depressive symptoms in EHR notes. The connectivity of annotated depressive symptoms is associated with the diagnosis of T2DM and hypertension.

The changes in the network of depressive symptoms generated by the T5-depression model could be used as an indicator for screening depression.

KEYWORDS

type 2 diabetes mellitus, depressive symptoms, natural language processing, network analysis, diabetes complication

1. Introduction

Depression is two times more common in patients with diabetes in the general population (1). Diabetic patients with depression have difficulty controlling their glycemic index (2), have a higher risk of dementia (3), and experience higher health care costs (4), especially in older adults (5). Depression has been reported to promote high risks of poor glucose control, comorbidities, and mortality in diabetic patients with depression (5, 6).

The duration of diabetes is associated with depression (7). A trial involving people who were newly diagnosed with type 2 diabetes mellitus (T2DM) found that the prevalence of depressive symptoms increased at least 1 year post diagnosis (8). Depressive symptoms are also associated with the presence of complications of diabetes, including cardiovascular disease, cerebrovascular disease, and neuropathy (9–12). This sentence highlights that the diagnosis events of complications, but the previous sentence describes about the relation between complications and depressive symptoms.

Depressive symptoms were estimated mostly using sum scores based on reported symptoms from screening tools (8, 13). The widely used validated tools for depression screening include the Patient Health Questionnaire-9 (PHQ-9), the Center for Epidemiologic Studies Depression Scale, and the World Health Organization-5 Well Being Index (WHO-5) (13, 14). Although treatment guidelines for patients with diabetes recommend regular depression screening (15), the rate of depression screening for such patients is low (16–18). However, owing to the heterogeneity of depression, the sum scores used in screening tools ignore the interactions among depressive symptoms when estimating the severity of symptoms (19). The low rate of depression screening and a lack of information on symptom interaction limit the identification of depressive symptoms and the understanding of their correlations in patients with diabetes.

The development of natural language processing (NLP) models and data mining in large-scale clinical real-world datasets of electronic health records (EHRs) has promoted screening for depression in patients with diabetes (18), especially screening based on admission notes. These notes contain a history of past illness, present illness, allergy, and birth information (20). Present illness includes the patient's main complaints, narratives of symptoms, and progress of treatment during their time in the hospital. During their hospital stay, patients will be checked for their status of spirit, sleep quality, and appetite, among others. Some researchers successfully used NLP tools to extract symptom data from unstructured free-text clinical documents in EHR. For example, Geraci et al. (21) extracted data from clinical notes through an NLP technique to predict the diagnosis of depression. Patel et al. (22) investigated the associations of depressive symptoms with clinical outcomes. These research studies provide opportunities for identifying depression-related symptoms and computer-aided diagnosis (23, 24).

In contrast to screening tools, network connectivity of symptoms focuses on estimating the associations among symptoms. The symptom–symptom interactions are used to form a network structure in the network analysis (25). Based on the network structure of depressive symptoms, the associations between symptoms and disease can be estimated from a part-whole perspective (26). Increases in network connectivity are associated with the severity of depression and persistent depressive symptoms (27, 28). Therefore, network analysis has recently been used as an alternative approach to assessing the severity of depressive symptoms.

In the present study, a model for classification and analysis of depression-related symptoms was proposed to directly identify depression symptoms from the EHRs of inpatients. Data were collected from an observational clinical dataset of inpatients at the First Affiliated Hospital of Nanjing Medical University over 8 years. The model integrated a transformer model with network analysis to facilitate an increased screening rate while retaining symptom interactions. The study examined depressive symptoms in patients with four complications of diabetes. The overall and local connectivities of the resulting networks were compared with the diagnosis of depression.

2. Methods

2.1. Study design and setting

The present study obtained medical record data from the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) at the First Affiliated Hospital of Nanjing Medical University (29). In this dataset, 61,471 inpatients with

valid present-illness notes were selected from among the 148,624 patients in the CDM who had been diagnosed with T2DM. We included data on patients' age at T2DM diagnosis, sex, diagnosis of depression (ICD-10 codes F32–F33), and diagnosis of complications: hypertension (ICD-10 code I10), ischemic heart disease (ICD-10 codes I20–I25), and cerebrovascular disease (ICD-10 codes I60–I69). The date of diagnosis of T2DM was defined as the earliest date of hemoglobin A1C $\geq$ 48 mmol/mol, or 6.5%, or use of insulin, or oral hypoglycemic drugs, or the first recorded diagnosis of T2DM. The date of diagnosis of complications was defined as the first recorded diagnosis of the complications. Ethical approval for the study was received from the Ethics Committee of the First Affiliated Hospital, Nanjing Medical University, Jiangsu, China.

We identified 52,139 inpatients who were first diagnosed with T2DM between 2008 and 2016 from a total of 61,471 patients. The complications (ischemic heart disease, hypertension, or cerebrovascular disease) of T2DM were confirmed after the diagnosis of T2DM had been made. To examine the difference in depressive symptoms before and after the diagnosis of T2DM or complications, a filtering rule (admission pairs, APs) was defined: patients were required to have admission records before and after the date of disease diagnosis during 2 years. For example, "patients have AP for hypertension" meant that patients had admission records 2 years before and after the date of diagnosis of hypertension. Eligible patients had AP for T2DM or its complications. Once the eligibility criteria had been met, 8,885 patients with T2DM, 1,357 patients with ischemic heart disease, 2,619 patients with hypertension, and 1,693 patients with cerebrovascular disease were selected for analysis. The procedure of patient selection is shown in Supplementary Figure S1. The year when patients were first diagnosed with T2DM, hypertension, ischemic heart disease, or cerebrovascular disease was coded as 0. Admissions in the preceding 2 years were coded as −2 and successive admissions as 2.

2.2. Depressive symptoms annotation

2.2.1. Processing of labeled datasets

To limit the cost of labeling, we randomly selected 10% of (15,615) notes from 156,156 admission notes of all inpatients (61,471 patients) to build and test the annotation model. Repeated notes of present-illness were excluded. Once the eligibility criteria had been met, 13,880 valid records of present-illness (dataset I) were labeled. To train, validate, and test the model, this dataset was split according to a ratio of 8:1:1. In addition, to internally evaluate the performance of the model, we randomly selected 4,658 admission notes (10% of 46,583 notes) as dataset II. These notes were extracted from the samples obtained in the previous patient selection process (see the "Study design and setting" section). Three annotators completed the labeling process of both datasets under the training of a clinical expert. A diagram illustrating this procedure is shown in Supplementary Figure S2.

We summarized depressive symptoms according to items described in previous research (30) and two commonly used screening tools namely, PHQ-9 (31) and WHO-5 (32). We included increased and decreased weights as symptoms because they were reported to have an effect on increasing the risk of depression in patients with T2DM (30). Another nine unique depressive symptoms were selected from PHQ-9 and WHO-5 scales, including feeling tired, difficulty in sleeping, a decrease in appetite, moving slowly, feeling irritable, a decline in memory or attention, feeling dispirited, depressed, or anxious, and feeling suicidal. The relationships of items in the screening tools and symptoms are shown in Supplementary Table S2. Antonyms were used for items in WHO-5 because these items are both positive expressions compared to PHQ-9. A total of 11 candidate depressive symptoms were evaluated by clinical experts. The synonyms of candidate depressive symptoms were also provided by clinical experts and were used in labeling (Supplementary Table S3).

Descriptive statistics for the manual labeling of datasets I and II are shown in Supplementary Table S4. Symptoms that occurred fewer than 10 times in any dataset were excluded. Finally, nine symptoms (feeling tired, difficulty in sleeping, a decrease in appetite, moving slowly, feeling irritable, a decline in memory or attention, a decrease in weight, an increase in weight, and feeling dispirited) were selected to build the model.

2.2.2. Annotation model development and evaluation

To annotate the depressive symptoms, we built a model named T5-depression based on a transformer model, Transfer Text-to-Text Transformer (T5 model) (33) model, with a sequence-to-structure paradigm. The architecture of T5-depression is shown in Figure 1. This model contains three parts: two multi-head attention modules (the encoder and decoder modules) and an auto rule-based result conversion module. The encoder module changes the input sentence x into a contextualized representation. The decoder module predicts the output sentence y on a token-by-token basis in the structured sequence. A constrained decoding algorithm for the symptom schema is injected during inference. The probability of the output is given in Equation 1, where T represents the size of the output and y_i represents each step of the output:

$$P(y|x) = \prod_{i=1}^{T} p(y_i|y_1, ..., y_{i-1}, x) \quad (1)$$

In the present study, each present illness note was regarded as the input, and all the related symptoms were formatted as the output. An example of formatted input and output is shown

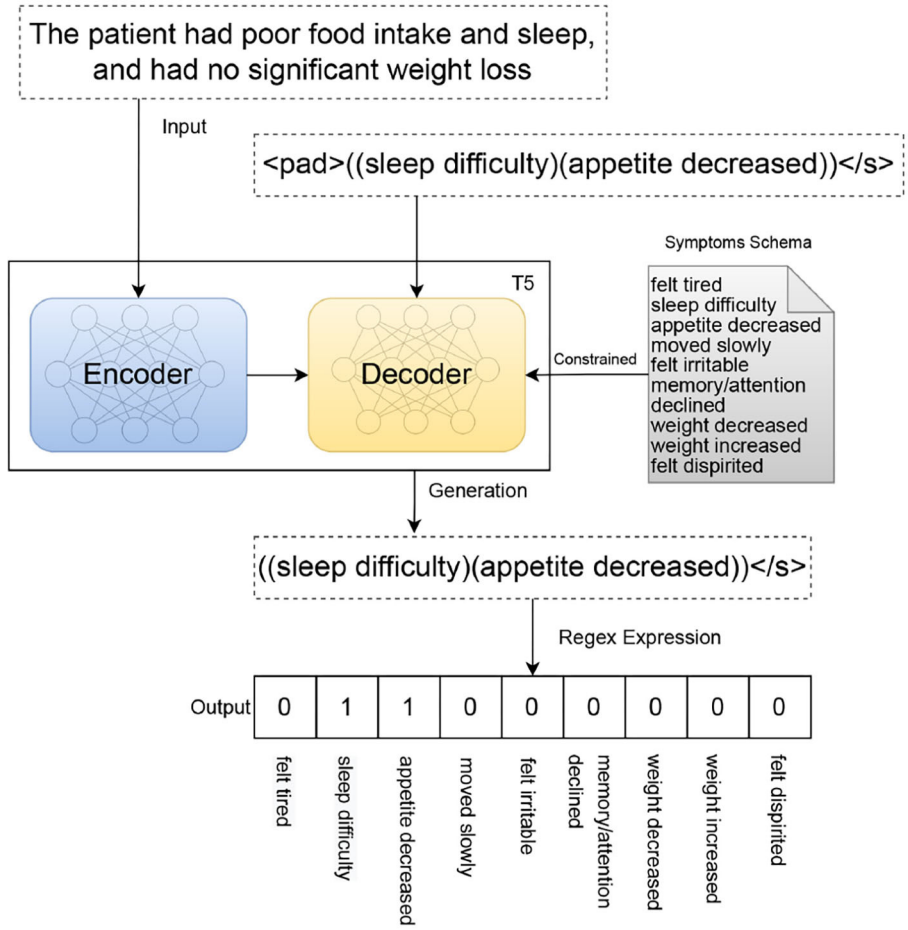

FIGURE 1
Architecture of the T5-depression model with formatted input and output.

in Figure 1. To support the Chinese language, we replaced the original pretrained model T5-base (33) with T5-Mengzi (34). Among the super-parameters used in T5-depression model, the learning rate was set to 5e-5, training epochs to 25, and batch size to 16. Other super-parameters were set as same as in Text2event.

We compared the performance of our model with a rule-based model, the Bidirectional Encoder Representations from Transformers (Bert) model (35), and the Roberta model (36) as benchmarks. The rule-based model was implemented using regular expressions derived from synonyms of each symptom in Supplementary Table S1. Roberta (36) was pretrained with Chinese-Roberta-wwm-ext (37) and Bert (35) was pretrained with Bert-base-Chinese. Bert is a contextualized word representation model that has been applied successfully to several tasks in the medical domain (38, 39). In the present study, we used the same number of epochs, batch size, and learning rate for Roberta and Bert. The implementation of the benchmark model was based on the Transformers package (40). All code for this study has been uploaded to https://github.com/inseptember/T5-depression.

To evaluate the performance of the models, precision, recall, F1-score, HammingLoss (41), and area under the receiver operating characteristic curve (AUROC) were used as metrics. Definitions of these metrics are given in Eqs. S1–S4 (Supplementary material). Precision is the ability to identify true positive samples among all positive prediction results. Recall is the ability to identify true positive samples among all positive results. F1 is the harmonic mean of the precision and recall. HammingLoss is the minimum number of substitutions required to change one sequence to another. This study indicates the fraction of symptoms that were incorrectly predicted. Owing to the unbalanced symptoms in our dataset (Supplementary Table S4), micro-averaging was performed on all symptoms. To prevent incorrect prediction of present illness notes, a model with higher recall and F1 is preferred to one with higher precision, AUROC, or HammingLoss. All metrics were calculated using the scikit-learn Python package (42).

Finally, T5-depression was used to process all present illness notes. The depressive symptoms, annotated from present illness notes within the range of admissions, were marked as binary values (1 for yes and 0 or no), depending on whether the notes contained the symptoms or not.

2.3. Statistical analysis

In depressive symptom networks, nodes represent symptoms and edges represent the associations between symptoms (26). We used the Ising models with the extended Bayesian information criterion from the R package *bootnet* (43) to construct and estimate the centrality of depressive symptoms before and after the diagnosis of each T2DM complication. We set the hyper-parameter tuning to 0 to estimate more connections (28). The weighted networks were illustrated using the R package *qgraph* (44).

Statistical assessment of the differences in overall connectivity of networks was performed using the R package *NetworkComparisonTest* (NCT) (27, 45). NCT is a two-tailed permutation-based hypothesis test to assess the difference between two groups (in our case, before and after the diagnosis of a disease or complication). The R package was run 1,000 times in our study to observe the differences in overall connectivity between the networks. In addition, differences in the importance of nodes were measured by node strength, closeness, and betweenness (44). Strength describes the degree to which a node is connected to other nodes. Closeness measures how close a node is to other nodes. Betweenness assesses the degree to which a node lies on the shortest path between nodes (46). In the present study, node strength was used as a local connectivity index. Furthermore, χ^2 test was conducted to determine depression associated difference for each complication. We compared the results from this test to the overall difference from the NCT package.

3. Results

3.1. Participants

A total of four cohorts with a diagnosis of T2DM or its complications (hypertension, ischemic heart disease, and cerebrovascular disease) were selected for this study. Descriptive statistics are shown in Table 1. The mean ages of participants in these four cohorts were 60.36 ± 15.58, 62.07 ± 13.03, 66.06 ± 14.15, and 66.52 ± 13.92, respectively. More than 59% of patients were men. Of the 8,885 patients in the T2DM cohort, 60 patients developed depression after diagnosis of T2DM within 2 years ($p < 0.001$). Of the 2,619 T2DM patients with hypertension, 24 developed depression after diagnosis with hypertension within 2 years ($p < 0.01$). There were no statistically significant differences in the diagnosis of depression after diagnosis with ischemic heart disease or cerebrovascular disease in patients with T2DM within 2 years.

3.2. Performance and annotation results of the T5-depression model

Table 2 reports the performance of the models for the annotation of depressive symptoms. Compared with other models, the T5-depression model achieved the best performance, with a micro-average F1 of 91.71% in dataset I and 95.53% in dataset II. The rule-based approach had the highest precision value of 95.39% and the lowest recall value of 79.23% in dataset I. The Roberta model achieved the best HammingLoss of 0.0027 in dataset I. The Bert model did not outperform other models in both datasets. We chose the T5-depression model as the auto-annotation model for the present-illness notes of patients.

According to annotation with the T5-depression model, the top three depressive symptoms in all cohorts were feeling tired, difficulty in sleeping, and a decrease in appetite (Table 1). The percentage of each depressive symptom increased significantly in the 2 years after diagnosis in the T2DM cohort, except for feeling irritable. Symptoms of a decrease in appetite ($p < 0.01$) and a decrease in weight ($p < 0.01$) showed a significant increase in the 2 years after diagnosis in the T2DM and hypertension cohort. Only a decrease in appetite ($p < 0.05$) showed a significant increase in the ischemic heart disease cohort. No change in symptoms was found in the cerebrovascular disease cohort.

3.3. Network analysis

A comparison of overall network connectivity before and after diagnosis (with T2DM, hypertension, ischemic heart disease, and cerebrovascular disease) is presented in Table 3. After diagnosis of diabetes ($p = 0.025$) and hypertension ($p = 0.013$) in patients, the overall connectivity of the symptom networks increased significantly during the 2 years. Due to consistent increase in overall connectivity, the number of patients with T2DM and hypertension diagnosed with depression also increased. With regard to symptoms, strong positive connections between a decline in memory/attention and feeling irritable were found after diagnosis of T2DM and hypertension (Figure 2). The strength of symptoms was measured as local connectivity (Supplementary Figure S2). The symptom of a decrease in appetite remained high and stable both before and after diagnosis. Weight-related symptoms had relatively lower values.

TABLE 1 Descriptive statistics for each diseases in these windows of years.

	T2DM			Hypertension			Ischaemic heart disease			Cerebrovascular disease		
	(−2,0]	(0,2]	*p*	(−2,0]	(0,2]	*p*	(−2,0]	(0,2]	*p*	(−2,0]	(0,2]	*p*
Total, n	8885			2619			1357			1693		
Age, Mean (SD)	60.36 (15.58)			62.07 (13.03)			66.06 (14.15)			66.52 (13.92)		
Sex, n (%)												
Men	5242 (59.00)		0.0000***	1643 (62.73)		0.0000***	911 (67.13)		0.0000***	1051 (62.08)		0.0000***
Women	3643 (41.00)			976 (37.27)			446 (32.87)			642 (37.92)		
Depression, n (%)	81 (0.91)	141 (1.59)	0.0001***	21 (0.80)	45 (1.72)	0.0044**	40 (2.95)	31 (2.28)	0.3360	55 (3.25)	69 (4.08)	0.2343
Depressive Symptoms, n (%)												
Feeling tired	1,569 (17.66)	1,797 (20.23)	0.0000***	555 (21.19)	589 (22.49)	0.2698	276 (20.34)	287 (21.15)	0.6359	531 (31.36)	498 (29.42)	0.2318
Difficulty in sleeping	1,225 (13.79)	1,396 (15.71)	0.0003***	443 (16.91)	479 (18.29)	0.2041	261 (19.23)	278 (20.49)	0.4414	345 (20.38)	347 (20.50)	0.9660
A decrease in appetite	1487 (16.74)	1,735 (19.53)	0.0000***	476 (18.17)	554 (21.15)	0.0074**	235 (17.32)	277 (20.41)	0.0443*	341 (20.14)	335 (19.79)	0.8298
Moving slowly	99 (1.11)	155 (1.74)	0.0005***	43 (1.64)	54 (2.06)	0.3054	14 (1.03)	19 (1.40)	0.4836	55 (3.25)	73 (4.31)	0.1256
Feeling irritable	47 (0.53)	61 (0.69)	0.2096	18 (0.69)	22 (0.84)	0.6340	12 (0.88)	9 (0.66)	0.6613	21 (1.24)	26 (1.54)	0.5568
A decline in Memory/attention	60 (0.68)	89 (1.00)	0.0212*	25 (0.95)	36 (1.37)	0.1978	12 (0.88)	15 (1.11)	0.6989	48 (2.84)	59 (3.48)	0.3259
A decrease in Weight	1051 (11.83)	1,138 (12.81)	0.0496*	417 (15.92)	331 (12.64)	0.0008**	118 (8.70)	137 (10.10)	0.2363	182 (10.75)	158 (9.33)	0.1885
An increase in Weight	99 (1.11)	179 (2.01)	0.0000***	36 (1.37)	55 (2.10)	0.0570	15 (1.11)	17 (1.25)	0.8589	18 (1.06)	23 (1.36)	0.5297
Feeling dispirited	358 (4.03)	472 (5.31)	0.0001***	146 (5.57)	160 (6.11)	0.4438	77 (5.67)	69 (5.08)	0.5515	140 (8.27)	148 (8.74)	0.6663

For age, standard deviation is in parentheses, mean value is outside. For sex and depressive symptoms, percentage value is in parentheses, amount value is outside.
(−2, 0], within 2 years before diagnosed date of each disease; (0, 2], within 2 years after diagnosed date of each disease.
p, p-values from χ2-test; *<0.05; **<0.01; ***<0.001.

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TABLE 2 Metrics for different models on Dataset I and II.

	Pretrained model	Datasets	AUROC	Hamming loss	P	R	F1
Rule-based	-	Dataset I - Train	89.74	0.0226	95.99	79.83	87.17
		Dataset I - Test	89.41	0.0242	95.39	79.23	86.57
		Dataset I - Validation	89.41	0.0243	96.57	79.14	86.99
		Dataset II	82.06	0.0263	92.91	64.45	76.11
Roberta	hfl/chinese-roberta-wwm-ext (37)	Dataset I - Train	93.78	0.012	94.8	89.39	92.02
		Dataset I - Test	93.21	0.0027	90.65	87.81	89.21
		Dataset I - Validation	92.98	0.0028	90.59	85.88	88.17
		Dataset II	89.32	0.0154	91.64	84.04	87.68
Bert	bert-base-chinese[a]	Dataset I - Train	90.51	0.0173	91.72	85.39	88.44
		Dataset I - Test	88.46	0.003	92.25	83	87.38
		Dataset I - Validation	91.2	0.0031	91.12	83.07	86.91
		Dataset II	88.38	0.0156	92.49	82.69	87.31
T5-depression	Langboat/mengzi-t5-base (34)	Dataset I - Train	99.3	0.0021	99.16	98.7	98.93
		Dataset I - Test	96.25	0.0166	89.84	93.65	91.71
		Dataset I - Validation	95.37	0.0173	91.43	91.72	91.58
		Dataset II	97.47	0.0058	95.83	95.23	95.53

P, Precision; R, Recall; F1, F-scores.
[a]: https://huggingface.co/bert-base-chinese.

TABLE 3 Comparison between network connectivity for each disease.

	Overall connectivity			Depression diagnosis		
	(−2,0]	(0,2]	*p*-value	(−2,0]	(0,2]	χ^2
T2DM	7.54	13.79	0.0250*	81	141	0.0001***
Hypertension	4.60	13.47	0.0130*	21	45	0.0044**
Ischaemic Heart Disease	3.91	5.37	0.3250	40	31	0.3360
Cerebrovascular Disease	7.21	8.83	0.5860	55	69	0.2343

P-values in overall connectivity are computed from the Network Comparison Test.
(−2, 0], within 2 years before diagnosed date of each disease; (0, 2], within 2 years after diagnosed date of each disease.
* < 0.05; ** < 0.01; *** < 0.001.

4. Discussion

In the present study, we compared depressive symptoms from the EHR notes of patients in the 2 years before and after the diagnosis of T2DM and complications (hypertension, ischemic heart disease, and cerebrovascular disease). To annotate depressive symptoms in EHR notes of patients with T2DM, we applied the T5-depression model to automatically label depressive symptoms. We used network analysis to examine the differences among depressive symptom networks. The diagnoses of T2DM and hypertension were associated with increased overall connectivity of the symptom network.

The T5-depression model was built using a sequence-to-structure paradigm. Classic methods used for symptom annotation include rule-based approaches and form part of pipelines including MedLEE (47), ClinREAD (48), and MTERMS (49). The rule-based methods mostly extract symptoms through keyword retrieval, which ignores the context semantics of each symptom. Recently, Bert (35) was applied to various clinical tasks (50–52). Through a multi-head attention mechanism, Bert-related models can obtain context features of each symptom. Moreover, methods used for annotation tasks train a classifier on the last layer of the model. However, this requires much effort when applied to medical notes with fine-grained token-level annotation. The sequence-to-structure paradigm model can generate all targets in one step and show competitive performance using only record-level annotations. This mechanism can reduce much of the effort involved in the annotation procedure and has generalizability (53).

In the present study, the T5-depression model achieved promising performance on our dataset. The architecture of T5-depression was designed to translate the input text to

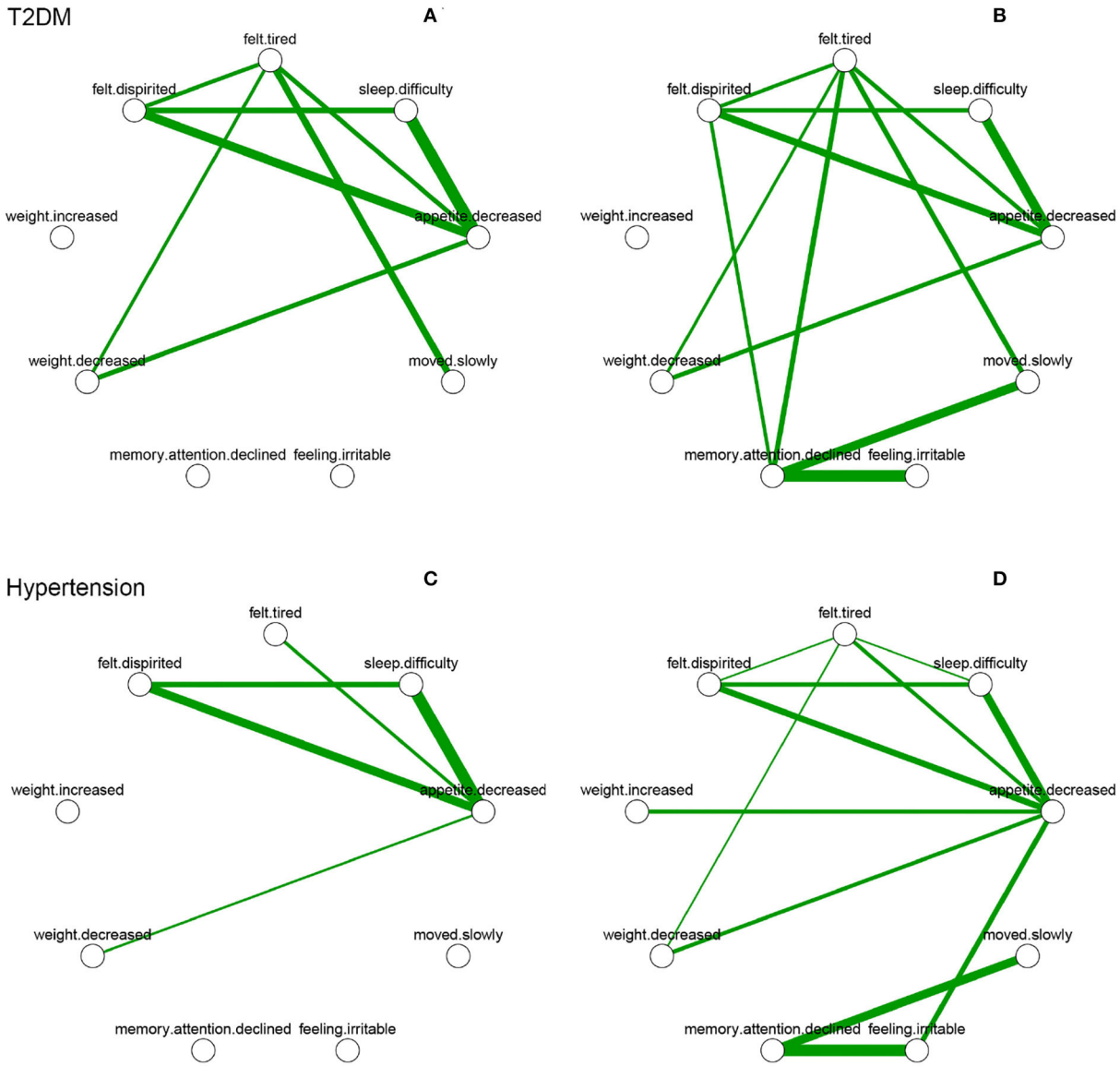

FIGURE 2
Depressive symptom networks within 2 years before and after the diagnosis of T2DM and hypertension. Green lines represent positive association, and thicker lines represent stronger association. **(A)** is within 2 years before diagnosed date of T2DM. **(B)** is within 2 years after diagnosed date of T2DM. **(C)** is within 2 years before diagnosed date of hypertension. **(D)** is within 2 years after diagnosed date of hypertension.

an augmented readable text, which makes the annotation procedure easier and enables the handling of labels of different sizes with less modification than classification models with one-hot labels. T5-depression can make full use of semantic information of labels by relative positional embeddings and use of an autoregressive decoder, unlike Bert-related models. Owing to the smaller number of annotations of certain symptoms, including feeling irritable and a decline in memory or attention (Supplementary Table S4), the rule-based model achieved the highest precision; however, it had a lower recall value than the T5-depression model. Through keyword searching, the rule-based approach could identify the exact same symptoms as labeled in notes but failed to identify symptoms in other formats. The T5-depression model showed poor performance related to symptoms including moving slowly (F1: 70.59) and feeling irritable (F1: 70.27) because these two symptoms had a more varied expression in the Chinese population and were reported in limited numbers compared with other symptoms in our dataset. The T5-depression model still achieved the best overall performance compared with regular rule-based

annotation methods. Thus, the model could be a reliable tool for identifying depressive symptoms in EHR of patients with T2DM, thereby saving time and effort on the part of medical experts.

This study showed a significant increase in the overall connectivity of depressive symptoms during the 2 years after diagnosis of T2DM and hypertension. Persistent depressive symptoms have been reported in the early stages of diabetes (8), and awareness of hypertension indicates a higher prevalence of depressive symptoms (54). It has been reported that persistent depressive symptoms are associated with stronger network connectivity (27), and the change in overall connectivity in this study was consistent with the diagnosis of depression in patients with T2DM and hypertension. Although some studies have reported that cerebrovascular disease has stronger associations with depressive symptoms in patients with diabetes (11, 55), the short-term prevalence of depression was unchanged (56), which is consistent with our results. The network connectivity of depressive symptoms in the early stages of T2DM could be an indicator for further monitoring of depression while current method for screening depression in patients with diabetes is insufficient. Although a study has suggested that the development of T2DM might not induce depressive symptoms (2), the increase in frequency of depressive symptoms after the diagnosis of T2DM illustrates the importance of mining EHR notes for psychiatric research.

High centrality of symptoms in the network could be considered as important parts in maintaining the mental disorders (25). We used the strength of nodes to measure local connectivity in this study. For patients diagnosed with T2DM and complications including hypertension, the centrality of the symptom of a decline in memory or attention ranked top among all depressive symptoms over 2 years. Depression is associated with concurrent cognitive decline (57) in patients with diabetes. Nonpharmacological treatments for behavioral and psychological symptoms of dementia have been shown to result in improvements in depression (58). Some studies also reported that anti-dementia drugs have antidepressant-like effects (59, 60) in animal models. Treatment of cognitive symptoms is thus a potential approach for the prevention of depression in patients with diabetes.

5. Limitations

Our study had some limitations. First, we included admissions only 2 years before and after the initial diagnosis; this time period might not be enough given that this was a study of chronic disease, in which some patients may have developed before their first admission or diagnosis in the hospital. Second, the annotation model for present illness in EHR notes has the potential to improve precision on some limited symptoms. In the current study, the semantics of tags helped to improve the performance of the model. In the future, we could inject a detailed description of each symptom obtained from multi-modal resources to the model and fuse vital indicators with symptom descriptions in the model. Third, the selected symptoms in this study might not cover the whole range of depressive symptoms compared with other screening tools like CES-D. Some associations of symptoms could therefore have been missed. More screening tools should be examined in the future to include more symptoms.

6. Conclusion

In the present study, depressive symptoms were annotated effectively from EHR notes by the T5-depression model, and network analysis was used to examine the effects of the diagnosis of T2DM and complications on depression. The model achieved acceptable performance on the annotation of depressive symptoms in all datasets, and the connectivity of depressive symptom networks was shown to be associated with the diagnosis of T2DM and hypertension during the past 2 years. In future research, the transition of symptoms during the course of T2DM should be examined, and more symptoms should be included in the model to estimate the relationships with other vital indicators.

Data availability statement

The datasets presented in this article are not readily available because data privacy and security requirements. Requests to access the datasets should be directed to YL, liuyun@njmu.edu.cn.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital, Nanjing Medical University (2020-SR-163). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

WF and CW contributed to conception and design of the study and performed the statistical analysis and wrote the first draft of the manuscript. HM and XZ organized the database. JW and RH prepared the figures in manuscript. HYa and HYu conducted the process of data collection. YL supervised the research activity planning and execution. RM and MJ annotated the datasets and participated in revising the manuscript. All

authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.966758/full#supplementary-material

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Wenhao Jiang,
Southeast University, China

REVIEWED BY
Gwendolyn Mayer,
Heidelberg University Hospital, Germany
Jung Kyung Hong,
Seoul National University, South Korea
Anabela Conceição Pereira,
University Institute of Lisbon (ISCTE), Portugal

*CORRESPONDENCE
Jing Wei
weijing@pumch.cn

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Validation of the Chinese version of the Somatic Symptom Scale-8 in patients from tertiary hospitals in China

Tao Li[1], Jing Wei[1]*, Kurt Fritzsche[2], Anne C. Toussaint[3], Lan Zhang[4], Yaoyin Zhang[5], Hua Chen[6], Heng Wu[7], Xiquan Ma[8], Wentian Li[9], Jie Ren[10], Wei Lu[11] and Rainer Leonhart[12]

[1]Department of Psychological Medicine, Peking Union Medical College Hospital (CAMS), Beijing, China, [2]Department of Psychiatry and Psychotherapy, University of Freiburg Medical Center, Freiburg, Germany, [3]Clinic for Psychosomatic Medicine and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [4]Mental Health Center, West China Hospital, Sichuan University, Chengdu, China, [5]Department of Psychosomatic Medicine, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China, [6]Department of Psychological Medicine, Zhongshan Hospital, Fudan University, Shanghai, China, [7]Department of Psychosomatic Medicine, Tongji Hospital, School of Medicine, Tongji University, Shanghai, China, [8]Department of Psychosomatic Medicine, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China, [9]Department of Clinic Psychology, Wuhan Mental Health Center, Wuhan, China, [10]Department of Rehabilitation, General Hospital of Jincheng Anthracite Coal Mining Group Co. Ltd., Jincheng, China, [11]Department of Psychosomatic Medicine, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, China, [12]Institute of Psychology, University of Freiburg, Freiburg, Germany

Objective: To validate the Chinese language version of the Somatic Symptom Scale-8 (SSS-8) in a sample of outpatients attending tertiary hospitals in China.

Materials and methods: A Chinese language version of the SSS-8 was completed by outpatients (n = 699) from psychosomatic medicine, gastroenterology/neurology, and traditional Chinese medicine clinics of nine tertiary hospitals between September 2016 and January 2018 to test the reliability. The Patient Health Questionnaire-15 (PHQ-15), the Somatic Symptom Disorder–B Criteria Scale (SSD-12), the Patient Health Questionnaire-9 (PHQ-9), the General Anxiety Disorder-7 (GAD-7) scale, the Medical Outcome Study 12-item Short Form Health Survey (SF-12) and the World Health Organization Disability Assessment Schedule (WHO DAS 2.0) were rated to test construct validity. The criterion validity was tested by using the Semi-structured Clinical Interview for DSM-5 (Research Version) (SCID-5-RV) for somatic symptom disorder (SSD) as the diagnostic gold standard to explore the optimal cutoff score of the SSS-8.

Results: The average age of the recruited participants was 43.08 (±14.47). 61.4% of them were female. The internal consistency derived from the sample was acceptable (Cronbach α = 0.78). Confirmatory factor analyses resulted in the replication of a three-factor model (cardiopulmonary symptoms, pain symptoms, gastrointestinal and fatigue symptoms) (comparative fit

index = 0.95, Tucker-Lewis index = 0.92, root mean square error of approximation = 0.10, 90% confidence interval = 0.08–0.12). The SSS-8 sum score was highly associated with PHQ-15 (r = 0.74, $p < 0.001$), SSD-12 (r = 0.64, $p < 0.001$), GAD-7 (r = 0.59, $p < 0.001$), and PHQ-9 (r = 0.69, $p < 0.001$). The patients with more severe symptoms showed worse quality of life and disability The optimal cutoff score of SSS-8 was 9 (sensitivity = 0.67, specificity = 0.68).

Conclusion: Our preliminary assessment suggests that the Chinese language version of the SSS-8 has reliability and validity sufficient to warrant testing further in research and clinical settings.

KEYWORDS

Somatic Symptom Scale-8, reliability, validation, psychometrics, somatic symptom disorder, Chinese version, screening tool

Introduction

Somatic symptoms are an important, subjective health-related experience and the most common reason for people seeking medical services (1). Somatic symptoms may be related to physical disease, but may also be a feature of a mental disorder, according to the classical medical concept of dualism. In recent decades, somatic symptoms have been considered a psychosomatic phenomenon. Somatic symptoms act as a precise key that can help doctors gain a profound understanding of a patient's suffering and identify health problems that need intervention. From the perspective of the clinical practice of mental health, distressing somatic symptoms are an important diagnostic criterion for somatic symptom disorder (SSD) in the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (DSM-5) and bodily distress disorder in the International Classification of Diseases (11th Revision) (ICD-11), and are significantly correlated with patients' quality of life.

Many scales have been designed to screen for somatic symptoms in daily clinical practice and epidemiological investigation (2). Previously, somatic symptoms were often included as part of general psychopathology measures, such as the 12 items in the Symptom Checklist-90 (SCL-90) somatization subscale (3). Since the 1980s, specific somatic symptom scales have been developed for the diagnosis of somatoform disorders, such as the Patient Health Questionaire-15 (PHQ-15) (4). Their common criteria include pain in different parts of the body, fatigue, dizziness, gastrointestinal discomfort, and breathing difficulties. These symptoms, which are the most common somatic symptoms, constitute the main content of the Somatic Symptom Scale-8 (SSS-8) as the short form of the PHQ-15 (5). In addition, sleep problems in the PHQ-15 are also retained in the SSS-8 (6).

In DSM-5 Cross Cutting Symptom Measure field trials, the SSS-8 was used as a reference measure for facilitating the diagnosis of SSD (7). Validated versions of the SSS-8 have been published in Germany, Japan, Korea, and Greece (6, 8–10). The SSS-8 has been recommended as a reliable and valid self-report measure of somatic symptom burden in the general population.

The aims of this study were (1) to investigate the reliability and validity of the Chinese version of SSS-8 in patients from tertiary hospitals in China, and (2) to explore the cutoff point of the sum score of SSS-8 to make it a valid screening tool for SSD.

Materials and methods

Sampling strategy

This study was a multicenter cross-sectional survey of somatic burden and the related mental well-being of outpatients attending tertiary hospitals in China between September 2016 and January 2018. Tertiary hospitals in China include general hospitals and specialized hospitals which provide advanced health care to patients. In most previous studies, the SSS-8 was proved to be a validate tool in general population (6, 8, 9). In this study, outpatients of tertiary hospitals were chosen to investigate if the SSS-8 is a validate tool for patients with relatively high somatic symptom burden. Based on geographic diversity, nine tertiary hospitals in Beijing, Shanghai, Chengdu, Wuhan, and Jincheng were selected, representing northern, southeastern, and southwestern regions of China. Outpatients were recruited from three different settings: psychosomatic medicine, gastroenterology/neurology, and traditional Chinese medicine. The neurology and gastroenterology departments were chosen to represent modern biomedical settings. In randomly selected work hours, the research assistant came to

these departments' outpatient clinics and invited all patients who came during that time to participate in the study by oral invitation. Eligible patients had to be aged 18 years or older, be seeking treatment voluntarily, and be able to read and sign the informed consent. People visiting for another person's problems, patients with difficulty communicating, a language barrier, or limited literacy; patients with cognitive impairment, an organic brain disorder or dementia, or psychosis; and patients with acute suicidal tendencies were excluded. All eligible patients were registered, including those who, owing to lack of time, lack of interest, or lack of trust in the researchers, did not participate.

Study procedure

Participants were asked to conduct self-rated questionnaires and an in-person interview on the spot and no extra visit for research was required.

The instruments administered in the study included a questionnaire on demographic characteristics, the SSS-8, the PHQ-15, the Patient Health Questionnaire-9 (PHQ-9), the General Anxiety Disorder-7 (GAD-7) scale, the Somatic Symptom Disorder–B Criteria Scale (SSD-12), the Medical Outcome Study 12-item Short Form Health Survey (SF-12), and the short-form self-administered World Health Organization Disability Assessment Schedule 2.0 (WHO-DAS 2.0). The Semi-structured Clinical Interview for DSM-5 (research version; SCID-5-RV) was used to conduct a diagnostic interview of each patient, and the results were used as the gold standard for SSD diagnosis, to measure the criterion validity of SSS-8.

All the questionnaires were print on papers with instructions in fixed order and filled by patients. The interview was conducted by research assistants from each tertiary hospital (students of psychology at the master's level, students of medicine in their final year of studies, and medical doctors) trained by experienced psychiatrists. They were blinded to the patients' questionnaire results.

Development of the Chinese version of the Somatic Symptom Scale-8

The SSS-8 scale has eight items, each of which is divided into five categories (0 = not at all to 4 = very much). Total score is between 0 and 32 points. The validated English version of the SSS-8 has been published in 2014 (6). The questionnaire was translated and then back-translated from English into Mandarin Chinese, using the "ITC-Test Adaptation Guidelines" of the International Test Commission. Three Mandarin Chinese native speakers fluent in both written and spoken English (one psychiatrist, one psychologist, and one educator) first completed independent translations. These preliminary translations were discussed during project meetings. A pilot of the revised questionnaire was tested on 10 patients and then back-translated into English for a final revision, from which the final version of the Chinese SSS-8 was established.

Other psychological measurements

The PHQ-15 is one of the most frequently used self-administered questionnaires, with 15 items assessing the burden of common somatic symptoms within the last 4 weeks (4). Each of the 15 items is scored on a three-point Likert-type scale with sum scores ranging from 0 to 30. A higher score indicates a heavier burden of somatic symptoms. The validity of the Chinese version was previously proven satisfactory (11).

The PHQ-9 is another widely used self-administered instrument and comprises nine items assessing depression symptoms within the last 2 weeks (12). Items are also scored on a four-point Likert-type scale with sum scores ranging from 0 to 27. Higher scores indicate more severe symptoms. The Chinese version of the PHQ-9 has demonstrated good validity in Chinese general hospital outpatients (13).

The GAD-7 self-administered questionnaire contains seven items measuring symptoms of general anxiety disorder and other common anxiety disorders (14). The items are scored on four-point Likert-type scale, and sum scores range between 0 and 21. The Chinese version of the GAD-7 has demonstrated satisfactory reliability and validity (15).

The SSD-12 consists of 12 self-administered items scored on a five-point Likert-type scale, and it assesses patients' perceptions of the symptom-related thoughts, feelings, and behaviors that they experience, based directly on the DSM-5 criteria (16). The total score is between 0 and 48 points and a higher score indicates greater psychological distress associated with somatic symptoms. The SSD-12 Chinese version has demonstrated satisfactory validity (17).

The SF-12 measures health-related quality of life (18). Twelve self-administered items are divided into six items reflecting a physical component (physical component score of SF-12, PCS of SF-12) and six items reflecting a mental component (mental component score of SF-12, MCS of SF-12), normalized to two subscales (mean [SD] = 50 [10]). Better health status is indicated by a higher score and the Chinese version has demonstrated good validity and reliability (19).

The WHO-DAS 2.0 comprises 12 self-administered items measuring disability and health at the population level and in clinical practice (20). A five-point Likert-type scale is used for scoring each item. The simple scoring method gives a total score of between 12 and 60 points. Higher scores indicate more severe disability, and a Chinese version has been validated (21).

The SCID-5-RV for SSD has previously been translated according to the procedures described for the translation of the

SSS-8. The validity of the Chinese version in assessing for SSD has been demonstrated (22).

Statistical analysis

SPSS version 25 was used for data analysis except factor analysis. The internal consistency of the scale was assessed with Cronbach's Alpha coefficients. Split-half reliability was estimated using Spearman-Brown coefficients.

Mplus 8.2 software was used for factor analysis to test the factorial structure of the SSS-8 for the Chinese samples. To test global model fits, comparative fit index (CFI), Tucker-Lewis index (TLI), and the root mean square error of approximation (RMSEA) were used. A CFI > 0.95, TLI > 0.95, and RMSEA < 0.08 were taken to indicate a good fit for the continuous data (23).

Pearson correlations coefficients were calculated to correlate the sum score of the SSS-8 with the PHQ-15, PHQ-9, GAD-7, and SSD-12, which assess construct validity of the SSS-8.

Receiver operating characteristic curve (ROC) was used to examine the effectiveness of the SSS-8 as a screening tool for SSD. The Youden Index was used to choose the optimal threshold value (cutoff point) of the SSS-8 for which the diagnostic specificity + sensitivity-1 is maximized for SSD (24).

The severity categories, general disability (WHO-DAS 2.0), the physical component score of SF-12 and the mental component score of SF-12 were analyzed by one-way analysis of variance followed by multiple comparisons using Scheffe test or Dunnett's T3 test according to the homogeneity state of variances.

Floor and ceiling effects were considered to be present if more than 60% of subjects achieved the lowest or highest score on each item and the sum score of the SSS-8 (8).

Results

A total of 1,269 patients were contacted, of whom 699 (55.1%) were enrolled (**Figure 1**). Sixty-eight (5.4%) patients were excluded according to the exclusion criteria, and 502 (39.6%) patients refused to participate in the study. Of those patients who refused, 53% indicated that they did not have time to participate, 29.5% were not interested in participating, and 8.4% indicated distrust of the researchers. A further 6.8% felt too unwell to participate and 2.4% gave other reasons. **Table 1** indicates the sociodemographic characteristics of the sample.

225 (32.2%) patients were enrolled from biomedical settings, 90 (40.0%) of which were SSD positive. 232 (33.2%) patients were enrolled from Traditional Chinese Medical settings, 44 (19.0%) of which were SSD positive. 242 (34.6%) patients were from psychosomatic medical settings, 102 (42.1%) of which were SSD positive. The prevalence of SSD in patients from different medical settings were significantly different ($\chi^2 = 34.049$, df = 2, $p \leq 0.001$).

Reliability of the Somatic Symptom Scale-8

The SSS-8 demonstrated an acceptable reliability for the sample, with Cronbach $\alpha = 0.78$. Additionally, Spearman-Brown split-half coefficient was 0.73. **Table 2** shows the overall item and subscale characteristics. The sum scores for 26 out of 699 participants were 0, for 1 out of 699 participants was 32. No remarkable floor or ceiling effects were observed for the total scores or individual item scores.

Validity of the Somatic Symptom Scale-8

Factorial validity

Previous studies have carried out factor analysis of the SSS-8. Confirmatory factor analysis (CFA) was adopted in our study. Three factor models were verified: a general-factor model, a three-factor model, and a second-order factor model that contained a global factor and four low-grade symptom clusters (6, 9). Fit indices for the three models from the CFA of the total included patients (n = 699) are shown in **Table 3** (see attachment). The relatively better fit indices were those derived from the three-factor model (Tucker-Lewis index, 0.92; CFI, 0.95; root mean square error of approximation, 0.10, 90% confidence interval [CI]: 0.08–0.12). The three-factor model consisted of three symptom clusters: (1) cardiopulmonary symptoms (Cronbach $\alpha = 0.71$) including headaches (item 4), chest pain or shortness of breath (item 5), and dizziness (item 6); (2) pain symptoms (Cronbach $\alpha = 0.64$) including back pain (item2) and painful legs, arms, or joints (item 3); and (3) gastrointestinal and fatigue symptoms (Cronbach $\alpha = 0.57$) including bowel or stomach problems (item 1), tiredness or having low energy (item 7), and sleeping difficulties (item 8).

Meanwhile, the fit indices for the general-factor model (TLI, 0.87; CFI, 0.91; RMSEA, 0.13, 90% CI: 0.11–0.14) and for the second-order factor model (TLI, 0.88; CFI, 0.92; RMSEA, 0.12, 90% CI: 0.11–0.14) were rejected.

Criterion validity

SSD diagnosed using the SCID-5-RV was used as the gold standard to test the criterion validity and threshold of the SSS-8. A total of 697 participants completed the interview. Of these, 236 (33.9%) participants were diagnosed with SSD. The diagnostic effectiveness of the SSS-8 for SSD was tested by using the sum score of the SSS-8 (**Figure 2**; **Table 4**). Area under curve (AUC) for detecting SSD was 0.729. The best

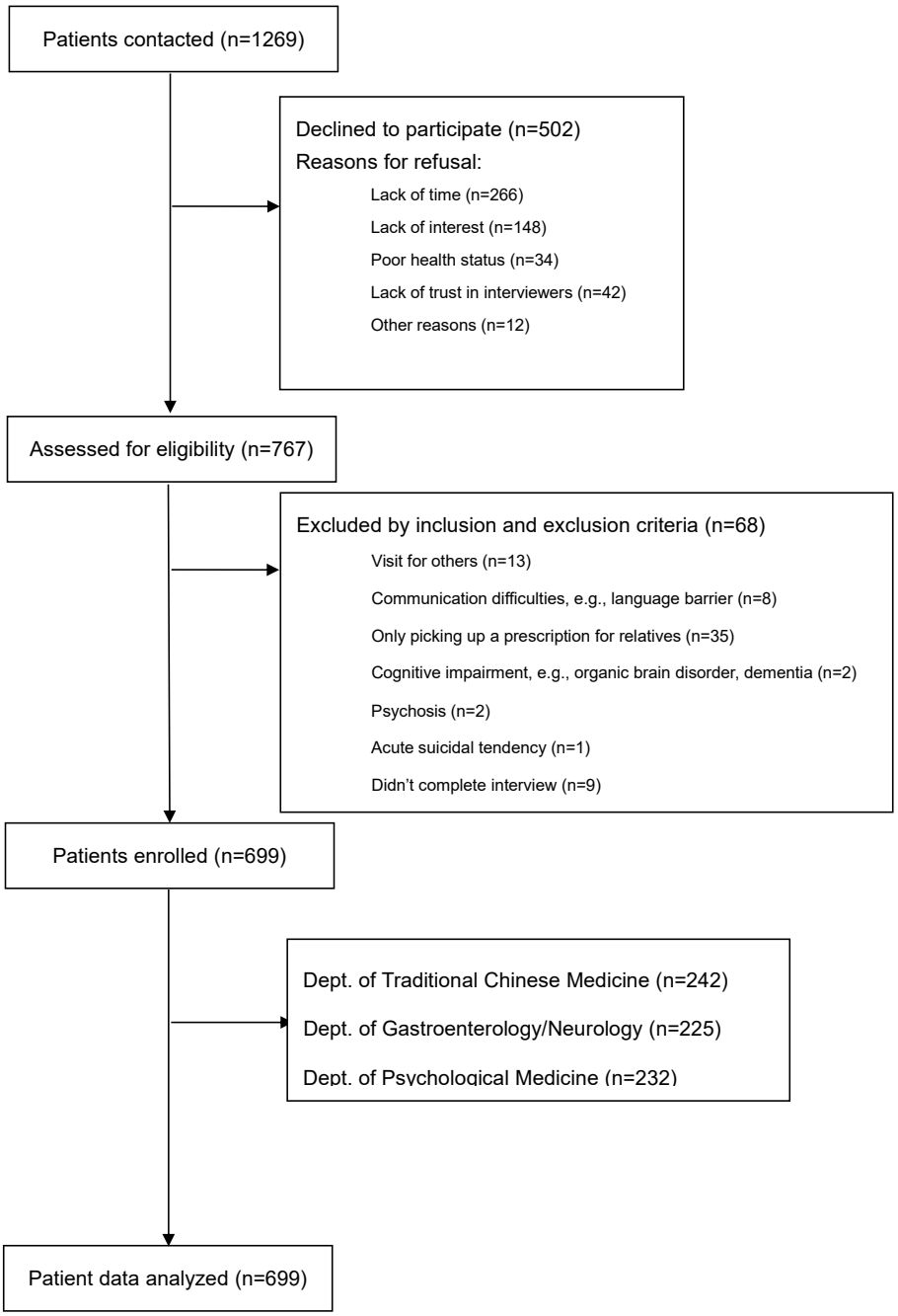

FIGURE 1
Flow chart of patient enrolment.

diagnostic performance of the SSS-8 sum score was achieved with a cutoff of ≥9 in the total sample (Youden index = 0.355, sensitivity = 0.674, and specificity = 0.681), with 0.520 positive predictive value (PPV) and 0.803 negative predictive value (NPV).

In previous studies, five categories of severity were defined according to SSS-8 sum scores of 0–3 (no to minimal severity), 4–7 (low), 8–11 (medium), 12–15 (high), and ≥16 (very high). Sensitivity and specifificity were calculated with each cut-off score. Detailed results are presented in Table 4.

Construct validity

The various well-established scales were used to assess construct validity of the SSS-8 Chinese version. The mean (SD) score for the PHQ-15 (n = 696) was 9.34 (5.40), which correlated highly with the SSS-8 sum score ($r = 0.74$, $p < 0.001$).

TABLE 1 Sociodemographic characteristics of outpatient sample from general hospitals in China.

	Total (n = 699)	With SSD (n = 236*)	Without SSD (n = 461*)	t/Chi^2	df	P
	Mean (SD) or N (%)	Mean (SD) or N (%)	Mean (SD) or N (%)			
Age	43.08 (14.47)	42.99 (14.04)	43.05 (14.69)	0.05	695	0.957
Sex (female)	429 (61.4)	143 (60.6)	284 (61.6)	0.07	1	0.795
Ethic group (Han)	650 (93.0)	219 (92.8)	429 (93.1)	0.02	1	0.898
Health insurance	602 (86.1)	200 (84.7)	400 (86.8)	0.69	1	0.406
Residence (city)	575 (82.3)	187 (79.2)	386 (83.7)	1.85	1	0.174
Marital status (married)	512 (73.3)	163 (69.1)	343 (74.4)	2.23	1	0.135
Monthly family income				3.26	2	0.196
Less than 4,000 RMB	235 (33.6)	89 (37.7)	145 (31.5)			
4,000–8,000 RMB	242 (34.6)	80 (33.9)	162 (35.1)			
More than 8,000 RMB	217 (31.0)	65 (27.5)	151 (32.8)			
Unknown	5 (0.7)	2 (0.8)	3 (0.7)			
Education level				2.16	2	0.340
Elementary	45 (6.4)	18 (7.6)	27 (5.8)			
Middle school	318 (45.5)	113 (47.9)	204 (44.2)			
University or higher	336 (48.1)	105 (44.5)	230 (49.9)			
Occupation				5.61	3	0.132
Employed/Student	382 (54.7)	119 (50.4)	262 (56.8)			
Unemployed	130 (18.6)	39 (16.5)	47 (10.2)			
Retired	150 (12.3)	51 (21.6)	98 (21.2)			
Others	37 (5.3)	27 (11.4)	54 (11.7)			
Department				34.05	2	<0.001
Biomedical settings	225 (32.2)	90 (38.1)	134 (29.1)			
Traditional medicine settings	232 (33.2)	44 (18.6)	187 (40.6)			
Psychosomatic medical settings	242 (34.6)	102 (43.2)	140 (30.4)			
Sum score of scales						
SSS-8	8.70 (6.08)	11.97 (6.50)	7.03 (5.09)	10.18	386.05	<0.001
PHQ-15	9.34 (5.40)	12.01 (5.53)	7.96 (4.77)	9.54	415.15	<0.001
SSD12	13.98 (12.23)	23.60 (11.43)	9.06 (9.38)	16.84	400.50	<0.001
PHQ-9	8.48 (6.59)	11.84 (6.76)	6.75 (5.78)	9.85	411.59	<0.001
GAD-7	6.64 (5.89)	9.70 (6.08)	5.09 (5.15)	9.94	408.48	<0.001
Physical component score of SF-12	43.07 (9.20)	39.14 (8.98)	45.14 (8.57)	8.58	691	<0.001
Mental component score of SF-12	41.35 (12.34)	34.86 (11.30)	44.64 (11.54)	10.63	691	<0.001
WHO-DAS 2.0 (SD)	19.08 (7.28)	22.65 (8.52)	17.25 (5.78)	8.75	346.93	<0.001

SSD, somatic symptom disorder; SD, Standard deviation; SSS-8, Somatic Symptom Scale-8; PHQ-15, The Patient Health Questionnaire-15; SSD-12, the Somatic Symptom Disorder–B Criteria Scal; PHQ-9, the Patient Health Questionnaire-9; GAD-7, the General Anxiety Disorder-7; SF-12, the Medical Outcome Study 12-item Short Form Health Survey; WHO DAS 2.0, the World Health Organization Disability Assessment Schedule. *2 of 699 participants had incomplete diagnostic information.

Moderate to high correlations were also found between the SSS-8 sum score and symptoms associated anxiety (SSD-12: $r = 0.61$, $p < 0.001$), general anxiety symptoms (GAD-7: $r = 0.56$, $p < 0.001$), depression symptoms (PHQ-9: $r = 0.67$, $p < 0.001$), health-related quality of life (PCS of SF-12: $r = -0.48$, $p < 0.001$; MCS of SF-12: $r = -0.52$, $p < 0.001$), and health-related disability (WHO DAS 2.0: $r = 0.55$, $p < 0.001$) as expected. The mean (SD) scores of the SSD-12, GAD-7, PHQ-9, PCS of SF-12, MCS of SF-12 and WHO DAS 2.0 were 13.98 (12.23), 6.64 (6.59), 8.48 (6.59), 43.07 (9.20), 41.35 (12.34) and 19.08 (7.28) respectively (Table 1).

Severity categories

The health-related quality of life and general disability of patients were caculated respectively based on the severity of categories of SSS-8 (6). The patients with more severe symptoms showed worse quality of life and disability. One-way analysis of variance followed by multiple comparisons using Scheffe test for the the mental component score of SF-12 and Dunnett's T3 test for the physical component score of SF-12 and the WHO-DAS 2.0 sum score was performed. Significant differences was observed between all pairs, except for the pair of the medium group and the high group (Table 5).

TABLE 2 Frequency distribution of responses (%), mean (SD), and item-total correlations for the items of the SSS-8.

Item	Not at all	A little bit	Some-what	Quite a bit	Very much	Mean (SD)	Cor_{iT}	Cron.α_{id}
1. Stomach or bowel problems	34.5	26.8	19.2	14	5.4	1.29 (1.23)	0.31	0.79
2. Back pain	56.8	22.2	11	6.2	3.9	0.78 (1.11)	0.48	0.76
3. Pain in your arms, legs, or joints	51.2	24.7	13.4	7	3.6	0.87 (1.11)	0.42	0.77
4. Headaches	52.3	23.1	11.6	9	4	0.89 (1.16)	0.55	0.75
5. Chest pain or shortness of breath	51.9	24.6	12.7	7.9	2.9	0.85 (1.10)	0.56	0.75
6. Dizziness	50.5	25	12	8.3	4.1	0.91 (1.15)	0.49	0.76
7. Feeling tired or having low energy	25.8	28.3	20.5	16.3	9.2	1.55 (1.28)	0.64	0.73
8. Trouble sleeping	31.9	22.3	16.5	16.9	12.4	1.56 (1.40)	0.47	0.76

Cor_{iT}, Corrected item-total correlation; Cron. α_{id}, Cronbach α if item deleted; SD, standard deviation.

Discussion

In the sample of our cross-sectional multicenter research, the SSS-8 demonstrated acceptable reliability (Cronbach α = 0.78). The confirmatory factor analysis shows that 3-factor model can be acceptable in our sample. The sum score for the SSS-8 was moderately to highly correlated with the PHQ-15, PHQ-9, GAD-7, SF-12, and WHO-DAS 2.0. This is consistent with previous studies and expectations (17, 25–27). The optimal cutoff score for SSD is 9 with sensitivity 0.674 and specificity 0.681. The severity category criteria set by Gierk (6) were valid in our Chinese language version of the SSS-8.

In psychometrics researches, the sampling range will have an important impact on the results. Previously, there were studies based on general population and study based on patient from psychosomatic department which had different baseline of somatic symptom burden (6, 8, 28). In Gierk's study, the mean score of SSS-8 was 3.23 (3.96). In Matsudaira's study, the mean score of SSS-8 was 4.5 (5.2). In Toussaint's study, the mean score of SSS-8 was 13.3 (5.6). We focused on outpatients from different medical settings of tertiary hospital, which were not only enrolled from psychosomatic clinics and biomedical settings with relatively high prevalence of SSD like gastroenterology department and neurology department, but also from traditional Chinese medicine department. The mean score of the SSS-8 in our study was 8.70 (6.08), which was in between the general population and patients from psychosomatic department.

We did not observe a significant floor or ceiling effect for any of the SSS-8 items, which can be observed in general population investigations and in patients from specific clinics (8, 10, 28).

In this study, the fit indices of all three models were generally worse than previous studies, and can't fully fit the criteria (CFI > 0.95, TLI > 0.95, and RMSEA < 0.08). In Gierk's research, the second-order factor model showed good fit indices (TLI, 0.95; CFI, 0.97; RMSEA, 0.08 [90% CI, 0.08–0.09]) (6). The fit indices of the general factor model in the same reseach were less ideal (TLI, 0.91; CFI, 0.94; RMSEA, 0.11 [90% CI, 0.10–0.12]). In Yang's research, 3-factor model was tested and showed excellent fit indices (TLI, 1.022; CFI, 1.000; RMSEA, 0.00) (9). It is possible that the selection of participants affected the distribution of symptoms. Nearly one third participants were recruited from gastrointestinal department and neurology department who could have specific symptoms like stomach or bowel problems; headache; and dizziness. Besides, the influence of cultural background on symptom distribution cannot be excluded.

The SSS-8 used as screening tools for SSD shows moderate diagnostic accuracy (AUC = 0.729). Similar conclusion was proved by Toussaint et al. (AUC = 0.71) (28). But the cutoff points are different: 12 in Toussaint's study, 9 in this study. As we mentioned above, the difference in the overall level of somatic symptom burden between the two groups of patient may influence the level of the cut-off value.

In Toussaint's study, the sensitivity and specificity (72 and 59%) were also similar with the results of our study. It came to the same conclusion that the efficiency of SSS-8 as a single tool for screening SSD was not very satisfactory, especially in patients with relatively high somatic symptom burden. The screening efficiency of SSS-8 for SSD in the general population remains to be explored in the future.

While the SSS-8 focused on the A-criteria of SSD, there is other scale be used to screen SSD, like SSD-12 which is focused

TABLE 3 Fit indices for three SSS-8 models from confirmatory factor analysis of total patients (n = 699).

	General-factor model	Three-factor model			Second-order factor model			
		Cardiopulmonary symptoms	Pain symptoms	Gastrointestinal and fatigue symptoms	General factor			
					Gastrointestinal	Pain	Cardiopulmonary	Fatigue
Loading								
Item 1	0.38**			0.40**	0.38**			
Item 2	0.61**		0.79**			0.69**		
Item 3	0.57**		0.71**			0.58**		
Item 4	0.73**	0.77**				0.74**		
Item 5	0.70**	0.74**					0.70**	
Item 6	0.70**	0.73**					0.71**	
Item 7	0.76**			0.83**				0.84**
Item 8	0.57**			0.60**				0.62**
Factor correlations								
Cardiopulmonary symptoms		1	0.63	0.85				
Pain symptoms		0.63	1	0.68				
Gastrointestinal and fatigue symptoms		0.85	0.68	1				
Model fits								
χ^2 (df)	245.27 (20)	132.32 (17)			218.86 (19)			
TLI	0.87	0.92			0.88			
CFI	0.91	0.95			0.92			
RMSEA (90% CI)	0.13 (0.11–0.14)	0.10 (0.08–0.12)			0.12 (0.11–0.14)			

SSS-8, Somatic Symptom Scale-8; TLI, Tucker-Lewis index; CFI, comparative fit index; RMSEA, the root mean square error of approximation; CI, confidence interval. **$P < 0.001$.

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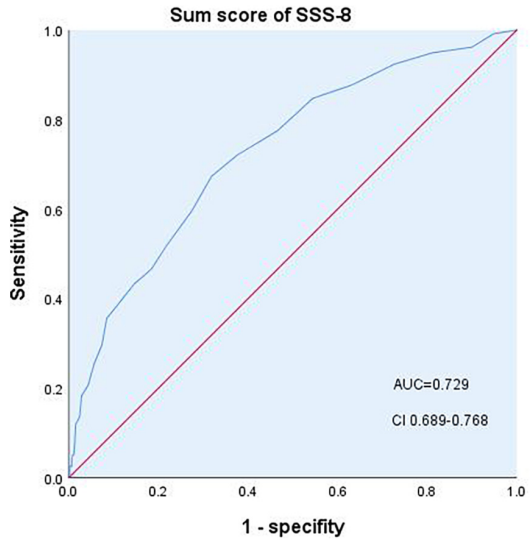

FIGURE 2
Diagnostic performance of the SSS-8 sum score. AUC, area under the curve; CI, confidence interval.

on the B-criteria of SSD. Based on the same sample of patients in this study, the criteria validity was tested with SSD-12. The SSD-12 showed higher criterion validity (AUC = 0.837) for SSD (17). According to our data, scale focus on B-criteria of SSD like SSD-12 may be more powerful for screening SSD than scale focus on A-criteria (SSS-8). In the sample of toussaint's study which was from the outpatient clinic of the department of Psychosomatic Medicine and Psychotherapy of the University Medical Center Hamburg, Germany, 86.8% of the participants fulfilled the A criterion of SSD, whereas a total of 56.2% met the full DSM-5 diagnostic criteria (27). The huge gap between the percentage of patients fulfilling A-criteria and fulfilling the diagnostic criteria of SSD in DSM-5 also indicated the limitation of the screening efficacy of SSS-8 for SSD. The combination of the two kinds of scale for screening is still worth further exploration. When SSS-8 is used alone in clinical work, it is necessary to carefully explain the suggestive significance of the results for SSD diagnosis.

We followed the method and criteria for categorizing severity developed by Gierk (6). In Gierk's study, patients with higher severity visited the hospital more frequently. In present study, patients with higher severity were found to have higher disability and worse quality of life. Due to the lack of statistically significant inter-group differences between the moderate and high severity groups, further studies are needed to determine whether the severity classification should be adjusted in Chinese patients.

Finally, the prevalence of SSD in this study population (33.9%) was relatively high (29). The results of prevalence were influenced by the sampling method. Departments selected in this study were the departments where patients with SSD most frequently visited. This would overestimate the prevalence of somatic symptom disorders among outpatients in tertiary hospitals in China.

There are several limitations of the present study. Limited departments of tertiary hospitals were selected to recruit patients. The symptom clusters of patients in these departments may have certain characteristics and cannot represent the outpatients in all departments of tertiary hospitals, which affects the distribution of symptoms and limit the generalizability of the

TABLE 4 Result of the ROC analysis of the SSS-8 sum score for the SSD diagnosis.

Cutoff	Sensitivity	Specificity	Youden Index	PPV**	NPV**
9*	0.674	0.681	0.355	0.520	0.803
4	0.924	0.273	0.197	0.394	0.875
8	0.720	0.625	0.345	0.496	0.814
12	0.466	0.816	0.282	0.564	0.749
16	0.297	0.926	0.223	0.730	0.745

ROC analysis: Receiver Operating Characteristic analysis; SSS-8, Somatic Symptom Scale-8; SSD, somatic symptom disorder; PPV, positive predictive value; NPV, negative predictive value. *Cut off score with the highest Youden's index value. **PPV and NPV was calculated based on the prevalence from the research data.

TABLE 5 Quality of life and disability according to SSS-8 severity category in tertiary hospital patients in China.

SSS-8 severity category (Range)	Number of patients, *n* (%)	SSD diagnosis, *n* (%)	Physical component score of SF-12 (SD)	Mental component score of SF-12 (SD)	WHO-DAS 2.0 (SD)
No to minimal (0–3)	144 (20.7)	18 (12.4%)	49.39 (7.06)	50.16 (9.95)	14.63 (3.88)
Low (4–7)	210 (30.3)	48 (22.9%)	44.96 (8.01)	44.74 (10.26)	17.02 (4.98)
Medium (8–11)	147 (21.2)	60 (40.5%)	41.06 (8.83)	38.98 (11.48)	19.70 (6.79)
High (12–15)	90 (13.0)	40 (44.0%)	40.57 (7.43)	34.85 (10.76)	21.65 (6.82)
Very high (≥16)	103 (14.8)	70 (66.7%)	35.43 (8.95)	31.20 (10.41)	26.22 (9.25)

SSS-8, Somatic Symptom Scale-8; SSD, somatic symptom disorder; SF-12, the Medical Outcome Study 12-item Short Form Health Survey; WHO DAS 2.0, the World Health Organization Disability Assessment Schedule; SD, Standard deviation.

result of this study. The high refusal rate for participation might also cause bias. Comorbid mental or physical disorders were not addressed in this study. This made it impossible to compare the difference in somatic symptom burden between patients with physical disorders and patients with SSD. However, because the diagnosis criteria of SSD in DSM-5 does not require the exclusion of physical diseases, it had little impact on the evaluation of diagnostic validity. The order of the questionnaires were fixed. The SSS-8 ranked second to last questionnaires (SF-12). The effect of sequence can't be avoid. It should be improved in the future by vary the orders of questionnaires which will be more convenient when using online way.

In addition, it is of great significance to test the psychometrics of Chinese SSS-8 in the general population of China for exploring the influence of cultural background on somatic symptoms.

In conclusion, the Chinese language version of the SSS-8 demonstrated satisfactory reliability and validity among outpatients attending tertiary hospitals. Our results indicate that it can be used as a screening tool to assess for the burden of somatic symptoms, not only in the general population but also with hospital patients.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by University of Freiburg (no. 494/17) and Peking Union Medical College Hospital (no. S-K276). The patients/participants provided their written informed consent to participate in this study.

Author contributions

TL was the project leader and responsible for the organization of data collection, analysis and drafted the manuscript. JW, KF, and AT contributed to the study conception and design. LZ, YZ, HC, HW, XM, WLu, JR, and WLi participated in its design and coordination and helped to draft the manuscript. RL participated in the study design and performed the statistical analysis. All authors have read and approved the final manuscript.

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Conflict of interest

Author JR was employed by General Hospital of Jincheng Anthracite Coal Mining Group Co. Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Wenhao Jiang,
Southeast University, China

REVIEWED BY
Ralf Ilchef,
Royal North Shore Hospital, Australia
Paul Desan,
Yale University, United States

*CORRESPONDENCE
Luigi Zerbinati
luigi.zerbinati@unife.it

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Changes of consultation-liaison psychiatry practice in Italian general hospitals: A comparative 20-year multicenter study

Luigi Zerbinati[1,2]*, Laura Palagini[1,2], Matteo Balestrieri[3], Martino Belvederi Murri[1,2], Rosangela Caruso[1,2], Armando D'Agostino[4,5], Maria Ferrara[1,2], Silvia Ferrari[6,7], Antonino Minervino[8], Paolo Milia[8], Maria Giulia Nanni[2,10], Stefano Pini[10], Pierluigi Politi[11], Matteo Porcellana[12], Matteo Rocchetti[11], Ines Taddei[13], Tommaso Toffanin[1,2], Luigi Grassi[1,2] and Italian Society of Consultation-Liaison Psychiatry

[1]Department of Neuroscience and Rehabilitation, Institute of Psychiatry, University of Ferrara, Ferrara, Italy, [2]University Hospital Psychiatry Unit, Integrated Department of Mental Health and Addictive Behavior, University S. Anna Hospital and Health Trust, Ferrara, Italy, [3]Psychiatric Clinic, Department of Medicine, University of Udine, Udine, Italy, [4]Department of Health Sciences, Università Degli Studi di Milano, Milano, Italy, [5]Department of Mental Health, ASST Santi Paolo e Carlo, Milan, Italy, [6]Section of Psychiatry, Department of Diagnostic-Clinical Medicine and Public Health, University of Modena and Reggio Emilia, Modena, Italy, [7]Dipartimento ad Attività Integrata di Salute Mentale e Dipendenze Patologiche, USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy, [8]Italian Society of Psychosomatic Medicine, Parma, Italy, [9]U.O. di Psichiatria, Dipartimento delle Fragilità, Azienda Ospedaliero-Universitaria, Sassari, Italy, [10]Department of Clinical and Experimental Medicine, Psychiatric Clinic, University of Pisa, Pisa, Italy, [11]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, [12]Department of Mental Health and Addiction Services, Niguarda Hospital, Milan, Italy, [13]Department of Psychiatric Sciences and Psychological Medicine, University La Sapienza, 3rd Psychiatric Clinic, Rome, Italy

Introduction: Conducted under the auspices of the Italian Society of Consultation Liaison Psychiatry (SIPC) the aim of this study was to describe the characteristics of Consultation Liaison Psychiatry (CLP) activity in Italy (SIPC-2—2018) over the past 20 years by comparing with data from the first Italian nation-wide study (SIPC-1—1998).

Methods: We collected data on CLP visits of 3,943 patients from 10 Italian hospitals over a period of 1 year. Data were compared with those from the SIPC-1 1998 study (4,183 participants). Patients were assessed with the same *ad hoc* 60-item Patient Registration Form recording information from five different areas: Sociodemographic, hospitalization-related, consultation-related, interventions and outcome.

Results: Compared with participants from the previous study, SIPC-2-2018 participants were significantly older (d = 0.54) and hospitalized for a longer duration (d = 0.20). The current study detected an increase in the proportion of referrals from surgical wards and for individuals affected by onco-hematologic diseases. Depressive disorders still represented the

most frequent psychiatric diagnosis, followed by adjustment and stress disorders and delirium/dementia. Also, CLP psychiatrists prescribed more often antidepressants (Φ = 0.13), antipsychotics (Φ = 0.09), mood stabilizers (Φ = 0.24), and less often benzodiazepines (Φ = 0.07).

Conclusion: CLP workload has increased considerably in the past 20 years in Italy, with changes in patient demographic and clinical characteristics. A trend toward increase in medication-based patient management was observed. These findings suggest that the psychiatric needs of patients admitted to the general hospital are more frequently addressed by referring physicians, although Italian CLP services still deserve better organization and autonomy.

KEYWORDS

liaison psychiatry, hospital psychiatry, medical psychiatry, Italy, Consultation-Liaison (C-L) psychiatry

Introduction

Consultation-Liaison Psychiatry (CLP), as the subspecialty of psychiatry liaising with other branches of medicine and stemming from the realization that some form of psychiatric comorbidity is evident in more than one third of patients admitted to the general hospital (GH) (1, 2), have grown considerably in many countries in the past decades (3). Appropriate CLP activity has positive effects in terms of length of hospital stay, health-related costs, and treatment adherence (4, 5).

This reflected a general interest in the CLP subspecialty at a European level, as evident from the involvement of international groups such as the European Consultation-Liaison Psychiatry Working Group (ECLW) (6) that led to the creation of the European Association of Consultation-Liaison Psychiatry and Psychosomatics (EACLPP) (7), further transformed into the European Association of Psychosomatic Medicine (EAPM) (8).

In Italy, the quest for efficient CLP models started after mental health legislation reform in 1978 with the development of CLP services within the GHs and CL activity only made by psychiatrists from psychiatric wards and some isolated University hospital experiences. More articulated CL services began in the 1990s in the form of integrated care programs and also highly specialized clinics. Pioneer examples were the services of Modena, Pavia and Udine for transplantation psychiatry (9–12), the psycho-oncology service of Ferrara and the psycho-gastroenterology service of Bari (13–15). In order to implement CLP in the country, a special CLP working group (CLP-WG.IT) within the Italian Society of Consultation-Liaison Psychiatry[1] was created with the aim to promote a nationwide research project on a 1-year period to better analyze the CLP situation in Italy (16). That was the first and the only multicenter investigation in Italy. Ever since, Italian CLP has significantly changed, partly because of the development of new services as clinical CLP sub-specialization (17), but also for the change in the health systems, cutting of resources and "rationalization" of the way hospital care and needs of medically ill patients are delivered and managed for, with the risk to jump back to the past rather than improving the level of CLP.

Following the initiative of other European countries (18, 19), the need for an up-to-date examination of CLP activity in Italy was felt to be a priority (17). Therefore, the aim of this study was to evaluate the activity of CLP in Italy, highlighting the major changes happened in a 20-year time-span since the cited first CLP Italian study.

Methods

The study aimed to compare data on current CLP activity in Italian GHs with those collected from the cited previous study by the CLP-WG-IT (16). To reach this aim, we used data from the nationwide CLP study conducted in 1998, referred to as Study 1, and the current CLP study conducted in 2018, referred to as Study 2.

Since we analyzed the data by using a form that is routinely employed in the CLP service after Study 1, ethical approval was operationalized by having each participant signing the information consent in agreement with the ethical regulations of the Committee for the Protection of Persons as adopted by the Local Health Trust and Hospital agencies of the participating centers.

1 www.sipc.eu

Study 1

The study was designed as a nationwide cross-sectional investigation involving 12 provinces (6 in the north of Italy, 3 in central Italy and 3 in southern Italy (**Supplementary Figure 1**), with a total of 17 GHs (19,804 beds overall) and 17 corresponding CLP services. The historical sample comprised 4,182 medically ill patients admitted to GH wards, recruited during a period of 12 consecutive months (1997–1998) for whom a psychiatric consultation was requested by hospital medical-surgical wards. A standardized Patient Registration Form (PRF-SF), previously used in CLP studies was used (16, 20, 21) to gather the following information: (1) Patient's sociodemographic data, previous psychiatric history, use of psychiatric services and medications; (2) data related to the index hospitalization such as its length, time to referral (Lagtime1), the time between referral and consultation (Lagtime 2), type of ward and somatic diagnosis; (3) data related to the consultation (e.g., reason for referral, psychiatric diagnosis); (4) data related to the CLP intervention, such as psychopharmacologic prescriptions and transfer to other medical or psychiatric wards; (5) data related to patient outcomes, such as post-discharge plans, including the referral to outpatient psychiatric care. Psychiatric and somatic diagnoses were recorded using the WHO ICD-10 system.

Study 2

The new CLP study, also run on a nationwide level, included 9 provinces, of whom 6 located in the Northern Italy, 2 in Central Italy, and 1 in Southern Italy (**Supplementary Figure 1**). A total of 10 GHs (8,338 beds in all) with a corresponding number of CLP Services were involved. From April 2018 to November 2019, CLP data were collected by using the same PRF-SF used in Study 1. Psychiatric and somatic diagnoses were also collected using the WHO ICD-10 system.

Statistical analysis

Descriptive statistics were conducted using bivariate analysis. Differences in estimates between the samples were explored using *t*-test and Chi-square. To evaluate the magnitude of effect sizes we computed Cohen's d, Kramer's V and Phi (Φ) coefficient as measures of statistical robustness, while percentage difference (PD) and mean difference (MD) were calculated as measures of absolute differences between the variables of interest. Statistical analyses were performed using SPSS (Statistical Package for the Social Science)—20 package. To aid visual comparisons, appropriate figures and graphs were created using *ggplot* R package.

Results

Sociodemographic characteristics

In Study 2 data pertaining to 3,943 patients were collected and were compared to the sample of 4,183 patients of Study 1. The distribution of the consultations at both times according to the region of provenance are shown in **Supplementary Figure 1**; the two populations significantly differed according to the region of origin ($\tilde{O}^2 = 2791.75$, df = 10, $p < 0.001$, V = 0.58).

Socio-demographic characteristics are shown in **Supplementary Table 1**. Compared with Study 1, patients in the present study were more frequently men (PD = 7.9%, Φ = 0.07) and older (MD = 9.98, Cohen's d = −0.54). Data regarding age according to sex and the distribution of age according to psychiatric and somatic diagnoses are displayed in **Supplementary Figures 2–4**. Overall, Study 2 patients were less likely to be married (PD = 10.1%, Φ = 0.12) and more likely to be retired (PD = 6.4%, Φ = 0.06), unemployed (PD = 2.2%, Φ = 0.03) and living alone (PD = 4.6%, Φ = 0.06). Data regarding education level were not comparable between the two groups.

Clinical characteristics

Data pertaining to somatic diagnoses regarding referred patients are presented in **Figure 1** and in **Supplementary Table 2**. Patients in Study 2 were more likely to suffer from cancer (PD = 12.8%, Φ = 0.20), hematological (PD = 2.3%, Φ = 0.07) or respiratory (PD = 3.9%, Φ = 0.08) diseases, and less likely to suffer from endocrine/metabolic disorders (PD = 4.4%, Φ = 0.09), dermatological conditions (PD = 2.5%, Φ = 0.08) or to show unspecified symptoms (PD = 5.9%, Φ = 0.09), including the effects of poisoning or intoxications (PD = 3.6%, Φ = 0.09). **Figure 2** shows the distribution of referrals across different wards (see also **Supplementary Table 3**).

Psychiatric consultation data

When comparing reasons for psychiatric referrals in Study 1 with Study 2, statistically significant changes were evident for the following reasons: Study 2 patients were more likely to be referred to psychiatric assessment for pharmacologic treatment (PD = 9.2%, Φ = 0.21), suicide risk (PD = 0.5%, Φ = 0.02), problems in patient's management or compliance (PD = 2.1%, Φ = 0.05) or the presence of active psychopathological symptoms (PD = 23.1%, Φ = 0.20); they were also less likely to be referred for pregnancy issues (PD = 1.7%, Φ = 0.07), medically unexplained symptoms (MUS, PD = 6.6%, Φ = 0.13) and alcohol or substance abuse (PD = 1.6%, Φ = 0.04) (**Table 1** and **Supplementary Figure 5**). Psychiatric referrals because of

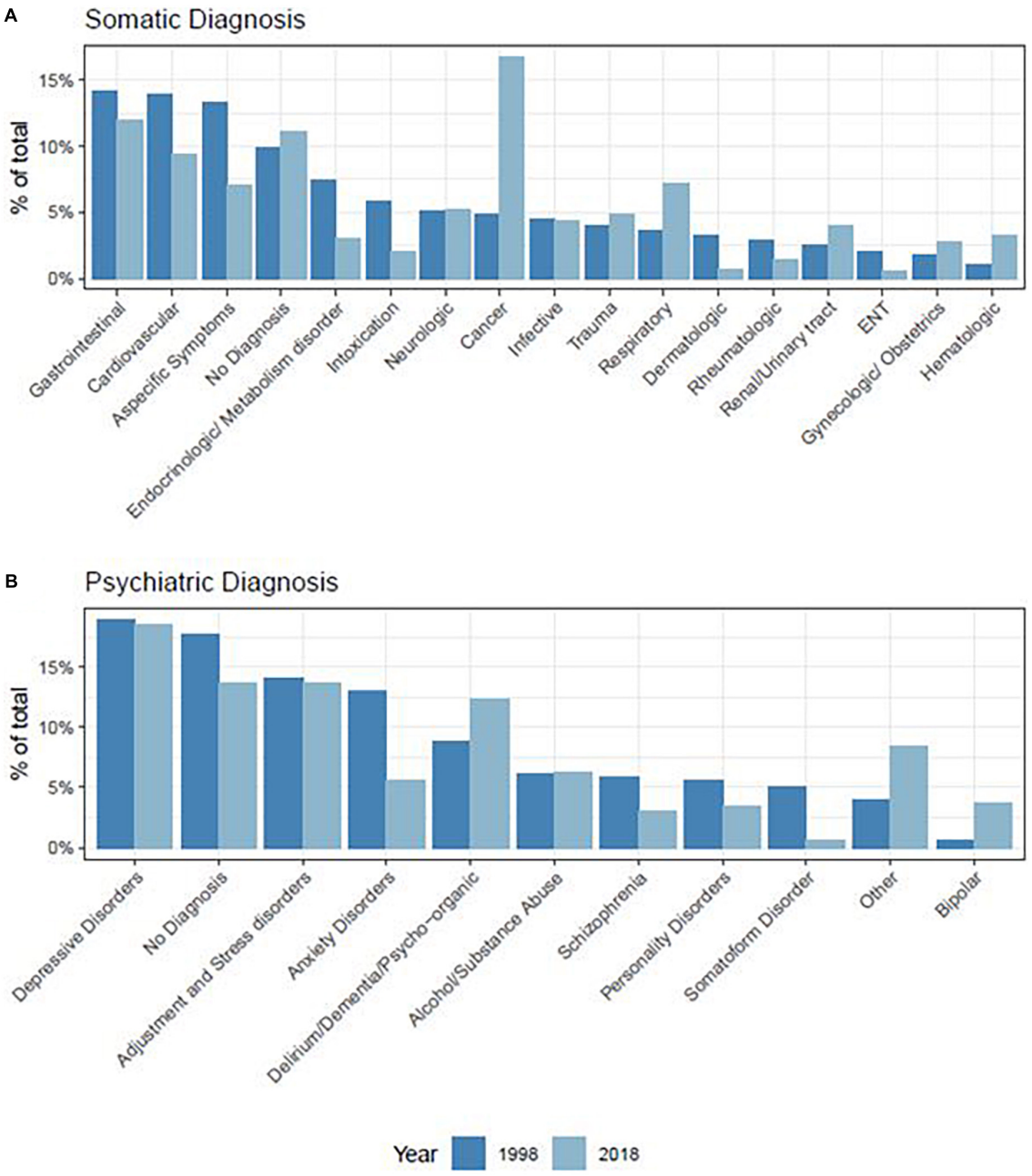

FIGURE 1
Percentage of somatic **(A)** and psychiatric **(B)** diagnoses of referred patients.

suicide attempt did not significantly differ between Study 1 and Study 2 ($p > 0.05$).

Patients were informed more often about psychiatric consultation referral in Study 2 with respect to Study 1 (PD = 12.4%, $\Phi = 0.14$).

Both groups showed comparable rates of psychiatric care in the 5 years preceding the consultation (PD = 1.4%, $p > 0.05$, $\Phi = 0.00$), although the pattern of mental health care in Study 2 patients was more prevalent in terms of psychiatric care at mental health outpatient services (PD = 5.4%, $\Phi = 0.07$) and psychiatric private practice (PD = 7.5%, $\Phi = 0.12$), and less prevalent at other services (PD = 2%, $\Phi = 0.03$). Also, Study 2 patients reported a lower number of hospitalizations in psychiatric units in the previous 5 years (PD = 3.5%, $\Phi = 0.07$) (**Supplementary Table 4**).

Time to CLP referral (Lagtime 1) was significantly higher in Study 2 (MD = 2.96, Cohen's $d = -0.23$), while the time from referral to consultation (Lagtime 2) was significantly lower than

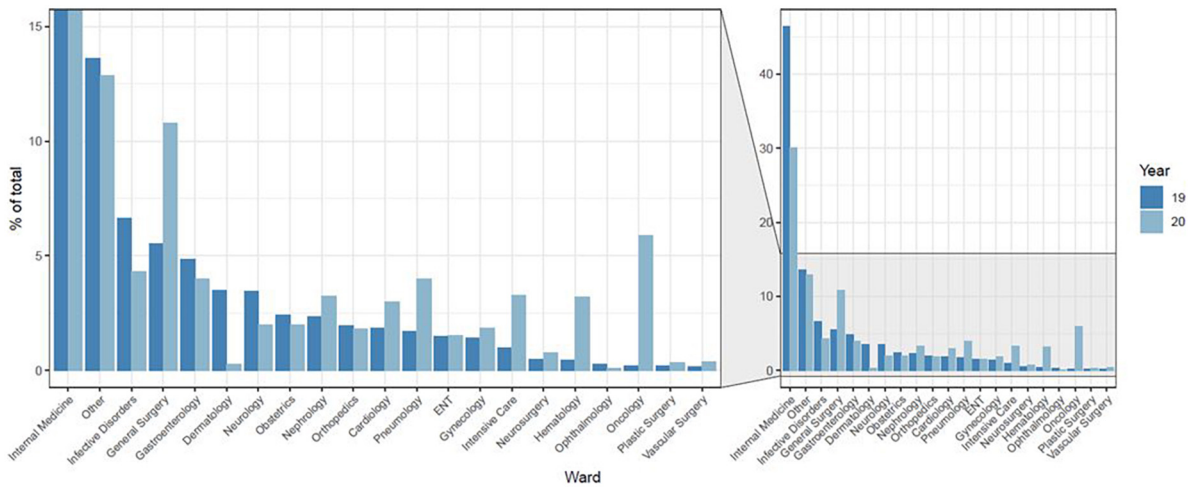

FIGURE 2
Distribution of referrals according to the ward.

in the Study 1 (MD = 0.57, Cohen's d = 0.27). Study 2 patients received slightly fewer follow-up visits during the hospital stay (MD = 0.11, Cohen's d = −0.11), with shorter consultation time (MD = 21.4, Cohen's d = 0.43) and longer hospitalization length (MD = 4.67, Cohen's d = −0.20) (Supplementary Table 5).

Supplementary Figure 6 shows the distribution of hospitalization length according to age, while the distribution of Hospitalization Length, Lagtime 1 and Lagtime 2 according to the psychiatric and somatic diagnosis are reported on the Supplementary Figures 7–12 and in Supplementary Tables 6–11.

Patients in Study 2 were more likely to be already treated with psychopharmacologic medications at the time of consultation than in Study 1 (PD = 17.7%, Φ = 0.17), especially with antidepressants (PD = 16.8%, Φ = 0.20), and mood stabilizers (PD = 8.9%, Φ = 0.19), but also with antipsychotics (PD = 8%, Φ = 0.11) and benzodiazepines (PD = 4.6%, Φ = 0.04) (Table 2 and Supplementary Figure 13A).

Regarding psychiatric diagnosis, it was more frequently made in Study 2 (PD = 2.5%, Φ = 0.03) and consisted of more frequent diagnosis of depressive disorder (PD = 1.8%, Φ = 0.02), bipolar disorder (PD = 3.5%, Φ = 0.11), behavioral syndrome due to delirium or dementia (PD = 4.9%, Φ = 0.07), and other disorders (PD = 5.4%, Φ = 0.11). Study 2 patients received less often a diagnosis of personality disorder (PD = 1.7%, Φ = 0.04), anxiety disorder (PD = 6.7%, Φ = 0.11), schizophrenia (PD = 2.5%, Φ = 0.05) or somatoform disorders (PD = 4.2%, Φ = 0.12), while adjustment disorder and substance abuse disorder did not significantly differ (all $p > 0.05$) between the 2 groups (Figure 1B and Supplementary Table 12).

TABLE 1 Main reason for psychiatric referral.

Reason for referral (%)	1998	2018	Difference
Suicide attempt	4.9%	4.9%	Φ = 0.00, PD = 0%
Risk of suicide	1.0%	1.5%	*, Φ = 0.02, PD = 0.5%
MUS	9.3%	2.7%	**, Φ = 0.13, PD = 6.6%
Psychiatric evaluation	27.9%	0.6%	**, Φ = 0.38, PD = 27.3%
Patient management and compliance	2.3%	4.4%	**, Φ = 0.05, PD = −2.1%
Psychiatric symptoms	36.1%	59.2%	**, Φ = 0.23, PD = 23.1%
Psychopharmacologic consultation	0.5%	9.7%	**, Φ = 0.21, PD = 9.2%
Positive psychiatric history	3.8%	3.7%	Φ = 0.01, PD = 0.1%
Alcohol or substance problems	4.7%	3.1%	**, Φ = 0.04, PD = 1.6%
Abortion evaluation	2.4%	0.7%	**, Φ = 0.07, PD = 1.7%
Patient's request	1.4%	1.0%	Φ = 0.01, PD = 0.4%
Other	5.2%	7.7%	**, Φ = 0.05, PD = 2.5%
Not specified	0.3%	0.6%	*, Φ = 0.02, PD = 0.3%
Patient informed about psychiatric referral	71.1%	83.5%	**, Φ = 0.14, PD = 12.4%

*$p < 0.05$; **$p < 0.01$.
PD, Percentage difference.

Intervention

Patients in Study 2 were more likely to be prescribed with psychopharmacological therapy (PD = 11.4%, Φ = 0.12) specifically, antidepressants (PD = 12.9%, Φ = 0.13), antipsychotics (PD = 8.2%, Φ = 0.09) and mood stabilizers (PD = 11.6%, Φ = 0.24) than Study 1, while benzodiazepines were less frequently prescribed (PD = 7.2%, Φ = 0.07) (Table 2 and Supplementary Figure 13B).

TABLE 2 Psychopharmacologic and liaison data.

	1998	2018	Difference
Psychopharmacologic treatment at the time of consultation	40.6%	58.3%	**, Φ = 0.17, PD = 17.7%
Patients on antidepressant treatment	12.4%	29.2%	**, Φ = 0.20, PD = 16.8%
Patients on benzodiazepines treatment	33.4%	38.0%	**, Φ = 0.04, PD = 4.6
Patients on antipsychotic treatment	11.2%	19.2%	**, Φ = 0.11, PD = 8%
Patients on mood stabilizer treatment	1.2%	10.1%	**, Φ = 0.19, PD = 8.9%
Psychopharmacologic prescription during the consultation	64.5%	75.9%	**, Φ = 0.12, PD = 11.4%
Antidepressant	27.2%	40.1%	**, Φ = 0.13, PD = 12.9%
Benzodiazepine	43.2%	36.0%	**, Φ = 0.07, PD = 7.2%
Antipsychotic	22.3%	30.5%	**, Φ = 0.09, PD = 8.2%
Mood stabilizer	0.4%	12.0%	**, Φ = 0.24, PD = 11.6%
Psychopharmacologic treatment at discharge	52.4%	46.6%	**, Φ = 0.05, PD = 5.8%
Antidepressant	27.9%	37.1%	**, Φ = 0.09, PD = 9.2%
Benzodiazepine	42.1%	29.8%	**, Φ = 0.12, PD = 12.3%
Antipsychotic	20.4%	24.9%	**, Φ = 0.05, PD = 4.5%
Mood stabilizer	0.5%	11.2%	**, Φ = 0.23, PD = 10.7%
Program at discharge/liaison intervention			
None	34.9%	38.6%	**, Φ = 0.03, PD = 3.7%
Social worker referral	3.2%	14.1%	**, Φ = 019, PD = 10.9%
GP referral	13.1%	0.0%	**, Φ = 0.25, PD = 13.1%
Psychiatric outpatient service	26.9%	20.3%	**, Φ = 0.07, PD = 6.6%
Consultation liaison service referral	13.2%	5.6%	**, Φ = 0.12, PD = 7.6%
Private practice psychiatrist	8.2%	14.5%	**, Φ = 0.07, PD = 6.3%
Other services (e.g., addiction clinics, child psychiatry service)	6.6%	11.9%	**, Φ = 0.09, PD = 5.3%
Psychiatric inpatient ward	2.9%	13.3%	Φ = 0.01, PD = 10.4%
Other medical ward	2.7%	1.7%	**, Φ = 0.03, PD = 1%

**$p < 0.01$.
PD, Percentage difference.

Outcome

At discharge, Study 2 patients were less likely to receive psychopharmacologic treatment than Study 1 (PD = 5.8%, Φ = 0.05); overall in Study 2 antidepressants (PD = 9.2%, Φ = 0.09), antipsychotics (PD = 4.5%, Φ = 0.05), and mood stabilizers (PD = 10.7%, Φ = 0.23) were prescribed more frequently while the prescription of benzodiazepines was lower (PD = 12.3%, Φ = 0.12) (Table 2 and Supplementary Figure 13C).

Compared to Study 1, a therapeutic program at discharge was offered slightly less frequently in Study 2 (PD = 3.7%, Φ = 0.03), with patients being referred more often to social workers (PD = 10.9%, Φ = 019) and other specialized services (e.g., addiction clinics, child and adolescent psychiatric services; PD = 5.3%, Φ = 0.09) and less frequently to their general practitioners (PD = 13.1%, Φ = 0.25), psychiatric outpatient services (PD = 6.6%, Φ = 0.07), consultation-liaison services (PD = 7.6%, Φ = 0.12) and private practitioners (PD = 6.3%, Φ = 0.07). Psychiatric hospitalization rates did not differ between the two groups ($p > 0.05$), while in Study 2 patients were less frequently recommended to be transferred to other medical wards (PD = 1%, Φ = 0.03) (Table 2).

Discussion

We report the results of a nationwide multicenter study describing CLP activity in Italy on almost four thousand patients, and comparing them to results from a previous CLP study adopting the same methodology of data collection carried out 20 years ago.

A first general result of the study is the increase of the ages of nearly a decade of the patients referred to CLP between the two studies. This finding seems to be in line with the general aging of the Italian population over the last 20 years and the increased life expectancy in Italy (22), as indicated in previous studies involving our centers (23, 24). This highlights the phenomenon of the general aging of the hospitalized population (25, 26), and the need of specific psychogeriatric training (27), since it has been estimated that up to 60% of old aged patients will develop a mental disorder during their hospital admission (28). Accordingly, this change had implications in the age of presentation of specific diagnosis and sub-populations of the sample (e.g., older patients with alcohol/substance abuse or personality disorders in Study 2), even though other differences can be attributed to specific epidemiological changes (e.g., the age of presentation of patients referred for infectious disorder in Study 2, while Study 1 coincided with the peak of HIV pandemic during the 90's, with younger patients referred to CLP).

A second finding regards psychiatric referrals. Compared Study 1, patients in Study 2 were referred more often from surgical wards. A possible explanation might include a better understanding and more education about the importance of psychiatric variables by surgeon colleagues, as highlighted by increasing literature in the surgical field (29–33). Alternatively, the older population in Study 2 might have resulted in an increased number of referrals for behavioral problems, since about 80% of elderly patients undergoing surgery is expected to develop delirium (34). The latter explanation is in line with the

modestly increased number of referrals from intensive care units and the higher number of referrals due to delirium, dementia or neurobehavioral syndromes, which, according to a recent nationwide Italian study, have been found to be present in 56.2% of the GH patients older than 65 (35).

Study 2 patients were also more likely to be referred from hematology-oncology settings. The almost quadrupled number of referrals for patients affected by these diseases reflects the important work done in the last two decades in the field psycho-oncology, with data showing a prevalence of psychiatric disorders in cancer care of 25–32% (36, 37). This is a major change of CLP activity in cancer setting that was shown to be lacking in Italy (38), while it seems to be a partially solved problem in more recent years (39).

A striking result is the lower rate of referrals for patients reporting MUS as the main reason for psychiatric evaluation and the low prevalence of somatoform disorders diagnosis in Study 2. There are different possible explanations for this finding. The first might be related to improvement in diagnostic tests (resulting in less "medically unexplained" symptoms, such as functional syndromes like fibromyalgia, functional gastrointestinal disorders and functional neurologic disorders), better understanding of these disorders, and improved education and management skills by non-psychiatrists, including rheumatologists, gastroenterologists and neurologists who have learned to treat common comorbidities like depression and anxiety (40). We cannot confirm this hypothesis though, since we do not have specific data in Italy. Another possible interpretation could be the older age of the sample. There is in fact evidence that MUS and somatic symptom disorders prevalence declines after the age of 65 years (41) and those older patients cope better with MUS than younger individuals (42), resulting in possibly less frequent referrals. Furthermore, since MUS in old-aged patients have been associated with frailty, the prevalence of these symptoms can be even lower because of misdiagnosis (43, 44). There is also the possibility that, given the complexity of the area, still with conflicts in the name and characteristics of the disorders and treatment, referring physicians may have less interest in requesting CLP consultation. This might be seen by referring physicians as only confirming the diagnosis but without concrete prospects of treatment in the usual organization of mental health service.

Regarding psychiatric diagnosis: the rates of adjustment and stress disorders, depressive disorders, and alcohol and substance abuse were comparable across the two studies. Depressive disorders still represent the most frequent psychiatric diagnoses, reflecting their high prevalence in the GH (45) and a general improvement in their recognition by non-psychiatrists (46). Similarly, the rates of adjustment and stress-related disorders, are comparable to other studies (47–50). The relatively high prevalence of alcohol and substance abuse disorders as reported in both the GH (51–54), and in CLP settings (55–57), highlight the fact that, at least in Italy, consultations for addictive disorders are still probably carried out by specific programs other than CL services. Anxiety disorders, compared with Study 1, were found to be significantly less prevalent, although with a similar rate found in other studies carried out in other countries (50, 58). This is consistent with a significant increase of antidepressants prescriptions in Italy during the last decades (59), as shown by the higher rates of patients being already in antidepressant treatment at the time of consultation. Patients may have already been prescribed antidepressants as outpatients, or by non-psychiatrists in the GH (60). Another possible explanation for this result again takes into account the older age of the population. It has been suggested that even though highly prevalent in old patients with chronic diseases (61), anxiety disorders might remain undetected in this particular population (62, 63). Bipolar disorders diagnoses showed a significant increase in prevalence at Study 2. This finding both contradicts (64, 65) and confirms (66) previous literature. Some hypotheses include the above-mentioned increase in antidepressant medications, with possible manic switching, and an improvement in the detection and diagnosis of bipolar disorders (67). Since it has been suggested that bipolar disorder can often be misdiagnosed as schizophrenia (68), this hypothesis might also explain the significantly decreased prevalence of schizophrenia and other psychotic disorders diagnoses in Study 2.

Further findings regard the length of stay, Lagtime1 and Lagtime2. Interestingly, while Hospitalization Length and Lagtime1 significantly increased in Study 2, Lagtime2 decreased. This last result probably indicates an overall improvement in the effectiveness of Italian CLP services, with psychiatric consultants able to deliver quicker visits. Increased Lagtime1 and hospitalization length can be interpreted in the light of the aging of the sample, since both age and Lagtime1 have been found to be predictors of Hospitalization Length (69–71) and, on the other hand, old age have been associated with increased Lagtime1 (69, 72). Patients displaying MUS may also require a higher number of investigations thus delaying the request of a psychiatric consultation (73). It should also be said that a still predominant tendency to consider CLP as a last resource, after all the possible medical investigations, can be found, with the need for implementation of proactive or integrated psychiatric care based services (3, 74).

Considering drug prescriptions, at the time of consultation patients were more likely to be already receiving psychoactive drugs, particularly antidepressants, mood stabilizers and benzodiazepines, compared with the previous study wave. CLP consultations resulted in an increase of antidepressants, antipsychotics and mood stabilizers prescription compared with 1998, and a relative decrease of benzodiazepines prescription. This pattern was relatively maintained at discharge, with a further decrease of benzodiazepines prescription in line with recent guidelines (75). With

regards to mood stabilizers, the increase in prescription could reflect a change in their use for analgesic purposes as gradually emerged in medical literature (76–78). Overall, these findings mirror the aforementioned change in antidepressants prescription in the last decades, the increased prevalence of bipolar disorders and confirm the frequent use of benzodiazepines in medical settings both for sleep control as well as a means for rapid tranquillization (79). These data underline the need to further train non-specialists in psychiatry, within and outside the hospital, about the risks of benzodiazepines use in medically ill patients, especially in the elderly (80, 81), as well as the need to further develop CLP services with general practitioners to monitor pharmacotherapy (82).

Finally, interesting differences were shown in the type of consultation and liaison interventions. While in Study 2 there was only a very small decrease in liaison intervention at discharge, compared to Study 1 there were significant changes in referral patterns, with comparable rates of psychiatric inpatient admissions. A first issue comes from the increased referral to social work services, which could be explained by a grown awareness of the importance of the social component of the problems presented by patients, especially if affected by somatic diseases (83–85) and in times of recession and socio-economical crisis (86).

Regarding the post-discharge plan, patients in Study 1 were more often referred to specialized services (e.g., addiction clinics, child/adolescence psychiatric services, dementia clinics, eating disorders clinics, psycho-oncology services). This seems to support the implementation over the last 20 years of more special services within community psychiatry and an improvement of the organization of mental health services in Italy.

The study is strengthened by adequate sampling and nationwide participation. There are, however, limitations which should be mentioned. First, although there is a similar characterization and representation of the CLP services included in both Study 1 and 2, there are also differences in regional participation, such as a higher presence of Northern Italian centers in Study 2. Future studies should include a larger sample of centers and extend the research to a larger representation of GHs, including CLP activity in small community hospitals, which are under-represented in CLP studies in several countries (17). For these reasons, the generalizability of our results is not possible.

In conclusion, this study provides information about the current status of CLP in Italy. The data presented here confirm a predominant consultation-based approach to the psychiatric care of the medically ill patient in Italian GHs. The changes over time discussed in this article may support a more proactive approach in the provision of CLP services, and more consistent to relevant changes in the epidemiology of medical-psychiatric comorbidity; also, we hope they could guide future research on the topic and pave the way for structural changes in the delivery of care for the patient affected by psychiatric and somatic co-morbidities.

Data availability statement

The datasets presented in this article are not readily available because of its proprietary nature. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee for the Protection of Persons as adopted by the University Hospital and Hospital Local Health Trust of the participating centers. The patients/participants provided their written informed consent to participate in this study.

Italian Society of Consultation-Liaison Psychiatry

The following persons participated as local coordinators of the Italian C-L Psychiatry working Group:

Jessica Bellucci[1,2], Emilio Bergamelli[3], Victor Attilio Campagna[3], Melissa Cherubini[1,2], Federica Folesani[4,5], Marta Gancitano[4,5], Francesca Giannetti[6], Gianluca Giovanna[7], Benedetta Gullotta[4,5], Lucia Massa[8] and Giulia Montardi[1,2]

[1]Section of Psychiatry, Department of Diagnostic-Clinical Medicine and Public Health, University of Modena and Reggio Emilia, Modena, Italy, [2]Dipartimento ad Attività Integrata di Salute Mentale e Dipendenze Patologiche, USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy, [3]Department of Health Sciences, Università Degli Studi di Milano, Milano, Italy; Department of Mental Health, ASST Santi Paolo e Carlo, Milan, Italy, [4]Department of Neuroscience and Rehabilitation, Institute of Psychiatry, University of Ferrara, Ferrara, Italy, [5]University Hospital Psychiatry Unit, Integrated Department of Mental Health and Addictive Behavior, University S. Anna Hospital and Health Trust, Ferrara, Italy, [6]Psychiatric Operative Unit n.25 of Casalmaggiore (Cremona), "Oglio Po" General Hospital, Cremona, Italy, [7]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, [8]Department of Clinical and Experimental Medicine, Psychiatric Clinic, University of Pisa, Pisa, Italy.

Author contributions

LG, LZ, MBe, and SF conceived the research. LZ, RC, MN, MR, MBa, AD'A, AM, MP, IT, LP, SP, PM, SF, and TT contributed to data collection. LZ carried out the statistical analysis and wrote the first draft. All authors contributed to the manuscript and approved the final version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.959399/full#supplementary-material

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EDITED BY
Wenhao Jiang,
Southeast University, China

REVIEWED BY
Francesco Monaco,
Azienda Sanitaria Locale Salerno, Italy
Geetha Desai,
National Institute of Mental Health and Neurosciences (NIMHANS), India

*CORRESPONDENCE
Jing Wei
weijing@pumch.cn

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Detecting DSM-5 somatic symptom disorder in general hospitals in China: B-criteria instrument has better accuracy—A secondary analysis

Jinya Cao[1], Jing Wei[1]*, Kurt Fritzsche[2], Anne Christin Toussaint[3], Tao Li[1], Lan Zhang[4], Yaoyin Zhang[5], Hua Chen[6], Heng Wu[7], Xiquan Ma[8], Wentian Li[9], Jie Ren[10], Wei Lu[11] and Rainer Leonhart[12]

[1]Department of Psychological Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [2]Center for Mental Health, Department of Psychosomatic Medicine and Psychotherapy, Faculty of Medicine, Medical Centre - University of Freiburg, Freiburg im Breisgau, Germany, [3]Department of Psychosomatic Medicine and Psychotherapy, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany, [4]Mental Health Centre, West China Hospital, Sichuan University, Chengdu, China, [5]Department of Psychosomatic Medicine, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China, [6]Department of Psychological Medicine, Zhong Shan Hospital, Fudan University, Shanghai, China, [7]Department of Psychosomatic Medicine, Tongji Hospital, School of Medicine, Tongji University, Shanghai, China, [8]Department of Psychosomatic Medicine, Dongfang Hospital, School of Medicine, Tongji University, Shanghai, China, [9]Department of Clinic Psychology, Wuhan Mental Health Centre, Wuhan, China, [10]Department of Rehabilitation, General Hospital of Jincheng Anthracite Coal Mining Group Co., Ltd., Jincheng, China, [11]Department of Psychosomatic Medicine, Beijing Hospital of Traditional Chinese Medicine, Capital University, Beijing, China, [12]Institute of Psychology, University of Freiburg, Freiburg im Breisgau, Germany

Objective: This study investigates the diagnostic accuracy of the PHQ-15, SSS-8, SSD-12 and Whitley 8 and their combination in detecting DSM-5 somatic symptom disorder in general hospitals.

Methods: In our former multicenter cross-sectional study enrolling 699 outpatients from different departments in five cities in China, SCID-5 for SSD was administered to diagnose SSD and instruments including PHQ-15, SSS-8, SSD-12 and WI-8 were used to evaluate the SSD A and B criteria. In this secondary analysis study, we investigate which instrument or combination of instrument has best accuracy for detecting SSD in outpatients. Receiver operator curves were created, and area under the curve (AUC) analyses were assessed. The sensitivity and specificity were calculated for the optimal individual cut points.

Results: Data from $n = 694$ patients [38.6% male, mean age: 42.89 years (SD = 14.24)] were analyzed. A total of 33.9% of patients fulfilled the SSD criteria. Diagnostic accuracy was moderate or good for each questionnaire (PHQ-15: AUC = 0.72; 95% CI = 0.68–0.75; SSS-8: AUC = 0.73; 95% CI = 0.69–0.76; SSD-12: AUC = 0.84; 95% CI = 0.81–0.86; WI-8: AUC = 0.81; 95% CI = 0.78–0.84). SSD-12 and WI-8 were significantly better at predicting SSD diagnoses. Combining PHQ-15 or SSS-8 with SSD-12 or WI-8 showed similar diagnostic

accuracy to SSD-12 or WI-8 alone (PHQ-15 + SSD-12: AUC = 0.84; 95% CI = 0.81–0.87; PHQ-15 + WI-8: AUC = 0.82; 95% CI = 0.79–0.85; SSS-8 + SSD-12: AUC = 0.84; 95% CI = 0.81–0.87; SSS-8 + WI-8: AUC = 0.82; 95% CI = 0.79–0.84). In the efficiency analysis, both SSD-12 and WI-8 showed good efficiency, SSD-12 slightly more efficient than WI-8; however, within the range of good sensitivity, the PHQ-15 and SSS-8 delivered rather poor specificity. For a priority of sensitivity over specificity, the cutoff points of ≥13 for SSD-12 (sensitivity and specificity = 80 and 72%) and ≥17 for WI-8 (sensitivity and specificity = 80 and 67%) are recommended.

Conclusions: In general hospital settings, SSD-12 or WI-8 alone may be sufficient for detecting somatic symptom disorder, as effective as when combined with the PHQ-15 or SSS-8 for evaluating physical burden.

KEYWORDS

somatic symptom disorder, PHQ-15, SSS-8, SSD-12, WI-8

Introduction

Somatic symptom disorder (SSD) was introduced in the DSM-5 in 2013 (1). The diagnosis of SSD is made when there are persistent (typically more than 6 months, Criteria C) and clinically significant somatic complaints (Criteria A) that are accompanied by excessive and disproportionate health-related thoughts, feelings, and behaviors regarding these symptoms (B-type criteria). Somatic complaints can be caused by medical diseases (organic) or not caused by them (functional). SSD is meant to substitute somatoform disorder in DSM-IV by avoiding the discussion of whether the somatic symptom can be medically explained or not. Moreover, the content of SSD is now further extended by including patients whose complaints can be explained by medical diseases. There have been doubts that SSD may be overinclusive as it includes medical patients with appropriate psychological reactions; however, it has been found that even in patients with a major medical burden, such as heart disease or arthritis, a diagnosis of SSD is not automatic (2). Only a fraction of such patients with chronic, persistent and distressing somatic complaints can be diagnosed with SSD. Indeed, it is the combination of somatic symptoms and B-type criteria that is associated with worsened quality of life and increased healthcare use (3). We think this diagnostic extension of including medical patients is especially meaningful, as this creates an opportunity to offer help to medical patients suffering from psychological burdens that are related to (and may also influence) medical complaints.

Clinical interviews are always most reliable in making diagnoses; however, they can be very time-consuming. In a real-world situation, in the limited time set of outpatient clinics, there is difficulty felt by both doctors and patients in achieving mutual empathy and understanding, not to mention to accomplish a full and extensive clinical interview. Thus, efficient screening tools of possible somatic symptom disorder can help greatly in clinic.

Well-established tools such as the Patient Health Questionnaire-15 (4) or the Somatic Symptom Scale-8 (5) can assist in assessing the A criteria of distressing somatic symptoms. The Somatic Symptom Disorder—B Criteria Scale (SSD-12) was developed to assess the psychological B criteria of SSD (6) and has been shown to have good validity in detecting SSD (7). A study in a German psychosomatic outpatient population showed that the combination of the PHQ-15 or SSS-8 with the SSD-12 increased the validity of identifying SSD compared with using each instrument alone (8).

In our former study (9), we found a prevalence of 33.6% (236/699) in a Chinese outpatient population and that SSD is associated high physical and psychological burdens and social function impairment. Drawing on the experience of Toussaint et al. (8), here we present a secondary data analysis of our former study (9) to investigate the predictive values of the PHQ-15, SSS-8, SSD-12 and WI-8 used alone or in combination for detecting SSD in Chinese general hospital outpatient clinics.

Methods

Study design and subjects

Our former multicenter cross-sectional study was conducted between May 2016 and March 2017 in the outpatient clinics of the neurology, gastroenterology, Traditional Chinese Medicine [TCM] and psychosomatic medicine departments of nine tertiary hospitals in Beijing, Jincheng, Shanghai, Wuhan, and Chengdu (located in the north, north-central, east, central, and southwest regions of China, respectively).

For inclusion in the study, the participants were required to be at least 18 years of age, to be visiting for treatment (i.e., not only picking up a prescription), to have adequate reading and writing skills and to have signed a written consent form. Exclusion criteria included the presence of language barriers, limited reading skills, cognitive impairment, acute psychosis or suicidal tendency.

The diagnosis of SSD was made by diagnostic SCID-5 interviews by trained clinical researchers blind to the screening scale results.

A detailed description of the procedure can be found in our previously published article (9).

Instruments

The PHQ-15 and SSS-8 for the A criteria and the SSD-12 and WI-8 for the B criteria were administered:

Somatic Symptom Severity Scale of the Patient-Health-Questionnaire (PHQ-15):

The PHQ-15 assesses 15 somatic symptoms, such as fatigue, pain, and gastrointestinal, musculoskeletal, and cardiopulmonary symptoms within the last 4 weeks. Each symptom is scored from 0 ("not bothered at all") to 2 ("bothered a lot"). Sum scores range from 0 to 30 and indicate the self-rated symptom burden (0–4 no to minimal; 5–9 low; 10–14 medium; 15–30 high). The Chinese version of the PHQ-15 exhibits satisfactory reliability (10) and validity (11).

Somatic Symptom Scale-8:

The SSS-8 is an abbreviated version of the PHQ-15, which was developed within DSM-5 field trials (12). A five-point response option (0–4) for each item and a 7-day time frame were used. The cutoff scores indicated whether a patient suffered from minimal (0–3 points), low (4–7), medium (8–11), high (12–15), or very high (16-32) somatic symptom burden. Previous studies demonstrated good item characteristics and excellent reliability, sound factor structures, and significant associations with related constructs such as depression, anxiety, quality of life, and health care use (5). These results have not been validated in China. In this sample, we estimated a Cronbach's alpha of 0.783.

Somatic Symptom Disorder—B Criteria Scale 12:

The Somatic Symptom Disorder—B Criteria Scale 12 (SSD-12) is composed of 12 items. Each of the three psychological sub-criteria is measured by four items with all item scores ranging between 0 and 4. The external and internal validity of this method have been established (6, 13). A cutoff point of 16 or 17 for SSD-12 has been found in Chinese studies for detecting SSD (7, 14).

Whiteley-8:

The Whiteley-8 test measures health-related anxiety in the previous 4 weeks. It has 8 items on a five-point Likert scale. In our study, each item score ranged between 1 and 5. The original well-validated 7-item scale WI-7 (15) was extended by one additional item: "Recurring thoughts about having a disease that is difficult to be rid of?" This item of rumination seemed to capture one core characteristic of health anxiety (16). The WI-8 was first used in the Danish study of functional disorders (17). The Chinese version of the WI-7 exhibited satisfactory reliability and internal validity in a general population sample (18, 19). The WI-8 has also been validated in China (20). In this sample, we estimated a Cronbach's alpha of 0.937.

Statistical procedures

The study center at Peking Union Medical College Hospital (PUMCH) stored all the data, regularly monitored all project sites and analyzed the data.

Analyses were carried out using the Statistical Package for the Social Sciences version 25.0 (SPSS Inc., Chicago, IL, USA) and MedCalc Version 20.

Results

Sample characteristics

In total, 1,269 participants were approached, and the response rate was 55.08%. A total of 697 participants were presented in our former study, as 3 of them had missed questionnaire data, a total of 694 participants who completed both the interview and the questionnaires of this study are presented in this study. Two hundred twenty-four participants came from the gastroenterology/neurology department, 239 from the psychosomatic medicine department, and 231 from the TCM department.

Among the 694 participants, 235 (33.9%) were diagnosed with SSD according to the SCID-5 interview. The average age of the participants was 42.89 years (SD = 14.24). Among them, 38.6% were male. There were no differences in age, sex, health insurance status, residence status, marital status, family income, occupation status, education, physical disease diagnosis or physical disease severity between the SSD group and the non-SSD group (Table 1).

The PHQ-15, SSS-8, SSD-12 and WI-8 scores were significantly different between the SSD group and the non-SSD group (Table 1). But these scores showed similar distribution between participants with physical disease and without physical disease, and these scores showed no correlation with physical disease severity (Supplementary Table S0).

Descriptive item reliability

The SSD-12 showed the highest reliability in this sample (α = 0.937). Cronbach's α values for the PHQ-15, SSS-8, SSD-12

TABLE 1 Baseline data of the study sample ($N = 694$).

		Total ($N = 694$)		With SSD ($N = 235$)		Without SSD ($N = 459$)				
		Mean	SD	Mean	SD	Mean	SD			*p*
Age		42.89	14.24	42.96	14.07	42.86	14.35			0.932
		N	%	*N*	%	*N*	%	Chi^2	*df*	*p*
Gender	Female	426	61.4	142	60.4	284	61.90	0.137	1	0.711
Health insurance	Yes	597	86.9	199	85.34	398	87.70	0.689	1	0.406
	No	90	13.00	34	14.50	56	12.30			
Residence	City	571	82.40	186	79.50	385	83.90	2.06	1	0.151
	Country	122	17.60	48	20.50	74	16.10			
Marital status	Single	129	18.60	45	19.10	84	18.30	7.38	5	0.194
	Married	503	72.50	162	68.90	341	74.30			
	Seperated	4	0.60	3	1.30	1	0.20			
	Divorced	38	5.50	17	7.20	21	4.60			
	Widowed	12	1.70	6	2.60	6	1.30			
	Others	8	1.20	2	0.90	6	1.30			
Family income	Low (under 4,000 RMB[a])	233	33.70	89	38.00	144	31.50	3.40	2	0.183
	Middle (4,000–8,000 RMB)	242	35.00	80	34.20	162	35.40			
	High (above 8,000 RMB)	216	31.30	65	27.80	151	33.00			
Occupation	Employed	341	49.10	105	44.70	236	51.40	6.78	5	0.238
	Unemployed	84	12.10	38	16.30	46	10.20			
	Retire	149	21.50	51	21.70	98	21.40			
	Housewife	44	6.30	16	6.80	28	6.10			
	Student	39	5.60	14	6.00	25	5.40			
	Others	37	5.30	11	4.70	26	5.70			
Education	Primary school	45	6.50	18	7.70	27	5.90	4.15	3	0.246
	Middle school	135	19.50	54	23.00	81	17.60			
	Higher school	179	25.80	58	24.70	121	26.40			
	University or higher	335	48.30	105	44.70	230	50.10			
Physical disease	No	417	60.1	143	60.9	274	59.7	0.087	1	0.769
	Yes	277	39.9	92	39.1	185	40.3			
Physical disease severity grade	0	417	60.1	143	60.9	274	59.7	2.075	3	0.557
	1	116	16.7	44	18.7	72	15.7			
	2	128	18.4	38	16.2	90	19.6			
	3	33	4.8	10	4.3	23	5.0			
Scale scores	Somatic symptom severity (PHQ-15) range = 0–30	9.33	5.38	12.00	5.53	7.96	4.77			<0.001
	Somatic symptom severity (SSS-8) range = 0–32	8.70	6.08	11.98	6.51	7.02	5.0			<0.001
	Psychological symptom severity (SSD-12) range = 0–48	13.98	12.24	23.58	11.45	9.07	9.38			<0.001
	Whiteley 8 (WI-8) range = 8–40	18.23	8.34	24.41	8.44	15.06	6.26			<0.001

Percentages are normally column percentages. [a]RMB: The renminbi is the currency of the People's Republic of China; 1,000 RMB is equivalent to ∼125 Euro.

and WI-8 assessments in this sample were 0.809, 0.783, 0.954, and 0.937, respectively. These predictors were moderately to very highly correlated (Supplementary Table S1).

Correlation of predictors

A Pearson correlation analysis showed that SSD-12 and WI-8 were very highly correlated, PHQ-15 and SSS-8 were highly correlated, PHQ-15 and SSD-12/WI-8 were moderately correlated, and SSS-8 and SSD-12/WI-8 were highly correlated (Table 2).

Combination of screening instruments

The combination of the PHQ-15/SSS-8 with the SSD-12/WI-8 in the regression analysis showed significantly more variance in predicting SSD than the PHQ-15/SSS-8 alone, while the combinations showed no improvement over SSD-12/WI-8 alone (as shown by the R^2 differences listed in Table 2).

ROC analysis

From ROC curve analysis with MedCalc, the cutoff point for PHQ-15 was found to be ≥8, with a sensitivity of 80%, specificity of 52%, and Youden Index of 0.32 (as there is an item related to menstruation, when considered separately, the cutoff point of PHQ-15 with highest Youden index should be 8 for women and 7 for men); the cutoff point for SSS-8 was ≥9, with a sensitivity of 67%, specificity of 68%, and Youden Index of 0.35; the cutoff point for SSD-12 was ≥16, with a sensitivity of 76%, specificity of 80%, and Youden Index 0.56; the cutoff point for WI-8 was ≥19, with a sensitivity of 73%, specificity of 76%, and Youden Index of 0.49.

The PHQ-15 (AUC = 0.715) and SSS-8 (AUC = 0.729) showed moderate diagnostic accuracy, while SSD-12 (AUC = 0.837) and WI-8 (AUC = 0.813) demonstrated good diagnostic accuracy. The differences between PHQ-15 or SSS-8 and SSD-12 or WI-8 were statistically significant (Supplementary Tables S2, S3, Figure 1).

The combination of the A and B criteria showed no significant improvement compared to the B criteria alone (PHQ-15 + SSD-12: AUC = 0.838; PHQ-15 + WI-8: AUC = 0.818; SSS-8 +SSD-12: AUC = 0.836; SSS-8 + WI-8: AUC = 0.816; Supplementary Tables S2, S3, Figure 1).

Diagnostic accuracy

However, since the potential harm of a false positive diagnosis and a false negative diagnosis is not equal in the case of SSD, the Youden Index may not be the best consideration when choosing cutoff points. A sensitivity priority should be considered, since a missed diagnosis would cause more harm than a false positive diagnosis, which would cause more clinical evaluation efforts but no damage. A diagnostic accuracy analysis according to Toussaint et al. (8) was performed to find a more sensitive cutoff point for each instrument (Supplementary Table S4). Only relevant ranges are shown.

Cutoff points of ≥13 for SSD-12 (sensitivity and specificity = 80 and 72%) and ≥17 for WI-8 (sensitivity and specificity = 80 and 67%) could be used.

Since previous studies reported severity thresholds of ≥10 (medium somatic symptom burden) and ≥15 (high somatic symptom burden) for both the PHQ-15 and the SSS-8 (21), and the corresponding thresholds for the SSD-12 can be determined at ≥20 and ≥25 (13), the cutoff points obtained with these combinations are also reported in Table 3. As there are no existing cutoff points for the WI-8 from other studies, no similar analysis was performed with the WI-8.

The application of higher severity cutoff points as determined by previous studies did not increase the efficiency but did decrease the sensitivity to an insufficient level.

Discussion

The present study evaluates and compares the diagnostic accuracy of the PHQ-15, SSS-8, SSD-12, and WI-8 and their combination for detecting DSM-5 somatic symptom disorder within a sample of general hospital outpatients. At their cutoff points from ROC analysis, SSS-8 (≥7) showed a relatively poor sensitivity and specificity; PHQ-15 (≥6) showed a high sensitivity, but a low specificity; however, SSD-12 (≥14) and WI-8 (WI ≥ 17) both showed good sensitivities and specificities. Combining the PHQ-15 or SSS-8 (to assess the A criteria) with the SSD-12 or WI-8 (to assess the B criteria) did not further increase the AUC compared to the use of the SSD-12 or WI-8 alone.

Previous studies investigating the use of PHQ-15, SSS-8, WI-7 and SSD-12 in detecting functional somatic symptoms or somatic symptom disorders in psychiatric populations or the general population have generally found good validity for these instruments (5, 8, 10, 11, 18, 19). The combination of an A criteria instrument (PHQ-15 or SSS-8) and a B criteria instrument (SSD-12) slightly improved the diagnostic accuracy (8).

In the study by Liao et al. (22) in psychiatric outpatients and healthy controls, the PHQ-15 scores of SSD patients and non-SSD patients were 10.04 (±6.03, $n = 200$) and 5.69 (±4.72, $n = 271$), respectively, and the cutoff point determined for the PHQ-15 was 4/5. The study by Toussaint et al. (8) was performed with psychiatric outpatients; the PHQ-15 scores of SSD patients and non-SSD patients were 14.6 (±5.0, $n =$

TABLE 2 Stepwise logistic regression analysis evaluating the PHQ-15/SSS-8 and SSD-12/WI-8 as predictors for SSD diagnosis ($n = 694$).

Variables	B	SE	*p*	OR	95% CI
PHQ-15 and SSD-12					
Step 1					
PHQ-15	0.151	0.017	<0.001	1.163	1.124–1.203
Constant	−2.151	0.196	<0.001	0.116	
Step 2					
PHQ-15	0.052	0.020	0.011	1.053	1.012–1.096
SSD-12	0.106	0.010	<0.001	1.112	1.091–1.134
Constant	−2.851	0.236	<0.001	0.058	
SSS-8 and WI-8					
Step 1					
SS-8	0.144	0.015	<0.001	1.155	1.121–1.190
Constant	−2.004	0.171	<0.001	0.135	
Step 2					
SSS-8	0.047	0.019	0.013	1.048	1.010–1.087
WI-8	0.139	0.015	<0.001	1.150	1.117–1.184
Constant	−3.781	0.278	<0.001	0.023	
SSD-12 and PHQ-15					
Step 1					
SSD-12	0.117	0.009	<0.001	1.124	1.104–1.144
Constant	−2.491	0.179	<0.001	0.083	
Step 2					
SSD-12	0.106	0.010	<0.001	1.112	1.091–1.134
PHQ-15	0.052	0.020	0.011	1.053	1.012–1.096
Constant	−2.851	0.236	<0.001	0.058	
WI-8 and SSS-8					
Step 1					
WI-8	0.158	0.013	<0.001	1.172	1.142–1.202
Constant	−3.708	0.274	<0.001	0.025	
Step 2					
WI-8	0.139	0.015	<0.001	1.150	1.117–1.184
SSS-8	0.047	0.019	0.013	1.048	1.010–1.087
Constant	−3.781	0.278	<0.001	0.023	

For the simplicity of data representation, only the PHQ-15 and SSD-12 combination and SSS-8 and WI-8 combination are listed here.
Model summary statistics:
PHQ-15 and SSD-12.
Step 1: step: χ^2 (1) = 89.67, p < 0.001; model: −2 log likelihood =798.81; Cox and Snell $R^2 = 0.12$; Nagelkerke $R^2 = 0.17$. Step 2: step: χ^2 (1) = 239.70, p < 0.001; model: −2 log likelihood = 648.78; Cox and Snell $R^2 = 0.29$; Nagelkerke $R^2 = 0.40$.
SSS-8 and WI-8.
Step 1: step: χ^2 (1) = 104.91, p < 0.001; model: −2 log likelihood = 783.56; Cox and Snell R2 = 0.14; Nagelkerke $R^2 = 0.19$. Step 2: step: χ^2 (1) = 212.09, p < 0.001; model: −2 log likelihood = 676.39; Cox and Snell $R^2 = 0.26$; Nagelkerke $R^2 = 0.37$.
SSD-12 and PHQ-15.
Step 1: step: χ^2 (1) = 233.21, p < 0.001; model: −2 log likelihood = 655.27; Cox and Snell $R^2 = 0.29$; Nagelkerke $R^2 = 0.40$. Step 2: step: χ^2 (1) = 239.70, p < 0.001; model: −2 log likelihood = 648.78; Cox and Snell $R^2 = 0.29$; Nagelkerke $R^2 = 0.40$.
WI-8 and SSS-8.
Step 1: χ^2 (1) = 205.89, p < 0.001; model: −2 log likelihood = 682.59; Cox and Snell $R^2 = 0.26$; Nagelkerke $R^2 = 0.36$. Step 2: step: χ^2 (1) = 212.09, p < 0.001; model: −2 log likelihood = 676.39; Cox and Snell $R^2 = 0.26$; Nagelkerke $R^2 = 0.37$.
B, unstandardized regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval.

209) and 11.1 (±4.7, $n = 163$), respectively, and the cutoff point determined for the PHQ-15 was ≥9. Physical symptoms such as pain, fatigue, heart palpitation, shortness of breath and gastroenterological symptoms are common and distressful in patients with depression and anxiety (23, 24). Depression and anxiety can also increase somatic symptom severity in organic disease patients (25). It is expected that the PHQ-15 score should be higher in the psychiatric outpatient group. The cutoff point

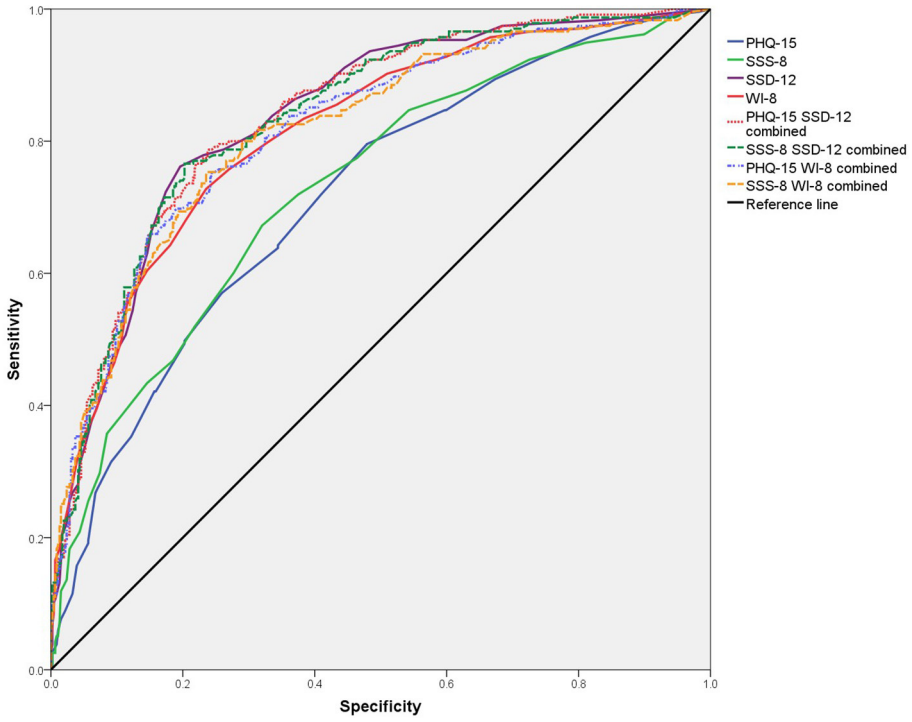

FIGURE 1
ROC curves of PHQ-15, SSS-8, SSD-12, WI-8, and their combinations.

TABLE 3 Combination of relevant cutoff points of PHQ-15 and SSD-12, and SSS-8 and SSD-12 ($n = 694$).

PHQ-15 and SSD-12	Optimal cutoff points determined in the current sample PHQ-15 ≥ 8 and SSD-12 ≥ 13	Pragmatic cutoff points based on established severity scores (medium severity) PHQ-15 ≥ 10 and SSD-12 ≥ 20	Pragmatic cutoff points based on established severity scores (high severity) PHQ-15 ≥ 15 and SSD-12 ≥ 25
Sensitivity	0.68	0.48	0.21
Specificity	0.80	0.92	0.98
NPV	0.64	0.76	0.82
PPV	0.83	0.77	0.71
Efficiency	0.76	0.77	0.72
SSS-8 and SSD-12	Optimal cutoff points determined in the current sample SSS-8 ≥ 9 and SSD-12 ≥ 13	Pragmatic cutoff points based on established severity scores (medium severity) SSS-8 ≥ 10 and SSD-12 ≥ 20	Pragmatic cutoff points based on established severity scores (high severity) SSS-8 ≥ 15 and SSD-12 ≥ 25
Sensitivity	0.62	0.50	0.25
Specificity	0.85	0.92	0.97
NPV	0.69	0.75	0.78
PPV	0.82	0.78	0.71
Efficiency	0.78	0.77	0.72

for the PHQ-15 determined in our study was ≥8, in between those found in the previous two studies.

SSS-8 is an abbreviated version of the PHQ-15. In past studies, it has been demonstrated to have a similar efficiency as the PHQ-15 in screening for bodily symptoms (21). This is the same case in our study: SSS-8 had similar AUC and efficiency as PHQ-15. Within a good range of sensitivity, PHQ-15 and SSS-8 would both show poor specificity. This may be because in general hospitals, "genuine" bodily symptoms are relatively more likely and more frequent than in general populations

or psychiatric hospitals; therefore, the A criteria would have a low specificity.

SSD-12 and WI-8 both showed good efficiency in our study, and the SSD-12 was slightly better than WI-8. This agrees with the core concept of SSD: that it is the psychological symptoms associated with the physical burdens, not the physical burdens themselves, that define SSD (2). In our sample, the finding that there is no difference of SSD diagnosis or instruments scores between different groups of physical disease status, also supports this idea that physical conditions themselves does not necessarily cause a higher chance of SSD or higher SSD severity. What defines SSD psychopathology is the psycho-behavior reaction to a somatic symptom, whether the symptom is organic or functional, whether the symptom is severe or not.

The cutoff point determined for SSD-12 (cutoff point $\geq$16) from the ROC analysis in our study was much lower than that found in the study by Toussaint et al. (8) (SSD-12 cutoff point $\geq$26). This difference could also be explained by participant selection differences. As the SSD-12 total sum-score was significantly associated with general anxiety and depressive symptoms (6, 26), it is expected that in a sample of psychiatric patients, the cutoff point for the SSD-12 would be higher.

In summary, the results from our study suggest that in general hospital outpatient settings, it's hard to find a good balance of sensitivity and specificity for PHQ-15 and SSS-8. So these instruments may be best used to evaluate SSD severity, but not as screening tools. In contrast, SSD-12 and WI-8 show good diagnostic accuracy. One B-criteria instrument seems to be sufficient by itself, with no further need or benefit of combining with one A-criteria instrument. When sensitivity is prioritized over specificity, the recommended cutoff points are $\geq$13 for SSD-12 and $\geq$17 for WI-8.

One limitation of our study is that only gastroenterological and neurological departments were chosen for biomedical departments, and approximately equal numbers of participants were selected from the biomedical, TCM and psychological departments, which may not represent the ratio of help-seekers to different departments in general hospitals. Different departments may have their own characteristic profiles of SSD presentation. Further detailed investigations in different clinical specialties from the perspective of consultation-liaison services may be warranted. Also, as our study was conducted in tertiary hospitals, the result may not be generalizable to primary care where patients with a less severe symptomatology present themselves.

Conclusion

In general hospital settings, SSD-12 or WI-8 alone may be sufficient for detecting somatic symptom disorder, as effective as when combined with PHQ-15 or SSS-8, while PHQ-15 and SSS-8 show a relatively poor diagnostic accuracy.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committees of Peking Union Medical College Hospital (PUMCH) and the University Medical Center, Freiburg, Germany (Protocol Number: S-K276). The patients/participants provided their written informed consent to participate in this study.

Author contributions

JW and KF designed this study. JW, TL, WLu, LZ, YZ, HW, XM, HC, WLi, and JR coordinated the study. JC made the drafting and statistic analysis. JW, KF, RL, and AT made critical reviews and improvement of the draft. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Author JR is employed by General Hospital of Jincheng Anthracite Coal Mining Group Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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EDITED BY
Wenhao Jiang,
Southeast University, China

REVIEWED BY
Jianwei Zhu,
Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, China
Huan Xiong,
Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, China
Zhaotao Wang,
The Second Affiliated Hospital of Guangzhou Medical University, China

*CORRESPONDENCE
Sunfu Zhang
neurosurgery.3rd.hospital@hotmail.com
Xuemei Li
470854563@qq.com

†These authors have contributed equally to this work and share first authorship
‡These authors have contributed equally to this work and share last authorship

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Deanxit and tandospirone relieved unexplained limb edema in a depressed pituitary adenoma survivor: A case report

Xingyu Dong[1†], Sheng Fang[1†], Wei Li[2], Xuemei Li[1*‡] and Sunfu Zhang[1*‡]

[1]Department of Neurosurgery, The Third People's Hospital of Chengdu, Chengdu, China, [2]Department of Neurology, The Third People's Hospital of Chengdu, Chengdu, China

Our case report describes a 45-year-old woman who suffered from limb edema for 2 months. We focused on tumor recurrence and other common potential diseases based on the pituitary adenoma history. However, none of the examinations showed any abnormality. Later, her continuous complaints about the family relationship and depressed mood came into sight, and a psychiatry consultation was arranged. Following that, she was diagnosed with major depressive disorder. After several days of Deanxit and tandospirone treatment, the patient's limb edema dramatically subsided. This is the first case of limb edema associated with depression. This highlights the importance of awareness of mental illness for non-psychiatrists, especially in patients with severe somatic symptoms, but with negative results.

KEYWORDS

limbs edema, Deanxit and tandospirone, major depressive disorder, somatic symptoms, antidepressant

Introduction

Edema is an accumulation of fluid in the interstitial space that occurs as the capillary filtration exceeds the limits of lymphatic drainage (1). It is usually seen in the eyelid, the infraorbital soft tissue, and the limbs, especially in the lower extremities. Edema can be caused by many somatic conditions, including endocrine and metabolic disease, cardiac disease, hepatic disease, renal disease, venous disease, and unspecific reasons (1, 2). Depression is a psychiatric condition associated with stratified psychological and somatic symptoms (3). Somatic symptoms prevailed in most patients with depression (4). Somatic symptoms vary from person to person. The most frequently presented ones are chronic pain, fatigue, and sleep disturbance. Limb edema associated with depression is rare. Herein, we report a case of a 45-year-old woman who had limb edema and was cured using Deanxit and tandospirone.

Case description

The patient suffered from limb edema for 2 months. She had pituitary adenoma for 7 years and underwent transsphenoidal pituitary surgery 4 years ago. She went to the

hospital for an endocrine review 2 years, which were within normal ranges.

Upon initial assessment, we observed mild to moderate edema in her hands and lower extremities, which the patient had complained about. She stated that she could not clench her fists and had recently felt that her pants were getting tight. However, her weight was stable from morning to evening. In addition to limb edema, she complained about feeling fatigued, depressed, and anxious and about having irregular menstruation in the last 2 months. The changes in her mental status and behavior prevented her from getting along with her family. Her vital sign and other physical examination were normal as well.

Diagnostic assessment and treatment

Considering her pituitary adenoma history and limb edema, we considered pituitary adenoma recurrence and secondary hypothyroidism as our initial diagnosis. Therefore, we scheduled a brain MRI with pituitary protocol and endocrine examination. However, the endocrine examination returned nearly normal results. Her thyroid hormone, sex hormone, growth hormone, and cortisol levels were within normal ranges. Moreover, the brain MRI only showed a slight enhancement in the pituitary gland, which was insufficient to diagnose tumor recurrence. As a result, the patient underwent further examinations, including liver and renal function tests, cardiac color Doppler ultrasonography, and internal organ ultrasonography. However, none of them displayed any abnormality. Thus, the common causes of limb edema, such as hypoalbuminemia, heart failure, renal failure, venous insufficiency, and idiopathic edema, were excluded.

Her continuous complaints, including about her daily life and family relationship, caught our attention on the fourth day of admission. Therefore, the psychiatry consultation was arranged immediately. At first, our psychiatry team performed PHQ-9, GAD-7, and Life Event Scale (LES) on her. The patient scored 20 in PHQ-9, 20 in GAD-7, and 65 in LES. These results indicated that the patient suffered severe mood problems in her daily life. The Hamilton Anxiety Rating Scale (HAMA) score was 25, and the Hamilton Depression Rating Scale (HAMD) score was 22. She was diagnosed with major depressive disorder.

The treatment that was given to her consisted of Deanxit (flupentixol/melitracen) 10.5 mg b.i.d. and tandospirone 10 mg t.i.d. The patient showed a significant improvement after 7 days of treatment. She felt much more relaxed. In addition, edema was relieved significantly. Then, she was discharged and referred to an outpatient psychiatric consultation with an indication for maintenance antipsychotic medication.

At the 3-week follow-up, the patient mentioned that she could wear her ring again (Figure 1). At the 2-month follow-up, her psychiatric symptoms further recovered. The HAMA and HADM scores were 8 and 9, respectively. The symptoms such as fatigue, depression, anxiety, and upset disappeared. In addition, she started to engage in more social activities, and her relations with family members improved. No relapse of psychiatric or edema was detected.

Discussion

Chronic limb edema is usually caused by systemic diseases like heart failure, renal disease, hepatic disease, or endocrine disease. The most frequent type is pitting edema, while myxedema is rare and often seen in Graves' disease and hypothyroidism. The thyroid hormone plays an essential role in many bodily functions. The extreme absence of this hormone is associated with a high mortality rate and has a broad spectrum of presenting symptoms (5). Thyroid hormone has several roles within the central and peripheral nervous systems, explaining the varying degrees of neurological symptoms associated with hypothyroidism, such as depression (6). Patients who underwent pituitary surgeries often suffer from hypopituitarism, which leads to secondary hypothyroidism. In addition to bilateral limb edema, this patient had a history of pituitary surgery and did not take hormone replacement therapy after the surgery. As a result, we suspected hypothyroidism to be the cause of limb edema and psychiatric symptoms. However, the levels of thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) of the patient were normal and negated our initial diagnosis.

The other common type of edema we need to differentiate is idiopathic edema. *Idiopathic edema* is a state that primarily affects women in the absence of hepatic, renal, and cardiac diseases (7–9). The diagnosis is made by physical and clinical assessments, and diuretics are the common treatment (10). The hallmark of this disease is orthostatic edema, accompanied by excessive weight gain from morning to evening due to fluid retention. It occurs almost exclusively in post-pubertal women and is independent of the menstrual cycle (11). However, in our case, the patient's weight was stable from morning to evening. She did not have orthostatic edema either. The clinical presentations are insufficient for the diagnosis of idiopathic edema.

Depression is a highly heterogeneous disorder with complicated clinical manifestations and biological mechanisms (12, 13). Two-thirds of patients with depression present only somatic symptoms at the early stage, and approximately half of the patients have unexplained medical symptoms (14). Sometimes lymphedema is accompanied by high depression and anxiety (15). However, unlike our case, this type of edema is usually caused by malignant tumors. In addition, some patients with idiopathic edema were more depressed and anxious, with a trend toward widespread neurotic symptoms (16). In these circumstances, diuretics are widely used to

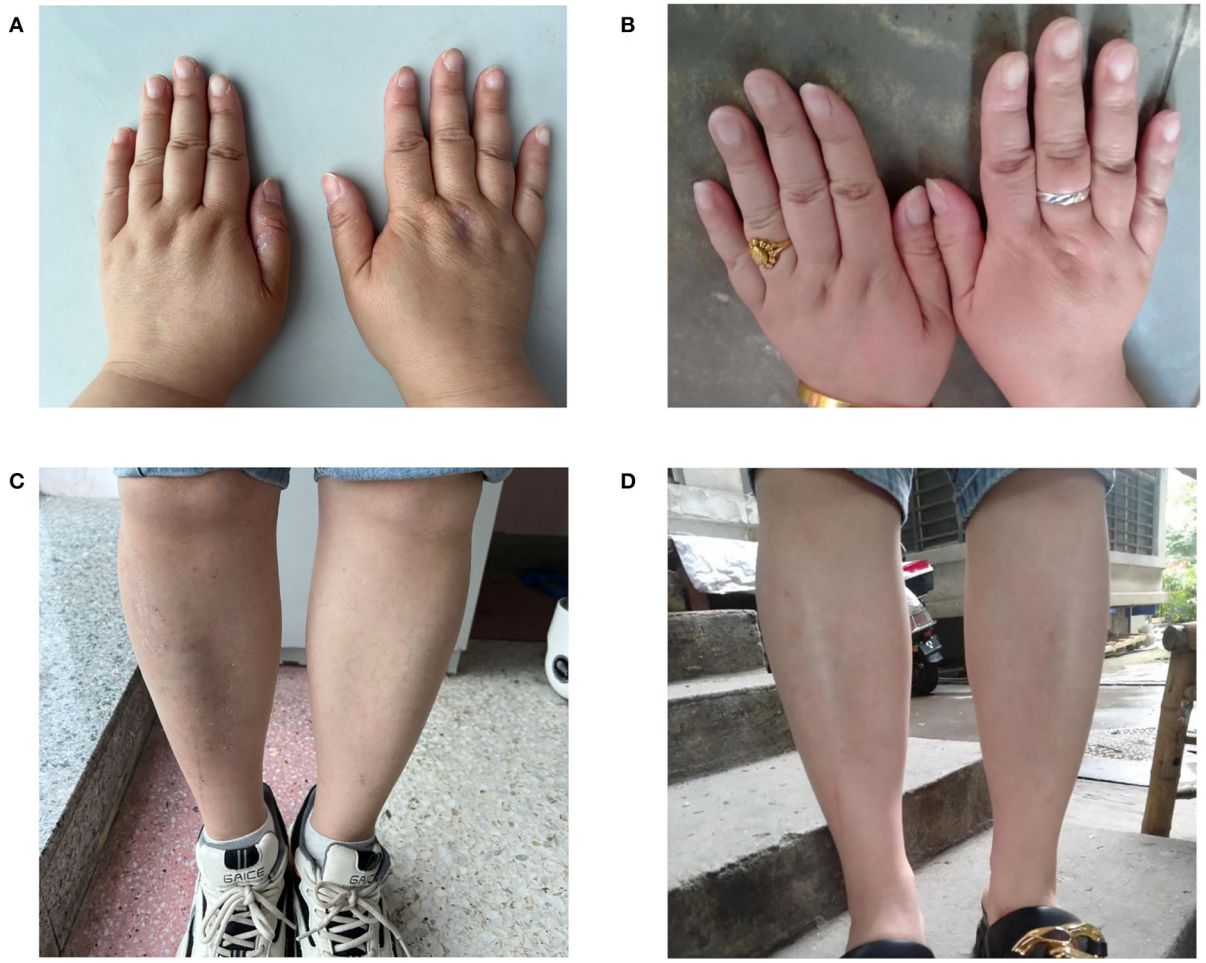

FIGURE 1
Limbs edema relived after antidepressant therapy at 7 days **(A,C)** and 3 weeks **(B,D)**.

relieve edema, which might also help release psychiatric symptoms. However, concurrent psychiatric symptoms were less recognized and treated.

Some researchers believed that excessive fluid retention in many patients with idiopathic edema might be related to the neuroendocrine abnormalities associated with psychiatric illness (16). We encountered similar situations in our case, and we discovered that edema was relieved at the same pace as her mood symptoms. However, there were hardly any published work suggesting Deanxit or tandospirone usage in such cases.

Moreover, neither of these medications has a diuretic effect. This evidence indicates that Deanxit and tandospirone do not relieve edema through a diuretic effect. We speculated that our patient had severe psychiatric problems at first. Then, primary emotional disturbances initiated some neuroendocrine changes and led to limb edema. Our treatment with Deanxit and tandospirone relieved depression, fixed neuroendocrine abnormalities, and reduced the limb edema. Our case might be the first report that limb edema, most likely associated with depression, dramatically remitted after antidepressant treatment. The underlying mechanism of this phenomenon is unknown, and further studies are needed.

People often present with somatic symptoms to clinical settings (17). Some non-specific symptoms may overlap with the somatic symptoms of psychiatric disorders, leading to misdiagnosis. Moreover, somatic symptoms could double the medical cost of examinations and treatment (18). As a result, physicians should consider psychiatric disorders when unexplainable symptoms appear. After treating limb edema, we turned to the psychiatrist for help as soon as we excluded the physical disorder of the patient, and the prescribed antidepressants finally solved the patient's problem.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Author contributions

XD and SF drafted this manuscript and treated the patient. WL conducted a psychological analysis. SZ and XL performed the case analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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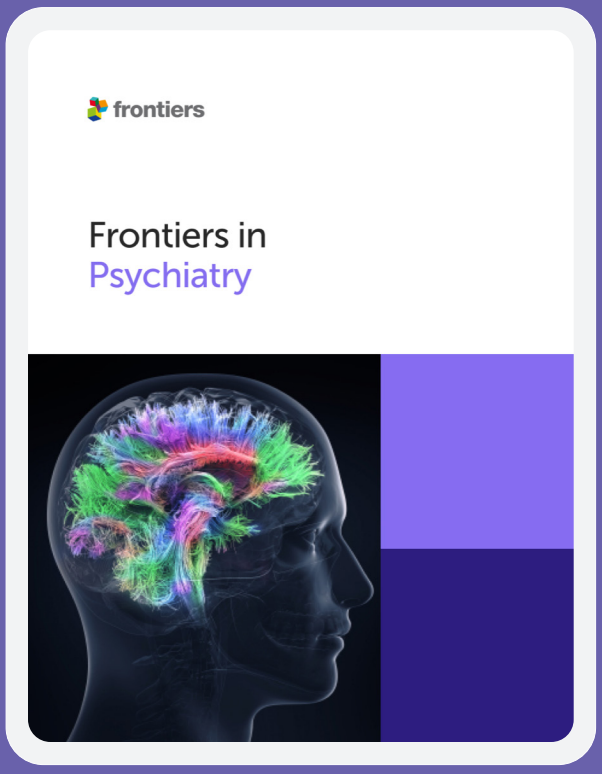

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