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# Insights in mood and anxiety disorders 2021

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Paul Stokes, Marco Grados and Alessandro Colasanti

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# Insights in mood and anxiety disorders: 2021

**Topic editors**

Paul Stokes — King's College London, United Kingdom

Marco Grados — Johns Hopkins University, United States

Alessandro Colasanti — Brighton and Sussex Medical School, United Kingdom

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# The Implications of the Diving Response in Reducing Panic Symptoms

*Peter Kyriakoulis[1]*, Michael Kyrios[2], Antonio Egidio Nardi[3], Rafael C. Freire[3,4] and Mark Schier[5]*

[1] School of Health Sciences, Swinburne University of Technology, Hawthorn, VIC, Australia, [2] College of Education, Psychology & Social Work, Orama Institute for Mental Health & Wellbeing, Flinders University, Adelaide, SA, Australia, [3] Institute of Psychiatry-Federal University of Rio De Janeiro, Rio De Janeiro, Brazil, [4] Department of Psychiatry and Centre for Neuroscience Studies, Queen's University, Kingston, ON, Canada, [5] School of Health, Swinburne University, Hawthorn, VIC, Australia

Increased $CO_2$ sensitivity is common in panic disorder (PD) patients. Free divers who are known for their exceptional breathing control have lower $CO_2$ sensitivity due to training effects. This study aimed to investigate the immediate effects of cold facial immersion (CFI), breath holding and $CO_2$ challenges on panic symptoms. Healthy participants and patients with PD were subjected to four experimental conditions in a randomly assigned order. The four conditions were (a) breath-holding (BH), (b) CFI for 30 s, (c) $CO_2$ challenge, and (d) $CO_2$ challenge followed by CFI. Participants completed a battery of psychological measures, and physiological data (heart rate and respiration rate) were collected following each experimental condition. Participants with PD were unable to hold their breath for as long as normal controls; however, this finding was not significant, potentially due to a small sample size. Significant reductions in both physiological and cognitive symptoms of panic were noted in the clinical group following the CFI task. As hypothesized, the CFI task exerted demonstrable anxiolytic effects in the clinical group in this study by reducing heart rate significantly and lessening self-reported symptoms of anxiety and panic. This outcome demonstrates the promise of the CFI task for clinical applications.

**Keywords: panic disorder, diving response, cold facial immersion, $CO_2$ sensitivity, anxiety**

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****Correspondence:***
*Peter Kyriakoulis*
*peter@positivepsychology.net.au*

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## INTRODUCTION

According to DSM-5, panic disorder (PD) is a severe and persistent anxiety disorder characterized by spontaneous and recurrent panic attacks (PAs) (1, 2). PD sufferers exhibit irregularities in respiratory rhythms, predominantly a thoracic pattern of breathing, abnormal variability, and irregularity in breathing (3, 4). In addition, several respiratory symptoms have been associated with PD, including air hunger, dyspnea, rapid breathing, and elevated heart rate (5).

$CO_2$ hypersensitivity theory proposes that PD sufferers have a lower physiological threshold for detecting $CO_2$ levels (5). It is proposed the existence of an evolved suffocation alarm system that helps the brain monitor useful air, consistent with the lowered threshold for detecting $CO_2$ levels (6). According to this model, PAs occur when the brain mistakenly detects a lack of useful air (increased $CO_2$), triggering the suffocation alarm system. This maladaptive response makes PD sufferers vulnerable to "false suffocation alarms," specifically PAs.

For PD sufferers, the $CO_2$ challenge has a more exaggerated response than normal controls, inducing a sharp and transitory rise in anxiety that has been compared to a PA (6–12). However, studies comparing PD patients with other anxiety disorders and normal controls have yielded mixed results. For instance, breath-hold times were lower in PD sufferers than in normal controls but no lower than in sufferers of other anxiety disorders (13). Meanwhile, PD patients exhibited shorter breath-hold times than patients with other anxiety disorders (14). Furthermore, PD sufferers experienced elevated physiological reactivity to the breath-hold challenge (15). Their findings support the false suffocation alarm system (6) present in PD sufferers.

More recently, research combining neuroimaging and panic provocation challenges provided further scientific insights into interoceptive sensory triggers and potential neural mechanisms that underlie spontaneous PAs (16). The role of acid-base and chemosensory mechanisms has been identified as an important internal homeostatic trigger for PAs. A large body of research proposes that the fear network, an association of fear circuits in the brain comprising the amygdala, hippocampus, medial prefrontal cortex, brain stem projections and insula, may be abnormally sensitive in PD patients and particularly sensitive to homeostatic changes (17, 18). More specifically, within the cycle of panic, a sensitivity in detecting threats to homeostasis, acidosis, may sensitize fear-arousal-stress regulatory circuits to other triggers leading to PD.

A research proposed the notion of a continuous trait based on one's physiological response to increasing $CO_2$ levels, where PD patients characterized by hypersensitivity to $CO_2$ are positioned at one end of the spectrum (19). At the other end are those individuals with low sensitivity to $CO_2$ increases. These include free divers (20, 21). Free divers are known for their exceptional breathing control and lower ventilatory response to $CO_2$, which has been related to training and diving experience (22).

Free divers practice the sport of diving on one breath and draw on a range of breathing techniques to assist them in attaining greater depths underwater, with some able to hold their breath underwater for 10 min (23). The extraordinary breath-hold ability found in free divers can be explained by an evolved physiological response that helps mammals stay underwater for long periods of time, known as the diving response (DR).

The DR is a physiological reflex that optimizes respiration, allowing humans to endure a lack of oxygen underwater. It is activated by apnea, also known as breath holding, and CFI (stimulation of the cold facial receptors with water) (24, 25). Research indicates that facial cold receptors are more strongly stimulated by immersion in water at temperatures ranging from 10 to 15°C (26).

The physiological adaptations associated with the DR include a decrease in heart rate (bradycardia) and cardiac output, vascular constriction, reduced blood flow to peripheral capillary beds and increased blood pressure. Cardiovascular adjustments and their pronounced bradycardic effect serve as an oxygen-conserving reflex that aims to maintain life during asphyxia by enhancing blood flow to vital organs (heart, brain, and lungs) (27–30). In many respects, the physiological adjustments comprising the nervous, cardiovascular and respiratory systems that act to promote oxygen conservation during the DR are the opposite of those triggered in PAs.

Long-term training of free diving is associated with several physiological adaptations, including a more pronounced DR, greater lung volume, lung oxygen, and carbon dioxide stores (25, 31). Trained breath-hold divers will endure the human DR during a breath hold until $PaO_2$ has fallen to 35 mmHg and $PaCO_2$ has increased to 50 mmHg, whereas non-divers when engaging in breath-hold activity can generally reduce their $PaO_2$ as low as 60 mmHg and their $PaCO_2$ as high as 45 mmHg (32). Further support that breath-hold training builds greater tolerance to $CO_2$ is found in trained synchronized swimmers who can sustain a normoxic breath hold for approximately twice the breath-hold time compared to non-diving controls (33). It was demonstrated that 2 weeks of daily apneic (breath-hold) training increased both the DR and the duration of breath-hold (34).

Cold water facial immersion is superior in reducing heart rate when compared to immersions of other body parts and that the water temperature is a significant stimulus for driving the DR (35): the greater the difference between ambient air temperature and water temperature, the more dramatic the bradycardic response will be (36). Given that there is a higher density of receptors in the ophthalmic region of the trigeminal nerve that includes the eyes, forehead, and nose, there is greater sensitivity to cold water when the face is fully submerged in water (37).

One of the cardinal features of PD when fear is elicited is a dysregulated ANS, characterized by sympathetic nervous system (SNS) arousal. It has been established that effecting reductions in heart rate can provide substantial acute symptomatic relief for persons in panic states. Frequently treatments are ineffective and costly, hence greater knowledge of the underlying pathophysiology of PD is required to assist with the development of effective treatments (38). PD patients may be able to benefit from simple and practical treatments aimed at regulating the ANS and reversing the fear response. Hence, this study explores whether the DR, activated through breath holding and CFI and its consequential bradycardic effect, is able to reduce the psychophysiological fear response associated with panic.

The current study investigated the immediate effects of breath holding and carbon dioxide challenge. The specific objectives are to (1) examine preliminary data on the short-term effects of CFI on physiological and psychological panic symptoms induced by respiratory challenges and (2) compare a group of PD participants with a control group to examine the magnitude of differences between these groups. This study is the first attempt to examine the relationship of $CO_2$ sensitivity threshold and panic symptoms in order to better understand possible applications of the DR and CFI to the treatment of panic symptoms.

# METHODS

## Participants and Sampling

Investigations were carried out with 32 participants: 16 patients with a primary diagnosis of PD with or without agoraphobia (DSM-5) (clinical group, or group 1) and 16 normal controls who did not meet the criteria for PD or mental illness (control group,

or group 2). Of these, 6 were male, and 26 were female. The clinical group comprised 1 male and 15 females, and the control group comprised 5 males and 11 females. The participants in the clinical group had an average age of 36.43 years ($SD = 2.82$), and the participants in the control group had an average age of 29.06 years ($SD = 1.79$). The cohort differences are reported in the results section.

Health screening assessments were carried out by a medical doctor (at Swinburne University) to establish medical eligibility to undergo the $CO_2$ challenge. The Mini-International Neuropsychiatric Interview (MINI) is a short structured diagnostic interview used to make diagnoses of Axis I disorders (DSM-IV) has demonstrated high reliability and validity (39). It was used to screen psychological disorders within the exclusion criteria and identify individuals with PD (DSM-IV). Exclusion criteria for both groups included psychotic disorders, substance abuse, prescription medication, habitual use of benzodiazepines, known allergies to latex, asthma or respiratory problems, cardiovascular problems, hypertension, hypotension, pregnancy, and cerebrovascular problems including epilepsy and organic brain disorder. Finally, other comorbidities to Axis I mental health disorders (DSM-IV) were excluded, along with those with first degree biological relatives with PD. The Panic Group was also assessed with the structured clinical interview (SCID-I) for the DSM-IV Axis I Disorders module for Panic Disorder and Agoraphobia (SCID-I) (40). The SCID-I is a comprehensive structured interview for diagnosis of psychiatric disorders according to DSM-IV criteria (41).

## Physiological Measures

A compact physiological monitoring system (Zephyr Bioharness) featuring a chest strap and external multirecording and monitoring device was used to measure heart rate, posture and respiration rate. Participants were connected to Zephyr Bioharness and measured throughout the experimental study. Participants' breath-hold ability was also measured during the experimental phase and included breath-hold ability after exhalation and breath-hold ability following maximum inhalation. All participants undertook all four conditions of the experimental study while wearing the chest strap connected to the Zephyr Bioharness, which was connected via Bluetooth to a multirecording and monitoring device (PowerLab). PowerLab version 7.0 data acquisition and analysis software were used as a multirecording device, and recorded data were sampled at a frequency of 60 Hz (60 samples per second).

## Research Design

Participants took part in four experimental conditions, where the order of conditions was randomly assigned. The experiment was conducted in a quiet clinical office. **Figure 1** displays the experimental conditions and data collection.

### Condition A: Breath-Hold Challenge

Participants wore a nose clip and were instructed to hold their breath for as long as possible, following an exhalation. Upon completion of this breath-hold challenge, they were given a 1-min rest period before being instructed again to hold their breath after taking a maximum inhalation. Physiological measures including breath-hold times, heart rate (HR) and respiration rate (RR) were recorded.

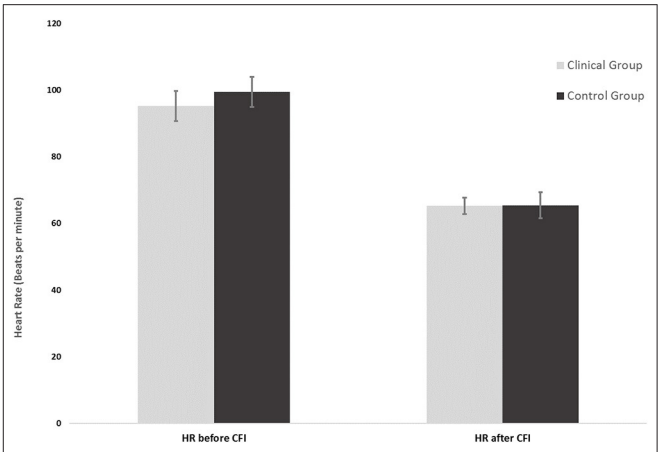


**FIGURE 1 |** Mean heart rates of the clinical group ($n = 16$) and control group ($n = 16$) before and after CFI.

### Condition B: CFI With 30 s of Apnea (CFI Challenge)

A sterilized container was filled with water and placed on the left side of a medical bed, which was cleared of any other apparatus. Sufficient space around the water container was allowed for participants to rest their arms on both sides of the container while completing the task. Participants were instructed to take a maximal inhalation and then immerse their entire face in the water (including the forehead) while holding their breath for 30 s. Participants were informed that they could terminate the exercise at any time if they felt discomfort or a strong urge to breathe. The researcher counted out aloud in intervals of 5 s until 30 s was reached, at which point participants were asked to lift their face from the water. The ambient air temperature was controlled at 22°C, and the water temperature was maintained between 7 and 12°C.

### Condition C: $CO_2$ Challenge

A single-breath $CO_2$challenge was used to evoke and rate participants' anxious response to the challenge. Participants were informed before the challenge that they would inhale a single breath of a $CO_2$ mix (comprising concentrations of 35% $CO_2$ and 65% $O_2$) via a Douglas bag and that while the procedure is completely safe, it may evoke some transient breathlessness or discomfort. Participants were instructed to wear a nose clip and exhale the air from the lungs before they inhaled a single maximum inhalation of the premixed air in the Douglas bag. The 35% $CO_2$ challenge is considered a valid procedure if the participant inhales at least 80% of their vital capacity (66). Participants were asked to hold their breath before exhaling for 4 s while the researcher counted aloud from 1 to 4. Participants were then asked to mark on the Visual Analog Scale (VAS) how anxious they felt. The VAS was a scale anchored by 0 (no anxiety at all) to 10 (worst anxiety). The researcher also rated (on a

similar VAS) how anxious the participant looked following the $CO_2$ challenge for concurrent external validity. Participants then sat down and completed the battery of psychological assessments.

### Condition D: $CO_2$ + CFI Challenge

$CO_2$ participants were then asked to perform the CFI task (as per Condition B) as soon as they felt comfortable enough. Once complete, both the participant and researcher independently rated the level of anxiety on the VAS. The participant was then asked to complete the battery of psychological measures.

## Data Cleaning

Prior to statistical analysis, all variables were assessed for the presence of missing data and univariate outliers. No outliers were identified in the clinical group or control group of participants, and no missing data were identified in any of the psychological measures or physiological measures collected during the premeasure phase or experimental phase. Non-parametric analyses were conducted in cases where data did not adequately meet the assumptions of normality and could not be transformed to normalize their distributions according to recommended procedures (42).

## Statistical Analyses

Physiological data, including RR and HR data, satisfied the assumptions for parametric analysis. Hence, *t*-tests and ANOVA analyses were used to investigate the differences between the clinical group and control on the experimental conditions. Examination of the scores across all self-report psychological measures taken at pretest, after Condition C ($CO_2$), and after Condition D (CFI plus $CO_2$), including Acute Panic Inventory (API), Anxiety Sensitivity Inventory (ASI), Beck Anxiety Inventory (BAI), Panic Attack Cognitions Questionnaire (PACQ), State Trait Anxiety Inventory (STAI), Visual Analog Scale—Researcher (VAS-R), and Visual Analog Scale—Participant (VAS-P), were not normally distributed; therefore, non-parametric tests were utilized. Spearman's correlation coefficient was used to investigate the relationships between psychological measures. Friedman's test was used to examine differences in the psychological measures collected across the experimental conditions. The Statistical Package for Social Sciences version 22.0 was used for all analyses. The alpha level was set at 0.05 for all parametric analyses. A Bonferroni adjustment was performed for parametric analyses, resulting in a significance threshold of $p < 0.016$.

# RESULTS

The analysis of this study is presented in two sections. The first section presents the comparison of demographic details between groups and correlations of the pretest measures. The second section presents analyses of the results.

## Participant Demographics and Correlations Between Pretest Measures

Age was significantly higher ($p = <0.05$) in the clinical group ($M = 36.4$ years; $SD = 11.3$) than in the control group ($M = 29.1$ years; $SD = 7.2$). **Tables 1**, **2** provide the means on categorical and continuous demographic variables for the clinical and control groups. No significant differences were found between the groups. Although the groups were matched statistically, there were apparent differences in gender and education that may not have been significant due to the small sample size.

The Spearman rank-order correlation coefficient was used as a non-parametric measure to determine the strength and

**TABLE 1 |** Demographic information: categorical variables.

| | | Clinical | | Control | |
|---|---|---|---|---|---|
| **Variable** | ***Fisher's z*** | ***N*** | **%** | ***N*** | **%** |
| **Gender** | $p = 0.172$ | | | | |
| Male | | 1 | 6.30 | 5 | 31.30 |
| Female | | 15 | 93.70 | 11 | 68.70 |
| **Education level** | $p = 0.156$ | | | | |
| No university degree | | 11 | 69.00 | 6 | 37.60 |
| University degree | | 5 | 31.00 | 10 | 62.40 |
| **Employment status** | $p = 0.479$ | | | | |
| Employed | | 10 | 62.50 | 7 | 43.80 |
| Unemployed/student | | 6 | 37.50 | 9 | 56.30 |
| **Smoking** | $p = 1.000$ | | | | |
| Yes | | 2 | 12.50 | 3 | 18.80 |
| No | | 14 | 87.50 | 13 | 81.20 |
| **Drinking** | $p = 1.000$ | | | | |
| Yes | | 13 | 81.30 | 14 | 87.50 |
| No | | 3 | 18.80 | 2 | 12.50 |
| **Physical fitness** | $p = 1.000$ | | | | |
| Poor/fair | | 7 | 43.75 | 7 | 43.75 |
| Good/very good | | 9 | 56.25 | 9 | 56.25 |
| **Physical activity at work** | $p = 0.252$ | | | | |
| Sedentary | | 9 | 56.30 | 13 | 68.80 |
| Non-sedentary | | 7 | 43.70 | 3 | 31.20 |
| **Weekly physical exercise** | $p = 1.000$ | | | | |
| <3 h | | 12 | 75.00 | 12 | 75.00 |
| >3 h | | 4 | 25.00 | 4 | 25.00 |
| **Weekly cycling** | $p = 1.000$ | | | | |
| None | | 12 | 75.00 | 13 | 81.25 |
| Some | | 4 | 25.00 | 3 | 18.75 |
| **Weekly walking** | $p = 0.242$ | | | | |
| <3 h | | 8 | 50.00 | 12 | 75.00 |
| >3 h | | 8 | 50.00 | 4 | 25.00 |
| **Weekly home duties** | $p = 0.273$ | | | | |
| <3 h | | 4 | 25.00 | 8 | 50.00 |
| >3 h | | 12 | 75.00 | 8 | 50.00 |
| **Weekly gardening** | $p = 1.000$ | | | | |
| None | | 11 | 68.75 | 10 | 62.50 |
| Some | | 5 | 31.25 | 6 | 37.50 |
| **Walking pace** | $p = 1.000$ | | | | |
| Slow/steady, average | | 4 | 25.00 | 5 | 31.25 |
| Brisk pace/fast (>6 km/h) | | 12 | 75.00 | 11 | 68.75 |

*N = 32 (group 1: n = 16; group 2: n = 16). Fisher's exact test (2-sided).*

**TABLE 2 |** Demographic information: continuous variables.

| | Clinical | | Control | |
|---|---|---|---|---|
| | *M* | *SD* | *M* | *SD* |
| Water comfort (Mann-Whitney, $p = 0.809$) (0 = Not at all comfortable−10 = Very comfortable) | 7.31 | 2.68 | 7.94 | 1.53 |
| Average no. of glasses per week (Mann-whitney, $p = 0.423$) | 3.00 | 2.88 | 2.00 | 1.63 |
| # of Push-ups (Mann-Whitney, $p = 0.140$) | 9.40 | 8.32 | 16.81 | 14.19 |
| Height (Mann-whitney, $p = 0.468$) | 167.25 | 7.46 | 169.12 | 8.30 |
| Weight (Mann-whitney, $p = 0.564$) | 74.22 | 17.97 | 70.47 | 17.02 |

*p-values (2-sided) are based on the Mann-Whitney test.*

**TABLE 3 |** Correlations between pre-measure assessments.

| | API | CESD | DIS | BAI | ASI | STAI T | STAI S | PACQ |
|---|---|---|---|---|---|---|---|---|
| API | – | 0.64** | 0.27 | 0.69 | 0.60 | 0.61 | 0.60 | 0.60 |
| CESD | | – | 0.18 | 0.71** | 0.84** | 0.93** | 0.83** | 0.74** |
| DIS | | | – | 0.41 | 0.46 | 0.13 | 0.12 | 0.48 |
| BAI | | | | – | 0.84** | 0.77** | 0.62 | 0.86** |
| ASI | | | | | – | 0.70 | 0.62 | 0.82** |
| STAI Trait | | | | | | – | 0.82** | 0.75** |
| STAI State | | | | | | | – | 0.64 |
| PACQ | | | | | | | | – |

*N = 30.*
***p < 0.001.*

direction of association that exists between the premeasure assessments. The magnitude of the relationship was determined by the following correlation coefficients: low (0–0.3), moderate (0.4–0.7), and high (≥ 0.8) magnitude of correlations. **Table 3** provides correlations between premeasures.

## Data Analyses

### Differences in Breath-Hold Duration Between Groups (Condition A)

Two independent samples *t*-tests were conducted to compare the differences in breath-hold durations between the clinical and control groups (**Table 4**).

The results revealed that there were no significant mean differences between the clinical participants and control participants in their breath-hold times following a maximum inhalation ($p > 0.05$). Furthermore, when comparing mean differences in breath-hold times following a passive exhalation, no significant mean differences were found between clinical participants and control participants ($p > 0.05$).

### Physiological Differences in Response to CFI Task (Condition B)

**Figure 2** shows the mean average HR measured just prior to the CFI task and the mean average HR measured upon completion of the CFI task. Simple main effects analysis showed that prior to the CFI task and upon completion of the CFI task, participants experienced a significant decrease in HR [$F_{(1,30)} = 58.87$, $p = 0.00$, $\eta^2 = 0.662$). However, there was no significant main effect of group, with clinical and control participants experiencing similar reductions in HR as a result of the CFI task [$F_{(1,30)} = 0.127$, $p = 0.724$, $\eta 2 = 0.007$].

### Physiological Differences in Response to the $CO_2$ Challenge (Condition C)

**Table 5** shows the mean RR measured 30 s before the $CO_2$ challenge (Time 1) and the mean RR measured 30 s after the $CO_2$ challenge (Time 2). There was no significant interaction between the effects of group and $CO_2$ challenge task on participants' RR [$F_{(1,30)} = 0.057$, $p = 0.814$, $\eta 2 = 0.002$]. Simple main effects analysis showed that between 30 s prior to the $CO_2$ challenge (Time 1) and 30 s following the $CO_2$ challenge (Time 2), participants experienced no significant increase in respiration rate [$F_{(1,30)} = 0.079$ $p = 0.780$, $\eta 2 = 0.003$]. No significant differences between respiration rates were observed between the clinical and control groups [$F_{(1,30)} = 1.062$, $p = 0.311$, $\eta 2 = 0.034$].

Furthermore, there was no significant interaction found between the effects of group and $CO_2$ on participants' HR [$F_{(1,30)} = 0.805$, $p = 0.377$, $\eta 2 = 0.026$]. Simple main effects analysis showed that between 30 s prior to the $CO_2$ challenge (Time 1) and 30 s following the $CO_2$ challenge (Time 2), participants experienced no significant change in HR [$F_{(1,30)} = 0.497$, $p = 0.486$, $\eta 2 = 0.016$]. In addition, no significant differences between HRs were observed between the clinical and control groups [$F_{(1,30)} = 0.130$, $p = 0.721$, $\eta 2 = 0.004$].

### Physiological Response Pre- and Post-$CO_2$ Administered Prior to CFI (Condition D)

**Table 6** shows the mean HRs and respiration rates for participants before and after the $CO_2$ challenge. A mixed ANOVA was conducted to compare the clinical and control groups in terms of the effect of the $CO_2$ challenge task and group on participants' RR and HR.

There was no significant interaction between the effects of group and $CO_2$ challenge task on participants' RR [$F_{(1,30)} = 0.002$, $p = 0.966$, $\eta 2 = 0.000$]. Simple main effects analysis showed that between 30 s prior to the $CO_2$ challenge (Time 1) and 30 s following the $CO_2$ challenge (Time 2), participants experienced no significant increase in respiration rate [$F_{(1,30)} = 4.381$, $p = 0.045$, $\eta^2 = 0.127$]. No significant differences between respiration rates were observed between the panic and normal groups [$F_{(1,30)} = 0.011$, $p = 9.19$, $\eta^2 = 0.000$].

No significant interaction was found between the effects of group and $CO_2$ on participants' HR [$F_{(1,30)} = 0.074$, $p = 0.788$, $\eta 2 = 0.002$]. Simple main effects analysis showed that between 30 s prior to the $CO_2$ challenge (Time 1) and 30 s following the $CO_2$ challenge (Time 2), participants experienced no significant

**TABLE 4 |** *T*-test results and descriptive statistics for breath-hold (BH) tasks for clinical and control groups.

| | Group | | | | 95% CI for mean difference | | | |
|---|---|---|---|---|---|---|---|---|
| | Clinical ($n = 16$) | | Control ($n = 16$) | | | | | |
| | *M* | *SD* | *M* | *SD* | | *t* | Df | *P* |
| BH p. max inhalation | 44.05 | 18.17 | 53.30 | 18.03 | −22.31, 3.82 | −1.45 | 30 | 0.912 |
| BH p. max exhalation | 24.18 | 9.84 | 26.32 | 15.53 | −11.53, 7.25 | −0.465 | 30 | 0.725 |

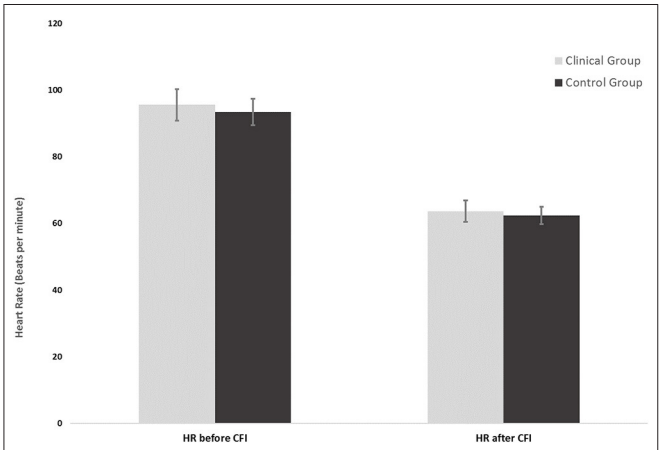


**FIGURE 2 |** Heart rates of the clinical group ($n = 16$) and control group ($n = 16$) at the start and end of the CFI task following $CO_2$ challenge.

**TABLE 5 |** Descriptive statistics for time 1 and time 2 of the $CO_2$ challenge.

| | Group | | | |
|---|---|---|---|---|
| | Clinical ($n = 16$) | | Control ($n = 16$) | |
| | *M* | *SD* | *M* | *SD* |
| RR Time 1 | 14.09 | 3.52 | 13.29 | 4.18 |
| RR Time 2 | 14.48 | 4.16 | 13.89 | 4.53 |
| HR Time 1 | 92.33 | 15.13 | 85.83 | 12.72 |
| HR Time 2 | 90.91 | 14.76 | 89.11 | 13.73 |

**TABLE 6 |** Descriptive statistics for heart rate and respiration rate before and after $CO_2$ challenge.

| | Group | | | |
|---|---|---|---|---|
| | Clinical ($n = 16$) | | Control ($n = 16$) | |
| | *M* | *SD* | *M* | *SD* |
| RR before $CO_2$ | 15.80 | 3.60 | 15.93 | 3.03 |
| RR after $CO_2$ | 14.74 | 3.61 | 14.83 | 3.36 |
| HR before $CO_2$ | 88.95 | 15.22 | 89.48 | 8.93 |
| HR after $CO_2$ | 91.16 | 15.11 | 90.96 | 12.31 |

change in HR [$F_{(1,30)} = 1.861, p = 0.183, \eta^2 = 0.058$]. In addition, no significant differences between HRs were observed between the clinical and control groups [$F_{(1,30)} = 0.001$, $p = 0.970$, $\eta^2 = 0.000$].

## Physiological Response Before and After the $CO_2$ + CFI Task (Condition D)

**Figure 2** shows the mean HR at the start of the CFI following the $CO_2$ challenge and the mean HR at the completion of the CFI task. A mixed ANOVA examined the effect of CFI following the $CO_2$ challenge on participants' HR and investigated whether differences between groups were observed. There was no significant interaction between the effects of group and CFI on participants' HR [$F_{(1,30)} = 0.222$, $p = 0.641$, $\eta^2 = 0.007$). Simple main effects analysis demonstrated that between Time 1 (start of CFI task following $CO_2$ challenge) and Time 2 (end of CFI task), participants experienced a significant HR reduction [$F_{(1,30)} = 58.878$, $p < 0.01$, $\eta^2 = 0.662$]. This was a very large effect size. However, no significant differences between the clinical and control groups were observed [$F_{(1,30)} = 0.127$, $p = 0.724, \eta^2 = 0.004$].

## Psychological Measures and the Effects of $CO_2$ and CFI

The Mann-Whitney U test was used to examine differences in the psychological measures collected across the three time periods. The PD group had significantly higher scores than the control group on all psychological measures at Time 1 (pretest), Time 2 ($CO_2$), and Time 3 (CFI after $CO_2$) ($p < 0.05$), with the exception of the Discomfort Intolerance Scale (DIS) ($p = 0.09$). **Table 7** provides the means for all self-reported psychological measures taken at Time 1 (pretest), Time 2 ($CO_2$), and Time 3 (CFI after $CO_2$).

All anxiety measures including the ASI, API, STAI, PACQ, BAI, VAS-P, and VAS-R were lower at Time 3 ($CO_2$ with CFI) compared to Time 1 (baseline) with the exception of API. This makes sense as control participants scored lower on the API, as they did not experience a PA in response to the $CO_2$ challenge. Furthermore, all participants reported a significant decrease in anxiety symptoms across all of the measures between Time 2 ($CO_2$ Challenge) and Time 3 ($CO_2$ with CFI). The findings of this study lend support to the application of the diving response and CFI in reducing panic cognitions and symptoms of anxiety and panic. Furthermore, these results indicate some promise in terms of the utility of CFI in assisting with the management and reduction of anxiety and panic symptoms.

**TABLE 7 |** Medians, minimum, maximum and interquartile ranges for psychological measures at time 1, time 2, and time 3.

| | Mdn | Min | Max | Interquartile range |
|---|---|---|---|---|
| **Acute Panic Inventory** | | | | |
| Time 1 (Pre-test) | 2.5 | 0 | 28 | 6 |
| Time 2 ($CO_2$ challenge) | 11.5 | 0 | 45 | 17.25 |
| Time 3 ($CO_2$ with CFI) | 1 | 0 | 39 | 6.5 |
| **Anxiety Sensitivity Index** | | | | |
| Time 1 (Pre-test) | 21.5 | 0 | 59 | 19 |
| Time 2 ($CO_2$ challenge) | 21.5 | 3 | 63 | 23 |
| Time 3 ($CO_2$ with CFI) | 10 | 0 | 63 | 22.5 |
| **Beck Anxiety Inventory** | | | | |
| Time 1 (Pre-test) | 11 | 0 | 47 | 28.1 |
| Time 2 ($CO_2$ challenge) | 17 | 2 | 60 | 27.25 |
| Time 3 ($CO_2$ with CFI) | 3 | 0 | 62 | 9 |
| **Panic Cognitions Questionnaire** | | | | |
| Time 1 (Pre-test) | 17 | 0 | 45 | 27.75 |
| Time 2 ($CO_2$ challenge) | 7 | 0 | 68 | 18.25 |
| Time 3 ($CO_2$ with CFI) | 0 | 0 | 69 | 5.5 |
| **State Anxiety Inventory** | | | | |
| Time 1 (Pre-test) | 38 | 21 | 71 | 17.5 |
| Time 2 ($CO_2$ challenge) | 44.5 | 24 | 79 | 22 |
| Time 3 ($CO_2$ with CFI) | 32 | 9 | 66 | 14.5 |
| **VAS—Participant** | | | | |
| Time 1 (Pre-test) | 7 | 0 | 9 | 5.38 |
| Time 2 ($CO_2$ challenge) | 6 | 0 | 10 | 6.13 |
| Time 3 ($CO_2$ with CFI) | 2 | 0 | 8 | 3.13 |
| **VAS—Researcher** | | | | |
| Time 1 (Pre-test) | 7.25 | 0 | 10 | 4.75 |
| Time 2 ($CO_2$ challenge) | 7 | 1 | 10 | 6.25 |
| Time 3 ($CO_2$ with CFI) | 2 | 0 | 7.5 | 2.75 |

*N = 32 (group 1: n = 16; group 2: n = 16).*

## DISCUSSION

The current study aimed to investigate the immediate effects of breath holding and $CO_2$ challenge on panic symptoms based on Klein's theory of false suffocation alarm, the principal findings of the current investigation do not support Klein's false suffocation alarm theory, which suggests that the brain's suffocation detector incorrectly signals a lack of useful air and increases vulnerability to false suffocation alarms and PAs. The study findings indicate that there were no significant differences in breath-hold durations among the clinical and control participants. Overall, the $CO_2$ challenge evoked anxiety and panic symptoms as self-reported by clinical participants, and the CFI task demonstrated anxiolytic effects by reducing heart rate (HR), as well as self-reported symptoms of anxiety and panic in both the clinical and control groups. The findings of this preliminary study revealed that there was no significant difference in breath-hold (BH) ability between the clinical and control groups. While the means of the BH durations in both the passive exhalation and the maximum deep inhalation BH tasks were slightly lower for the clinical group than for the control group, these differences were not significant. One possible explanation for this finding may have been the relatively small sample size that comprised this study. Previous research that has tested this hypothesis has used different methodologies and yielded varied findings (13, 43–46). The varied results found in previous studies may be explained by many of the studies comprising small, heterogeneous samples, diverse inclusion and exclusion criteria, and different criteria for assessing panic attacks (PAs). Lung capacity decreasing with age is also another known factor that may reduce breath-hold (BH) ability. Despite lung volumes being different, there are no gender differences in BH ability (47).

Furthermore, these findings do not support the BH challenge as a potential marker for hypersensitivity to $CO_2$ and susceptibility to $CO_2$-induced panic. Hypersensitivity to $CO_2$ may be more notable in the PD respiratory subtype (4, 48–53). The small sample in this study and our recruitment method (general rather than selecting subgroups) precluded subgroup analysis. Respiratory symptoms may play a role in both PAs and $CO_2$-induced panic (44). Their study reported that with a single breath of 35% $CO_2$/65% $O_2$ inhalation, participants with PD reported significantly stronger symptoms of panic and anxiety than the control group. These findings were in line with those of Griez et al. (2) and Perna et al. (11). The results of the current study support this hypothesis and found that both clinical and control participants demonstrated a significant bradycardic effect (a drop of ∼30–35 beats per minute) following the CFI task. This is in line with previous research that has demonstrated that the diving response (DR) elicits a strong autonomic response characterized by a pronounced HR reduction and blood centralization to the organs that are most in need of oxygen (i.e., heart, lungs and brain) (25, 34, 54–57). The findings of the current study suggest that the DR is a powerful physiological adaptation that is innate to all humans. This is consistent with previous research that has found that the DR is augmented by the CFI task or by facial cooling (30, 36, 58).

Furthermore, our study found no significant differences between the clinical and control groups in HR in response to $CO_2$. Previous research has yielded mixed results, with some $CO_2$ studies reporting an increase in HR (59–63) and some reporting a decrease or no change in HR (64).

In addition, this study reported no significant difference in respiration rates between the clinical and control groups. Although previous research examining the respiration rate (RR) after $CO_2$ challenge has yielded mixed results, our findings lend support to those of existing research (6, 65–67), which revealed no significant differences in respiration rates following $CO_2$ inhalation. Contrary to the findings of van den Hout and Griez's study, the $CO_2$ challenge did not induce a significant increase in RR in clinical and control participants (12). Respiratory rate may not be the best measure of respiratory response to $CO_2$ but rather the increase in respiratory tidal volume. Previous studies have reported that 50% of clinical panic participants describe difficulties with taking a deep inhalation of $CO_2$ and feeling breathlessness (68). This difficulty was also observed with the clinical group in this study, with some participants reporting discomfort in breathing and with the bad odor. Hence, it is plausible that the full effects of $CO_2$ were not observed, as some

participants may not have taken full inhalation of $CO_2$. For the 35% $CO_2$ test to be valid, a participant needs to inhale at least 80% of their vital capacity (66).

With regard to BH durations, our findings were not in line with the findings of Asmundson and Stein's, who found that patients diagnosed with PD had significantly shorter BH durations than healthy participants (43). Our findings were not in line with Klein's theory of the suffocation false alarm theory (6) and the findings of Asmundson and Stein, who suggested that participants with PD terminate their BH earlier to avoid activation of the suffocation alarm (43). A relatively small sample size of the clinical group may have been a plausible explanation for this finding. Future research on BH durations between clinical and control groups should look at investigations with a larger sample size that is adequately powered.

The current findings are consistent with the finding from a study that showed no significant differences in HR changes between panic patients and controls following the $CO_2$ challenge, even though there was a trend for the heart rate increasing (69). It is well-established in the literature that $CO_2$-induced inhalation elicits a sudden increase in ventilation accompanied by a surge of anxiety that mimics a PA (6, 66) and triggers arousal of the conditioned fear response in panic patients (70, 71). It was demonstrated that panic patients who experienced $CO_2$-induced PAs showed HR responses to $CO_2$ that were significantly greater than those of non-panic patients, perhaps reflecting greater cardiac sympathetic stimulation by $CO_2$ (63).

Limitations of this study included recruitment challenges, and the extensive list of exclusion criteria for individuals to be eligible to participate in the study which limited the sample size and matching of participants. A pragmatic approach was pursued in an attempt to match participants for age and gender however this was not possible due to recruitment challenges. There were also some difficulties noted with the breathing apparatus for the $CO_2$ challenge and with the provocation method used. Amongst some of the challenges some participants reported included: disliking the taste of the $CO_2$ gas, feeling anxious or panicky when doing the task, difficulty with inhaling as deeply as instructed, whilst others were not able to hold their breath with the inhaled gas mixture for a period of 4 s before exhaling it, as instructed. Given that to be considered a valid test, participants need to inhale at least 80% of their vital capacity of $CO_2$ (66). Our results may have been impacted by the inability of some participants to achieve this. Given the brevity of the task, it was not anticipated that participants would experience difficulty in carrying out the $CO_2$ challenge as per instructions. Future studies should emphasize to participants the importance of maximum inhalation and holding their breath for 4 s. Another important limitation was the variability in participants' heart rate and respiration rate changes in response to the $CO_2$ challenge, which made data interpretation difficult when comparing 30 s of physiological data 30 s prior to the $CO_2$ challenge to 30 s following the $CO_2$ challenge. Nonetheless, when data were examined on a case-by-case basis, a trend was depicted, characterized by a more elevated RR and HR in the clinical participants in response to the $CO_2$ challenge compared to the control group.

It is noteworthy that by activating the diving response and subsequently reducing one's heart rate, one may achieve reductions in physiological and cognitive symptoms of panic and potentially in $CO_2$ sensitivity. This study demonstrated that the CFI task was able to reduce anxiety and panic symptoms induced by the $CO_2$ challenge. One of the most frightening symptoms reported by sufferers of panic disorder is heart racing or pounding. Hence, reducing the heart rate and autonomic sympathetic nervous system arousal may have a positive impact on self-reported anxiety. Another common fear-associated symptom reported by panic sufferers is the feeling of suffocation and dyspnea. In contrast, when the diving response is activated, it exerts an oxygen-conserving effect that extends breath-holding time with the aim of assisting the survival of the organism. Hence, CFI may prove to be an effective treatment for panic disorder and other anxiety disorders. Furthermore, the diving response can be easily activated with cold moisture (i.e., ice packs), making it an easily administered treatment. Further investigations are warranted to explore the anxiolytic effects induced by the activation of the diving response.

## 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 Swinburne University Human Research Ethics Committee. The participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

PK provided the conceptualization, methodology, analysis, investigation, writing, reviewing and editing, and funding of the research. MK and MS provided supervision and review. AN and RF provided the review and editing. All authors contributed to the article and approved the submitted version.

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# Dysfunctional Attitudes Mediate the Relationship Between Childhood Emotional Neglect and Anhedonia in Young Adult Major Depression Patients

*Peilin Wang, Nan Zhang, Simeng Ma, Lijun Kang, Wei Wang, Xiaofen Zong, Hanping Bai, Ruiting Li*† and Zhongchun Liu*†*

*Department of Psychiatry, Renmin Hospital of Wuhan University, Wuhan, China*

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***Correspondence:**
*Zhongchun Liu*
*zcliu6@whu.edu.cn*
*Ruiting Li*
*736213684@qq.com*

†*These authors share last authorship*

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**Background:** Childhood traumas are well-established risk factors for major depressive disorder (MDD). However, the relationship between childhood traumas types and MDD symptoms is unclear. The present study tested the hypothesis that childhood traumas affect specific types of anhedonia in depression and the mediating role of dysfunctional attitude.

**Methods:** Within this cross-sectional study, 310 young adult patients with MDD completed the PHQ-9, CTQ-SF, DAS, and SHAPS. The statistical analyses used the Mann-Whitney U test, Spearman's rank correlation, and multiple regression analysis. Mediation analyses were tested by the structural equation model (SEM).

**Results:** Spearman's rank correlation analysis showed positive correlations between the SHAPS, CTQ-SF, and DAS total score ($p < 0.05$). The EA, EN, PN, and SHAPS scores were positively correlated ($p < 0.05$). Among the four factors of anhedonia, social interaction and interest/pastimes were positively correlated with EA, EN, and PN ($p < 0.05$), the sensory experience was positively correlated with EN ($p < 0.01$), and diet did not correlate with childhood traumas. Stepwise regression analysis showed that dysfunctional attitude and emotional neglect were the main influencing factors of sensory experience ($p < 0.001$) and social interaction ($p < 0.001$). Dysfunctional attitude and physical neglect were the main factors influencing interest/pastimes ($p < 0.001$). SEM analysis found that dysfunctional mediated between childhood traumas and anhedonia.

**Conclusions:** The degree of anhedonia was related to dysfunctional attitudes and childhood traumas. The childhood emotional neglect experience was the most important and was related to sensory and social anhedonia. Dysfunctional attitudes played a mediating role between childhood neglect and anhedonia. Early psychotherapy targeting young adult MDD patients with childhood emotional neglect may help decrease symptoms of anhedonia.

**Keywords: depression, anhedonia, dysfunctional attitudes, structural equation model, childhood trauma**

# INTRODUCTION

Anhedonia is one of the core features of major depressive disorder (MDD), according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (1). Anhedonia refers to people's loss of the ability to experience happiness or a decline in the ability to experience happiness, including lack of pleasure in interest and success (2). The presence of symptoms of anhedonia, as a predictor of poor treatment response (3), can change independently of other symptoms of depression (4, 5).

Childhood traumas have become major social public-health problems worldwide (6, 7). As critical early-life adverse events, childhood traumas link to various adult psychopathologies, such as the first onset of depression (8, 9), bipolar disorder, anxiety, psychosis, disruptive behavior, substance abuse, and eating disorders (10, 11). Further, childhood maltreatment exposures predict a more chronic, treatment-resistant, and severe depression than individuals with depression but without a maltreatment history (12). Among Chinese young adults, the prevalence rate of childhood traumas exposures is as high as 18.6% (13). Several studies revealed the association between childhood traumas and high anhedonia (14, 15). These studies suggested that when considering the symptom dimension, childhood traumas may mainly affect the anhedonia aspect of MDD. Childhood traumas include physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect (13). At present, physical and emotional neglect has attracted more and more attention (7). Current knowledge about the impact of childhood traumas on specific anhedonia is limited, such as the state anhedonia (16) and social anhedonia (17).

According to Beck's schema-based cognitive model, an individual's emotional experiences depend on the content of thoughts and beliefs activated by life experiences (18). According to the diathesis-stress model, childhood traumas may cause vulnerable individuals to form negative cognitive schemas (19). These negative thinking styles are typically conceptualized as dysfunctional attitudes, rigid and maladaptive beliefs about oneself, the world, and the future (20, 21). Dysfunctional attitudes, as cognitive vulnerabilities, interact with adverse life events to affect depression (22). Current research showed that dysfunctional attitudes are not only related to the severity of depression and the risk of recurrence (23) but can also persist as stable features (24) and mediate the impact of childhood traumas on depression (25).

In the current study, we first determined the effects of different types of childhood traumas on different domains of anhedonia. Then examined the mediating role of dysfunctional attitudes between different types of childhood traumas and anhedonia. Our hypotheses were as follows: (a) specific types of childhood traumas were associated with severe anhedonia; (b) dysfunctional attitudes mediated the relationship between childhood traumas and anhedonia in MDD patients.

# METHOD

## Study Design and Participants

This study was based on China's Early Warning System and Comprehensive Intervention for Depression (ESCID) project from April 2019 to January 2020. A total of 310 participants were included. Two experienced psychiatrists diagnosed all participants and met the DSM-5 diagnostic criteria for major depressive disorder. The inclusion criteria of participants were: 18–30 years of age, having a junior high school education or higher. The exclusion criteria were as follows: other mental illnesses, substance dependence or abuse, severe physical illness or craniocerebral trauma, or severe excitement, impulsivity, or non-cooperation. This experiment was examined and approved by the Ethics Committee of the Renmin Hospital of Wuhan University. All the participants were informed and agreed to participate in this study.

## Measures

The nine-item Patient Health Questionnaire (PHQ-9) is a self-assessment questionnaire for patients with depression. The PHQ-9 has been widely used and is a valid measure of depression in clinical populations (26–28). The total score ranges from 0–27, with the following grades: no depression (0–4), mild depression (5–9), moderate depression (12–16), and severe depression ($\geq$ 15) (29). In our study, the PHQ-9 demonstrated strong internal consistency ($\alpha = 0.875$).

The Snaith-Hamilton Pleasure Scale (SHAPS) is a self-report scale containing 14 items designed to evaluate a person's enjoyment experience (food/drink, interest/pastimes, social interactions, and pleasurable sensory experiences) in the past few days (30). The SHAPS is not influenced by participants' demographic and clinical characteristics, possesses excellent psychometric properties, and appears appropriate for clinical and research settings (31). The Chinese version of SHAPS is answered according to a Likert-style 4-point system (1 point, absolutely agree; 2 points, agree; 3 points, disagree; 4 points, absolutely disagree), with a total score of 14 to 56 points (32). The higher the score, the more obvious anhedonia. According to the research of Zhang et al. (33), the Spanish four-factor structure (34) was used in this study: sensory experience (items 6, 7, 11, 12, 13), food/drink (items 4, 5, 9, 10), social interaction (items 2, 8, 14), and interest/pastimes (items 1, 3). This model provides the best fit for both Chinese non-clinical and clinical samples. In our study, Cronbach's α coefficients ($\alpha = 0.913$) for the total SHAPS reached accepted standards ($\alpha > 0.70$), and all four subscales scored above 0.60.

The Childhood Trauma Questionnaire-Short Form (CTQ-SF) is a self-report scale containing 28 items (25 clinical items and 3 validation items). It is used to retrospective evaluate traumatic experiences in childhood (35), including physical abuse (PA), emotional abuse (EA), sexual abuse (SA), physical neglect (PN), and emotional neglect (EN). It is a 5-point Likert scale, from "Never" (score = 1) to "Always" (score = 5). The total score ranges from 25 to 125 points. The higher the score, the higher the experience of abuse/neglect. According to previous studies (36), cutoff points for CTQ-SF subscales are EA score $\geq$ 13, PA score $\geq$ 10, SA score $\geq$ 8, EN score $\geq$ 15, and PN score $\geq$ 10, and CTQ-SF total $\geq$ 50. The Chinese version of CTQ-SF has good reliability and validity in college students and depression (37). In our study, Cronbach's α coefficients for the total CTQ-SF was 0.870, and all five subscales scored above 0.60, indicating that CTQ-SF has good structural validity in the Chinese depression sample.

The Chinese version of the Dysfunctional Attitude Scale (DAS) is a self-report scale consisting of 40 items. Designed to assess the cognitive vulnerability of depression, it may reflect the impact of early adverse events on a person's perception of self and the world. Each item includes a statement on the subject and a 7-point Likert scale to assess the degree of agreement (1 point = completely disagree; 7 points = completely agree). Among them, 10 items are scored in reverse (items 2, 6, 12, 18, 24, 29, 30, 35, 37, 40). The scoring range is 40 to 280 points, and the total normal score is ≤ 130 points. The higher the score, the more distorted the subject's cognition (38). DAS has good reliability and validity in Chinese MDD patients (13). In our study, Cronbach's α coefficients (α = 0.917) for the total DAS reached accepted standards (α > 0.70).

Suicidality was assessed by asking participants if they ever had suicidal ideation, plans, or attempts in their lifetime. Self-injury was assessed by asking participants if they ever had self-injury attempts in their lifetime. We asked about the use of the substance, including having ever used a substance, tobacco, or alcohol. Family history was assessed by asking participants whether their biological parents and siblings ever had depression.

## Statistical Analysis

Categorical data were expressed in frequency and percentage (N, %), and the Chi-square test was used to compare differences between groups. Kolmogorov-Smirnov test was used to test the normality of the continuous data (39), showing that the survey result data were non-normally distributed ($p < 0.05$). So non-normal data was represented by Median and IQR. The non-parametric Mann-Whitney *U*-test was used to compare differences between groups. Spearman's rank correlation test was used to explore the relationships between variables. Stepwise multiple linear regression analysis was used to test the impact of different types of childhood traumas and dysfunctional attitudes on anhedonia when demographic characteristics were controlled.

A structural equation model (SEM) including full information maximum likelihood (FIML) estimation was used to examine the mediation model with gender and age as covariates. Standardized direct, indirect, and total effects were estimated for all pathways. We calculated a 95% bootstrap confidence interval (*CI*) with 5000 bootstrapped samples to examine the significance of direct and indirect effects. The following fit criteria were used to evaluate the goodness-of-fit of the model (40): $\chi^2/df \leq 3$, the root-mean-square error of approximation (RMSEA) ≤ 0.08, the Standardized Root-Mean-Square Residual (SRMR) ≤ 0.08 (41), the Comparative Fit Index (CFI) ≥ 0.90(42), the goodness of fit index (GFI) ≥ 0.90.

SPSS 25.0 was used for single factor and multivariate statistical analysis, and AMOS 23.0 was used for SEM analysis. A two-tailed significance level of overall $p < 0.05$ was considered statistically significant in this study.

# RESULTS

## Participants' Socio-Demographic Characteristics

In total, 310 patients were participated, including 65 males (20.97%) and 245 females (79.03%). When a subscale score was higher than the cut-off point, we analyzed the frequencies of childhood traumas. In survey 175 (56.5%) participants reported at least one type of trauma. The prevalence rates of childhood emotional abuse (EA), physical abuse (PA), sexual abuse (SA), emotional neglect (EN), and physical neglect (PN) were 24.52, 17.1, 11.94, and 41.61, and 31.61%. Among those people, 85 (37.1%) participants reported more than one type of trauma. The two most reported trauma types were emotional neglect ($n = 129$, 41.61%) and physical neglect ($n = 98$, 31.61%).

According to CTQ-SF total ≥ 50, patients were divided into no childhood trauma group ($n = 100$, 32.3%) and childhood traumas group ($n = 210$, 67.7%), and the socio-demographic differences between the two groups were compared (**Table 1**). Patients with childhood traumas showed more childhood separation from their parents ($p < 0.001$), a lower education level ($p = 0.026$), higher substance use ($p < 0.001$), more suicide plans/behaviors in the lifetime ($p < 0.001$), and more self-harm behaviors ($p = 0.023$). Although there was no significant difference in age between the two groups ($p = 0.188$), patients with childhood traumas had younger onset age ($p = 0.001$) with a longer duration of illness ($p = 0.003$). It showed that childhood traumas were associated with early-onset depression. We also assessed the gender differences in five childhood traumas (**Table 2**) and found that the prevalence of EA in female patients was higher than males ($\chi^2 = 10.384$, $p = 0.001^{**}$). Therefore, age, gender, and education level were used as control variables in the subsequent analysis.

## Correlation's Analysis

Spearman's rank correlation tests were used to analyze the relationship between childhood traumas, anhedonia, and dysfunctional attitudes with age, gender, and education level as control variables. There were positive correlations between SHAPS total score, DAS total score, and CTQ-SF total score ($rho = 0.150$–$0.254$, $p < 0.001$–$0.01$). SHAPS total score was positively correlated with EA, EN, and PN scores ($rho = 0.113$–$0.186$, $p < 0.01$–$0.05$). Therefore, these three items were included in the subsequent analysis. Among the four factors of anhedonia, social interaction and interest/pastimes were positively correlated with EA, EN, and PN ($rho = 0.121$–$0.223$, $p < 0.001$–$0.05$), the sensory experience was positively correlated with EN ($rho = 0.177$, $p < 0.01$), however, food/drink was not correlated with childhood traumas. DAS total score was positively correlated with 4 factors of SHAPS ($rho = 0.174$–$0.262$, $p < 0.001$–$0.01$), and CTQ-SF total score and 4 factors ($rho = 0.159$–$0.239$, $p < 0.001$–$0.01$) except SA ($rho = 0.106$, $p = 0.063$). Complete results of the correlation analysis between childhood traumas and other scales are shown in **Table 3**.

## Multiple Regressions Analysis

Four stepwise multiple linear regression models were calculated with the SHAPS total score and four subscales: sensory experience, social interaction, and interest/pastimes as the dependent variable. The independent variables included the DAS total score, EA, EN, PN, age, gender, and education level. The results showed that dysfunctional attitudes and emotional neglect were the main influencing factors of SHAPS total score ($R^2 = 0.092^{***}$), sensory

**TABLE 1 |** The socio-demographic and clinical characteristics.

| | No CT ($n = 210$) | CT ($n = 100$) | | |
|---|---|---|---|---|
| **Variables** | **N (%)** | **N (%)** | $\chi^2$ | ***p*** |
| Female | 159 (64.90%) | 86 (35.10%) | 4.325 | 0.038* |
| First episode | 156 (67.20%) | 76 (32.80%) | 0.106 | 0.745 |
| **Education level** | | | | |
| Undergraduate | 176 (65.40%) | 93 (34.60%) | 4.986 | 0.026* |
| Graduate | 34 (82.90%) | 7 (17.10%) | | |
| **Residence** | | | | |
| City | 164 (68.30%) | 76 (31.70%) | 0.234 | 0.890 |
| Town | 32 (66.70%) | 16 (33.30%) | | |
| Village | 14 (63.60%) | 8 (36.40%) | | |
| Separated from parents | 45 (48.90%) | 47 (51.10%) | 21.225 | <0.001*** |
| Substance use in the lifetime | 12 (34.30%) | 23 (65.70%) | 20.058 | <0.001*** |
| Suicide[a] | 58 (54.20%) | 49 (45.80%) | 13.701 | <0.001*** |
| Self-injury[b] | 59 (59.00%) | 41 (41.00%) | 5.163 | 0.023* |
| Family history | 28 (60.90%) | 18 (39.10%) | 1.167 | 0.280 |
| **Variables** | **Median (IQR)** | **Median (IQR)** | ***Mann-Whitney U*** | ***p*** |
| Age (year) | 22 (21,23) | 21 (20,23) | 9,511.5 | 0.188 |
| Age of onset (year) | 19 (17,20) | 17 (15,19) | 8,054 | 0.001** |
| Duration of illness (year) | 1 (0,2) | 2 (1,3) | 8,310 | 0.003** |
| HAMD-17 | 19 (12,23) | 21 (16,25) | 8,151 | 0.001** |
| PHQ-9 | 16 (10,20) | 18 (14,23) | 8,301.5 | 0.003** |
| DAS | 163 (146,182) | 176 (159,197) | 7,736.5 | <0.001*** |
| SHAPS | 31 (27,36) | 35 (28,39) | 8,280.5 | 0.003** |
| Sensory experience | 11 (10,13) | 12 (10,14) | 8,530 | 0.007** |
| Food/drink | 9 (8,11) | 10 (8,11) | 9,479.5 | 0.162 |
| Social interaction | 6 (5,7) | 7 (6,8) | 7,730.5 | <0.001*** |
| Interest/pastimes | 4 (4,5) | 5 (4,6) | 8,743 | 0.014* |
| CTQ-SF scores | 36 (31,41) | 61 (54,68) | 0 | <0.001*** |
| EA | 7 (6,9) | 14 (11,18) | 1,859 | <0.001*** |
| PA | 5 (5,7) | 8 (6,13) | 4,442.5 | <0.001*** |
| SA | 5 (5,5) | 5 (5,8) | 7,351.5 | <0.001*** |
| EN | 10 (7,13) | 20 (17,21) | 785.5 | <0.001*** |
| PN | 6 (5,8) | 11 (9,14) | 2,239 | <0.001*** |

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ (2-tailed). [a]Suicide plans/behaviors in the life time. [b]Self-injury behaviors in the life time. PHQ-9, nine-item Patient Health Questionnaire; SHAPS, Snaith-Hamilton Pleasure Scale; CTQ-SF, Childhood Trauma Questionnaire–Short Form; EA, emotional abuse; PA, physical abuse; SA, sexual abuse; EN, emotional neglect; PN, physical neglect; DAS, Dysfunctional attitude scale.*

**TABLE 2 |** Prevalence of five childhood traumas in different genders.

| | Female ($n = 245$) | Male ($n = 65$) | $\chi^2$ | ***p*** |
|---|---|---|---|---|
| EA | 70 (28.6%) | 6 (9.2%) | 10.384 | 0.001** |
| PA | 46 (18.8%) | 7 (10.8%) | 2.323 | 0.127 |
| SA | 33 (13.5%) | 4 (6.2%) | 2.616 | 0.106 |
| EN | 105 (42.9%) | 24 (36.9%) | 0.745 | 0.388 |
| PN | 77 (31.4%) | 21 (32.3%) | 0.018 | 0.892 |

**$p < 0.01$ (2-tailed). EA, emotional abuse; PA, physical abuse; SA, sexual abuse; EN, emotional neglect; PN, physical neglect.*

experience ($R^2 = 0.084$***), and social interaction ($R^2 = 0.092$***). Dysfunctional attitudes and physical neglect were the main influencing factors of interest/pastimes ($R^2 = 0.065$***). **Table 4** shows the complete results of the multiple regressions.

## Mediating Effect Analysis

To test the mediating role of dysfunctional attitudes between childhood traumas and anhedonia, we used SEM to test two mediation models with DAS being the mediator. We first included the overall sample, and then we separately analyzed in female and male groups. Age was controlled in all models.

Model 1 examined the mediating role of dysfunctional attitudes between EN and anhedonia. Since food/drink and childhood traumas were not significantly correlated, and EN was not included in the regression equation of interest/pastimes, only sensory experience and

**TABLE 3 |** Spearman's rank correlation between childhood traumas, anhedonia and dysfunctional attitudes.

| | SHAPS | Sensory experience | Food/drink | Social interaction | Interest/pastimes | DAS |
|---|---|---|---|---|---|---|
| EA | 0.113* | 0.084 | 0.054 | 0.163** | 0.121* | 0.238*** |
| PA | 0.076 | 0.062 | 0.015 | 0.122* | 0.083 | 0.211*** |
| SA | −0.045 | −0.055 | −0.025 | −0.069 | 0.012 | 0.106 |
| EN | 0.186** | 0.177** | 0.112 | 0.223*** | 0.137* | 0.159** |
| PN | 0.141* | 0.112 | 0.079 | 0.142* | 0.202*** | 0.163** |
| CTQ-SF | 0.15** | 0.126* | 0.077 | 0.187** | 0.158** | 0.239*** |
| DAS | 0.254*** | 0.246*** | 0.262*** | 0.174** | 0.18** | 1 |

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ (2-tailed). Age, gender, and education level as control variables. SHAPS, Snaith-Hamilton Pleasure Scale; CTQ-SF, Childhood Trauma Questionnaire–Short Form; EA, emotional abuse; PA, physical abuse; SA, sexual abuse; EN, emotional neglect; PN, physical neglect; DAS, Dysfunctional attitude scale.*

**TABLE 4 |** Stepwise multiple linear regressions analyses: associations of childhood traumas and dysfunctional attitudes with anhedonia.

| | Predictors | Unstandardized coefficients | | Standardized coefficients | | |
|---|---|---|---|---|---|---|
| **Dependent** | **Independent** | ***β*** | ***SE*** | ***B(95%CI)*** | ***t*** | ***$R^2$*** |
| SHAPS | DAS | 0.061 | 0.014 | 0.240(0.033–0.089) | 4.343*** | 0.092*** |
| | EN | 0.194 | 0.071 | 0.150(0.054–0.335) | 2.718** | |
| Sensory experience | DAS | 0.023 | 0.006 | 0.230(0.012–0.034) | 4.151*** | 0.084*** |
| | EN | 0.073 | 0.029 | 0.142(0.017–0.130) | 2.562* | |
| Social interaction | EN | 0.065 | 0.018 | 0.197(0.029–0.101) | 3.564*** | 0.092*** |
| | DAS | 0.009 | 0.004 | 0.134(0.002–0.016) | 2.399* | |
| Interest/pastimes | PN | 0.068 | 0.022 | 0.173(0.025–0.112) | 3.09** | 0.065*** |
| | DAS | 0.008 | 0.003 | 0.162(0.002–0.013) | 2.901** | |

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ (2-tailed). SHAPS, Snaith-Hamilton Pleasure Scale; EA, emotional abuse; PA, physical abuse; SA, sexual abuse; EN, emotional neglect; PN, physical neglect; DAS, Dysfunctional attitude scale.*

social interaction were taken as latent variable models of anhedonia.

As shown in **Figure 1**, the overall model showed a good fit: $\chi^2/df = 2.331$, GFI = 0.991, CFI = 0.986, RMSEA = 0.066, SRMR = 0.0232. The SEM analysis revealed that a standardized total effect of EN on anhedonia was 0.231 (*95% CI* (0.075, 0.357), $p = 0.005$), with the significant direct effect of EN on anhedonia being 0.198 (*95% CI* (0.034, 0.329), $p = 0.018$), and the significant indirect effect being 0.033 (*95% CI* (0.004, 0.081), $p = 0.020$) in the pathway of EN-DAS-anhedonia. This indirect effect suggested that higher EN increased the anhedonia via the DAS. In addition, we found that dysfunctional attitudes also had a partial mediation role in female patients (see **Supplementary Figure 1**). However, there was no significant correlation between EN, DAS, and anhedonia in male patients (see **Supplementary Figure 2**).

Model 2 examined the mediating role of dysfunctional attitudes between PN and interest/pastimes. As shown in **Figure 2**, the overall model showed a good fit: $\chi^2/df = 0.409$, GFI = 0.999, CFI = 1.000, SRMR = 0.0120. The SEM analysis revealed that a standardized total effect of PN on interest/pastimes was 0.198 (*95% CI* (0.088, 0.303), $p = 0.001$), with the significant direct effect of PN on interest/pastimes being 0.173 (*95% CI* (0.065, 0.282), $p = 0.002$), and the significant indirect effect being 0.026 (*95% CI* (0.005, 0.062), $p = 0.011$) in the pathway of PN-DAS-interest/pastimes. This indirect effect suggested that higher PN increased the interest/pastimes via the DAS. In addition, dysfunctional attitudes also had a partial mediation role in female patients (see **Supplementary Figure 3**). Nevertheless, there was no significant correlation between PN, DAS, and anhedonia in male patients (see **Supplementary Figure 4**).

## DISCUSSION

In the present study, we investigated if different types of childhood traumas were associated with different dimensions of anhedonia in depressive patients and the role of dysfunctional attitudes in contributing to childhood traumas and anhedonic symptoms. Our findings indicated that dysfunctional attitudes were significant mediators between childhood traumas and anhedonia, indicating cognitive dissonance as a mechanism of anhedonia caused by childhood traumas.

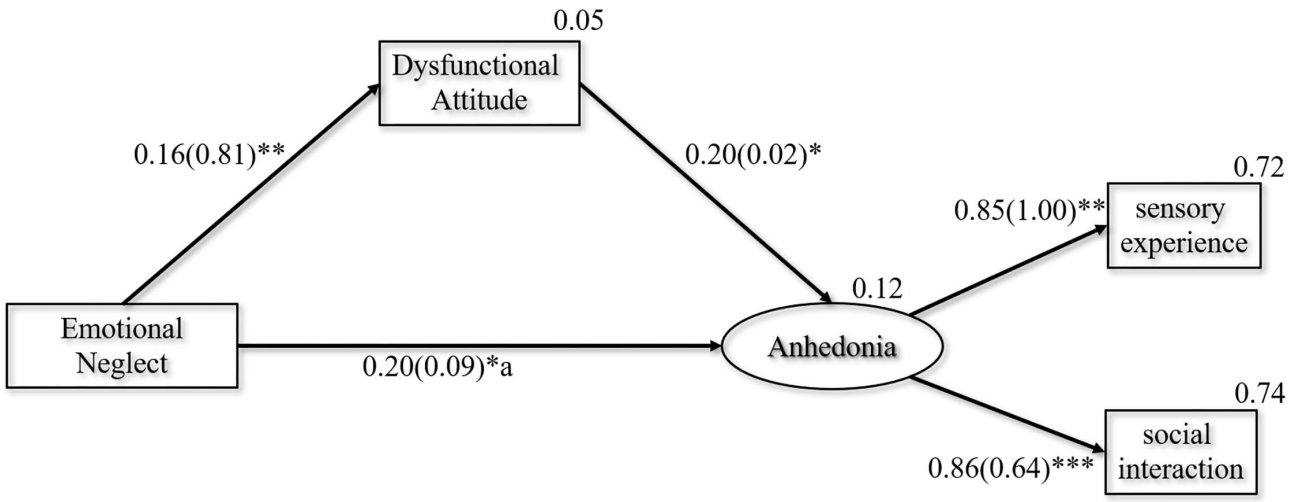


**FIGURE 1 |** Final path model with the standardized and unstandardized coefficients presented in the parentheses. $\chi^2/df = 2.331$, GFI = 0.991, CFI = 0.986, RMSEA = 0.066, SRMR = 0.0232. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

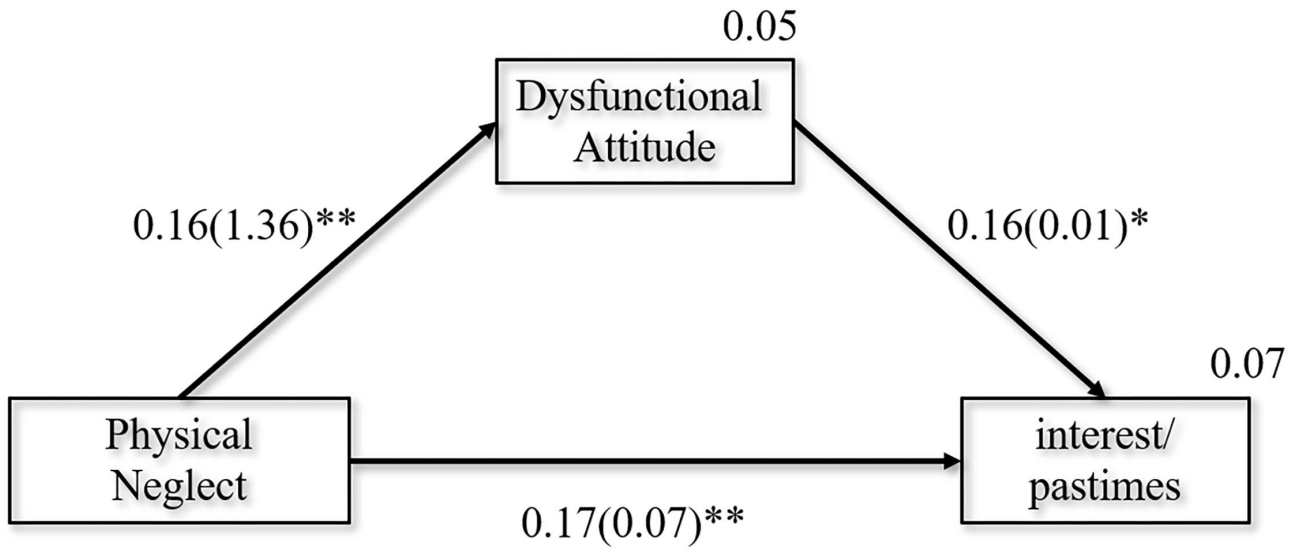


**FIGURE 2 |** Final path model with the standardized and unstandardized coefficients presented in the parentheses. $\chi^2/df = 0.409$, GFI = 0.999, CFI = 1.000, SRMR = 0.0120. $^*p < 0.05$, $^{**}p < 0.01$.

Our findings indicated that anhedonia was related to specific types of childhood traumas. The stronger association came from specific trauma types of emotional abuse and neglect and physical neglect. Among them, the incidence of childhood emotional neglect was the highest in both men (36.9%) and women (42.9%), with no gender difference. Emotional neglect also had a stronger correlation with anhedonia in depression ($rho = 0.186$, $p < 0.01$), consistent with the previous reports (43, 44). Emotional neglect often coexists with emotional abuse, collectively called Childhood Emotional Abuse and Neglect (CEAN). This kind of childhood emotional maltreatment, different from sexual or physical abuse, is more insidious but more common in depression patients (45, 46).

Interestingly, our study found that physical neglect was associated with interest/pastimes of anhedonia. At present, there are few studies on childhood physical neglect. Physical neglect is not associated with mental health problems in early adulthood, such as depression, anxiety, and stress (47). Therefore, the specific reasons for this association need to be further studied. These results reiterate the importance of

distinguishing between childhood misfortunes and clusters of symptoms when describing the relationship between maltreatment and depression.

We found that childhood traumas had main effects on specific domains of consummatory anhedonia. Consummatory anhedonia includes the source of enjoying many things and being able to appreciate the positive stimuli entirely (48). Specifically, we found that individuals with childhood traumas had higher sensory experience, social interaction, and interest/pastimes but not food/drink than participants with a low level of childhood traumas. According to the contents engender pleasure, anhedonia includes physical and social anhedonia. Our analysis showed that childhood emotional neglect was related to sensory experience and social interaction. Sensory experience and social interaction reflect social anhedonia to some extent (49). Therefore, childhood traumas are more likely to cause social anhedonia in patients with depression. Patients with social anhedonia showed decreased social connections, decreased social functioning, and decreased returns from social interactions. Social anhedonia may play an etiological role in developing adolescent depression (50). It is associated with increased severity of depression and poor treatment response (51).

Our study suggested that dysfunctional attitudes mediated the impact of childhood traumas on anhedonia. A recent systematic review also showed that negative cognitive styles could be used as mediating factors in the association between children's emotional abuse and depression (52). The anhedonia-centered model of depressive vulnerability suggests that childhood decreases positive reinforcements and increases negative reinforcements lead to an individual's personality and cognition disorder (53). In comparison, Beck's theory focuses on negative schema and dysfunctional attitudes (54). Childhood maltreatment is deemed to act as a severe environmental risk that may contribute individuals to the development of cognitive vulnerabilities (55) through ruminating and negative reasoning. These abnormal cognitive schemata will become a risk factor for depressive symptoms in adolescence. In addition, other forms of cognitive patterns may also relate to the association between childhood adversities and affective symptoms. Mansueto et al. (56) found that childhood abuse or neglect may be related to negative metacognitive beliefs, mediating the association between childhood adversities and negative emotions. A systematic review suggested that repetitive negative style may be involved in the association between childhood traumas and psychological symptoms in a clinical and non-clinical population: childhood abuse is related to worry and rumination; in contrast, childhood neglect is related to rumination (57).

Therefore, correcting cognitive disorders can reduce the severity of anhedonia for young adult patients who report childhood adversity. Psychotherapy can help improve patients' functional attitude disorders, such as interpersonal psychotherapy (IPT) (58) and cognitive-behavioral therapy (CBT) (59). Considering that depression patients with childhood traumas may have a greater risk of recurrence or treatment resistance, clinicians should provide them with tailor-made interventions to reduce the severity of depressive symptoms. Sequential combination of psychotherapy has a relative advantage in preventing relapse/recurrence of depression (60).

In addition, we found the mediating role of dysfunctional attitudes in the overall sample and the female sample, but not in males since gender differences play an important role in childhood traumas and dysfunctional attitudes. Sonmez et al. (15) found that female adolescents with MDD have a more significant association between anhedonia and sexual abuse than males. Similarly, females with MDD have higher DAS scores and more severe cognitive distortion in seeking applause, dependence, and self-determination than males (61), suggesting that gender differences should be considered when providing interventions. Future research should analyze different gender groups separately.

Our results have some shortcomings. First, our study was a cross-sectional study with no further follow-up to assess patient outcomes, and the CTQ-SF is a recall questionnaire. There might be recall bias in our study's assessment of childhood traumas. Second, the SHAPS focuses exclusively on consummatory pleasure and lacks an assessment of anticipatory anhedonia. Third, some confounding clinical variables that may affect the severity of depression symptoms and cognitive style were not investigated. Growing studies have explored the impact of COVID-19 exposures (62), and recent stressful life events combined with cognitive vulnerability can lead to depression (63). In addition, our study did not include information about pharmacological treatments. Considering pharmacological treatment side effects (64, 65) and that anhedonia often persists after antidepressant treatment (66), evaluating drug efficacy and psychosocial factors in future studies will suggest psychotherapy. Fourth, a larger sample size is needed to validate the results.

## CONCLUSION

Childhood maltreatment, especially emotional neglect, was related to the anhedonia in which sensory experience and social interaction are affected. The dysfunctional attitudes play a mediating role between childhood neglect and anhedonia. For young depression patients with childhood trauma, especially female patients, early cognitive therapy may help to improve the symptoms of anhedonia. Future research needs to explore the impact of childhood traumas on anhedonia with different reward mechanisms and the impact of recent stressful life events.

## 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 Renmin Hospital of Wuhan University. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

PW, NZ, LK, and ZL drafted the manuscript. PW, SM, and WW contributed to data analysis, results, and finalized the manuscript. All authors make important contributions to data collection, read, and approved the final manuscript.

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## SUPPLEMENTARY MATERIAL

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# Anxiety and Depression in Patients With Pulmonary Arterial Hypertension in Northwest China: A Cross-Sectional Study

*Juxia Zhang*[1†], *Yuhuan Yin*[2†], *Yujie Wen*[3], *Fugui Shi*[4] *and Jiancheng Wang*[5*]

[1] Clinical Educational Department, Gansu Provincial Hospital, Lanzhou, China, [2] School of Nursing, Gansu University of Chinese Medicine, Lanzhou, China, [3] Cardiovascular Department, Gansu Provincial Hospital, Lanzhou, China, [4] Lanzhou Hand and Foot Surgery Hospital, Lanzhou, China, [5] Geriatrics Department, Gansu Provincial Hospital, Lanzhou, China

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Ali-Akbar Salari,
Salari Institute of Cognitive and Behavioral Disorders (SICBD), Iran

***Correspondence:**
Jiancheng Wang
juxia2008@hotmail.com

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

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**Objective:** Pulmonary arterial hypertension (PAH) is a rare life-threatening and incurable disease. Although symptoms of depression and anxiety have been widely reported, these traits and associated factors have not been systematically assessed in Northwest China.

**Methods:** A cross-sectional study was conducted between March 2020 and February 2021. 106 PAH patients in Northwest China were evaluated by Self-rating Anxiety Scale (SAS) and the Self Rating Depression Scale (SDS) questionnaire.

**Results:** Overall, the included patients had particularly high depressive symptoms (70.09%), while anxiety among them was 17.55%. Multivariate linear regression revealed that patients with lower age ($p = 0.04$), female ($p < 0.01$), smoking ($p < 0.01$), WHO functional class III/IV ($p < 0.01$), higher mean pulmonary hypertension ($p < 0.01$), lower left ventricular ejection fraction ($p < 0.01$), and lower 6-min walking distance ($p < 0.01$) had higher anxiety scores. Patients who lived in rural areas ($p = 0.01$), smoking ($p < 0.01$), WHO functional class III/IV ($p < 0.01$), higher mean pulmonary hypertension ($p = 0.04$), lower 6-min walking distance ($p < 0.01$), and college degree or above had higher depression scores ($p = 0.02$).

**Conclusions:** Mental health problems such as depression are common among patients with PAH in Northwest China. Patients' characteristics such as smoking status, WHO functional class, and 6-min walking distance were related to anxiety and depression scores. Thus, early detection of mental health problems such as depression and anxiety should be detected in PAH patients. Meanwhile, interventions against these problems should be used to improve such patients' mental status.

**Keywords: depression disorder, anxiety disorder, pulmonary arterial hypertension, patients, China**

## INTRODUCTION

Pulmonary hypertension (PH) is defined as mean pulmonary artery pressure (PAP) at rest of >25 mmHg (1). It is divided into five major categories (2). Currently, one that is of particular clinical relevance is pulmonary arterial hypertension (PAH) (1). An internationally registered epidemiological data on PAH showed that the prevalence of PAH was 15 cases per million adults

(2), making it a rare disease. However, even with PAH-specific drug treatment, there is yet no cure for it and survival for PAH patients remains poor (3). Koudstaal et al.'s study showed that among newly diagnosed PAH cases, the 5-year survival rate was 61.2% (4).

PAH patients can experience multiple symptoms, including shortness of breath (5), fatigue, chest discomfort, and decreased physical function (6). These changes can significantly affect psychological and physical conditions of patients in different ways. For example, PAH patients may have feelings of uncertainty about their future, significant economic burden (7), a high risk of maternal mortality (30–55%) (7, 8), and heavy side effects of medical therapies (9). All of these could have a negative effect on a patient's mental status, resulting in the occurrence of depression and anxiety symptoms. To better understand the health of PAH patients, mental status (depression and anxiety) is increasingly considered as an important indicator of an individual's psychological health (7). In other countries, PAH patients showed a high mental health burden. For example, a study in Japan reported 64% of candidates had depression and 28% had anxiety (10). A study in Beijing, China, found 66.3% of samples had depression and anxiety (11), while 38.2% of PAH patients reported these symptoms in Germany (12). Some studies also have suggested that patients' anxiety and depression symptoms may further lead to deterioration of physical function (11, 13), poor cardiac function (14), poor prognosis (11), worsening quality of life, and increased health-related costs (10).

The present study was produced in Gansu Provincial Hospital. The tertiary hospital is located in Lanzhou, the capital of Gansu Province, which is located in Northwest China. Affected by geographical and regional conditions, compared with other provinces in China, the development of economy, culture, and information as well as medical resources supplying Gansu has been relatively less. According to China's comprehensive economic competitiveness development report, Gansu was listed as 27th among 31 provinces (15). The average altitude of Gansu Province is 2,158 m (3,370.6–421.9 m). At present, there are no detailed epidemiological data of PAH in Gansu. In 2017, Gansu Provincial Hospital took the lead in setting up an outpatient clinic for pulmonary hypertension in the province, and carried out a voluntary activity to care for "Blue Lips," so that this group of people receive attention. In 2020, about 300 inpatients with pulmonary hypertension have been diagnosed and treated in the hospital. With the standardization of disease diagnosis and treatment, the number of patients with pulmonary hypertension is increasing. However, these patients are mostly treated by cardiologists who had less experience in detecting the patients' mental status (16). Guidelines for the diagnosis and treatment of pulmonary hypertension in China (2021 edition) suggest the standard management for PAH patients (17), and the psychological aspects of the disease are often neglected due to the lack of structured psychosomatic support, which also showed in other countries (16). Many mental health epidemiological studies in patients with PAH have been conducted. However, only a few surveys exist in China. With the increase of patients diagnosed with PAH, in addition to clinical treatment, we should investigate the following: (1) How many patients with PAH have symptoms of depression and anxiety? (2) Is there any association between patients' characteristics and incidence of depressive and anxiety, so as to provide effective interventions and lead to improved comprehensive healthcare for PAH patients?

# METHODS

## Study Design

This is a cross-sectional study that uses a questionnaire to evaluate symptoms of depression and anxiety in selected PAH patients.

## Setting and Participants

The study included hospitalized patients diagnosed with PAH at Gansu Provincial Hospital from March 2020 to February 2021.

For inclusion, patients should meet the following criteria: (1) diagnosed with PAH; (2) aged 18 years or older; (3) under optimized medical therapy for PAH for at least 2 months. The diagnosis of PAH was established according to the current guidelines (18). Exclusion criteria were: (1) impaired cognition and judgment; (2) history of diagnosed psychological problems (such as depression and anxiety)—this information was obtained through asking for medical history of mental disorders; (3) unable to communicate; (4) severe comorbidity (such as untreated left heart disease). The nature of the study was explained to all samples, and subsequently, all of them gave verbal consent.

## Questionnaire

A questionnaire was formed to collect information from samples. The first section was demographic data of selected patients, which include age, gender, marital status, education level, home location, smoking, drinking, WHO functional class, mean arterial pressure (mean PAP), left ventricular ejection fraction (LVEF%) and 6-min walking distance (6MWD). The second part consisted of 20 items from Self-rating Anxiety Scale (SAS) to assess symptom of anxiety current or in the last week (19). Each item was answered with "a little of the time," "some of the time," "good part of the time," or "most of the time." For scoring of the answer, items 5, 9, 13, 17, and 19 were positive rated on a 4–1 scale whereas others were negative rated on a 1–4 scale. Based on standardized scoring algorithm, symptom of anxiety was defined if the SAS score $\geq$50 points (50–59 mild, 60–69 moderate, $\geq$70 severe). The third part included 20 items from the Self Rating Depression Scale (SDS) that used to measure symptoms of depressive using a 4-point scale "none" for 1, "a little of the time" for 2, "most of the time" for 3, and "all of the time" for 4 (20). Under standardized scoring algorithm, depression symptom was defined if the SAS score was $\geq$53 points (53–62 mild, 63–72 moderate, $>$72 severe). The higher scores indicate more severe symptoms.

## Sample Size

According to a preliminary survey, the prevalence of depression in patients with pulmonary hypertension was 40.2%. We assume $p = 50\%$ and a precision level of 10% ($50 \pm 10\%$). The sample size was calculated as follows (19):

$$n = \frac{Z^2_{\alpha/2}(1-p)p}{\delta^2} \quad (1)$$

where confidence level $Z_{(\alpha/2)} = 1.96$ and δ is the allowable error (0.10). The resulting sample size of 96 was increased to 10–12% to account for questionnaires discarded due to lack of information and filling errors.

## Data Collection

Two trained researchers performed the survey. Patients' demographic and clinical symptom data including gender, age, WHO functional class, 6MWD, mean PAP, and main symptoms were traced from medical records. Then, the researchers invited individual patients to a single room next to the cardiovascular medicine department. One of the researchers explained the nature of the study and verbal agreement was acquired from patients. Each respondent was given 20 min to fill in the questionnaire. If someone cannot correctly answer for some reasons (such as illiteracy), one of the family members would be invited to assist. After all patients completed the survey, the two researchers entered the data into Excel 2007.

## Statistical Methods

Data were imported from Excel to SPSS 21 for analyses. Categorical variables were expressed in absolute ($n$) and relative (%) frequencies, and numerical variables were expressed in mean ($\bar{x}$) and SD. $T$-test and one-way ANOVA were performed to preliminarily analyze various independent variables related to anxiety and depression scores. Next, multiple linear analysis was used to examine the independent factors related to anxiety and depression scores. The dependent variable was anxiety or depression scores, taking into account confounding factors; all demographic and disease-related characteristics were included in the regression model. During multivariable modeling, tolerance and the variance inflation factor (VIF) were used to detect multicollinearity. Any predictor with a tolerance below 0.1 and/or a VIF above 10 was excluded from the final model. A $p$-value $< 0.05$ was considered to be statistically significant.

# RESULTS

## Basic Information of the Participants

As shown in **Table 1**, of 129 included patients, 20 were excluded as WHO functional class or 6MWD was not performed. Furthermore, three patients were excluded for not completing the SAS. Finally, 106 patients were enrolled (consent rate = 82.17%) with mean age 54.74 ± 14.43 (range: 23–85). Of them, 54.72% were female. According to WHO functional classifications (WHO FC), the majority (62.26%) of patients were classified as WHO FC III/IV. The mean PAP was 43.62 ± 13.24 (range: 26–73). Regarding common symptoms, 75.47% reported shortness of breath, followed by cough (35.85%) and chest pain (13.21%).

**TABLE 1** | Participant demographics.

| Characteristics | | Participants ($N = 106$) $n$ (%) |
|---|---|---|
| Age (years), $\bar{x} \pm SD$, range | | 54.74 ± 14.43, 23–85 |
| Gender | Male | 48 (45.28) |
| | Female | 58 (54.72) |
| Marital status | Unmarried | 10 (9.43) |
| | Married | 96 (90.57) |
| Home location | Rural | 48 (45.28) |
| | Urban | 58 (54.72) |
| Educational level | High school or below | 74 (69.81) |
| | College degree or above | 32 (30.19) |
| Profession | Worker or farmers | 60 (56.60) |
| | Cadre or retired | 46 (43.40) |
| Smoking | Yes | 18 (16.98) |
| Drinking | Yes | 14 (13.21) |
| WHO-FC, $n$ (%) | Class I/II | 40 (37.74) |
| | Class III/IV | 66 (62.26) |
| Mean PAP (mmHg), $\bar{x} \pm$ SD, range | | 43.62 ± 13.24, 26–73 |
| LVEF%, $\bar{x} \pm$ SD, range | | 51.51 ± 8.07, 32–69 |
| 6MWD (m), $\bar{x} \pm$ SD, range | | 354.03 ± 80.47, 136–489 |
| Common symptom | Shortness of breath | 80 (75.47) |
| | Chest pain | 14 (13.21) |
| | Cough | 38 (35.85) |
| Antidepressant drug (yes) | | 0 (0.00) |
| Oxygen therapy (yes) | | 106 (100) |

*PAP, pulmonary arterial pressure; LVEF%, left ventricular ejection fraction; 6MWD, 6-min walking distance; WHO-FC, World Health Organization functional class.*

## Symptoms of Depression and Anxiety

Of the 106 participants, 70.09% had symptoms of depression with 28.22% moderate to severe (**Figure 1**); however, no one used antidepressant drugs or accepted non-drug interventions (**Table 1**).

The incidence of depressive symptoms in urban PAH patients was significantly higher than those in rural areas ($t = 3.42$, $p < 0.01$). Non-smokers had significantly higher depression scores than smokers ($t = 3.29$, $p < 0.01$), while the depression scores were higher among those with LVEF% <50 ($t = 2.60$, $p = 0.01$) and higher mean PAP (**Table 2**). Anxiety symptoms were found by 17.55% of the participants, and they were all mild anxiety, while none were found to have moderate or greater anxiety (**Figure 1**). The incidence of anxiety was significantly higher among PAH patients whose homes were located in an urban area ($t = 2.13$, $p = 0.03$). Anxiety symptoms were significantly higher among participants who were not smoking ($t = 5.11$, $p < 0.01$) and not drinking ($t = 2.46$, $p = 0.01$) compared with those who did (**Table 2**).

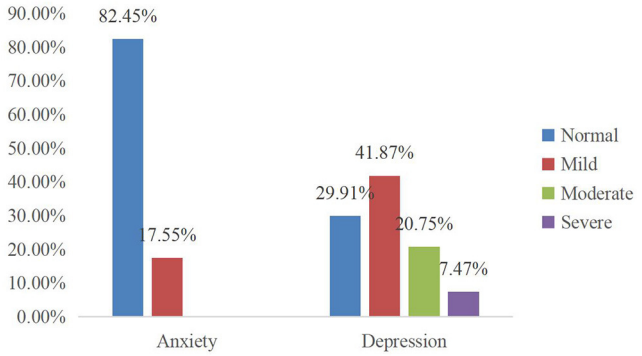


**FIGURE 1 |** The percentage of anxiety and depression levels.

## Influencing Factors for Symptoms of Anxiety and Depression

The results of multivariate linear regression analysis (**Table 3**) showed that the significant influencing factors of anxiety scores were age (95% CI, −0.12, −0.002; $p = 0.04$), gender (95% CI, −4.59, −0.92; $p < 0.01$), smoking (95% CI, −10.18, −4.17; $p < 0.01$), WHO-FC (95% CI, 1.13, 2.81; $p < 0.01$), mean PAP (95% CI, 1.07, 3.19; $p < 0.01$), LVEF% (95% CI, −0.39, −0.16; $p < 0.01$), and 6MWD (95% CI, −0.05, −0.008; $p < 0.01$) (**Table 3**).

The significant influencing factors of depression scores were home location (95% CI, −5.91, −0.81; $p = 0.01$), smoking (95% CI, −10.27, −2.09; $p < 0.01$), WHO functional class (95% CI, 1.36, 3.48; $p < 0.01$), mean PAP (95% CI, 0.46, 3.92; $p = 0.04$), 6MWD (95% CI, −0.09, −0.03; $p < 0.01$), and educational level (95% CI, 0.10, 1.61; $p = 0.02$) (**Table 4**).

# DISCUSSION

This study is the first to provide evidence regarding prevalence of psychiatric disorders in patients with PAH in Northwest China, thus providing essential references for the psychological treatment of PAH patients.

Our study suggested that the prevalence of depression was considerably high in patients with PAH. Notably, we found that the state of depression and anxiety was significantly related to social characteristics including smoking status, WHO functional class, mean PAP, and 6MWD in these patients.

## Anxiety and Depression Symptoms of Patients With PAH

A previous study estimated that the incidence of moderate to severe depression in PAH patients has been between 20 and 50% (21). Our study also found similar results: 70.09% of patients were judged to have depressive symptoms on the depression score, and 28.22% had moderate to severe depression. The result of the high incidence of depressive symptoms in present study was consistent with a previous study in Beijing, China (11), and in other countries (12). These may be because of the poor prognosis, significant side effects, and activity limitations of patients diagnosed of PAH that may expose patients to higher stressors, leading to the development of depression and anxiety (21). High levels of such status can adversely affect health outcomes (22), increase the chance of unhealthy behaviors (23), cause adverse events to occur more frequently (11), and reduce quality of life (10). However, there was a lack of psychological support for PAH patients with depression in the present population, who have not received any type of intervention, and similar observations have been made in the study of Harzheim et al. (24). It is noteworthy that these patients in our hospital are mostly treated by pulmonologists or cardiologists with limited experience in the detection of mental illness, and similar limited sources of medical care have been observed in other developing countries (22). The lack of mental health detection for PAH patients will lead to inadequate diagnosis, treatment, and intervention for these problems. Since this negative mental status will bring adverse outcomes to PAH patients, and psychological support has not been the standardized management in most pulmonary hypertension institutions (22), as a high-risk group for developing emotional problems in the literature, we suggest that early screening and diagnosis of mental disorders in this group is essential. Meanwhile, to improve mental symptoms of patients with PAH, the need for a psychological support and counseling would be beneficial (25).

In contrast, the anxiety was less prevalent than depression in the present study with prevalence of 17.55%, which was similar to the finding from Japan (10). One study found that patients who had long been diagnosed and followed in a reference center have a lower frequency of psychological disorders than those who had recently been diagnosed with PAH (25). Although a small proportion of patients experienced anxiety in the present study, our study was a survey at a given point of time and did not compare mental health change with the disease progression. In addition, the present study only focused on depression and anxiety symptoms, it will be necessary to analyze the association between mental status and quality of life in the future.

## Effect of Social Characteristics on Symptoms of Depression and Anxiety

Our study observed that PAH patients from urban areas were more likely to have psychological problems than those from rural areas. Similar outcomes were also found in residents of China (26–28) and other countries (29). A meta-analysis concluded that the odds of depression increased by about 30% in cities compared with rural areas (30). Even though urban living can offer benefits [such as convenient transportation, access to medical resources (28)], it is characterized by a lack of green space, intensive social activity, intense competition, and social fragmentation (lack of social connections between individuals in a particular geographical area) (31, 32), which may have a negative impact on those susceptible to mental illness (29). Thus, appropriate interventions are needed for PAH patients with mental disorders in different geographic regions. Our study found that patients who smoked had lower

**TABLE 2 |** Univariate analysis of anxiety, depression scores, and general characteristics.

| Characteristics | | Anxiety score | | | Depression score | | |
|---|---|---|---|---|---|---|---|
| | | $\bar{x} \pm SD$ | *F/t* | *p* | $\bar{x} \pm SD$ | *F/t* | *p* |
| Age | <40 | 38.89 ± 6.25 | 1.45[a] | 0.23 | 45.28 ± 3.31 | 1.02[a] | 0.36 |
| | 40 ∼ 60 | 39.88 ± 3.72 | | | 48.50 ± 7.05 | | |
| | >60 | 41.68 ± 5.05 | | | 47.40 ± 6.56 | | |
| Gender | Male | 39.84 ± 5.41 | −0.89[b] | 0.37 | 46.46 ± 6.86 | −1.17[b] | 0.24 |
| | Female | 41.90 ± 4.34 | | | 48.28 ± 5.86 | | |
| Marital status | Single | 37.25 ± 5.75 | 1.75[b] | 0.08 | 45.25 ± 2.61 | 1.82[b] | 0.08 |
| | Married | 40.50 ± 4.70 | | | 47.69 ± 6.59 | | |
| Home location | Rural | 39.06 ± 5.20 | 2.13[b] | **0.03** | 44.69 ± 6.78 | 3.42[b] | **<0.01** |
| | Urban | 41.55 ± 4.38 | | | 49.74 ± 5.36 | | |
| Educational level | High school or below | 40.44 ± 4.87 | 0.72[b] | 0.48 | 48.69 ± 6.81 | 2.02[b] | 0.13 |
| | College degree or above | 41.53 ± 4.54 | | | 50.84 ± 5.59 | | |
| Profession | Worker or farmers | 38.55 ± 4.35 | 2.92[b] | 0.09 | 46.35 ± 7.850 | 1.03[b] | 0.36 |
| | Cadre or retired | 42.40 ± 3.65 | | | 47.89 ± 4.352 | | |
| Smoking | No | 41.65 ± 4.46 | 5.11[b] | **<0.01** | 48.55 ± 5.488 | 3.29[b] | **<0.01** |
| | Yes | 34.45 ± 3.79 | | | 42.09 ± 8.444 | | |
| Drinking | No | 40.98 ± 4.86 | 2.46[b] | **0.01** | 47.91 ± 5.757 | 1.52[b] | 0.13 |
| | Yes | 36.79 ± 3.80 | | | 44.46 ± 9.296 | | |
| WHO-FC | Class I/II | 39.78 ± 4.41 | 1.42[b] | 0.15 | 47.63 ± 8.044 | 0.15[b] | 0.87 |
| | Class III/IV | 41.50 ± 5.41 | | | 48.35 ± 5.125 | | |
| Mean PAP (mmHg) | 26 35 | 41.86 ± 5.69 | 2.14[a] | 0.12 | 46.64 ± 7.694 | 7.65[a] | **<0.01** |
| | 36 45 | 41.96 ± 3.50 | | | 46.94 ± 4.794 | | |
| | >45 | 42.15 ± 4.71 | | | 48.40 ± 6.085 | | |
| LVEF% | <50 | 43.63 ± 5.08 | −0.11[b] | 0.90 | 50.06 ± 5.067 | 2.60[b] | **0.01** |
| | 50 70 | 38.64 ± 4.11 | | | 45.99 ± 6.717 | | |
| 6MWD (m) | >426 | 38.58 ± 6.80 | 1.24[a] | 0.29 | 40.89 ± 9.414 | 1.03[a] | 0.36 |
| | 150 425 | 40.49 ± 4.52 | | | 47.99 ± 5.488 | | |
| | <150 | 42.50 ± 4.16 | | | 52.25 ± 4.185 | | |

[a]*Equal to F value.*
[b]*Equal to t value.*
*WHO-FC, World Health Organization functional class; PAP, pulmonary arterial pressure; LVEF%, left ventricular ejection fraction; 6MWD, 6-min walking distance.*
*Bold values are those indicating statistical significance.*

scores for depression and anxiety compared with those who did not. This is probably because nicotine, the main ingredient in cigarettes, binds to nicotinic acetylcholine receptors, which increases the amount of dopamine secreted by neurons in the brain's reward centers, leading to feelings of happiness and relaxation (33). Besides, some studies have also found that withdrawal from cigarettes after nicotine addiction can lead to increased anxiety and depression symptoms (34, 35).

Our multiple linear regression showed that the likelihood of depression and anxiety in patients with better functional status (WHO FC I or II) was significantly lower. FC and 6MWD are two measures to assess patients' functional exercise capacity and treatment efficacy (36), which are also specific treatment goals for PAH patients as guidelines recommend with FC I–II and 6MWT ≥380–440 m (37). One study has shown that the prevalence of depression increased with functional class (FC) worsening (38) and 6MWT decreasing (22). Exercise and physical activity are useful to gain self-confidence (39), which are also good opportunities to meet or socialize with others and can help improve one's mood (40). However, severe physical capacity impairment was common in patients with PAH (21). In the present study, most individuals had FC III/IV, and the average of 6MWD was 354.03 ± 80.47 m, which was similar to the results in America (41), Brazil (42), and France (43). For many individuals diagnosed with PAH, impaired exercise tolerance is a prominent feature that can lead to increased sense of social isolation (22). The occurrence of mental disorders is obviously related to the restriction of daily activities (11). However, it is still difficult to determine whether exercise restriction is the cause of mental illness. It has been reported that proper exercise training is an adjunct to improving the exercise capacity of PAH patients (11); in addition, patients who were followed at PAH centers were less likely to develop mental disorders than those who were not (11), further demonstrating the positive role of psychological support. Diagnosed patients are prone to emotional problems due to the type and severity of PAH; in the future, there should be more evidence on

**TABLE 3 |** Multiple linear regression analysis of anxiety scores and general characteristics.

| Characteristics | Unstandardized coefficients | | Standardized coefficients | t | *p* | 95% CI | |
|---|---|---|---|---|---|---|---|
| | B | SE | Beta | | | Lower | Upper |
| Age | −0.06 | 0.03 | −0.19 | −2.06 | **0.04** | −0.12 | −0.002 |
| Gender (male) | −2.75 | 0.95 | −0.28 | −2.98 | **<0.01** | −4.59 | −0.92 |
| Marital status (married) | 0.94 | 1.79 | 0.05 | 0.52 | 0.60 | −2.62 | 4.51 |
| Home location (rural) | −1.64 | 0.94 | −0.17 | −1.74 | 0.08 | −3.52 | 0.22 |
| Educational level (college degree or above) | 0.21 | 0.31 | 0.05 | 0.68 | 0.49 | −0.40 | 0.82 |
| Profession (cadre or retired) | 0.08 | 0.26 | 0.03 | 0.31 | 0.75 | −0.44 | 0.61 |
| Smoking (yes) | −7.17 | 1.51 | −0.55 | −4.74 | **<0.01** | −10.18 | −4.17 |
| Drinking (yes) | 2.15 | 1.46 | 0.15 | 1.47 | 0.14 | −0.75 | 5.05 |
| WHO-FC (class III/IV) | 1.97 | 0.42 | 0.36 | 4.66 | **<0.01** | 1.13 | 2.81 |
| Mean PAP | 2.13 | 0.53 | 0.39 | 4.03 | **<0.01** | 1.07 | 3.19 |
| LVEF% | −0.27 | 0.05 | −046 | −4.72 | **<0.01** | −0.39 | −0.16 |
| 6MWD | −0.02 | 0.01 | −0.35 | −2.73 | **<0.01** | −0.05 | −0.008 |

*Adjusted $R^2 = 0.536$, $p < 0.01$.*
*Bold values are those indicating statistical significance.*
*95% CI, 95% confidence interval for B.*

**TABLE 4 |** Multiple linear regression analysis of depression scores and general characteristics.

| Characteristics | Unstandardized coefficients | | Standardized coefficients | t | *p* | 95% CI | |
|---|---|---|---|---|---|---|---|
| | B | SE | Beta | | | Lower | Upper |
| Age | −0.03 | 0.04 | −0.07 | −0.79 | 0.42 | −0.11 | 0.05 |
| Gender (male) | −1.99 | 1.26 | −0.15 | −1.58 | 0.11 | −4.49 | 0.50 |
| Marital status (married) | −1.02 | 2.44 | −0.04 | −0.41 | 0.67 | −5.88 | 3.84 |
| Home location (rural) | −3.36 | 1.28 | −0.26 | −2.61 | **0.01** | −5.91 | −0.81 |
| Educational level (college degree or above) | 0.85 | 0.38 | 0.27 | 2.25 | **0.02** | 0.10 | 1.61 |
| Profession (cadre or retired) | 0.36 | 0.36 | 0.11 | 1.00 | 0.31 | −0.35 | 1.08 |
| Smoking (yes) | −6.18 | 2.06 | −0.36 | −3.00 | **<0.01** | −10.27 | −2.09 |
| Drinking (yes) | 1.98 | 1.98 | 0.10 | 1.00 | 0.32 | −1.96 | 5.94 |
| WHO functional class (class III/IV) | 2.42 | 0.53 | 0.45 | 4.58 | **<0.01** | 1.36 | 3.48 |
| Mean PAP | 2.19 | 0.86 | 0.31 | 2.55 | **0.04** | 0.46 | 3.92 |
| LVEF% | −0.14 | 0.08 | −0.18 | −1.85 | 0.06 | −0.30 | 0.01 |
| 6MWD | −0.06 | 0.01 | −0.62 | −4.65 | **<0.01** | −0.09 | −0.03 |

*Adjusted $R^2 = 0.498$, $p < 0.01$.*
*Bold values are those indicating statistical significance.*
*95% CI, 95% confidence interval for B.*

the role of interventions, including psychological counseling and appropriate social support for PAH patients with anxiety and depression.

There are limitations in this study. First, this was a cross-sectional study and did not prove a causal relationship between the prevalence of mental disorders and social characteristics. Second, the samples were chosen from a tertiary hospital in Northwest China, and the use of a single site may result in sampling bias that affects the representativeness of the study. Third, our study focused on inpatients who may have higher rates of depression and anxiety than outpatients. Finally, the use of self-reported patient data may lead to some bias because the answers may be exaggerated or underreported.

## CONCLUSIONS

The study concluded that although optimized treatments for PAH were available, these patients often experience symptoms of depression and anxiety, which were associated with impaired cardiac function and mobility. Also, these problems were underestimated due to a lack of standardization in the psychological detection. The study calls for screening and diagnosis of anxiety and depression to be included in routine

clinical testing. In addition, more randomized controlled trials should be conducted to explore the effects of interventions such as psychological counseling, psychosocial support, and drugs on PAH patients with anxiety and depression.

## 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 Research Committee of Gansu Provincial Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

JZ was responsible for study design, implementation of the study, and drafting of the article. JW and YY were responsible for study design, statistical analysis, data interpretation, and drafting of the article. YW was responsible for data collection and data interpretation. YY and FS were responsible for implementation of the study and data interpretation. YY revised the contents of the article. 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.2021.758120/full#supplementary-material

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# Serum Neurofilament Light Predicts 6-Month Mental Health Outcomes in a Cohort of Patients With Acute Ischemic Stroke

*Duo-Zi Wang*[1†], *Fu-Qiang Guo*[1†], *Lei Guo*[1], *Shu Yang*[1], *Neng-Wei Yu*[1], *Jian Wang*[2] *and Jian-Hong Wang*[1*]

[1] *Department of Neurology, The Affiliated Hospital of University of Electronic Science and Technology, Sichuan Provincial People's Hospital, Chengdu, China,* [2] *Department of Neurology, Ya'an People's Hospital, Ya'an, China*

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*Marco Grados, Johns Hopkins University, United States*

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***Correspondence:**
*Jian-Hong Wang*
*jhwangneurology@yeah.net*

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

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**Background:** Mental health problems after acute ischemic stroke (AIS) have caused wide public concerns, and the study on early identification of these disorders is still an open issue. This study aims to investigate the predictive effect of circulating neurofilament light (NfL) on long-term mental health status of AIS patients.

**Methods:** This study collected demographic information and mental health measurements from 304 AIS patients from May 1, 2016 to Dec 31, 2019. Baseline serum neurofilament light (NfL) was determined within 2 h since patient admission. Six months after AIS onset, the degree of symptoms of depression, anxiety, and insomnia was assessed by the Chinese versions of the 9-item Patient Health Questionnaire (PHQ-9), the 7-item Generalized Anxiety Disorder scale (GAD-7), the 7-item Insomnia Severity Index (ISI), respectively. Subjects were divided into the high NfL group and the low NfL group. Multivariate logistic regression analysis was performed to identify factors associated with these mental health problems.

**Results:** The high NfL group had significantly higher PHQ-9, GAD-7, and ISI scores than the low NfL group. The prediction of serum NfL for major depression generated a sensitivity of 70.27%, a specificity of 67.79% and an AUC of 0.694. The prediction of serum NfL for anxiety generated a sensitivity of 69.23%, a specificity of 64.02%, and an AUC of 0.683. The prediction of serum NfL for insomnia generated a sensitivity of 75.00%, a specificity of 66.43% and an AUC of 0.723. Higher serum NfL was a risk factor of post-AIS depression [ORs (95% CI): 4.427 (1.918, 10.217)], anxiety [ORs (95% CI): 3.063 (1.939, 6.692)], and insomnia [ORs (95% CI): 4.200 (1.526, 11.562)].

**Conclusions:** These findings imply that circulating NfL might be a potential biomarker of long-term mental health problems after AIS.

**Keywords: post-stroke, neurofilament light, depression, anxiety, insomnia**

## INTRODUCTION

Acute ischemic stroke (AIS) is among the leading causes of death and disability worldwide (1). Except for neurological deficits, AIS patients also experience a variety of mental health problems, such as anxiety (2), depression (3), and insomnia (4) during the rehabilitation of the disease. Although these post-AIS consequences do not directly cause death or disability, they are closely related to the quality of life after stroke. Therefore, early identification of patients with risk of developing neuropsychological disorders is of significance for timely intervention to improve the mental health outcomes. Recent studies have identified a panel of blood-based biomarkers that is associated with stroke severity and prognosis (5). However, few convenient and effective biomarkers are available to evaluate the risk of neuropsychological problems after stroke.

Neurofilaments, including neurofilament light (NfL), neurofilament medium (NfM), and neurofilament heavy (NfH) are components of the neuronal cytoskeleton. Together with NfH and NfM, NfL represents one of the scaffolding proteins of the neuronal cytoskeleton and is released into the extracellular space following neuronal damage (6). NfL is increased in multiple neurological diseases, such as Alzheimer's disease (7), Parkinson's disease (8), and multiple sclerosis (9). It is also a well-validated prognostic biomarker of functional outcomes of AIS (10). But it is not clear yet whether NfL could predict mental health outcomes of this disease. This study aims to investigate the association between circulating NfL and mental health outcomes of AIS, including major depression, anxiety, and insomnia.

## SUBJECTS AND METHODS

### Patients

This study used the same cohort of patients in our previous study (11). Briefly, inpatients with AIS from the Department of Neurology, Sichuan Provincial People's Hospital and Ya'an People's Hospital during May 1, 2016 and Dec 31, 2019, were screened for eligibility for this study. Patients were excluded if they have one of the following conditions: (1) Have previously diagnosed depression, anxiety, and insomnia before AIS onset; (2) have other psychological disorders, such as schizophrenia and bipolar disorders et al. before AIS onset; (3) Cannot complete psychological tests due to hearing, language, or communicating disabilities; (4) Other severe neurological diseases which may affect circulating NfL levels, such as Parkinson's disease, Alzheimer's disease, and traumatic brain injury; (5) Refused to participate in this study. Written informed consent for participation was obtained from patients or their legal relatives. This study conformed with the principles of the Declaration of Helsinki and was approved by the investigational review board of the Sichuan Provincial People's Hospital.

### Clinical Assessment and Data Collection

The demographic information, including age, sex, education level, body mass index (BMI), smoking history, medical history, including oral anticoagulion or antiplatelet drug use, comorbidities such as hypertension, diabetes mellitus, hypercholesteremia, and arial fibrillation were collected from the medical records. AIS was diagnosed according to the World Health Organization (WHO) Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (WHO-MONICA) criteria and was verified by magnetic resonance imaging (MRI) performed within 24 h since symptom onset. The neurological deficits of patients were examined with the National Institutes of Health Stroke Scale (NIHSS) upon admission (12), performed by a certified stroke neurologist. AIS subtype was determined with the TOAST criteria.

### Assessment of Mental Health Outcomes

We focused on symptoms of depression, anxiety, and insomnia for all participants 6 months after AIS onset, using Chinese versions of validated measurement tools. Accordingly, the 9-item Patient Health Questionnaire (PHQ-9; range, 0–27) (13), the 7-item Generalized Anxiety Disorder (GAD-7) scale (range, 0–21) (14), the 7-item Insomnia Severity Index (ISI; range, 0–28) (15), were used to assess the severity of symptoms of depression, anxiety, and insomnia, respectively. The total scores of these measurement tools were interpreted as follows: PHQ-9, normal (0–4), mild (5–9), moderate (10–14), and severe (15–27) depression; GAD-7, normal (0–4), mild (5–9), moderate (10–14), and severe (15–21) anxiety; ISI, normal (0–7), subthreshold (8–14), moderate (15–21), and severe (22–28) insomnia. These categories were based on cutoff values established in the literature (13–15). The cutoff value for detecting symptoms of major depression, anxiety, and insomnia distress were 10, 7, and 15, respectively. Participants with scores above the cutoff threshold were characterized as having major depression, anxiety and insomnia, respectively.

### NfL Concentration Determination

Blood was sampled within 2 h since admission, and serum was separated within 30 min after sampling and stored at −80°C until further analysis. Serum NfL was determined using the single-molecule (Simoa) array according to manufacturer's instructions (16). Each test was done in duplicates and the means of each test were used for statistical analysis. Monoclonal antibodies and purified bovine NFL were used as calibrators.

### Statistical Analysis

Continuous variables were tested for normality, and if they were normally distributed, an independent *t*-test was used, but if they were not normally distributed, a Mann-Whitney *U*-test was used. For categorical data, two-sample tests of proportions were used to compare proportions. Logistical regression models were utilized to investigate the association between serum NfL concentrations at baseline and mental health outcomes. We first fitted univariate models with a single candidate variable at one time. The potential risk factors as determined by a $p$-value $< 0.2$ were included in the final multivariate regression models. The receiver operating characteristic (ROC) curve analysis were utilized to test the predictive effects of baseline serum NfL on mental health outcomes at follow-up. Optimal sensitivity and specificity were determined *via* a non-parametric approach. The Youden index was calculated for the cutoff value to determine the

cutoff value that maximized the discriminating power of the test. Statistical analyses were conducted using SPSS statistical package version 24 (IBM SPSS Statistics for Windows, Armonk, NY, USA) and a $p$-value $< 0.05$ was regarded as statistically significant.

# RESULTS

## Demographic Characteristics of Subjects

We categorized the patients into two groups according to serum NfL concentrations, the high NfL group and the low NfL group. There was no significant difference in the mean age, median BMI, the frequency of family history of stroke, frequencies of antiplatelet drug use and anticoagulation drug use between the high NfL and low NfL group. Frequencies of hypertension, diabetes mellitus, hypercholesteremia and arial fibrillation between the high NfL and low NfL group were also not significantly different between groups. No significant difference was not observed in the distribution of infarction region and stroke etiology between the high and low NfL group. No significant difference was also not observed in the incidences of hemorrhagic transformation and recurrent AIS during follow-up between groups. The high NfL group had significantly higher incidences of PSD, PSA, and PSI than the low NfL group during follow-up (**Table 1**).

**TABLE 1 |** Demographic information of subjects.

| Variables | Low NfL group ($n = 152$) | High NfL group ($n = 152$) | *P*-value |
|---|---|---|---|
| Age, mean (SD) | 64.81 (9.25) | 65.02 (9.25) | 0.843[a] |
| Female, No. (%) | 88 (57.89) | 86 (56.58) | 0.908[b] |
| BMI, median (IQR) | 24.51 (23.08–25.59) | 24.24 (23.08–25.54) | 0.483[c] |
| Smoking history, No. (%) | 11 (7.24) | 17 (11.18) | 0.321[b] |
| Antiplatelet drug use, No. (%) | 20 (13.16) | 20 (13.16) | 1.000[b] |
| Antithrombotic drug use, No. (%) | 5 (3.29) | 14 (9.21) | 0.055[b] |
| Family history of stroke, No. (%) | 7 (4.61) | 11 (7.24) | 0.467[b] |
| **Comorbidities** | | | |
| Hypertension, No. (%) | 49 (32.24) | 55 (36.18) | 0.546[b] |
| Diabetes Mellitus, No. (%) | 28 (18.42) | 21 (13.82) | 0.349[b] |
| Hypercholesteremia, No. (%) | 14 (9.21) | 14 (9.21) | 1.000[b] |
| Arial fibrillation, No. (%) | 5 (3.29) | 14 (9.21) | 0.055[b] |
| Post stoke anxiety, No. (%) | 17 (11.18) | 48 (31.58) | <0.001[b] |
| Post stroke depression, No. (%) | 8 (5.26) | 29 (19.08) | <0.001[b] |
| Post stroke insomnia, No. (%) | 5 (3.29) | 19 (12.50) | <0.001[b] |
| DWI hyperintensity volume, ml (SD) | 24.37 (1.52) | 24.26 (1.50) | 0.544[b] |
| **Infarction region*** | | | |
| Cerebral lobe, No. (%) | 29 (19.08) | 23 (15.13) | 0.447[b] |
| Cerebral white matter, No. (%) | 26 (17.11) | 20 (13.16) | 0.424[b] |
| Striatocapsule, No. (%) | 103 (67.76) | 112 (73.68) | 0.313[b] |
| Thalamus, No. (%) | 4 (2.63) | 8 (5.26) | 0.378[b] |
| Cerebellum, No. (%) | 4 (2.63) | 6 (3.95) | 0.750[b] |
| **Stroke etiology** | | | |
| Atherothrombotic, No. (%) | 132 (86.84) | 125 (82.24) | 0.341[b] |
| Cardioembolic, No. (%) | 5 (3.29) | 14 (9.21) | 0.055[b] |
| Lacunar, No. (%) | 9 (5.92) | 8 (5.26) | 1.000[b] |
| Unknown, No. (%) | 6 (3.95) | 5 (3.29) | 1.000[b] |
| **Complication** | | | |
| Hemorrhagic effect, No. (%) | 4 (2.63) | 6 (3.95) | 0.750[b] |
| Recurrent AIS, No. (%) | 3 (1.97) | 2 (1.32) | 1.000[b] |
| Post-stroke depression, No. (%) | 8 (5.26) | 29 (19.08) | <0.001[b] |
| Post-stroke anxiety, No. (%) | 17 (11.18) | 48 (31.58) | <0.001[b] |
| Post-stroke insomnia, No. (%) | 5 (3.29) | 19 (12.50) | 0.005[b] |

*IQR, Inter-Quartile Range; BMI, Body Mass Index; NIHSS, National Institutes of Health Stroke Scale.*

**It is notable that the infarctions may involve multiple brain regions.*

[a] *Unpaired t-test.*

[b] *Pearson $\chi^2$-test.*

[c] *Mann-Whitney U-test.*

## Mental Health Outcomes of AIS Patients and Their Associations With Serum NfL Levels

High NfL group had significantly higher PHQ-9, GAD-7, and ISI scores than low NfL group (**Figure 1**). Serum NfL concentrations were positively associated with PHQ-9, GAD-7, and ISI scores (**Figure 2**). Furthermore, serum NfL predicted major depression with a sensitivity of 70.27%, a specificity of 67.79% and an AUC of 0.694 (**Figure 3A**). Serum NfL predicted anxiety with a sensitivity of 69.23%, a specificity of 64.02% and an AUC of 0.683 (**Figure 3B**). Serum NfL predicted insomnia with a sensitivity of 75.00%, a specificity of 66.43% and an AUC of 0.723 (**Figure 3C**).

## Risk Factors of Mental Health Problems

We utilized three logistic regression models to investigate risk factors of major depression, anxiety and insomnia. In univariate analyses, family history of stroke [ORs (95% CI): 3.053 (1.021, 9.125)], DWI hyperintensity volume [ORs (95% CI): 1.037 (0.998, 1.077)], cerebral lobe infarction [ORs (95% CI): 1.984 (0.894, 4.402)], and high NfL level [ORs (95% CI): 4.244 (1.871, 9.625)] were found to be potential risk factors of major depression. Male sex was found to be a protective factor against major depression [ORs (95% CI): 0.526 (0.262, 1.053)]. However, only high NfL level remained to be a significant risk factor of major depression [ORs (95% CI): 4.427 (1.918, 10.217)] in the final multivariate model (**Table 2**).

In univariate analyses, family history of stroke [ORs (95% CI): 2.502 (0.929, 6.736)], thalamus infarction [ORs (95% CI): 2.762 (0.847, 9.008)], and high NfL level [ORs (95% CI): 3.665 (1.993, 6.742)] were found to be potential risk factors of anxiety. Male sex was found to be a protective factor against anxiety [ORs (95% CI): 0.522 (0.300, 0.908)]. However, only high NfL level [ORs (95% CI): 3.063 (1.939, 6.692)] remained to be a significant risk factor of anxiety and male sex [ORs (95% CI): 0.514 (0.288, 0.917)] remained to be a protective factor against that in the final multivariate model (**Supplementary Table 1**).

In the analysis of risk factors of insomnia, only high NfL level [ORs (95% CI): 4.200 (1.526, 11.562)] was found to be a risk factor in both univariate and multivariate analyses. Collectively, these findings indicate that high serum NfL level might be a potential risk factor of major depression, anxiety, and insomnia (**Supplementary Table 2**).

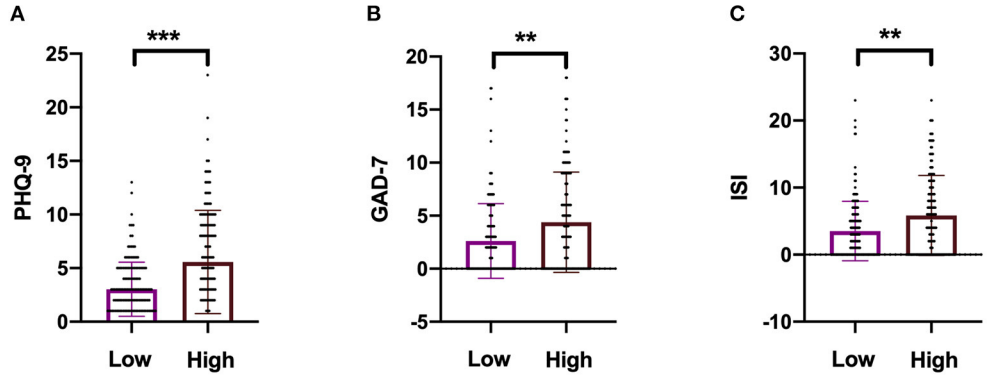


**FIGURE 1 |** Comparison of the severity of depression, anxiety, and insomnia between high and low NfL group. **(A)** Comparison of PHQ-9 score between high and low NfL group. **(B)** Comparison of GAD-7 score between high and low NfL group. **(C)** Comparison of ISI score between high and low NfL group. PHQ-9, GAD-7, and ISI scales were used to determine the severity of depression, anxiety, and insomnia of subjects. Unimpaired *t*-test. $^{**}p < 0.01$, $^{***}p < 0.001$.

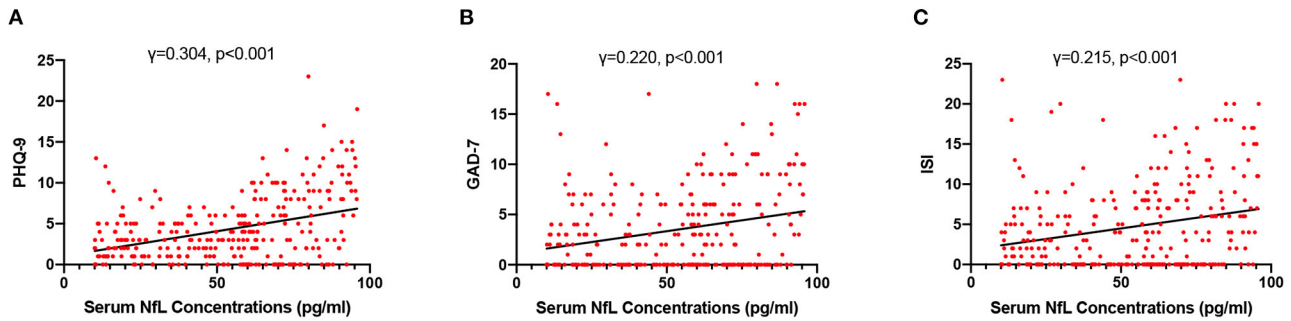


**FIGURE 2 |** Association between serum NfL levels and post-AIS mental health outcomes. **(A)** Association between serum NfL concentrations and PHQ-9 score. **(B)** Association between serum NfL concentrations and GDA-7 score. **(C)** Association between serum NfL concentrations and ISS score. Spearman correlation analysis.

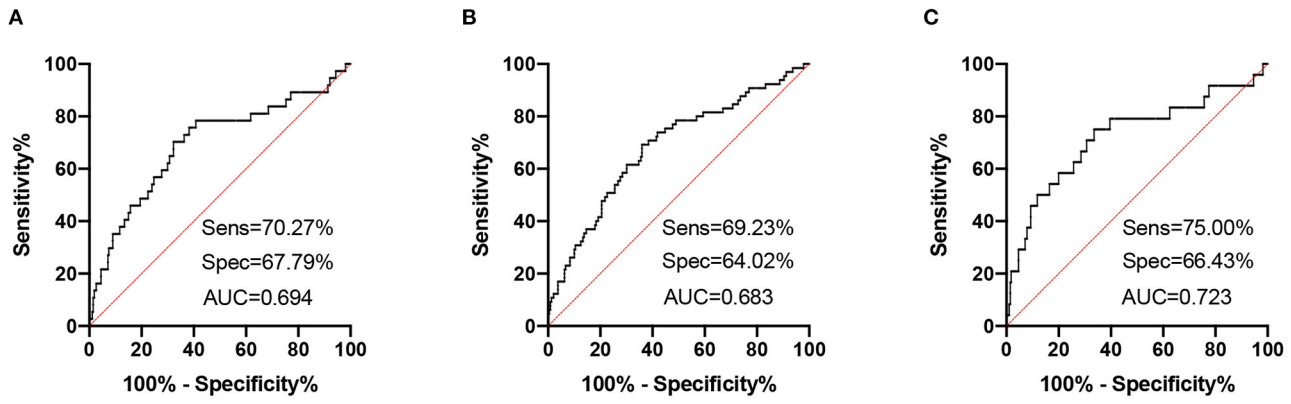


**FIGURE 3 |** Receiver operating characteristic (ROC) curves of serum NfL for post-AIS mental health outcomes. **(A)** ROC curve of serum NfL and PHQ-9 score. **(B)** ROC curve of serum NfL and GAD-7 score. **(C)** ROC curve of serum NfL and ISI score.

## DISCUSSION

In the present study, we investigated the associations between circulating NfL levels and mental health outcomes of AIS. We found that the incidences of mental health disorders after AIS, including anxiety, depression and insomnia, were significantly higher in the high NfL group in comparison with the low NfL group. ROC analyses found that serum NfL had a relatively high accuracy of predicting the occurrence of major depression, anxiety and insomnia. Furthermore, regression

**TABLE 2 |** A logistic regression model to evaluate the association between serum NfL and post-stroke major depression.

| Variables | Univariate ORs (95%CI) | *P*-value | Multivariate ORs (95%CI) | *P*-value |
|---|---|---|---|---|
| Age, year | 1.004 (0.968, 1.042) | 0.817 | | |
| Sex, male | **0.526 (0.262, 1.053)** | **0.070** | 0.613 (0.287, 1.312) | 0.208 |
| BMI, kg/m$^2$ | 0.963 (0.767, 1.209) | 0.746 | | |
| Smoking history, vs. no | 1.227 (0.401, 3.758) | 0.720 | | |
| Antiplatelet drug use, vs. no | 1.655 (0.673, 4.069) | 0.273 | | |
| Family history of stroke, vs. no | **3.053 (1.021, 9.125)** | **0.046** | 2.698 (0.851, 8.557) | 0.092 |
| **Co-existing disorders** | | | | |
| Hypertension, vs. no | 1.197 (0.588, 2.438) | 0.620 | | |
| Diabetes Mellitus, vs. no | 0.792 (0.292, 2.145) | 0.646 | | |
| Hypercholesteremia, vs. no | 0.530 (0.120, 2.330) | 0.400 | | |
| Arial fibrillation, vs. no | 0.840 (0.186, 3.794) | 0.821 | | |
| DWI hyperintensity volume, ml | **1.037 (0.998, 1.077)** | **0.066** | 1.031 (0.975, 1.091) | 0.281 |
| Stroke etiology | 0.913 (0.551, 1.513) | 0.725 | | |
| **Infarction region** | | | | |
| Cerebral lobe infarction, vs. no | **1.984 (0.894, 4.402)** | **0.092** | 1.146 (0.326, 4.025) | 0.832 |
| Cerebral white matter infarction, vs. no | 1.364 (0.560, 3.322) | 0.494 | | |
| Striatocapsule infarction, vs. no | 0.562 (0.277, 1.143) | 0.111 | | |
| Thalamus infarction, vs. no | 2.259 (0.653, 9.803) | 0.179 | | |
| Cerebellum infarction, vs. no | 0.796 (0.098, 6.472) | 0.831 | | |
| Delirium, vs. no | 1.033 (0.225, 4.737) | 0.967 | | |
| Hemorrhagic transformation, vs. no | 0.000 (0.000, ∼) | 0.999 | | |
| Recurrent stroke, vs. no | 1.826 (0.199, 16.796) | 0.595 | | |
| High NfL level, vs. low NfL level | **4.244 (1.871, 9.625)** | **0.001** | **4.427 (1.918, 10.217)** | **<0.001** |

*In univariate analyses, variables with a p-value < 0.100 were included in the multivariate analysis. The bold caption represented meaningful association.*

models identified high NfL level as a risk factor of these mental health disorders.

Post-stroke mental health disorders, including PSD (17), PSA (18), and PSI (19), are harmful to the quality of life in patients with AIS. Furthermore, these neuropsychological consequences of AIS have adverse effects on functional improvement of AIS. Therefore, early identification of patients at risk of developing these disorders is essential for timely intervention to achieve better prognosis. However, currently no reliable biomarker is available to predict the mental health outcomes of AIS.

Mounting evidence has demonstrated the association between circulating NfL levels and functional outcomes of AIS (10, 20). NfL is also suggested to be a reliable biomarker predicting post-stroke cognitive impairment (11, 21, 22). Mental health disorders, including depression, anxiety and insomnia, are commonly observed during the rehabilitation of AIS (23–25). The prevalence of PSD, PSA, and PSI was 12.17, 21.38, and 7.89%, respectively in this study, which is comparable to other reports in the Chinese population (2, 26). Therefore, in this study, we investigated the predictive value of circulating NfL for the 6-month neuropsychological outcomes of AIS.

We categorized the AIS patients into two subgroups according to serum NfL level, and it is interesting to see that high NfL group had substantially higher incidences of PSD, PSA, and PSI than low NfL group. Circulating NfL could predict post-AIS mental health disorders with a relatively high accuracy. In a recent study, it is demonstrated that elevated level of circulating NfL is associated with an increased risk of depression 3 months after stroke onset (27), which is consistent with our present findings. Although patients with anxiety (28) and insomnia (29) are found to have increased NfL levels, the association of circulating NfL with these disorders in AIS has not been reported yet.

The mechanisms underlying the associations between NfL and post-stroke mental health disorders could be multifactual and have not been thoroughly illustrated. NfL is also found to be increased in other psychiatric disorders, such as bipolar disorders (30), chronic insomnia disorder (29), and depression not due to stroke (31). These findings suggest that mental health disorders might contribute to neuronal damage, thus promoting the increase of NfL. In return, it is not clear why AIS patients with high circulating NfL levels are more prone to develop these mental illnesses. But we could speculate that mental health disorders are associated with the severity of neuroaxonal damage, as reflected by NfL levels. We propose that the disruption of the equilibrium of neurotransmitters induced by ischemic attack may induce neuroaxonal damage and promote might contribute to post-AIS mental health disorders (32).

This study has several limitations. First, this is a simple correlation analysis with a relatively small sample size, further large-scale investigations are needed to confirm the present findings. Second, only baseline NfL levels were determined, thus the association between the dynamic change of NfL and neuropsychological outcomes of AIS patients has not been illustrated. But in conclusion, this study found NfL as a potential

biomarker of post-stroke mental health disorder, including depression, anxiety and insomnia. Furthermore, the median age of participants in this study is more than 60, thus it is unclear whether NfL could predict long-term mental health disorders in young AIS patients. Patients with increased NfL levels should be intensively monitored for delayed neuropsychological disorders.

## 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 Investigational Review Board of the Sichuan Provincial People's Hospital. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

J-HW designed the study and drafted the manuscript. D-ZW and F-QG collected the samples and patients' information. D-ZW, SY, and N-WY participated in the determination of NfL. D-ZW and N-WY conducted the statistical analysis. GL and WJ contributed to the revision of the manuscript. 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.2021.764656/full#supplementary-material

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# Domain-Based Functional Improvements in Bipolar Disorder After Interpersonal and Social Rhythm Therapy

*William Moot, Marie Crowe, Maree Inder, Kate Eggleston, Christopher Frampton and Richard J. Porter**

*Department of Psychological Medicine, University of Otago, Christchurch, New Zealand*

**Background:** Studies typically report overall change in function when assessing bipolar disorder (BD) interventions, but individual domains are not analyzed. Which aspects of functioning are impacted is clearly important and may differ between treatments.

**Methods:** Data were analyzed from two previous clinical trials of Interpersonal and Social Rhythm Therapy (IPSRT) for BD patients. Change in total and subscale scores on the Social Adjustment Scale Self-Report (SAS-SR) from 0 to 78 weeks, were analyzed.

**Results:** 152 BD patients took part in randomized controlled trials of IPSRT ($n = 38$) vs. Specialist Supportive Care (SSC) ($n = 43$), and of IPSRT ($n = 41$) vs. treatment as usual (TAU) which was discharge to primary care ($n = 30$). IPSRT was superior to TAU on change in the social and leisure activities and extended family subscales, and SAS-SR total score over 18 months.

**Limitations:** Studies were not designed to be pooled. Patients in study 1 were younger and symptomatic at baseline. Patients assigned to TAU were more likely to drop-out. Patients did not respond to subscales that were not personally applicable (work, marital, children).

**Conclusion:** IPSRT had a positive impact on two SAS-SR subscales compared to TAU over 18 months. Other subscales were limited by the lack of respondents due to individual applicability. Different psychotherapy may have differential effects on different domains of function. Measures of function and research into functioning in BD should include domain-based measures, and report the numbers of participants who respond to questions in each domain.

**Keywords: bipolar disorder, psychotherapy, domain-based, function, functional improvements, IPSRT**

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*Alessandro Colasanti, Brighton and Sussex Medical School, United Kingdom*

***Correspondence:**
*Richard J. Porter*
*richard.porter@otago.ac.nz*

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## INTRODUCTION

Patients with symptoms of bipolar disorder (BD) are more likely to experience impaired occupational (1), relational (2), and cognitive functioning (3). Furthermore, functional impairment can persist even when symptomatic remission has been achieved (4). A review of 17 studies of psychosocial outcomes in BD found 30–60% of patients experience functional impairment even during remission of symptomatic episodes (5). For many patients with BD, functional improvement

is more important than symptomatic outcomes (6). Recognizing this, the traditional clinical emphasis on acute symptom reduction in BD has shifted to include longer-term focus on recovery of functioning in everyday life (7).

An important issue is how to consistently and accurately measure function. A recent review indicates ambiguity in the definition and measurement of functioning in BD (4). Researcher's personal definitions of functioning (8), and ability to interpret findings (9) may contribute to their choice of measure. There is no clear consensus on the most appropriate measure, despite a wide variety having been developed. Currently, the majority of studies use clinician-rated measures with far fewer including a self-report measure (4).

One self-report measure is the Social Adjustment Scale Self-Report (SAS-SR) (10). The SAS-SR is a measure of social functioning that was developed by adapting existing scales that had demonstrated sensitivity and utility in assessing role impairment. Development was driven by increased interest in social adjustment as opposed to symptomatology. The SAS-SR contains 45 questions (updated from the initial 42) that measure six major areas of functioning: work (as a paid worker, home-maker, or student); social and leisure activities; relationships with extended family; marital role; parental role; and role within the family unit. Each question is rated on a five-point Likert scale with a higher score indicating impairment (patients may leave questions blank if they are not applicable). Early and ongoing independent research found a high level of consistency between patient self-report and clinician assessment of patient function (11–13). Studies using the SAS-SR in BD samples have found significant baseline impairment in work-related performance, social and leisure activities, and family unit interactions compared with psychologically healthy population samples (14, 15).

Studies of psychotherapy for BD such as Interpersonal and Social Rhythm Therapy (IPSRT) have often examined effects of treatment on global function. Few have, however, examined the effects on individual domains. For example, Hoberg et al. (16) found a significant improvement in BD patient function from baseline to 12 weeks after 2 weeks of intensive group IPSRT [using the Sheehan Disability Scale (SDS)], but did not examine individual domains. Hlastala et al. (17) found significant improvements in overall function on the children's Global Assessment Scale (C-GAS) in a group of BD adolescents undergoing modified IPSRT for adolescents over 20 weeks and Steardo et al. (18) found BD patients had global improvements in function on the Global Assessment of Functioning (GAF) over 12 weeks of IPSRT. Frank et al. (19) however, examined functioning in a particular domain and found that BD patients receiving IPSRT showed a rapid initial improvement in occupational functioning (measured on the UCLA Social Attainment Scale) compared with those assigned to Intensive Clinical Management (ICM). However, this difference was not sustained after 2-years of follow-up.

Domain-specific assessment provides additional information regarding functioning, as it is likely that individual patients experience impairment in different domains. For instance, a recent systematic review and meta-analysis demonstrated that a higher proportion of BD patients experience impairment in occupational functioning (65.6%) than global functioning (58.6%) or other domains (20).Residual symptoms appear to have negative effects on some domains of functioning but not others (21). Additionally, while the GAF is the most commonly used global functioning measure in BD research (4), service users rate it as inappropriate and poorly relevant (22). Clinically, identifying which domains of functioning are most impaired and providing treatment that is aimed at improving these areas is of importance. Therefore, understanding which domains of functioning are improved by current treatment is highly relevant.

We used the SAS-SR as the primary measure of functioning in two previous Randomized Control Trials (RCTs) examining the efficacy of Interpersonal and Social Rhythm Therapy (IPSRT) compared with Specialist Supportive Care (SSC) (23) and IPSRT compared with treatment as usual (TAU) (24). Both studies found significant improvements in social functioning as measured by mean SAS-SR total score when undergoing psychotherapy (IPSRT or SSC), whilst patients randomized to TAU did not improve. In the second study, there was a significantly greater improvement during treatment with IPSRT compared with TAU. In this *post-hoc* analysis we have pooled the data from both RCTs, providing the opportunity to examine functional outcomes in a larger number of patients receiving psychotherapy for BD. Here we report a secondary analysis of these studies, examining the effects of IPSRT on domains within the SAS-SR and comparing these effects with SSC and TAU. We hypothesized that there may be greater changes in particular areas of function related to interpersonal relationships, such as extended family, family unit and marital domains, as a result of IPSRT.

# METHODS

Data are from two randomized control trials (RCTs) of IPSRT for BD referred to as study 1 (23) and study 2 (24). All patients who participated in 18 months of structured therapy or TAU during these trials were considered eligible for *post-hoc* combined analysis.

## Inclusion/Exclusion Criteria

In study 1, patients were aged 15–36 years with BD-I, BD-II or BD not otherwise specified (defined as fulfilling the criteria for BD-II, with 2 days of hypomania). There were no criteria regarding mood state at entry. In study 2, patients had a diagnosis of BD-I or BD-II, were aged 18–64 years and did not meet the criteria for an episode of depression, mania, or mixed state at baseline. Exclusion criteria for both studies were minimal and included a primary diagnosis of schizophrenia, schizoaffective disorder, or severe substance use disorder (SUD).

## Assessment

The Structured Clinical Interview for DSM–IV Axis I Disorders (SCID-I) (25) and for Axis II Disorders (SCID-II) (26) were used to confirm psychiatric diagnoses. The cumulative burden of mood symptoms was measured using the Longitudinal Interval Follow-up Examination (LIFE). The LIFE is used to retrospectively rate the severity of depression and mania on a

weekly basis over the previous 6 months (27). Ratings were carried out by a trained research assistant, by telephone, blind to treatment. In both studies, mood was also rated at baseline using the Young Mania Rating Scale (YMRS) (28).

Patients completed the SAS-SR, a 45-item self-report questionnaire measuring patient function over the previous 2 weeks. A score is derived from 7 subscale scores, which are averaged to give a final score in the range of 1–5, with a lower score reflecting greater social adjustment (10). In order that they appear on the SAS-SR the subscales are: How things have been going at work (work), how household tasks have been going (housework), how relationships with friends have been going and how spare time has been spent (social and leisure activities), how relationships with family excluding partners or children living at home have been going (extended family), how things have been going with a partner who lives with you (marital), how things have been going with children living at home (children) and how things have been with immediate family living at home (family unit). We examined change in SAS-SR subscale scores between baseline and 78 weeks.

## Psychotherapeutic Intervention

In study 1 (23) patients were randomized to receive IPSRT or Specialist Supportive Care (SSC). In study 2 (24) patients were randomized to IPSRT or Treatment as Usual (TAU).

In both studies IPSRT was delivered according to a manualized protocol. IPSRT combines Interpersonal Psychotherapy with Social Rhythm Therapy to help patients reduce stressors that lead to relapse and to learn to live with bipolar disorder and its impact on their lives (29). The timing of sessions was flexible based on clinical need, usually consisting of 10–12 weekly sessions, followed by 6–8 fortnightly sessions, and 4–5 monthly sessions thereafter, with a total of ∼24 sessions.

SSC was designed as a control psychotherapy based on American Psychiatric Association (APA) guidelines for the management of BD (30). SSC combines supportive psychotherapy and psychoeducation, with the focus of each session initiated by the patient. It is not organized around a systematic exploration of interpersonal issues or social rhythms.

Patients assigned to TAU remained under usual care from their general practitioner and were provided with information about education and services by Bipolar Support Canterbury.

For all psychotherapy patients, treating psychiatrists made medication changes using clinical judgment and guided by a decision tree to optimize psychopharmacological treatment. Medication decisions were consistent with the APA (30) and Royal Australian and New Zealand College of Psychiatrists (RANZCP) Guidelines (7) for the treatment of BD.

## Ethics

Both studies gained ethical approval from the Canterbury Ethics Committee (study 1) and New Zealand Health and Disability Commission (study 2). They were registered prospectively with the Australia and New Zealand Clinical Trials Registry (study 1—ACTRN12605000722695; study 2—ACTRN12611000961943).

## Primary Outcome Measures

In study 1 the primary outcome was the cumulative burden of depressive symptoms as measured by the LIFE. Study 2 had two primary outcomes: time to relapse and readmission to hospital. In this pooled analysis, outcome measures determined a priori were changes in function as measured by SAS-SR subscale scores.

## Statistical Analyses

Analyses used the Statistical Package for the Social Sciences (SPSS) version 25. Baseline demographic and clinical characteristics of patients in the four treatment arms were recorded using means, standard deviations, counts and frequencies where appropriate. Between group differences were examined using Fisher's protected least significant difference test for continuous variables, and *post-hoc* Chi-square tests for categorical variables.

The primary analysis used a univariate general linear model (GLM). For this analysis, patients randomized to IPSRT in study 1 and study 2 were grouped, as the primary goal was to examine a pooled group of participants receiving 18 months of IPSRT. These Dependent variables were SAS-SR subscale score changes from 0 to 78 weeks (work, housework, social and leisure activities, extended family, marital, children and family unit). Data distribution was then assessed with Kolmogorov-Smirnov and Shapiro-Wilk Tests of Normality. Pearson's correlations for parametric continuous variables, Spearman's correlations for non-parametric continuous variables, and One-Way ANOVA for categorical variables were used to test for significant correlations of sample characteristics with SAS-SR subscale score change. Variables identified as significantly correlated with each subscale score change were then entered in the GLM as co-variates. Work was co-varied for BD Type (BDI/BDII/BD-NOS). Housework was co-varied for Gender and BD Type (BDI/BDII/BD-NOS). Marital was co-varied for the presence of rapid-cycling. Children was co-varied for Gender. All dependent change variables were co-varied for their corresponding score at baseline. Each GLM was also co-varied by age, age of onset of first affective episode, baseline LIFE score, history of lifetime anxiety disorder, and mood state at baseline (not in episode/manic/hypomanic/depressive) to control for the significant differences between treatment arms at baseline. Randomization was entered as a fixed factor (IPSRT study 1 + study 2/ SSC study 1/ TAU study 2).

A secondary analysis of the IPSRT groups (IPSRT study 1 + IPSRT study 2) was performed, using a one sample *t*-test for each SAS-SR subscale score change. SSC and TAU were excluded, as the intention of this secondary analysis was to examine whether IPSRT had a significantly positive impact on each of the SAS-SR subscale scores.

# RESULTS

## Sample Characteristics

In study 1, 100 patients were randomized to IPSRT ($n = 49$) or SSC ($n = 51$). Eighty-one patients completed the study, 38 (78%) and 43 (84%) in each respective arm. In study 2, 88 patients were randomly assigned to IPSRT ($n = 43$) or TAU ($n = 45$).

**TABLE 1 |** Clinical characteristics by treatment randomization.

| | IPSRT 1 (*N* = 38) | | SSC (*N* = 43) | | IPSRT 2 (*N* = 41) | | TAU (*N* = 30) | |
|---|---|---|---|---|---|---|---|---|
| **Characteristic** | ***N*** | **%** | ***N*** | **%** | ***N*** | **%** | ***N*** | **%** |
| Age (M ± SD) | 27.3 ± 6.1[a] | | 26.8 ± 5.8[a] | | 40.8 ± 14.0[b] | | 42.2 ± 12.8[b] | |
| Gender (F) | 29 | 76 | 33 | 77 | 31 | 76 | 23 | 77 |
| Ethnicity (Pākehā) | 33 | 87 | 34 | 79 | 31 | 76 | 22 | 73 |
| Bipolar 1/2 | 30/4 | 79/11 | 35/8 | 81/19 | 28/13 | 68/32 | 23/7 | 77/23 |
| Index episode (depressive) | 33 | 84 | 41 | 93 | 33 | 83 | 23 | 79 |
| Rapid cycling | 13 | 34 | 13 | 30 | 7 | 17 | 3 | 10 |
| Age at onset (M ± SD) | 16.7 ± 5.1[A] | | 14.9 ± 5.6[A] | | 17.3 ± 6.9[A] | | 20.7 ± 9.9[B] | |
| Lifetime anxiety disorder | 19[A,B] | 50 | 26[B] | 60 | 11[A] | 27 | 7[A] | 23 |
| Lifetime substance use disorder | 18 | 47 | 23 | 53 | 14 | 34 | 11 | 37 |
| Medication use[†] | | | | | | | | |
| Lithium | 13 | 34 | 13 | 30 | 12 | 29 | 11 | 37 |
| Anticonvulsant mood stabilizer | 14 | 37 | 17 | 40 | 17 | 41 | 6 | 20 |
| Antipsychotic | 19 | 50 | 22 | 51 | 21 | 51 | 21 | 70 |
| Antidepressant | 21 | 55 | 20 | 47 | 23 | 56 | 16 | 53 |
| Drop out | 11[A,B] | 22 | 7[A,B] | 14 | 3[B] | 7 | 16[A] | 36 |
| SAS total score[†] (M ± SD) | 2.3 ± 0.5 | | 2.3 ± 0.5 | | 2.1 ± 0.4 | | 2.1 ± 0.5 | |
| Cumulative mood score (LIFE)[‡] (M ± SD) | 2.1 ± 1.1[A] | | 1.8 ± 1.4[A] | | 1.1 ± 1.2[B] | | 0.8 ± 1.2[B] | |
| YMRS[†] (M ± SD) | 1.7 ± 3.9 | | 2.5 ± 3.0 | | 1.5 ± 2.9 | | 2.3 ± 3.1 | |

[†]*At 0 weeks.*

[‡]*Retrospective from 0 to 26 weeks.*

[a,b]*Rows with differing superscript letters denote a significant difference at the p < 0.001 level.*

[A,B]*Rows with differing superscript letters denote a significant difference at the at p < 0.05 level.*

Seventy-one patients completed the study, 41 (95%) and 30 (67%) in each respective arm. Therefore, 152 patients were included in the analyses.

Baseline demographic and clinical characteristics of all patients grouped by treatment arms are presented in **Table 1**. Given study 1 specifically recruited younger patients (aged 15–35), as expected there was a difference ($p < 0.001$) in age between the study groups. Differences were also demonstrated in lifetime rates of Anxiety Disorders ($p < 0.05$) and LIFE score at baseline ($p < 0.05$) between treatment arms. Age of onset was later in the TAU group compared with the other treatment arms ($p < 0.05$). In study 2, patients were specifically recruited out of episode resulting in a less symptomatic population at baseline.

Patients were significantly more likely to drop out of the study if they were randomized to TAU. Analysis of the drop-out group's baseline demographics and clinical characteristics showed similar characteristics as patients were more likely to be older ($p < 0.05$) and older at age of onset of any affective episode ($p < 0.05$) in TAU than other treatment randomization. There were no significant differences found in mood-related measures and no significant differences found between dropouts and completers.

## Outcomes

The primary analysis was of the effect of treatment randomization on change in SAS-SR subscale score from 0 to 78 weeks (see **Figure 1**).

Initial GLM results (see **Table 2**) showed a significant association of treatment randomization on the social and leisure activities subscale ($p = 0.030$), extended family subscale ($p = 0.018$) and SAS-SR total score ($p = 0.011$). Sub analysis using pairwise comparisons (see **Table 3**) showed IPSRT had a significant effect compared with TAU on the social and leisure activities subscale ($p = 0.009$), extended family subscale ($p = 0.020$) and SAS-SR total score ($p = 0.002$). There was no difference between IPSRT and SSC. There were significantly fewer degrees of freedom in the work, marital, children and family unit subscales due to the lower number of people who completed these sections.

Secondary analysis examined the effect of IPSRT from baseline to 18 months on SAS-SR subscale score change for all participants (see **Table 4**). Housework ($p = 0.012$) and social and leisure activities ($p < 0.001$) showed statistically significant mean score improvements of 0.249 and 0.374 respectively.

After completing these analyses, power calculations were performed on each SAS subscale change and SAS Total Score change. **Table 5** shows that sufficient power to detect an effect of IPSRT over TAU was present in the Social and Leisure Activities, Extended Family and SAS Total Score change scales.

# DISCUSSION

In this pooled analysis of two RCTs examining psychotherapy in BD, there was a significant effect of treatment randomization on

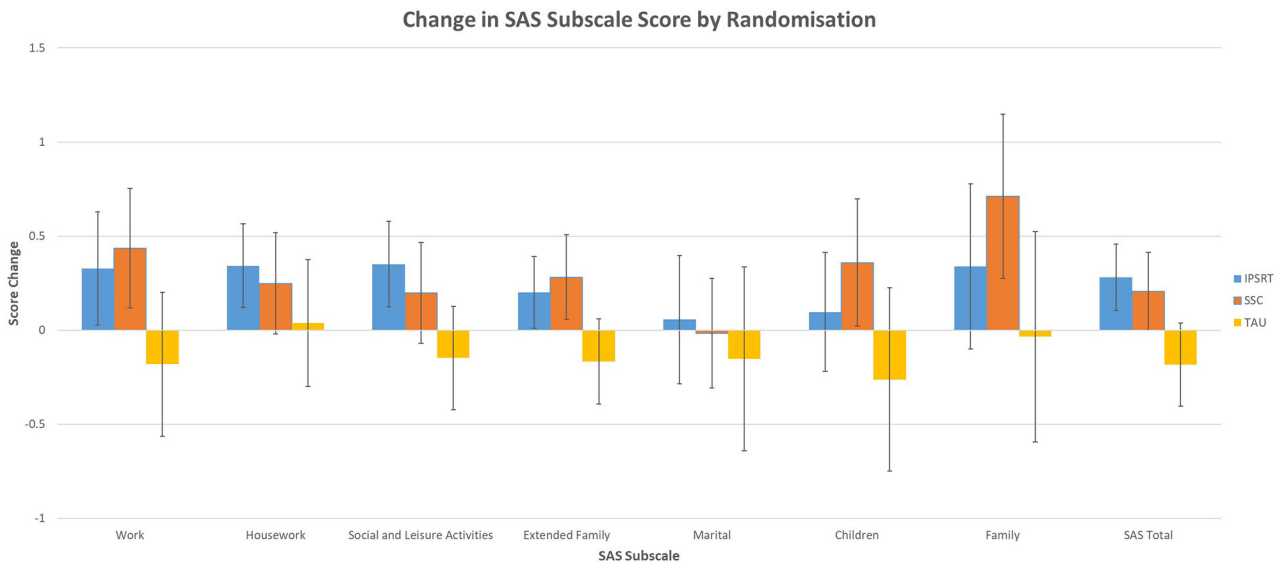


**FIGURE 1 |** Treatment randomization on SAS subscale score change—Estimated Marginal Means (EMM) with 95% Confidence Intervals (CIs) from GLM.

**TABLE 2 |** Treatment randomization on SAS subscale score change—significant predictive values from GLM.

| | | 95% confidence interval of the difference | | | | |
|---|---|---|---|---|---|---|
| | EMM[†] (IPSRT/SSC/TAU) | Lower (IPSRT/SSC/TAU) | Upper (IPSRT/SSC/TAU) | df | *F* | *p* |
| Work ($n = 74$) | 0.329/0.436/−0.181 | 0.028/0.119/−0.564 | 0.629/0.753/0.202 | 2, 49 | 1.424 | 0.250 |
| Housework ($n = 149$) | 0.343/0.249/0.038 | 0.122/−0.021/−0.298 | 0.564/0.519/0.374 | 2, 101 | 0.067 | 0.856 |
| Social and leisure activities ($n = 152$) | 0.351/0.197/−0.148 | 0.123/−0.071/−0.422 | 0.578/0.465/0.126 | 2, 130 | 3.598 | 0.030 |
| Extended family ($n = 150$) | 0.200/0.282/−0.166 | 0.009/0.056/−0.393 | 0.390/0.507/0.061 | 2, 128 | 4.165 | 0.018 |
| Marital ($n = 58$) | 0.056/−0.017/−0.152 | −0.286/−0.307/−0.640 | 0.398/0.274/0.337 | 2, 32 | 0.521 | 0.599 |
| Children ($n = 54$) | 0.097/0.359/−0.262 | −0.219/0.021/−0.749 | 0.413/0.697/0.225 | 2, 30 | 2.084 | 0.142 |
| Family ($n = 74$) | 0.339/0.712/−0.035 | −0.101/0.274/−0.595 | 0.779/1.149/0.524 | 2, 54 | 2.054 | 0.138 |
| SAS total ($n = 152$) | 0.280/0.206/−0.183 | 0.103/−0.002/−0.405 | 0.457/0.414/0.038 | 2, 130 | 4.712 | 0.011 |

[†] *Estimated Marginal Means.*

**TABLE 3 |** Secondary pairwise comparison analysis of IPSRT with SSC and TAU based on significant predictive values from GLM.

| | Pairwise comparison with SSC | | Pairwise comparison with TAU | |
|---|---|---|---|---|
| | Dif. ± SE[†] | *p* | Dif. ± SE[†] | *p* |
| Social and leisure activities | 0.154 ± 0.173 | 0.375 | 0.499 ± 0.188 | 0.009 |
| Extended family | −0.082 ± 0.147 | 0.577 | 0.365 ± 0.155 | 0.020 |
| SAS total | 0.078 ± 0.133 | 0.559 | 0.465 ± 0.144 | 0.002 |

[†] *Difference between Estimated Marginal Means ± Standard Error, as estimated by GLM.*

the social and leisure activities SAS-SR subscale and extended family SAS-SR subscale. Effect of treatment randomization was also found on SAS-SR Total score, confirming findings from our previous analyses (23, 24). Further examination of adjusted score change in the different therapy arms suggested that this is driven by a greater effect of IPSRT in these domains, with *post-hoc* analysis showing a significant difference between IPSRT and TAU on the social and leisure activities subscale and extended family subscale. No significant differences were found on the other subscales. No significant differences were found between

**TABLE 4 |** SAS subscale score change from baseline for IPSRT.

| | One sample *t*-test | | | | |
|---|---|---|---|---|---|
| | | 95% confidence interval of the difference | | | |
| **SAS subscale score change** | **Mean difference** | **Lower** | **Upper** | ***t*** | ***p*** |
| Work ($n = 38$) | 0.097 | −0.196 | 0.389 | 0.668 | 0.509 |
| Housework ($n = 78$) | 0.249 | 0.056 | 0.442 | 2.564 | 0.012 |
| Social and leisure activities ($n = 79$) | 0.374 | 0.209 | 0.548 | 4.517 | <0.001 |
| Extended family ($n = 78$) | 0.094 | −0.058 | 0.246 | 1.237 | 0.220 |
| Marital ($n = 22$) | 0.171 | −0.038 | 0.379 | 1.703 | 0.103 |
| Children ($n = 28$) | 0.259 | −0.075 | 0.593 | 1.590 | 0.123 |
| Family ($n = 38$) | 0.149 | −0.184 | 0.482 | 0.908 | 0.370 |
| SAS total ($n = 79$) | 0.318 | 0.181 | 0.456 | 4.612 | <0.001 |

**TABLE 5 |** Power calculations for SAS total and subscales—IPSRT compared with TAU.

| | Power calculations | | |
|---|---|---|---|
| **SAS subscale score change** | **Observed effect size** | **Observed differences** | **Detectable differences (80% power) with the observed Ns** |
| Work | 0.820 | 0.509 | 0.54 |
| Housework | 0.467 | 0.297 | 0.39 |
| Social and leisure activities | 0.818 | 0.453 | 0.34 |
| Extended family | 0.663 | 0.35 | 0.34 |
| Marital | 0.456 | 0.244 | 0.53 |
| Children | 0.591 | 0.312 | 0.56 |
| Family | 0.571 | 0.472 | 0.76 |
| SAS total | 0.995 | 0.438 | 0.27 |

IPSRT and SSC. It is important to note that housework, social and leisure activities, and extended family subscales had the greatest number of respondents, close to the total number of respondents at follow-up. In contrast, work, marital, children, and family unit subscales each had less than half the number of respondents at baseline and follow-up, which will have contributed to the lack of statistically significant findings in these domains.

Examination of baseline scores compared with follow up scores in the IPSRT groups showed significant improvement from baseline to 18 months in the housework and social and leisure activities SAS-SR subscales, and SAS-SR total score. The improvements seen in the social and leisure activities and extended family subscales may be attributable to the enhanced interpersonal skills, promoted by IPSRT. The establishment of circadian stability is promoted by the Social Rhythm component of IPSRT and the therapeutic mechanisms of the IPT component are related to decreasing interpersonal stress, facilitating emotional processing, improving interpersonal skills and enhancing social support (31). It is interesting to note, however, that other Interpersonal SAS-SR subscales (marital, children and family unit) did not see significant improvements with IPSRT compared with TAU which involved no psychotherapy. There were significantly fewer respondents in several of the SAS-SR subscales (work, marital, children and family unit) (see **Table 2**). This is likely due to the design of the SAS-SR, where participants do not respond to items that are not relevant to them (e.g., non-response to marital subscale if single).

Previous studies using the SAS-SR have detailed only results of overall score change, and used this as a proxy for improvement in social functioning. It is of interest that many of our patients did not answer questions across several domains, due to the lack of individual applicability. The SAS-SR is scored by averaging scores across all the questions answered. These results emphasize the fact that what is measured and reflected in this score varies across individuals depending on which domains are applicable. Individuals may not be working, married, or have children and therefore are unable to answer questions on these subscales. These scores are then unlikely to change over the course of treatment, limiting the ability of the SAS-SR to demonstrate improvement in functioning in these areas over time.

Two previous studies employed a different measure, the Functional Assessment Short Test (FAST), to assess domain-specific functional improvements after intervention (24, 25). The FAST scale is (in contrast to the SAS-SR) a quick, clinician-rated measure comprising 24 items divided into six domains of function; autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time with a higher score denoting a poorer outcome (32). The FAST scale does not have any questions that may not be answered due to applicability, for example in the occupational functioning section, patients who do not have a job are assigned a 3: the highest possible score. Rosa et al. (24) examined results over 6 months of engagement in the Bipolar Disorders Program of the Hospital Clinic at the University of Barcelona, which included pharmacotherapy, biophysical therapies such as electroconvulsive therapy, and psychoeducation as appropriate. They found improvements in autonomy, cognitive functioning, and interpersonal relationships at 21 days, with improvements in the work subscale at 3 months, and financial and leisure

subscale improvements at 6 months. Torrent et al. (25) found improvements in only 2 of the 6 domains assessed by the FAST scale (interpersonal and occupational) when comparing 21 weeks of a weekly functional remediation program (intervention addressing neurocognitive issues with focus on enhancing function in daily routine) with TAU.

Miklowitz et al. (33) employed the Longitudinal Interval Follow-Up Evaluation–Range of Impaired Functioning Tool (LIFE-RIFT) to compare domain-specific functional improvements between 30 one-hour sessions (21 weekly and nine biweekly) of intensive psychosocial treatment (IPSRT, Family-Focused Therapy, or Cognitive Behavioral Therapy) and collaborative care (a 3-session psychoeducational treatment). The LIFE-RIFT is a quick, clinician-rated tool of nine items divided into four domains: relationships (family, children, or friends), satisfaction (contentment and fulfillment from activities with family and friends, job, and finances), work/role performance (employment, household, or student roles), and recreational activities/hobbies (34). Patients were recruited from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (32) who were able to respond to all questions on the LIFE-RIFT. They found improvements in 2 of 4 domains: relationships and satisfaction, when comparing IPSRT alone and intensive psychotherapy as a whole, with collaborative care. Our study falls broadly in line with these studies, in that there were improvements on the social and leisure activities and extended family subscales when compared to treatment as usual. Both Rosa et al. and Torrent et al. identified improvements in interpersonal skills and associated this with exercises completed as part of the assigned therapy. Miklowitz et al. (33) postulated that changes in life conditions, self-esteem, mood, and functioning often occur among bipolar disorder patients undergoing intensive treatments, although these changes do not necessarily occur at the same time or as a direct result of each other.

The discrepancies between our own findings and results published by Rosa et al., Torrent et al., and Miklowitz et al. may be attributable to the differences in functional measurements and therapies implemented. Clinician-based measures inherently bias understanding of patient functioning, as the perception of the relationship between symptoms and psychosocial functioning differs significantly between clinicians and patients (35). We used a self-report measure which may have aided in avoiding sources of clinician bias. Both studies (36, 37) using the FAST scale did not have any difficulties with non-respondents, as the FAST scale relies on generally applicable questions. Miklowitz et al. (33) had a very large BD population to sample patients from, and recruited specifically for patients that were able to answer every question on the LIFE-RIFT. This further highlights the difficulty in accurately assessing patient function, as typically not all domains of function will apply to every patient. Assessment of occupational function has proven to be particularly problematic—for example the SAS-SR does not account for job loss or gain over the study period, which would impact statistical and individual results. Similarly, the FAST assigns a score of 3 to patients who are unemployed, however it does not assess whether unemployed patients have the capacity to engage in work, and subsequent work gainers of this nature could be transitioned from a poor score of 3 to the top score of 0 by virtue of gaining employment. It is unclear what the optimal method of assessing occupational function is. In terms of the treatments examined, IPSRT consisted of more sessions over a longer period of time than either study. In addition, compared with the functional remediation program used by Torrent et al., IPSRT did not have focus on addressing neurocognitive issues, and was conducted in individual sessions which were necessarily more focused on the problems presented by each individual. Rosa et al. (24) found a significant improvement in all 6 domains of the FAST scale over 6 months of intervention. The global improvements in functioning may be due to the hospital-based multi-disciplinary nature of the program, which had greater contact time during the study period than our own trials.

One review of disability in BD found only 5 of 34 studies examined assessed occupational outcomes, suggesting limited effort in addressing occupational problems associated with BD (38). Frank et al. (19) showed an initial improvement in occupational functioning on the UCLA Social Attainment Scale, when comparing patients assigned to acute IPSRT with acute ICM. We did not find a significant improvement of occupational outcomes measured by the work SAS-SR subscale. This difference may relate to stage of illness given Frank et al. examined patients who were in episode at baseline. In our studies, 68% of patients in study 1 were in episode while in study 2 none were in episode. Early gains in occupational functioning may be more likely when people are unwell at baseline, particularly as patients who are unemployed may be able to seek employment after early remission of mood symptoms and functional impairment as a result of psychotherapy. In our study, 19 patients gained employment over the course of 18 months and had work SAS-SR subscale scores recorded at week 78. However, they were unable to be included in analyses of the work subscale due to the lack of a baseline score. This clearly represents significant improvement which was not, however, measured using the SAS-SR. Conversely, 17 patients lost employment over the course of 18 months and did not have work SAS-SR subscale scores recorded at week 78, and were therefore excluded from analyses. This likely represents deterioration in patients' ability to work, but is unable to be interpreted by the SAS-SR. There were no significant differences between treatment randomizations for number of work gainers or losers.

Our results indicate that BD patients undergoing IPSRT as opposed to TAU achieved improved functional outcomes of social and leisure activities and extended family relationships. Similarly, patients undergoing IPSRT demonstrated significant improvements over time in the housework and social and leisure activities subscales. As many BD patients prioritize functional outcomes over symptomatic recovery (6), identifying patients who exhibit significant impairment in these domains may be beneficial in implementing appropriate therapies for patient-prioritized outcomes. We did not demonstrate any significant improvements in the work, marital, extended family, children or family SAS-SR subscale scores after 18 months treatment with IPSRT. This result may indicate the

lack of global applicability for functional assessments in BD, as the number of respondents for each of these subscales dropped dramatically. As the topic of functional assessment and functional improvement gains traction in psychotherapeutic research, our results suggest that a closer examination of domain-specific outcomes is warranted to accurately understand improvements in function. Clarification of the concept of functioning in BD, and refinement of measures, is therefore needed (39).

This secondary analysis of two RCTs for BD has several limitations. Firstly, it should be noted that the studies were not designed to be pooled. Each had different inclusion and exclusion criteria and primary outcome measures. Patients were younger, more unwell at baseline and had poorer functioning in study 1. We adjusted for this by covarying in our analyses for variables that were significantly different between treatment arms at baseline. However, this may not correct for unmeasured differences between the samples. In addition the determinants of functional impairment may be important mediators of change and while we measured and examined several clinical variables, we did not, for example, examine stage of illness. Staging models have suggested progressive functional impairment in some individuals with BD (40). Future studies assessing domain-specific effects of treatment could usefully incorporate staging into their design.

Secondly, our analyses was limited by the number of patients that dropped out over the 18 month period, particularly in the TAU group. Patients in this study were relatively well at baseline, and TAU patients had less interaction with the study team which may account for this discrepancy. We compared baseline characteristics between dropout groups and found significant differences between treatment arms only on characteristics which were identified as likely to be different based on the different inclusion criteria of the studies analyzed (age, age of onset of any affective episode, and current episode). Thirdly, the age range captured in our studies was narrow with patients predominantly aged between 20 and 40 years, despite the lack of age restriction in study 2. This may contribute to the lower number of respondents in the work, marital, children and family unit subscales. Fourthly, the loss of data from particular subscales of course reduces power in the analysis of these subscales and potentially explains the lack of statistical improvement demonstrated in these domains of functioning and the lack of difference between IPSRT and TAU in the same domains (see **Table 5**).

In summary, in this *post-hoc* combined analysis of 152 BD patients undergoing 18 months of psychotherapy, there was a significant effect of IPSRT compared with TAU on the SAS-SR social and leisure activities subscale and extended family subscale, and a significant effect of IPSRT over 18 months on the SAS-SR housework and social and leisure activities subscale. This finding has similarities and divergences from previous functional domain-based studies. There are few studies that have assessed function in BD patients from a domain perspective, limiting understanding of patient function and improvement as a result of psychotherapy. We recommend that studies assessing patient function need to reflect the domains identified as relevant rather than those identified by clinicians.

## DATA AVAILABILITY STATEMENT

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

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

WM analyzed the data and wrote the first draft. RP supervised analysis and writing. CF supervised analysis. MC, MI, and KE were involved in planning of the analysis. All authors contributed to subsequent drafts. All authors contributed to the article and approved the submitted version.

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# Treatment-Resistant Depression in Portugal: Perspective From Psychiatry Experts

*João M. Bessa[1,2,3†], Serafim Carvalho[4†], Inês B. Cunha[5†], Milene Fernandes[6*], Ana Matos-Pires[7,8†], Rui Neves[9†], Albino J. Oliveira-Maia[10,11†], Susana Santos[12] and Vítor Santos[13†]*

[1] School of Medicine, Life and Health Sciences Research Institute (ICVS), University of Minho, Braga and Guimarães, Portugal, [2] ICVS/3B's, PT Government Associate Laboratory, Braga and Guimarães, Portugal, [3] Clinical Academic Center – Braga, Braga, Portugal, [4] Department of Psychiatry, Hospital de Magalhães Lemos, Porto, Portugal, [5] Department of Psychiatry, Hospital Júlio de Matos - Psychiatric Hospital Centre of Lisbon, Lisbon, Portugal, [6] Real World Evidence and Late Phase, CTI Clinical Trial and Consulting Services, Lisbon, Portugal, [7] Department of Psychiatry, Unidade Local de Saúde do Baixo Alentejo, Beja, Portugal, [8] Comprehensive Health Research Center (CHRC), NOVA Medical School - NMS, Universidade Nova de Lisboa, Lisboa, Portugal, [9] Casa de Saúde da Idanha, Instituto das Irmãs Hospitaleiras do Sagrado Coração de Jesus, Lisbon, Portugal, [10] Champalimaud Research and Clinical Centre, Champalimaud Foundation, Lisbon, Portugal, [11] NOVA Medical School - NMS, Universidade Nova de Lisboa, Lisbon, Portugal, [12] Janssen-Cilag Farmacêutica Lda, Porto Salvo, Portugal, [13] Department of Psychiatry, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

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**Edited by:**
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***Correspondence:**
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*mfernandes@ctifacts.com*

*† These authors have contributed equally to this work*

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Guidance about treatment-resistant depression (TRD) in Portugal is very limited, even though depression prevalence is among the highest in European countries. A questionnaire was conducted, followed by two advisory boards with seven Portuguese psychiatry experts, to characterize and discuss MDD and TRD epidemiology, diagnosis, patient journey, treatment options, and unmet clinical needs. Consensus was reached on the main issues. In daily practice, TRD can be defined as moderate to severe MDD episodes with insufficient clinical improvement after two antidepressant treatments, taken in adequate doses and duration. TRD diagnosis and treatment are mostly decided by psychiatrists at public hospitals. Treatment type and duration must be adjusted to characteristics of the patient and the depressive episode, including symptoms, number of previous episodes, comorbidities, and previous treatment response and side effects. The most relevant objectives of TRD treatment are reaching response and remission, prevention of suicide, and improvement of quality of life, functionality, and wellbeing. Regarding pharmacotherapy, antidepressant switch occurs more frequently with non-response, while optimization, combination, and augmentation are considered for patients with partial response. Psychotherapy should be considered in parallel to pharmacological treatment. Brain stimulation techniques are underused. Lifelong treatment is required for recurrent or more chronic TRD episodes, but patient adherence is also poorer in these cases. In Portugal, TRD management is limited by lack of access to specialist care and to many treatment options. These aspects highlight that conventional pharmacotherapy does not lead to remission in many patients and that optimization strategies are frequently necessary to achieve satisfactory treatment outcomes.

**Keywords: treatment-resistant depression, major depressive disorder, patient journey, expert opinion, Portugal**

## INTRODUCTION

Depressive disorders are among the most frequent psychiatric disorders, with a prevalence of 4.4% worldwide (1), and around 7–9% in Portugal, which is one of the most affected European countries (2–4). In addition to the high prevalence and associated burden, treating major depressive disorder (MDD) presents several challenges due to its heterogenous manifestations, existence of comorbidities, and the variability and unpredictable nature of response to treatment (5). As a result, ∼50–80% of treated patients are reported to have a recurring episode throughout their lives, with only 30–45% of patients reaching complete remission of symptoms after first-line antidepressant treatment (6, 7). The *Sequenced Treatment Alternatives to Relieve Depression* (STAR*D) study is the most comprehensive assessment of MDD treatment outcomes, consisting of a randomized controlled trial that ran between July 2001 and September 2006, and providing a demonstration of the latter point (8). The remission rate after two, three, and four sequential trials of antidepressants was 30.6, 13.7, and 13.0%, respectively. Other European studies also included inpatients, resulting in lower rates of remission (9). Hence, although antidepressant drugs have repeatedly been shown to be very effective in several meta-analyses (10), these results demonstrate that they fail to achieve remission in up to one-third of MDD patients (8).

Treatment-resistant depression (TRD) has been defined as a disorder where a moderate to severe MDD episode does not respond to at least two different treatments with antidepressants, at an appropriate dose and treatment duration (9, 11–14), but still with some debate regarding this definition (11, 15). Nevertheless, when compared to treatment-responsive MDD episodes, TRD was associated with higher impact on daily activities, family relationships, and quality of life, in addition to a higher risk of suicide and higher treatment costs (16–18). In fact, some clinical manifestations that are frequently observed in TRD patients (e.g., suicidality, psychotic features, comorbidity anxiety, and among others) complicate patient management and limit response to treatment (9). The low quality of life and reduced productivity of TRD patients were also observed at the baseline of a recent European cohort study, where 46% of TRD patients had failed three or more drugs during the current episode (19). After 6 months of treatment, only 17% of TRD patients achieved remission and 74% showed no response to treatment (12, 19). Information about MDD and TRD management worldwide is still very limited, including in Portugal, where depressive disorders are the third cause of disability (20). This project aimed to provide a first characterization of the clinical practice in Portugal regarding diagnosis, epidemiology, patient journey, and treatment of MDD patients with TRD episodes.

## METHODS

An individual questionnaire was sent in May 2020 to a panel of seven psychiatrists (of about 750 psychiatrists in Portugal) (21) with clinical expertise in the treatment of TRD, as well as academic and health decision experience. The seven experts (JB, SC, IC, AMP, RN, AOM, and VS) estimated to have followed, at public and/or private healthcare settings, a total of 2,858 patients with MDD during 2019, corresponding to a median number per expert of 270 (min–max: 150–468) patients with MDD without TRD and 130 (min–max: 20–200) MDD patients with TRD.

The questionnaire included quantitative and qualitative open questions, regarding definitions and diagnosis, epidemiological estimates, patient journey, treatment strategies, and unmet needs. Standardized mean estimates of proportions were calculated by (1) multiplying the estimates of each expert by their respective number of patients followed (i.e., determining expected number of patients with the variable of interest) and (2) dividing the sum of expected patients with the variable of interest by the total number of patients of all experts. After the descriptive analysis of the questionnaire and identification of the key conclusions, two meetings with all experts were conducted online in December 2020, to discuss the main findings and define consensus, whenever possible. This manuscript presents the conclusions of the questionnaire and advisory boards, framed by the most relevant literature.

## RESULTS AND DISCUSSION

### A Pragmatic Approach to MDD and TRD Diagnosis and Treatment Definitions

MDD is a highly heterogenous mood disorder (13, 22). In daily practice, MDD diagnosis results from patient observation and identification of signs and symptoms of depression (depressed mood; anhedonia; fatigue; cognitive, psychomotor, and neurovegetative symptoms, among others), assessment of impact on daily life, and exclusion of other disorders or diseases. In fact, the criteria of the *ICD-10 Classification of Mental and Behavioral Disorders* or *Diagnostic* (23) and the *Statistical Manual of Mental Disorders of the American Psychiatric Association* (DSM-5) (24) are important for the classification and validation of the diagnosis (e.g., in the context of clinical studies) but, in daily practice, MDD diagnosis is not strictly bound to verification of these criteria.

Another complexity of MDD management is related to episodes with an inadequate response to treatment or that fail to achieve remission. The lack of a consensus around an operational definition for TRD weakens the generalization of TRD recommendations, despite its burden on patient, caregivers, and services (11, 25, 26). In the European regulatory setting, TRD is defined as an MDD episode for which "treatment with at least two different antidepressant agents (of the same or a different class), prescribed in adequate dosages for adequate duration and with adequate affirmation of treatment adherence, showed lack of clinically meaningful improvement" (27). The experts agreed that TRD definition should refer to the index major depressive episode, detail its severity, and consider other treatment modalities besides antidepressant medication. Hence, from a pragmatic perspective, TRD can be defined as moderate to severe MDD episode with insufficient clinical improvement after two antidepressant treatments taken in adequate doses and duration. Furthermore, the assessment of clinically significant improvement and of episode severity should consider the global assessment of the patient, clinical history, level of disability, and nature of the symptoms that remain after treatment, with

particular attention to suicidal ideation, psychotic symptoms, and psychomotor inhibition.

A more global assessment should also be reflected on the assessment of treatment outcomes. Experts agreed with the proposed definitions for remission, i.e., regression of depressive symptoms and return to premorbid functioning, and response, i.e., the occurrence of a substantial clinical improvement that may or may not reach remission (28). However, the definition of these outcomes should extend beyond a defined cutoff in instruments assessing episode severity (overall and in terms of baseline and persistent symptom dimensions). The experts were aware of other proposed concepts, namely, "difficult-to-treat depression", that integrates a comprehensive and patient-centered assessment of treatment barriers, the illness, and the treatment (29). Importantly, the experts reported that their practice on TRD management already reflects a comprehensive assessment of the patient/episode/treatment triad, although laboratory tests and biomarker determination are not routinely performed in clinical practice across centers (30).

## TRD Patient Profile and Patient Journey

The experts estimated a point prevalence of 9.7% for MDD, which agrees with the data published for the adult Portuguese population (3, 21, 31), with additional estimates that ∼32% of patients in Portugal would develop a TRD episode during the course of MDD. This proportion is consistent with the 29% of patients with TRD observed in the previous 12 months as per the experts' estimate (830 TRD cases among 2,858 patients with MDD) and, after adjusting for the number of patients observed by each expert, with the 42% of patients that failed to respond to at least two treatments during the last MDD episode. This TRD estimate of 29–42% is similar to those reported from UK studies (32), from the multicenter *European Group for Study of Depression* trial (33), and from the STAR*D trial (6, 34).

Regarding patients with MDD observed during the previous 12 months, the experts estimated that 64% of the patients without TRD episodes were female, with a mean age of 47 years (25% were 65 years or older), and 30% were new diagnoses of MDD. When considering patients with at least one TRD episode during the same period, the experts estimated that 56% were female, aged 52 years old on average (34% were 65 years or older), and 34% were new diagnoses of TRD. Observational studies from other counties have shown similar mean age and proportion of female patients (19, 35, 36). Among factors associated with TRD, the experts acknowledge those reported in the literature (25, 26, 37, 38), and highlighted the characteristics of depression itself (e.g., number of episodes, failure to achieve total remission between episodes, type of depression, persistence of symptoms), having had stressful life events and traumatic experiences (especially during childhood), psychiatric comorbidities (e.g., anxiety and substance abuse), and non-psychiatric comorbidities (e.g., cancer), besides socioeconomic factors (e.g., unemployment), potential genetic determinants (39), and neural biomarkers (40).

The panel estimated that MDD diagnosis is first done on average 11 months (min–max: 6–24 months) after onset of symptoms, suggesting an improvement from the 4 years reported in a 2008 national survey (41). At the index TRD episode, the median time from the onset of symptoms to the recognition of treatment resistance was estimated as 12 months, similar to that observed in UK (42). While it was acknowledged that TRD can be diagnosed during the first episode of MDD, the index episode of TRD was proposed to occur most often after other non-TRD episodes MDD. This estimate of an interval between MDD diagnosis and first episode of TRD is aligned with the 13.7 ± 11.2 months reported by others (19).

The experts also predicted that the majority of TRD diagnoses (83%) and treatment initiation (87%) are made by psychiatrists, namely, at public hospitals (**Figure 1**), and that most patients continue follow-up with the same physician until remission/recovery (73%) and after recovery (56%). TRD patients are referred to psychiatry outpatient care at public hospitals mainly from primary healthcare units, often before the criteria of resistance to treatment are observed. Furthermore, the experts estimated that patients with TRD referred by other physicians (non-psychiatrists) were frequently under antidepressant medication (81%) but that only 23% were identified with TRD and 32% have never had a prior psychiatry appointment.

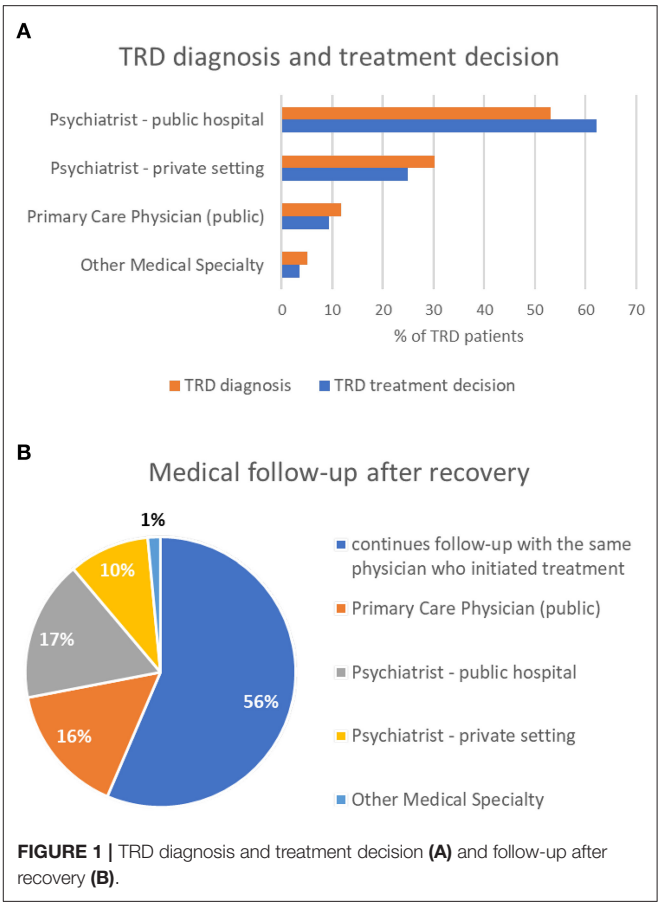


**FIGURE 1 |** TRD diagnosis and treatment decision **(A)** and follow-up after recovery **(B)**.

## Strategies for MDD and TRD Treatment

The experts acknowledge the relevance of guidelines on MDD treatment such as those from the *National Institute for Health*

*and Care Excellence*, the *Canadian Network for Mood and Anxiety Treatments*, and the *American Psychiatric Association* (13, 43, 44). Other guidelines also referred a hierarchy of treatment strategies and proposed treatment algorithms (45, 46). However, in daily practice, guidelines and therapeutic recommendations must be integrated with clinical experience and adapted to the characteristics of each patient with MDD, especially in TRD episodes. Hence, the choice of an antidepressant for MDD treatment must consider the patient's symptomatic profile, psychiatric and non-psychiatric comorbidities, as well as response to previous treatments and possible side effects. The experts identified the following intrinsic factors as having the greatest impact on the management of MDD, here listed in decreasing order of relevance: suicide risk, severity of the depressive episode, psychotic symptoms or personality disorder, stressful life events, and episode characteristics. Substance abuse and other significant medical conditions, namely, neurological disease and cancer, were also identified as the most challenging comorbidities when treating depressive episodes, and often require a multidisciplinary approach with other medical specialists. These factors have also been described by others, namely, when considering the need for hospitalization (26).

Regarding MDD treatment options in Portugal, antidepressant monotherapy is the most frequent strategy for the first two lines on treatment. As a general guidance, most experts refer that MDD episodes with greater agitation/anxiety component show better results with first-line treatment based on serotonergic drugs, while episodes with melancholic/slowing symptoms may benefit more from treatment with noradrenergic or dual agents. Tricyclic antidepressants were viewed as an option after insufficient response to more recent antidepressants, namely, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), or dual inhibitors. When considering treatment of TRD episodes, the experts reinforced that there is no defined strategy but rather that the therapeutic decision should depend on the patient and episode characteristics, comorbidities, level of response to previous therapies, side effects, and non-adherence. In their practice, antidepressant switch is the most frequent option after non-response, while optimization, combination, and augmentation (by decreasing order of frequency) are the usual options in cases of partial response.

The perspective of experts on MDD and TRD treatment is consistent with some registry-based studies that identified monotherapy with SSRIs followed by SNRIs as the most frequent options for the first lines of MDD therapy (19, 36, 47). Other guidelines proposed a similar rationale for deciding switching vs. optimization/combination/augmentation strategies, according to the level of previous treatment responses (26, 43–45). However, the available evidence suggests that further research is necessary to define the most appropriate treatment pathways for TRD episodes (48).

Non-pharmacological strategies were also debated. Psychotherapy—among which cognitive-behavioral techniques are the most frequently used—is considered as a parallel axis to pharmacological strategies, being strongly recommended to be carried out by psychiatrists or psychologists with appropriate training. The use of brain stimulation techniques should be considered as a treatment option for TRD, depending on the severity of the depressive episode, previous and current non-response or side effects of the medication, as well as patient choice. It was also noted that, in the pandemic context in Portugal, accessibility to brain stimulation worsened considerably. Other studies indicated that neurostimulation techniques are underused, including in TRD episodes (19, 36, 49).

## Treatment Objectives and Response/Remission Estimates From the Clinical Practice

For the experts, the main treatment objectives are reaching response and remission, prevention of suicide, and improvement of quality of life, functionality, self-perceived wellbeing, and family relationships. Individual definition of these goals is based on unstructured patient observation and assessment, with rating scales most often used for monitoring treatment with brain stimulation techniques and in more severe cases.

Overall, rates of response, remission, and maintenance of remission decrease with the progression of therapeutic lines, especially in the context of pharmacological treatment (**Figure 2**). When the remission is not achieved, potential pseudo-resistance—by insufficient plasma levels, patient non-compliance, or relevant psychiatric and/or somatic comorbidities—has to be excluded before treatment optimization (45, 46). In line with other recommendations (26), maintenance treatment is extended in recurrent episodes (compared to first episodes without risk of recurrence) and for patients with TRD episodes: up to 36 months for patients with response to a 3rd or 4th line of treatment and lifelong for patients on a 5th or later line of treatment. However, the experts also estimate that patients leave treatment more frequently with the progression of therapeutic lines and mostly in the maintenance phase, with loss to follow-up of 32–40% vs. 12–28% of patients during acute treatment. Psychoeducation, the involvement of caregivers, and a strong patient–physician relationship are seen as crucial to promote adherence to treatment.

# CONCLUSION

The high number of relapses, poor adherence to treatment, difficult access to psychotherapy, and other non-pharmacological treatment strategies and insufficient efficacy of available medication for treatment of TRD were identified by the experts as the main barriers to treatment success. In fact, even though antidepressants have proven their efficacy on MDD treatment, TRD episodes, frequently recurrent, are still a challenge for clinical practice (50). These aspects highlight that conventional psychopharmacotherapy does not lead to remission in every patient and that optimization strategies are frequently necessary to achieve satisfactory treatment outcome, whereby recent international recommendations may further contribute to successful treatment (45). TRD is a high burden for patients, caregivers, and healthcare services, and there is a need for improvement of access to treatment options that provide

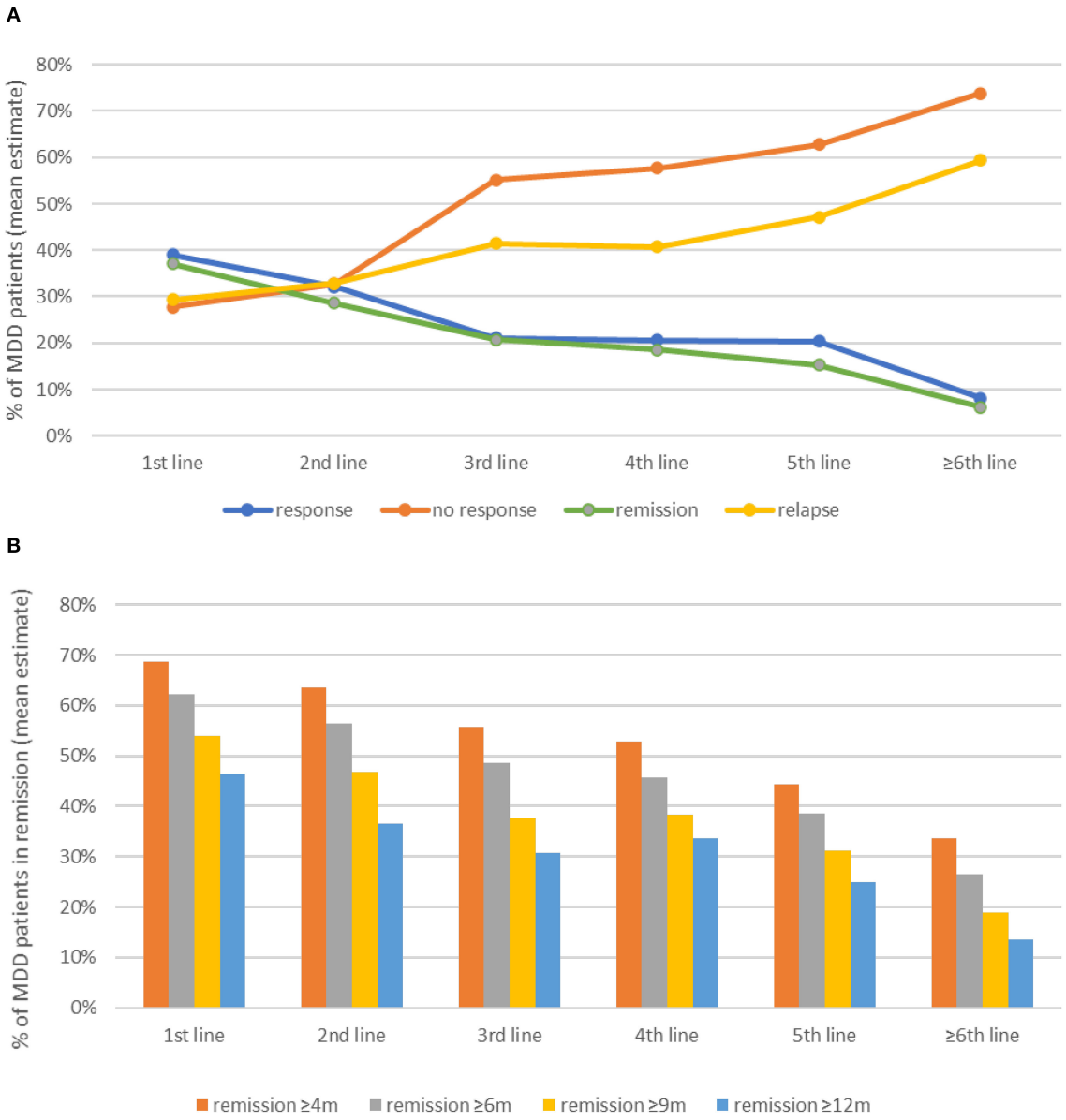


**FIGURE 2 |** Rates of response and remission **(A)** and duration of remission after successful treatment **(B)**.

sustained responses, as well as development of novel therapeutic options for the future (17, 51).

Some limitations are acknowledged, as this was an advisory board, based on expert consensus and opinion, rather than strong data from an empirical study. Nevertheless, care was taken to reduce potential bias from dominant opinions among experts, namely, through the use of the initial individual questionnaire, assuring that answers from all experts were considered. It is also possible that the perspective of the experts involved here may lack the insight of other clinicians involved in MDD and TRD management, namely, primary care physicians. Nevertheless, there is some consensus that, in Portugal, TRD diagnosis and treatment are usually performed by psychiatrists. Hence, based on the clinical experience of the experts involved here, as well as data available in the literature, this manuscript provides an insight into the Portuguese context of MDD management, while also providing estimates of clinical characteristics and treatment results in the context of TRD.

Overall, the expert consensus was consistent with observational studies and recommendations that have started to unveil the barriers to successful treatment of TRD episodes (12, 14), which were augmented by the COVID-19 pandemic (52, 53). Mental health services and MDD management in Portugal require an urgent investment, namely,

by providing patients with facilitated access to available treatment options, including psychotherapy, neurostimulation, and novel pharmacological strategies.

## 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, SC, IC, AM-P, RN, AO-M, and VS: expert participation and critical revision of the manuscript. SS: questionnaire development and revision of the manuscript. MF: questionnaire development, data analysis, and drafting the manuscript. All authors revised the manuscript draft and approved the submitted version.

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# Resilience Among Parents of Adolescents With Type 1 Diabetes: Associated With Fewer Parental Depressive Symptoms and Better Pediatric Glycemic Control

*Dan Luo[1]*, Yubing Wang[2], Xue Cai[3], Ruxue Li[3], Mingzi Li[3], Haiyan Liu[4]* and Jingjing Xu[5]**

[1] School of Nursing, Nanjing University of Chinese Medicine, Jiangsu, China, [2] Department of Endocrinology, Children's Hospital Affiliated to Nanjing Medical University, Jiangsu, China, [3] School of Nursing, Peking University, Beijing, China, [4] Department of Neurology, The Second Affiliated Hospital of Xuzhou Medical University, Jiangsu, China, [5] Department of Endocrinology, The First Affiliated Hospital With Nanjing Medical University (Jiangsu Province Hospital), Jiangsu, China

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**Edited by:**
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***Correspondence:**
Dan Luo
501710014@qq.com
Haiyan Liu
xiaohu4531@163.com
Jingjing Xu
dsnxjj@njmu.edu.cn

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**Background:** Although pediatric resilience plays a significant role in resisting negative moods and improving glycaemic control, little research exists regarding resilience among the parents of adolescents with Type 1 diabetes.

**Objective:** To investigate parental resilience's correlations with parental depressive symptoms, parental diabetes distress, and pediatric glycaemic control.

**Methods:** This cross-sectional study recruited adolescents with Type 1 diabetes and their parents from two hospitals. The parents completed questionnaires. The 10-item Connor-Davidson Resilience Scale measured resilience; the Problem Areas in Diabetes Survey-Parent Revised version measured diabetes distress; the Patient Health Questionnaire-9 measured depressive symptoms. Standard glycated hemoglobin tests were performed on the adolescents.

**Results:** Data from 224 parents (77.2% female, $M_{age}$ = 39.88 [SD = 5.02], age range = 30–56 years) of adolescents (50.9% boys, $M_{age}$ = 13.54 years [SD = 2.48], age range = 10–19 years) were available. More than half (52.7%) of parents exceeded the criterion score for high resilience. Parental resilience was significantly negatively associated with parental depressive symptoms and diabetes distress. Parents from the high-resilience group reported fewer depressive symptoms than those from the low-resilience group. In multivariate regressions, greater parental resilience is consistently related to better pediatric glycaemic control beyond parental psychological risk factors.

**Conclusions:** This study highlights the importance of parental resilience for parental mental health and glycaemic control among adolescents with Type 1 diabetes. The appropriate resilience support programme might be developed for parents, especially for those existing depressive symptoms and diabetes distress.

**Keywords: resilience, depressive symptoms, diabetes distress, parents, diabetes mellitus Type 1**

## INTRODUCTION

Type 1 diabetes is one of the most common childhood diseases which requires lifelong insulin treatment (1). The incidence of Type 1 diabetes has been increasing worldwide, especially among children under 19 (2). Deteriorating glycemic control is shared among adolescences with Type 1 diabetes due to hormonal changes and problematic self-management behavior (3). The pivotal Diabetes Control and Complications Trial demonstrated that elevated glycosylated hemoglobin (HbA1c) was associated with long-term complications, impaired neurocognitive function, and increased mortality (4, 5).

Parents of adolescents with Type 1 diabetes are responsible for the complex management of diabetes, leading to caregiver burden and stress (6). Moreover, they bear a heavy financial burden, experience frequent family conflict, and fear the complications of diabetes (7–9). In a systematic review, 19% of parents experienced psychological distress lasting 1–4 years after their children were diagnosed with Type 1 diabetes (10). Bassi (11) reported that the prevalence of depression among the parents of adolescents with Type 1 diabetes ranged from 13 to 74% in different studies. Evidence from empirical research suggests that parental depressive symptoms and diabetes distress are negatively associated with pediatric glycaemic control (12, 13). Identifying protective factors that could play dual roles to relieve parents' depressive symptoms and diabetes distress and improve glycaemic control among adolescents is crucial to improving the quality of life for these families.

One factor that has attracted considerable attention in pediatric chronic diseases is caregiver resilience, typically defined as an individual's capacity to resist adverse psychological reactions and demonstrate positive outcomes when caring for a child with chronic illness (14). Among parents of children with cancer, those in the high-resilience group displayed fewer depressive symptoms and reported lower levels of uncertainty regarding the illness than those in the low-resilience group (15). Similarly, Rodríguez-Rey et al. (16) conducted a longitudinal study. They found that parental resilience was a strong negative predictor of anxiety, depression, and posttraumatic stress disorder following their child's treatment in intensive care. On the other hand, parental resilience has been linked to the health outcomes of children in recent studies. Khu et al. (17) reported that parental resilience was positively associated with pediatric pain indicators among adolescents diagnosed with chronic pain. In contrast, Gmuca et al. (18) argued that no significant correlation existed between parental resilience and adolescents' pain levels.

According to the pediatric transactional theory (19), the health status of children is deeply affected by the bidirectional interactions that occur between parents and children. Most type 1 diabetes studies have focused primarily on adolescents' resilience and proved that greater resilience was associated with better glycemic control and quality of life (20, 21). Only one survey has specifically examined the association between parental resilience and depressive symptoms. Edraki and Rambod (22) reported that parents in the lowest resilience group experienced extremely severe stress and depression. No study has explored the association between parental resilience and pediatric glycaemic control.

In summary, glycaemic control is suboptimal among adolescents with Type 1 diabetes. There is a well-documented association between parents' negative emotions and the glycaemic control of the children. Therefore, identifying the key variables that correlate with both negative parental emotions and pediatric glycaemic control may provide a rational basis for developing effective interventions. This study hypothesized that higher parental resilience would be associated with fewer parental depressive symptoms, lower parental diabetes distress, and better pediatric glycaemic control.

## MATERIALS AND METHODS

### Participants and Procedure

This cross-sectional survey study was conducted from February 2020 to July 2021. Participants were consecutively recruited from two academic hospitals in China. The eligibility requirements included: being the parents of adolescents (aged 10–19 years) who were diagnosed with Type 1 diabetes for over 6 months; responsible for adolescents who receive either multiple daily injections or continuous subcutaneous insulin infusions; being mentally and physically competent to answer the study questionnaires; able to read and speak Chinese; being willing to participate in the study. Parents were excluded if they had any psychiatric disorders or comorbid organic diseases or if their children were taking any medications that could influence glycaemic control (such as glucocorticoid drugs). The study sample size was calculated based on a pilot study. Among the 20 parents of adolescents with Type 1 diabetes in the pilot study, Pearson's correlation coefficients between parental resilience and depressive symptoms, diabetes distress, and adolescents' HbA1c value were −0.38, −0.31, −0.23, respectively. Therefore, based on $\alpha = 0.05$, $\beta = 0.90$, and $r = 0.23$, a 195-subject sample size was estimated to be necessary (23).

A total of 407 adolescents with Type 1 diabetes visited the endocrine clinic of these hospitals during the study period. All parents were contacted by a diabetes specialist nurse and asked if they were interested in participating in the study. Of the 262 parents interested in participating and screened for eligibility, 240 were eligible. Eligible parents signed the informed consent and finished the questionnaires. Because of the incompletely filled questionnaires, 16 respondents were excluded from the study. Finally, the data of 224 participants were used for the data analysis. **Figure 1** shows the participant recruitment process in detail.

### Data Collection

The parents who signed the informed consent form completed the pen-and-paper survey in a quiet room. The self-reported questionnaires included five parts: parental resilience, depressive symptoms, diabetes distress, demographic characteristics, and adolescents' demographics and disease information. Well-trained diabetes education nurses instructed the parents to respond to the questionnaires. The entire survey took ∼20 min to complete, and all questionnaires were reviewed on-site to improve quality and

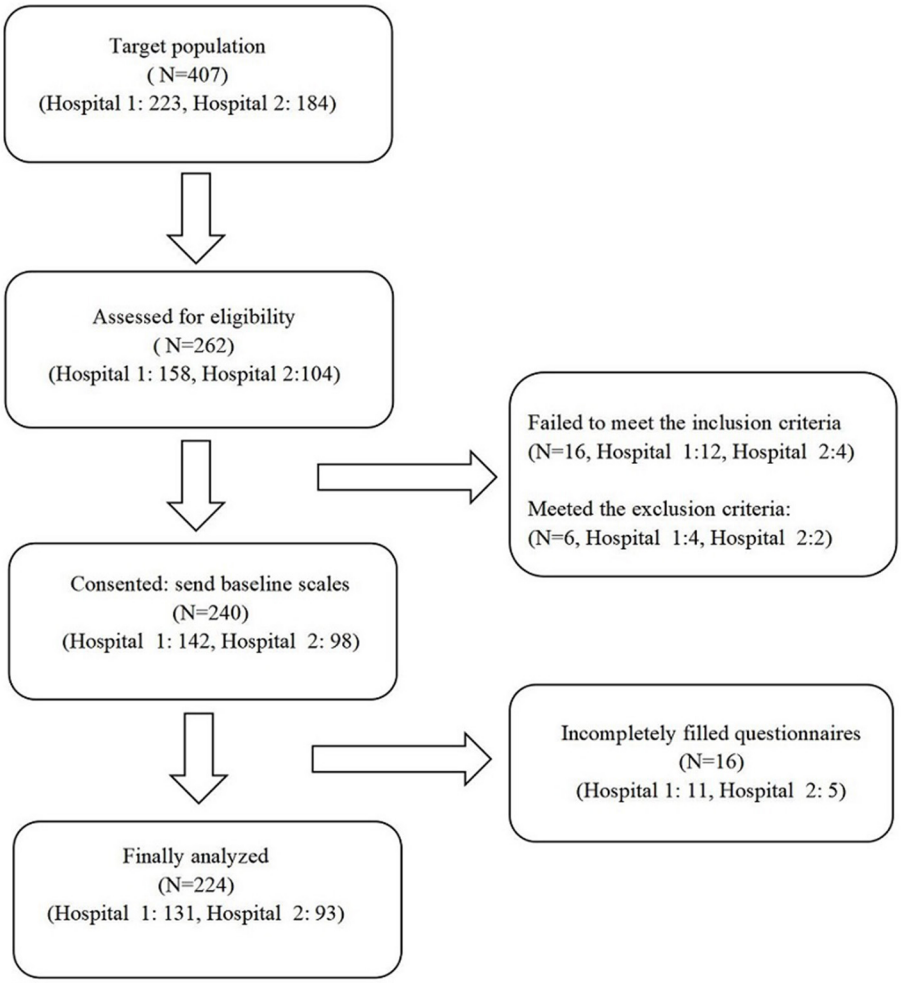


**FIGURE 1 |** Participant recruitment flow chart.

completeness. While the parents filled out the questionnaires, the adolescents underwent HbA1c testing.

## Instruments

### Demographics

The self-designed questionnaire used in this study consisted of two separate sections. The first section asked about parent demographic characteristics (age, gender, education level, marital status, family income, work conditions, the number of children, and whether the parent is the only caregiver). The second section included questions regarding the demographic and disease-related information of the adolescents with Type 1 diabetes (age, gender, duration of Type 1 diabetes, insulin therapy method, whether they monitor blood glucose daily, and self-management level).

### Resilience

The Chinese version of the 10-item Connor-Davidson Resilience Scale (CD-RISC-10) was used to assess parental resilience (24). The CD-RISC-10 is a 5-point Likert scale (0: never to 4: almost always) that measures the personal capacity to tolerate difficulty and achieve positive outcomes. All item scores were summed to obtain a total score, with higher scores reflecting greater resilience. The scores of the Chinese version of the CD-RISC-10 can also be divided into two levels: 0–25 indicates low resilience, whereas 26–40 indicates high resilience. The Chinese version of the CD-RISC-10 has well-documented reliability (Cronbach's $\alpha = 0.88$, the 2 week test-retest = 0.73) (24).

### Depressive Symptoms

The depressive symptoms of parents were evaluated using the Chinese version of the Patient Health Questionnaire-9 (PHQ-9) (25). The PHQ9 is not a diagnostic instrument but does give an indication of the severity of depressive symptoms experienced. A four-point scale (0: not at all to 3: nearly every day) was used for all nine items. The total scores ranged from 0 to 27, with higher scores indicating more depressive symptoms. Parents with a PHQ-9 score of 10 or higher are considered to be suffering from severe depression symptoms. They are offered assistance to obtain further assessment and treatment. The Cronbach's $\alpha$

for the Chinese version of the PHQ-9 was 0.86, and the 2-week test-retest was also 0.86.

### Diabetes Distress

To measure the diabetes distress of parents, we used the Problem Areas in Diabetes Survey-Parent Revised version (PAID-PR), which was designed by Markowitz et al. (26). Two subscales for immediate distress and theoretical distress were examined, each consisting of nine items. The 18-item PAID-PR utilizes a 6-point Likert scale (1: no concern to 6: serious concern), with total scores ranging from 18 to 108, and higher scores indicate more diabetes distress. We translated the original PAID-PR into Chinese through the following four stages: (1) forward translation, (2) back translation, (3) committee discussion, and (4) pilot test. The Chinese version of PAID-PR in this study demonstrated good construct validity ($\chi^2/DF = 2.29$; CFI = 0.90; RMSEA = 0.08) and reliability (Cronbach's $\alpha = 0.91$).

### Glycaemic Control

Capillary blood samples were collected from adolescents through finger sticks. HbA1c values were measured at a central laboratory shared by both recruitment sites utilizing the standard method (Clover A1c Analyzer, Bio-Rad D10 hemoglobin testing system Specifications).

### Ethical Considerations

The Bioethics Committee of the Peking University Health Science Center approved this study (IRB00001052-19108). All study procedures were following the Declaration of Helsinki (World Medical Association, 2013).

## Statistical Analyses

Statistical analyses werfgv5©[1]e conducted using SPSS 22.0 (IBM Corporation, New York, NY, USA). The study population is described by mean (Standard deviation, SD) and *n* (%). The Pearson correlation coefficients (*r*) was calculated to evaluate the associations among parental resilience and depressive symptoms and diabetes distress. The difference between *r* for resilience-depressive symptoms and *r* for resilience-diabetes distress were explored following the method provided by Lee et al. (27). The odds ratios (ORs) and 95% confidence intervals (CIs) for risk of low resilience (CD-RISC-10 score $\leq$ 25) in relation to every 1-SD higher of depressive symptoms and diabetes distress were obtained using logistic regression analyses. The subgroup analysis was employed to evaluate the impact of parental gender on the associations that depressive symptoms and diabetes distress had with the risk of low resilience. We established three linear regression models to evaluate the independent association between parental resilience and pediatric glycemic control. We centered all predictor variables for testing two-way interactions. The collinearity test was performed using the Variance Inflation Factor (VIF) and Tolerance (TOI), and the results showed no overlapping. Model 1 was adjusted for variables including child age, gender, disease duration, insulin regimen, daily blood glucose monitoring, and self-management level that demonstrated a correlation with pediatric glycaemic control in previous studies (28, 29). For example, insulin pump therapy, higher adherence for blood glucose monitoring, and better self-management were associated with lower HbA1c (30). Model 2 was adjusted for variables in Model 1 plus parental depressive symptoms and diabetes distress. Model 3 was adjusted for variables in Model 2 plus interaction effects between parental resilience and depressive symptoms and diabetes distress. For the unranked variables, dummy variables were created. For all anal yes, $p < 0.05$ indicated significance.

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# RESULTS

## The Characteristics of the Participants

The mean age of the parents was 39.88 (SD = 5.02) and ranged from 30 to 56 years. Most respondents were mothers (77.2%), and almost all (95.0%) of the parents reported being married. In addition, 31.2% of the parents were unemployed, and 52.2% had a family monthly income of <5,000 Yuan. Over half (53.1%) of the parents reported having more than one child. Additionally, 21.0% of parents care for adolescents alone. Among the adolescents with Type 1 diabetes, 49.1% were boys, and 61.6% were younger than 15 (ranged from 10 to 19), with a mean age of 13.54 (SD = 2.48) years. Their average Type 1 diabetes duration was 3.91 (SD = 2.77) years, and 76.3% were currently using an insulin pen for insulin injection. Parents reported that 88.4% of adolescents monitored their blood glucose levels daily, and 30% had low levels of self-management. The mean HbA1c was 8.0 ± 1.8%, and 52.7% of adolescents did not reach the glycaemic goal (HbA1c < 7.5%) (31). See detail in **Table 1**.

## Resilience, Depressive Symptoms and Diabetes Distress Among Parents

The Cronbach's $\alpha$ of CD-RISC-10, PHQ-9, and PAID-PR in this sample were 0.88, 0.88, and, 0.91, respectively, indicating excellent reliability. Just over half of parents (52.7%) were highly resilient with a CD-RISC-10 score above 26, and a mean score was 28.36 (SD = 6.81); 12.9% experienced severe depression symptoms, PHQ-9 score $\geq$ 10, and the mean score was 4.67 (SD = 4.49). The means score for diabetes distress was 65.68 (SD = 19.82). Regarding gender differences, mothers reported more depressive symptoms than fathers ($t = -2.12$, $p = 0.032$). No significant differences were found between mothers and fathers regarding resilience and diabetes distress.

The results of Pearson correlation analysis were shown in **Table 2**, parental resilience was moderately negatively associated with parental depressive symptoms ($r = -0.43$, $p < 0.001$) and diabetes distress ($r = -0.37$, $p < 0.001$). There was no statistical difference between the $r_1$ (resilience and depressive symptoms) and $r_2$ (resilience and diabetes distress) ($z = -1.10$, 95%CI: −0.21, - 0.06).

Following the bivariate analysis, we included parental depressive symptoms and diabetes distress in a logistic regression model, in which the dichotomous dependent variable was parental resilience level (low resilience: CD-RISC-10 score $\leq$ 25). More parental depressive symptoms were associated with an OR of 1.15 (95% CI: 1.06–1.25, $p = 0.001$) for the low level of resilience. The prevalence of low resilience was significantly

**TABLE 1 |** Participants' characteristics.

| Participants | Characteristic | Classification | Number (n) | Percentage (%) |
|---|---|---|---|---|
| Parents | Gender | Female | 173 | 77.2 |
| | | Male | 51 | 22.8 |
| | Age(years)[†] | <40 | 108 | 48.2 |
| | | ≥40 | 116 | 51.8 |
| | Education level | Primary education | 17 | 7.6 |
| | | Secondary education | 134 | 59.8 |
| | | Higher education | 73 | 32.6 |
| | Marital status | Married | 212 | 95.0 |
| | | Divorced | 12 | 5.0 |
| | Work status | Employed | 154 | 68.8 |
| | | Unemployed | 70 | 31.2 |
| | Family monthly income | <5,000 Yuan | 117 | 52.2 |
| | | ≥5,000 Yuan | 107 | 47.8 |
| | Number of children | 1 | 105 | 46.9 |
| | | ≥ 2 | 119 | 53.1 |
| | Sole caregiver | Yes | 177 | 79.0 |
| | | No | 47 | 21.0 |
| Adolescents | Gender | Girl | 114 | 50.9 |
| | | Boy | 110 | 49.1 |
| | Age(years)[‡] | <15 | 138 | 61.6 |
| | | ≥15 | 86 | 38.4 |
| | Diabetes duration(years)[§] | <5 | 164 | 73.2 |
| | | ≥5 | 60 | 26.8 |
| | Insulin regimen | Pen | 171 | 76.3 |
| | | pump | 53 | 23.7 |
| | Daily blood glucose monitoring | Yes | 198 | 88.4 |
| | | No | 26 | 11.6 |
| | Self-management level | Low | 60 | 26.8 |
| | | Moderate | 156 | 69.6 |
| | | High | 8 | 3.6 |
| | HbA1c, % [¶] | ≤7.5 | 106 | 47.3 |
| | | >7.5 | 118 | 52.7 |

*SD, Standard deviation; HbA1c, Glycated hemoglobin; [†] The mean (SD) for parents' age was 39.88 (5.02) years; [‡] The mean (SD) for adolescents' age was 13.54 (2.48) years; [§] The mean (SD) for diabetes duration was 3.91 (2.77) years; [¶] The mean (SD) for HbA1c was 8.0 (1.8)%.*

**TABLE 2 |** Levels and associations of parental resilience with parental depressive symptoms and diabetes distress.

| | Mean | SD | Correlation Matrix | | |
|---|---|---|---|---|---|
| | | | 1 | 2 | 3 |
| Resilience | 28.36 | 6.81 | 1 | | |
| Depressive symptoms | 4.67 | 4.49 | −0.43** | 1 | |
| Diabetes distress | 65.68 | 19.82 | −0.37** | 0.53** | 1 |

***Correlation is significant at the 0.01 level (2-tailed).*

higher in parents who had severer diabetes distress (OR = 1.02, 95%CI: 1.01–1.04, $p = 0.036$). Subgroup analysis showed that the association between depressive symptom and resilience was significant in both mothers (OR = 1.11, 95%CI: 1.02–1.21, $p = 0.019$) and fathers (OR = 1.40, 95%CI: 1.08–1.82, $p = 0.012$). Furthermore, diabetes distress did not lead to an increased risk of low resilience in fathers ($p = 0.902$), while did in mothers (OR = 1.02, 95%CI: 1.00–1.04, $p = 0.032$).

## Multivariate Analysis of the Association Between Parental Resilience and Pediatric Glycemic Control

Three linear regression models were established to evaluate the association between parental resilience and pediatric glycaemic control (**Table 3**). The model 1 showed that greater parental resilience was correlated with lower pediatric HbA1c after controlling for adolescents' demographic and disease characteristics ($\beta = -0.06$, $p = 0.002$, Cohen's $d = 0.44$). The same association was observed in model 2, adjusted for variables in Model 1 plus parental depressive symptoms and

**TABLE 3 |** Regression analyses testing parent resilience as predictor of HbA1c.

| Variables | Model 1[†] | | Model 2[‡] | | Model 3[§] | |
|---|---|---|---|---|---|---|
| | *β* | *p* | *β* | *p* | *β* | *p* |
| Child gender | 0.44 | 0.059 | 0.40 | 0.082 | 0.42 | 0.075 |
| Child age | 0.04 | 0.475 | 0.02 | 0.694 | 0.02 | 0.642 |
| Disease duration | 0.02 | 0.693 | <0.00 | 0.923 | <0.00 | 0.945 |
| Insulin regimen | −0.32 | 0.261 | −0.25 | 0.375 | −0.29 | 0.318 |
| Daily blood glucose monitoring | −0.60 | 0.117 | −0.63 | 0.092 | −0.64 | 0.089 |
| Self-management level (1) | −0.07 | 0.792 | −0.05 | 0.860 | −0.03 | 0.911 |
| Self-management level (2) | −1.29 | 0.052 | −1.17 | 0.077 | −1.27 | 0.062 |
| Resilience | −0.06 | 0.002 | −0.05 | 0.008 | −0.05 | 0.007 |
| Diabetes distress | | | 0.02 | 0.008 | 0.02 | 0.006 |
| Depressive symptoms | | | −0.05 | 0.104 | −0.06 | 0.107 |
| Resilience × Diabetes distress | | | | | <-0.01 | 0.625 |
| Resilience × Depressive symptoms | | | | | <-0.01 | 0.816 |
| R2 | | 0.11* | | 0.13* | | 0.13* |

*HbA1c, glycosylated hemoglobin; *, P < 0.01.*

*[†] Model 1: adjusted for child age, disease duration, insulin regimen(pen or pump), daily blood glucose monitoring (no or yes), and self-management level(low or moderate, low or high).*

*[‡]Model 2: Model 1 plus diabetes distress and depressive symptoms.*

*[§]Model 3: Model 2 plus interactions between resilience and depressive symptoms and distress.*

diabetes distress ($\beta = -0.05$, $p = 0.008$, Cohen's d = 0.37). Two-way interactions between parental resilience and depressive symptoms and diabetes distress were added in model 3, and results found no significant interactions. The association between parental resilience and pediatric glycemic control remained unchanged ($\beta = -0.05$, $p = 0.007$, Cohen's d = 0.38).

## DISCUSSION

The primary aim of the present study was to explore the correlations that parental resilience has with parental depressive symptoms, parental diabetes distress, and pediatric glycaemic control. Our analysis provided support for our hypotheses. Among parents of adolescents with Type 1 diabetes, higher parental resilience was associated with fewer parental depressive symptoms and lower diabetes distress. Moreover, parental resilience had an independent effect on pediatric glycaemic control after statistically controlling for adolescents' demographic and disease variables and parental depressive symptoms and diabetes distress.

The mean PHQ-9 score of parents in this study was higher than that of a Chinese community population (25). Complex, diabetes-specific daily tasks, and frequent hospital visits increase parents' vulnerability to experiencing depressive symptoms (13). Specifically, mothers of adolescents with Type 1 diabetes reported more depressive symptoms than fathers. Women's susceptibility to depression and a higher level of maternal involvement in diabetes care may account for this difference (32). The mean score of parental diabetes distress in our study was much higher than the results reported for a cohort in the United States (26). The lower incidence of Type 1 diabetes in China may result in specific challenges for parents and adolescents with Type 1 diabetes in this country. In a cross-national survey, 19.1% of Chinese participants reported being discriminated against because of their diabetes, compared with 10.6% of participants in the United States (33). Moreover, Chinese universities and junior colleges are allowed to refuse admission to students with Type 1 diabetes according to government regulations, which may increase parents' uncertainty about their children's futures (34). Another significant finding of our study was the relatively high level of resilience identified among the parents of adolescents with Type 1 diabetes compared to a general Chinese population (35). Resilience theory emphasizes that stressful circumstances will provide opportunities to improve resilience, allowing the individual to maintain their physical and psychological well-being (36). From a cultural perspective, Chinese people typically regard suffering and hardships as necessary conditions for growth and success. They attempt to stay positive and pay less attention to unwelcome thoughts.

In addition, we found that parental resilience was negatively correlated with parental diabetes distress and depressive symptoms. This finding was similar to the findings of the studies conducted by Tully (37) and Ye et al. (38), who surveyed the parents of children with asthma and cancer, respectively. Mason et al. (39) conducted a longitudinal qualitative study examining the mothers of children with an autism spectrum disorder and reported that higher baseline resilience among mothers predicted lower stress trajectories over 18 months. The neuro mechanism of resilience could explain these results. An increasing body of evidence suggests that resilience could invoke specific brain structures and neural circuits to help the individual to regulate mood (40, 41). Although parental psychosocial screening is becoming more common at diabetes clinics, the medical staff is more likely to recognize and relieve negative emotions than evaluate and improve positive psychological qualities (42).

Identifying the resilient characteristics of parents can help medical staff to provide specific family-centered education and support.

The current study provides initial evidence that parental resilience was positively correlated with better pediatric glycaemic control among adolescents with Type 1 diabetes. This finding extends previous work regarding the correlation between parental psychological variables and adolescents' diabetes-related outcomes. The mechanisms underlying this positive relationship may be partly explained by pediatric transactional theory (19). The transactional theory highlights the interactions between the parents' characteristics and children's behaviors and health outcomes. Greater resilience can lead to higher self-efficacy and more positive coping strategies when individuals encounter traumatic circumstances (43). Lohan and Mitchell (44) demonstrated that parental self-efficacy was positively associated with adolescents' diabetes self-management behavior. Speculatively, parents with higher resilience may have more confidence in diabetes care, providing more freedom and support to their children, which might sequentially improve self-care behavior and glycaemic control of adolescents (45).

This study has several strengths. First, our results may enable cross-cultural comparisons because our measures are well-established and have good psychometric properties among people from different countries. Second, the HbA1c values were tested using a standard method. Third, we included demographic, disease-related, and psychological covariates in serial multivariable regression models and demonstrated that parental resilience was independently correlated with pediatric glycaemic control. We also acknowledge several limitations of our study. First, the cross-sectional design makes it impossible to determine causal relationships between parental resilience and other variables. More longitudinal studies and randomized controlled trials remain necessary. Second, the study consists of samples from two Chinese hospitals, and our observations could be characteristic of that specific population studied. The reader may need to be cautious in interpreting the results, and more extensive studies are needed to explore whether our conclusions are replicable in different countries with diverse cultures. Third, the sample size of fathers was small, reducing the statistical power to detect differences in resilience and diabetes distress between mothers and fathers. More evenly sized samples and the inclusion of both parents from a family unit might allow a more accurate examination of gender differences. Last, the parents of the presents study were invited on a voluntary and anonym basis. Volunteers usually have a better mental function, and this means that our results could have been biased.

The current study demonstrated that in parents of adolescents with Type 1 diabetes, resilience might be a promising focus for interventions to improve parental mental health and pediatric glycaemic control. As applied to clinical care, we recommend incorporating resilience in the routine assessment of parental psychological symptoms. Standard screening of parents in diabetes clinics may help identify those who need emotional support to address depressive symptoms and diabetes distress and are most likely to benefit from resilience intervention. Some resilience strengthening strategies that medical staff can adopt include discovering and utilizing parental internal strengths (optimistic, self-efficacy and calm) and organizing activities to promote interaction between parents and children (46, 47). In addition, the findings from parents of adolescents with Type 1 diabetes could be generalized to the parents of children with chronic disease. There is an urgent need for research focusing on the relationship between parental positive psychological variables and pediatric disease-related health outcomes.

In conclusion, the parents of adolescents with Type 1 diabetes showed relatively high resilience. Higher parental resilience was associated with fewer parental depressive symptoms and lower levels of diabetes distress. Parental resilience appears to play a significant role in pediatric glycaemic control, adjusting for adolescents' demographic and clinical parameters and parental risk psychological variables. Future research should further explore the effects of parental resilience on parental mental health and pediatric diabetes management and examine whether resilience-focused interventions can improve the health outcomes of parents and adolescents.

## 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 Peking University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

DL designed the study, enrolled participants, analyzed and interpreted the data, and wrote the manuscript. YW, XC, RL, and JX were responsible for collecting data. ML, HL, and JX supervised this research project.

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# White Matter Network Disruption Is Associated With Melancholic Features in Major Depressive Disorder

*Mengxin He*[1,2], *Yuqi Cheng*[1,2], *Zhaosong Chu*[1,2], *Xin Wang*[1], *Jinlei Xu*[1], *Yi Lu*[3], *Zonglin Shen*[1,2,4*] *and Xiufeng Xu*[2*]

[1] Department of Psychiatry, First Affiliated Hospital of Kunming Medical University, Kunming, China, [2] Yunnan Clinical Research Center for Mental Disorders, Kunming, China, [3] Department of Medical Imaging, First Affiliated Hospital of Kunming Medical University, Kunming, China, [4] Mental Health Institute of Yunnan, First Affiliated Hospital of Kunming Medical University, Kunming, China

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Tianmei Si,
Peking University Sixth Hospital, China

***Correspondence:**
Xiufeng Xu
xfxu2004@sina.com
Zonglin Shen
shenzl1987@163.com

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**Background:** The efficacy and prognosis of major depressive disorder (MDD) are limited by its heterogeneity. MDD with melancholic features is an important subtype of MDD. The present study aimed to reveal the white matter (WM) network changes in melancholic depression.

**Materials and Methods:** Twenty-three first-onset, untreated melancholic MDD, 59 non-melancholic MDD patients and 63 health controls underwent diffusion tensor imaging (DTI) scans. WM network analysis based on graph theory and support vector machine (SVM) were used for image data analysis.

**Results:** Compared with HC, small-worldness was reduced and abnormal node attributes were in the right orbital inferior frontal gyrus, left orbital superior frontal gyrus, right caudate nucleus, right orbital superior frontal gyrus, right orbital middle frontal gyrus, left rectus gyrus, and left median cingulate and paracingulate gyrus of MDD patients. Compared with non-melancholic MDD, small-worldness was reduced and abnormal node attributes were in right orbital inferior frontal gyrus, left orbital superior frontal gyrus and right caudate nucleus of melancholic MDD. For correlation analysis, the 7th item score of the HRSD-17 (work and interest) was positively associated with increased node betweenness centrality (aBC) values in right orbital inferior frontal gyrus, while negatively associated with the decreased aBC in left orbital superior frontal gyrus. SVM analysis results showed that abnormal aBC in right orbital inferior frontal gyrus and left orbital superior frontal gyrus showed the highest accuracy of 81.0% (69/83), the sensitivity of 66.3%, and specificity of 85.2% for discriminating MDD patients with or without melancholic features.

**Conclusion:** There is a significant difference in WM network changes between MDD patients with and without melancholic features.

**Keywords: melancholic depression, non-melancholic depression, diffusion tensor imaging, WM network, small-world**

## INTRODUCTION

Major depressive disorder (MDD) is a commonly recurring psychiatric disorder with a high disability rate. The clinical features of MDD include persistent depression, decreased vitality, decreased response to external stimuli, and changes in sleeping habits (1). In the DSM, a subtype of MDD is described: pervasive anhedonia (reduction or complete loss of external and inner pleasure experiences), circadian mood fluctuations, guilt, early awakening, psychomotor excitement/retardation, loss of appetite/weight loss (2). MDD with these highly consistent clinical features is categorized as melancholic MDD (3). Compared with non-melancholic MDD patients, melancholic MDD patients have worse cognitive and social functions (4), higher suicide risk (5), and lower clinical cure rate (4). Melancholic MDD is proposed to be a special subtype of MDD, and this diagnosis may predict treatment efficacy and prognosis (6).

A series of studies have suggested changes in brain function and structure in patients with MDD (7, 8), such as interruption of functional homogeneity and decreased effective connectivity of cortical regions involved in emotion regulation (9). At the same time, many studies have revealed the alterations of brain structure or function in patients with melancholic. For example, its melancholic severity is positively correlated with the orbitofrontal cortex (OFC) activation (10, 11) and negatively correlated with the anterior volume of the caudate nucleus (12). The evaluation of melancholic features may be mainly regulated by OFC (13). Melancholic MDD may have lower mean fractional anisotropy (FA) of OFC (14), and higher FA of the inner capsule of the right forelimb outside the head of the caudate nucleus and inside the lenticular nucleus, than non-melancholic MDD patients (15). However, these studies are only based on the analysis of the function or structure of a single brain area, ignoring the synergy between the various areas of the brain as a network as a whole. The brain network alterations of melancholic MDD are unclear.

Recently, a neuroimaging analysis revealed functional and structural defects in the brains of patients with MDD (16). Research by the Enhancing Neuro Imaging Genetics through Meta-Analysis consortium showed consistent neuroimaging results of MDD brain structure in a multi-site alignment study (17). Functional abnormalities and changes in the cortical structure of non-adjacent brain regions (18), white matter (WM) tract connections between the cortex and subcortical regions between seemingly non-adjacent regions (19), and altered WM tract integrity (disconnection-syndrome) (20) were discovered in patients with MDD. Abnormal transmission of information and nutrients between regions leads to cortical and functional changes in patients with MDD.

Most neuroimaging studies use traditional voxel-based analyses (21), which may not detect subtle and balanced interactions between brain regions or extensive and subtle pathological changes (22). However, the global connection pattern of the brain as well as local connection patterns among brain regions can be evaluated using large-scale network analyses of each brain region (23). This complex brain network analysis (graph theory)—has been widely used in connection group studies of mental disorders (22), such as MDD (24), schizophrenia (25), and bipolar disorder (26), to compare complex brain networks between people with and without these disorders. Small-world network attributes are helpful to explain complex neural connection states between regions (global). The complex brain network of each region (local) can be analyzed through brain networks formed at the connection (edge) between each brain region (node) (27). Compared with voxel-based single brain region analyses, investigating connections between regions may be a more reliable technique for detecting changes in the WM structure in MDD (28), and maybe a helpful method to uncover the pathological mechanism of MDD. In brief, considering the clinical manifestations were different between melancholic depression and non-melancholic depression, the WM structure, which is associated with the pathological mechanism of MDD, may be different between these two subtypes, and associated with different manifestations. We hypothesized that there is a special network model of melancholic depression, the orbitofrontal cortex may play a key role in the network. Thus, we use a complex WM structure brain network based on graph theory to verify this hypothesis. First-episode untreated adult depression patients with and without melancholic characteristics were recruited in our study to avoid the influence of medication.

## METHODS

### Participants

Between 2015 and 2017, 82 MDD patients (aged 18–45) were recruited from the outpatient and inpatient departments of the First Affiliated Hospital of Kunming Medical University. Independent diagnoses by at least two professional psychiatrists were conducted according to the structured clinical interviews based on the mood disorders sections of "Structured Clinical Interview for DSM-IV axis I disorders" (SCID-I). Patients were included in this study if they were newly diagnosed with MDD; scored 12 or higher on the Montgomery–Åsberg Depression Rating Scale (MADRS) (29) and 17 or higher on the Hamilton Rating Scale for Depression (HRSD-17) (30); and had no history of taking antipsychotics, undergoing electric shock therapy or psychotherapy, brain injury, or other mental and neurological diseases. Pregnant and left-handed individuals were excluded. Sixty-three healthy controls matched for age, gender, and years of education were also recruited. Healthy patients with a family history of mental illness, any neurological disease, history of mental disorders, drug abuse, or symptoms of mental illness were excluded. It has been approved by the Ethics Committee of Kunming Medical University in Yunnan, China [Ethics Review L No. 50 (2016)]. The study was described in detail to the recruited participants and written informed consent was obtained.

### Subgroups

An M-MDD subgroup was identified based on the DSM description of MDD with melancholic characteristics. Criterion A (at least one item): almost or complete loss of pleasure in all activities or lack of emotional response to pleasant stimuli;

criterion B (at least three items): day and night mood changes; extreme guilt; easy to wake up early; psychomotor agitation or retardation; anorexia symptoms or weight loss (2).

The DSM also recommends using the MADRS and HRSD-17 criteria to distinguish between NM- and M-MDD. MADRS criterion A: MADRS 8th item score $\geq$ 4 (inability to feel), or MADRS 1th or 2th item score $\geq$ 6 (apparent or reported sadness); concurrent with HRSD-17 criterion B: 1th (depressed mood) or 7th (work and interest) item scores $\geq$ 3 and at least three of the following: (1) HRSD-17 6th item score $\geq$ 1 (insomnia-delayed); (2) HRSD-17 8th or 9th item scores $\geq$ 2 (psychomotor retardation or agitation); (3) HRSD-17 12th or 16th item scores $\geq$ 2 (anxiety—somatic or loss of weight); (4) HRSD-17 2th item score $\geq$ 2 (feelings of guilt). Because neither the MADRS nor the HRSD-17 assesses mood changes within 1 day, we were unable to assess diurnal mood variation (31–33).

## Image Acquisition

Magnetic resonance imaging (MRI) was performed using an Achieva 3.0 Tesla MRI system with 16 channels (Philips, Eindhoven, The Netherlands). Diffusion tensor imaging (DTI) was conducted using a single-echo planar imaging sequence in 50 axial planes. DTI scans consist of 32 independent directions, a diffusion weighting factor with non-collinear diffusion sensitization gradient ($b$ = 1,000 s/mm$^2$), and a reference image without diffusion weighting (b0 image). DTI data were captured using an axial section parallel to the front and rear axis. The imaging parameters were set as follows: TR = 6,800 ms (shortest), TE = 80 ms (shortest), slice thickness = 3 mm (no slice gap), FOV = 230 × 230 mm, matrix size = 116 × 112, voxel size = 2 × 2 × 3 mm, flip angle = 90°, scan time = 8 min 29 s.

## Data Preprocessing

Data preprocessing was performed in MATLAB 2016b using the integrated data processing software PANDA. The preprocessing was performed using the following steps. (1) Correction of head movement and eddy current distortion: registration of the diffusion-weighted image to the b0 image (34). (2) Calculation of the FA to reduce the influence of motion artifacts. (3) Whole-brain fiber bundle imaging: a continuous tracking algorithm for fiber distribution (starting from the deep WM area; voxels with a turning angle >45°; stop tracking at FA < 0.15) (35). (4) Matching of participants with WM fiber tract imaging using an automatic anatomical marker segmentation scheme (AAL90) to construct a WM network (36). (5) Assuming that each brain area is regarded as a node, the number of fibers (FN) multiplied by the average FA between the corresponding cortical areas is regarded as the edge weight ($w_{ij}$): $w_{ij} = FA_{ij} \times FN_{ij}$ (37, 38). A weighted WM network (90 × 90) was constructed for each participant.

## Network Analysis

Using the GRETNA package (http://www.nitrc.org/projects/gretna/) to perform small-world network operations, healthy human WM networks were found to exhibit the attributes of small-world networks, which are between random networks and regular networks and enable more efficient local specialization and optimally balanced global integration (39). To better understand the characteristics of the small-world network, we analyzed the global attributes (small-worldness) and local attributes (node attributes) (22, 26). Small-worldness includes the normalized clustering coefficient ($\gamma$), normalized characteristic path length ($\lambda$), characteristic path length, clustering coefficient, global efficiency, and local efficiency (40). Small-worldness ($\sigma$) is $\gamma > 1$ and $\lambda \approx 1$, or $\sigma = \frac{\gamma}{\lambda} = \frac{\frac{C_p^{real}}{C_p^{rand}}}{\frac{L_p^{real}}{L_p^{rand}}}$, where $C_p^{rand}$ and $L_p^{rand}$ are the averaged values of cluster coefficients and shortest path length of 100 random networks with the same N, V, and degree distribution as the real network (39). We assessed the following six node parameter attributes: node betweenness centrality (aBC), node degree centrality (aDC), node clustering coefficient (aCP), node efficiency (aEfficiency), node local efficiency (aEloc), and node shortest path length (aLP). aBC refers to the number of times a node acts as the shortest bridge between the other two nodes ($B_{nod}(i) \frac{1}{(N-1)(N-2)} \sum_{h=1}^{N} \sum_{j=1, h \neq j \neq i}^{N} \frac{\rho_{hj(i)}}{\rho_{hj}}$, where $\rho_{hj(i)}$ is the total number of the shortest path lengths between nodes $h$ and $j$, which pass through $h$ for a specific node $i$) (40). Additional details are provided as **Supplementary Materials**.

## Statistical Analyses

Analysis of variance was performed to analyze group differences in age and years of education using SPSS18.0, and a two-sample $t$-test was used to analyze group differences in MDD and MADRS scores. A chi-square test was performed to describe the gender distribution. The significance level for all tests was $p < 0.05$.

Analysis of covariance (ANCOVA) was performed to assess the small-world network differences among the three groups with gender, age, and years of education as covariates, then *post-hoc* analysis was used to find out the alterations between each group with gender, age, years of education, and MADRS total score as covariates. We tested the topological small-world network attributes using a sparsity threshold of 5% < sparse < 50% to reduce the influence of deviation caused by a single threshold. The measurement network was calculated as the area under the entire curve (sparse threshold range). The result was corrected for multiple comparisons using FDR (false discovery rate) to $p <$ 0.05 (41, 42).

To assess the node attributes differences among the three groups with gender, age, and years of education as covariates by ANCOVA analysis. And then use *post-hoc* analysis was used to look for changes between each group with gender, age, years of education, and MADRS total score as covariates. To reduce the error in node parameters analysis, non-parametric tests (10,000 times) are used for correction, and the distribution of identification data confirms the application of non-standard test statistics (43), to correct for multiple comparisons, using FDR correction.

GRETNA (http://www.nitrc.org/projects/gretna/) was used to extract relevant values from brain regions with abnormal node attributes. Pearson's correlation analysis was conducted to assess the relationship between anomalous node attributes and HRSD item scores (FDR correction $p < 0.05$).

**TABLE 1 |** Demographic and clinical characteristics of all participants.

| Variables (mean ± SD) | Control ($n = 63$) | NM-MDD ($n = 59$) | M-MDD ($n = 23$) | $F/t$ or $\chi^2$ | $P$-value |
|---|---|---|---|---|---|
| Handedness (R/L) | 63/0 | 59/0 | 23/0 | - | - |
| Age (years) | 34.3 ± 10.4 | 33.7 ± 10.3 | 32.4 ± 11.2 | 0.68 | 0.50[a] |
| Gender (M/F) | 38/25 | 43/16 | 16/7 | 2.26 | 0.32[c] |
| Education (y) | 13.0 ± 4.2 | 11.7 ± 4.5 | 11.1 ± 4.4 | 2.18 | 0.12[a] |
| Duration of illness (mo) | - | 12.0 ± 17.9 | 9.3 ±1 2.9 | 0.77 | 0.44[b] |
| MADRS total score | - | 28.1 ± 6.4 | 37.5 ± 4.9 | 7.0 | <0.001[b] |
| MADRS Item 1th | - | 3.0 ± 1.3 | 4.1 ± 1.1 | 3.70 | 0.001[b] |
| MADRS Item 8th | - | 3.3 ± 1.0 | 4.2 ± 0.42 | 5.5 | <0.001[b] |

*SD, standard deviation; MADRS, Montgomery and Asberg Depression Rating Scale; MADRS Item 1th (0–6 score): Apparent Sadness; MADRS Item 8th (0–6 score): Inability to Feel. R, right; L, left; mo, month; M, male; F, female.*

[a] *The P-values were obtained by ANOVA.*

[b] *The P-values were obtained by two-sample t-test.*

[c] *The P values were obtained by chi-square test.*

## Support Vector Machine Analysis

Using LIBSVM software (https://www.csie.ntu.edu.tw/~cjlin/libsvm/), a support vector machine (SVM) was used to classify healthy people and people with MDD, as well as people with non-melancholic MDD and melancholic MDD, based on the anomalous node attributes of the identified abnormal brain regions.

# RESULTS

## Demographic and Clinical Characteristics

Demographic and clinical characteristic data are presented in **Table 1**. No significant differences in age, gender, or years of education were detected among the three groups, and no statistical difference in illness duration was detected between the two MDD groups. Significant differences in MRADS scores were observed between MDD groups. The MRADS scores of the M-MDD group were significantly higher than those of the NM-MDD group.

## Small-Worldness Differences Between Groups

The ANCOVA analysis with gender, age, and years of education as covariates revealed differences in small-worldness between the three groups. Small-worldness was significantly reduced at the threshold 0.45–0.05 ($\sigma$, $\gamma$, clustering coefficient, and global efficiency) in the two MDD groups. Compared with the control group, the M-MDD group had significantly reduced local efficiency and significantly increased characteristic path length at the threshold 0.40–0.05 ($p < 0.05$, FDR corrected). No significant difference was found in NM-MDD (**Figure 1**).

## Node Attributes

### Node Attribute Differences Between M-MDD, NM-MDD, and Healthy Controls

Compared with the control, six abnormal brain regions in NM-MDD group are as follows: right orbital inferior frontal gyrus (ORBinf.R) (increased aBC), left orbital superior frontal gyrus (ORBsup.L) (decreased aBC, aDC, and aEloc), right caudate nucleus (CAU.R) (increased aBC), left dorsolateral superior frontal gyrus (SFGdor.L) (decreased aDC), right orbital superior frontal gyrus (ORBsup.R) (decreased aBC and aDC; increased aCP), right orbital middle frontal gyrus (ORBmid.R) (decreased aBC), and left rectus gyrus (REC.L) (decreased aCP; increased aBC) (**Table 2**; **Figure 2**).

Compared with the control, eight abnormal brain regions in M-MDD group are as follows: ORBinf.R (decreased aCP; increased aBC aDC and aLP), ORBsup.L (decreased aBC, aDC, aEfficiency and aEloc), CAU.R (decreased aEloc; increased aBC), SFGdor.L (decreased aDC and aEfficiency; increased aCP), ORBsup.R (decreased aBC and aDC; increased aCP), ORBmid.R (decreased aBC; increased aDC), REC.L (decreased aCP; increased aBC), and left median cingulate and paracingulate gyrus (DCG.L) (increased aDC) (**Table 2**; **Figure 2**).

### Node Attribute Differences Between NM-MDD and M-MDD

Compared with NM-MDD, in the M-MDD group right orbital inferior frontal gyrus had significantly increased node attributes (aBC and aDC) and decreased attributes (aCP and aEloc). The left orbital superior frontal gyrus had significantly decreased attributes (aBC, aDC, aEfficiency, and aEloc). The right caudate nucleus had significantly decreased node attributes (aBC and aEloc) (**Table 2**; **Figure 2A**).

## Correlations Between aBC and Clinical Characteristics

Increased aBC in right orbital inferior frontal gyrus was positively correlated with the HRSD-17 total score ($r = 0.373$, $p = 0.002$), 7th item score (work and interest; $r = 0.373$, $p = 0.003$) and 12th item score (gastrointestinal somatic symptoms $r = 0.233$, $p = 0.030$) (**Figures 3A,C**). Decreased aBC in left orbital superior frontal gyrus was negatively correlated with the HRSD-17 total score ($r = -0.228$, $p = 0.0034$) and 7th item score ($r = -0.230$, $p = 0.034$) (**Figures 3B,C**). There was no significant difference in other items in HRSD-17 (see the **Supplementary Materials** for the correlation to the MADRS items).

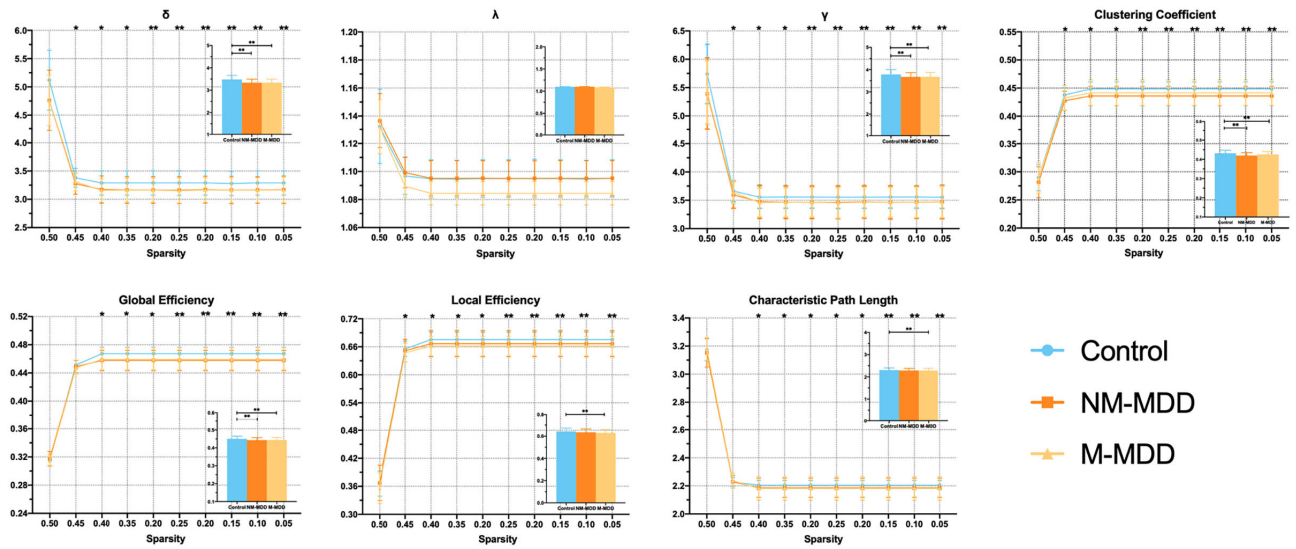


**FIGURE 1 |** Group comparison of small-world network measures among NM-MDD, M-MDD, and control groups. MDD groups showed significantly decreased σ, γ, clustering coefficient, and global efficiency; M-MDD group showed significantly decreased local efficiency and increased characteristic path length ($p < 0.05$, FDR corrected). σ, small-worldness; λ, normalized characteristic path length; γ, normalized clustering coefficient. $^{*}p < 0.05$; $^{**}p < 0.005$.

**TABLE 2 |** ANCOVA results of nodal parameters differences among patients with healthy groups.

| **NM-MDD vs. M-MDD** | **aBC** | | **aDC** | | **aCP** | | **aEiffiency** | | **aEloc** | | **aLP** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***T*** | ***P*** | ***T*** | ***P*** | ***T*** | ***P*** | ***T*** | ***P*** | ***T*** | ***P*** | ***T*** | ***P*** |
| ORBinf.R | −5.271 | **<0.0001*** ** | −5.130 | **<0.0001*** ** | 5.061 | **<0.0001*** ** | 1.869 | 0.06 | −4.653 | **<0.0001*** ** | 3.022 | **0.001**** |
| ORBsup.L | 2.152 | **0.019*** | 2.431 | **0.015*** | −0.992 | 0.325 | 2.370 | **0.017*** | 0.490 | 0.621 | −0.750 | 0.457 |
| CAU.R | 2.235 | **0.017*** | 1.452 | 0.154 | 0.384 | 0.712 | 1.001 | 0.32 | 0.503 | 0.624 | −0.883 | 0.381 |
| **Three groups** | **aBC** | | **aDC** | | **aCP** | | **aEiffiency** | | **aEloc** | | **aLP** | |
| | ***F*** | ***P*** | ***F*** | ***P*** | ***F*** | ***P*** | ***F*** | ***P*** | ***F*** | ***P*** | ***F*** | ***P*** |
| ORBinf.R | 13.90 | **<0.0001*** ** | 11.74 | **<0.0001*** ** | 11.320 | **<0.0001*** ** | 2.494 | 0.086 | 8.206 | **0.0004**** | 7.018 | **0.001**** |
| ORBsup.L | 7.292 | **0.0009**** | 15.35 | **<0.0001*** ** | 0.587 | 0.557 | 4.385 | **0.014*** | 7.019 | **0.001**** | 1.536 | 0.219 |
| CAU.R | 5.512 | **0.004**** | 2.15 | 0.12 | 0.744 | 0.477 | 0.511 | 0.601 | 3.495 | **0.033*** | 0.491 | 0.613 |
| SFGdor.L | 1.003 | 0.374 | 3.27 | **0.04*** | 5.412 | **0.005*** | 3.503 | **0.032*** | 2.248 | 0.109 | 2.780 | 0.065 |
| ORBsup.R | 4.521 | **0.013*** | 3.13 | **0.04*** | 4.387 | **0.014*** | 2.764 | 0.066 | 2.780 | 0.065 | 0.414 | 0.661 |
| ORBmid.R | 5.591 | **0.004**** | 2.10 | 0.13 | 3.653 | **0.028*** | 2.108 | 0.125 | 2.299 | 0.104 | 1.561 | 0.213 |
| REC.L | 5.554 | **0.004**** | 2.48 | 0.09 | 5.369 | **0.006**** | 1.090 | 0.339 | 2.881 | 0.059 | 0.653 | 0.522 |
| DCG.L | 1.195 | 0.313 | 4.02 | **0.02*** | 0.130 | 0.878 | 2.334 | 0.101 | 0.622 | 0.538 | 2.366 | 0.097 |

*ORBinf, Orbital inferior frontal gyrus; ORBsup, Orbital superior frontal gyrus; CAU, Caudate nucleus; SFGdor, Dorsolateral superior frontal gyrus; ORBmid, Orbital middle frontal gyrus; REC, Gyrus rectus; and DCG, Median cingulate and paracingulate gyrus; L, Left hemisphere; R, Right hemisphere.*
*FDR corrected, $^{*}p < 0.05$, $^{**}p < 0.005$, $^{***}p < 0.0001$. Bold indicates that FDR correction is statistically significant.*

## SVM Classification Analysis

The SVM results showed that abnormal right orbital inferior frontal gyrus and left orbital superior frontal gyrus aBC values could distinguish between M-MDD patients and NM-MDD patients with accuracies of 79.5% (66/83) and 73.5% (61/83), sensitivities of 45.1 and 33.3%, and specificities of 83.0 and 83.2%, respectively. The combination of abnormal aBC in right orbital inferior frontal gyrus and left orbital superior frontal gyrus could better distinguish between MDD groups, showing the highest accuracy [81.0% (69/83)], sensitivity (66.3%), and specificity (85.2%). The accuracy, sensitivity, and specificity for distinguishing between healthy and MDD populations were not high (**Figure 4**).

## DISCUSSION

This study explored the characteristic model of the orbitofrontal lobe WM structure brain network in MDD patients with

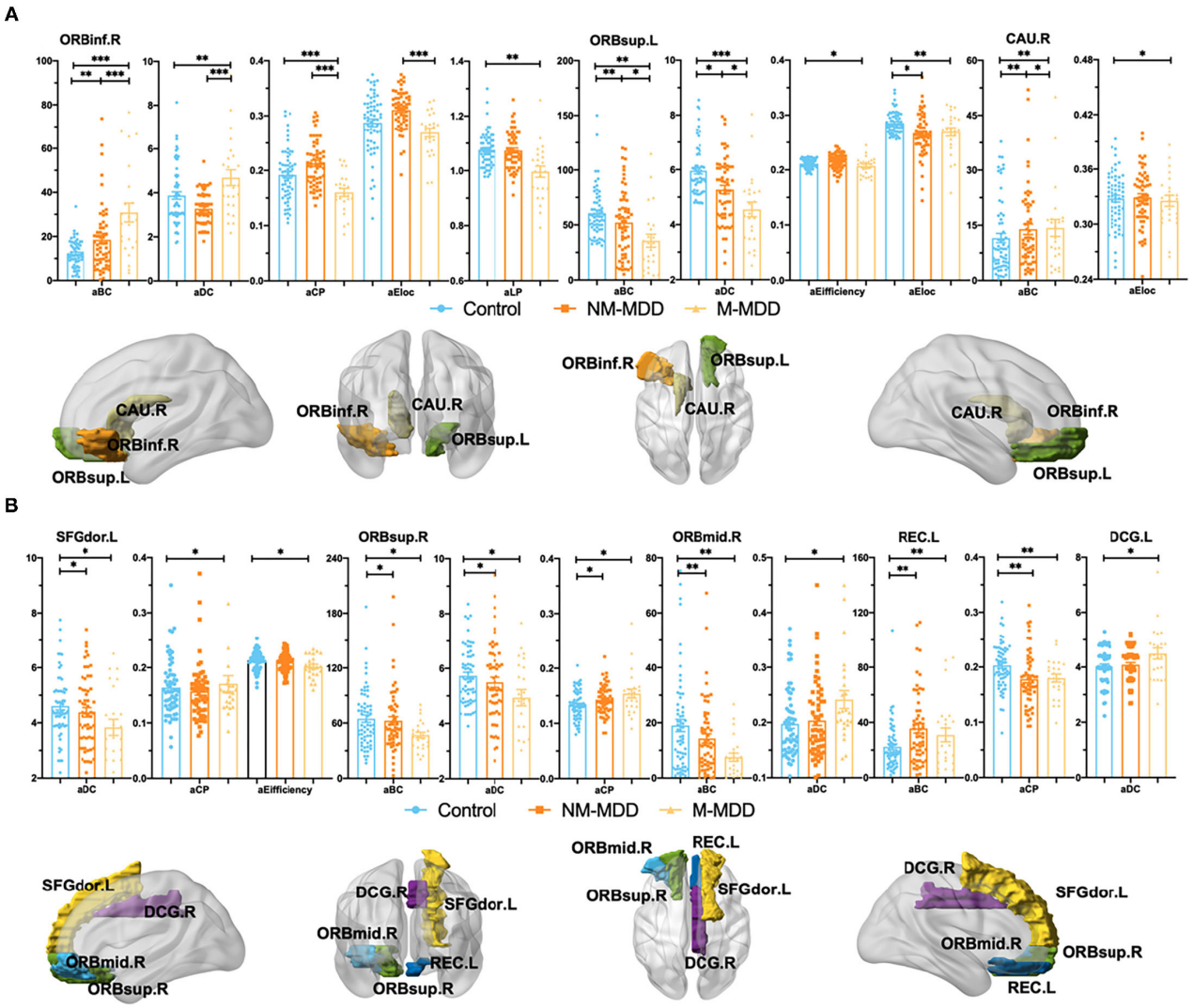


**FIGURE 2 |** Group comparison of Node attributes among NM-MDD, M-MDD, and control groups. **(A,B)**: MDD groups showed significantly decreased aBC (ORBsup.L, ANG.R, ORBsup.R and ORBmid.R), aDC (ORBsup.L, SFGdor.L and ORBsup.R), aEifficiency (ORBsup.L and SFGdor.L), aCP (ORBinf.R and REC.L), aEloc (ORBsup.L and CAU.R) and increased aBC (ORBinf.R, CAU.R and REC.L), aDC (ORBinf.R, ORBmid.R and DCG.L), and aCP (SFGdor.L and ORBsup.R). **(A)** Group comparison of Node attributes between NM-MDD and M-MDD showed abnormal brain regions in ORBinf.R ORBsup.L and CAU.R. **(B)** Only compared with the control group, MDD groups showed abnormal brain regions SFGdor.L, ORBsup.R,O RBmid.R, REC.L, and DCG.L. FDR corrected, $^{*}p < 0.05$, $^{**}p < 0.005$, $^{***}p < 0.0001$. ORBinf (Orange, Orbital inferior frontal gyrus) ORBsup (Green, Orbital superior frontal gyrus), CAU (Earthy, Caudate nucleus), SFGdor (Yellow, Dorsolateral superior frontal gyrus), ORBmid (Sky-blue, Orbital middle frontal gyrus) REC (Dark-blue, Rectus gyrus) and DCG (Purple, Median cingulate and paracingulate gyrus); L, Left hemisphere; R, Right hemisphere.

and without melancholic features. The WM network of MDD patients conforms to the attribute of small-world network, but compared with the healthy control, the global information efficiency of MDD patients is weakened, which refers to the overall efficiency of parallel information transmission in the network (σ, γ, clustering coefficient, and global efficiency) (22) and the node attributes of some brain regions, such as the prefrontal lobe and cingulate gyrus, are ill-conditioned (26). We observed microscopic structural differences in the WM structure network between MDD types. Compared with non-melancholic MDD, the global information efficiency was weaker, and the WM structure network was more random and inefficient in melancholic MDD. Although anomalies of multiple node attributes are observed in the WM network, node betweenness centrality (aBC) is a metric that reflects the importance of a single node, which can better measure the influence of brain regions on information transmission in the network (25). Abnormal aBC was found in almost all abnormal brain regions. In the MDD patients with melancholic features, increased aBC in the right orbital inferior frontal gyrus was

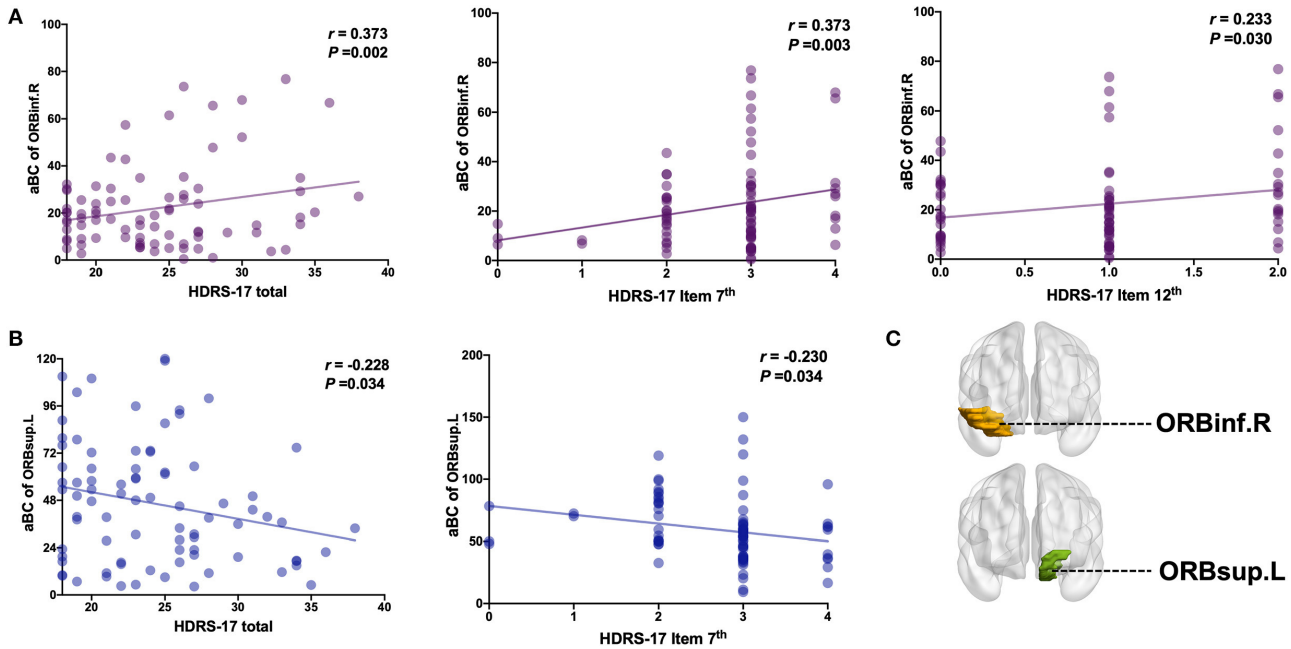


**FIGURE 3 |** Correlation analysis of HRSD-17 factor scores on aBC of ORBinf.R and ORBsup.L. **(A)** aBC of ORBinf.R is positively correlated with HRSD-17 total score or factor score. **(B)** aBC of ORBsup.L is negatively correlated with HRSD-17 total score or factor score. **(C)** Brain regions visualization. L, Left hemisphere; R, Right hemisphere; ORBinf (Purple, Orbital inferior frontal gyrus); ORBsup (Blue, Orbital superior frontal gyrus). HRSD Item 7th (0–4 score): Reduced Work and Activities; HRSD Item 12th (0–2 score): Gastrointestinal Somatic Symptoms.

positively correlated with the 7th item score of the HRSD-17 (work and interest). It is a measure of the severity of anhedonia, the main characteristic symptom in MDD patients with melancholic features (2). Additionally, decreased aBC in the left orbital superior frontal gyrus was negatively correlated with the 7th item score of the HRSD-17. These results suggest that abnormal aBC in the right orbital inferior and left orbital superior frontal gyri may be the neurobiological features associated with melancholic features.

Compared with healthy controls, patients with MDD have weaker small-world attributes, and the network information transmission order is interrupted, and the efficient information network is transformed into a random network which weakens of information transmission efficiency (26). Additionally, the melancholic MDD group had a lower local efficiency (aEloc) and longer node shortest path length (aLP) than HC. Although the difference between the two MDD subgroups is not obvious, this trend shows that the small-world network attribute of the melancholic subtype is developing more disorderly (24).

The orbitofrontal cortex believed that it is mostly related to the problems of cognition (44) and pleasure experience (information processing ability and response to external stimuli) (45). The caudate nucleus associated with rewarding process and pleasure experience (12). Our study found that compared with non-melancholic MDD and healthy controls, the increased aBC were found in right inferior orbital frontal gyrus and right caudate nucleus while the decreased aBC was found in left superior orbital superior frontal gyrus in melancholic MDD patients group. This can explain the more serious cognitive and pleasure experience problems experienced in melancholic MDD (low information processing ability and weaker response to external stimuli) (4). Therefore, we can speculate that the increase of aBC in the right inferior orbital frontal gyrus and the right caudate nucleus, and the decrease of aBC in the left superior orbital frontal gyrus may be the stable and unique neurobiological characteristics of melancholic MDD.

Compared with non-melancholic MDD patients, the abnormal network betweenness centrality in right inferior orbital frontal gyrus, the left orbital superior frontal gyrus and the right caudate nucleus was found in MDD patients with melancholic featured. Node betweenness centrality (aBC) refers to the number of times a node acts as the shortest bridge between the other two nodes. The abnormal aBC of two regions indicates that the information transmission balance is disturbed (46). The right inferior orbital frontal gyrus and the left superior orbital frontal gyrus belong to the orbitofrontal cortex (47). The caudate nucleus is part of the striatum (46). Previous study has shown the dysfunction and structure deficits of orbital frontal lobe were associated with the decision/reward deficits, lack of emotion/behavior control, and negative cognition in MDD patients (41), as well as the reward neural circuits are affected by the prefrontal–striatal pathway (48). The caudate nucleus (49), and orbital frontal lobe (48) are involved in the process of emotional and cognitive regulation. When MDD patients process positive emotional task information, the severity of anhedonia is related to the activation of the orbital frontal

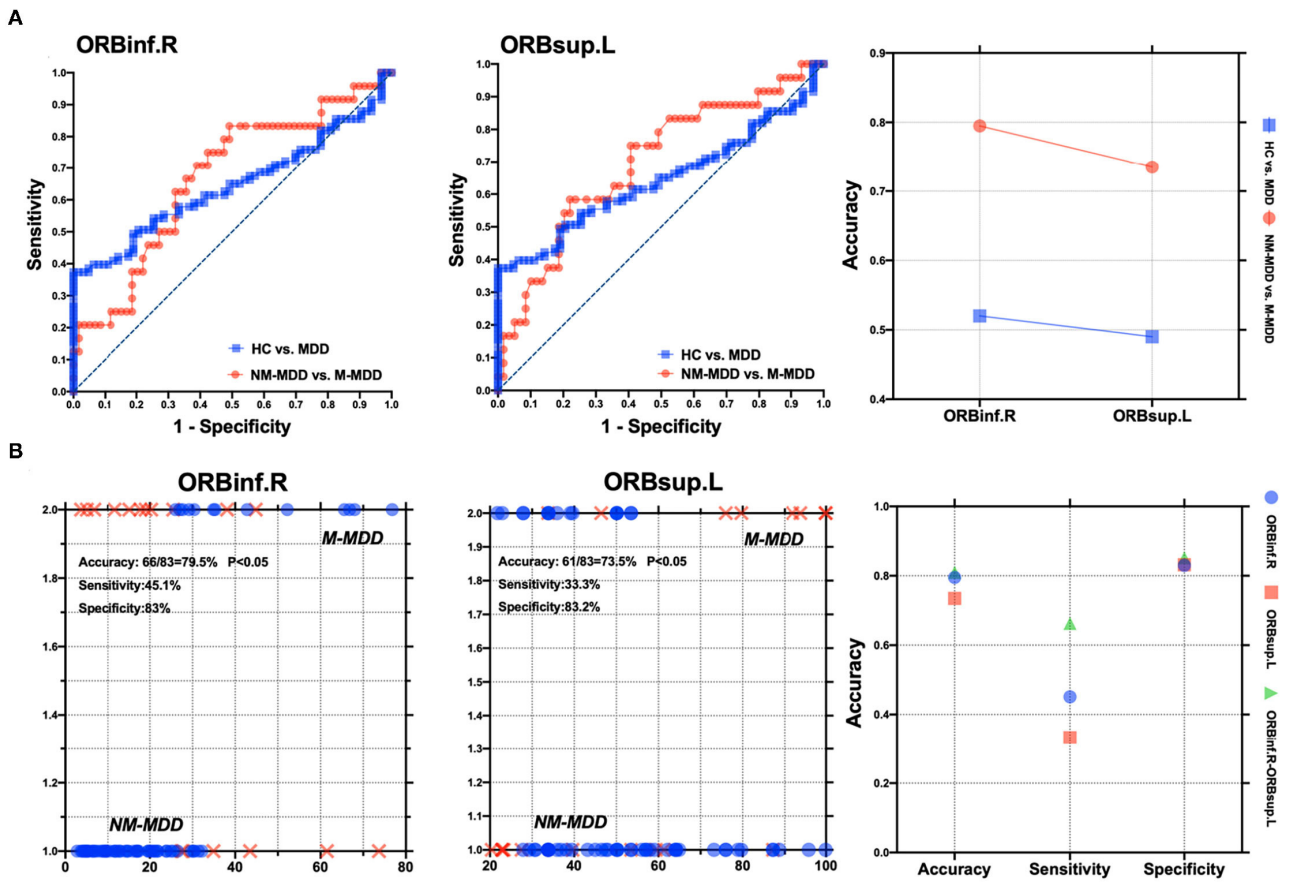


**FIGURE 4 |** Visualization of classification by using support vector machine (SVM) using the aBC values of ORBinf.R and ORBsup.L. **(A)** Visualization of parameters from healthy controls vs. MDD patients and NM-MDD vs. M-MDD. **(B)** Classification map of aBC values in ORBinf.R and ORBsup.L and SVM parameters as two features. L, Left hemisphere; R, Right hemisphere; ORBinf, Orbital inferior frontal gyrus; ORBsup, Orbital superior frontal gyrus.

lobe and is negatively related to the volume of the anterior caudate nucleus (31). A study of brain function in depression with loss of appetite reported enhanced activation of the right orbital frontal lobe in the reward loop (50). Therefore, the interruption of these brain regions transmitting information may lead to severe anhedonia, negative cognition, and loss of appetite (weight loss) in melancholic depression (49). This may be the neuropathological basis for the obvious and poorer cognitive performance of melancholic MDD compared with HC or non-melancholic depression (51).

The right orbit inferior frontal gyrus aBC was positively correlated with the HRSD-17 total score, 7th item (work and interest), and 12th item score (gastrointestinal somatic symptoms). The left orbit superior frontal gyrus aBC was negatively correlated with the HRSD-17 total score and 7th item score. non-melancholic and melancholic MDD subtypes were grouped according to strict criteria (A and B) while meeting the requirements of two groups (32). The significant difference in the orbitofrontal gyrus between the two MDD groups may explain the more severe anhedonia experienced and loss of appetite in non-melancholic MDD. The main symptoms of melancholic MDD are anhedonia and reduced or absent internal and external reaction emotions (3), as well as more severe cognitive deficits than non-melancholic MDD (4), it also showed a significant loss of appetite (3), which may be due to a weakened response to external/internal stimuli. This may be the main reason for the obvious difference between the two MDD subtypes (6). Therefore, we speculate that abnormal aBC in the right orbital inferior frontal gyrus and left orbital superior frontal gyrus may be potential imaging markers for distinguishing melancholic MDD from non-melancholic MDD.

SVMs are widely used in biomedical research to diagnose severe mental illnesses (52), such as major depression, schizophrenia, and bipolar disorder (53–55). Generally, the accuracy, sensitivity, and specificity are not below 65%, indicating fair reliability. When these parameters are >70%, the SVM can be used as a reliable diagnostic index (56, 57). In this study, the SVM analysis showed that the melancholic and non-melancholic MDD groups could be distinguished based on aBC abnormalities of either the right orbital inferior frontal gyrus or the left orbital inferior frontal gyrus with accuracies >70% but low sensitivities. However, by combining the right

orbital inferior frontal gyrus and left orbital inferior frontal gyrus aBC values, the SVM could distinguish the MDD subtypes with high accuracy (81.0%), sensitivity (66.3%), and specificity (85.2%). Therefore, the combination of the right orbital inferior frontal gyrus and left orbital inferior frontal gyrus aBC values can be used as a reliable biomedical indicator to distinguish MDD patients with and without melancholic features.

Compared with non-melancholic MDD, melancholic MDD is characterized by worsened clinical symptoms, including universal anhedonia, mood, cognition, and loss of appetite (3). There are other subtypes of non-melancholic MDD patients, with other characteristics (such as anxiety, atypical sleep disorders, physical symptoms, etc.) rather than melancholic MDD patients (6). This may be the right inferior orbital frontal gyrus and the left superior orbital frontal gyrus can only be used as one of the reasons to distinguish between non-melancholic and melancholic depression. Therefore, there can be a misfit when distinguishing between health and depression. To improve diagnosis accuracy, future applications should focus not only on single voxel-based brain imaging technology (7, 8) but also on the relationships between brain regions and multi-modal brain network technology (58), combining functional and structural brain network data (40).

As shown in our series of studies, melancholic depression can be classified as a special subtype of depression (6). Future research could further explore the different subtypes of depression. Imaging analysis based on the WM structure of the brain network provides an objective basis for distinguishing between melancholic and non-melancholic depression and provides evidence that different subtypes of depression may have different neuropathological mechanisms.

## CONCLUSION

In the WM structure network of MDD patients, the information transmission efficiency is lower and more disordered. The differences in WM structure in the MDD patient group were mainly in the orbitofrontal gyrus and cingulate gyrus regions. Our results demonstrate that MDD patients with melancholic depression have a unique WM structure network pattern that differentiates them from patients with non-melancholic features. The WM structure network in melancholic depression is more biased toward random networks and less efficient. aBC defects in the right orbital inferior and left orbital superior frontal gyri may be stable and unique neurobiological features of melancholic depression, representing potential imaging markers for distinguishing melancholic and non-melancholic depression subtypes.

## LIMITATIONS AND FUTURE DIRECTIONS

An important limitation of this study is its cross-sectional design; longitudinal research is required to confirm our findings. Changes in the WM network structure are not as sensitive as changes in a single structure and function, and further large-scale research and evidence are needed. Although the number of patients with melancholic depression is small, our results also provide a certain reference value for distinguishing melancholic depression from non-melancholic depression. In the future, we can expand the sample size to verify the results of this study. Melancholic and non-melancholic dependence were distinguished using an objective scale evaluation. The questionnaire of the supervisor is not used for the distinction. In the future, it can be verified in the sample using questionnaires to verify the reliability of the results of this study. Additionally, MDD subtypes may be related to the prognosis; therefore, long-term follow-up studies are needed to evaluate differences in treatment outcomes between patients with different subtypes. Future research should explore and verify the multi-modal brain network using larger cohorts and datasets.

## 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 First Affiliated Hospital of Kunming Medical University [Ethics Review L No. 50 (2016)]. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

All authors provided have made strong, direct, effective contributions to this research, and agree to publish it.

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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.2022.816191/full#supplementary-material

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# Association Between Clinical Competencies and Mental Health Symptoms Among Frontline Medical Staff During the COVID-19 Outbreak: A Cross-Sectional Study

*Qing Chang*[1,2,3†], *Han Su*[1,3†], *Yang Xia*[1,3], *Shanyan Gao*[1,3], *Ming Zhang*[4], *Xiaoyu Ma*[1,3], *Yashu Liu*[1,3] *and Yuhong Zhao*[1,3*]

[1] *Department of Clinical Epidemiology, Shengjing Hospital of China Medical University, Shenyang, China,* [2] *Department of Graduate Medical Education, Shengjing Hospital of China Medical University, Shenyang, China,* [3] *Clinical Research Center, Shengjing Hospital of China Medical University, Shenyang, China,* [4] *Office of Medical Administration and Management, Health Commission of Liaoning Province, Shenyang, China*

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***Correspondence:**
*Yuhong Zhao*
*zhaoyuhong@sj-hospital.org*

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

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**Background:** In China, mental health of frontline medical staff might be influenced by clinicians' ability to handle the outbreak of coronavirus disease 2019 (COVID-19). Few studies to-date have addressed the association between clinicians' competencies and mental health in this context. This cross-sectional study was to examine the prevalence of mental health symptoms among frontline medical staff that fought against the COVID-19 outbreak, and explore the associations between their competencies, and separate and concurrent depressive and anxiety symptoms.

**Methods:** A total of 623 frontline medical staff was included in this study. Competencies, depressive symptoms, and anxiety symptoms were assessed using a self-reported short form of the Chinese clinical physicians' competency model, Patient Health Questionnaire-9, and Generalized Anxiety Disorder-7 questionnaire, respectively. Logistic regression models were used to evaluate the associations between one SD increase in competency scores and the prevalence of mental health problems.

**Results:** The prevalence of depressive, anxiety, and comorbid depressive and anxiety symptoms was 40.93, 31.78, and 26.00%, respectively. Among the medical staff with higher total competency scores, the prevalence of depressive [odds ratios (ORs) = 0.67, 95% confidence intervals (CIs): 0.55–0.81], anxiety (OR = 0.68, 95% CI: 0.56–0.83), and comorbid anxiety and depressive symptoms (OR = 0.69, 95% CI: 0.55–0.83) was lower than among their lower-scoring counterparts. Subgroup analyses stratified by core competency scores revealed similar associations as the main analyses.

**Conclusion:** The present findings highlight the association between high core competency scores and lower prevalence of depressive, anxiety, and comorbid anxiety and depressive symptoms.

**Keywords: COVID-19, competency, frontline staff, medical staff, mental health**

## INTRODUCTION

Coronavirus disease 2019 (COVID-19), was initially reported in Wuhan, the capital of Hubei Province in China, has rapidly spread globally (1–4). The World Health Organization Emergency Committee declared COVID-19 outbreak an international public health emergency in late January 2020 (5). Wuhan soon became an epicenter of COVID-19 in China. By March 1, 2020, there have been 79,968 confirmed COVID-19 cases, including 2,873 associated deaths in China (6). The entire health care system in Wuhan, even in Hubei Province was almost paralyzed by then due to this rapidly evolving epidemic. The government of China took active measures to call for support to fight against the rapid transmission of COVID-19. Thus, over 30,000 volunteered healthcare workers from all over China were sent to Hubei Province and provided medical support to combat the COVID-19 outbreak (7, 8).

Such large-scale public health threat associated with infectious disease poses several challenges to frontline healthcare workers, who are generally medical workers treating patients with major contagious diseases. For instance, frontline medical workers are under tremendous physical and psychological pressure, higher risk of being infected, considerable work intensity, in particular, and have to cope with unknown causes and pathogens of the diseases, especially in the early stage of the COVID-19 outbreak (9, 10). The present COVID-19 epidemic has features comparable to the 2003 outbreak of severe acute respiratory syndrome (SARS-CoV), which was caused by another coronavirus, resulting in 349 deaths out of 5,327 confirmed cases in China (11). Previous studies have reported that in the initial phase of the SARS outbreak, medical staff felt vulnerable, uncertain, and concerned for their lives, which manifested with physical and psychological symptoms (12–16). It is demonstrated that frontline medical workers fighting against COVID-19 are susceptible to mental illnesses, such as depression and anxiety (10). Another study found that during the COVID-19 outbreak, frontline healthcare workers were more likely to have psychosocial issues and risk factors for developing them (17). A study carried out in Wuhan indicated that poor mental health status and sleep quality were common among frontline medical workers during the COVID-19 outbreak (18). Another survey reported that the prevalence of depression, anxiety, insomnia, and distress symptoms was 50.7, 44.7, 36.1, and 73.4%, respectively, among frontline healthcare workers in China (19). Moreover, frontline medical workers who experienced symptoms of depression were at increased risk of making errors in patient care (20). Maintaining good mental health among medical staff is essential to prevent infectious disease from spreading and ensure long-term wellbeing of staff (21, 22). Therefore, the mental health of frontline medical staff should be placed more emphasis during the outbreak of COVID-19.

Competence is a concept that refers to the ability to perform a specific activity, integrating knowledge, skills, values, and attitudes, often used to distinguish average and outstanding performance of a role (23, 24). Competence is measurable and can be developed through training. In the early stages of the COVID-19 outbreak, frontline medical workers have experienced substantial challenges with their competencies (25). Evidence shows that the core competencies are essential for healthcare workers to combat major infectious diseases outbreak (26, 27). It is demonstrated that the core competencies of nursing personnel are identified as a important factor affecting nursing effectiveness (28). Another study indicates that core competencies of nurse, including their knowledge, skills and experiences to handle unknown infectious disease, have a substantial impact on the prevention and control of the COVID-19 outbreak in China (29). In addition, it is suggested that a training program is required to improve core competencies of healthcare providers in regard to infectious disease outbreaks (30). Therefore, it is hypothesized that the high prevalence of mental disorders among frontline healthcare workers might be influenced by their competencies to handle the outbreak of COVID-19 in China. However, to the best of our knowledge, the association between competencies and mental health symptoms among frontline medical workers during the COVID-19 outbreak still remains unknown.

Therefore, the present cross-sectional study intends to examine the prevalence of mental health problems among frontline medical staff responding to the COVID-19 outbreak, and explore the associations between core competency scores and prevalence of depressive, anxiety, and comorbid anxiety and depressive symptoms in this population.

## MATERIALS AND METHODS

### Participants

According to the COVID-19 pandemic isolation regulations, this cross-sectional study avoided the face to face interview and adopted online survey using an electronic questionnaire tool named "Questionnaire Star", which was a mini-programme based on WeChat (a social media app widely used in China). Participants were able to fill out the questionnaire after scanning a quick response (QR) code by their mobile phones. Questionnaires were distributed by the directors of the medical aiding teams in WeChat group. In order to guarantee quality control of answering questionnaire, a 5-min time-frame was set in Questionnaire Star. In the pilot study, the average time of finishing the questionnaire was 5 min. Those who completed the questionnaire within 5 min would not be able to submit. Those who did not answer the questionnaire in the opening hours, or exceed the time limit for questionnaire, or have incomplete answer for the questions would be ruled out. In addition, several simple repeated questions, including age, years of service, marriage status, were set automatically in questionnaire. If the answers of the repeated questions were inconsistent, the questionnaire would be considered invalid. The entry criteria were as follows: (1) individuals aged 18 years or older; (2) frontline healthcare workers who were volunteers from different hospitals in Liaoning Province and offered medical support to cope with COVID-19 in Hubei Province; (3) without serious mental illness, such as schizophrenia. The exclusion criteria were as follows: (1) Those who did not answer the questionnaire in the opening hours; (2) Exceeding the time limit for questionnaire; (3) incomplete answer for the questions. (4) Those who failed to

answer the repeated questions correct. From January 20, 2020 to February 20, 2020, which basically was the early stage of COVID-19 outbreak in China, a total of 669 frontline medical staff coping with the COVID-19 outbreak participated in the present study. Participants who failed to provide information on any of the variables were ruled out ($n = 46$). Overall, data from 623 participants were collected in the analyses. The study protocol was approved by the ethics committee of Shengjing Hospital of China Medical University, and all participants provided written informed consent to participate. The study protocol conformed to the principles of the 1975 Declaration of Helsinki.

## Assessment of Depressive Symptoms

Depressive symptoms were assessed using the Chinese version of the Patient Health Questionnaire-9 (PHQ-9), a nine-item questionnaire designed to screen for depression in primary care and other medical settings (31). Questionnaire items were scored from 0 (not at all) to 3 (nearly every day). The sum of these scores produced an overall score, ranging from 0 to 27; higher scores indicated greater depressive symptoms. The degree of depressive symptoms was classified into four categories according to the score: 0–4 points: no depression; 5–9 points: mild depression; 10–14 points: moderate depression and $\geq$ 15 points: severe depression (31). Those participants with an overall PHQ-9 score $\geq$ 5 were considered to suffer depressive symptoms (31).

## Assessment of Anxiety Symptoms

Anxiety symptoms were assessed using the Chinese version of the Generalized Anxiety Disorder-7 (GAD-7) questionnaire, which consists of 7 questions and reflects the frequency of symptoms during the preceding 2 weeks (32). Questionnaire items were scored from 0 (not at all) to 3 (nearly every day). The sum of these scores produced an overall score, ranging from 0 to 21, with higher scores indicating greater anxiety symptoms. The degree of anxiety was evaluated in accordance with the score: 0–4 points: no anxiety: 5–9 points: mild anxiety; 10–14 points: moderate anxiety and $\geq$ 15 points or above: severe anxiety (32). Those individuals with an overall GAD-7 score $\geq$ 5 were considered to suffer anxiety symptoms (32).

## Assessment of Clinicians' Competencies

Competencies among frontline medical staff were assessed using the short version of the Chinese clinical physicians' competency model, which was comprised of 12 items, classified into 8 components: clinical skills and patient care, mastery of medical knowledge, information and management, professionalism, interpersonal communication, health promotion and disease prevention, academic research, and teamwork (33, 34). In general, the items of abundant clinical experiences, skills of curing respiratory diseases, skills of treating infectious disease, skills of dealing with critical illnesses, nursing operating skills were classified into the dimension of clinical skills and patient care. The items of teamwork abilities, communication skills, good work ethic, knowledge and skills of public health, scientific research ability, accumulated medical knowledge, ability in organization and coordination and management, were categorized into the components of teamwork, interpersonal communication, professionalism, health promotion and disease prevention, academic research, mastery of medical knowledge, Information and management, respectively. Each component was weighed from 1 to 9, generating a global score from 8 to 72. Higher scores indicated greater competencies. The overall scale reliability (Cronbach's alpha) of the short version (12 items) of the Chinese Clinical physicians' competency model was 0.874 with dimensions ranged from 0.737 to 0.892. The test-retest reliability examined after 2 weeks was 0.905. The validity of the short version of the Chinese Clinical physicians' competency model was also examined. The Spearman correlation coefficient with the full version (103 items) was 0.833. Correlation coefficients at the item level between the two versions of scale ranged from 0.810 to 0.975.

## Assessment and Definitions of Confounding Factors

All confounding factors (age, gender, profession, department, marital status, relative infected by COVID-19, working location, household income, years of service, working time after the COVID-19 outbreak, and sleeping time after COVID-19) were collected using a questionnaire. For analyses, profession was classified as "physician", "nurse", or "public health practitioner"; department was classified as "intensive care unit", "general ward", or "other"; household income was classified as "$\geq$1,00,000 Yuan/year" or below; marital status was classified as "currently married" or "currently unmarried"; working location was classified as "Hubei province" or "other".

## Statistical Analysis

Participant characteristics were reported stratified by depressive or anxiety symptoms status. Continuous variables were presented as least-square means and 95% confidence intervals (CIs); categorical variables were presented as counts and percentages. Logistic regression models were used to estimate the associations between one standard deviation increase in clinicians' competency scores, and the prevalence of depressive and anxiety symptoms. Odds ratios (ORs) and 95% CIs were calculated. The crude model was used to calculate the crude OR (95% CI) without any adjustments. Model 1 was adjusted for age and sex. Model 2 was further adjusted for profession, department, marital status, relative infected by COVID-19, working location, household income, years of service, working time after COVID-19, and sleeping time after COVID-19. Moreover, in order to increase analytic rigor, we also conducted the Benjamini-Hochberg procedure to calculate adjusted *P*-values. All analyses were performed using the Statistical Analysis System 9.3 edition for Windows (SAS Institute Inc., Cary, NC, USA). All *P*-values were two-tailed, and *P*-values $<0.05$ were considered statistically significant.

# RESULTS

## Participant Characteristics

Among 623 participants, the prevalence of depressive, anxiety, and comorbid depressive and anxiety symptoms was 40.93, 31.78, and 26.00%, respectively. The mean age was 33.93 (95% CI: 33.74–34.49) years.

Participant characteristics are presented in **Tables 1**, **2**, divided by depressive and anxiety symptoms status, respectively. Participants with depressive or anxiety symptoms had lower clinicians' competency scores. Participants with depressive symptoms tended to be younger ($P = 0.01$), not married ($P = 0.03$), and have a shorter length of service ($P = 0.01$). Moreover, participants with anxiety symptoms were more likely to be men ($P = 0.02$), younger ($P < 0.01$), working at departments other than intensive care or general wards ($P < 0.001$), based in provinces other than Hubei ($P < 0.001$), with a shorter length of service ($P < 0.01$), and a higher likelihood of having a relative infected by COVID-19 ($P = 0.02$).

## Clinicians' Competencies and Depressive Symptoms

Associations between clinicians' competency scores and prevalence of depressive symptoms are presented in **Table 3**. Among participants with higher total competency scores, the prevalence of depressive symptoms was lower. The multivariate-adjusted OR (95% CI) for depressive symptoms per one standard deviation increase in total scores of competencies was 0.67 (0.55–0.81). Furthermore, subgroup analyses stratified by eight core competency categories revealed similar associations as the total score. After corrected for multiple comparisons, the results were not changed.

**TABLE 1 |** Participant characteristics, stratified by the presence of depressive symptoms[a].

| Characteristic | Depressive symptoms status | | *P*-value[b] | *P adj.* |
|---|---|---|---|---|
| | No | Yes | | |
| PHQ-9 scores (≥5, %) | 368 (59.07) | 255 (40.93) | | |
| PHQ-9 scores (mean value) | 1.53 (1.26, 1.81)[c] | 8.83 (8.50, 9.16) | | |
| Total competencies score | 61.75 (60.64, 62.87) | 57.48 (56.14, 58.82) | <0.001 | <0.01 |
| Information and management | 7.77 (7.60, 7.93) | 7.27 (7.08, 7.47) | <0.001 | <0.01 |
| Professionalism | 8.40 (8.25, 8.54) | 7.92 (7.47, 8.09) | <0.001 | <0.01 |
| Clinical skills and patient care | 7.21 (7.03, 7.40) | 6.59 (6.37, 6.81) | <0.001 | <0.01 |
| Interpersonal communication | 8.13 (7.97, 8.28) | 7.53 (7.35, 7.72) | <0.001 | <0.01 |
| Health promotion and disease prevention | 7.71 (7.54, 7.89) | 7.18 (6.97, 7.39) | <0.001 | <0.01 |
| Mastery of medical knowledge | 7.99 (7.83, 8.15) | 7.51 (7.32, 7.70) | <0.001 | <0.01 |
| Academic research | 6.23 (6.01, 6.46) | 5.73 (5.46, 6.01) | <0.01 | <0.05 |
| Teamwork | 8.31 (8.17, 8.46) | 7.75 (7.57, 7.93) | <0.001 | <0.01 |
| Sex (male, %) | 32.88 | 38.04 | 0.18 | 0.25 |
| Age (years) | 34.54 (33.81, 35.26) | 33.06 (32.19, 33.92) | 0.01 | <0.05 |
| Years of service | 11.18 (10.51, 11.86) | 9.80 (8.98, 10.61) | 0.01 | <0.05 |
| Married (yes, %) | 79.62 | 72.16 | 0.03 | 0.06 |
| Household income (≥100,000 Yuan/year, %) | 54.62 | 50.20 | 0.28 | 0.35 |
| Working time after COVID-19 (hours/day) | 8.45 (8.17, 8.72) | 8.13 (7.79, 8.46) | 0.15 | 0.23 |
| Sleeping time after COVID-19 (hours/day) | 6.82 (6.67, 6.98) | 6.67 (6.49, 6.86) | 0.22 | 0.29 |
| Profession | | | | |
| Physician | 28.80 | 27.06 | 0.63 | 0.69 |
| Nurse | 60.60 | 61.96 | 0.73 | 0.76 |
| Public health practitioner | 10.60 | 10.98 | 0.88 | 0.88 |
| Department | | | | |
| Intensive care unit | 38.86 | 36.86 | 0.61 | 0.7 |
| General ward | 34.24 | 30.59 | 0.34 | 0.41 |
| Other | 26.90 | 32.55 | 0.13 | 0.21 |
| Relative infected by COVID-19 | 5.71 | 9.80 | 0.05 | 0.09 |
| Working location (Hubei province, %) | 75.54 | 69.02 | 0.07 | 0.12 |

[a] *PHQ-9, Patient Health Questionnaire-9; COVID-19, Coronavirus disease 2019.*

[b] *Analysis of variance or chi-square test.*

[c] *Least square mean (95% confidence interval) (all reported values).*

**TABLE 2 |** Participant characteristics, stratified by the presence of anxiety symptoms[a].

| Characteristic | Anxiety symptoms status | | *P*-value[b] | *P adj.* |
|---|---|---|---|---|
| | No | Yes | | |
| GAD-7 scores (≥5, %) | 425 (68.22) | 198 (31.78) | | |
| GAD-7 scores (mean value) | 1.33 (1.13, 1.53)[c] | 8.04 (7.75, 8.33) | | |
| Total competencies score | 61.57 (60.54, 62.61) | 56.64 (55.13, 58.16) | <0.001 | <0.01 |
| Information and management | 7.78 (7.63, 7.93) | 7.11 (6.88, 7.33) | <0.001 | <0.01 |
| Professionalism | 8.43 (8.30, 8.56) | 7.71 (7.52, 7.90) | <0.001 | <0.01 |
| Clinical skills and patient care | 7.16 (6.99, 7.33) | 6.52 (6.27, 6.77) | <0.001 | <0.01 |
| Interpersonal communication | 8.09 (7.95, 8.24) | 7.43 (7.22, 7.64) | <0.001 | <0.01 |
| Health promotion and disease prevention | 7.69 (7.53, 7.85) | 7.09 (6.85, 7.32) | <0.001 | <0.01 |
| Mastery of medical knowledge | 8.00 (7.85, 8.14) | 7.35 (7.13, 7.56) | <0.001 | <0.01 |
| Academic research | 6.11 (5.90, 6.32) | 5.86 (5.55, 6.17) | 0.19 | 0.28 |
| Teamwork | 8.31 (8.17, 8.45) | 7.59 (7.39, 7.79) | <0.001 | <0.01 |
| Sex (male, %) | 32.00 | 41.41 | 0.02 | <0.05 |
| Age (years) | 34.48 (33.81, 35.15) | 32.75 (31.77, 33.73) | <0.01 | 0.02 |
| Years of service | 11.19 (10.56, 11.82) | 9.38 (8.46, 10.30) | <0.01 | 0.02 |
| Married (yes, %) | 77.88 | 73.74 | 0.26 | 0.35 |
| Household income (≥100,000 Yuan/year, %) | 54.59 | 48.99 | 0.19 | 0.28 |
| Working time after COVID-19 (hours/day) | 8.26 (8.00, 8.52) | 8.44 (8.06, 8.82) | 0.43 | 0.52 |
| Sleeping time after COVID-19 (hours/day) | 6.76 (6.62, 6.91) | 6.76 (6.55, 6.97) | 0.96 | 0.96 |
| Profession | | | | |
| Physician | 28.47 | 27.27 | 0.76 | 0.79 |
| Nurse | 61.65 | 60.10 | 0.71 | 0.77 |
| Public health practitioner | 9.88 | 12.63 | 0.30 | 0.38 |
| Department | | | | |
| Intensive care unit | 42.12 | 29.29 | <0.01 | 0.02 |
| General ward | 33.41 | 31.31 | 0.60 | 0.69 |
| Other | 24.47 | 39.39 | <0.001 | <0.01 |
| Relative infected by COVID-19 | 5.65 | 11.11 | 0.02 | <0.05 |
| Working location (Hubei province, %) | 77.18 | 63.64 | <0.001 | <0.01 |

[a] *GAD, Generalized Anxiety Disorder-7; COVID-19, Coronavirus disease 2019.*
[b] *Analysis of variance or chi-square test.*
[c] *Least square mean (95% confidence interval) (all reported values).*

## Clinicians' Competencies and Anxiety Symptoms

As shown in **Table 3**, total clinicians' competency scores were negatively associated with the prevalence of anxiety symptoms. After adjustments for confounding factors, the OR (95% CI) for anxiety symptoms per one standard deviation increase in the total competency score was 0.68 (0.56–0.83). Moreover, scores on seven core competency categories (all except academic research) were negatively associated with the prevalence of anxiety symptoms. After corrected for multiple comparisons, the results were not changed.

## Clinicians' Competencies and Comorbid Anxiety and Depressive Symptoms

We examined associations between clinicians' competency scores and comorbid anxiety and depressive symptoms (**Table 4**). Among participants with higher total competency scores, the prevalence of comorbid anxiety and depressive symptoms was lower than among their counterparts. The OR (95% CI) for comorbid anxiety and depressive symptoms per one standard deviation increase in total clinicians' competency score was 0.68 (0.55–0.83). Seven core competency categories (all except academic research) were negatively associated with the prevalence of comorbid anxiety and depressive symptoms. After corrected for multiple comparisons, the results were not changed.

# DISCUSSION

To the best of our knowledge, the present study is the first study to explore the associations between competencies and mental health symptoms among frontline healthcare workers fighting against the COVID-19 outbreak. Mental health problems, including depressive, anxiety, and comorbid depressive and anxiety symptoms are highly prevalent in frontline healthcare workers. Our findings suggest that higher competency scores are associated with lower prevalence of depressive, anxiety, and

**TABLE 3 |** Associations between competencies, anxiety, and depressive symptoms among frontline medical staff during the COVID-19 outbreak.

| | Crude model | *P* | *P* adj. | Adjusted model 1[a] | *P* | *P* adj. | Adjusted model 2[b] | *P* | *P* adj. |
|---|---|---|---|---|---|---|---|---|---|
| **Depressive symptoms** | | | | | | | | | |
| Total competencies score | 0.67 (0.57, 0.80)[c] | <0.0001 | 0.0003 | 0.70 (0.58, 0.83) | <0.0001 | 0.0005 | 0.67 (0.55, 0.81) | <0.0001 | 0.0004 |
| Information and management | 0.74 (0.63, 0.87) | 0.0003 | 0.0003 | 0.77 (0.65, 0.90) | 0.0017 | 0.0019 | 0.76 (0.63, 0.90) | 0.0021 | 0.0025 |
| Professionalism | 0.71 (0.59, 0.83) | <0.0001 | 0.0003 | 0.74 (0.62, 0.88) | 0.0007 | 0.0011 | 0.71 (0.58, 0.85) | 0.0004 | 0.0007 |
| Clinical skills and patient care | 0.71 (0.60, 0.83) | <0.0001 | 0.0003 | 0.73 (0.62, 0.86) | 0.0002 | 0.0005 | 0.69 (0.57, 0.83) | <0.0001 | 0.0004 |
| Interpersonal communication | 0.67 (0.56, 0.79) | <0.0001 | 0.0003 | 0.70 (0.58, 0.83) | <0.0001 | 0.0005 | 0.68 (0.56, 0.82) | <0.0001 | 0.0004 |
| Health promotion and disease prevention | 0.73 (0.62, 0.86) | 0.0001 | 0.0002 | 0.75 (0.63, 0.88) | 0.0006 | 0.0011 | 0.74 (0.62, 0.88) | 0.0008 | 0.0012 |
| Mastery of medical knowledge | 0.73 (0.62, 0.86) | 0.0002 | 0.0003 | 0.76 (0.64, 0.90) | 0.0012 | 0.0015 | 0.76 (0.63, 0.90) | 0.0021 | 0.0025 |
| Academic research | 0.80 (0.68, 0.94) | 0.0060 | 0.0060 | 0.81 (0.69, 0.96) | 0.0130 | 0.0130 | 0.82 (0.69, 0.97) | 0.0179 | 0.0179 |
| Teamwork | 0.67 (0.56, 0.80) | <0.0001 | 0.0003 | 0.70 (0.58, 0.83) | <0.0001 | 0.0005 | 0.67 (0.55, 0.81) | <0.0001 | 0.0004 |
| **Anxiety symptoms** | | | | | | | | | |
| Total competencies score | 0.65 (0.55, 0.77) | <0.0001 | 0.0002 | 0.68 (0.57, 0.81) | <0.0001 | 0.0003 | 0.68 (0.56, 0.83) | 0.0001 | 0.0003 |
| Information and management | 0.67 (0.57, 0.79) | <0.0001 | 0.0002 | 0.70 (0.59, 0.83) | <0.0001 | 0.0003 | 0.70 (0.58, 0.84) | 0.0001 | 0.0003 |
| Professionalism | 0.61 (0.51, 0.72) | <0.0001 | 0.0002 | 0.64 (0.53, 0.76) | <0.0001 | 0.0003 | 0.63 (0.52, 0.77) | <0.0001 | 0.0006 |
| Clinical skills and patient care | 0.71 (0.60, 0.84) | <0.0001 | 0.0002 | 0.74 (0.62, 0.87) | 0.0004 | 0.0005 | 0.74 (0.61, 0.89) | 0.0019 | 0.0023 |
| Interpersonal communication | 0.66 (0.55, 0.78) | <0.0001 | 0.0002 | 0.69 (0.58, 0.82) | <0.0001 | 0.0003 | 0.70 (0.58, 0.85) | 0.0003 | 0.0005 |
| Health promotion and disease prevention | 0.71 (0.60, 0.84) | <0.0001 | 0.0002 | 0.74 (0.62, 0.88) | 0.0005 | 0.0006 | 0.75 (0.62, 0.90) | 0.0019 | 0.0023 |
| Master of medical knowledge | 0.67 (0.57, 0.79) | <0.0001 | 0.0002 | 0.70 (0.59, 0.83) | <0.0001 | 0.0003 | 0.72 (0.59, 0.86) | 0.0004 | 0.0006 |
| Academic research | 0.90 (0.76, 1.06) | 0.1926 | 0.1926 | 0.92 (0.78, 1.09) | 0.3335 | 0.3335 | 0.92 (0.77, 1.10) | 0.3668 | 0.3668 |
| Teamwork | 0.62 (0.52, 0.74) | <0.0001 | 0.0002 | 0.66 (0.55, 0.78) | <0.0001 | 0.0003 | 0.66 (0.54, 0.80) | <0.0001 | 0.0006 |

[a] *Adjusted for age and gender.*

[b] *Adjusted for age, gender, profession, department, marriage status, relative infected by COVID-19, working location, household income, years of service, working time after COVID-19, and sleeping time the COVID-19outbreak.*

[c] *Odds ratio (95% confidence interval) per one standard deviation increase of scores of clinicians' competencies (all reported values).*

comorbid depressive and anxiety symptoms. Subgroup analyses stratified by different domains of competencies yielded results similar to the results of the main analyses.

It is well established that the outbreak of severe infectious diseases may exert adverse psychological impact on ordinary people and healthcare staff. A number of studies have confirmed that medical staff suffered mental illnesses during the outbreak of SARS in 2003 (14–16). The present findings suggest that frontline healthcare workers with depressive and anxiety symptoms tend to be younger and have a shorter length of service. The risk of depressive and anxiety symptoms appears to be influenced by frontline healthcare workers' age and length of service (35, 36). Possible factors that account for these findings are age- and service duration-related decrease in emotional responsiveness, and increase in emotional control and psychological resilience.

In the present study, the prevalence of depressive, anxiety, and comorbid depressive and anxiety symptoms among Chinese frontline medical workers fighting against the COVID-19 outbreak was 40.93, 31.78, and 26.00%, respectively, which was higher than reported peacetime estimates as well as estimates from the initial phase of the SARS epidemic (37–41). A previous study conducted in southern China has reported that 28.13% of physicians had depressive symptoms, 25.67% had anxiety symptoms, and 19.01% had comorbid depressive and anxiety symptoms (38). Another study has explored the impact of the SARS epidemic on healthcare workers in Taiwan, reporting the prevalence of depressive symptoms at 17.3% during the SARS epidemic (41). In a recent multi-center survey, high prevalence of depressive (50.7%) and anxiety (44.7%) symptoms of frontline medical workers has been reported during the COVID-19 outbreak in China (21). Mental health problems among medical staff might hinder their professional performance and affect the quality of response to COVID-19. Concurrently, deterioration in medical workers' wellbeing is likely to negatively affect on patients and professionals' overall health. Protecting mental health of medical staff is crucial for epidemic control and maintaining staff wellbeing.

In recent years, clinical core competencies, including clinical skills and patient care, mastery of medical knowledge, health promotion and disease prevention, information and management, professionalism, interpersonal communication, academic research, and teamwork have played a key role in defining medical staff's ability worldwide (42–45). High competency scores indicate good clinical performances.

**TABLE 4 |** Associations between competencies, and comorbid anxiety and depressive symptoms among frontline medical staff during the COVID-19 outbreak.

| | Crude model | *P* | $P_{adj.}$ | Adjusted model 1[a] | *P* | $P_{adj.}$ | Adjusted model 2[b] | *P* | $P_{adj.}$ |
|---|---|---|---|---|---|---|---|---|---|
| **Comorbid anxiety and depressive symptoms** | | | | | | | | | |
| Total competencies score | 0.64 (0.53, 0.76)[c] | <0.0001 | 0.0002 | 0.68 (0.56, 0.81) | <0.0001 | 0.0003 | 0.68 (0.55, 0.83) | 0.0001 | 0.0003 |
| Information and management | 0.69 (0.58, 0.82) | <0.0001 | 0.0002 | 0.73 (0.61, 0.88) | 0.0006 | 0.0009 | 0.73 (0.61, 0.89) | 0.0014 | 0.0021 |
| Professionalism | 0.58 (0.49, 0.69) | <0.0001 | 0.0002 | 0.62 (0.51, 0.74) | <0.0001 | 0.0003 | 0.62 (0.50, 0.75) | <0.0001 | 0.0006 |
| Clinical skills and patient care | 0.72 (0.60, 0.85) | 0.0002 | 0.0002 | 0.75 (0.63, 0.90) | 0.0015 | 0.0017 | 0.76 (0.62, 0.92) | 0.0061 | 0.0069 |
| Interpersonal communication | 0.64 (0.54, 0.76) | <0.0001 | 0.0002 | 0.68 (0.57, 0.81) | <0.0001 | 0.0003 | 0.70 (0.57, 0.84) | 0.0003 | 0.0007 |
| Health promotion and disease prevention | 0.70 (0.59, 0.84) | <0.0001 | 0.0002 | 0.74 (0.62, 0.88) | 0.0008 | 0.0010 | 0.75 (0.62, 0.91) | 0.0031 | 0.0040 |
| Master of medical knowledge | 0.66 (0.55, 0.78) | <0.0001 | 0.0002 | 0.69 (0.58, 0.83) | <0.0001 | 0.0003 | 0.71 (0.58, 0.86) | 0.0004 | 0.0007 |
| Academic research | 0.85 (0.71, 1.02) | 0.0736 | 0.0736 | 0.88 (0.73, 1.05) | 0.1584 | 0.1584 | 0.87 (0.72, 1.05) | 0.1455 | 0.1455 |
| Teamwork | 0.60 (0.50, 0.72) | <0.0001 | 0.0002 | 0.64 (0.53, 0.77) | <0.0001 | 0.0003 | 0.64 (0.52, 0.78) | <0.0001 | 0.0006 |

[a]*Adjusted for age and gender.*

[b]*Adjusted for age, gender, profession, department, marriage status, relative infected by COVID-19, working location, household income, years of service, working time after COVID-19, and sleeping time after the COVID-19 outbreak.*

[c]*Odds ratio (95% confidence interval) per one standard deviation increase of scores of clinicians' competencies (all reported values).*

Moreover, the present study found that lower competency scores have been associated with increased prevalence of anxiety, depressive, and comorbid anxiety and depressive symptoms. Competency scores were negatively associated with the prevalence of mental health problems among frontline medical staff. These findings suggest that improving core competencies among frontline medical workers coping with the epidemic might help contain the spread of COVID-19. To control the epidemic, health authorities would ensure that frontline workers are competent and equipped with up-to-date knowledge and information.

To the best of our knowledge, the present study is the first to use a competency-based survey to investigate the associations between core competency scores and the prevalence of mental health problems among frontline medical workers. The present findings highlight the importance of clinicians' competencies in maintaining mental health. Suitable training should be provided to frontline medical workers. Nevertheless, this study has several limitations, which should be considered when interpreting its findings. Firstly, the cross-sectional design of the present study limits discussions about causality and generalizability of the findings. For example, participants with worse mental health may assess their competencies more negatively. Secondly, the use of an online survey might have resulted in a biased participant sample. However, given the high transmission rate of the virus, which has restricted the opportunities to conduct face-to-face surveys, WeChat-based survey programme Questionnaire Star has been widely implemented in China (21). Thirdly, unmeasured confounding factors might have affected the observed findings. Fourthly, in the present study, considering the heavy work for the frontline medical staff in the early stage of COVID-19 outbreak, we used a short version of the Chinese Clinical physicians' competency model to evaluate the competencies. Even though the short version has been validated in medical staff (including doctor, nurse and other types of medical staff), comparing to the full version, it cannot reflect all the characteristics of frontline medical staff's competencies. Fifthly, due to the COVID-19 pandemic isolation regulations and the risk of virus transmission, a self-reported clinical competency scale was used in the present study. Even though the scale showed decent reliability and validity, due to the nature of self-reported questionary, recall bias and reporting bias exist and the associations between clinical competency and depression may be overestimated. Future cohort studies with objective assessments of clinical competencies are needed to classify the results.

In conclusion, mental health problems associated with core competencies are highly prevalent among frontline medical workers combating the COVID-19 outbreak. Protecting mental health of medical workers is of great importance for epidemic control. Our study has highlighted the importance of clinicians' core competencies in maintaining staff well-being during an epidemic. Providing additional training to frontline medical staff might help prevent the onset of mental health problems and make efforts to contain COVID-19. To address the COVID-19 epidemic, health authorities would ensure competent staff, equipped with up-to-date information are volunteered to combat in the frontline.

## 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 Committee of Shengjing Hospital of

China Medical University. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

QC and YZ designed the study and formulated the clinical question. YZ had full access to all data in the study and is responsible for data integrity and the accuracy of data analysis. All authors collected, managed, analyzed the data, prepared, reviewed, revised, and read and approved the final manuscript.

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# The Impact of Service Dogs on Military Veterans and (Ex) First Aid Responders With Post-traumatic Stress Disorder

*Emmy A. E. van Houtert[1]*, T. Bas Rodenburg[1], Eric Vermetten[2,3,4] and Nienke Endenburg[1]*

[1] *Animals in Science and Society, Faculty of Veterinary Medicine, Utrecht University, Utrecht, Netherlands,* [2] *Department of Psychiatry, Leiden University Medical Centre, Leiden, Netherlands,* [3] *Arq Psychotrauma Expert Group, Diemen, Netherlands,* [4] *Department of Militaire Geestelijke Gezondheidszorg (MGGZ), Ministry of Defence, Utrecht, Netherlands*

Due to its novelty and lack of empirical study it remains unclear if a service dog truly mitigates the burden of post-traumatic stress disorder (PTSD) symptoms. To cross sectionally investigate the effect of service dogs on veterans and first aid responders with PTSD, we studied subjective and physiological parameters in 65 individuals divided over four groups. These groups were: veterans and first aid responders with PTSD and a service dog ($n$ = 20), with PTSD and a companion dog ($n$ = 10), with PTSD without a dog ($n$ = 12) and a group without PTSD ($n$ = 23). We found that veterans and first aid responders with PTSD who had a service dog showed significantly less PTSD related symptoms, better sleep quality, and better wellbeing experience, than those with a companion dog. Those with a service dog additionally experienced fewer PTSD related symptoms than those without a service dog and tended to walk more than individuals without PTSD. No differences were found in cortisol levels between groups though and changes in both salivary cortisol and activity were not linked to improved welfare experience. Though the use of physiological measurement methods thus warrants more research, our study indicates that the subjective experience of wellbeing, sleep quality and PTSD related symptoms is improved by the presence of a service dog.

**Keywords: service dog, PTSD, veteran, dog, post-traumatic stress disorder**

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*University of Vienna, Austria*
*Daniel Berckmans,*
*KU Leuven, Belgium*

****Correspondence:***
*Emmy A. E. van Houtert*
*e.a.e.vanhoutert@uu.nl*

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## INTRODUCTION

PTSD in veterans typically is a chronic disorder, that manifests in a general negative mood, periods of depression, periods of anxiety, flashes of anger, reckless behavior, sleeplessness, and general increased arousal causing impairment or distress (1). A novel way in which the symptoms of PTSD can be lessened is through the provision of a PTSD service dog. Service dogs are specialized assistance animals, which have learned to respond to various verbal and non-verbal communication ques of their handler. As a response they will act as both a social support and behavioral mirror, and help their handler in coping with the consequences of their PTSD. Service dogs are further known to work as a social facilitator *via* their learned behaviors (2) and their presence as a companion animal

(3–5). This function is related to the principles of Behavioral Activation (BA), which has been shown to be an effective treatment for depression (6, 7). Because there is also empirical support for BA as a treatment for PTSD (7), the principles of BA may provide evidence for PTSD service dog effect. The most compelling evidence of the effectiveness of service dogs to date however, seems to be in the form of self-report by those who are supported by a service dog (8–11). In these reports handlers state that their service dog helps them reclaim control of their life and obtain a sense of worth by promoting responsibility and self-efficacy through the care the service dog needs (12). Service dogs are further stated to help handlers reconnect with society, improve individual quality of life, and therefore help their handlers reach opportunities in life they previously deemed unreachable (2).

All these effects seem to speak in high favor of the provision of service dogs to individuals with PTSD. In our literature study from 2018 we however concluded that the presented evidence of service dog effectiveness at that time was insufficient to definitively attribute any improved wellbeing in individuals with PTSD to service dog presence (13). This attribution was difficult because, as stated above, the influence of service dogs is mostly measured *via* self-report measurements. Although very valuable in the determination of individual wellbeing, these measurements do not indicate physiological changes that might be influenced by both PTSD and presence of a PTSD service dog. We further determined that many studies on service dogs were conducted among small sample sizes, did not have control groups, and had vastly varying measurement methodologies, which made them difficult to compare to one another (13). All this led to the conclusion that further study regarding the effect of service dogs on individuals with PTSD needed to address the above uncertainties by not only introducing standardization in methodology, but also by introducing the use of quantifiable measurements to complement and frame the subjective experience of service dogs by individuals with PTSD.

One study which has since addressed some of the uncertainties in service dog research is that of Rodriguez et al. (14). In their study they compared the morning awakening cortisol response in 45 veterans with a service dog with that of 28 individuals on a waiting list to receive one. By doing so, they found that individuals with a service dog had a higher morning awakening cortisol level than those on the waiting list. Morning awakening cortisol is a measure related to the human circadian cortisol rhythm. In this rhythm a basal release of the hormone is regulated throughout the day by the suprachiasmatic nucleus in the hypothalamus (15, 16). In individuals with PTSD this basal release of cortisol is known to deviate from that of non-PTSD individuals. Though differences in the overall circadian average are disputable between groups (17), evening peak and early morning levels of cortisol were found to be lower in individuals with PTSD (18–20). The results of Rodriguez et al. (14) therefore suggest that the difference in presence or absence of a service dog between their two subject groups influenced the manner in which PTSD affected the subjects' cortisol response, and brought the service dog group closer to what could be expected of non-PTSD afflicted individuals. If this conclusion is correct, they have provided one of the first measurements that can be used to quantify the influence of service dog presence on an individual with PTSD and have therefore created interest in the use of other PTSD symptom related measurement techniques in service dog research.

One of these other measurement techniques is through the observation of changes in behavioral patterns and overall functioning of individuals with PTSD (21). Although PTSD can express differently between individuals, it generally alters observable behavior and functioning in an individual compared to non-PTSD individuals. Especially overall activity and activity intensity are known to decrease in those with PTSD since they are less inclined to leave their house or safe environment. The degree in which an individual undertakes activities and is active in his or her daily life is could therefore be seen as an indicator of how he or she is affected by PTSD. Combined with a record of service dog presence, an individual's activity level or changes therein can thus be used to evaluate the effect of the service dog on PTSD related symptoms (21).

All in all, there are various measurements with which the effect of PTSD on human physiology and psychology can be quantified. The objective of this study was therefore to identify the influence of a service dog on activity levels and morning salivary cortisol levels of individuals with PTSD. More specifically we asked several questions regarding these measurements. The first question was whether the presence or absence of a service dog is measurable in the 24 h activity pattern of individuals with PTSD? We hypothesized that individuals with PTSD and a service dog would be more active than those with PTSD without a dog, though not necessarily more than those with PTSD and a pet dog. Our second question concerned cortisol levels and whether or not the presence or absence of a service dog is measurable in the morning and evening cortisol of individuals with PTSD. Our hypothesis for this question was that individuals with PTSD and a service dog would approach cortisol levels expressed by individuals without PTSD, while levels in those with PTSD without a service dog would deviate. Our third question finally was whether or not the morning waking cortisol and 24 h activity pattern of those with PTSD were positively correlated to wellbeing experience as reported. Our hypothesis for this question was that individuals with PTSD who evaluate their own wellbeing the highest also are the most active and have cortisol levels that approach those of individuals without PTSD, If these questions could be answered, they could provide insight in the effects that provision of a service dog might have on individuals with PTSD.

# MATERIALS AND METHODS

## Subjects

Four groups were identified for this study (Total $n$ = 65). The first group ($n$ = 20) consisted of military veterans or (ex) first aid responders (ambulance workers, firefighters, police officers) who were currently matched with a service dog from the service dog provider Stichting Hulphond Nederland. We chose to only work with individuals who had received a service dogs from a

single provider as to eliminate the influence of different training, education, selection, and support strategies on the performance of service dogs as an extra variable in this study. It was further chosen to only work with veterans or (ex) first aid responders with PTSD, as the origin, development, and support offered for PTSD is relatively similar between individuals in this group.

The second group ($n$ = 12) consisted of military veterans or (ex) first aid responders with PTSD who were currently waiting to be matched with a service dog from the abovementioned service dog provider. Individuals in the second group were additionally not in the possession of a companion dog, as those who already had a companion dog (besides waiting for a trained service dog) were considered a separate third group ($n$ = 10). This division between groups two and three was made to see if the presence of a companion dog had a positive influence on veterans/(ex) first aid responders with PTSD, and if so, to see if this influence was different from the influence of a service dog. The fourth and final group of participants ($n$ = 23) consisted of military veterans without PTSD. Details of each group can be found in **Table 1**.

Contact with potential participants to the study was sought *via* various channels. All individuals of group one were contacted *via* the above mentioned service dog provider. This was also done for a number of individuals belonging to groups two and three who were on a waiting list to receive a service dog from that same service dog provider. The remaining participants in groups two, three, and four were finally found *via* a mixture of personal connections, and communication channels targeted at veterans.

## Experimental Design

All participants were instructed to perform several measurements at home. These measurements were: collecting 10 salivary samples at set timepoints over the course of 2 days, wearing an accelerometer for a period of 36 h, and filling out a maximum of five questionnaires. Individuals who had a service dog finally also collected 10 salivary swabs from their dog, made sure it wore an activity measuring collar and filled out an additional questionnaire. These dog based measurements were used for a study on service dog welfare. The results and full design of this study will be published separately.

To ensure the instructions for home measurements were clear, a researcher visited each participant in their home and explained every measurement before handing over the necessary equipment to perform them. This same researcher collected the used equipment after a period of at least a week, and answered any questions the participants might ask before, during, and after their participation to the study.

**TABLE 1 |** Details on the participants of the four subject groups in this study.

| Group | Male | Female | Age | Veteran* | First aid responder* | PTSD | Service dog |
|---|---|---|---|---|---|---|---|
| | % | % | Years | % | % | % | % |
| 1 | 90 | 10 | 52 | 84 | 47 | 100 | 100 |
| 2 | 75 | 25 | 20 | 80 | 58 | 100 | 0 |
| 3 | 100 | 0 | 47 | 67 | 60 | 100 | 0 |
| 4 | 91 | 9 | 51 | 100 | 26 | 0 | 0 |

*The first group consisted of veterans/(ex) first-aid responders with PTSD and a service dog (n = 20), the second group consisted of veterans/(ex) first-aid responders with PTSD but without any dog (companion or service dog) (n = 12), the third group consisted of veterans/(ex) first-aid responders with PTSD and a companion dog (n = 10), and the fourth group consisted of veterans without PTSD (n = 23).*

**The percentages of veterans and first aid responders do not add up because some participants were part of both groups (e.g., veterans who joined the police force after their deployment).*

## Questionnaires

The five questionnaires used during this study were filled out by all subjects in all groups as long as the questionnaire was applicable to their situation. This means that questionnaires regarding dogs were not filled out by subjects without a dog. The five questionnaires were:

- An intake questionnaire used to register general information on each subject like age, sex, whether they were a veteran or (ex) first aid responder, whether or not they were diagnosed with PTSD, and if so whether they were assisted by a service dog or not.
- The PTSD Check List—version DSM 5 (PCL-5). The PCL-5 is a 20 item questionnaire concerning the prevalence or severity of trauma associated symptoms in individuals. Each answer can be given on a 5-point scale which indicates increasing prevalence or severity. If points for all answers are combined a score between zero and 80 points should be achieved (22), with a cut-off point at 31–33 points for PTSD diagnosis (23). Analysis of this questionnaire was performed *via* its included instructions which resulted in four component scores and a final score for each questionnaire.
- The Pittsburg Sleep Quality Index (PSQI) questionnaire. The PSQI is a 21 item self-report questionnaire which questions the frequency of disruptive nocturnal behaviors (DNB). It is made up of seven components; subjective sleep quality, sleep latency, habitual sleep efficiency, sleep duration, sleep disturbance, use of sleep medication and daytime functioning (24, 25). Analysis of this questionnaire was performed *via* its included instructions which resulted in a final score.
- The 36-Item Short Form Survey Instrument (SF36) questionnaire. The SF36 is a 36-item self-reflective wellbeing measurement tool with multiple choice answer format. Shiner et al. (26) found the SF36 to reproduce reliable results when filled out by a subject group of military veterans with PTSD. It was later also applied by Stern and Chur-Hansen (8) to evaluate experienced quality of life by military veterans in relation to service dog intervention. Analysis of this questionnaire was performed by first mirroring negative question scores before adding all answer scores into a final score.
- A Dutch translation of the Monasch Dog Owner Relationship Score (MDORS) (27, 28). The Dutch translation of the MDORS has 16 items divided over 2 factors; perceived emotional closeness and perceived costs

of dog ownership. Answers can be given on a five-point multiple choice format which produces a score between 16 and 80 points. Analysis of this questionnaire was performed by first mirroring the score of negative questions before adding all answer scores into a final score. The MDORS questionnaire was only filled out by the participants that either had a service dog or a pet dog.

## Salivary Cortisol

To study deviations in normal morning and evening peripheral cortisol level between subject groups, salivary cortisol level was measured on 10 occasions divided over 2 days. On the first day, the first sample was taken in the morning directly after waking up. The next sample was taken 15 min later, the third 30 min after waking up, and the fourth 60 min after waking up. The fifth and final sample was taken right before going to sleep, after which the whole procedure was repeated the next morning and evening.

Sample collection by participants occurred in their individual home environment through passive drooling into a new collection tube at each time point. Participants were instructed not to eat, smoke, or consume any other fluid than clear water 30 min before each measurement, as this might influence sample quality (19). After collection, a sample was marked with its order-number and stored at −20°C until retrieval by the researcher. Retrieved samples were then transported to the general storage facility at Utrecht University, where they were again stored at −20°C.

Extraction of cortisol from samples was performed by spinning the samples at 3,000 rpm for 5 min. This resulted in a clear supernatant of low viscosity. Visual inspection was performed at this stage for any signs of contamination (discoloration). No samples were rejected because of this. Cortisol concentrations were finally measured using a commercially available chemiluminescence immunoassay with high sensitivity (IBL International, Hamburg, Germany). The average intra-assay coefficient was 5%.

The 10 samples over 2 days were finally reduced to five datapoints. This was done by averaging the sample of day 1 and day 2 for each time point. This resulted in a total of five datapoints per participant, one for each timepoint. If a participant missed a measurement on either 1 of the 2 days the final datapoint was based on a single measurement instead.

## Activity Measurements

Overall activity in all human subjects was monitored *via* the Empatica E4. Participants wore the E4 for a continuous period of at least 36 h. During those 36 h the device had to be worn at all time, both while awake and while sleeping, unless there was a high chance of damage to the devices (showering, swimming, working heavy tools). All registered data were stored on the device's internal storage capacity until extraction *via* Empatica's specialized E4 software. Data analysis was performed *via* the EDA explorer scripts of Taylor et al. (29). This entailed that each dataset was run through a step detection script which returned the estimated total number of steps, mean step time during movement and percentage of time spent inactive during the first 24 h.

## Statistical Analysis

Statistical analysis was performed in R version 4.0.3 with R studios (30). A total of 12 numeric variables were analyzed for differences between four participant groups. The variables were: salivary cortisol levels at five different timepoints, the number of steps taken in a 24 h time period, the mean time spent walking in a 24 h time period, the percentage of time an individual was inactive in a 24 h time period, an individual's PCL5 questionnaire score, an individual's PSQI questionnaire score, an individual's SF36 questionnaire score, and an individual's MDORS questionnaire score. For all these variables normality was judged by plotting a histogram and observing if the resulting figure neared normal distribution. From these histograms it became apparent that normality could not be assumed for any of the variables. A choice was therefore made for statistical analysis *via* non-parametric methods. This analysis was started with a Levene's test of homogeneity of variances for each variable. None of these tests were significant which meant that equal variances could be assumed. To check if pairs of two participant groups differed from one another, a series of Mann-Whitney tests was performed per variable ($\alpha = 0.05$). This resulted in six Mann-Whitney tests per variable according to the following schedule: group 1–2, 1–3, 1–4, 2–3, 2–4, 3–4. Significant results of these tests are represented in the results section *via* a *p*-value and an effect size r. r is based on the z scores of the Mann-Whitney tests (formula $r = z/\sqrt{N}$). Effect sizes around 0.8 are considered large, around 0.5 medium, and around 0.2 small (31).

A series of Spearman correlations ($\alpha = 0.05$) was finally used to evaluate possible correlations between the questionnaire scores (PCL5, PSQI, SF36, MDORS) and the other variables.

## Ethics Statement

Ethical review and approval for this study was obtained from the medical ethical committee of the Utrecht Medical Centre, Utrecht, The Netherlands under number NL64117.041.18. Each participant further gave informed consent before participation to the study.

# RESULTS

## Dataset Description

All but a few datasets were fully complete. This resulted in a reduced n for several measurements compared to the total participant number. Regarding salivary cortisol, a total of 60 out of 65 participants had at least one sample at all five timepoints. A further three had a sample for at least four timepoints, one had a sample for three timepoints, and one missed samples for all timepoints. The main reason for these missing samples was insufficient saliva volume.

Activity measurements were successful for 47 out of 65 participants. The most common reason for activity measurement to fail was due to (premature) battery failure of the measurement equipment.

The full set of questionnaires was finally retrieved for 55 out of 65 participants. The intake questionnaire missed one or more items for three participants, the PCL5 questionnaire missed

one or more items for one participant, the PSQI missed one or more items for nine participants, and the SF36 questionnaire missed one or more items for two participants. Regarding the PSQI, missing values were often caused by one missing answer out of the total 21 items on the questionnaire. This missing item prevented a total score from being calculated, resulting in a missing value. To reduce the number of missing values for this questionnaire we decided to substitute the missing item, in questionnaires with only a single missing item, with the average of the treatment group that particular participant was assigned to. This substitution made it possible to calculate a PSQI score for an additional seven participants leaving only two fully missing datapoints.

## Salivary Cortisol Differences Between Groups

The salivary cortisol levels at all five timepoints were compared between participant groups using a series of Mann-Whitney tests between group pairs. No significant differences were found (**Figure 1**).

## Activity Differences Between Groups

The number of steps taken, mean time walking and percentage of stillness were compared between participant groups using a series of Mann-Whitney tests between group pairs. These tests showed that the total number of steps taken tended to be higher for participants with PTSD and a service dog (**Figure 2**) than for individuals without PTSD or service dog ($p = 0.05$). No other differences between groups were found.

## Questionnaire Differences Between Groups

The questionnaire scores of the PCL5, PSQI, and SF36 were compared between participant groups using a series of Mann-Whitney tests between group pairs. Regarding the PCL5 questionnaire, it was found that participants without PTSD or service dog had significantly lower PCL 5 scores (**Figure 3A**) than participants with PTSD and a service dog ($p < 0.01$, $r = 0.85$), participants with PTSD and a companion dog ($p < 0.01$, $r = 0.76$), and participants with PTSD without a dog ($p < 0.01$, $r = 0.84$). It was additionally found that individuals with PTSD who were supported by a service dog had significantly lower PCL5 scores than those with a companion dog ($p < 0.01$, $r = -0.51$) or with PTSD without a dog ($p = 0.01$).

Regarding the PSQI it was found that participants without PTSD had significantly lower PSQI scores (**Figure 3B**) than participants with PTSD and a service dog ($p < 0.01$, $r = 0.78$), with PTSD and a companion dog ($p < 0.01$, $r = 0.76$), and PTSD without a dog ($p < 0.01$, $r = 0.81$).

Regarding the SF36 it was found that participants without PTSD had significantly lower SF36 scores (**Figure 3C**) than participants with PTSD and a service dog ($p < 0.01$, $r = 0.70$), participants with PTSD and a companion dog ($p < 0.01$, $r = 0.66$), and without a dog ($p < 0.01$, $r = 0.77$). It was additionally found that individuals with PTSD who were supported by a service dog had significantly lower SF36 scores than those with a companion dog ($p = 0.04$).

Regarding the MDORS it was finally found that participants without PTSD had significantly lower MDORS scores (**Figure 3D**) than participants with PTSD and a service dog ($p < 0.01$, $r = 0.59$), and participants with PTSD and a companion dog ($p = 0.03$).

## Relations Between Questionnaire Scores and Other Variables

To see if there was a relation between the PCL5, PSQI or SF36 or MDORS questionnaire scores of participants and either their activity or salivary cortisol measurements, a series of spearman correlations were calculated. These showed that the correlation between cortisol level taken right before an individual went to bed and their PSQI score showed a trend ($p = 0.07$, rho $= -0.24$). All other correlations were non-significant.

# DISCUSSION

## Subjective Measurements of Service Dog Influence

In our study we found that individuals with PTSD and a service dog had the lowest level of PTSD related symptoms among observed individuals with PTSD. This is in line with earlier studies by Stern and Chur-Hansen (8), Kloep et al. (9), Vincent et al. (10), and Yarborough et al. (11), who all found that individuals with PTSD and a service dog judged their own wellbeing to be better than that of those with PTSD without a service dog. Our study thus demonstrates that individuals with PTSD can experience a service dog as a positive influence on their wellbeing. Because individuals with a pet dog showed more PTSD related symptoms than individuals with a trained service dog, our study furthermore hints that this effect might not an inherent effect of dog presence but a result of service dog training and/or guidance by the organization that provided the service dog. Further study on this topic is still very much needed though to evaluate if this conclusion is true for all service dogs or only those trained by a select number of organizations who follow similar protocols. Additionally it is also possible that those with a service dog suffer from positive bias toward the animal and therefore answered more favorably to questionnaires than those without a service dog. We therefore performed additional measurements to see if the above effects extend beyond the experience of wellbeing and PTSD symptom severity.

## Biological Parameters

The additional measurements performed in this study were measurements of morning salivary cortisol levels and activity levels between groups. Neither of these measurements showed differences between participant groups though, which is interesting when compared to earlier research. Two earlier studies by Rodriguez et al. (14) and Lessard et al. (21) have also studied similar measurements in similar participant groups. Rodriguez et al. (14) studied the influence of service dogs on

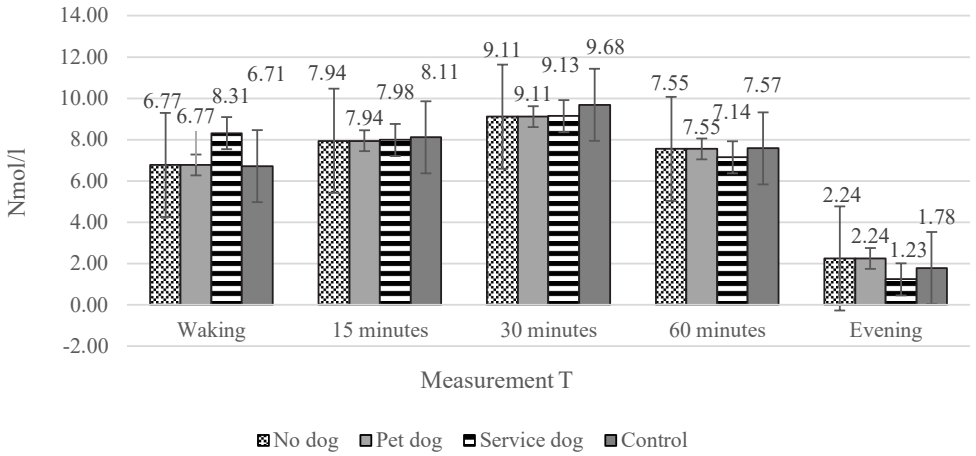


**FIGURE 1 |** The salivary cortisol levels for the four different subject groups during five different measurement points. The four groups are: individuals with PTSD and a service dog, individuals with PTSD and a companion dog, individuals with PTSD without a dog, Individuals without PTSD. The five measurement moments are: Just after waking up (*n* = 19, 10, 11, 21), 15 min after waking up (*n* = 20, 10, 12, 22), 30 min after waking up (*n* = 20, 10, 12, 22), 60 min after waking up (*n* = 17, 10, 12, 22), just before going to bed in the evening (*n* = 19,10,12,22).

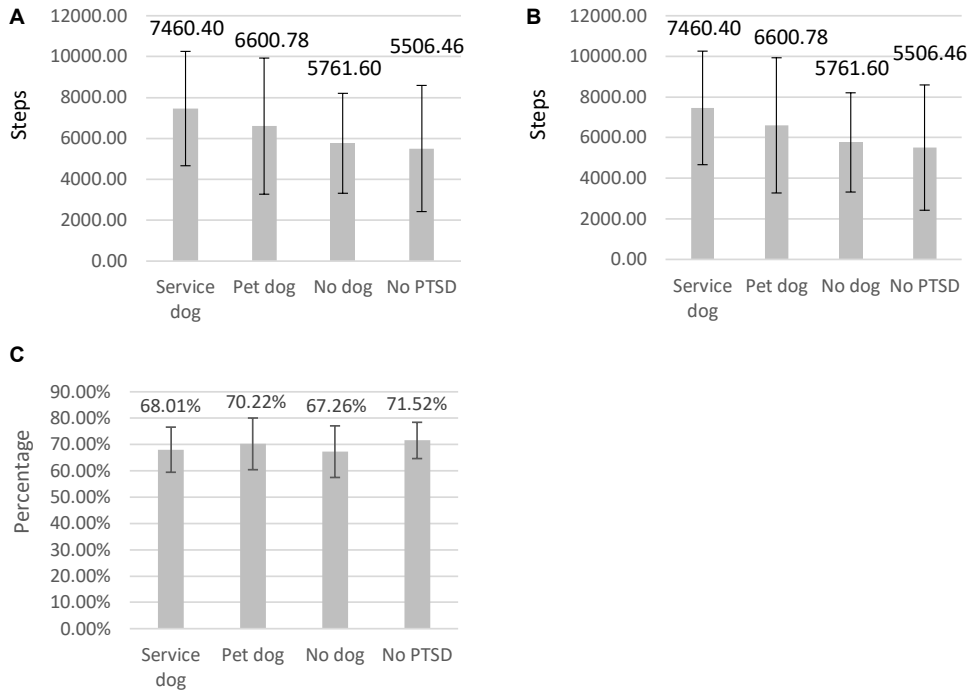


**FIGURE 2 |** The number of steps taken during 24 h **(A)**, mean step time **(B)**, and percentage stillness **(C)** per participant group. The four groups are: individuals with PTSD and a service dog (*n* = 15), individuals with PTSD and a companion dog (*n* = 9), individuals with PTSD without a dog (*n* = 10), Individuals without PTSD (*n* = 13).

morning salivary levels while Lessard et al. (21) studied the effect of service dogs on activity levels in those with PTSD. Both studies found an effect of service dogs on these respective measurements which is in contrast to our results. This could be due to the manner in which these parameters were evaluated though. Lessard et al. (21) for example studied activity within individuals while we studied activity between individuals. It is therefore possible that the effect of service dogs on activity levels is small or differs between individuals which makes it easier to measure within than between individuals.

Another possibility for the differences in found results could have been a difference in study populations. In some populations PTSD is known to lower morning cortisol levels (17–20). This was true for the population observed in the study by Rodriguez

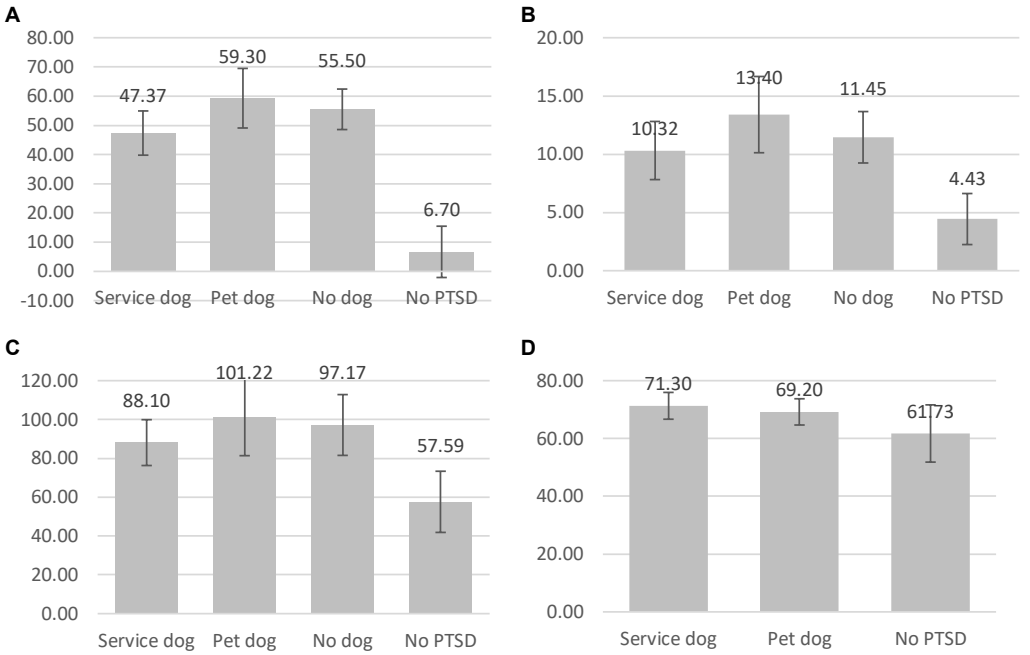


**FIGURE 3 |** The average scores for the PCL5 **(A)**, PSQI **(B)**, SF36 **(C)**, and MDORS **(D)** questionnaires per participant group. The four groups are: individuals with PTSD and a service dog (*n* = 19, 13, 20, 20), individuals with PTSD and a companion dog (*n* = 10, 9, 9, 10), individuals with PTSD without a dog (*n* = 11, 12, 12), Individuals without PTSD (*n* = 23,22,22,11).

et al. (14), which made it possible for them to observe an elevating effect of service dog presence on salivary cortisol levels. No lowering of salivary cortisol levels in those with PTSD was observed in our study though, which made it impossible to measure an effect of service dogs on this parameter.

An explanation for why a non-lowered group was observed might be due to a limitation of our study. Out of all approached individuals with PTSD without a service dog, about half of them agreed to participate. The other half stated that they did not feel well enough to participate, and that they wanted to focus on their own recovery instead. Because of these statements it is possible that only individuals with PTSD in relative good welfare participated.

## Correlation Between Subjective and Physiological Parameters

In addition to the above salivary cortisol and activity level as measured in this study also failed to show a correlation with subjective measurements of welfare. Of course it is possible that this was due to the absence of difference within the physiological parameters, though it is also possible that the effects of PTSD on wellbeing and bodily function are truly separate (14). The PTSD service dog itself might for example influence different consequences of PTSD *via* different routes. The activity level of an individual with PTSD for example, might not solely be influenced by the severity of PTSD symptoms and the service dog's reduction thereof. Measurements of activity level might instead be independently influenced by a dog's intrinsic need for exercise. This possibility is supported by data found in this study which showed that both those with a service dog and a companion dog walked more than those who did not have a dog. Though this difference was not significant, the absence of a correlation with measurements of wellbeing in this study suggests that dog presence does increase activity in its own right independent of changes in wellbeing.

To accurately measure a correlation between the subjective experience of wellbeing and physiological changes however, repeated measurements over longer periods of time are needed. This was not done within this study, which might also explain a lack of found differences in this variable. It is therefore advisable that future research focusses on repeated measurements over longer periods of time to more accurately establish which effects can be expected of service dogs and whether or not these effects are limited to the experience of wellbeing or can also be measured in physiological parameters.

# CONCLUSION

In conclusion, our results showed that the presence of a service dog improved the reported quality of life, and lowered the level of reported PTSD symptoms in those with PTSD. No effects of service dog presence were found on activity level and salivary cortisol levels though. These variables were furthermore not linked to measurements of wellbeing. The possibility of bias and placebo that could explain significant differences between the experienced wellbeing of those with and without a service dog effect is therefore difficult to counter *via* our results. Most likely this is due to the used measurement methods which

might be more suited for the detection of changes within an individual than they are between individuals. Future research might therefore consider alternative methodology in the study of PTSD service dog effect. Additionally future studies should question though if bias and placebo are truly present in the registration of wellbeing and how big its effect is. Several studies have repeatedly shown a positive influence of service dog presence on those with PTSD. This effect was additionally greater than that of pet dog presence as shown by our results. It can therefore be questioned how big the influence of bias and/or placebo would truly be on our results since similar results have been found across populations. Though the possibility of this influence seems to be small, it is advisable that in future a meta-analysis or similar study is performed on these parameters, to establish a definitive answer to this question.

## 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 Medisch Ethische Toetsingscommissie (METC) Utrecht. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

EH: conceptualization, primary writing, data gathering, and statistics. TR, EV, and NE: conceptualization, review, and funds acquisition. All authors contributed to the article and approved the submitted version.

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# Comparison of Patterns of Non-suicidal Self-Injury and Emotion Dysregulation Across Mood Disorder Subtypes

*So Yung Yang*[1,2], *Dongbin Lee*[3], *Hyewon Jeong*[4], *Yunji Cho*[3], *Jae Eun Ahn*[4], *Kyung Sue Hong*[3,5] *and Ji Hyun Baek*[3,5]*

[1] Department of Psychiatry, National Health Insurance Service Ilsan Hospital, Goyang-si, South Korea, [2] Institute of Behavioral Sciences in Medicine, College of Medicine, Yonsei University, Seoul, South Korea, [3] Department of Psychiatry, Samsung Medical Center, Sungkyunkwan University, Seoul, South Korea, [4] Center for Clinical Research, Samsung Biomedical Research Institute (SBRI), Seoul, South Korea, [5] School of Medicine, Sungkyunkwan University, Suwon, South Korea

**Introduction:** Non-suicidal self-injury (NSSI) is frequently encountered in patients with mood disorders. Emotion dysregulation (ED), frequently observed in mood disorders, could be a major mediating factor in NSSI. The aim of this study was to explore differences in NSSI behavior and ED across mood disorder subtypes. The relationships between childhood trauma and NSSI and ED were also explored.

**Methods:** A total of 191 patients with mood disorders were included in this study. The patterns of NSSI behavior and ED across patients with bipolar I disorder (BD-I), bipolar II disorder (BD-II), and major depressive disorder (MDD) were compared.

**Results:** More than half (54%) of the subjects experienced NSSI. Patients with BD-II and MDD engaged in NSSI behavior more frequently than those diagnosed with BD-I. NSSI behaviors in patients with BD-II most commonly included cutting, whereas hitting behaviors were most common among other groups. Patients with BD-II and MDD reported more severe ED than those with BD-I. In the case of childhood trauma, those with BD-II and MDD reported greater emotional neglect than those with BD-I. Structural equation modeling revealed that ED mediated the association between childhood trauma and NSSI.

**Conclusion:** BD-I was associated with less frequent NSSI behavior and less severe ED than BD-II and MDD. ED mediated the association between childhood trauma and NSSI. Promoting emotion regulation strategies could prevent NSSI behavior in patients with mood disorders.

**Keywords: mood disorders, non-suicidal self-injury (NSSI), emotional dysregulation, bipolar II disorder (BD-II), childhood trauma**

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***Correspondence:**
*Ji Hyun Baek*
*jihyunbaek@skku.edu*

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## INTRODUCTION

Non-suicidal self-injury (NSSI) has been defined as the deliberate and self-inflicted destruction of body tissues without suicidal intent (1). The prevalence of NSSI among the clinical samples of adults ranged from 13 to 37% (2–4). Typical NSSI behaviors include cutting, scraping skin, skin-picking, self-hitting and biting, burning, and tying (5, 6). NSSI usually begins in adolescence. It has the highest prevalence during adolescence and early adulthood, but it can manifest at any age

(4, 7, 8). Although by definition, NSSI occurs without an intent to commit suicide, it is strongly associated with suicidal thoughts and behaviors (8, 9).

NSSI has received increasing attention over the past several decades (10) with growing evidence suggesting that it is a transdiagnostic symptom commonly associated with psychiatric disorders including mood disorders (11–13). While self-harm is a diagnostic criterion of borderline personality disorder, studies have shown that mood disorders and NSSI frequently co-exist (14, 15). Individuals who engaged in NSSI exhibited elevated levels of anxiety and depression compared to those who did not engage (16, 17). A meta-analysis showed that individuals with mood disorders exhibited more than twice the odds (odds ratio = 2.09) of engaging in NSSI compared to those without such disorders (18).

Emotion dysregulation (ED) is a factor that could mediate the relationship between mood disorders and NSSI behavior (19). ED refers to "an individual's ability to modify an emotional state so as to promote adaptive, goal-oriented behaviors" (20). Therefore, ED refers to the failure to change the reactivity of emotions or the unacceptance and devaluing of emotions (21). ED has been proposed as a critical component in the development and maintenance of mood disorders (19). NSSI is often used to regulate affect to reduce or escape from an aversive or negative affective state (22, 23). It may provide relief from emotional distress (24). Thus, NSSI is often intended to avoid the negative emotional experiences associated with mood disorders.

Previous studies demonstrated the association of mood disorders with NSSI and ED (13, 19). However, little is known about whether the patterns of NSSI behavior and ED differ by mood disorder subtypes such as bipolar disorder (BD) and major depressive disorder (MDD). In addition, differences in NSSI behavior and ED between patients with bipolar I disorder (BD-I) and bipolar II disorder (BD-II) remain unclear. Considering that BD-I, BD-II, and MDD differ clinically in terms of long-term illness trajectory (25–27), they might show different patterns of ED and NSSI behavior.

Childhood trauma is generally accepted as a risk factor for NSSI (28, 29) and mood disorders (30). Some studies have suggested that depression (31) and ED (24, 32) might play a potential role in the association between NSSI and childhood trauma. However, previous studies investigating the relationship between NSSI and childhood trauma mainly targeted adolescents (29). Few studies involved adult clinical samples.

The aim of this study was to determine differences in NSSI patterns and association with ED according to mood disorder subtypes (i.e., BD-I, BD-II, and MDD). The relationship between childhood trauma and NSSI and the possible mediating effects of ED on the relationship were also explored.

# MATERIALS AND METHODS

## Study Participants

Study participants were recruited from the psychiatry outpatient clinic of Samsung Medical Center from January 2019 to November 2020. Subjects aged between 18 and 60 years who were diagnosed with BD-I, II, or recurrent MDD were included. Board-certified psychiatrists who had at least one year of research experience evaluated the participants' psychiatric diagnoses using DSM-V criteria. These study participants were clinically stable, i.e., they scored 3 (mildly ill) or lower on the Clinical Global Impression of Severity scale (33) at the time of assessment. Clinical severity was evaluated by the same psychiatrists who made the clinical diagnosis. Based on comprehensive psychiatric evaluations, we only included individuals who could reliably report their symptoms and past histories. All participants were undergoing standard pharmacological treatment, which included mood stabilizers or antidepressants. The other inclusion criterion was the absence of evidence of schizophrenia, organic mental disorder, intellectual disability, and substance or medical illness-induced mood disorders. Patients who could not reliably report their lifetime history were excluded. Information was collected using a checklist of demographic data, as well as psychiatric and medical history. The participants completed self-reported questionnaires related to childhood trauma, emotion regulation, and the lifetime frequency of NSSI. Written informed consent was obtained from all subjects after a complete explanation of the study. This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB no. 2018-11-019).

## Measures

### Non-suicidal Self-Injury

NSSI behaviors and functions were assessed using the Korean version of the Inventory of Statements about Self-Injury (ISAS) (5, 34). The first section of the ISAS measures the lifetime frequency of 12 NSSI behaviors including cutting, biting, carving, burning, pinching, pulling hair, severe scratching, banging or hitting self, interfering with wound healing, rubbing skin against a rough surface, sticking self with needles, and swallowing dangerous substances. In this section, the participants are also asked about the frequency of each behavior and the method they most commonly used.

### Emotion Dysregulation

The Korean version of Difficulties in Emotion Regulation Scale (DERS) (35, 36) was used to measure ED. This 36-item scale asked the relevance of each item based on a 5-point scale. Difficulties in emotion regulation were assessed using six subscales: impulse control difficulties, lack of emotional awareness, non-acceptance of emotional response, lack of emotional clarity, limited access to emotion regulation strategies, and difficulties engaging in goal-directed behavior. The cumulative scores of the DERS subscales were also calculated.

### Childhood Trauma

A childhood history of abuse was assessed retrospectively using the Korean version of the Child Trauma Questionnaire (CTQ) (37, 38). The CTQ is a 28-item self-reported assessment of the severity and frequency of childhood maltreatment, including physical, sexual, and emotional abuse, and physical and emotional neglect. The items were scored using a 5-point Likert scale ranging from 1 (never true) to 5 (very often true). The total score of the CTQ subscales was also calculated.

**TABLE 1 |** Participants' sociodemographic characteristics.

| | Total subjects (*N* = 191) | 1. BD-I (*N* = 56) | 2. BD-II (*N* = 104) | 3. MDD (*N* = 31) | F or $\chi^2$ | *p*-value |
|---|---|---|---|---|---|---|
| Sex, male, n (%) | 67 (35.1) | 20 (35.7) | 38 (36.5) | 9 (29.0) | 0.605[a] | 0.739 |
| Age, year, mean (SD) | 30.3 (9.6) | 32.1 (10.6) | 29.5 (9.2) | 29.7 (8.9) | 1.495[b] | 0.227 |
| Education, high school graduate or more, n (%) | 132 (69.5) | 40 (71.4) | 73 (70.2) | 19 (63.3) | 0.66[a] | 0.719 |
| Marital state, married (%) | 56 (29.6) | 22 (39.3) | 24 (23.3) | 10 (33.3) | 4.68[a] | 0.096 |
| Occupation, present, n (%) | 135 (71.4) | 44 (78.6) | 69 (67.0) | 22 (73.3) | 2.448[a] | 0.294 |

*BD-I, bipolar I disorder; BD-II, bipolar II disorder; MDD, major depressive disorder; SD, standard deviation.*
[a]*Groups were compared using the one-way ANOVA test.*
[b]*Groups were compared using the χ2-test.*

**TABLE 2 |** Descriptive statistics and differences in NSSI and DERS and CTQ scores between diagnostic groups.

| | Total subjects (*N* = 191) | 1. BD-I (*N* = 56) | 2. BD-II (*N* = 104) | 3. MDD (*N* = 31) | F or $\chi^2$ | *p*-value[a] | *Post-hoc* test[b] |
|---|---|---|---|---|---|---|---|
| NSSI, present, *n* (%) | 104 (54.5) | 19 (33.9) | 67 (64.4) | 18 (58.1) | 13.843 | **0.001** | 1<2, 1<3 |
| DERS | | | | | | | |
| Total score, mean (SD) | 107.9 (27.6) | 97.2 (26.8) | 112.2 (27.5) | 113 (24.7) | 6.326 | **0.002** | 1<2, 1<3 |
| Impulse, mean (SD) | 14.2 (5.8) | 12.9 (5.4) | 15 (6) | 13.7 (5.6) | 2.594 | 0.077 | |
| Awareness, mean (SD) | 19.8 (6.4) | 18.8 (7) | 20 (6.1) | 20.9 (5.9) | 1.257 | 0.287 | |
| Acceptance, mean (SD) | 22.8 (9) | 20.3 (8.8) | 23.6 (9.2) | 24.8 (8) | 3.337 | **0.038** | 1<2, 1<3 |
| Clarity, mean (SD) | 8 (3.3) | 6.6 (3.2) | 8.6 (3.3) | 8.2 (2.9) | 7.246 | **0.001** | 1<2, 1<3 |
| Strategy, mean (SD) | 19.1 (7.5) | 16.4 (5.5) | 20.1 (8.4) | 20.5 (6.3) | 5.306 | **0.006** | 1<2, 1<3 |
| Goal, mean (SD) | 13.9 (4.4) | 12.3 (4.6) | 14.7 (4) | 14 (4.8) | 5.494 | **0.005** | 1<2 |
| CTQ | | | | | | | |
| Total score, mean (SD) | 54.5 (19.1) | 49.2 (17.5) | 56.2 (19.7) | 58.4 (18.4) | 3.252 | **0.041** | 1<2, 1<3 |
| Emotional abuse, mean (SD) | 12.2 (5.9) | 10.8 (5.5) | 12.8 (6.1) | 13 (5.9) | 2.37 | 0.096 | |
| Physical abuse, mean (SD) | 10.5 (5.6) | 9.4 (5.9) | 10.9 (5.4) | 10.8 (5.4) | 1.444 | 0.238 | |
| Emotional neglect, mean (SD) | 15.4 (6.2) | 13.7 (6.5) | 15.8 (6.1) | 17 (5.2) | 3.492 | 0.032 | 1<2, 1<3 |
| Physical neglect, mean (SD) | 9.5 (4) | 8.8 (3.4) | 9.7 (4.1) | 10.5 (4.6) | 2.034 | 0.134 | |
| Sexual abuse, mean (SD) | 6.9 (3.9) | 6.6 (3.5) | 7 (4.2) | 7.1 (3.6) | 0.295 | 0.745 | |

*BD-I, bipolar I disorder; BD-II, bipolar II disorder; MDD, major depressive disorder; CTQ, child trauma questionnaire; SD, standard deviation; NSSI, non-suicidal self-injury; DERS, difficulties in emotion regulation scale.*
[a]*Bold fonts indicate statistically significant differences with a* $p < 0.05$.
[b]*Fisher's LSD post-hoc comparisons (1, BD-I; 2, BD-II; 3, MDD).*

## Statistical Analysis

All statistical analyses were executed using IBM SPSS statistics version 23 (IBM Corp., Armonk, NY, USA) and SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). The Shapiro-Wilk test was used to determine the normality of parametric variables. Variables that were normally distributed with equal variance among groups were compared using the Student's *t*-test or one-way ANOVA followed by Fisher's LSD *post-hoc* comparison. Data that were neither normally distributed nor had equal variance were tested using Mann-Whitney's U-test. Categorical variables were compared using the χ2-test.

The relationship between childhood trauma and NSSI and the mediating effect of ED on such relationships were explored via structural equation modeling (SEM) analysis using Markov Chain Monte Carlo (MCMC) with 1000 bootstrap samples in SPSS AMOS. Age and sex variables were included in the model as covariates to control for their potential confounding effects. Model fit was examined using the Comparative Fit Index (CFI), the Root Mean Square Error of Approximation (RMSEA), and the Standardized Root Mean Square Residual (SRMR). The acceptable fit of SEM was defined as CFI values above 0.90, RMSEA values <0.08, and SRMR values less than 0.08 (39, 40).

# RESULTS

## Patterns of NSSI Behaviors and Emotion Dysregulation in Patients With Mood Disorders

No significant differences in sociodemographic variables including sex and age were found between the diagnostic groups (**Table 1**). Of all participants, 54% had a lifetime NSSI history (**Table 2**). When statistically analyzing the proportion of patients who experienced NSSI by diagnosis, patients with BD-I were less likely to engage in NSSI compared to other diagnostic groups (BD-I: 33.9%, BD-II: 64.4%, MDD: 58.1%, $\chi^2 = 13.843$, $p = 0.001$) (**Table 2**).

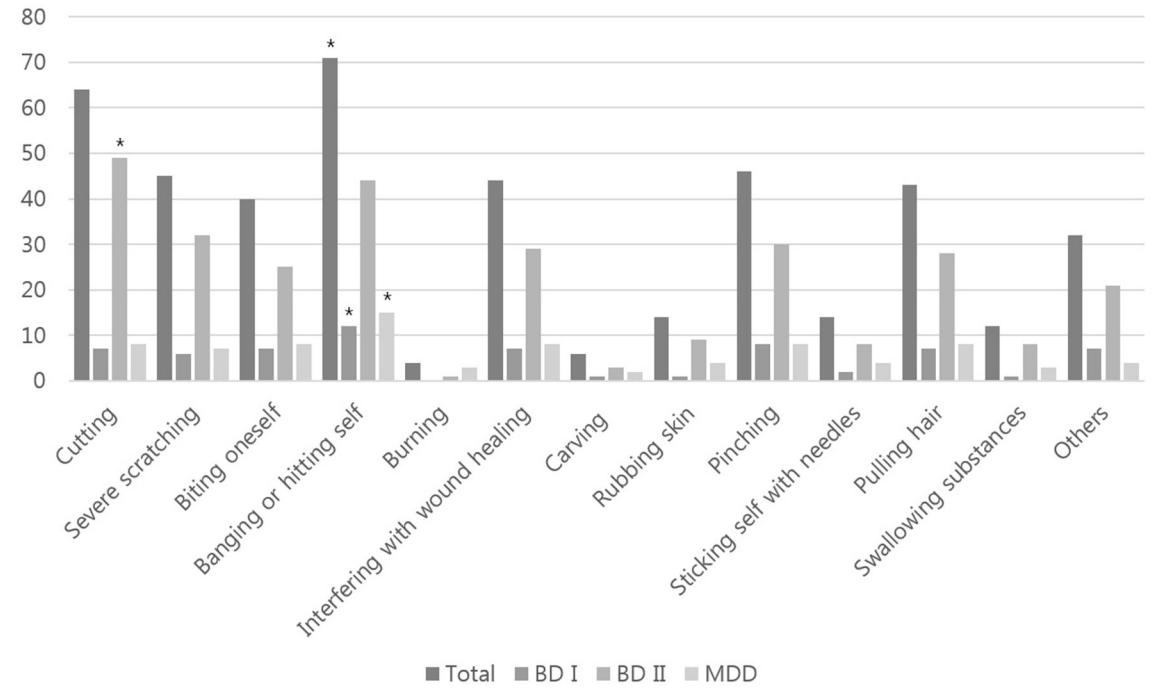


**FIGURE 1 |** Types of NSSI behavior based on diagnostic group (multiple responses were allowed). BD-I, bipolar I disorder; BD-II, bipolar II disorder; MDD, major depressive disorder. Asterisk indicates the most commonly used self-injury method by the diagnostic group.

**Figure 1** shows the different types of NSSI behavior (ISAS section 1) according to the diagnostic groups. When the methods ever used in their lifetime were queried (multiple responses allowed), "cutting" was the most common method, followed by "banging or hitting self" and "severe scratching" in patients with BD-II. In patients with BD-I or MDD, "banging or hitting self" was the most commonly used self-harm method, followed by "cutting," "pinching," and "severe scratching." "Cutting" was the most commonly used method of self-harm, followed by "banging or hitting self," "others," and "interfering with wound healing" in patients with BD-II. However, "banging or hitting self" was the mainly used self-harm method in patients with BD-I and MDD (**Supplementary Table 1**).

Statistically significant differences between the diagnostic groups were detected in total DERS scores. The BD-I group reported lower DERS total scores, indicating less severe ED compared to the other diagnostic groups ($F = 6.326$, $p = 0.002$) (**Table 2**). This overall pattern was repeated for the DERS subscales except for impulse control difficulties and the lack of emotional awareness subscales. Patients with BD-I also reported a lower CTQ total score, indicating less severe overall childhood trauma experience compared to the other groups (CTQ total score: $F = 3.252$, $p = 0.041$). In sub-score analyses, the BD-I group scored significantly lower on the emotional neglect subscale than the other groups ($F = 3.492$, $p = 0.032$).

## Comparison Between Patients With and Without a Lifetime History of NSSI

**Table 3** shows differences in the variables based on NSSI experience. A significantly greater proportion of females than males reported engaging in NSSI ($\chi^2 = 5.189$, $p = 0.023$). The NSSI group was younger ($z = -3.659$, $p < 0.001$) and more frequently unmarried ($\chi^2 = 8.345$, $p = 0.004$). Participants with and without NSSI did not differ in educational level or occupational status. As for the clinical variables, the NSSI group reported significantly higher levels of childhood traumatic experience ($t = -6.145$, $p < 0.001$) and difficulties in emotion regulation ($t = -5.457$, $p < 0.001$).

## Structural Equation Modeling Analysis

**Table 4** presents the correlation of age with the total CTQ and DERS scores. Since age is known to be related to DERS scores, it was included in the correlation analysis. The rate of childhood trauma and severity of emotion dysregulation showed a significant positive correlation ($r^2 = 0.419$, $p < 0.001$). Age was negatively correlated with ED ($r^2 = -0.229$, $p = 0.001$) and childhood trauma ($r^2 = -0.177$, $p = 0.014$). **Figure 2** presents a conceptual model of the relationship between childhood trauma and ED and NSSI. Age and sex were included in the model as covariates to control for its potential confounding effect. The results showed that all paths were statistically significant. The model explained 36.4% of the NSSI of patients with mood disorders (total effect coefficient = 0.437). An increased incidence of childhood trauma directly predicted increased levels of NSSI (coefficient = 0.3286, 95% confidence interval (CI): 0.1629–0.4832). Childhood trauma was related to ED (coefficient = 0.4204, 95% CI: 0.2959–0.5334), which in turn, was significantly predictive of NSSI (coefficient = 0.2582, 95% CI: 0.0829–0.4256). Mediation analysis revealed that ED mediated the relationship between childhood trauma and

**TABLE 3 |** Descriptive statistics and differences in variables between non-NSSI and NSSI groups.

| | NSSI (*N* = 104) | non-NSSI (*N* = 87) | *t* or $\chi^2$ | *p*-value |
|---|---|---|---|---|
| Sex, male (%) | 29 (27.9) | 38 (43.7) | 5.189 | 0.023 |
| Age, mean (SD) | 27.63 (7.266) | 33.46 (11.046) | 4.215 | <0.001 |
| Education, high school graduate or more, *n* (%) | 74 (71.2) | 58 (67.4) | 0.306 | 0.58 |
| Marital state, married (%) | 20 (19.4%) | 33 (38.4%) | 8.345 | 0.004 |
| Occupation, present, *n* (%) | 68 (66.0) | 67 (77.9) | 3.245 | 0.072 |
| CTQ total score, mean (SD) | 61.54 (18.90) | 46.11 (15.79) | 6.145 | <0.001 |
| DERS total score, mean (SD) | 117.23 (24.44) | 96.82 (27.23) | 5.457 | <0.001 |

*NSSI, non-suicidal self-injury; SD, standard deviation; CTQ, child trauma questionnaire; DERS, difficulties in emotion regulation scale.*

**TABLE 4 |** Pearson product-moment correlation coefficients of variables.

| | 1 | 2 | 3 |
|---|---|---|---|
| 1. Age | - | | |
| 2. CTQ total score | −0.177* | - | |
| 3. DERS total score | −0.229** | 0.419** | - |

*$P < 0.05$.
**$P < 0.01$.

NSSI (standardized indirect effect coefficient = 0.1086, 95% CI: 0.0332–0.1919; standardized total effect coefficient = 0.4372, 95% CI: 0.2857–0.5742). The model fit including all diagnostic groups was as follows: CFI = 0.943, RMSAEA = 0.103 (90% CI:0.029–0.183), SRMR = 0.045. The SEM results and fitness in each diagnostic group are presented in **Supplementary Figure 1**.

## DISCUSSION

NSSI is a widespread phenomenon without diagnostic boundaries. However, previous studies did not explore the differences across mood disorder subgroups. The current study investigated NSSI and ED patterns among patients with BD-I, BD-II, and MDD. We additionally analyzed the association of NSSI and ED with childhood trauma in patients with mood disorders.

Approximately 54% of the participants in our study reported a lifetime history of NSSI. The rate of NSSI in our study was comparable to that of a previous study (13). A previous study involving patients seeking treatment at a general practice clinic in the United States (U.S.) reported a higher prevalence of NSSI in patients with mood disorders than in those with other psychiatric disorders (43 vs. 20%, respectively) (13). The prevalence of NSSI was especially high in subjects with bipolar disorder (up to 52%) (13).

This was the first study that compared the rates and patterns of NSSI in patients with BD-I, BD-II, and MDD. Notably, patients with BD-I showed substantially lower rates of lifetime NSSI behavior than the other groups. The rate of lifetime NSSI behavior was the highest in the BD-II group. Previous studies evaluating the rate of NSSI behavior in patients with psychiatric diagnoses reported mixed results regarding NSSI rates in patients with BD (18, 41). The contrasting results of NSSI frequency between BD-I and BD-II patients might have contributed to the mixed results. The patterns of NSSI behavior also differed among the three groups. Patients diagnosed with BD-II manifested cutting as the most common method of NSSI, which is potentially associated with a high degree of tissue damage compared to the other methods.

Consistent with the higher rate of NSSI behavior in patients with BD-II and MDD, difficulties in ED were more severe in those groups. BD-II was associated with profound ED, similar to MDD, rather than BD-I. A meta-analysis revealed that ED was common in patients with BD, but the differences in ED between patients with BD-I and BD-II were not clear (42). A single study reported the absence of differences in DERS scores between patients with BD-I and BD-II (43). However, the small sample size affected the results. Previous studies reported significant ED in patients with mood disorders compared to the general population, which was pervasive across diverse mood states including manic, depressive, and euthymic conditions (44, 45). In particular, mood dysregulation is more severe in BD-II than in BD-I (46, 47), which corroborates our study findings. Decreased ED correlated with a decrease in depression and anxiety (42), suggesting an association between negative affect and persistent ED. Depressive episodes are known to be more frequent in patients with BD-II than BD-I (27). The more frequent depressive episodes and mood swings observed in patients with BD-II often resemble severe ED found in borderline personality disorder (48, 49). A neuroimaging study also suggested differences in mood regulation circuitry between patients with BD-I and BD-II (50).

Consistent with the significant differences in total DERS scores, patients with BD-I showed better emotion regulation than those manifesting BD-II and MDD on all subscales of the DERS, and the difference reached a significant level in four domains (non-acceptance of emotion response, lack of emotional clarity, limited access to emotion regulation strategies, and difficulties engaging in goal-directed behavior). In contrast to our study, no previous studies analyzed the differences in DERS subscales between mood disorder subtypes. In a previous meta-analysis, subjects with BD showed significantly higher DERS subscale scores except for the awareness subscale score compared to healthy controls (42). Compared to borderline personality disorder, BD was associated with significantly lower scores on all the DERS subscales. A previous study investigating the latency profiles of DERS reported that the awareness subscale did not correlate with other subscale scores (51). Understanding the ED profiles across mood disorder subtypes will facilitate treatment strategies for these populations. Further studies are needed to confirm the study findings.

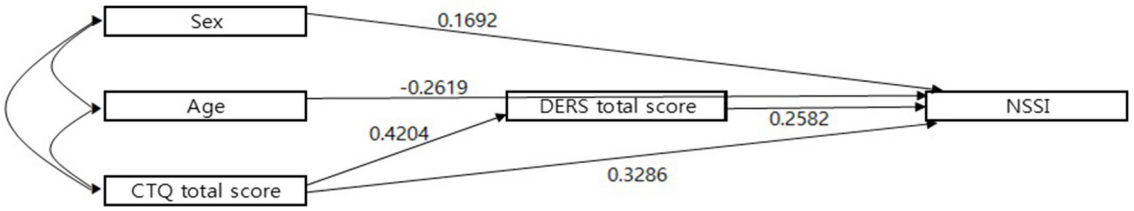


**FIGURE 2 |** A conceptual model of the relationship between childhood trauma and emotion dysregulation (ED) and NSSI using standardized beta coefficients. Age and sex variables were included in the model as covariates. All paths were statistically significant. CTQ, child trauma questionnaire; DERS, Difficulties in Emotion regulation scale; NSSI, non-suicidal self-injury.

Although NSSI implies non-suicidal intent, it is associated with an increased risk of suicidal attempts (8, 9). The higher the rate of NSSI behavior, the more frequent the use of methods with the potential for a high degree of tissue damage, and greater ED in patients with BD-II might contribute to the increased suicide risk in patients with BD-II. A recent clinical study with the largest-ever sample size (52) and a meta-analysis (53) confirmed the higher prevalence of suicide attempts in patients with BD-II. In a recent prospective study of patients diagnosed with BD and MDD (54, 55), suicide attempts were more frequently observed in patients with BD than in those with MDD mainly because of the higher duration of high-risk illness, i.e., more frequent depressive episodes. Subjects in the MDD group in our study showed NSSI rates comparable to those in the BD-II group, reinforcing the association between NSSI behavior and recurrent depression.

In our study, the CTQ scores were also higher in patients with BD-II and MDD than in patients with BD-I. However, in the sub-scale analyses, such differences were significant only for the emotional neglect subscale. Emotional neglect is arguably the most subjective and difficult to define among the forms of abuse (56). A prior study reported no differences in the rate of childhood traumatic experience of patients with BD-I and BD-II (57). Further studies are needed to confirm our findings.

In accordance with previous studies (8, 58), the NSSI group was younger and included proportionately higher numbers of females than the non-NSSI group. The CTQ and DERS scores differed depending upon the diagnosis, with NSSI being more prevalent in the group with higher CTQ and DERS scores. These results support the mediating role of ED on the association between childhood trauma and NSSI. As hypothesized, the SEM results revealed that ED mediated the relationship between childhood trauma and NSSI. When evaluating the model fit using total subjects including all diagnostic groups, a single indicator was not acceptable (RMSAEA), probably due to heterogeneity between the diagnostic groups. Subgroup analyses showed a better fit except for the BD-II group for unknown reasons. Diagnostic characteristics may also affect the model fit. The correlation between CT and NSSI has been confirmed in studies enrolling various subjects as well as clinical samples (29). A single study explored the mediating role of ED in the relationship between CT and NSSI, although it involved adolescent inpatients (59). A study of adult clinical samples has yet to be reported. The current study further emphasized the importance of ED as a mediating factor by limiting the patient group to those with mood disorders. ED is a major independent risk factor for NSSI (21, 60). The functional aspects of ED in NSSI have been studied, especially in terms of behavioral theory. Based on the behavioral model, the positive reinforcement function (e.g., to feel something) and negative reinforcement function (e.g., to relieve depression or uncomfortable internal experiences) of NSSI might be relevant to individuals with ED (22, 61). In this respect, individuals who experience negative emotions may use NSSI as a coping strategy. A group skills training program in dialectical behavior therapy is one possible treatment option that appears to be effective in decreasing emotional reactivity and improving psychological wellbeing in patients with bipolar disorder (62). A further study is needed to identify better strategies to decrease ED and NSSI in patients with mood disorders.

This study had several limitations. First, all measures were evaluated using self-reported questionnaires. In particular, the retrospective study may be associated with recall bias. However, a previous study showed that recall bias accounted for <1% of the reported variance in measures of childhood abuse (63). Second, since the data included patients with mood disorders only, it was not clear if the current study results apply only to mood disorders or the findings could be generalized to other clinical samples. Third, this study was performed as a cross-sectional and single-center study of patients who were treated in a single hospital. Therefore, prospective and multicenter studies are needed before the results can be generalized. Fourth, SEM showed that childhood trauma and ED only explained part of the mechanism of NSSI. Further studies that include diverse factors that contribute to the development of NSSI are needed.

## CONCLUSIONS

In conclusion, NSSI is common across diverse mood disorders subtypes. Patients with BD-I had the lowest prevalence of NSSI and significantly less ED compared to those diagnosed with BD-II and MDD. The association between NSSI and childhood trauma was also mediated by ED. Thus, it could be beneficial to promote emotional coping skills in patients with mood disorders and a history of childhood trauma to prevent NSSI.

## 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 Institutional Review Board (IRB) of Samsung Medical Center. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

JB designed the study and wrote the protocol. JB and KH obtained the funding. DL, YC, and JA collected and managed the data. SY managed the literature searches and analyses. SY, DL, and HJ performed the statistical analysis, and SY and JB wrote the first draft of the manuscript. All authors contributed to the final manuscript and have approved it.

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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.2022.757933/full#supplementary-material

**Supplementary Figure 1 |** A conceptual model of the relationship between childhood trauma and emotion dysregulation and NSSI in each diagnostic group. Age and sex were included in the model as covariates. Statistically significant paths are indicated with an asterisk (*). The BD-I and MDD models showed acceptable fit (CFI = 1.000, RMSAEA = 0.000 (90% CI: 0.000–0.169), with SRMR = 0.024 and CFI = 1.000, RMSAEA 0.000 (90% CI: 0.000–0.329) and SRMR = 0.053, respectively). The BD-II model showed poor fit (CFI = 0.850, RMSAEA = 0.213 (90% CI: 0.105–0.340), SRMR = 0.079). CTQ, child trauma questionnaire; DERS, difficulties in emotion regulation scale; NSSI, non-suicidal self-injury; BD-I, bipolar I disorder; BD-II, bipolar II disorder; MDD, major depressive disorder; CFI, comparative fit index; RMSEA, root-mean-square error of approximation; SRMR, standardized root-mean-square residual.

**Supplementary Table 1 |** Main form of individual's NSSI behaviors by diagnotic groups.

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# The Influence of Self-Esteem and Psychological Flexibility on Medical College Students' Mental Health: A Cross-Sectional Study

*Jiamei Guo[1†], Xin Huang[2†], Anhai Zheng[1], Wanjun Chen[1], Zhongli Lei[1], Chenglu Tang[1], Hongyu Chen[1], Hongyan Ma[1] and Xuemei Li[1*]*

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

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***Correspondence:**
Xuemei Li
181770478@qq.com

[†] These authors have contributed equally to this work

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**Background:** Mental health problems has become a major public health issue among medical students. Self-esteem and psychological flexibility were important associated factors for mental health, but their relations have not been discussed in medical students. The present study aimed to assess the status of mental health problems among medical students and identified whether psychological flexibility had a mediating role in the effects of self-esteem on the top three most common psychological symptoms.

**Methods:** A total of 810 undergraduate students from 18 classes comprised in the sample. Nine dimensions of psychological symptoms was assessed by the Symptom Checklist-90-revised (SCL-90-R). Self-esteem was measured by the Self-esteem Scale (SES) and psychological flexibility was evaluated by the Acceptance and Action Questionnaire 2nd Edition (AAQ-II) and Cognitive Fusion Questionnaire (CFQ-F). Univariate analysis and logistic regression analysis were used to determine the relationship among the top three common psychological symptoms, self-esteem, psychological flexibility, and participants' characteristics. The mediating effect of psychological flexibility between self-esteem and psychological symptoms was detected by bootstrap method.

**Results:** 57.8% of the medical undergraduate students reported positive at least one of the nine psychological symptom dimensions assessed by the SCL-90-R and 13.8% of students had moderate or more severe symptoms. The symptoms of obsessive-compulsiveness, interpersonal sensitivity, and depression were the three most common psychological symptoms among the medical students. Meanwhile, self-esteem and psychological flexibility were negatively associated to the symptoms of obsessive-compulsiveness, interpersonal sensitivity, and depression. And, almost 50% effects of self-esteem on these three symptoms in medical students exert indirect effects through psychological flexibility.

**Conclusions:** Psychological distress was quite common in the Chinese medical students. The three most common psychological symptoms were successively

obsessive-compulsiveness, interpersonal sensitivity, and depression. Low self-esteem and psychological inflexibility might be the risk factors for these top three symptoms, and psychological flexibility might play a mediating role in the effects of self-esteem on these psychological symptoms.

**Keywords: self-esteem, psychological flexibility, mental health, empirical avoidance, cognitive fusion**

## INTRODUCTION

Mental health is an essential component of health (1). Yet, mental health problems have become a major public health issue worldwide due to its increasing prevalence and great burden to their own families or the society (2, 3). Most mental health problems arise in early adulthood. However, young adults rarely receive any treatment or support from professionals (4). It is reported that college students are facing greater mental health challenges than general population due to high expectations of families and society (5, 6). Worldwide, it is estimated that 12%−50% of college students present at least one diagnostic criterion for one or more mental disorders (7). And even more, medical students are at a higher rate of mental health problems than non-medical undergraduates, such as anxiety, depression, stress, suicide and so on (8). These problems might lead to a range of adverse effects, such as poor academic performance, bad relationships with peers, and increasing risk of suicide and non-suicidal self-injury (NSSI) behavior (9, 10). Moreover, they might also potentially increase the incidence of drug abuse, medical errors, and unethical behavior after graduation (11). Therefore, early identification and management of psychological distress may be critical for long-term knowledge accumulation and development of medical students as future health care professionals.

Studies have suggested that self-esteem plays an important role in mental health (12). Self-esteem is an overall self-evaluation of an individual's worth and ability, strongly affected by social feedback from parents, teachers, and peers (13). It influences interactions and feelings toward oneself and others. Strong evidence shows that low self-esteem is a non-specific risk factor for mental health, such as anxiety, depression, stress or aggression (14). Choi et al. (15) suggested that different levels of self-esteem was related to the development of depression, and also related the social support. Meanwhile, Self-esteem is also associated to substance abuse, suicidal ideation, suicidal attempted, and other mental health conditions (16, 17). Therefore, improving the level of self-esteem is helpful to promote the mental health for young adults.

Psychological flexibility, a fundamental aspect of health (18), is the central construction of Acceptance and Commitment Therapy (ACT) proposed by Hayes et al. (19). Psychological flexibility is defined as an individual's "ability to contact with the present environment and internal psychological activities, to persist or change in behavior when doing so serves valued ends, and to tolerate, accept, or overcome interference (19). Empirical avoidance and cognitive fusion are the features of psychological inflexibility. Experiential avoidance refers to an unwillingness to maintain contact with unwanted experiences and acting to avoid them (20), and cognitive fusion refers to the tendency for behavior to be over-regulated and affected by cognition (21). Psychological flexibility has been found to be closely associated with psychopathology and wellbeing (22). Apart for that, psychological flexibility also mediate the development of mental disorders. Over the past two decades, ACT have gained a amount of attention in clinical psychotherapy and was widely used in the treatment of anxiety, depression, chronic physical pain, and so on (23–25). The core treatment target in ACT is to promote psychological flexibility. A high level of psychological flexibility can enhance a positive evaluation of oneself, feelings of continuous growth and development, purposeful and meaningful beliefs in life, and satisfaction with one's relationship (26). To some extent, these are all closely related to self-esteem. Hence, we speculated that the level of self-esteem may be improved by an increased psychological flexibility.

As mentioned above, both self-esteem and psychological flexibility are important related factors for mental health. However, so far, no studies have been reported on the relations between self-esteem, psychological flexibility, and mental health problems. Self-esteem, as a central part of human personality, whether it can modulate mental health by mediating psychological flexibility is unknown. So, in the study, we would explore the link between self-esteem, psychological flexibility, and mental health problems, and further confirm whether psychological flexibility had a mediating effect between self-esteem and mental health. Although, there have been some studies on the prevalence of and risk factors for mental health problems among medical students (27, 28), but little is known about the role of psychological flexibility on the mental health problems in this specific group. Secondly, most studies focused on the incidence of depression, anxiety, stress and their related factors, and little attention was paid to other psychological symptoms. Therefore, our study would also clarify the status of psychological symptoms among medical students, and analyze the related risk factors for the top three psychological symptoms respectively. Our findings might be helpful to provide valuable information for mental health services in medical student.

**Abbreviations:** SCL-90-R, Symptom Checklist-90-revised; SES, Self-esteem Scale; AAQ-II, Acceptance and Action Questionnaire 2nd Edition; CFQ-F, Cognitive Fusion Questionnaire; ACT, Acceptance and Commitment Therapy; NSSI, non-suicidal self-injury (NSSI); Y-BOCS, Yale-Brown obsessive compulsive scale(Y-BOCS); OCD: obsessive-compulsive disorder.

## METHODS

### Subjects and Study Design

A Cross-sectional study was conducted in Chongqing, a major city in southwest China during June 1 to December 31, 2019.

Participants were medical students from Chongqing medical university. A stratified cluster sampling method was used to draw a 25% sample of undergraduate students in the university. All the students in the chosen class were enrolled into the study. With this sampling procedure, a total of 810 medical university students from 18 classes comprised the study population. All the subjects were informed about the purpose of the study, the confidentiality of personal information, the principle of volunteering and written informed consent was obtained from all study participants before evaluation. Study protocols were approved by the ethics committee of Chongqing Medical University, China.

## Measurement Process

Data collection was conducted by two trained members of the research group. Before the assessments, the testers introduced the purpose and significance of the survey and declared the principle of confidentiality to all the participants. After obtaining the students' informed consent, questionnaires were distributed centrally and unified instructions were informed. The participants answered the questionnaires independently and anonymously. During the assessments, the testers were always on the spot to answer any questions raised by the participants. The answer time for the questionnaires was within 30 min. Psychological assessments were composed of four parts: demographics, self-esteem assessments, psychological distress, and psychological flexibility. Before assessing each scale, identified instructions were provided.

## Measures

### Demographics

General information covered age, gender, grades, registered residence (urban or rural), relationship with roommates (good, not bad, bad), being the only child or not, being a poor student or not, joining the student clubs or not.

### Symptom Checklist-90-Revised Scale (SCL-90-R)

Psychological symptoms of study participants were assessed using the Chinese version of the Symptom Checklist-90-revised (SCL-90-R), which was widely used in mental health screening (29). The scale has a total of 90 items and is divided into nine dimensions for evaluating participants' self-reported psychopathological symptoms, including somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Each item is scored using a 5-point Likert-type scale according to the severity to which the subjects had suffered from the item in the last week (0 = "not at all", 1 = "a little bit", 2 = "moderately", 3= "quite a bit", 4 = "extremely"). Higher scores indicate a greater severity of psychiatric symptoms. The scores of the nine subscales were categorized as follows: average score $<1$ were classified as "normal"; $1 \leq$ average score $< 2$ were classified as "mild"; and average score $\geq 2$ were classified as "moderate or high". In the present study, the Cronbach's alpha coefficient for this scale was 0.975 and ranged from 0.746 (paranoid ideation) to 0.904 (depression) across the nine subscales.

### Self-Esteem Scale

Self-esteem Scale (SES) was compiled by Rosenberg in 1965. The Chinese version of self-esteem scale was used to measure the self-esteem levels (30). It consists of 10- item self-reported questionnaire with a 4-point scale. The questions are about participants' overall feelings of self-worth and self-acceptance. The total scores range from 10 to 40, with the higher scores indicating higher self-esteem. In this survey, the Cronbach coefficient of the scale in the present research was 0.836.

### Psychological Flexibility Assessments

Psychological flexibility was assessed *via* the Chinese version of Acceptance and Action Questionnaire 2nd Edition (AAQ-II) and Cognitive Fusion Questionnaire (CFQ-F). AAQ-II was used to assess experiential avoidance using a 7-item self-reported questionnaire with a 7-point scale (31). The total scores range from 7 to 49, with the higher scores indicating greater psychological inflexibility. CFQ-F was used to measure cognitive fusion using a 9-items self-reported questionnaire with a 7-point scale (32). The total scores range from 9 to 63, with the higher scores indicating higher psychological inflexibility. In this study, the Cronbach coefficient of the AAQ-II and CFQ-F questionnaires were 0.883 and 0.946, respectively.

## Statistical Analysis

Data were analyzed in IBM SPSS Statistics 22.0. Descriptive statistics was applied to the study variables and general characteristics. Univariate analyses were used to identify any relations between sociodemographic characteristics, self-esteem, psychological flexibility and the psychological symptoms. Additionally, linear regressions analysis was constructed to analyze the relationship between psychological symptoms and self-esteem and psychological flexibility. Bootstrap procedure was used to explore the mediating effects of psychological flexibility on the self-esteem and psychological symptoms. $P$ (two-tailed) $< 0.05$ was considered statistically significant.

# RESULTS

In total, 810 questionnaires were distributed to medical students, and 788 valid questionnaires were used for the next analysis. Hence, the effective rate of valid data received for the present analysis was 97.28%. The participants were aged between 17 and 24 years, with an average age of 19.93 (SD = 1.27), and 60.7% of the participants were female. Among them, the proportions of freshmen, sophomores, and juniors 33.9, 34.1, and 32.0%, respectively. Most participants were rural residents ($n$ = 537; 68.1%), and had one or more siblings ($n$ = 607; 77%). 81.9% of the participants had a good relationship with their roommates, and only 13.2 of participants were poor students (**Table 1**).

Of our participants, 50.5% had symptoms of obsessive-compulsiveness (8.5% with moderate or more severe), 38.1% had symptoms of interpersonal sensitivity (6.9% with moderate or more severe), 26.6% had symptoms of depression (5.7% with moderate or more severe), and 21.6% had symptoms of anxiety (3.3% with moderate or more severe). These psychological symptoms were more common in the medical students. The

**TABLE 1 |** The study sample description ($N = 788$).

| Sociodemographic | Total ($N = 788$) |
|---|---|
| **Age (years), Mean (SD)** | 19.931 ± 0.27 |
| **Residence, *n* (%)** | |
| Urban | 250 (31.7) |
| Rural | 537 (68.1) |
| **Sex, *n* (%)** | |
| Male | 310 (39.3) |
| Female | 478 (60.7) |
| **Grades, *n* (%)** | |
| First | 267 (33.9) |
| Second | 269 (34.1) |
| Third | 252 (32) |
| **Being the Only child or not, *n* (%)** | |
| Yes | 181 (23) |
| No | 607 (77) |
| **Joining a student club or not, *n* (%)** | |
| Yes | 546 (81.9) |
| No | 136 (17.3) |
| **Relationships with roommates, *n* (%)** | |
| Good | 645 (81.9) |
| Not bad | 136 (17.3) |
| Bad | 7 (0.9) |
| **Bing a poor student or not, *n* (%)** | |
| Yes | 104 (13.2) |
| No | 684 (86.8) |

**TABLE 2 |** Distribution of SCL-90-R.

| SCL-90-R | Distribution of all participant, *n* (%) |
|---|---|
| **Somatization** | |
| Normative | 721 (91.5) |
| Mild | 64 (8.1) |
| Moderate or high | 3 (0.4) |
| **Obsessive-compulsiveness** | |
| Normative | 390 (49.5) |
| Mild | 331 (42) |
| Moderate or high | 67 (8.5) |
| **Interpersonal sensitivity** | |
| Normative | 488 (61.9) |
| Mild | 246 (31.2) |
| Moderate or high | 54 (6.9) |
| **Depression** | |
| Normative | 578 (73.4) |
| Mild | 165 (20.9) |
| Moderate or high | 45 (5.7) |
| **Anxiety** | |
| Normative | 618 (78.4) |
| Mild | 144 (18.3) |
| Moderate or high | 26 (3.3) |
| **Hostility** | |
| Normative | 647 (82.1) |
| Mild | 121 (15.4) |
| Moderate or high | 20 (2.5) |
| **Phobia** | |
| Normative | 644 (81.7) |
| Mild | 124 (15.7) |
| Moderate or high | 20 (2.5) |
| **Paranoid** | |
| Normative | 620 (78.7) |
| Mild | 148 (18.8) |
| Moderate or high | 20 (2.5) |
| **Psychoticism** | |
| Normative | 610 (77.4) |
| Mild | 155 (19.7) |
| Moderate or high | 23 (2.9) |
| **Overall of each dimension** | |
| Normative | 332 (42.1) |
| Mild | 347 (44) |
| Moderate or high | 109 (13.8) |

prevalence of other psychological symptoms is shown in **Table 2**, such as symptoms of hostility, somatization, phobia, paranoid, and psychoticism. Besides, 57.8% of participants reported positive at least one dimension of symptoms (13.8% with moderate or more severe).

**Table 3** shows that experiential avoidance and cognitive fusion were positively correlated with the symptoms of obsessive-compulsiveness, interpersonal sensitivity, and depression ($P < 0.001$), and self-esteem was negatively correlated with these three symptoms ($P < 0.001$). **Table 3** also shows that age, sex, grades and relationships with roommates were related with symptoms of obsessive-compulsiveness and depression ($P < 0.05$). Additionally, joining a student club was associated with symptoms of depression ($P = 0.044$). But, we only observed grades ($P = 0.028$) and relationships with roommates ($P < 0.001$) was related with the symptoms of interpersonal sensitivity.

Linear regression analysis further showed the self-esteem was negatively associated with the symptoms of obsessive-compulsiveness ($B = -0.024$, $\beta = -0.163$, $P < 0.001$), interpersonal sensitivity ($B = -0.034$, $\beta = -0.234$, $P < 0.001$) and depression ($B = -0.043$, $\beta = -0.292$, $P < 0.001$). **Table 4** also shows that cognitive fusion and empirical avoidance were positively related with the symptoms of obsessive-compulsiveness ($B = 0.013$, $\beta = 0.25$, $P < 0.001$; $B = 0.025$, $\beta = 0.32$, $P < 0.001$), interpersonal sensitivity ($B = 0.01$, $\beta = 0.195$, $P < 0.001$; $B = 0.027$, $\beta = 0.348$, $P < 0.001$) and depression ($B = 0.01$, $\beta = 0.188$, $P < 0.001$; $B = 0.025$, $\beta = 0.324$, $P < 0.001$) after adjusted for age, sex, grades, roommate relationship, family economic status.

In order to further understand the relationship among self-esteem, psychological flexibility and the top three psychological symptoms in the medical students, we explored whether psychological flexibility has a mediating effect between self-esteem and these three psychological symptoms. First, the

**TABLE 3 |** Factors influencing obsessive-compulsiveness, interpersonal sensitivity, and depression symptoms (mean ± SD).

| Sociodemographic | Obsessive-compulsiveness | *r/t/F* | *P* | Interpersonal sensitivity | *r/t/F* | *P* | Depression | *r/t/F* | *P* |
|---|---|---|---|---|---|---|---|---|---|
| **Age (years)** | | 0.114 | **0.001**[c] | | 0.061 | 0.089[c] | | 0.11 | **0.002**[c] |
| **Place of birth** | | −1.003 | 0.316[a] | | −0.635 | 0.526[a] | | 0.546 | 0.585[a] |
| Urban | 1.020 ± 0.65 | | | 0.810 ± 0.65 | | | 0.700 ± 0.69 | | |
| Rural | 1.070 ± 0.65 | | | 0.840 ± 0.63 | | | 0.670 ± 0.62 | | |
| **Sex** | | −2.197 | **0.028**[a] | | −1.338 | 0.181[a] | | −2.903 | **0.004**[a] |
| Male | 0.990 ± 0.64 | | | 0.790 ± 0.64 | | | 0.600 ± 0.60 | | |
| Female | 1.090 ± 0.65 | | | 0.860 ± 0.64 | | | 0.730 ± 0.67 | | |
| **Grades** | | 10.107 | **<0.001**[b] | | 3.597 | **0.028**[b] | | 9.241 | **<0.001**[b] |
| Freshman year | 0.960 ± 0.59 | | | 0.780 ± 0.61 | | | 0.570 ± 0.57 | | |
| Sophomore year | 1.010 ± 0.63 | | | 0.800 ± 0.64 | | | 0.670 ± 0.65 | | |
| Junior year | 1.200 ± 0.71 | | | 0.920 ± 0.66 | | | 0.680 ± 0.64 | | |
| **Being the only child or not** | | −0.937 | 0.349[a] | | −0.223 | 0.824[a] | | −0.301 | 0.764[a] |
| Yes | 1.010 ± 0.71 | | | 0.820 ± 0.71 | | | 0.670 ± 0.71 | | |
| No | 1.060 ± 0.63 | | | 0.830 ± 0.62 | | | 0.680 ± 0.62 | | |
| **Joining a student club or not** | | −1.759 | 0.079[a] | | −0.846 | 0.398[a] | | −2.015 | 0.044[a] |
| Yes | 1.020 ± 0.64 | | | 0.810 ± 0.63 | | | 0.640 ± 0.59 | | |
| No | 1.100 ± 0.66 | | | 0.850 ± 0.65 | | | 0.730 ± 0.70 | | |
| **Relationships with roommates** | | 19.92 | **<0.001**[b] | | 32.42 | **<0.001**[b] | | 42.786 | **<0.001**[b] |
| Good | 1.990 ± 0.61 | | | 1.750 ± 0.58 | | | 1.590 ± 0.55 | | |
| Not bad | 2.290 ± 0.72 | | | 2.140 ± 0.72 | | | 2.060 ± 0.82 | | |
| Bad | 2.961 ± 0.07 | | | 2.861 ± 0.24 | | | 2.71 ± 0.16 | | |
| **Bing a poor student or not** | | −1.05 | 0.294[a] | | 1.602 | 0.11[a] | | 0.984 | 0.326[a] |
| Yes | 1.110 ± 0.67 | | | 0.920 ± 0.71 | | | 0.740 ± 0.68 | | |
| No | 1.040 ± 0.65 | | | 0.820 ± 0.63 | | | 0.670 ± 0.64 | | |
| Empirical avoidance | | 0.615 | **<0.001**[c] | | 0.643 | **<0.001**[c] | | 0.657 | **<0.001**[c] |
| Cognitive fusion | | 0.586 | **<0.001**[c] | | 0.587 | **<0.001**[c] | | 0.601 | **<0.001**[c] |
| Self-esteem scale(SES) | | −0.466 | **<0.001**[c] | | −0.527 | **<0.001**[c] | | −0.588 | **<0.001**[c] |

[a] *t-value.*
[b] *F-value.*
[c] *r-value.*
*The bold values indicate $p < 0.05$.*

**TABLE 4 |** Linear regression of SES and psychological flexibility for the top three most common symptoms.

| Independent variables | Obsessive-compulsiveness score | | | Interpersonal sensitivity score | | | Depression score | | |
|---|---|---|---|---|---|---|---|---|---|
| | *B* | 95% CI | | *B* | 95% CI | | *B* | 95% CI | |
| | | Lower | Upper | | Lower | Upper | | Lower | Upper |
| SES | −0.024 | −0.034 | −0.015 | −0.034 | −0.043 | −0.026 | −0.043 | −0.052 | −0.035 |
| Empirical avoidance | 0.025 | 0.018 | 0.032 | 0.027 | 0.02 | 0.033 | 0.025 | 0.019 | 0.031 |
| Cognitive fusion | 0.013 | 0.008 | 0.017 | 0.01 | 0.006 | 0.014 | 0.01 | 0.006 | 0.013 |

*After adjusted for age, sex, grades, roommates relationship, family economic status.*

predictive variables were standardized. The scores of obsessive-compulsiveness, interpersonal sensitivity, and depression were chosen as the dependent variable, respectively. The scores of SES scores were chosen as the predictive variable. Meanwhile, AQQ-II scores and CFQ-F scores were chosen as the mediating variable to conduct the mediation effect test, and Bootstrap self-sampling times were set as 5,000. The mediating role of psychological flexibility in the effects of self-esteem on the symptoms of compulsive symptoms, obsessive-compulsiveness, and interpersonal sensitivity was −0.286 (experiential avoidance −0.173; cognitive fusion −0.113), −0.278 (experiential avoidance −0.193; cognitive fusion −0.085), and −0.265 (experiential avoidance −0.183; cognitive fusion −0.082), respectively. The proportion of mediation effects ranged from 45.14 to 61.36%, and experience avoidance accounted for a higher proportion of mediation effects compared with cognitive fusion (**Table 5**).

**TABLE 5 |** Mediation effect of psychological flexibility on self-esteem and the top three most common symptoms.

| Effects | Obsessive-compulsiveness | | | | Interpersonal sensitivity | | | | Depression | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Value | Bootstrap 95% *CI* | | Relative effect proportion(%) | Value | Bootstrap 95% *CI* | | Relative effect proportion(%) | Value | Bootstrap 95% *CI* | | Relative effect proportion(%) |
| | | Lower | Upper | | | Lower | Upper | | | Lower | Upper | |
| Total effects | −0.466 | −0.528 | −0.405 | 100 | −0.527 | −0.586 | −0.467 | 100 | −0.588 | −0.644 | −0.531 | 100 |
| Direct effects | −0.180 | −0.243 | −0.118 | 38.64 | −0.249 | −0.309 | −0.189 | 47.2 | −0.322 | −0.379 | −0.265 | 54.86 |
| Indirect effects | −0.286 | −0.343 | −0.236 | 61.36 | −0.278 | −0.327 | −0.228 | 52.8 | −0.265 | −0.316 | −0.219 | 45.14 |
| Empirical avoidance | −0.173 | −0.232 | −0.118 | 37.01 | −0.193 | −0.250 | −0.139 | 36.61 | −0.1830 | −0.237 | −0.134 | 31.15 |
| Cognitive fusion | −0.114 | −0.158 | −0.074 | 24.35 | −0.085 | −0.127 | −0.046 | 16.19 | −0.082 | −0.122 | −0.049 | 13.99 |

## DISCUSSION

To our knowledge, this was the first study to estimate the relationship among self-esteem, psychological flexibility, and mental health in a sample of Chinese medical students. SCL-90 is one of the most famous mental health scales for mental disorders screening in the world (33). This scale is mainly used to assess whether a person has psychological symptoms and its severity, and it has a good discriminatory ability for people with psychological symptoms (34). In our study, we found that psychological distress was a serious problem among Chinese medical students, with 57.8% of medical students reported positive of psychological symptoms, including 44% reporting mild and 13.8% reporting moderate or more severe psychological distress in at least one dimension assessed by SCL-90-R. Our findings indicated that a significant proportion of medical students are experiencing a variety of psychiatric symptoms, which was consistent with previous reported domestic and foreign studies. For example, Yang et al. (27) reported that 24.45% of medical students in southeast China might have mental health problems according to the total score of SCL-90 ($\geq$160). Tang et al. showed that 40.7% of the university students screened positive for at least one of the nine psychological symptom dimensions assessed by the SCL-90-R (35). Shao et al. (3) used Zung self-rating depression scale and Zung Self-Rating Anxiety Scale to evaluate the depression and anxiety symptoms among Chinese medical students, and found that 57.5 and 30.8% of students might be experiencing the symptoms of depression and anxiety, respectively. Meanwhile, foreign researches also find that medical students have a high prevalence of mental health problems, and multiple countries have proposed it is time to act mental health services for medical students (36). Such as a study from Brazilian reported that 34.6% of medical students had depressive symptoms, 37.2% showed anxiety symptoms, and 47.1% had stress (37). Another study from Nigeria showed that 25.2% of the medical students had psychological distress, depression in 33.5%, anxiety in 28.8%, and psychoactive substance in up to 44.2% (38). However, we also noticed that there were some inconsistencies in the reported prevalence rates. These discrepancies might be partly explained by the unbalanced economic development between different regions, different cultures, varied screening methods and different population.

Our present study also found that obsessive-compulsive symptoms were most prevalent among medical students, followed by interpersonal sensitivity and depression. This finding was consistent with previous study reported by Yang (22) using the same scale (SCL-90) to assess the mental health of medical students in Huazhong University of Science and Technology, China. However, Yang's study just simply reported the prevalence of the psychological symptoms (22). They didn't examine the associated factors for the three top psychological symptoms, respectively. To our knowledge, this was the first study to examine the related factors of the three most common psychological symptoms among medical students. Previous studies have also shown that these three psychiatric symptoms seriously affect the mental health of

medical students. For example, Esan et al. reported that 51.4% were aware of obsessive-compulsive disorder based on Yale-Brown obsessive compulsive scale(Y-BOCS) among 1,172 medical students (39). Another cross-sectional study with 471 Brazilian medical students found that possible obsessive-compulsive disorder (OCD) identified by Obsessive-Compulsive Inventory-Revised score >27 among medical students is more common (40). Moreover, obsessive-compulsive symptoms were also relevant to suicidal ideation and depressive symptoms among medical students (41). Interpersonal sensitivity is a type of personality trait, characterized by over-awareness of the actions and feelings of others and sensitivity to perceived criticism or rejection (42). Individuals with this trait have a sense of discomfort and inferiority in interpersonal communication, which leads the individuals to often avoid social interactions (43). Interpersonal sensitivity plays an important role in human mental health, and it has some negative impact on individual mental health and social adaptive functions (44). Additionally, it is also a susceptibility factor for many mental disorders such as depression, anxiety, paranoia, and compulsion (45, 46). Thus, obsessive-compulsiveness and interpersonal sensitivity are negligible mental health problems among medical students. Unfortunately, the current domestic and foreign researches on the mental health mainly focused on professional burnout, depression, suicide and anxiety (47). The attention paid to obsessive-compulsiveness and interpersonal sensitivity is still insufficient. Therefore, comprehensive assessment of individual mental health might be more conducive to meet the requirements of WHO for mental health. We considered that screening and intervention for the symptoms of obsessive-compulsive and interpersonal sensitivity should be emphasized in the studies and mental health care among medical students.

In addition, the present study also found a negative association all existed between self-esteem and obsessive-compulsiveness, interpersonal sensitivity, or depression. It means that low self-esteem was a risk factor for these three psychological symptoms. Self-esteem is the positive affirmation and acceptance of self-worth (48). Good self-esteem helps individual maintaining psychological balance and avoiding the psychological response caused by the pressure. Our results are consistent to the previous studies. A large number of studies showing that low self-esteem increases the risk of mental health problem, such as depression, anxiety (14, 49). In addition, low self-esteem was reported to be a risk factor for OCD, and enhancing self-esteem could significantly reduces OCD symptoms (50). Meanwhile, self-esteem played a mediating role in the relationship between left-behind experience and obsessive-compulsive symptoms (51). Too weak self-esteem is called inferiority, which would affect the self-evaluation, reduce social interaction, and increase interpersonal sensitivity (43). In the present study, we also found that low self-esteem increased the symptoms of interpersonal sensitivity, which are closely related to interpersonal relationships and social support. There are some evidence shows that low self-esteem is associated with interpersonal sensitivity. For example, Zavala et al. (52) reported that collective narcissism, a high but contradictory form of group self-esteem was associated with threats to group image and sensitivity to retaliatory aggression. And, Preti et al. (53) also found self-esteem was related to interpersonal relationships. Strong evidence shows that interpersonal relationships and social support are closely related to mental health (54). Good interpersonal relationships and social support reduce the incidence of mental health problems, otherwise increase the risk. A recent review reported by Gilligan et al. (55) concluded that the interventions on improving interpersonal communication skills among medical students had positive effects on most outcomes in most studies.

Moreover, we also found cognitive fusion and empirical avoidance are positively associated with obsessive-compulsiveness, interpersonal sensitivity, or depression. That means psychological flexibility was a protective factor for these three psychological symptoms. Studies have shown that the levels of cognitive fusion and empirical avoidance in patients with depression are higher than in health control group, and both psychological inflexibility are positively associated with depression level (56). Acceptance and commitment therapy (ACT) is a psychological intervention that aims at increasing psychological flexibility (22). Extensive evidence shows that ACT can improve depression, stress, and physical pain (23–25). Some studies shows that ACT can reduce OCD symptoms (57). Such as a randomized controlled trial study reported that SSRI combined with ACT treatment showed a greater decrease in the severity of OCD, compared with OCD patients with SSRI alone (58). However, researches on the relationship of ACT or psychological flexibility and interpersonal sensitivity are very lack. Oró et al. found mindfulness-based programme could significantly improve the symptoms of compulsion, interpersonal sensitivity of medical students (59). Our study might be the first study to report that interpersonal sensitivity was positively associated with psychological inflexibility. We speculated that enhancing the psychological flexibility by ACT or mindfulness would be helpful to reduce the symptoms of interpersonal sensitivity and increase social interaction.

The bootstrap method further showed that psychological flexibility played a partial mediating role between the self-esteem and the three most common psychological symptoms among medical students. The proportion of indirect effects fluctuated from 45.14 to 61.36%, which means that approximately 50% effects of self-esteem on the three most common psychological symptoms exert indirect effects through psychological flexibility. Empirical avoidance accounted for a higher proportion of indirect effects compared with cognitive fusion. Individuals with good self-esteem are more likely to recognize their abilities, objectively evaluate their value, and actively seek resources and methods to resist negative factors in the face of failure (60). However, the individuals with low self-esteem are prone to fall into rumination, become self-derogatory, and avoid solving problems when faced with pressure or conflicts (61). These manifestations are associated with psychological flexibility and psychological inflexibility, respectively (62). Similarly, according to the ACT treatment model, improving the level of the openness and acceptance might also improve the level of self-efficacy, which is positively associated with self-esteem (63). These theories support the finding that psychological flexibility might

be a mediator between self-esteem and mental health. Therefore, we speculated that ACT intervention might be one of the effective methods to reduce the impact of low self-esteem on the mental health among medical students.

There were some limitations in the present study. Firstly, this study just used experiential avoidance and cognitive fusion to assess psychological flexibility. Future studies might use multidimensional measurement tools to comprehensively reflect the psychological flexibility of participants. Secondly, the participants enrolled in the study were from the same medical university. Thus, our finding might be more likely to reflect the prevalence of psychiatric symptoms among medical students in a region. Last, the study was a cross-sectional survey, so the causal relationship between variables could not be proven. Therefore, longitudinal follow-up study could be performed to verify the mediating effect of psychological flexibility on self-esteem and the symptoms of obsessive-compulsive disorder, interpersonal sensitivity and depression in the following studies.

## CONCLUSION

We found medical students displayed a considerable prevalence of psychopathological symptoms. Among the nine dimensions of psychological symptoms assessed by SCL-90-R, obsessive-compulsive was most prevalent, followed by interpersonal sensitivity and depression in the medical students. In addition, we identified a number of factors associated with the top three symptoms, factors including age, sex, grades, roommate relationship, family economic status, self-esteem, experiential avoidance and cognitive fusion. Furthermore, we found that psychological flexibility is a mediator in the relationship between self-esteem and mental health. We argue it is time to comprehensive identification of the mental health problems among medical students, followed by assessment-based psychological interventions to promote mental health.

## 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 study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (2019-270). The participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

JG and XH analyzing the data and writing the paper. AZ helping modifying the paper. WC helping designing the questionnaire. ZL, CT, HC, and HM helping collecting the data. XL: conceived and designed the experiments; fund provider; writing—review. All authors contributed to the article and approved the submitted version.

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# Protocol for a Pragmatic Trial of Pharmacotherapy Options Following Unsatisfactory Initial Treatment in OCD (PROCEED)

*Pei Wang[1], Wenjie Gu[1], Jian Gao[1], Changhong Wang[2], Jianqun Fang[3], Maorong Hu[4], Hui Xiang[5], Bin Li[6], Na Liu[7], Wenxin Tang[8], Xijin Wang[9], Yanbin Jia[10], Yi Li[11], Yuqi Cheng[12], Zhen Tang[13], Helen Blair Simpson[14], Dan J. Stein[15] and Zhen Wang[1,16]**

[1] Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2] Department of Psychiatry, The Second Affiliated Hospital of Xinxiang Medical University, Henan, China, [3] Mental Health Center, General Hospital of Ningxia Medical University, Ningxia, China, [4] Psychiatry Department, The First Affiliated Hospital of Nanchang University, Jiangxi, China, [5] Guizhou Provincial People's Hospital, Guizhou, China, [6] Mental Health Center, West China Hospital, The Sichuan University, Sichuan, China, [7] Department of Medical Psychology, The Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China, [8] Hangzhou Seventh People's Hospital, Mental Health Center Zhejiang University School of Medicine, Zhejiang, China, [9] The First Psychiatric Hospital of Harbin, Heilongjiang, China, [10] Department of Psychiatry, The First Affiliated Hospital of Jinan University, Guangzhou, China, [11] Wuhan Mental Health Center, Hubei, China, [12] First Affiliated Hospital of Kunming Medical University, Kunming, China, [13] Suzhou Guangji Hospital, Jiangsu, China, [14] Department of Psychiatry, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, United States, [15] Department of Psychiatry and South African Medical Research Council Unit on Risk & Resilience in Mental Disorders, University of Cape Town, Cape Town, South Africa, [16] Institute of Psychological and Behavioral Science, Shanghai Jiao Tong University, Shanghai, China

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**Edited by:**
Pedro Morgado,
University of Minho, Portugal

**Reviewed by:**
Brian P. Brennan,
Massachusetts General Hospital and Harvard Medical School, United States
Zezhi Li,
Guangzhou Medical University, China

***Correspondence:**
Zhen Wang
wangzhen@smhc.org.cn

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**Background:** Selective serotonin reuptake inhibitors (SSRIs) are the first-line pharmacotherapy for obsessive-compulsive disorder (OCD), but a large proportion of patients do not achieve remission after an adequate SSRI trial. To the best of our knowledge, there have been no well-powered randomized controlled trials (RCTs) of sequenced pharmacotherapy using pragmatic research designs. China provides a unique context for undertaking such a trial that will recruit the largest treatment-naïve participants and systematically compare the efficacy of different sequenced pharmacotherapy.

**Methods:** A pragmatic research design will be adopted, with $n = 1{,}600$ treatment-naïve OCD patients initially treated for sertraline for 12 weeks, and with non-remitters then randomized to 5 different augmentation or switching pharmacotherapy options for another 12 weeks. The 5 arms will include: (1) treatment with higher than usual doses of sertraline, (2) switch to fluvoxamine, (3) switch to venlafaxine, (4) augmentation with memantine, and (5) augmentation with aripiprazole.

**Discussion:** China is uniquely positioned to recruit sufficiently large sample sizes of treatment-naïve OCD patients to compare different pharmacotherapy options; data from the proposed trial promises to help inform current clinical practice guidelines by providing important information about optimal pharmacotherapy choice for those who demonstrate no response or response but no remission to first line pharmacotherapy.

**Trial Registration:** The trail was registered on 27 August 2020 in ClinicalTrials.gov (https://register.clinicaltrials.gov/) (NCT04539951).

**Keywords: obsessive-compulsive disorder, treatment-naïve, pharmacotherapy, alternatives, remission**

# INTRODUCTION

Obsessive-compulsive disorder (OCD) is a common and disabling disorder that has a 12-month and lifetime prevalence of 1–3% worldwide, and that is accompanied by significant morbidity, impairment and huge economic burden (1–4). OCD is characterized by obsessions and compulsions; obsessions are comprised of unwanted, intrusive and persistent thoughts and images, while compulsions are comprised of repetitive behaviors, often executed with the purpose of relieving anxiety and distress caused by obsessions (5). There is a strong evidence-base demonstrating the efficacy and tolerability of selective serotonin reuptake inhibitors (SSRIs) in OCD, and these agents are therefore viewed as a first-line pharmacotherapy in OCD treatment guidelines (6–9).

Nevertheless, a large proportion of OCD patients are response only partially or not at all to an adequate trial of an SSRI (10–12). The literature on randomized controlled trials (RCTs) of pharmacotherapy approaches to OCD when response to an SSRI is unsatisfactory is relatively sparse, with little attention to pragmatic or "real-world" research designs, or to those who respond but do not remit to treatment. Pragmatic trials are important for obtaining data on representative samples (13), while remission entails improvements in both symptoms and function and so is an important goal for patients (14–16).

On the basis of the existing sparse literature, several pharmacotherapy options for OCD patients who do not respond, or who respond but do not remit, have been outlined in current treatment guidelines. These include (1) treatment with higher than usual doses of an SSRI, (2) switch to a different SSRI, (3) switch to a different class of medication, (4) augmentation with a dopamine blocker, and (5) augmentation with a glutamatergic agent. There is a need for additional data, particularly real-world data, on how best to choose between these options.

China provides a unique context for undertaking appropriately powered RCTs to compare different pharmacotherapy options for those who do not remit following an adequate SSRI initial trial. Our research will be able to recruit the largest treatment-naïve sample in a clinical trial to date, and such data may be extremely useful for informing evidence-based treatment guidelines on optimal pharmacotherapy of treatment-naïve OCD. The proposed RCT will adopt a pragmatic treatment design, recruiting OCD patients for a 12-week trial of sertraline, and then randomizing non-remitters to 5 different treatment options.

# METHODS

## Design

This study is a multi-center clinical study with a total of 13 clinical centers that specialize in the management of patients with OCD. In the Chinese context, such centers evaluate and manage many treatment-naïve patients. This allows such centers to undertake well-powered pragmatic research trials.

A randomized block design will be used in this study and all eligible participants accepted into this study will undergo an initial course of pharmacotherapy (phase I), and non-remitters will be randomly allocated to five treatment arms (phase II). In phase II, the 5 arms will comprise (1) treatment with higher than usual doses of sertraline, (2) switch to fluvoxamine, (3) switch to venlafaxine, (4) augmentation with memantine, and (5) augmentation with aripiprazole. Physician and patients will know which treatment arm is employed, but change in OCD symptoms will be assessed at several different time points by independent evaluators (IEs) who will be blind to treatment assignment. The flow diagram of the study protocol is shown in **Figure 1**.

## Inclusion/ Exclusion Criteria

Participants will be recruited from Shanghai Mental Health Center and twelve other specialized OCD sites in China. Individuals will be included in the study if they (1) meet the Diagnostic and Statistical Manual of Mental Disorder, fifth Edition (DSM-5) criteria for OCD as the primary diagnosis (17); (2) are in the age range from 18 to 65 years; (3) have a score of at least 20 on Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (18); (4) have never received medication for OCD, and have not received any form of psychotherapy for OCD in the past 6 month; (5) have provided written informed consent.

Participants will be excluded if they (1) have met the DSM-5 diagnostic criteria for Schizophrenia Spectrum and Other Psychotic Disorders, or the Bipolar and Related Disorders; (2) have a moderate or higher risk of suicide (?9 on the Suicide Module in the Mini-International Neuropsychiatric Interview (MINI) (19); (3) have substance use that is sufficiently severe to possibly impact negatively on treatment adherence in the past 1 year; (4) have severe depression with Beck Depression Inventory-II (BDI-II) score of $\geq$29 (20); (5) have comorbid psychiatric or medical disorders that may impact negatively on adherence to or on the efficacy of medication (e.g., borderline personality disorder, CNS disorders); (6)are pregnant or lactating females.

## Screening and Baseline Visit

All recruited patients will be diagnosed as having OCD as the primary diagnosis by a psychiatrist, using DSM-5 criteria. The Y-BOCS (18) will be used to assess the severity of OC symptoms, and the MINI (19) will be used to screen history of comorbid DSM-5 psychiatric disorders. At baseline, demographic data (including age, gender and education) will be collected, and participants will undergo a brief physical examination including blood routine and liver function tests. In addition, participants will complete the self-administered

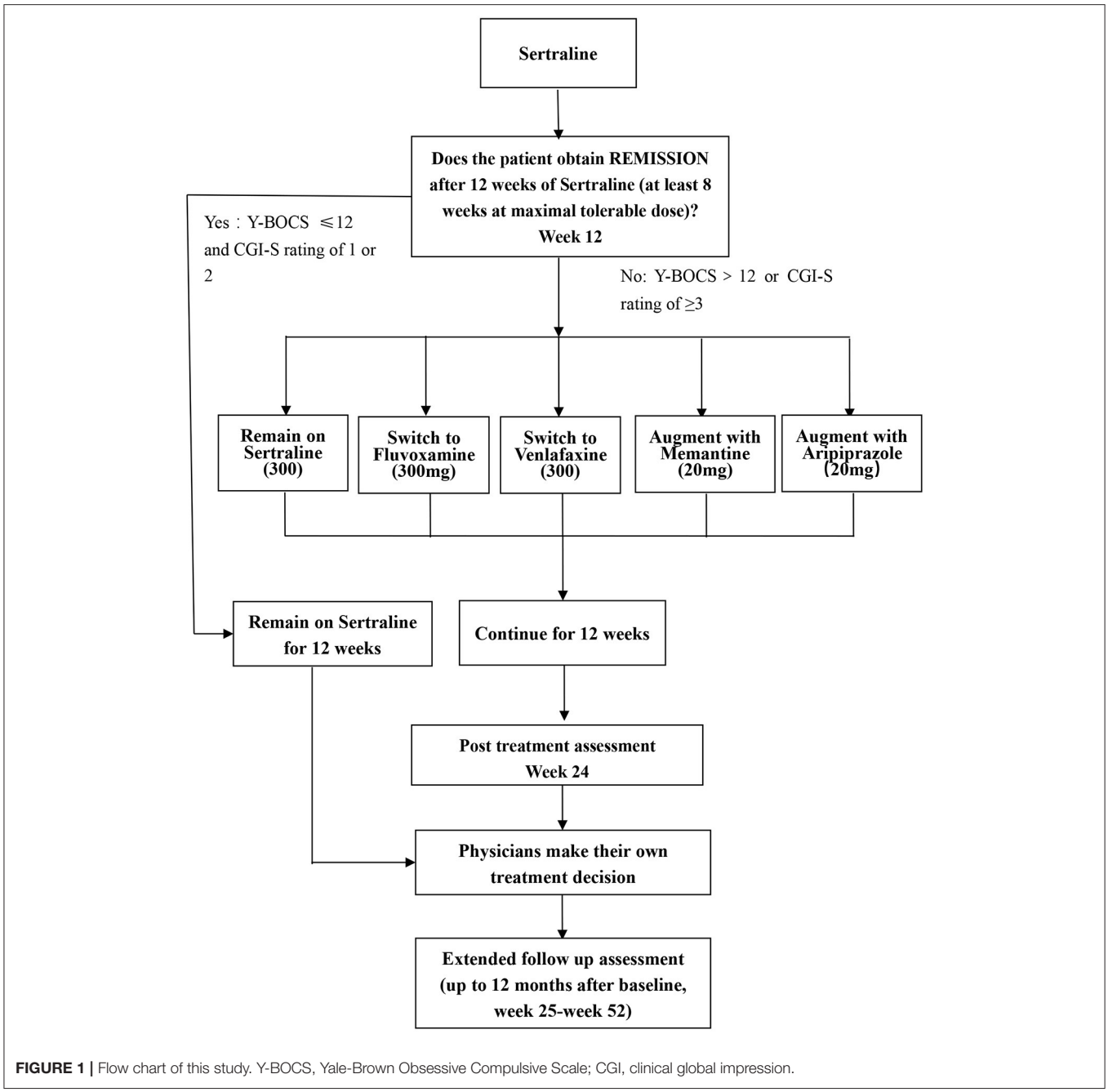


**FIGURE 1 |** Flow chart of this study. Y-BOCS, Yale-Brown Obsessive Compulsive Scale; CGI, clinical global impression.

Obsessive-Compulsive Inventory Revised (OCI-R) (21), BDI-II, Beck Anxiety Inventory (BAI) (22) and Sheehan Disability Scale (SDS) (23) to measure the severity of clinical symptoms. The Chinese versions of all measures have been proved to be reliable and eligible (24–27).

## Interventions

### Experimental Phase I: Initial Treatment

The protocol will be approved by the Institutional Review Board of all participating centers. All recruited participants will provide written informed consent before any study procedures are undertaken. Participants will be made fully aware of the design of the study, and of possible adverse effects of the medications under investigation.

Sertraline was chosen to represent the SSRIs as the initial treatment. The rationale for this chosen is as following: First, sertraline is one of four SSRIs approved by the National Medical Products Administration (NMPA) for the treatment of OCD in China, and is recommended as first-line agent by the Chinese Practice Guideline on OCD (9). Second, in terms of drug metabolism, sertraline demonstrates linear pharmacokinetics when daily dose is between 50 and 200 mg (28), so it is

straightforward for physicians to adjust the dose according to the patient's condition. Third, there is good evidence of the safety and tolerability of sertraline, and this medication has few drug interactions. In addition, sertraline is considered the medication treatment of choice for OCD in the clinical practice in China.

In phase I, participants will receive sertraline, initially at 50 mg/d, with a weekly 50 mg/d further increase, to the maximum recommended dosage (200 mg/d) or to the maximum tolerated dosage (<200 mg/d). Patients will be on their maximum dose by week 4, so allowing an assessment of response at 12 weeks (29).

- If the patients achieved remission in the first-step treatment [scores of ≤12 on the Y-BOCS and Clinical Global Impression –Severity (CGI-S) rating of 1 or 2 at week 12], participants will be continued on sertraline for another 12 weeks (30).
- Participants who do not achieve remission in the first-step treatment (scores of >12 on the Y-BOCS or CGI-S ≥3) will be randomly assigned to the second-step treatment. However, participants who do not achieve remission because they cannot tolerate a high dose of sertraline (200 mg) will not enter the second phase.

## Experimental Phase II: Sequenced Treatment Alternatives

The second-step therapy will consist of five treatment options including higher-than-usual-maximal dosage of sertraline, switching to fluvoxamine, switching to venlafaxine, augmentation with memantine, and augmentation with aripiprazole. The rationale for each of these treatment options follows.

- *Higher-than-usual-maximal dosage of sertraline:* Previous evidence from a meta-analysis of OCD pharmacotherapy suggested that higher doses of SSRI may allow a more optimal response with similar adverse effects, when compared with lower doses of SSRI (31). Furthermore, a multicenter double-blind randomized controlled trial revealed that a higher-than-usual dose of sertraline (250–400 mg/d) was more efficacious than a standard dose (200 mg/d), but with similar tolerability (32). In view of this literature, but also considering the precautionary principle, we set an intermediate dose (300 mg/d) as the upper limit.
- *Switching to fluvoxamine:* Research suggests that different SSRIs may have equal efficacy in OCD, but treatment guidelines note that different SSRIs may have slightly different pharmacological profiles and suggest that some patients who do not responds to a particular SSRI may respond to a different one (33). There is good evidence for the efficacy of fluvoxamine in OCD. In addition, fluvoxamine is considered the second medication treatment choice for OCD in China (34).
- *Switching to venlafaxine:* Although venlafaxine is not considered a first-line agent for OCD, this serotonin-norepinephrine reuptake inhibitor (SNRI) has a different pharmacological mechanism from the SSRIs, and so is recommended for patients who do not remit after treatment with an SSRI in a number of practice guidelines (6, 8). A randomized double-blind study also showed that venlafaxine (300 mg/d) was equally effective to paroxetine (60 mg/d) in treating patients with OCD (35). A real-world research also suggested that venlafaxine may be useful in a proportion of patients with poor response to SSRIs (36). In addition, the maximum dose of venlafaxine approved for clinical practice in China is 300 mg/d. So, we set the target dose at 300 mg/d although the recommendation for venlafaxine is 350 mg/d in some countries.
- *Augmentation with memantine or aripiprazole:* Augment treatment strategies have widely been recommended and studied in patients who have not had an adequate response to SSRIs. Randomized controlled trials (RCTs) and open-label data have both demonstrated that SSRI augmentation with memantine, a glutamatergic agent, is superior to placebo in OCD (37, 38). Similarly, RCTs and open-label data have demonstrated that SSRI augmentation with aripiprazole, an atypical antipsychotic, is efficacious in OCD (39). There is some evidence that aripiprazole has a superior efficacy and tolerability profile compared to other antipsychotic agents when used to augment SSRIs in OCD (39). Thus, a number of practice guidelines suggest that SSRI augmentation with memantine and aripiprazole may be considered in the management of OCD (6, 8, 40).

In summary, during phase II, the treatment options will be:

- Remain on sertraline (higher dosage): where sertraline 200 mg has been tolerated, dosage will be increased by 50 mg fortnightly to a maximal dose of 300 mg/d or to the maximum tolerable dose (<300 mg/d).
- Switch to fluvoxamine: fluvoxamine will be initiated at a dose of 50 mg/d, increasing quickly to a maximal dose of 300 mg/d or the maximum tolerated dose by week 4 (41).
- Switch to venlafaxine: venlafaxine will be initiated at 75 mg/d, increasingly weekly by 75 mg/day, to a maximal dose of 300 mg/d or the maximum tolerated dose (35).
- Augment with memantine: sertraline will be augmented with memantine initially at 5 mg/d, and increasing by 5 mg/d weekly to a maximal dose of 20 mg/d (10 mg twice daily) or the maximum tolerated dose (42).
- Augment with aripiprazole: sertraline will be augmented with aripiprazole, initially at 5 mg/d, and increasing by 5 mg/d weekly to a maximal dose of 20 mg/d or the maximum tolerated dose (43).

At the conclusion of phase II at week 24, physician may choose to continue the current treatment regime, or to make appropriate changes, as per the principles of the Chinese Practice Guideline on OCD (which are similar to those of other practice guidelines from around the world) (6–9). The extended follow up assessment will last up to the month 12 after baseline (i.e., week 25-week 52) if participants are willing to stay in the program.

Adjuvant therapy with benzodiazepines or non-benzodiazepines for insomnia will be allowed during the course of the study, but other psychotropic agents will not be

permitted. Participants can withdraw from the study at any time if they wish to do so, without any consequences.

## Sample Size

To determine the detectable effect size, sequential multiple-assignment randomized clinical trials (SMART) were used to verify the design of pharmacotherapy options following unsatisfactory initial treatment in OCD. Given preliminary data and literature retrieval, an expected remission rate to Y-BOCS (phase I) (44). In phase II, there are 5 groups. Through multiple comparisons, the clinical remission rate of the two groups with the smallest difference was evaluated, P_T = 20%, P_C = 10%. We use the type I error at 0.05 ($\alpha = 0.05$), type II error at 0.2 ($\beta = 0.2$) and get a sample size of 199 in each group [total sample size is 199*5/(1–20%) = 1,244] using PASS software version V11. Consider a 20% drop-out rate, the minimum sample size of $N = 1{,}600$ for Phase I was calculated according to the possible combination.

## Primary Outcome

The primary outcome will be OCD symptoms severity as measured by the Y-BOCS (18) and by IEs. The Y-BOCS has been shown to have good psychometric properties, is sensitive for measuring treatment effects, and is regarded as the gold standard for symptom severity assessment in trials of OCD.

## Secondary Outcome

The secondary outcomes will comprise clinical severity (anxiety, depression, and obsessive-compulsive symptoms), functional impairment and side effects at different time, as assessed with the following measures:

### Clinical Global Impression

The Clinical Global Impression (CGI; National Institute of Mental Health) (45) is a clinician-rated scale to assess treatment response in patients with mental disorders. It requires the clinician to rate how much the patient's illness has improved or worsened relative to a baseline measurement (phase I: week 0; phase II: week 12).

### Beck Anxiety Inventory

The Beck Anxiety Inventory (BAI) (22) is a 21-item, self-report inventory which identifies anxiety symptoms and quantifies their intensity. Respondents are asked to rate how much they have been bothered by each item over the past week.

### Beck Depression Inventory-II

The Beck Depression Inventory-II (BDI-II) (46) is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression. It includes both cognitive and somatic symptoms of depression.

### Obsessive-Compulsive Inventory-Revised

The Obsessive-Compulsive Inventory Revised (OCI-R) (21) is a 18-item self-report measure of obsessive-compulsive measures. It is chosen because of its psychometric properties and the short time that its administration requires.

### Sheehan Disability Scale

Sheehan Disability Scale (SDS) (23) is a reliable, brief self-report scale that assesses disability or functional impairment on 3 items: work, social life and family life.

### Treatment Emergent Symptom Scale

The Treatment Emergent Symptom Scale (TESS) (47) is widely used to record side effects. We will use it to assess tolerability of the different treatment arms.

### Tolerability

The tolerability of treatment will be defined as side effect discontinuation in this study. as defined by the proportion of patients who discontinued treatment due to adverse events during the study (48).

## Medication Management

Screening visit will include Informed consent, demographic data, MINI Psychiatric Interview, symptom measures. All the recruited participants of this study are interviewed and evaluated by IEs who are blind to randomization every two or four weeks after enrollment and following-up evaluation will be up to week 24. If participants are willing, we will continue to extend follow up interview for up to 12 months after baseline (week 25-week 52). Details are provided below (**Table 1**).

1. Interview 1 (week 0): verification of inclusion/exclusion criteria, assessment of insight, symptom measures, laboratory investigation (e.g., electrocardiogram, blood testing, and other necessary tests).
2. Interviews 2–8 (week 2, 4, 8, 12, 16, 24): follow up with symptoms measures, laboratory investigation, recording adverse events, ending record.
3. Extended interview (up to 12 months after week 0): follow up with symptom measures, laboratory inspection, recording adverse events.

All participants will complete the self-reports mentioned above and will be administered the clinician-rated scales either face-to-face or via telephone or by remote video conferencing.

## Adherence

To increase adherence to pharmacotherapy, the clinician treating the patient will emphasize the importance of continuous administration of medication at each visit. In addition, all participants will be asked to record their daily medication intake in standard forms. Drug dosage reduction, increase or missing administration will be recorded. From all records the participants will be divided into three categories: good compliance, defined as medication taken as intended; moderate compliance, defined as reduced medication to one to two tablets per day for a maximum of 4 weeks and/or no tablets for a maximum 2 weeks as projected; and poor compliance, defined as reduced medication to one to two tablets per day more than 4 weeks and/or no tablets more than 2 weeks.

## Safety and Monitoring

The TESS will be used by the clinician treating the patients to evaluate side effects at each visit following initiation of treatment.

**TABLE 1 |** Timing of assessments and data collection.

| | Baseline | Treatment and follow-up phase | | | | | | | Extended follow up |
|---|---|---|---|---|---|---|---|---|---|
| **Timepoint (Weeks)** | **0** | **2** | **4** | **8** | **12** | **16** | **20** | **24** | **25–52** |
| Informed consent | X | | | | | | | | |
| MINI | X | | | | | | | | |
| demographic data | X | | | | | | | | |
| **Primary endpoint** | | | | | | | | | |
| Y-BOCS | X | X | X | X | X | X | X | X | X |
| **Secondary endpoint** | | | | | | | | | |
| OCI-R | X | X | X | X | X | X | X | X | X |
| BDI-II | X | X | X | X | X | X | X | X | X |
| BAI | X | X | X | X | X | X | X | X | X |
| SDS | X | X | X | X | X | X | X | X | X |
| CGI | | X | X | X | X | X | X | X | X |
| TESS | | X | X | X | X | X | X | X | X |
| Tolerability | | X | X | X | X | X | X | X | X |
| Ending record | | | | | | | | X | |

*MINI, the Mini-International Neuropsychiatric Interview; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; OCI-R, Obsessive-Compulsive Inventory Revised; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory-; SDS, Sheehan Disability Scale; CGI, Clinical Global Impression; TESS, Treatment Emergent Symptom Scale. X represents must-done item.*

Adverse and secondary events will be recorded from the baseline visit and throughout the follow-up visits. All adverse events will be report to the administration agency of the hospital. Serious adverse events will be reported to the Ethics Committee at each site and to the lead site. The association of an event with study drugs will be evaluated based on a temporal and biological correlation analyses.

## Data Collection and Management

Participants in this study will be interviewed and evaluated by IEs in the study, and the data will be directly collected using the electronic data management system.

- Electronic Case Report Form (eCRF): Data administrators will build eCRFs according to the research protocol.
- Permission Assignment: Data administrators will create accounts and grant different permissions to access the system according to different identities of researcher, rater and inspector. For example, researchers of each center will only be able to browse and modify the data they collect themselves. The case situation at each center will be read by the supervisor, who has no authority to modify the data, but who can comment or raise questions.
- Data input: Clinical researchers or coordinators will promptly and accurately enter the data into the eCRF.
- Data Questions and Answers: For the questions in the case report, the independent supervisor will issue the Q&A form, and the researcher or evaluator should answer and return it as soon as possible. The data administrator will modify the data according to the answers of the researcher and may issue the Q&A form again if necessary.
- Data Locking and Exporting: After each participant completes the experiment and is verified by the supervisor, the data manager will lock the data. During the experiment, real-time lock data was exported for interim analysis as required. After all the test data were locked, the data manager will export them to the designated database for final statistical analysis.

## Statistical Methods

Descriptive analysis and statistics will be undertaken with SPSS 20.0. All the relevant data of patients meeting the inclusion criteria will be used as the data set for analysis. Comparison among the clinical and demographic characteristics of the samples will conducted by chi-square test and *t*-test. The patient's adherence to treatment and the factors affecting prognosis will be classified and counted by SPSS combined with R. Ordinal multi-categorical logistic regression model will be used to construct the index system of symptom severity. Mixed-effect models will be used to evaluate the efficacy of treatment on both the primary treatment outcome measure (the YBOCS) as well as on secondary treatment outcome measures.

## Informed Consent

The researcher needs to explain in detail the purpose of this study, research contents, the potential risk and benefit, alternative therapies available and the rights and obligations of the participants in line with the Helsinki Declaration to all screening participants (compulsive disorder patients willing to participate in the study). The medical treatment of patients who do not agree to enter the study will not be impacted. Participants have the right to withdraw at any stage after they enter the study. The explanation should also include the necessary matters to protect the individual rights and interests of the participants. With full explanation, after confirming that the patient fully understands the study and clearly knows the informed consent, the participant can enter the research process only by signing the informed consent and indicating the date.

If the informed consent is revised during the study, the modified content of the informed consent shall have an impact on the patients out of the group after the end of the study, and patients undergoing treatment or follow-up shall sign the newly revised informed consent again.

## Quality Control

Research coordinator of each research center is responsible for the coordination in the research, and the implementation of the project schedule management. The independent supervisor will monitor the quality of the work by reviewing informed consents, and completion of eCRFs. They will visit site every 6 months. 25% of all cases are randomly selected for checking by the independent monitor. In addition, all sites will submit a brief description of the clinical features of their patients at time of recruitment to monitor accuracy of diagnosis (for example, excluding patients with body dysmorphic disorder). In addition, all IEs will receive online training in administration of the YBOCS and CGI. The training process will comprise introductory lectures and demonstrations by experienced raters, followed by repeated rating of videos until such time as inter-rater reliability is obtained. To maintain reliability of ratings, raters will receive additional training up to four times per year and inter-rater reliability will be assessed.

# DISCUSSION

The current clinical trial is being conducted to compare different approaches to the pharmacological treatment of OCD patients who do not respond, or who respond but do not remit, to first line SSRI pharmacotherapy. To the best of our knowledge, this will be the first study to compare the efficacy of several switching or augment strategies for medications in such patients, and the largest prospective randomized pragmatic trial of OCD to date. Our hope is that this study will provide useful evidence to inform clinical practice and international guidelines on the pharmacological management of OCD.

There are several unique features of this study. First, the design is pragmatic in several respects, for example, patients with secondary major depression will be included, and physicians and patients will not be double-blind to treatment. Second, the design is rigorous, with randomization to different treatment arms, and with raters being kept blind to treatment randomization in Phase II. Third, the trial will compare several augmentation and switching strategies. Finally, this will be the largest RCT of OCD ever conducted to date.

In conclusion, this pragmatic study is the first randomized trial that compares 5 different pharmacotherapy options in patients who do not have remission after treatment with an SSRI, and it should provide data that are useful in informing the optimal pharmacotherapeutic approach to such patients. It hopes to complement the existing literature on large pragmatic trials of schizophrenia, bipolar disorder, and major depression, by contributing equally informative data on OCD.

# TRIAL STATUS

This trial is recruiting and is expected to be complete in December 2024.

# ETHICS STATEMENT

Ethical approval for this trial has been granted by the Institutional Review Boards of Shanghai Mental Health Center and other participating institutions 20/04/2020 (2020- 11), and written informed consent will be obtained from all participants. The trial is registered as NCT04539951.

# AUTHOR CONTRIBUTIONS

Preparation of the original manuscript draft was conducted by PW and WG, with reviewing and editing by HS, DS, and ZW. JG, CW, JF, MH, HX, BL, NL, WT, XW, YJ, YL, YC, and ZT are responsible for study assessments and monitor the participants at 13 clinical centers. The design of the study was done jointly by all authors. All authors have read and agreed to the published version of the manuscript.

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# Glutamic Acid Decarboxylase 1 Gene Methylation and Panic Disorder Severity: Making the Connection by Brain Gray Matter Volume

*Huiqin Wu[1†], Yuan Zhong[2†], Huazhen Xu[1], Huachen Ding[1], Shiting Yuan[1], Yun Wu[1,2,3], Gang Liu[1], Na Liu[1*] and Chun Wang[1,2,3*]*

[1] Nanjing Brain Hospital Affiliated to Nanjing Medical University, Nanjing, China, [2] School of Psychology, Nanjing Normal University, Nanjing, China, [3] Cognitive Behavioral Therapy Institute of Nanjing Medical University, Nanjing, China

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***Correspondence:**
*Na Liu*
*happyliun@126.com*
*Chun Wang*
*chun_wang@njmu.edu.cn*

[†]*These authors share first authorship*

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**Objective:** This study aimed to test the hypothesis that the relationship between glutamic acid decarboxylase (GAD) 1 gene methylation and severity of clinical symptoms of panic disorder (PD) is mediated by the effect of GAD1 gene methylation on gray matter volume (GMV) and the effect of GMV on PD.

**Methods:** Panic disorder ($n$ = 24) patients were recruited consecutively from the Affiliated Brain Hospital of Nanjing Medical University through outpatient and public advertising, eligible healthy controls (HCs) ($n$ = 22) were recruited from public advertising. We compared GMV and GAD1 gene methylation in PD and HCs to estimate the differences, and on the basis of the relationship between gray matter volumes and GAD1 gene methylation in PD patients was evaluated, the role of GMV as a mediator of GAD1 gene methylation and PD clinical symptoms was analyzed.

**Results:** Panic disorder patients had significantly lower methylation in the GAD1 promoter region on Cytosine-phosphate-guanine (CPG) 7 than HCs ($t$ = 2.380, $p$ = 0.021). Pearson correlation analysis found a significant negative association between cg171674146 (cg12) site and clinical severity ($n$ = 24, $r$ = −0.456, $p$ = 0.025). Compared to HCs, patients with PD had decreased gray matter volumes in several brain regions, which were also associated with PD severity. Left postcentral gyrus (PoCG) GMV mediated the association between cg12 methylation and PD severity, and there was a significant mediation effect of right angular gyrus (ANG) gray matter volumes on the relationship between cg12 methylation and PD severity.

**Limitation:** No direct results can be derived for methylation patterns in different brain regions; the study is cross-sectional; relatively small size.

**Keywords: panic disorder, glutamic acid decarboxylase 1, gray matter volumes, DNA methylation, mediation effect**

## INTRODUCTION

Panic disorder (PD) is defined as episodic, unexpected panic attacks with no clear trigger that includes worry about further attacks and modifications to behavior in maladaptive ways to avoid them (1). Panic disorder is a common mental illness with a lifetime prevalence rate of 0.5%; the China Mental Health Survey reports estimates a 12-month prevalence of 0.3% (2).

The pathogenesis of PD is complex, comprised of an interaction of biological factors, particularly genetic factors (heritability estimates: 48%) (3) and brain structure (4). Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter of the central nervous system, and its dysfunction is considered to be one of the main neurobiological pathomechanisms of anxiety (5), especially patients with anxiety and panic disorder (6). GAD is the key rate-limiting enzyme that catalyzes the decarboxylation of glutamate to synthesize Gamma -aminobutyric acid, it has two isozyme forms–GAD67 (GAD1) and GAD65 (GAD2). The GAD1 gene is the rate-limiting enzyme for glutamate synthesis of GABA in the brain, GAD2 gene is present in membranes and nerve endings, so it is more sensitive to the effects of GABA levels (7). GAD's role in the pathogenesis of PD has been well-established. One study analyzed the association of the GAD1 and GAD2 genes with genetic risk for a range of diseases. They found that variations in the GAD1 gene may affect susceptibility across a range of anxiety disorders (8). Another study suggested that patients with panic disorder exhibited significantly lower average GAD1 methylation than HCs, though no methylation alterations were observed for the GAD2 gene (9). A third study tested the genetic association of 93 single nucleotide polymorphisms (SNPs) with anxiety disorders in the Finnish population-based Health 2000 sample (282 cases and 575 matched controls), they showed that several SNPs in the GAD1 gene (rs769401, rs3791851, and rs769395) were associated with PD, with GAD1 having the most obvious association (10). Gorman (11) proposed a fear network model (FNM) of panic disorder based on an animal model of fear. FNM is centered in the amygdala and includes the thalamus (THA), hypothalamus, and hippocampus, as well as the locus ceruleus, periaqueductal gray area, and other brainstem sites. However, more extended regions of FNM have been identified in recent imaging studies. For example, Lai (12) suggests FNM also includes sensory regions of occipital lobe, temporal cortex, insula, and parietal cortex.

A previous meta-analysis of PD conducted by our research group revealed significant volume reductions in the right insula [extending to the PoCG, right inferior frontal gyrus, rolandic operculum, superior temporal gyrus (STG) and putamen], median cingulate/paracingulate gyrus, and SFG (13). In addition, some researchers have reported significant volume reductions in parietal regions (14) and the THA (15) in PD patients,
whereas significant increases in volume have been found in the left inferior frontal gyrus (IFG), midbrain (16) and cuneus (17). The PoCG has been associated with functions of receiving, integrating, and interpreting most of the sensory information in the human body (18). Gorman et al. (11) showed that abnormalities in PoCG could potentially lead to misinterpretation of somatosensory information, thus allowing inappropriate activation of the FNM through misleading excitatory inputs to the amygdala (11). Another region that has gained attention is the ANG. ANG is important in empathic response, emotional regulation, mood, anxiety, and is associated with meditation and calmness (19). Previous studies reported that not only do PoCG and ANG play an important role in panic disorder, a correlation between GMV of those regions and clinical symptoms in PD exists as well (20).

Although evidence suggests that epigenetic alterations of GAD1 gene and gray matter volumes alterations of PoCG and ANG play an important role in the onset and maintenance of panic disorder, whether GAD1 methylation influences GMV of PoCG and ANG in PD has not yet been confirmed. Thus, the current study sought to explore the differences in whole brain gray matter volume and GAD1 gene promoter methylation levels between patients with panic disorder and the normal population. And furthermore, to explore the correlation between GAD1 methylation, brain gray matter volume and Panic Disorder Severity Scale (PDSS) scores. We hypothesized that GMV of PoCG and ANG mediates the relationship between GAD1 methylation and panic disorder severity.

## MATERIALS AND METHODS

### Participants

This study was approved by the Ethics Committee Institute of the Brain Hospital of Nanjing Medical University, and all participants will receive a detailed explanation of the process before signing the written informed consent.

Panic disorder patients were recruited consecutively from the Affiliated Brain Hospital of Nanjing Medical University through outpatient and public advertising. The inclusion criteria for patients in the PD group were as follows: (1) A diagnosis of PD by a psychiatrist according to the fourth edition of the DSM (Diagnostic and Statistical Manual of Mental Disorders); (2) Filter by Mini-international Neuropsychiatric Interview Chinese version; (3) Ability to read and write Chinese at least in 6th grade, right handedness; (4) 18–55 years old; (5) Cooperation with psychological tests and completion of questionnaires. Exclusion criteria were: (1) Any other psychiatric illnesses or disorders of the nervous system; (2) Any serious comorbidity; (3) Any psychotherapy or medical treatment in the past 6 months; (4) Pregnancy and/or breastfeeding; (5) Inability to complete MRI. In HC group. The inclusion criteria for patients were as follows: (1) 18–55 years old; (2) Hamilton Anxiety Rating Scale (HAMA) score $\leq$ 7; (3) Right handedness; (4) Ability to complete all examinations. Exclusion criteria were: (1) Any other psychiatric illnesses or disorders of the nervous system; (2) Any serious comorbidity; (3) Any psychotherapy or medical treatment in the past 6 months; (4) Pregnancy and/or breastfeeding; (5) Inability to complete MRI.

### Measure

A self-report questionnaire was used to collect demographic data on the subjects, including: gender, age, years of education,

duration of illness, ethnicity, contact information, history of psychological counseling, history of physical illness, and so on. The PDSS (21) was used to assess panic symptom severity for patients with PD. The HAMA (22) is a well-established reliability and validity instrument used to assess the severity of anxiety for each subject.

## DNA Methylation Data

After obtaining informed consent, 5 ml of peripheral blood was retained from all subjects and stored in a refrigerator at −80°C. Blood samples that passed DNA quality testing were subjected to DNA sequencing. Based on the software primer3, amplification was performed using the technique of multiplex PCR, using the standard human genome as a template. The samples were processed using EZ DNA Methylation-Gold Kit reagent to convert genomic DNA unmodified by methylation from cytosine C to uracil U, and multiplexed PCR amplification was performed. High-throughput sequencing was performed in a 2 × 150 bp double-end sequencing mode using the Illumina Hiseq platform for detection of GAD1 methylation levels and analysis of the results.

## MRI Acquisition and Processing

While waiting for the scans, the researcher communicated with the subjects about precautions and reminded them to remove metal-type jewelry. During the scans, each subject was asked to remain still and close their eyes, use foam pads on both sides of their head to reduce head movement, and wear earplugs to protect their hearing. The magnetic resonance scanning involved in this study used the latest ultra-high field VerioMRI machine (magnetic field strength 3.0T, gradient field strength 45mT, and switching rate 150mT) from the Department of Radiology, Affiliated Brain Hospital of Nanjing Medical University. The sagittal images cover the entire brain with the following parameters: field of view (FOV) = 240 × 240 mm, repetition time (TR)/echo time (TE) = 1900/2.48 ms, matrix size = 128 × 128, slice thickness = 3 mm, interslice gap = 0.5 mm.

In order to minimize the errors caused by the data acquisition process, the CAT12 software package (C. Gaser, Structural Brain Mapping group, Jena University Hospital, Jena, Germany) based on the MATLAB platform was used to perform a series of original images of the 3D structure image. The preprocessing program was performed according to the following protocol: (1) Use the MATLAB platform-based SPM12 (Statistical Parametric Mapping) software package[1] to view the 3D structure image of each subject, and manually rotate and re-create the image orientation to ensure that the structural images of each subject are aligned in space; (2) Remove the unevenness and noise of the MRI scanning process to normalize the image; (3) Based on the DARTEL algorithm, register all images to the default Template; (4) Divide the image after spatial normalization into three components of white matter, gray matter and cerebrospinal fluid (23), and calculate the total intracranial volume (TIV). This segmentation method used partial volume estimation (PVE) to deal with partial volume effects (24); (5) Use the CAT12 quality inspection process to evaluate the quality of the gray matter image after segmentation to ensure the subsequent data analysis process is based on good data quality; (6) Use a smoothing kernel (full width at half maximum, FWHM) of 8 mm to smooth all gray matter images.

[1]www.fil.ion.ucl.ac.uk/spm/

## Statistical Analysis

This study used SPSS 22.0 software to analyze the general demographic data and questionnaire data, the difference in gender between PD patients and HCs was estimated with Chi square test, and an independent *t*-test was utilized to determine the potential differences in age, education duration, duration of illness, HAMA scores, and GAD1 methylation between PD patients and HCs. SPSS 22.0 was used to calculate the Pearson correlation between differentially methylated sites of GAD1 gene and PDSS scores. Differential analysis of whole brain gray matter volume between PD and HCs was performed using SPM 8, and no covariates were included because none of the demographic variables were significantly different. The minimum cluster size was 50 voxels, and differences were considered significant if $p < 0.05$. Multiple regression analysis using SPM8 was used to calculate the correlation between gray matter volumes and GAD1 methylation sites in PD patients, as well as the correlation between PDSS scores and GMV in panic disorder patients, with no covariate. Based on the above two correlations, the correlation loci were extracted using the image caculator in REST1.8 with the formula i1. *i2. Simple mediation analyses were performed using PROCESS, no covariates in the model. The Model4 intermediary model was constructed using the PROCESS plug-in in SPSS 22.0 software based on the Bootstrap method (25). The methylation level of GAD1 gene was used as the independent variable (X), the gray matter volume of each brain region was the mediating variable (M), and the total PDSS score was the dependent variable (Y). All analyses are based on a bootstrap sample of 5,000 Q20, and the mediation effect is considered significant when the confidence interval (CI) does not include zero (26).

# RESULTS

## Demographic and Clinical Characteristics

We recruited 24 patients with PD (age ± SD: 31.6 ± 6.8, 12 males) and 22 HCs (age ± SD: 33.1 ± 7.1, 11 males) in this study, and all signed informed consents. The demographic and clinical characteristics of participants are presented in **Table 1**. Sex, age, and education did not differ among groups (all $p > 0.05$), whereas differences in HAMA total scores did ($p < 0.001$). The cumulative illness duration of the patients was 2.9 ± 3.6 years (**Table 1**). The average PDSS score in patients was 16.6 ($n = 24$, SD = 2.2), and ranged from 9 to 20. Eight patients did not complete the clinical measurement completely; 46 subjects had DNA methylation data, and 16 patients and 10 HCs had neuroimaging data.

**TABLE 1 |** Demographic data of patients with panic and healthy controls.

| | Patients | Controls | *p*-values |
|---|---|---|---|
| Gender(number) | M (12)/F (12) | M (11)/F (11) | 0.087[a] |
| Age, mean (SD), years old | 31.6 (6.8) | 33.1 (7.1) | 0.466[b] |
| Education duration, mean (SD), years | 13.9 (3) | 15.6 (3.8) | 0.110[b] |
| Duration of illness, years | 2.9 (3.6) | – | <0.001[b] |
| HAMA | 20.6 (7.7) | 2.2 (2.9) | |
| PDSS | 16.6 (2.2) | – | |

*a = $\chi^2$ b = independent sample t-test. SD, standard deviation; F, female; M, male; HAMA, Hamilton rating scale for anxiety; PDSS, panic disorder severity scale.*

## Lower Methylation in the Promoter of Glutamic Acid Decarboxylase 1 Gene in Panic Disorder Compared With Healthy Controls

Average methylation across CPG7 island of GAD1 gene promoter was significantly lower in patients compared to healthy controls ($p$ = 0.02) (**Figure 1A**). There were 20 cg sites in CPG7 region and of them, the *t*-test identified 10 (5, 7–10, 12, 13, 16, 17, 19) differential cg sites that displayed significantly lower methylation (**Figure 1B**). These 10 cg sites were analyzed for correlation with clinical symptoms.

Pearson correlation analysis found a significant negative association between cg 12 site and clinical severity ($n$ = 24, $r = -0.456$, $p = 0.025$) (**Figure 2**). No significant differences were found in other sites.

## Whole-Brain Differences in Gray Matter Volumes in Patients With Panic Disorder Versus Healthy Controls

First, whole-brain differences in GMV between PD patients and HCs were examined. Significant group differences (50 or more voxels, $p < 0.05$) are identified in **Table 2**. The largest GMV increases associated with panic disorder were in a left hemisphere cluster encompassing the superior medial frontal gyrus (SFGmed) and middle temporal gyrus (MTG). Additional differences were detected in the right inferior frontal gyrus of the orbital region (ORBinf) and the right pars opercularis. The reverse contrast (HCs > PD) identified clusters in bilateral THA, and regions of the left parahippocampal gyrus (PHG), left

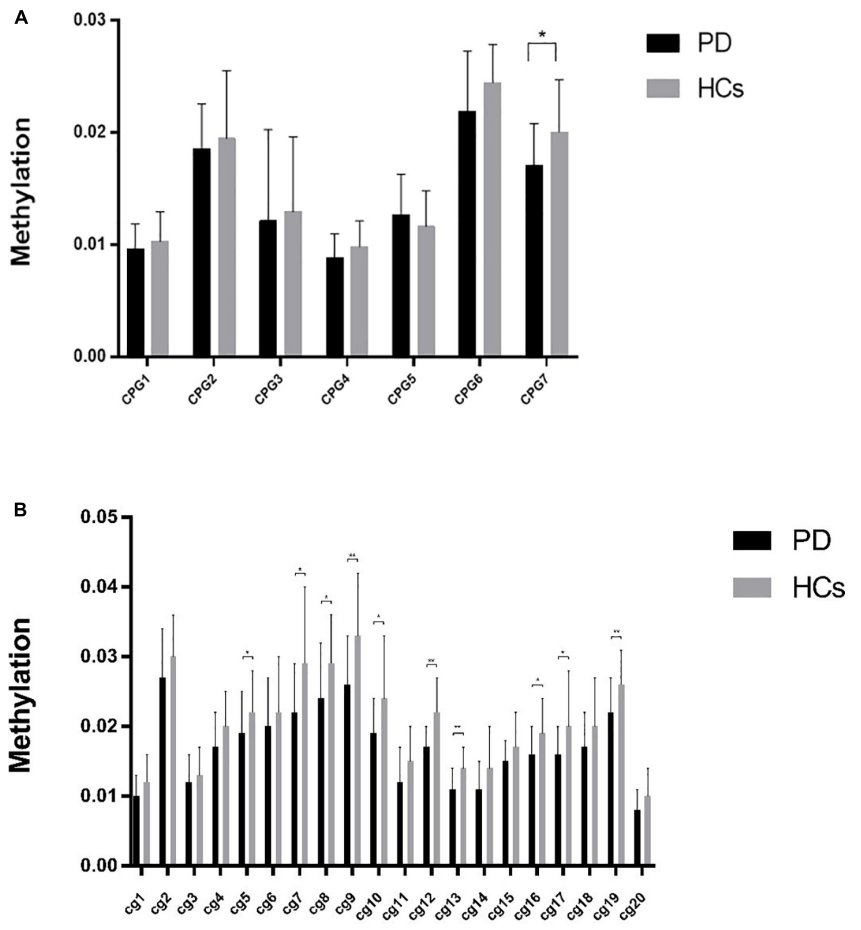


**FIGURE 1 | (A)** The methylation of CPG islands in GAD1 gene in the discovery sample of patients with PD and HCs. **(B)** Lower methylation in PD compared with controls. "*" Significant at $p < 0.05$; "**" significant at $p < 0.01$.

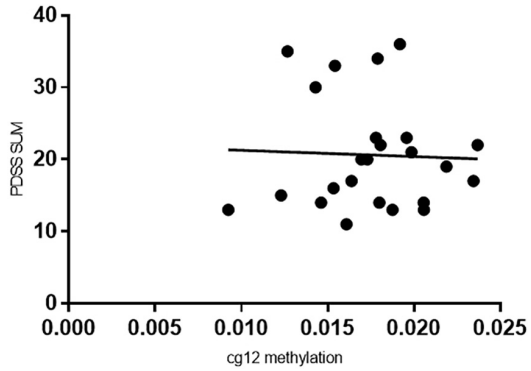


**FIGURE 2 |** Correlation between PDSS and GAD1 cg 12 methylation. Higher PDSSSUM scores were associated with relatively decreased cg171674146 GAD1 CPG7 island methylation ($r$ = –0.456, $p$ = 0.025) in the total sample of 24 patients.

**TABLE 2 |** Gray matter volume (GMV) abnormalities associated with panic disorder (PD).

| Brain areas | Laterality | MINI coordinates | | | Voxels in cluster | *t* |
|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | | |
| SFGmed | L | 0 | 60 | 34.5 | 106 | 8.339 |
| ORBinf | R | 54 | 45 | −10.5 | 95 | 8.170 |
| MTG | L | −70.5 | −45 | −12 | 94 | 7.075 |
| IFGoperc | R | 63 | 18 | 10.5 | 56 | 7.400 |
| THA | R | 18 | −16.5 | 10.5 | 1040 | −9.868 |
| THA | L | −15 | −24 | 6 | 942 | −9.067 |
| PHG | L | −18 | −21 | −19.5 | 163 | −11.300 |
| SMG | L | −60 | −48 | 33 | 154 | −8.252 |
| STG | L | −61.5 | −48 | 21 | 154 | −7.306 |
| SPG | R | 16.5 | −58.5 | 69 | 112 | −8.556 |
| TPOsup | R | 31.5 | 12 | −30 | 77 | −8.851 |

*$p < 0.05$; $k = 50$; $N = 26$ (17 PD, 9 HCs); Clusters surviving whole brain correction are indicated as follows: $p < 0.05$; Clusters are listed in order of descending size; coordinates refer to the voxel with the peak t-value in the cluster. SFGmed, Frontal_Sup_Media; ORBinf, Frontal_Inf_Orb, MTG, Temporal_Mid; IFGoperc, Frontal_Inf_Oper; THA, Thalamus; PHG, ParaHippocampal; SMG, SupraMarginal; STG, Temporal_Sup; SPG, Parietal_Sup; TPOsup, Temporal_Pole_Sup. The largest GMV increases associated with PD were in a left hemisphere cluster encompassing the SFGmed and MTG. Additional differences were detected in right inferior frontal gyrus of orbital region, and right pars opercularis. The reverse contrast (HCs > PD) identified clusters in bilateral THA, and regions of the left PHG, left SMG, STG, SPG, and TPOsup.*

supramarginal gyrus (SMG), STG, superior parietal gyrus (SPG), and superior temporal gyrus of pole (TPOsup).

## Correlation Between Panic Disorder Clinical Severity, Gray Matter Volumes, and DNA Methylation of Glutamic Acid Decarboxylase 1

In order to more accurately detect the effects of GMV on PD severity, we performed a multiple regression analysis and found several correlations (30 or more voxels, $p < 0.05$), as shown in **Table 3** and **Figure 3**. The left precuneus (PCUN), the right middle frontal gyrus (MFG), and the right cuneus (CUN) were

**TABLE 3 |** Correlation between whole-brain GMV and PDSS scores in PD patients.

| Brain areas | Laterality | MINI coordinates | | | Voxels in cluster | *t* |
|---|---|---|---|---|---|---|
| | | *x* | *y* | *z* | | |
| PCUN | Left | −7.5 | −37.5 | 60 | 140 | −3.8653 |
| MOG | Right | 36 | −82.5 | 42 | 51 | 3.4301 |
| MFG | Right | 33 | 25.5 | 34.5 | 131 | −4.5548 |
| PoCG | Left | −51 | −15 | 27 | 245 | 3.8506 |
| CUN | Right | 12 | −84 | 19.5 | 34 | −3.7738 |
| ACG | Left | 0 | 39 | 9 | 38 | 3.4499 |

*$p < 0.05$; $k = 30$; $N = 17$; Clusters surviving whole brain correction are indicated as follows: $p < 0.05$; Clusters are listed in order of descending size; coordinates refer to the voxel with the peak t-value in the cluster. PCUN, Precuneus; MOG, Occipital_Mid; MFG, Frontal_Mid; PoCG, Postcentral; CUN, Cuneus; ACG, Cingulate_Ant. The left PCUN, the right MFG, and the right CUN were negatively correlated with PD severity. In contrast, the right MOG, the left PoCG, the left ACG were positively correlated with PD severity.*

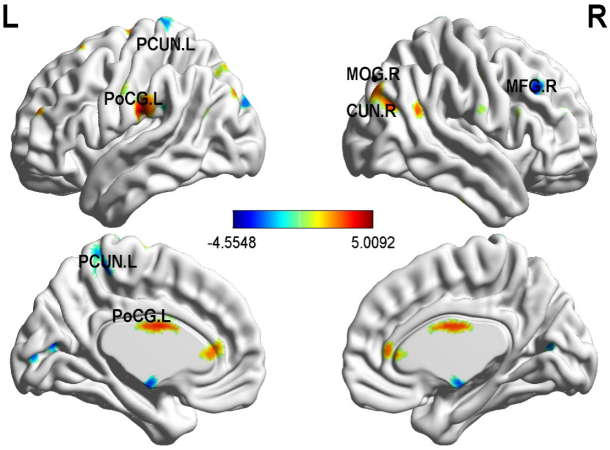


**FIGURE 3 |** Correlation between whole-brain gray matter volume (GMV) and PDSS scores in PD patients. The left PCUN, the right middle frontal gyrus, and the right cuneus were negatively correlated with PD severity. In contrast, the right MOG, the left PoCG, the left ACG were positively correlated with PD severity. $p < 0.01$; $N = 17$.

negatively correlated with PD severity. In contrast, the right middle occipital gyrus (MOG), the left PoCG, the left anterior cingulate and paracingulate gyri (ACG) were positively correlated with panic disorder severity.

As for the correlation of cg 12 site methylation and whole-brain GMV, multiple regression analysis showed a negative correlation with the left PHG, the bilateral MTG, the left ANG, the left PoCG, and so on (**Figure 4** and **Table 4**).

## Gray Matter Volumes as a Mediator of the Relationship Between Glutamic Acid Decarboxylase 1 Methylation and Greater Panic Disorder Severity

Of the regions included in the analysis, GMV of 2 regions (PoCG, ANG) were found to significantly mediate the relationship between cg171674146 (cg12) methylation and PD severity.

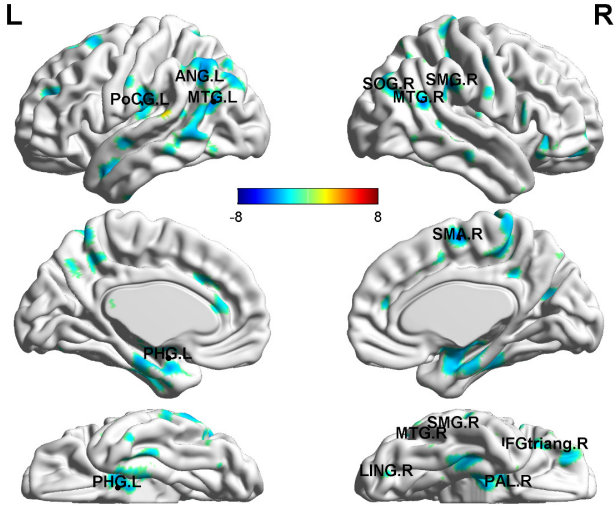


**FIGURE 4 |** Gray matter volume abnormalities associated with cg171674146 methylation. Correlation between whole-brain GMV and cg171674146 methylation in PD patients. The multiple regression analysis showed negative correlations with the left PHG, the bilateral MTG, the left ANG, the left PoCG, and so on. $p < 0.01$; $N = 17$.

**TABLE 4 |** Correlation between whole-brain GMV and cg171674146 methylation in PD patients.

| Brain areas | Laterality | MINI coordinates | | | Voxels in cluster | *t* |
|---|---|---|---|---|---|---|
| | | x | y | z | | |
| PHG | Left | −12 | 0 | −21 | 1178 | −7.341 |
| MTG | Left | −46.5 | −66 | 21 | 391 | −4.7865 |
| SMA | Right | 7.5 | −6 | 60 | 169 | −4.6112 |
| LING | Right | 21 | −81 | −3 | 60 | −4.2328 |
| PAL | Right | 13.5 | 6 | −4.5 | 160 | −3.6446 |
| MTG | Right | 48 | −55.5 | 21 | 355 | −5.1142 |
| ANG | Left | −42 | −57 | 36 | 679 | −4.2585 |
| SMG | Right | 55.5 | −33 | 33 | 126 | −4.2056 |
| IFGtriang | Right | 40.5 | 33 | 1.5 | 68 | −3.7796 |
| PoCG | Left | −57 | −16.5 | 19.5 | 141 | −3.3132 |
| SOG | Right | 22.5 | −75 | 25.5 | 113 | −4.6351 |

*$p < 0.05$; $k = 50$; $N = 17$; Clusters surviving whole brain correction are indicated as follows: $p < 0.05$; Clusters are listed in order of descending size; coordinates refer to the voxel with the peak t-value in the cluster. PHG: Parahippocampal; MTG: Temporal_Mid; SMA: Supp_Motor_Area; LING: Lingual; PAL: Pallidum; ANG: Angular; SMG: SupraMarginal; IFGtriang: Frontal_Inf_Tri; PoCG: Postcentral; SOG: Occipital_Sup. The multiple regression analysis showed negative correlations with the left PHG, the bilateral MTG, the left ANG, the left PoCG, and so on.*

As shown in **Figure 5** and **Table 5**, the cg12 methylation level had a significant predictive effect on the clinical severity of PD patients (β = −0.548, $t = -2.537$, $p < 0.05$), while the direct predictive effect of cg12 gene methylation level on the clinical severity of PD patients was not significant when mediating variables were put in (β = −0.193, $t = -0.779$, $p > 0.05$). cg12 methylation level had a significant negative predictive effect on left PoCG gray matter volumes (β = −0.636, $t = -3.194$, $p < 0.01$), and a significant positive predictive effect of PoCG GMV on clinical severity in PD patients (β = 0.557, $t = 2.240$, $p < 0.05$). In addition, the bootstrap indirect effect was−0.354 (95% CI = −0.873, −0.068), since the CI does not include zero, indicating that the cg12 methylation level was able to predict the clinical severity of PD patients through the mediating effect of left PoCG GMV with a completed mediating effect. The direct effect (−0.194) and mediating effect (−0.354) accounted for 35.34 and 64.66% of the total effect (−0.548).

In the second model (**Figure 6** and **Table 6**), when the mediating variable right ANG gray matter volumes was put into the model, the cg12 methylation level was a significant negative predictor of right ANG gray matter volumes (β = −0.727, $t = -4.105$, $p < 0.001$), and the positive predictor of right ANG GMV on the clinical severity of PD patients was not significant (β = 0.566, $t = 1.960$, $p > 0.05$). In addition, the bootstrapped indirect effect was−0.411 (95% CI = −0.983, −0.114), since the CI does not include zero, indicating that the cg12 methylation level was able to predict the clinical severity of PD patients through the mediating effect of ANG GMV. The direct effect (−0.137) and mediating effect (−0.411) accounted for 24.92% and 75.08% of the total effect (−0.548).

## DISCUSSION

The present study investigated whether GAD1 gene methylation impacted panic disorder severity and whether GMV played a mediating role in this relationship. Results point to a significant yet indirect relationship between GAD1 gene methylation and severity of PD. Importantly, the effects of GAD1 gene methylation on PDSS scores were mediated by gray matter volumes.

The question of whether and how GAD1 gene methylation affects PD has tremendous importance for improving our understanding of the pathogenic mechanism of panic disorder. We found that PD patients had lower gene methylation in ten GAD1 CPG sites compared to HCs. In general, DNA hypomethylation probably promotes gene expression (27). GAD1 gene hypomethylation increases GABA levels, it is possible that GAD1 hypomethylation of PD patients is not the cause of the panic behavior but a compensation for it. In view of the above results, we examined the link between methylation of ten CPG sites and PD severity. Results showed a significant negative association between methylation of cg12/171674146 site of GAD1 with clinical severity. This finding is supported by a recent study suggesting that GAD1 gene hypermethylation may play a compensatory role in panic disorder and may mediate the effect of negative life events on panic disorder (9). These results provide further evidence for the belief that GAD1 gene methylation plays an important role in the occurrence and development of PD.

The differences in GMV in the brains of PD and HCs imply that many structures are involved in the cognitive regulation of anxiety, the fear response, and the generation of threat perception, while also replicating and extending previous findings. Abnormal gray matter volumes in panic disorders has been reported in several studies (28, 29), and their results are consistent with our findings of decreased GMV in the regions

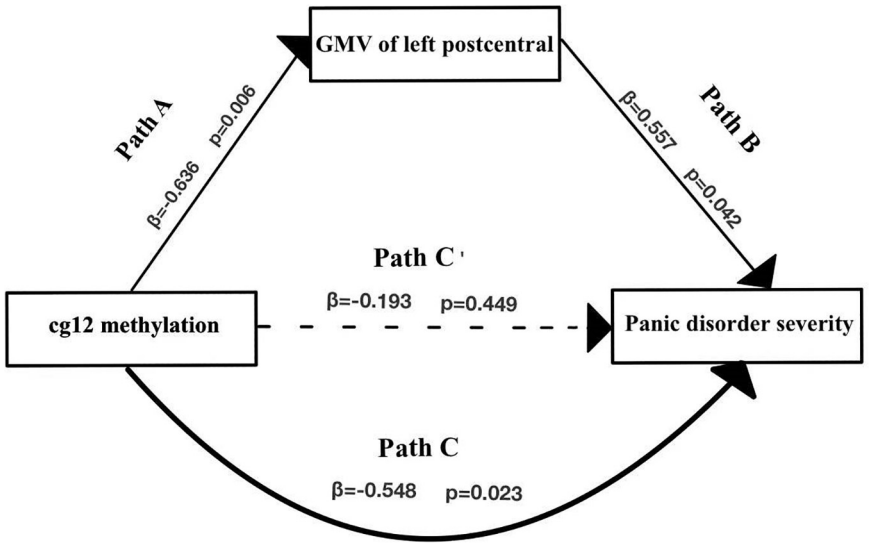


**FIGURE 5 |** Mediation effect model with three variables in the model. Mediation analysis suggested that cg12/171674146 CpG methylation mediated the relationship between GMV in the left PoCG and PD severity. Indirect effect of cg171674146 on PDSSSUM = 95% CI: –0.873 to –0.068. Direct effect of cg171674146 on PDSSSUM (Path C′) = 95% CI: –0.619 to 0.298. Total effect of cg171674146 on PDSSSUM (Path C) = 95% CI: –0.813 to –0.157.

of the left PHG, left SMG, left STG, right SPG, and right TPOsup, and bilateral THA in PD subjects compared to HCs. As we all know, the THA regulates emotional and cognitive functions (30). FNM suggests that changes in the temporal lobe may affect the transmission of sensory information to the THA for further filtering and subsequent "top-down" modulation of the frontal system (11). The THA interacts with temporal, parietal, subcortical limbic structures, and other FNM structures to modulate the noradrenergic system response toward fear (19, 31, 32, 33). Sensory areas of the brain, such as the occipital and temporal lobes, transmit sensory information to the FNM in order for the FNM to recognize and process facial and physical fear signals (34). Thus, the reduction of gray matter volumes in these brain regions affects the processing of fear information and the response to fear in patients with panic disorder. The results of multiple regression analysis also showed a negative correlation between cg12 site methylation with GMV of left PHG, the bilateral MTG, the left ANG, the left PoCG, and so on. Although the relationship between GAD1 gene methylation with gray matter volumes in PD remains unclear, the reduction in GABA receptor binding or reduced GABA activity occurs mainly in the frontal, limbic, temporal, and insula regions (35, 36). Consequently, anticipatory anxiety and panic attacks may be triggered by reduced GABAergic inhibition in different brain areas (37). Therefore, aberrant methylation of cg12 may be an important molecular mechanism underlying the anatomical changes in PD.

The results of the multiple regression analysis showed a significant positive correlation between right GMV of MOG, left PoCG, left anterior cingulate, and paracingulate gyri with panic disorder severity, and a negative correlation between gray matter volumes of left PCUN, the right middle frontal gyrus, and the right cuneus with PD severity. Interestingly, further mediation analysis demonstrated that GMV in the left PoCG totally mediated the association between cg12 methylation and PD severity. The PoCG has been associated with functions of receiving, integrating, and interpreting most of the sensory information in the human body (18). Abnormalities in PoCG could potentially lead to misinterpretation of somatosensory information, resulting in misleading excitatory input to the amygdala and inappropriate activation of the FNM (11). Notably, postcentral abnormalities were also seen when panic disorder was compared with MDD and generalized anxiety, suggesting that brain areas involved in somatosensory processing are more likely to be specific to patients with somatic symptoms, primarily in perceptual processing, rather than the general chronic and excessive feelings of anxiety and worry which is core features of generalized anxiety (38). Indeed, structural alterations in the PoCG may explain the specific symptoms of PD, which include

**TABLE 5 |** Mediation effect model of left postcentral GMV with cg171674146 methylation in PD.

| Outcome variable | Predictor variable | R | $R^2$ | F | β | *t* |
|---|---|---|---|---|---|---|
| PDSS(c) | Cg12(a) | 0.696 | 0.485 | 6.590 | −0.193 | −0.779 |
| | Postcentral GMV(b1) | | | | 0.557 | 2.240* |
| c | a | −0.548 | 0.300 | 6.438 | −0.548 | −2.537* |
| b1 | a | 0.636 | 0.405 | 10.201 | −0.636 | −3.194** |

*Cg12 methylation was negatively associated with left postcentral GMV (β = −0.636, t = −3.194, p = 0.006), and left postcentral GMV was positively associated with PD severity (β = 0.557, t = 2.240, p = 0.042). The standardized indirect effect was (-0.636)*0.557 = −0.354. The standardized direct effect was −0.193 after controlling for mediation, and the standardized total effect was −0.548. *p < 0.05, **p < 0.01, ***p < 0.001.*

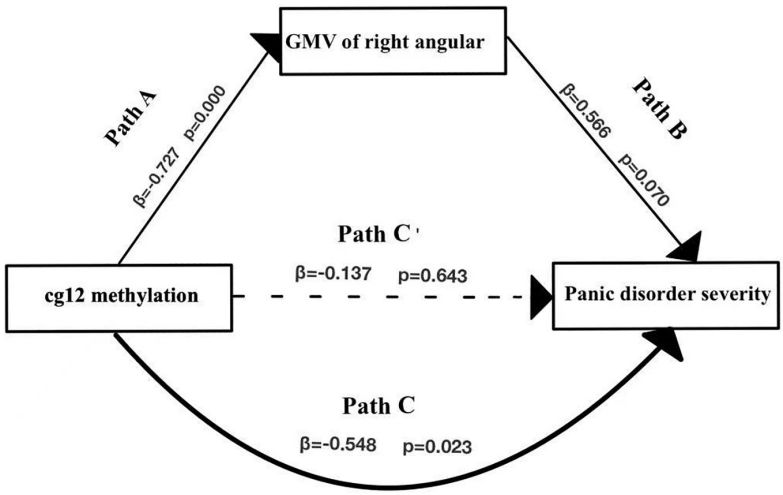


**FIGURE 6 |** Mediation effect model with three variables. Mediation analysis suggested that cg12/171674146 CpG methylation mediated the relationship between GMV in the right ANG and PD severity. Indirect effect of cg171674146 on PDSSSUM = 95% CI: –0.983 to –0.114. Direct effect of cg171674146 on PDSSSUM (Path C′) = 95% CI: –0.652 to 0.626. Total effect of cg171674146 on PDSSSUM (Path C) = 95% CI: –0.813 to –0.157.

abnormal perception of body signals and extreme sensation of the heartbeat. Thus, we suggest that a reduction in the volume of PoCG gray matter leads to more severe alterations in PD and this process is associated with cg12 methylation.

Path analysis showed that GMV of the ANG mediated the relationship between cg12 methylation and PD severity. The ANG plays an important role in affective regulation, empathic response, anxiety, and mood and is associated with meditation and calmness (19). In patients with panic disorder, abnormal gray matter volumes of ANG (part of parietal lobe) have been reported. For example, one study on voxel-based morphometry found reduced gray matter volumes in the parietal and temporal lobes of patients with PD (14, 15). These results provide further evidence for the idea that GMV in the right ANG potentially mediated the association between GAD1 gene methylation and PD severity.

The present study has the following limitations. First, epigenetic studies using peripheral blood do not allow for direct conclusions about the respective methylation patterns in brain tissue. Second, the study is cross-sectional and the direction of the relationship between brain structure and diseased state is uncertain. Third, the relatively small size might affect the significance of our results.

**TABLE 6 |** Mediation effect model of right angular GMV with cg171674146 methylation in PD.

| Outcome variable | Predictor variable | R | $R^2$ | F | β | *t* |
|---|---|---|---|---|---|---|
| PDSS(c) | Cg12(a) | 0.672 | 0.451 | 5.750 | −0.137 | −0.473 |
| | Angular GMV(b2) | | | | 0.566 | 1.960 |
| c | a | 0.548 | 0.300 | 6.438 | −0.548 | −2.537* |
| b2 | a | 0.727 | 0.529 | 16.853 | −0.727 | −4.105*** |

*Right angular GMV was negatively associated with cg12 methylation (β = −0.727, t = −4.105, p = 0.000). The standardized indirect effect was (−0.727)*0.566 = −0.411. The standardized direct effect was −0.137 after controlling for mediation, and the standardized total effect was −0.548. *p < 0.05, **p < 0.01, ***p < 0.001.*

## CONCLUSION

In conclusion, the results of this study confirmed a significant negative relationship between cg12 methylation and PD severity. Further, we revealed that gray matter volumes of PoCG and ANG mediated this relationship, which has not been found in previous PD research. Our findings suggest that cg12 site methylation of GAD1 may affect the development of PoCG and ANG GMV and further participate in the pathophysiology of panic disorder. Future PD research should combine epigenetics with neuroimaging, which is conducive to a more comprehensive understanding of the pathogenesis of panic disorder from the epigenetic level to the neural network level.

## DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: NCBI, PRJNA793355.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institute of Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University. The

patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

CW and NL designed the study and supervised the conduct of the study. GL and HD contributed to the data collection. HX, YW, SY, and YZ provided the methodological advice. HW and HX performed the data analysis and results interpretation. HW and CW drafted the manuscript, which all authors reviewed and approved for publication. 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.2022.853613/full#supplementary-material

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# Identifying the Subtypes of Major Depressive Disorder Based on Somatic Symptoms: A Longitudinal Study Using Latent Profile Analysis

*Xiaohui Wu[1], Yuncheng Zhu[1], Zhiguo Wu[1], Jia Huang[1], Lan Cao[1], Yun Wang[1], Yousong Su[1], Hongmei Liu[1], Maosheng Fang[2], Zhijian Yao[3], Zuowei Wang[4], Fan Wang[1], Yong Wang[1], Daihui Peng[1], Jun Chen[1]* and Yiru Fang[1,5,6]**

[1] Clinical Research Center and Division of Mood Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2] Wuhan Mental Health Centre, Wuhan, China, [3] Nanjing Medical University Affiliated Brain Hospital, Nanjing, China, [4] Department of Psychiatry, Hongkou District Mental Health Center of Shanghai, Shanghai, China, [5] CAS Center for Excellence in Brain Science and Intelligence Technology, Shanghai, China, [6] Shanghai Key Laboratory of Psychotic Disorders, Shanghai, China

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Marco Grados,
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**Reviewed by:**
Xingguang Luo,
Yale University, United States
Chutima Roomruangwong,
Chulalongkorn University, Thailand

***Correspondence:**
Jun Chen
doctorcj2010@gmail.com
Yiru Fang
yirufang@aliyun.com

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**Background:** Two-thirds of major depressive disorder (MDD) patients initially present with somatic symptoms, yet no study has used approaches based on somatic symptoms to subtype MDD. This study aimed to classify MDD *via* somatic symptoms and tracked the prognosis of each subtype.

**Methods:** Data were obtained from the study of Algorithm Guided Treatment Strategies for Major Depressive Disorder (AGTs-MDD). We recruited 395 subjects who received monotherapy of mirtazapine or escitalopram and conducted 2-, 4-, 6-, 8-, and 12-week follow-up assessments ($n = 311$, 278, 251, 199, and 178, respectively). Latent profile analysis (LPA) was performed on somatic symptom items of the depression and somatic symptoms scale (DSSS). Generalized linear mixed models (GLMM) were used to study the longitudinal prognosis of the subtypes classed by LPA. Primary outcome measures were the Hamilton Depression Rating Scale (HAMD), HAMD score reduction rate, as well as somatic and depressive items of DSSS.

**Results:** Three subtypes of MDD were found, namely, depression with mild somatic symptoms (68.9%), depression with moderate somatic symptoms (19.2%), and depression with severe somatic symptoms (11.9%). Scores of HAMD ($F = 3.175$, $p = 0.001$), somatic ($F = 23.594$, $p < 0.001$), and depressive ($F = 4.163$, $p < 0.001$) DSSS items throughout the 12-week follow-up showed statistical difference among the three subtypes. The moderate group displayed a higher HAMD-17 score and a lower reduction rate at the 6th week, and more severe depressive symptoms both at the 4th and 6th weeks.

**Conclusion:** The results indicate that somatic symptoms should be emphasized in patients with MDD, and more attention is needed for those with moderate somatic symptoms, which may be relevant to a worse prognosis.

**Keywords: major depression disorder, somatic symptom, latent profile analysis, subtype, GLMM**

## INTRODUCTION

For all ages and both sexes combined, the prevalence of major depressive disorder (MDD) was approximately 2.21% globally in 2017 (1). A nationwide cross-sectional epidemiological survey across China showed that the lifetime prevalence of MDD is around 3.36% (2). A multicenter international study reported that two-thirds of MDD patients initially present with somatic symptoms (3). Moreover, patients with somatic symptoms tended to co-exist with both depressive and anxiety disorders. It has been reported that depressed patients are 4.43 times more likely to have somatoform disorders than non-depressed ones (4). Indeed, Chinese respondents were more likely to complain about somatic symptoms rather than psychological symptoms in comparison with patients in western countries. Due to the influence of culture, over 50% of Chinese MDD patients with somatic symptoms first seek for medical consultation (5, 6). Previous evidence proved the strong associations between depression and somatic symptoms; however, most research has focused only on depression (7).

Somatic symptoms of MDD can be grouped into (1) vegetative symptoms, including sleep disturbance, changes in appetite, and lack of energy; (2) painful symptoms, including headache, backache, gastrointestinal disturbances, and musculoskeletal aches; and (3) non-painful symptoms, including dizziness, palpitations, dyspnea, and shortness of breath (8, 9). Neurovegetative symptoms are included in the most core symptoms of depression (10). Complaints of multiple pain in patients with MDD were reported to be positively related to severe emotional symptoms (11). Besides, the symptom of pain may worsen the treatment response of depression, and this residual symptom could largely increase the disease burden (12). Previous studies have demonstrated that somatic symptoms were predictors for greater severity, worse prognosis, and poorer treatment response, as well as the chronicity and delayed remission of MDD. It has been reported that the cardiopulmonary, gastrointestinal, and general symptomatic cluster could predict the 2-year persistence of MDD. The presence of multiple somatic symptoms was a significant predictor (OR = 1.69, 95%CI = 1.07–2.68, $p = 0.03$) (13–15). Even after appropriate treatment, somatic symptoms may remain as residual symptoms, hindering the remission and increasing the risk of relapse (16).

In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), MDD is classified into 13 subtypes by clinical features. However, MDD is a heterogeneous syndrome, with which patients differ remarkably in symptoms, treatment responses, and pathophysiological mechanisms. In clinical practice, patients with MDD often show opposite profiles of symptoms, such as increase or decrease in appetite, hyposomnia, or hypersomnia. Therefore, DSM-5 diagnostic classifications may not be specific enough to generalize sophisticated phenotypes of MDD. Over the decades, researchers have been trying to categorize depression into different subgroups. In general, previous studies have already tried to classify depression based on clinical symptoms, medication responses, neuroimaging, genetics, and neurotransmitter distributions (17–20). To the best of our knowledge, somatic symptoms have been neglected or haven't been mainly considered when subdividing MDD.

In clinical practice, diagnosis of MDD mainly depends on emotional symptoms rather than somatic symptoms, which may be influenced by different expressions of depressive symptoms, especially in China, where people tend to express their somatic symptoms rather than emotional problems (9). The Depression and Somatic Symptoms Scale (DSSS) is a reliable questionnaire, which can assess and monitor the severity of both depressive and somatic symptoms. DSSS is composed of two major subscales, namely, the depressive subscale (DS), including 12 items, and the somatic subscale (SS), including 10 items (21). The DS, SS, and Hamilton Depression Rating Scale (HAMD) scores at baseline were reported to be significantly associated with the long-term outcome of depression. Besides, the scales or subscales for assessing somatic symptoms might be more strongly associated with the outcome of depression (22). The total score of DSSS ranges from 0 to 66, in which DS ranges from 0 to 36 and SS ranges from 0 to 30. The items of SS are designed to reflect the common somatic symptoms of MDD, which can reflect the severity of depression and have a significant impact on the prognosis of patients (23). Therefore, in this study, we selected DSSS as the major scale to acquire patients' information on somatic symptoms.

On account of the importance of somatic symptoms in the mechanism and prognosis of MDD, as well as the reconsideration of existing nosology, we aimed to classify MDD based on the somatic symptoms only. We hypothesized that there could be different trends of somatic symptoms in patients with MDD, and these subtypes would show differences in emotional or other symptoms, as well as treatment responses.

## METHODS

### Participants and Procedure

The Algorithm Guided Treatment Strategies for Major Depressive Disorder (AGTs-MDD) study (ClinicalTrials.gov NCT01764867) was a multisite naturalistic cohort, which aimed to compare treatment outcomes between strategies of AGT and Treatment as Usual (TAU) for MDD patients. In brief, the AGTs-MDD cohort screened 1,746 subjects from 8 mental health institutes during 2012 to 2014, in which 964 subjects were diagnosed with MDD according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision* (DSM-IV-TR). Finally, 845 subjects of Han Chinese were recruited, and they were randomized into AGT (escitalopram or mirtazapine) or TAU group. All procedures complied with the ethical standards of the relevant national and institutional committees on human experimentation and the Helsinki Declaration of 1975, as revised in 2008. The research was approved by the Institutional Review Board of Shanghai Mental Health Center, and all respondents provided written informed consent.

For this study, those with scores of HAMD-17 below 14 or lack of major baseline data were excluded. Besides, we only included subjects that received monotherapy of mirtazapine

**TABLE 1 |** Description of symptoms in the questionnaire of DSSS.

| Item | Somatic subscale | Item | Depression subscale |
|---|---|---|---|
| 01 | Headache | 02 | Loss of interest in daily or leisure activities |
| 03 | Tightness in the chest | 04 | Insomnia |
| 05 | Muscle tension | 06 | Irritable mood |
| 07 | Back pain | 08 | Unable to feel happy or decreased ability to fell happy |
| 09 | Dizziness | 10 | Depressed mood or tearful |
| 11 | Chest pain | 12 | Feeling of self-reproach or guilt |
| 13 | Neck or shoulder pain | 14 | Loss of interest in sex |
| 15 | Shortness of breath or difficulty breathing | 16 | Anxious or nervous |
| 17 | Soreness in more than half of the body's muscles | 18 | Unable to concentrate |
| 19 | Palpitations or increased heart rate | 20 | Thoughts of death or suicidal ideas |
| | | 21 | Fatigue or loss of energy |
| | | 22 | Decreased appetite or loss of appetite |

or escitalopram. Different antidepressants may have different effects on somatic symptoms. For example, escitalopram, as a selective serotonin reuptake inhibitor (SSRI), may cause somatic side effects, such as headache, lower heart rate, and some gastrointestinal symptoms (24). Mirtazapine, as a norepinephrine–serotonin modulator, may cause somatic side effects like some gastrointestinal symptoms and sympathetic activation-related symptoms (25). In this study, the classification of MDD by somatic symptoms was constructed at the baseline, where patients had not accepted any medication. Therefore, the effects on the classification from medications could be neglected. Finally, 395 MDD patients with complete baseline information were selected, in which 311 patients finished a 2-week follow-up, 278 patients finished a 4-week follow-up, 251 patients finished a 6-week follow-up, 199 patients finished an 8-week follow-up, and 178 patients completed a 12-week follow-up.

## Measurements

All patients were assessed using the Depression and Somatic Symptoms Scale (DSSS), the 17-item Hamilton Depression Rating Scale (HAMD-17), the Hamilton Anxiety Rating Scale (HAM-A), the Quality of Life (QOL) Scale, the Global Assessment Function (GAF) Scale, and the International Neuropsychiatric Interview (M.I.N.I.) at baseline. The assessment of DSSS and HAMD-17 scales was completed at every follow-up point. DSSS consists of two subscales, namely, the depression subscale and the somatic subscale (**Table 1**). Besides, the risk level of suicide was assessed by the total score of M.I.N.I. item C (SUICIDALITY). The total score of HAMD-17 and its reductive rate of score were used to evaluate the treatment responses of subjects.

## Statistical Analysis

Latent profile analysis (LPA) was carried out *via* Mplus 8.3 to explore somatic symptoms-related subtypes of MDD. In the process of LPA, 10 items in the somatic subscale of DSSS were designed as the original items. We fitted one to five latent class models to determine the optimal number of latent classes. A total of six model fit indexes were used to help evaluate the optimal model of LPA: Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), sample-size adjusted Bayesian Information Criterion (SSABIC), Lo-Mendell-Rubin (LMR), Bootstrapped Likelihood Ratio Test (BLRT), and Entropy. The AIC, BIC, and SSABIC are the information criterion indices used to compare different counterpart models. A lower value indicates a better fitting model. LMR and BLRT are two likelihood ratios used to make a comparison of model fit improvement between models with κ classes and κ-1 classes. A lower and significant *p*-value indicates that the model is superior to the one less class model. Simulation studies have shown that BIC and BLRT are the best indices. Entropy evaluates how well each class could result from LPA. Value exceeding 0.8 is preferred, and approaching 1.0 demonstrates a much better result (26, 27).

Kruskal-Wallis and chi-square ($\chi^2$) tests were applied for comparing descriptive variables at baseline, including age, sex, body mass index (BMI), medication, depressive subscale items of DSSS, and scores of HAMD-17 and HAM-A, GAF, and QOL scores. The *post-hoc* test, adjusted by the Bonferroni method, was used to conduct a pairwise analysis. Generalized linear mixed models (GLMMs) were adopted to analyze the treatment outcomes of subjects in different subtypes during the 12-week longitudinal follow-ups, and pairwise contrast was performed by the Bonferroni method. The score and reduction rate of HAMD-17 were compared across different LPA subtypes at each follow-up, as well as the scores of depressive and somatic subscales of DSSS. All the statistical analyses were tested bilaterally, with the original significance value set to 0.05.

**TABLE 2 |** Fit indices of latent profile models of DSSS somatic symptom clusters.

| Model | FP | AIC | BIC | SSABIC | LMRA (*p*) | BLRT (*p*) | Entropy |
|---|---|---|---|---|---|---|---|
| 1 | 20 | 10,397.106 | 10,476.684 | 10,413.224 | | | |
| 2 | 31 | 9,532.997 | 9,656.342 | 9,557.979 | 0.001 | <0.001 | 0.907 |
| 3 | 42 | 9,146.262 | 9,313.375 | 9180,.109 | 0.183 | <0.001 | 1.000 |
| 4 | 53 | 9,175.764 | 9,386.645 | 9,218.476 | 0.526 | <0.001 | 0.883 |
| 5 | 64 | 9,125.107 | 9,379.756 | 9,176.683 | 0.513 | >0.05 | 0.883 |

*FP, Free parameters; AIC, Akaike's information criterion; BIC, Bayesian information criterion; SSABIC, sample size-adjusted BIC; BLRT, bootstrapped likelihood ratio test; LMRA, Lo-Mendell-Rubin-adjusted likelihood ratio test.*

# RESULTS

## Identification and Description of the Best-Fitting Latent Class

The results of five models (one-class model to five-class model) are presented in **Table 2**. The 1-class model had the largest AIC, BIC, and ABIC, suggesting the worst model. The 5-class model had the lowest AIC and SSABIC, while with the


**FIGURE 1 |** Profiles of latent profile analysis of major depressive disorder by somatic symptoms.

smallest entropy value. In the 4-class model, BIC, SSABIC, and entropy were smaller than those of the 3-class model, whereas the *P*-value of LMRA was the largest. In view of the LMRA, the 2-class model showed statistical significance; however, the AIC, BIC, and SSABIC were smaller than those of the 3-class model. As shown in **Table 2**, the 3-class model showed excellent entropy. Therefore, the 3-class model solution pattern yielded optional model values. Ultimately, we decided that the 3-class pattern of the somatic subscale of DSSS was the best-fitting model based on the results from all the six model fit indicators. The correct class assignment probabilities for the 3-class model were excellent, suggesting a good discriminability and a reliable result of LPA with the 3-class model.

**Figure 1** illustrates the profiles of subtypes of somatic symptoms for the 3-class model, in which the Y-axis shows the score of each item, and the X-axis represents different DSSS somatic items that are used for LPA. Participants from class-1 ($n$ = 272, 68.9%) were characterized by the lowest scores of somatic items of DSSS, with each item getting the lowest score, especially the symptom of muscle soreness (mean = 0.000). Thus, the 1-class model was labeled as the Mild Group of somatic symptoms. The 2-class model ($n$ = 76, 19.2%) showed a similar pattern, with more neck or shoulder pain. Symptoms of muscle tension, dizziness, and body's muscle soreness in 2-class model were moderate between the 1-class model and 3-class model. Given the characteristics of 2-class model, we used the Moderate Group of somatic symptoms to represent it. Participants in the 3-class model ($n$ = 47, 11.9%) showed statistically significantly higher somatic symptoms compared with other subtypes, muscle soreness of which was particularly severe (mean = 2.255). Therefore, we named 3-class model as the Severe Group of somatic symptoms.

## Comparison of Clinical Characters of the 3-Class Subtypes at Baseline

As shown in **Table 3**, age, sex, and BMI of the three groups displayed no statistically significant difference. Besides, the three subgroups showed no difference in medication allocation. We compared the depressive items of DSSS across the three subtypes of MDD, with all items $p$-values $< 0.01$. The 2-class and 3-class models showed higher scores in the symptoms of irritable mood, loss of interest in sex, anxiety or nervousness, unable to concentrate, fatigue or loss of energy, and decreased appetite or loss of appetite. The Severe Group had more problems in losing interest in daily or leisure activities than the other groups. Besides, compared with the Mild Group, the Severe Group showed higher scores in insomnia, unable to feel happy or decreased ability to feel happy, and feeling of self-reproach or guilt. The Moderate Group got the highest score of depressed mood or tearfulness, which was statistically significantly higher than the Mild Group. The total depressive subscale score of the Moderate and Severe Groups was higher than that of the Mild Group. The 3-class subtypes exhibited no differences in the level of sleep problems, suicide risk levels, and GAF ($p > 0.05$). The HAMD-17 scores ascended from 1-class model to 3-class model, and the 1-class model showed the lowest score of HAM-A, which also had better life qualities.

## The Longitudinal Comparison of Treatment Outcome Measures Across Subtypes of MDD

There were dropout rates of 21.3, 29.6, 36.5, 49.6, and 54.9%, respectively, at the 2nd, 4, 6, 8, and 12th weeks. The proportion of patients treated with Escitalopram and Mirtazapine exhibited no difference among the three subgroups both at baseline and at each follow-up point ($p > 0.05$). Scores of HAMD-17 ($F = 0.2047$,

**TABLE 3 |** Comparison of demographic and clinical characteristics across the three subtypes.

| Variable | Class 1 mild $n = 272$ | Class 2 moderate $n = 76$ | Class 3 severe $n = 47$ | $\chi^2$ or $Z$ | $p$ |
|---|---|---|---|---|---|
| Age | 40.26 (14.23) | 38.64 (15.31) | 36.68 (12.85) | 2.753 | 0.252 |
| Sex | | | | 0.489 | 0.783 |
| Male | 90 (33.1%) | 26 (34.2%) | 18 (38.3%) | | |
| Female | 182 (66.9%) | 50 (65.8%) | 29 (61.7%) | | |
| BMI | 21.66 (3.36) | 21.02 (2.78) | 21.69 (3.53) | 0.943 | 0.624 |
| Medication | | | | 0.131 | 0.937 |
| Escitalopram | 165(61.0%) | 46 (61.1%) | 27 (58.1%) | | |
| Mirtazapine | 107 (39.0%) | 30 (38.9%) | 20 (41.9%) | | |
| DSSS | | | | | |
| 02 | 1.99 (0.81)[a] | 1.93 (0.81)[a] | 2.36 (0.74)[b] | 9.824 | 0.007 |
| 04 | 1.74 (1.02)[a] | 2.04 (0.96)[a,b] | 2.23 (0.81)[b] | 12.619 | 0.002 |
| 06 | 1.13 (0.98)[a] | 1.66 (0.96)[b] | 1.81 (1.17)[b] | 26.272 | <0.001 |
| 08 | 2.01 (0.77)[a] | 2.14 (0.86)[a,b] | 2.43 (0.74)[b] | 14.276 | 0.001 |
| 10 | 1.95 (0.79)[a] | 2.17 (0.93)[b] | 2.15 (0.93) | 8.832 | 0.012 |
| 12 | 1.17 (0.92)[a] | 1.41 (1.00)[a,b] | 1.62 (0.95)[b] | 10.737 | 0.005 |
| 14 | 0.75 (0.94)[a] | 1.26 (0.96)[b] | 1.74 (1.09)[b] | 45.177 | <0.001 |
| 16 | 1.62 (0.86)[a] | 2.03 (0.82)[b] | 2.17 (0.99)[b] | 25.463 | <0.001 |
| 18 | 1.45 (0.85)[a] | 1.83 (0.93)[b] | 2.09 (0.97)[b] | 27.046 | <0.001 |
| 20 | 0.86 (0.92)[a] | 1.20 (0.91)[b] | 1.43 (0.97)[b] | 20.386 | <0.001 |
| 21 | 1.78 (0.78)[a] | 2.08 (0.81)[b] | 2.30 (0.66)[b] | 23.08 | <0.001 |
| 22 | 0.97 (0.90)[a] | 1.42 (0.91)[b] | 1.51 (0.98)[b] | 23.236 | <0.001 |
| Depressive | 17.42 (5.36)[a] | 21.17 (5.75)[b] | 23.83 (5.75)[b] | 57.126 | <0.001 |
| Somatic | 5.21 (3.94)[a] | 11.11 (3.84)[b] | 16.57 (5.83)[c] | 173.481 | <0.001 |
| HAMD-17 | 20.44 (4.32)[a] | 22.56 (5.59)[b] | 24.43 (4.11)[c] | 32.819 | <0.001 |
| HAM-A | 16.39 (6.39)[a] | 21.99 (6.61)[b] | 24.45 (5.92)[b] | 78.051 | <0.001 |
| GAF | 55.89 (9.74) | 55.60 (6.56) | 51.11 (11.56) | 8.314 | 0.160 |
| QOL | 15.48 (2.89)[a] | 14.64 (2.77)[b] | 13.87 (3.23)[b] | 12.949 | 0.002 |

*Classes with different alphabets at the top right corner show statistically significant differences in assessment, $p < 0.05$.*

$p = 0.026$), somatic ($F = 23.594$, $p < 0.001$), and depressive ($F = 4.163$, $p < 0.001$) items of DSSS among the three groups were statistically different during the follow-up period, while the reduction rate of HAMD-17 score for the three subtypes showed no difference throughout 12 weeks ($F = 1.303$, $p = 0.238$). At the 6th follow-up point, MDD patients with moderate somatic symptoms at baseline (Class 2) had higher scores of HAMD-17 and a lower reduction rate of HAMD-17 than the other two groups (**Table 4**). Somatic symptoms of the three groups were statistically different until the 12th week, while their depressive symptoms showed similar levels since the 8th week. Besides, from the 4 to 6th weeks, DS scores of the 2-class model were higher than that of the 1-class model and 3-class model (**Table 4**).

## DISCUSSION

The LPA found three subtypes of MDD, namely, depression with mild somatic symptoms, depression with moderate somatic symptoms, and depression with severe somatic symptoms. The 3-class model showed excellent membership classification with an entropy score of 1.000. This finding indicated that the severity of somatic symptoms might be a basis for MDD classification. Comparisons among the three groups showed that MDD patients with severer somatic symptoms had more problems with depressive symptoms and anxiety. Notably, cohort comparison among the three subtypes found that it was the Moderate Group rather than the Severe Group that had the worst remission. The Moderate Group displayed a higher HAMD-17 score at the 6th week and severer depressive symptoms both at the 4 and 6th weeks follow-up points.

Due to the population heterogeneity of MDD, researchers have been motivated to identify homogeneous clinically useful subtypes of MDD for purchasing a better prognosis and understanding of this disease. Although biological parameters seem to be more objective and have less bias, symptoms are what psychiatrists directly assess in clinical practice. Early symptom-based subtyping studies have labeled and validated the "melancholic" and the "non-melancholic" subtypes of MDD (28, 29). Later on, researchers found three stable subtypes of MDD, including the moderate subtype and the severe subtype with hypersomnia, increased appetite, and weight, and the severe subtype with diurnal variation, insomnia, early morning awakening, and decreased appetite and weight (30, 31). A recent study used both depressive and anxiety symptomatic items to

**TABLE 4 |** Longitudinal assessments among the three subtypes by GLMM.

| Week | Assessment | Class 1 | Class 2 | Class 3 | *F* | *p* |
|---|---|---|---|---|---|---|
| 2 | HAMD-17 | 13.52(6.09) | 15.08(4.66) | 13.89(6.17) | 1.622 | 0.198 |
| $n = 311$ | Reduction rate | 0.34(0.26) | 0.31(0.25) | 0.40(0.28) | 1.502 | 0.223 |
| | SS | 3.83(3.97)[a] | 7.08(4.97)[b] | 7.56(5.49)[b] | 27.660 | **<0.001** |
| | DS | 11.77(5.54)[a] | 14.00(5.80)[b] | 14.00(5.86)[b] | 7.177 | **0.001** |
| 4 | HAMD-17 | 9.96(5.40) | 12.00(4.87) | 10.35(6.00) | 2.937 | 0.053 |
| $n = 278$ | Reduction rate | 0.50(0.26) | 0.45(0.25) | 0.55(0.27) | 2.264 | 0.104 |
| | SS | 2.57(2.89)[a] | 5.09(4.71)[b] | 5.79(5.44)[b] | 16.870 | **<0.001** |
| | DS | 8.68(5.13)[a] | 11.43(5.79)[b] | 10.18(5.49)[a,b] | 6.074 | **0.002** |
| 6 | HAMD-17 | 8.20(5.32)[a] | 11.29(5.62)[b] | 8.45(6.52)[a] | 5.973 | **0.003** |
| $n = 251$ | Reduction rate | 0.59(0.27)[a] | 0.47(0.28)[b] | 0.63(0.30)[a] | 4.576 | **0.010** |
| | SS | 2.13(2.93)[a] | 4.63(4.68)[b] | 4.87(5.90)[b] | 12.634 | **<0.001** |
| | DS | 7.44(5.13)[a] | 9.56(6.10)[b] | 8.27(5.88)[a,b] | 3.018 | **0.049** |
| 8 | HAMD-17 | 5.62(4.21) | 7.29(4.96) | 7.71(5.58) | 2.650 | 0.071 |
| $n = 199$ | Reduction rate | 0.71(0.22) | 0.67(0.22) | 0.67(0.25) | 0.691 | 0.501 |
| | SS | 1.41(2.34)[a] | 2.69(3.22)[b] | 3.88(4.47)[b] | 5.709 | **0.003** |
| | DS | 5.33(4.34) | 5.89(5.06) | 7.42(5.45) | 1.269 | 0.282 |
| 12 | HAMD-17 | 4.76(4.32) | 6.97(5.42) | 5.45(4.87) | 2.954 | 0.052 |
| $n = 178$ | Reduction rate | 0.75(0.24) | 0.67(0.27) | 0.78(0.21) | 2.669 | 0.070 |
| | SS | 1.11(1.69) | 2.38(2.85) | 2.76(3.40) | 2.955 | 0.052 |
| | DS | 3.97(3.87) | 5.56(5.12) | 5.75(4.59) | 1.422 | 0.241 |

*Bold values indicate $p < 0.05$. SS, somatic subscale of DSSS; DS, depressive subscale of DSSS. Classes with different alphabets at the top right corner show statistically significant differences in assessment, $p < 0.05$.*

cluster MDD (32). Besides, some studies have tried to combine clinical questionnaire scores and biological parameters, such as plasma indexes and gene expressions, to cluster MDD subjects at a high dimension (33, 34). Unlike previous studies, this study focused only on the somatic symptoms of MDD subtyping, which displayed a new aspect for understanding MDD.

This study provided evidence of the comorbidity of somatic and depressive symptoms in patients with MDD. Those with more severe somatic symptoms also had more serious problems with depressive symptoms. The presence of major depressive episode has been proved to be strongly correlated with the loss of interest (35), which is also a distinguishing feature for the subgroup with severe somatic symptoms. The Severe Group had more complaints of insomnia than the Mild Group, while previous research reported that in both adolescents and adults, subjects with insomnia scored higher on somatic symptom measurements than non-insomnia ones (36). Guidi et al. found two clusters of MDD, including depressed somatizers and irritable/anxious depression (37). This study further proved that patients with milder somatic symptoms also suffered less from irritable mood. Previously, a study demonstrated that somatic symptoms of depression had an influence on the ability of being happy (38), which was reconfirmed in this study that the Severe Group exhibited more problems in feeling happy. What surprised us is that it was the Moderate Group rather than the Severe Group that showed heavier depressed mood, which suggested that the more severe somatic symptoms might cover the symptoms of emotion to some degree. Subjects in the Severe Group were found to be more likely to feel guilt or self-reproach. It has been reported that guilt may function as a mediator between childhood trauma and adult somatic symptoms (39), suggesting that patients with more severe somatic distress might have experienced something unusual in their childhood, which should not be neglected by psychiatrists in clinical practice. We found that the interest in sex also differed among the three groups. However, a previous report declared that the severity of sexual dysfunction was uncorrelated with the somatic dimension (40). The reason might be that the loss of interest in sex is more related to the lack of pleasure but not sexual functions. The three groups were found to have ascending levels of anxiety, which was consistent with previous studies (41). The Moderate and Severe groups showed heavier concentration problems; however, there existed an argument on whether to divide concentration into the cognitive or somatic cluster (42). A recent study reported that heavier burdens of somatic symptoms were associated with the risk of suicide (43), which has been further proved in this study. As indicated by previous studies (44), subjects with different degrees of somatic symptoms also differ in the symptom of energy and appetite loss.

The outcomes of the three subtypes were compared in a clinical trial. The STAR*D Study reported that patients with somatic depression exhibited low remission rates in response to citalopram (45). Mirtazapine was reported to be an effective and safe antidepressant for depressive patients with somatic symptoms (46). Although mirtazapine shows stronger effects for somatic symptoms, in this study, medication allocation of the three subgroups displayed no statistical difference both at baseline and at each follow-up point. Therefore, the impact

of drugs on curative effects among groups could be excluded. After the 6-week medication, the group with moderate somatic symptoms exhibited the highest score of HAMD-17, as well as the lowest reductive rate. A previous study reported that patients with no/mild somatic symptoms (84.1%) achieved the highest proportion of remission than those with moderate or severe somatic symptoms (72.0 and 55.3%) (47). In this study, we found that patients with moderate somatic symptoms actually had the worst remission and severe depressive symptoms. It provides a warning for psychiatrists that more attention is needed for MDD patients with moderate somatic symptoms (somatic subscale of DSSS scores from 11.11 to 16.57) in clinical work.

Previous evidence has proved that there is an association between neurovegetative symptoms of depression and inflammation (48). Besides, in patients with MDD, inflammation-related proteins, such as C-reactive protein (CRP) and interleukin-6 (IL-6), were positively connected to somatic symptoms (49). In this study, patients with moderate to severe somatic symptoms tended to have problems with fatigue or loss of energy and decreased appetite or loss of appetite. Alessandro et al. observed a strong association between altered appetite/eating symptoms with CRP and white blood cell count (WBC), as well as between tiredness/low energy with granulocyte-to-lymphocyte ratio (GLR) (50). Therefore, there could be potential inflammation-related changes among the three groups, which might imply clues for the mechanism under the classification and their prognosis. In future studies, inflammatory proteins of patients with different levels of somatic symptoms are supposed to be examined for a better understanding of MDD and seeking for more specific treatment target.

## LIMITATIONS

There were several main limitations of this study to be noted. First, there was a relatively high dropout rate, especially for the longer treatment follow-ups. A high dropout rate may be due to that patients were required to stick at least 6 weeks to monotherapy, and those who could not receive ideal remission might choose another drug and then drop out of the study. Second, this study only focused on the treatment outcome of the acute phase of 12 weeks, not on a long-term outcome, and further studies are required to explore a longer follow-up period of MDD patients with different levels of somatic symptoms. Third, this study failed to make a validation of the 3-class subtype model with external data, such as patients from other hospitals. Finally, the number of participants varies significantly among the three subgroups, which, to some degree, is due to the characteristics of the subtypes, and it might also result from the small sample size. Thus, a future study with a larger sample size is needed to assure the accuracy of the subtype model.

## CONCLUSION

This study focused only on the somatic symptoms of MDD subtyping, which displayed a new aspect for understanding MDD. The results of this study identified three subtypes of MDD by their somatic symptoms: MDD patients with mild somatic symptoms, MDD patients with moderate somatic symptoms, and MDD patients with severe somatic symptoms. We found that patients with more severe somatic symptoms showed more problems with depressive symptoms and anxiety. The cohort comparison of the three subtypes found that it was the Moderate Group rather than the Severe Group that had the worst remission. The Moderate Group had higher HAMD-17 scores at the 6th week. It provides a warning that in clinical practice, somatic symptoms should be emphasized both to patients and doctors, and more attention is needed for MDD patients with moderate somatic symptoms, to whom a longer medication is supposed to be applied. Since few antidepressants have been studied for targeting somatic symptoms, future studies should pay more attention to somatic symptoms in MDD patients, and figure out more evidence of accurate pharmacotherapy for MDD with somatic symptoms.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from SMHC. Restrictions apply to the availability of these data, which were used under license for this study.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Shanghai Mental Health Center Institution Review Board Office. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

XW: data analysis, methodology, writing original draft, reviewing, and editing. YZ, YW, DP, and JC: conceptualization, methodology, reviewing, and editing. ZW: conceptualization, methodology, data analysis, reviewing, and editing. JH: conceptualization, methodology, and project administration. LC, YW, YS, and HL: conceptualization, reviewing, and editing. MF, ZY, ZW, and FW: data curation, investigation, and methodology. YF: conceptualization, funding acquisition, investigation, methodology, project administration, resources, supervision, reviewing, and editing. All authors contributed to the article and approved the submitted version.

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EDITED BY
Alessandro Colasanti,
Brighton and Sussex Medical School, United Kingdom

REVIEWED BY
Reiji Yoshimura,
University of Occupational and Environmental Health, Japan
Toru Hosoi,
Sanyo-Onoda City University, Japan

*CORRESPONDENCE
Yanqing Tang
tangyanqing@cmu.edu.cn
Fei Wang
fei.wang@cmu.edu.cn

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# The role of leptin in indirectly mediating "somatic anxiety" symptoms in major depressive disorder

Yue Zhu[1,2], Yange Wei[1,2], Jia Duan[1,2], Jianing Li[3], Ran Zhang[1,2], Jiaze Sun[1,2], Pengshuo Wang[1,2], Zhuang Liu[4], Jing Lv[1,2,5], Shengnan Wei[1,2], Xiaowei Jiang[1,2], Fei Wang[1,2,6]* and Yanqing Tang[1,2,7]*

[1]Department of Psychiatry, The First Affiliated Hospital of China Medical University, Shenyang, China, [2]Brain Function Research Section, The First Affiliated Hospital of China Medical University, Shenyang, China, [3]China Medical University and Queen's University of Belfast Joint College, China Medical University, Shenyang, China, [4]School of Public Health, China Medical University, Shenyang, China, [5]Department of Psychiatry, Corning Hospital, Shenzhen, China, [6]Department of Radiology, The First Affiliated Hospital of China Medical University, Shenyang, China, [7]Department of Gerontology, The First Affiliated Hospital of China Medical University, Shenyang, China

**Background:** Leptin is a multifunctional hormone secreted from adipose tissue, which plays a core role in regulating energy intake and expenditure. Evidence has demonstrated that leptin receptors are located in brain areas involved in emotional processing, and major depressive disorder (MDD) is characterized by dysfunction of emotional processing. Taken together, these features suggest that leptin may play a potential role in the pathophysiology of MDD. However, the precise roles of leptin in modulating depressive symptoms in MDD remain unclear.

**Methods:** Participants [18 drug-naïve MDD patients, 15 unaffected first-degree relatives of MDD patients (FDR-MDD), and 40 healthy controls] completed clinical assessments and provided blood samples for measurement of leptin levels. We evaluated the effect of leptin on clinical status (MDD or FDR-MDD) and symptomatic dimensionalities of MDD using mediation analysis.

**Results:** We found that leptin was increased in MDD patients and this only predicted "somatic anxiety" symptoms. Furthermore, leptin was a significant and indirect mediator of the association between clinical status (MDD or FDR-MDD) and "somatic anxiety" symptoms.

**Conclusion:** Our finding that leptin was a significant and indirect mediator of clinical status (MDD or FDR-MDD) and "somatic anxiety" symptoms suggests that leptin may indirectly affect somatic depressive symptoms in MDD. Our findings may provide a theoretical basis for novel clinical interventions in MDD.

KEYWORDS

**drug-naïve major depressive disorder, first-degree relatives, leptin, somatic anxiety symptoms, mediation analysis**

## Background

Major depressive disorder (MDD) is one of the most prevalent and disabling mental disorders worldwide (1). Genetic epidemiological research has indicated that compared with the general population, people with one first-degree relative with a mood disorder are approximately 2.8 times more likely to suffer from MDD (2). However, despite this increased genetic risk, most first-degree relatives of individuals with MDD (FDR-MDDs) do not develop MDD. Importantly, examination of FDR-MDDs may be useful for determining whether there are candidate markers of vulnerability in individuals with risk genes of MDD.

There is a bidirectional relationship between depressive disorder and obesity, such that the presence of one disorder increases the risk of developing the other (3). Furthermore, patients with obesity and their first-degree relatives frequently experience depression, anxiety, and other psychiatric disturbances (4, 5). Leptin is secreted by adipocytes in peripheral tissues and plays a core role in regulating energy intake and expenditure (6). Circulating leptin can permeate the blood–brain barrier (BBB) to exert its central effects *via* participating in synaptic activity, neuronal morphology, and neuronal development in the central nervous system (7, 8), and circulating leptin is partly from the human brain (9). Leptin receptors participate in emotional processing and exhibits high expression in the cortex, amygdala, and hippocampus (10, 11). The distribution of leptin signaling in the brain is related to emotional and cognitional processes, which has sparked an increased interest in the role of leptin in mood disorders (12–14). However, studies have provided conflicting results with both high and low levels of circulating leptin in depressed patients (15–17), suggesting that circulating leptin levels are influenced by age, sex, body mass index (BMI), and treatment with antidepressants (18, 19).

The relationship between depressive and anxiety symptoms of MDD and leptin remains unclear. A cross-sectional study indicated that metabolic syndrome was associated with the severity of depressive symptoms and the prevalence of depression (20). In patients with metabolic syndrome, leptin is positively associated with somatic depressive symptoms but not total depressive symptoms (21). Moderate-severe anxiety symptoms are associated with high serum leptin levels in patients with type 2 diabetes (22). Higher phobic anxiety scores are associated with increased levels of serum leptin in women with diabetes (23). These above studies focused on the relationship between leptin and depressive symptoms in patients with metabolic syndrome. MDD studies have reported conflicting findings on the relationship between leptin levels and the severity of depressive or anxiety symptoms in MDD, as these studies have found both positive and negative relationships, as well as no relationship whatsoever (24, 25). Higher leptin levels were associated with an atypical MDD subtype, but not with overall MDD or the typical subtype (26). These mixed results may be attributed to different symptomatic profiles of MDD; additionally, most studies have aimed to study total depressive symptoms of MDD without elucidating the symptom dimensions more commonly associated with leptin. Hence, it may be helpful to understand the role of leptin in MDD *via* the multidimensional clinical character of MDD.

In this study, we aim to investigate whether drug-naïve MDD patients and FDR-MDDs exhibit dysregulation of leptin, to identify whether there is a specific symptomatic dimension affected by leptin in MDD, and to explore whether leptin is an indirect mediator in this specific symptomatic dimension.

**Abbreviations:** MDD, major depressive disorder; FDR-MDDs, first-degree relatives of MDD; BBB, blood–brain barrier; HC, healthy control; KSADS-PL, Schedule for Affective Disorders and Schizophrenia for School-Age Children; HAMD-17, 17-item Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; ANOVA, one-way analysis of variance; BMI, body mass index; ANCOVA, one-way analysis of covariance; SD, standard deviation; CI, confidence interval; HPA, hypothalamic–pituitary–adrenal.

## Materials and methods

### Participants

Participants included drug-naïve patients with MDD ($n$ = 18), FDR-MDDs ($n$ = 15), and healthy controls (HCs) ($n$ = 40), all aged between 13 and 45 years. Drug-naïve MDD patients were recruited from 2014 to 2017 in the Department of Psychiatry at the First Affiliated Hospital of China Medical University and Shenyang Mental Health Center. Sixteen MDD patients were in a depressive state, and two MDD patients were in a remissive state. FDR-MDDs were all first-degree relatives of patients presenting with MDD at the Department of Psychiatry at the First Affiliated Hospital of China Medical University and Shenyang Mental Health Center. HCs were recruited from the local community *via* advertisements. All participants provided written consent that was approved by the Ethics Committee of China Medical University.

Participants with MDD were diagnosed by two trained psychiatrists individually and were included if they met the following criteria: (1) they fulfilled the Schedule for Affective Disorders and Schizophrenia for School-Age Children (KSADS-PL) criteria if younger than 18 years; (2) they fulfilled the Structured Clinical Interview DSM-IV criteria for MDD if 18 years or older; and (3) they had no comorbid diagnosis of psychosis or bipolar disorder, and no history of psychotropic medications. FDR-MDD participants were all first-degree relatives of individuals with MDD who did not meet the criteria for any DSM-IV Axis-I disorder. HCs were individuals who did not have a current or previous history of Axis-I disorders and did not have any first-degree relatives with a history

of Axis-I disorders. The severities of depression and anxiety of all participants were assessed using the 17-item Hamilton Depression Rating Scale (HAMD-17) and the Hamilton Anxiety Rating Scale (HAMA). The multidimensional characteristics ("somatic anxiety," "psychic anxiety," "core depressive," and "anorexia") of the HAMD-17 determined *via* factor analysis have been deemed to be useful for better understanding psychopathological dimensions of MDD (27). The "somatic anxiety" psychopathological dimension of MDD in the HAMD-17 includes somatic anxiety, hypochondria, early insomnia, middle insomnia, late insomnia, general somatic symptoms, and gastrointestinal symptoms.

The present study was approved by the Institutional Review Board of China Medical University and was performed in accordance with the Declaration of Helsinki. All experiments and methods were performed in accordance with approved guidelines and regulations. Demographic and clinical details are presented in **Table 1**.

## Determination of plasma leptin levels

Blood collection was carried out according to standardized protocols, with samples taken between 10:00 a.m. and 3:00 p.m. Participants should not have consumed food for at least 2 h before the blood collection. EDTA was used as an anticoagulant. Plasma samples were centrifuged for 10 min at 2,000 rpm and were stored at −80°C until further analysis. A Human Premixed Multi-Analyte Kit (R&D Systems, Inc., Minneapolis, MN, United States) with a Human Magnetic Luminex Assay was used to measure plasma leptin levels. Samples were magnetically labeled using a human magnetic premixed microparticle cocktail of antibodies (Kit Lot Number L120614). The assay was performed in duplicate according to the manufacturer's directions, and intra- and inter-assay coefficients of variation were <10% for leptin. Detailed information on this method can be found in **Supplementary Material**.

## Statistical analyses

We separated the participants into three groups (HCs, FDR-MDDs, and MDD patients). Group effects on demographic characteristics (age, gender, and BMI) and clinical characteristics (duration of illness, first episode, and HAMD and HAMA scores) were examined using one-way analyses of variance (ANOVAs) or Chi-square tests. Leptin concentrations were analyzed using a one-way analysis of covariance (ANCOVA), with age, gender, and BMI as covariates. *Post hoc* analyses were performed among the HC, FDR-MDD, and MDD groups using a general linear model. Bonferroni correction was used for multiple comparisons.

We used partial correlation to analyze the correlation between leptin levels and clinical symptoms, age, gender, and BMI as covariates in the MDD group. We then used multiple stepwise regression analysis to examine the effects of leptin on clinical symptom scores with potential confounding factors (age, gender, and BMI) in the MDD group. Based on these results, a mediation analysis was used to explore whether leptin (as a mediator variable) potentially influenced the association between clinical status-MDD or FDR-MDD (causal variable) and clinical symptoms (outcome variable). For the mediation analysis, the PROCESS procedure for SPSS Version 3.2 (written by Andrew F. Hayes, Ph.D.[1]) was used,

1 www.afhayes.com

TABLE 1 Demographic and clinical characteristics of HC, HR-MDD, and drug-naïve MDD.

| | HC | GHR-MDD | MDD | $F/\chi^2$ value | *P*-value |
|---|---|---|---|---|---|
| *n* | 40 | 15 | 18 | | |
| Age | 25.22 (4.84) | 30.00 (7.46) | 23.89 (7.55) | 4.517 | 0.014 |
| Gender, female% | 47.50% | 53.30% | 77.80% | 4.684 | 0.098 |
| BMI | 21.83 (4.04) | 23.11 (3.90) | 21.77 (3.49) | 0.663 | 0.518 |
| Duration, months | – | – | 14.24 (20.05) | – | – |
| First episode, yes | – | – | 83.30% | – | – |
| **HAMD** | | | | | |
| Somatic anxiety | 0.33 (0.69) | 0.60 (1.18) | 5.59 (4.68) | 31.12 | <0.001 |
| Psychic anxiety | 0.13 (0.52) | 0.27 (0.80) | 5.18 (8.01) | 10.77 | <0.001 |
| Core depressive | 0.13 (0.34) | 0.13 (0.52) | 4.06 (2.93) | 47.74 | <0.001 |
| Anorexia | 0.15 (0.43) | 0.20 (0.56) | 1.00 (1.17) | 9.38 | <0.001 |
| HAMD total | 0.65 (1.27) | 1.13 (2.23) | 14.88 (10.34) | 48.39 | <0.001 |
| **HAMA** | | | | | |
| HAMA total | 0.57 (1.55) | 1.33 (2.16) | 13.06 (11.55) | 29.56 | <0.001 |

Data are mean (SD) or %. HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale.

with a 5,000 bias-corrected bootstrap sample for significance testing. We summarized mediators using means, standard deviations (SD), and 95% confidence interval (CI). Significance was set at $p < 0.05$ (two-tailed) for all tests. All analyses were performed using SPSS.

# Results

## Demographic and clinical characteristics

There were significant differences in age ($p = 0.014$) among the HC, FDR-MDD, and MDD groups. There were no significant differences in gender or BMI ($p > 0.05$) among the HC, FDR-MDD, and MDD groups. The effects of diagnosis on HAMD ("somatic anxiety," "psychic anxiety," "core depressive," "anorexia," and total scores) (27) and HAMA scores were significant among the HC, FDR-MDD, and MDD groups (all $p$-values $< 0.001$; Table 1).

## Comparison of plasma leptin levels

After controlling for age, gender, and BMI, significant group effects were observed in leptin levels in the three-group analysis ($p = 0.004$). *Post hoc* analysis revealed significantly higher leptin levels in the MDD group compared with those in FDR-MDD ($p = 0.003$) or HC ($p = 0.008$) group after Bonferroni correction ($p_{Bonferroni} = 0.017$), but there was no significant difference in leptin levels between the FDR-MDD and HC groups (Figure 1).

## Relationship between leptin levels and clinical symptoms

In the MDD group, correlation analysis identified a significant positive correlation between leptin levels and "somatic anxiety" scores on the HAMD ($r = 0.550$, $p = 0.024$), but no significant correlation between leptin levels and scores for "psychic anxiety," "core depressive," "anorexia," or total scores on the HAMD and HAMA (Table 2). Regression analyses further confirmed that plasma leptin levels were only significantly positively associated with "somatic anxiety" scores on the HAMD ($\beta = 0.520$, $t = 2.355$, $p = 0.033$) in the MDD group after controlling potential confounding factors (age, gender, and BMI) (Figure 2).

## Mediated moderation analysis

Based on the results of the multiple regression analyses, we established a mediation model and found that leptin (Path AB, $\beta = -0.4752$; 95% CI: $-1.0395$ to $-0.0062$) significantly mediated clinical status in "somatic anxiety" as measured by the HAMD. As shown in Figure 3, clinical status was significantly related to leptin levels (Path A, $\beta = -1570.4384$, $t = -2.3583$, $p = 0.0251$), and leptin was significantly positively associated with "somatic anxiety" on the HAMD (Path B, $\beta = 0.0003$,

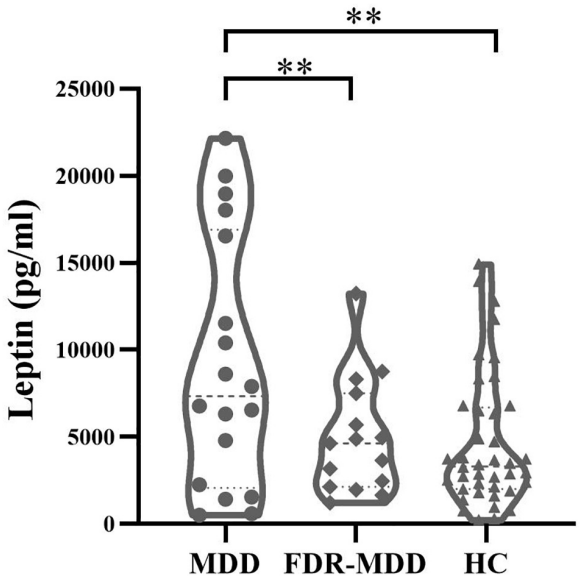


FIGURE 1
Comparison of plasma leptin levels by groups. Higher plasma leptin levels in drug-naïve MDD (9,163.11 ± 7,184.88 pg/ml) compared with FDR-MDD (4,956.07 ± 3,320.44 pg/ml, $p = 0.003$) and HC (4,633.3 ± 3,836.81 pg/ml, $p = 0.008$) after Bonferroni correction. **$p < 0.01$.

$t$ = 2.9956, $p$ = 0.0056). The total effect (effect of clinical status on "somatic anxiety") was also significant (Path C, β = −1.6627, $t$ = −4.0111, $p$ = 0.0004). After accounting for leptin as a mediator, the direct effect of clinical status on "somatic anxiety" was significant (Path C′, β = −1.1875, $t$ = −2.9603, $p$ = 0.0061). Leptin played an indirect effect (Path AB, β = −0.4752), which accounted for 28.58% (Path AB/Path C) of the total effect.

## Discussion

To the best of our knowledge, our present study is the first to investigate leptin levels in drug-naïve MDD patients, FDR-MDDs, and HCs to determine if there is a specific symptomatic dimension in MDD influenced by leptin levels and to further explore the precise role of leptin in mediating this specific symptomatic dimension of MDD. We found that leptin was increased in participants with MDD. Subsequently, we found leptin predicted "somatic anxiety" symptoms in MDD, and leptin could be a significant and indirect mediator in the association between clinical status (MDD or FDR-MDD) and "somatic anxiety" symptoms.

### Dysregulation of leptin in major depressive disorder

We found that leptin was increased in the drug-naïve MDD group but failed to find the same change in the FDR-MDD group, suggesting that increased leptin levels in MDD may indicate that elevated leptin may play an important pathophysiological role in MDD. Consistent with our finding, previous studies demonstrated elevated circulating leptin levels in patients with MDD (15, 28, 29). Circulating leptin as an adiposity negative signal could transmit peripheral energy homeostatic information to the brain. Peripheral hyperleptinemia related to central leptin resistance could explain the reason for anomalous appetite/weight changes in MDD. Central leptin resistance could occur at several levels, including debilitated transport of leptin across the BBB, the diminished function of the leptin receptor, and defects in leptin signal transduction (30). However, other studies reported reduced plasma leptin in MDD patients with a normal BMI (16, 17); this is consistent with rats or mice models of depression, which exhibited low circulating leptin levels (31, 32). Animal model data support the hypothesis that leptin insufficiency may underlie depression-like behavioral deficits. The conflicted findings in circulating leptin in humans may be related to the emergence of

TABLE 2 Correlations between levels of leptin and clinical symptoms in MDD.

| | HAMD | | | | | HAMA total |
|---|---|---|---|---|---|---|
| | Somatic anxiety | Psychic anxiety | Core depressive | Anorexia | Total | |
| $r$-value | 0.550 | 0.230 | 0.425 | −0.162 | 0.388 | 0.417 |
| $p$-value | 0.024* | 0.374 | 0.089 | 0.535 | 0.124 | 0.095 |

*Correlation coefficients statistically significant at $p < 0.05$.

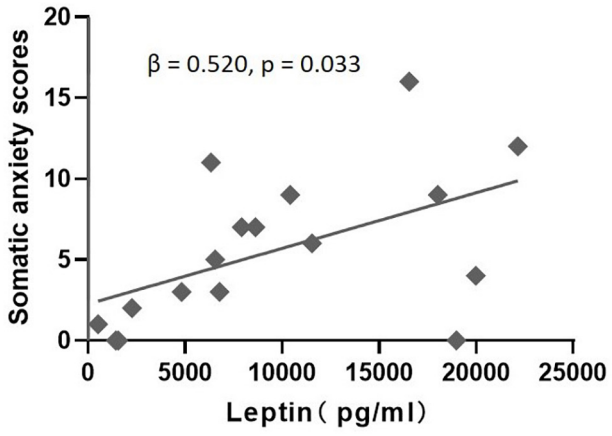


FIGURE 2
Multiple regression analysis to examine the effect of leptin on somatic anxiety scores after accounting for age, gender, and BMI in the MDD group.

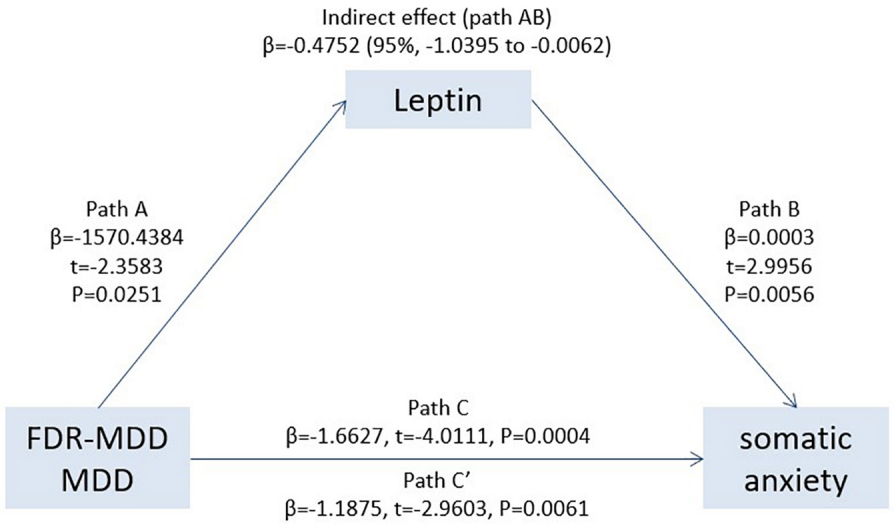


FIGURE 3
Leptin significantly mediated the association between clinical status (MDD or FDR-MDD) and "somatic anxiety," providing further evidence that there was an indirect way to influence patient "somatic anxiety" by leptin. Path C represents the variance in clinical state associated with "somatic anxiety," and Path C′ represents the association between clinical status and "somatic anxiety" after taking into account leptin as a mediator. Path AB in the mediation effect and is significant at $p < 0.05$ based on confidence intervals from bias-corrected bootstrapping of 5,000 samples.

leptin insufficiency in a subpopulation of depressed patients. Another interpretation may be that circulating leptin levels are influenced by multiple factors. Sexual dimorphism may affect leptin levels, with leptin levels being higher in females than in males (33, 34). A meta-analysis by Cao et al. indicated that males who expressed lower adiponectin and leptin levels had a higher likelihood of developing MDD (35). In their meta-analysis, they also found that there was no significant difference in leptin levels between MDD subjects and HCs (SMD = 0.13; 95% CI: −0.06, 0.31; $p = 0.170$); however, there was high heterogeneity for leptin ($I^2 = 91.8\%$, $p < 0.001$). After excluding six Asian studies, significantly higher levels of leptin were found in MDD subjects compared to those in HCs. The geographic location of participants may contribute to the heterogeneity of reported leptin levels (35). One previous study has posited that dysfunction of central leptin signaling, rather than the absolute concentration of leptin, may be more associated with effects on mood (13). Paz-Filho et al. systematically reviewed that there are possible therapeutic uses of leptin in conditions where leptin levels were normal, low, or high, and also suggested that a better understanding of the physiological roles of leptin may contribute to the development of leptin-based treatments for depression (36). Therefore, further investigations are needed to better elucidate the mechanisms of leptin in modulating the neurobiological substrates of MDD and in the potential application of leptin levels in the clinical application of MDD.

## Leptin indirectly mediates depressive symptoms in major depressive disorder

In the present study, we found a positive correlation between leptin and "somatic anxiety" but not for other symptoms in the MDD group. "Somatic anxiety" includes somatic anxiety, sleep disturbances, general somatic symptoms, gastrointestinal symptoms, and hypochondria. A previous study indicated that increased leptin levels were accompanied by sleep disturbances (37). The irregularity of the sleep-wake rhythm would affect energy homeostasis, and the energy homeostasis could be regulated by leptin (38). Leptin expression in the gastric mucosa could be associated with gastrointestinal symptoms (39). Our finding is also consistent with previous research which indicated that there is a significantly positive association between leptin and somatic depressive symptoms after adjusting for relevant confounding factors such as age, gender, BMI, insulin resistance, and inflammatory factors (21). Unfortunately, the mechanisms of the relationship between leptin and somatic depressive symptoms remain unknown. Based on the neuroendocrine functions of emotion regulation of leptin, mediation analysis showed that leptin was an indirect mediator in the association between clinical status and "somatic anxiety" symptoms. Similar to any application of regression analysis, our mediation analysis proves that the model is correctly specified but does not generate evidence that establishes causality (40). Therefore, we cannot bluntly arrive at a conclusion that leptin plays a causal role in

somatic anxiety symptoms in MDD, due to other factors that may influence the relationship between leptin and "somatic anxiety" symptoms. Leptin may provide feedback information on the nutritional status *via* integrated regulation of energy balance (41). In this study, all participants were informed to not consume food for at least 2 h prior to the blood collection to reduce short-term effects of eating on leptin. Peripheral leptin was affected by longer periods of fasting and overfeeding but was not changed immediately in the following food within 3 h (42). Additionally, nutritional status is linked to depression. However, it is difficult to conclude a causal relationship in human subjects since it is unclear whether depressed patients changing their healthy or unhealthy dietary habits may increase the risk of depression. A previous study also found that leptin levels were associated with chronic stress conditions (depressive mood and social isolation), while this association was not influenced by other lifestyle factors (smoking status, alcohol consumption, physical activity, and low income) (43). The associations among depression, unhealthy lifestyle factors (e.g., chronic stress conditions and unhealthy dietary habits), and leptin are complex. Chronic stress activates the hypothalamic–pituitary–adrenal (HPA) axis (44) and induces low-grade inflammation (45). Inflammation can reduce leptin signals to the central nervous system that influence depression and leptin may modulate HPA function (12, 46). Leptin modulates energy homeostasis *via* gut-brain circuits (47) and also regulates reward processing of food by modulating dopaminergic mesolimbic systems (48). MDD patients may be more vulnerable to dysfunctional food-reward processing, which may trigger stress-induced eating, and this phenomenon may be related to altered leptin levels in MDD. Therefore, there seems to be a complex interacting relationship among the following: MDD-unhealthy lifestyle factors (e.g., chronic stress conditions and unhealthy dietary habits), HPA dysfunction, inflammation, leptin dysregulation, mood disturbances, and MDD. Although our findings suggest that leptin may play a role in mediating somatic anxiety symptoms in MDD, the mechanisms of leptin-related somatic anxiety symptoms in MDD remain unclear.

### Limitations

Our present study had some limitations. Firstly, we selected drug-naïve MDD patients to minimize the influence of treatments, resulting in an extremely small sample size that may have limited the generalizability of our findings. Therefore, we performed power analyses of ANOVA and correlation analyses in the MDD group. ANOVA achieved the power of 0.67 and correlation analyses achieved the power of 0.51. Another limitation of the present study is that this was a cross-sectional study; therefore, subsequent developments in the included FDR-MDDs remain unknown. A longitudinal study of FDR-MDDs with long-term follow-ups is required to make such determinations, with comparisons between individuals who do and do not develop MDD, allowing for the possibility of developing a better mechanism to determine the genetic susceptibility of MDD.

## Conclusion

In summary, we found that leptin was increased in MDD patients and that elevated leptin may play an important pathophysiological role in MDD. Additionally, we found a correlation between leptin and "somatic anxiety" symptoms in MDD patients, and leptin was found to be a significant and indirect mediator between clinical status (MDD or FDR-MDD) and "somatic anxiety" symptoms, suggesting that leptin plays an indirect effect in somatic depressive symptoms in MDD. Taken together, our findings may provide a theoretical basis for novel clinical interventions for treating MDD.

## Data availability statement

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

## Ethics statement

All participants provided written consent that was approved by the Ethics Committee of China Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## Author contributions

YZ, YW, FW, and YT designed the study. RZ, JS, PW, JL, SW, and XJ have collected participants. YZ, JD, JNL, and ZL did the analysis plan. YZ drafted the manuscript. All authors read, contributed, 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



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.757958/full#supplementary-material

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EDITED BY
Alessandro Colasanti,
Brighton and Sussex Medical School, United Kingdom

REVIEWED BY
Marianna Mazza,
Agostino Gemelli University Polyclinic (IRCCS), Italy
Siraj Wali,
King Abdulaziz University, Saudi Arabia
Beata Gavurova,
Tomas Bata University in Zlín, Czechia

*CORRESPONDENCE
Ahmad Aldobyany
ahmad2145@hotmail.com

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# Prevalence of depression and its associated factors among patients with confirmed COVID-19 in Makkah, Saudi Arabia

Eid Alqurashi[1], Ahmad Aldobyany[1]*, Abdelfattah Touman[1], Abdullah Alqahtani[1], Rajaa Alsaggaf[1], Omar Alnashiwaaty[1], Nabil Ghaleb[1], Hanan Mabar[1] and Amr S. Albanna[2,3]

[1]Department of Medicine, King Abdullah Medical City, Makkah, Saudi Arabia, [2]Department of Medicine, King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Jeddah, Saudi Arabia, [3]Department of Medicine, McGill University, Montreal, QC, Canada

**Background:** In early December 2019, a cluster of acute pneumonia of viral etiology had been identified in Wuhan, China. Later on, it has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing a worldwide pandemic. This pandemic triggered unprecedented health-related psychiatric sequalae. We aim in this study to evaluate the prevalence of depression and its associated factors among confirmed patients with COVID-19.

**Methodology:** This is a cross-sectional study, we included adult patients more than 18 years old who have been diagnosed with PCR-confirmed COVID-19 and managed in a hospital, home, or hotel. A self-administered online questionnaire based on Patient Health Questionnaire (PHQ-9) Quick Depression Assessment questionnaire was used.

**Results:** A total of 143 subjects completed the PHQ-9 questionnaire. The prevalence of moderate to severe depression was 34%. Prevalence of depression was positively associated with the female gender ($p$-value = 0.013). Location of COVID-19 management and financial status did not affect the prevalence of depression.

**Conclusion:** The prevalence of depression among patients with COVID-19 is high, which underscores the importance of active screening and management of depression in this population.

KEYWORDS

**depression, COVID-19, SARS-CoV-2, PHQ-9, psychiatric sequalae**

## Highlights

- The prevalence of depression among patients with COVID-19 is high at 33.6%.
- Prevalence of depression was positively associated with the female gender.
- Location of COVID-19 management and financial status did not affect the prevalence of depression.

## Introduction

In early December 2019, a cluster of acute pneumonia of unknown etiology had been identified in Wuhan, China. The pathogen was identified as a new RNA virus, which was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). After the rapid global spread of this virus, the WHO declared COVID-19 a pandemic on 12 March 2020 (1).

This outbreak triggered unprecedented health-related anxiety (2). During the pandemic, the rapid spread of SARS-CoV-2 during the pandemic resulted in a great burden on health and the economy, which prompted countries and health agencies to apply strict measures to decrease viral transmission. These measures included community lockdown, social distancing, and other strict measures which resulted in psychosocial and health-related sequences.

It has been demonstrated in various research that infection outbreaks affect people's mental and psychosocial health significantly. In the initial phase of COVID-19 spread, people started to have symptoms of anxiety especially younger individuals with chronic diseases. These psychosocial and mental symptoms increased particularly after implementing the community lockdown (3), affecting both general populations and healthcare workers. The effect was more prominent among persons who lack social support and those who have been living with a suspected case of COVID-19 (4). As opposed to an influenza outbreak, where the anxiety was ranging from 10 to 33% in the general population (5). Alsaqri and colleagues found that around 67% of the study population were suffering from a degree of social anxiety during the COVID-19 pandemic (6).

In addition to the COVID-19-related strict precautionary measures that can cause mental health problems, COVID-19 disease itself can trigger mental health disorders like depression. It has been found that the prevalence of depression was 43% in clinically stable patients with COVID-19 (7). In a systematic review that evaluated infected patients with COVID-19, the pooled prevalence of depression was 45% (8).

Different studies have shown that depression can be associated with a depressed immune system, especially cellular immunity, which may have a negative impact on COVID-19 disease progression (9). This underscores the importance of screening patients with COVID-19 for any sign of depression. Symptoms of depression can persist even after the resolution of the disease. In one study that evaluated patients with COVID-19 after one month of their discharge from the hospital, the prevalence of depression was 18% (10). A substantial percentage of patients with COVID-19 have persistent symptoms of depression 3–6 months after COVID-19 symptoms onset (11). Thus, awareness and effective management of mental health-related disorders in patients with COVID-19 is strongly required.

The location of isolation either at home or in hospital settings may also have an impact on mental health. This, however, was not sufficiently evaluated in previous studies. We aim in this study to evaluate the prevalence of depression and its associated factors among COVID-19 confirmed patients and the factors, including isolation location that may influence mental health.

## Materials and methods

This is a cross-sectional study that included adult patients more than 18 years old who have been diagnosed with SARS-CoV-2 PCR confirmed COVID-19 and managed based on Saudi ministry of health guidelines in hospitals, homes, or hotels were involved. Patients were recruited from the COVID-19 clinic over a period of 3 months (March, April, and May, 2020). Critically ill patients, patients with previous diagnoses of depression, and patients with cognitive impairment such as dementia or delirium were excluded. A self-administered online questionnaire based on Patient Health Questionnaire (PHQ-9) Quick Depression Assessment questionnaire was used. This questionnaire has been validated, and it relies on patient self-report (12, 13). An electronic questionnaire was sent to 300 patients using their e-mails and cell phones. A total of 143 patients out of 300 patients (47.7%) responded and completed the questionnaire. The questionnaire contains questions related to demographic, social, educational, and financial status. We used PHQ-9 which is categorized as the following: A score of 1–4 is minimal depression, a score of 5–9 is mild depression, a score of 10–14 is moderate depression, a score of 15–19 is moderately severe depression, and a score of 20–27 is severe depression.

## Statistical analysis

Data were analyzed by using Statistical Package for Social Studies (SPSS 22; IBM Corp., New York, NY, United States). Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as percentages. The *t*-test and the one-way ANOVA were used for continuous variables. The chi-square test was used for categorical variables. A $p$-value of $<0.05$ was considered statistically significant.

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## Ethics and confidentiality

Ethical approval, as well as the informed consent form for the study, was taken from the KAMC Institutional Review Board (Approval number: 20-643).

TABLE 1 Patient's characteristics ($n$ = 143).

| | | Number | % |
|---|---|---|---|
| Gender | Male | 65 | 45.5 |
| | Female | 78 | 54.5 |
| Age (Mean, SD) | | 41.57 | 15.08 |
| Education | Illiterate | 16 | 11.2 |
| | Primary | 10 | 7.0 |
| | Intermediate | 14 | 9.8 |
| | Secondary | 29 | 20.3 |
| | University | 53 | 37.1 |
| | Post-bachelor | 21 | 14.7 |
| **Chronic disease** | | | |
| DM | Yes | 38 | 26.6 |
| HTN | Yes | 36 | 25.2 |
| Heart diseases such as ischemic heart disease, heart failure, or other | Yes | 6 | 4.2 |
| Chronic lung disease | Yes | 15 | 10.5 |
| Chronic kidney disease | Yes | 3 | 2.1 |
| Stroke | Yes | 1 | 0.7 |
| Cancer (any type) | Yes | 1 | 0.7 |
| Other chronic diseases not mentioned above | Yes | 12 | 8.4 |
| When have you been diagnosed with COVID-19? | 1 day | 2 | 1.4 |
| | 2 days | 3 | 2.1 |
| | 3 days | 4 | 2.8 |
| | 4 days | 9 | 6.3 |
| | 5 days | 10 | 7.0 |
| | 6 days | 10 | 7.0 |
| | One week ago, or more | 105 | 73.4 |
| Where were you treated for COVID-19? | Stayed at home | 61 | 42.7 |
| | Admitted at a hospital | 71 | 49.7 |
| | In a hotel or other place designated for quarantine | 11 | 7.7 |
| What is your assessment of your current financial status? | Good | 60 | 42.0 |
| | Average | 69 | 48.3 |
| | Low | 14 | 9.8 |

## Results

A total of 143 subjects completed the PHQ9 questionnaire and were included. The baseline demographic and disease characteristics are shown in Table 1. The mean age is 41 years, and the majority (78%) of the subjects were women. Most of the subjects (73%) were diagnosed with COVID-19 for more than 1 week and half of them (49.7%) were hospitalized. Subjects with a previous diagnosis of depression represented only 2%.

The prevalence of different depression severity categories is shown in Table 2. The prevalence of moderate to severe depression was 34%. The distribution of subjects across different degrees of depression severity is shown in Figure 1.

The severity degree of depression among confirmed patients with COVID-19 by their characteristics is shown in Table 3. The mean score of PHQ-9 for confirmed patients with COVID-19 by their characteristics is shown in Table 4. The prevalence of depression was positively associated with the female gender ($p$-value = 0.013). Location of COVID-19 management and financial status did not affect the prevalence of depression.

## Discussion

We found that around one-third (34%) of patients diagnosed with COVID-19 suffered from moderate to severe depression, which was positively associated with the female gender. Location of COVID-19 management (hospital, home, or hotel) and financial status did not affect the prevalence of depression.

Our findings are consistent with what has been found in other studies. Ma and colleagues found that the prevalence of depression among patients with COVID-19 using the PHQ-9 questionnaire was 43.1%. Female gender and family history of severe COVID-19 disease have been found to be strong predictors of depression (7). In another cross-sectional study that was conducted on 1,002 patients with COVID-19 using PHQ-9, the prevalence of moderate to severe depression was as high as 48%. Depression was positively associated with lower family income, sleep disturbance, lack of physical activity, fear of COVID-19 re-infection, and persistent COVID-19 symptoms (14). In our study, female

TABLE 2 The severity degree of depression among confirmed patients with COVID-19.

| | Number | Prevalence (%) |
|---|---|---|
| Minimal depression (1–4) | 37 | 25.9 |
| Mild depression (5–9) | 46 | 32.2 |
| Moderate depression (10–14) | 30 | 21.0 |
| Moderately severe depression (15–19) | 13 | 9.1 |
| Severe depression (20–27) | 5 | 3.5 |

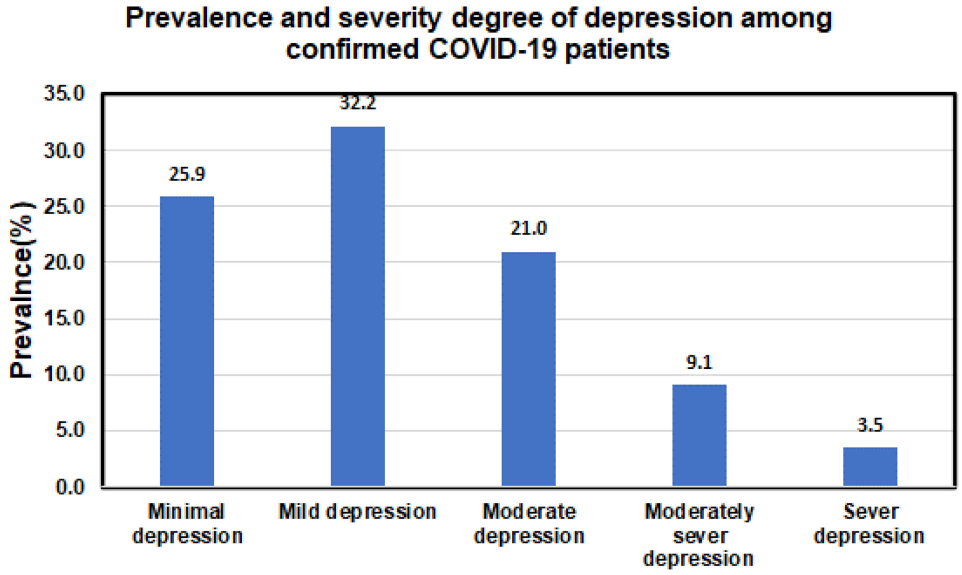


FIGURE 1
Prevalence and severity degree of depression among confirmed patients with COVID-19.

gender was a significant risk factor for depression. Other factors including financial status, comorbidities, duration of having COVID-19, and location of isolation did not affect the prevalence of depression.

Prevalence of depression has been found to be higher in patients with COVID-19 as compared to the general population. Alamri and colleagues found that the prevalence of depression among the general population in Saudi Arabia during the COVID-19 pandemic is 17% (15). It is low as compared to our finding in this study which is 34%. In a systematic review that involved multiple studies in different countries, the overall prevalence of depression in the general population was ranging from 14.6 to 48.3% (16). While in patients with COVID-19, the prevalence was higher as demonstrated in a systematic review and meta-analysis that evaluated infected patients with COVID-19, which found that the pooled prevalence of depression was 45% (8).

During the COVID-19 pandemic prevalence of depression was relatively high compared to the pre-pandemic period. The prevalence of depression symptoms in the United States of America was more than threefold higher during the COVID-19 pandemic compared to the pre-pandemic period (17). In one survey of the general population before the COVID-19 pandemic in Saudi Arabia, the prevalence of depression was 3.8% (18), which increased significantly during the pandemic as indicated in this study is 34%.

Some studies showed a higher prevalence of depression in actively hospitalized patients. Samrah and colleagues did a survey on patients with COVID-19 after 10 days of hospital isolation which showed a very high prevalence of 44% (19). In another study, 97.2% of hospitalized patients with COVID-19 with stable conditions had some degree of depression (20). In our study, the location where the patient received COVID-19 management at home, hotel, or hospital did not affect the prevalence of depression.

Although the high prevalence of depression among patients with COVID-19 could be explained by the quarantine and fear of disease, the inflammatory process of COVID-19 has been found to play a role in the psychiatric sequalae. Baseline systemic immune-inflammation index has positively associated with the prevalence of depression in 402 adults surviving COVID-19 at 1-month follow-up after hospital treatment (21).

It is important to acknowledge the limitations of our study, which include small sample size and an online self-assessment questionnaire rather than a face-to-face meeting and evaluation. Also, the absence of a control group from the general population during the same period is one of the limitations. On the other hand, we used a well-validated questionnaire and assessed different important variables that might affect the mental status.

Our study findings have important clinical implications as they indicate that the prevalence of depression is high in patients with COVID-19 as compared to the general population during the COVID-19 pandemic. This raises the importance of good assessment and evaluation of those patients for health-related psychiatric sequalae. This can be conducted through telemedicine or web-based care. In one study, digitally enabled remote care for people with long COVID-19 syndrome showed promising results; and there are ongoing studies to assess the online cognitive behavioral therapy that will be more accessible with less cost (22–24).

TABLE 3 The prevalence and severity degree of depression among confirmed patients with COVID-19 by their characteristics.

| | | Minimal depression | | Mild depression | | Moderate depression | | Moderately severe depression | | Severe depression | | *P*-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Number | % | Number | % | Number | % | Number | % | Number | % | |
| Gender | Male | 21 | 32.31 | 17 | 26.15 | 13 | 20.00 | 4 | 6.15 | 1 | 1.54 | 0.247 |
| | Female | 16 | 20.51 | 29 | 37.18 | 17 | 21.79 | 9 | 11.54 | 4 | 5.13 | |
| Education | Illiterate | 5 | 31.25 | 4 | 25.00 | 1 | 6.25 | 3 | 18.75 | 1 | 6.25 | 0.137 |
| | Primary | 2 | 20.00 | 6 | 60.00 | 2 | 20.00 | 0 | 0.00 | 0 | 0.00 | |
| | Intermediate | 2 | 14.29 | 4 | 28.57 | 6 | 42.86 | 0 | 0.00 | 0 | 0.00 | |
| | Secondary | 12 | 41.38 | 4 | 13.79 | 6 | 20.69 | 2 | 6.90 | 0 | 0.00 | |
| | University | 9 | 16.98 | 20 | 37.74 | 11 | 20.75 | 6 | 11.32 | 4 | 7.55 | |
| | Post-bachelor | 7 | 33.33 | 8 | 38.10 | 4 | 19.05 | 2 | 9.52 | 0 | 0.00 | |
| **Chronic disease** | | | | | | | | | | | | |
| DM | Yes | 8 | 21.05 | 15 | 39.47 | 4 | 10.53 | 2 | 5.26 | 2 | 5.26 | 0.274 |
| | No | 29 | 27.62 | 31 | 29.52 | 26 | 24.76 | 11 | 10.48 | 3 | 2.86 | |
| HTN | Yes | 8 | 22.22 | 13 | 36.11 | 6 | 16.67 | 1 | 2.78 | 2 | 5.56 | 0.484 |
| | No | 29 | 27.10 | 33 | 30.84 | 24 | 22.43 | 12 | 11.21 | 3 | 2.80 | |
| Heart diseases such as ischemic heart disease, heart failure, or other | Yes | | 0.00 | 3 | 50.00 | 2 | 33.33 | 0 | 0.00 | 0 | 0.00 | 0.439 |
| | No | 37 | 27.01 | 43 | 31.39 | 28 | 20.44 | 13 | 9.49 | 5 | 3.65 | |
| Chronic lung disease | Yes | 3 | 20.00 | 6 | 40.00 | 2 | 13.33 | 1 | 6.67 | 0 | 0.00 | 0.801 |
| | No | 34 | 26.56 | 40 | 31.25 | 28 | 21.88 | 12 | 9.38 | 5 | 3.91 | |
| Chronic kidney disease | Yes | | 0.00 | 1 | 33.33 | 2 | 66.67 | 0 | 0.00 | 0 | 0.00 | 0.425 |
| | No | 37 | 26.43 | 45 | 32.14 | 28 | 20.00 | 13 | 9.29 | 5 | 3.57 | |
| Stroke | Yes | | 0.00 | 1 | 100.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0.761 |
| | No | 37 | 26.06 | 45 | 31.69 | 30 | 21.13 | 13 | 9.15 | 5 | 3.52 | |
| Cancer (any type) | Yes | | 0.00 | 1 | 100.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 0.761 |
| | No | 37 | 26.06 | 45 | 31.69 | 30 | 21.13 | 13 | 9.15 | 5 | 3.52 | |
| Other chronic diseases not mentioned above | Yes | 1 | 8.33 | 4 | 33.33 | 5 | 41.67 | 1 | 8.33 | 0 | 0.00 | 0.320 |
| | No | 36 | 27.48 | 42 | 32.06 | 25 | 19.08 | 12 | 9.16 | 5 | 3.82 | |
| Non-chronic disease | | 23 | 28.40 | 22 | 27.16 | 19 | 23.46 | 9 | 11.11 | 3 | 3.70 | 0.517 |

*(Continued)*





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TABLE 3 (Continued)

| | | Minimal depression | | Mild depression | | Moderate depression | | Moderately severe depression | | Severe depression | | *P*-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Number | % | Number | % | Number | % | Number | % | Number | % | |
| When have you been diagnosed with COVID-19? | 1 day | 1 | 50.00 | 0 | 0.00 | 0 | 0.00 | 1 | 50.00 | 0 | 0.00 | 0.599 |
| | 2 days | 0 | 0.00 | 1 | 33.33 | 1 | 33.33 | 0 | 0.00 | 0 | 0.00 | |
| | 3 days | 1 | 25.00 | 3 | 75.00 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | |
| | 4 days | 2 | 22.22 | 2 | 22.22 | 1 | 11.11 | 0 | 0.00 | 1 | 11.11 | |
| | 5 days | 3 | 30.00 | 3 | 30.00 | 2 | 20.00 | 1 | 10.00 | 0 | 0.00 | |
| | 6 days | 1 | 10.00 | 3 | 30.00 | 1 | 10.00 | 3 | 30.00 | 0 | 0.00 | |
| | One week ago or more | 29 | 27.62 | 34 | 32.38 | 25 | 23.81 | 8 | 7.62 | 4 | 3.81 | |
| Where were you treated for COVID-19? | Stayed at home | 17 | 27.87 | 19 | 31.15 | 11 | 18.03 | 7 | 11.48 | 3 | 4.92 | 0.646 |
| | Admitted at a hospital | 15 | 21.13 | 25 | 35.21 | 16 | 22.54 | 6 | 8.45 | 2 | 2.82 | |
| | In a hotel or other place designated for quarantine | 5 | 45.45 | 2 | 18.18 | 3 | 27.27 | | 0.00 | | 0.00 | |
| What is your assessment of your current financial status? | Good | 17 | 28.33 | 19 | 31.67 | 11 | 18.33 | 6 | 10.00 | 2 | 3.33 | 0.979 |
| | Average | 16 | 23.19 | 24 | 34.78 | 16 | 23.19 | 6 | 8.70 | 2 | 2.90 | |
| | Low | 4 | 28.57 | 3 | 21.43 | 3 | 21.43 | 1 | 7.14 | 1 | 7.14 | |



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TABLE 4 Mean score of PHQ-9 depression questionnaire for confirmed patients with COVID-19 by their characteristics.

| | | Mean** | SD | *P*-value |
|---|---|---|---|---|
| Gender | Male | 6.42 | 4.92 | 0.013* |
| | Female | 8.73 | 5.91 | |
| Education | Illiterate | 8.06 | 7.08 | 0.290 |
| | Primary | 7.20 | 3.43 | |
| | Intermediate | 7.50 | 5.23 | |
| | Secondary | 5.83 | 5.12 | |
| | University | 8.92 | 6.04 | |
| | Post-bachelor | 7.14 | 4.39 | |
| **Chronic disease** | | | | |
| DM | Yes | 6.76 | 5.63 | 0.239 |
| | No | 8.01 | 5.55 | |
| HTN | Yes | 7.03 | 5.79 | 0.421 |
| | No | 7.90 | 5.52 | |
| Heart diseases such as ischemic heart disease, heart failure, or other | Yes | 7.50 | 5.01 | 0.731 |
| | No | 7.69 | 5.62 | |
| Chronic lung disease | Yes | 6.13 | 5.17 | 0.259 |
| | No | 7.86 | 5.62 | |
| Chronic kidney disease | Yes | 11.00 | 3.61 | 0.299 |
| | No | 7.61 | 5.60 | |
| Stroke | Yes | 6.00 | 0.00 | 0.764 |
| | No | 7.69 | 5.60 | |
| Cancer (any type) | Yes | 9.00 | | 0.813 |
| | No | 7.67 | 5.60 | |
| Other chronic disease not mentioned above | Yes | 9.17 | 4.51 | 0.236 |
| | No | 7.54 | 5.66 | |
| When have you been diagnosed with COVID-19? | 1 day | 9.00 | 9.90 | 0.874 |
| | 2 days | 6.67 | 6.11 | |
| | 3 days | 5.25 | 3.30 | |
| | 4 days | 6.22 | 8.00 | |
| | 5 days | 6.70 | 4.90 | |
| | 6 days | 8.90 | 6.59 | |
| | One week ago or more | 7.88 | 5.39 | |
| Where were you treated for COVID-19? | Stayed at home | 7.84 | 6.09 | 0.519 |
| | Admitted at a hospital | 7.83 | 5.30 | |
| | In a hotel or other place designated for quarantine | 5.82 | 4.38 | |
| What is your assessment for your current financial status? | Good | 7.45 | 5.68 | 0.845 |
| | Average | 7.96 | 5.51 | |
| | Low | 7.29 | 5.85 | |
| Overall score | | 7.68 | 5.58 | |

*Significant *p*-value.
**Out of 27.

## Conclusion

The prevalence of depression among patients with COVID-19 is high (34%), which underscores the importance of active screening and management of depression in this population that can be provided through telemedicine or web-based care. Depression was positively associated with the female gender in our population; however, the location of COVID-19 management and financial status did not influence the prevalence of depression.

## 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 Institutional Review Board (IRB) of King Abdullah Medical City (KAMC) (Approval number: 20-643). The patients/participants provided their written informed consent to participate in this study.

## Author contributions

EA and AA designed and supervised the study. EA, AMA, AT, ASA, and RA contributed to protocol development, data collection, interpretation of the analyzed data, and manuscript writing. OA, NG, and HM were involved in data collection and entry as well as manuscript editing. All authors reviewed and approved the final version of the 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.

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Alessandro Colasanti,
Brighton and Sussex Medical School,
United Kingdom

REVIEWED BY
Çiçek Hocaoğlu,
Recep Tayyip Erdoğan University,
Turkey
Rikinkumar S. Patel,
Duke University Medical Center,
United States

*CORRESPONDENCE
Kabtamu Nigussie
kabtamuali@gmail.com

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# Depression and anxiety among people with hypertension on follow-up in Eastern Ethiopia: A multi-center cross-sectional study

Lemesa Abdisa[1], Shiferaw Letta[1] and Kabtamu Nigussie[2]*

[1]Department of Nursing, School of Nursing and Midwifery, College of Health and Medical Science, Haramaya University, Harar, Ethiopia, [2]Department of Psychiatry, School of Nursing and Midwifery, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia

**Background:** People with hypertension have a high risk of developing mental disorders, such as depression and/or anxiety. However, there is a paucity of data regarding comorbid depression and anxiety symptoms among people with hypertension in study settings.

**Objective:** The study determined the prevalence and associated factors of depression, and anxiety symptoms among people with hypertension on follow-up at public hospitals, in Eastern Ethiopia.

**Materials and methods:** A cross-sectional study was carried out among 471 people with hypertension who were randomly chosen from four public hospitals in Harar town and the Dire Dawa Administration. The data were collected by interviewer-administered structured questionnaires. A validated nine-item Patient Health Questionnaire and Generalized Anxiety Disorder scales were used to assess depression and anxiety symptoms, respectively. A logistic regression model was used to identify the association among depression, anxiety, and their predictors. An adjusted odds ratio and a 95% confidence interval were used to report the association. The statistical significance was set at a $p$-value of $< 0.05$.

**Results:** Depression and anxiety symptoms were present in 27.2 and 32.7% of people with hypertension, respectively. Being women (AOR = 1.74, 1.09–2.78), having no formal education (AOR = 2.19, 1.19–4.81), presence of other medical illnesses (AOR = 2.23, 1.39–3.56), having a family history of depression (AOR = 2.01, 1.25–3.19), and poor social support (AOR = 2.80, 1.60–5.22) were statistically associated with depressive symptoms, whereas being women (AOR = 1.54, 1.01–2.35), widowed and divorced (AOR = 2.22, 1.41–3.52), presence of other medical illnesses (AOR = 1.64, 1.06–2.53), and poor social support (AOR = 3.54, 2.09–6.01) were statistically associated with anxiety symptoms.

**Conclusion:** More than a quarter of people with hypertension reported symptoms of depression and anxiety. Findings demonstrated that being a

woman, having an additional medical illness and having poor social support were statistically associated with depressive and anxiety symptoms. Regular screening, early detection, and offering the proper intervention should be on top priorities for healthcare professionals.

KEYWORDS

hypertension, depression, anxiety, magnitude, Eastern Ethiopia, follow-up

# Introduction

Non-communicable diseases (NCDs) accounted for 41 million population deaths worldwide. Among these deaths, 32.8 million were attributed to cardiovascular diseases, diabetes, cancers, and chronic respiratory diseases (1). About 80% of these NCD deaths were recorded in low- and middle-income countries (2).

Hypertension is one of the NCDs, which is defined as abnormally high arterial blood pressure. Hypertension is diagnosed when the systolic blood pressure readings on 2 different days are greater than 140 mmHg or more, and/or the diastolic blood pressure readings on both days are greater than 90 mmHg or more (3). Each year, hypertension causes approximately 7.5 million deaths (4). The systematic review study revealed that hypertension (HTN) remains stable in developed countries, whereas it is rising in middle- and low-income countries (5). Adults with hypertension account for roughly a quarter of the population, and by 2025, that figure will rise to roughly one-third (6).

People with hypertension are at an increased risk of mental health disorders, including depression and/or anxiety (7). Changes in appetite and weight, sleep and activity patterns, energy levels, feelings of guilt, difficulty thinking clearly and making decisions, and recurring thoughts of death or suicide are all symptoms that indicate depression (8, 9). Anxiety is defined as the existence of excessive worry about several events or activities on the majority of days, as well as somatic symptoms like muscle tension, irritability, difficulty sleeping, and restlessness (9, 10).

The co-occurrence and the impact of psychological and psychosocial issues related to HTN are challenging in diagnosis and management (7). Depression likely causes a 5.7% increase in the global burden of diseases by 2020 and become the leading cause of disability worldwide by the year 2030 (6). Depression comorbidity decreases the quality of life and increases the risk of myocardial infarction and stroke in people with hypertension (11). Anxiety influences medication adherence in people with hypertension and limits the feature treatment options worsens the prognosis and increases mortality (12). Several studies showed that depression was found in 40.1% (13) to 58% (1), while anxiety ranged from 28.5% (14, 15) to 42.3% (1) in people with hypertension. Moreover, the prevalence of comorbid depression in Africa accounted for 33.3% (16).

Different studies showed that biological and psychosocial factors were associated with comorbid depression and anxiety among people with hypertension. These included gender, physical activity, socioeconomic status (13), concern about medication and poor BP control (17), comorbid chronic illness (1), weight change, low income (18), older age, family history of depression (19) and being a woman (1), stressful life event, comorbid diabetic poor social support (14), weight change, and low income (18). Though comorbid depression and anxiety adversely affect health outcomes, there is limited information about the prevalence and determinants in people with hypertension in Ethiopia, particularly in Eastern Ethiopia. Therefore, this study aimed to determine the prevalence and associated factors of depression and anxiety among people with hypertension, as well as to make important recommendations that will likely improve future intervention programs.

# Materials and methods

## Study design and setting

An institutional-based cross-sectional study design was conducted in four public hospitals found in Harar and Dire Dawa Administration, namely Hiwot Fana Specialized University Hospital, Jugal Hospital, Dilchora Referral Hospital, and Sabian General Hospital from June 15 to July 15, 2021. All these hospitals provide both in-patient and out-patient services for the population of Eastern Ethiopia including the surrounding regions and zones. Around 3,848 people with hypertension receive their services each year (20, 21).

## Eligibility criteria

All adults aged ≥18 years people who had been clinically diagnosed with hypertension and who were on follow-up during the study period at selected hospitals were included in the study. People who were critically ill, unable to communicate, and

patients currently on antidepressants and anxiolytic medication were excluded from the study.

## Sample size determination and sampling procedure

The sample size was calculated by using a single population proportion formula, considering the following statistical assumptions: $z$ = the standard value of confidence level of alpha 95%, $d$ = the margin of error between the sample and the population (0.04). For this study, $p$ (the estimated proportion of anxiety) = 24.7%, which was the prevalence of anxiety symptoms among people with hypertension conducted in Hawassa University Comprehensive Specialized Hospital, Southern Ethiopia (19).

$$n = \frac{(Z_{\alpha/2})^2 P (1 - P)}{d^2} \quad n = \frac{(1.96)^2 0.247(1 - 0.247)}{0.04^2} = 447$$

Accordingly, adding 10% for non-the response rate gives the total calculated sample size is 491. The data from each public hospital indicated that 363, 216, 239, and 205 people with hypertension were on follow-up at Dilchora Referral Hospital, Sabian General Hospital, Hiwot Fana Specialized University Hospital, and Jugal Hospital, respectively. Next, they were proportionally allocated to the sample size. As per allocation, 174, 104, 115, and 98 patients were from Dilchora Referral Hospital, Sabian General Hospital, Hiwot Fana Specialized University Hospital, and Jugal Hospital, respectively. A systematic random sampling method was used to select study participants from the designated public hospitals. The first study participant was selected by a lottery method from each hospital independently, and the subsequent study participants were chosen for every two people.

## Data collection procedure and measurements

Data were collected using face-to-face interviews, and a review of the patient's chart for other comorbid medical illnesses, duration of treatment, and the number of antihypertensive medications. The questionnaire contains four parts: sociodemographic, clinical, psychosocial, and substance-related characteristics of the patients that were adapted and modified after reviewing similar literature.

Depression was measured by the nine items of the Patient Health Questionnaire (PHQ-9), validated in Ethiopia with Cronbach's alpha of 0.84 (22, 23). Scores for each item are 0, "not at all"; 1, "several days"; 2, "more than half days" to 3, "nearly every day" with a total score ranging from 0 to 27. The respondent who scored above or equal to 10 was considered as having depression (24). Anxiety was assessed by generalized anxiety disorder 7-items (GAD-7), which was validated in Ethiopia and its Cronbach's alpha was 0.95 (25, 26). Scores for each item were 0, "not at all"; 1, "several days"; 2, "more than half days" to 3, "nearly every day" with a total score ranging from 0 to 21. The respondents who scored above or equal to 10 were considered as having anxiety disorder (25).

Social support was assessed by Oslo Social Support Scale containing three items (Oslo-3). It is a three item questionnaire, commonly used to assess social support and it has been used in several studies. The sum score scale ranged from 3 to 14, which had 3 categories: poor support 3–8, moderate support 9–11, and strong support 12–14 (27), and it was validated in Ethiopia (28). Substance-related factors were assessed by alcohol, smoking, and substance involvement screening test (ASSIST), which is a brief screening questionnaire developed and validated by the World Health Organization (WHO) to find out people's use of psychoactive substances currently and a history of ever substance use (29). Regular physical activity was assessed by 2 items of days in the last 7 days in a week. Then, the responses were added up (range, 0–14). Participants who scored ≥8 were coded as adhering to the physical activity recommendations (30). The medication side effect was assessed by asking patients and review patient's chart. Data were collected by eight trained B.Sc nurses and supervised by two M.Sc nurses. Coronavirus disease (COVID-19) prevention protocol was completely applied during data collection.

## Data quality control

Data collectors and supervisors were trained for 2 days on the data collection approaches of the study. The questionnaire was translated into the local language Amharic by an expert and back to translated into English by another person to check it for consistency. A pretest was conducted on 5% of the sample size at Haramaya General Hospital to see the applicability of the instruments and feedback was incorporated into the final tool to improve the quality. The result was not included in the result of this study found. Throughout the data collection period, supervision was carried out, and the completeness and consistency of the questionnaire were looked over daily.

## Statistical analysis

The data were coded, cleaned, and entered into Epi Data version 3.1 and then exported to SPSS (Statistical Package for Social Science) version 20 for analysis. Bivariate and multivariate logistic regression analyses were performed to identify factors associated with the outcome variable. All variables with a $p$-value less than 0.05 in bivariate analysis were entered into the multivariate logistic regression analysis. A $p$-value of less than 0.05 was considered statistically significant, and the

adjusted odds ratio (AOR) with a 95% confidence interval (CI) was calculated. The Hosmer–Lemeshow goodness test showed model fitness.

## Ethical consideration

Ethical clearance was obtained from the Institutional Health Research Ethics Review Committee (IHRERC) of Haramaya University College of Health and Medical Sciences. A formal letter of permission and support was provided to all four public hospitals in which the study was conducted. Participants were informed of the study's objective, procedures, and information confidentiality, as well as their right to withdraw and stop the interview at any time. A written informed consent was taken from each study participant before data collection began. Confidentiality was maintained at all levels of the study through anonymous data collection. During data collection, the COVID-19 prevention protocol was strictly kept.

# Results

## Sociodemographic characteristics of participants

A total of 471 participants were included in the study, making a response rate of 96%. The median age of respondents was 50 years, interquartile range (IQR, 40–75) with the age range of 18–90 years. Around half of them, 51.2% (241) and 57.1% (269) were men and married, respectively. More than half, 59.9% (282) of participants were living with family, 201 (42.7%) were Muslim by religion, and nearly two-thirds 67.7% (319) were urban residents as presented in **Table 1**.

## Clinical, psychosocial, and substance-related factors of respondents

About two-thirds, 63.9% of participants were reported as having no family history of hypertension. Around half, 54.4% (256) of respondents had up to 5 years duration of treatment and 53.8% (254) of them were taking two antihypertensive medications, whereas more than half 55.6% (260) were with controlled hypertension. More than two-thirds, 67.7% (319) of participants with hypertension had no regular physical activities. From all study respondents, 61.8% (291) and 36.7% (173) had 18.5–24.9 kg/m$^2$ body mass index and moderate social support, respectively, whereas 42.5% (200) had a history of other comorbid medical illnesses. Concerning substance use, nearly one-third 34.8% (164) of them smoke a cigarette as presented in **Table 2**.

## Factors associated with depression symptoms in people with hypertension

In multivariable logistic regression analysis, variables, such as being a woman, not attending formal education, comorbid medical illness, family history of depression, and poor social support were statistically significantly associated with depression symptoms. In this study, the odds of having depression among respondents with being women was about 1.7 times higher compared with participants those being men (AOR = 1.74; 95% CI: 1.09–2.78), and the odds of having depression among participants who did not attend formal education was 2.2 times higher compared with the respondents who attended college and above education (AOR = 2.19; 95% CI: 1.19–4.81). The odds of having depression among respondents who had other medical illnesses was 2.23 times higher compared with the respondents who had no other medical illness (AOR = 2.23; 95% CI: 39–3.56) and odds of having depression among participants who had a family history of depression was 2.0 times higher compared with the participants those who had no family history of depression (AOR = 2.01; 95% CI: 1.25–3.19). The finding of this study indicated that the odds of having depression among respondents who had poor social support was about 2.8 times (AOR = 2.80; 95% CI: 1.60–5.22) higher compared with the participants who had strong social support as presented in **Table 3**.

## Factors associated with anxiety symptoms in people with hypertension

In this study, variables, such as being a woman, widowed/divorced, having a comorbid medical illness and having poor social support were significantly associated with anxiety symptoms. The odds of having anxiety among woman participants were about 1.5 times higher as compared with men participants (AOR = 1.54; 95% CI: 1.01–2.35), and the odds of having anxiety among divorced/widowed participants were 2.2 times higher as compared with married participants (AOR = 2.22; 95% CI: 1.41–3.52). The finding also indicated that the odds of having anxiety among participants who had comorbid other medical illnesses were about 1.6 times higher as compared with participants who had no comorbid other medical illness (AOR = 1.64; 95% CI: 1.06–2.53) and the odds of having anxiety among respondents who had poor social support was 3.5 times higher as compared with participants who had good social support (AOR = 3.54; 95% CI: 2.09–6.01) (**Table 4**).

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TABLE 1 Demographic information of people with hypertension on follow-up in Eastern Ethiopia ($n$ = 471).

| Variables | Categories | Frequency ($n$ = 471) | Percentage (%) |
|---|---|---|---|
| Sex | Men | 241 | 51.2 |
| | Women | 230 | 48.8 |
| Age category in year | 18–39 | 92 | 19.5 |
| | 40–49 | 140 | 29.7 |
| | 50–59 | 124 | 26.3 |
| | ≥60 | 115 | 25.3 |
| Marital status | Single | 67 | 14.2 |
| | Divorced/widowed | 135 | 28.7 |
| | Married | 269 | 57.1 |
| Living arrangement | Alone | 189 | 40.1 |
| | With family | 282 | 59.9 |
| Religion | Muslim | 201 | 42.7 |
| | Orthodox | 171 | 36.3 |
| | Protestant | 70 | 14.9 |
| | Others | 29 | 6.2 |
| Occupation | Framer | 59 | 12.5 |
| | Merchant | 136 | 28.9 |
| | Civil servant | 180 | 38.2 |
| | Household worker | 77 | 16.3 |
| | Jobless | 19 | 4.0 |
| Education | No formal education | 58 | 12.3 |
| | Primary school (1–8) | 85 | 18.0 |
| | Secondary school (9–12) | 107 | 27.7 |
| | College and above | 221 | 46.9 |
| Place residence | Urban | 319 | 67.7 |
| | Rural | 152 | 32.3 |
| Monthly income, ETB | ≤1400 | 119 | 25.3 |
| | 1401–3500 | 124 | 26.3 |
| | 3501–5000 | 12999 | 27.421.0 |
| | ≥5000 | 99 | 21.0 |

NB: one Ethiopian Birr = 0.023 US dollar.

## Discussion

This study indicated that the prevalence of comorbid depression among people with hypertension was 27.2% (95% CI: 22.9–31.2). Being a woman, having other medical illnesses, a family history of depression, and having poor social support showed the association with comorbid depression. Similarly, the prevalence of anxiety in the current finding was 32.7 % (95% CI: 28.2.3–36.9). Being a woman, divorced and widowed, having other medical illnesses, and having poor social support were predictors of comorbid anxiety in people with hypertension.

The prevalence of depressive symptoms in the current study was high, and this finding was in line with the study conducted in Nigeria (31), Pokhara Metropolitan City (32), and Hawassa, Ethiopia (19). However, it was lower than the study conducted in Saudi Arabia (19) and Nepal (33). The possible reason for the discrepancy might be the study design, as this study was an institutional-based cross-sectional study, whereas a study conducted in Saudi Arabia was a community-based cross-sectional study. In addition, data collection instruments and the economic status of the population might contribute to this variation. On the other hand, the finding of the current study was higher than the study conducted in Saudi Arabia (34), Korea (35), Shenzhen, China (36), and Northwest Ethiopia (37). The reason for the disparity might be the instrument used: the Beck Depression Inventory and the World Health Organization's five wellbeing index were used in Saudi Arabia and Shenzhen, China, respectively, whereas the patient health questionnaire was used in this study.

The prevalence of anxiety symptoms in the current finding was high which was in line with the study conducted in China, Iran (38), and Addis Ababa, Ethiopia (14). However,

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TABLE 2 Clinical, substance use, and psychosocial characteristics of people with hypertension on follow-up in Eastern Ethiopia ($n$ = 471).

| Variables | Categories | Frequency ($n$ = 471) | Percentage |
|---|---|---|---|
| Family history of hypertension | Yes | 170 | 36.1 |
| | No | 301 | 63.9 |
| Duration of treatment | Up to 5 years | 256 | 54.4 |
| | 5–10 years | 146 | 31.4 |
| | ≥10 years | 67 | 14.2 |
| Family history of depression | Yes | 180 | 38.2 |
| | No | 291 | 61.8 |
| Number antihypertensive medication | One | 175 | 37.2 |
| | Two | 254 | 53.8 |
| | Three | 42 | 8.9 |
| Hypertension status | Controlled | 260 | 55.2 |
| | Uncontrolled | 211 | 44.8 |
| Comorbid medical illness | Yes | 200 | 42.5 |
| | No | 271 | 57.5 |
| Medication side effect | Yes | 201 | 42.7 |
| | No | 270 | 57.3 |
| Regular physical activity | Yes (regular) | 152 | 32.3 |
| | No (irregular) | 319 | 67.7 |
| BMI | <18.5 | 65 | 13.8 |
| | 18.5–24.9 | 291 | 61.8 |
| | 25–29.9 | 91 | 19.3 |
| | ≥30 | 24 | 5.1 |
| Alcohol use | Yes | 139 | 29.5 |
| | No | 332 | 70.5 |
| Smoking | Yes | 164 | 34.8 |
| | No | 307 | 65.2 |
| Social support | Poor | 135 | 28.7 |
| | Moderate | 173 | 36.7 |
| | Strong | 163 | 34.6 |

the finding of the current study was higher than the previous studies conducted in Egypt (39), South Africa (40), Qatar (38), Germany (41), and Malaysia (42). The possible reason for the discrepancy might be sample size, study design, and study setting, a prospective cohort study and community-based survey were used in Germany (41) and Egypt (39), while this study used an institutional-based cross-sectional study design. Another possible reason for the difference might be the data collection instruments used, which were a Composite International Diagnostic Interview to measure DSM-IV mental disorders (40) and the Hospital Anxiety and Depression Scale (HADS) used in Malaysia (42). On the other hand, the result of the current study was lower than the study conducted in two hospitals in Ghana (42, 43). The possible reason for the discrepancy might be the difference in study participants, study design, and data collection tools, which were the Depression Anxiety Stress Scale (DASS) (42), Zung Self-Rating Anxiety Scale test (43), and Generalized Anxiety Disorder (GAD-7).

It was identified that poor social support was associated with depression and anxiety symptoms. Previous research conducted in Ethiopia provided evidence to support these findings (14, 19). This might be because the perceived feeling of being unsupported (isolated) and having a somatic illness (like hypertension) leads to increased psychosocial stress, and on the contrary, good social support reduces the risk of depression and anxiety (44).

In this study, having no formal education was associated with depression symptoms. This result was supported by the studies conducted in China (36), Saudi Arabia (34), and Ethiopia (19). The argument could be that people who had no formal education might have limited awareness about disease and poor coping mechanisms toward stress and psychosocial problems.

Having a family history of depression was correlated with depression symptoms. This might be that if one parent has a mood disorder (such as depression), the child has a risk of developing it (8) since they share similar life and psychosocial stress (19).

TABLE 3 Factors associated with depressive symptoms in people with hypertension on follow-up in Eastern Ethiopia ($n$ = 471).

| Explanatory variables | Depression | | COR (95% CI) | AOR (95% CI) |
|---|---|---|---|---|
| | Yes | No | | |
| **Sex** | | | | |
| Men | 52 | 189 | 1 | 1 |
| Women | 76 | 154 | 1.79 (1.19–2.71) | 1.74 (1.09–2.78)* |
| **Marital status** | | | | |
| Single | 24 | 43 | 1.86 (1.05–2.35) | 1.71 (0.91–3.24) |
| Divorced/widowed | 42 | 93 | 1.51 (0.95–2.39) | 1.27 (0.75–2.13) |
| Married | 62 | 207 | 1 | 1 |
| **Educational status** | | | | |
| No formal education | 24 | 34 | 2.29 (1.25–4.21) | 2.19 (1.19–4.81)* |
| Primary school | 26 | 59 | 1.43 (0.82–2.49) | 1.25 (0.67–2.33) |
| Secondary school | 26 | 81 | 1.04 (0.61–1.79) | 0.79 (0.43–1.48) |
| College and above | 52 | 169 | 1 | 1 |
| **Hypertension status** | | | | |
| Uncontrolled | 75 | 136 | 2.15 (1.43–3.26) | 1.45 (0.88–2.41) |
| Controlled | 53 | 270 | 1 | 1 |
| **Comorbid illness** | | | | |
| Yes | 77 | 123 | 2.70 (1.78–4.09) | 2.23 (1.39–3.56)** |
| No | 51 | 220 | 1 | 1 |
| **Body mass index in (kg/m$^2$)** | | | | |
| <18.5 | 11 | 54 | 1 | 1 |
| 18.5–24.9 | 77 | 214 | 1.77 (0.88–3.55) | 1.49 (0.69–3.18) |
| 25–29.9 | 34 | 57 | 2.93 (1.35–6.36 | 2.21 (0.93–5.28) |
| ≥30 | 6 | 18 | 1.64 (0.53–5.06) | 1.79 (0.44–1.14) |
| **Family history of depression** | | | | |
| Yes | 67 | 113 | 2.24 (1.48–3.38) | 2.01 (1.25–3.19)* |
| No | 61 | 230 | 1 | 1 |
| **Smoking** | | | | |
| Yes | 54 | 110 | 1.55 (1.02–2.35) | 0.71 (0.44–1.14) |
| No | 74 | 233 | 1 | 1 |
| **Social support** | | | | |
| Poor | 51 | 84 | 2.81 (1.65–4.77) | 2.80 (1.60–5.22)** |
| Moderate | 48 | 125 | 1.77 (1.05–2.99) | 1.73 (0.97–3.09) |
| Strong | 29 | 134 | 1 | 1 |

*$p < 0.05$, **$p < 0.001$, Chi square = 11.80; DF = 8 and Hosmer-Lemeshow test = 0.46.

Being a woman was associated with depression and anxiety symptoms. This was supported by a study conducted in Karachi, Pakistan (45). The possible justification could be women are more vulnerable to psychosocial related problems due to hormonal effects (8). Those respondents, who had divorced/widowed higher risk to have anxiety because when they feel lonely, lack hope, are worthless and become anxious.

Other comorbid medical illnesses were associated with depression symptoms. This result was consistent with the number of studies conducted in different countries like Egypt (39), Pakistan (45), and central Ethiopia (14, 19). It is possible that metabolic factors, such as fasting blood glucose and systolic blood pressure, independently contribute to anxiety and depression (45), in addition to the direct pathophysiological effect of inflammation and metabolic factors on the hypothalamic-pituitary axis and autonomic nervous systems (46).

## Limitations of the study

The use of retrospective elements in the questionnaire may have incurred recall bias like duration of illness and duration of treatment. Because of the cross-sectional nature of the

TABLE 4 Factors associated with anxiety symptoms in people with hypertension on follow-up in Eastern Ethiopia ($n$ = 471).

| Explanatory variables | Anxiety | | COR (95% CI) | AOR (95% CI) |
|---|---|---|---|---|
| | Yes | No | | |
| **Sex** | | | | |
| Men | 66 | 175 | 1 | 1 |
| Women | 88 | 142 | 1.64 (1.11–2.42) | 1.54 (1.01–2.35)* |
| **Marital status,** | | | | |
| Single | 17 | 50 | 0.89 (0.49–1.65) | 0.79 (0.42–1.50) |
| Divorced/widowed | 63 | 72 | 2.31 (1.49–3.55) | 2.22 (1.41–3.52)** |
| Married | 74 | 195 | 1 | 1 |
| **Hypertension status** | | | | |
| Uncontrolled | 85 | 126 | 1.87 (1.27–2.76) | 1.46 (0.95–2.27) |
| Controlled | 69 | 191 | 1 | 1 |
| **Comorbid illness** | | | | |
| Yes | 81 | 119 | 1.85 (1.25–2.73) | 1.64 (1.06–2.53)** |
| No | 73 | 198 | 1 | 1 |
| **Social support** | | | | |
| Poor | 69 | 66 | 3.66 (2.16–5.86) | 3.54 (2.09–6.01)** |
| Moderate | 48 | 125 | 1.31 (0.79–2.14) | 1.39 (0.84–2.34) |
| Strong | 37 | 126 | 1 | 1 |

*$p < 0.05$, **$p < 0.001$, Chi square = 6.05; DF = 8 and Hosmer-Lemeshow test = 0.79.

study and the lack of a control group, determining the cause–effect relationship between the outcome variable and predictive variables was difficult. The COVID-19 pandemic might also affect the result of this study.

## Future directions

With the existing study limitations, we recommended that researchers in the field of mental health and public health need to conduct an additional study about the prevalence of depression and anxiety through longitudinal studies and investigate the relationship between medication adherence and the grade of hypertension.

## Clinical and research implications of the study

This study might be an essential contribution in giving insight to the healthcare providers to evaluate the people with hypertension in the study area for psychiatric disorders and improve mental health services. The findings of this study will further motivate researchers to conduct the longitudinal study.

# Conclusion

The finding of this showed that depressive and anxiety symptoms were common among people with hypertension. Being a woman, having a family history of depression, having no formal education, having an additional medical illness, and having poor social support were significantly associated with depression. Likewise, being women, divorced/widowed, having other comorbid medical illnesses, and having poor social support were significantly associated with anxiety symptoms. Regular screening, early identification, diagnosis, and providing appropriate intervention might reduce adverse health outcomes resulting from depression and anxiety through a collaborative care model. In addition, an appropriate and timely referral from primary care to specialist care is recommended. Moreover, people with hypertension who were women, had an additional medical illness and poor social support need special attention.

# 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 Research Ethics Review Committee of

College of Health and Medical Sciences, Haramaya University. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

LA conceived the research idea. KN was involved from inception to design, acquisition of data, analysis, interpretation, and drafting and editing of the manuscript. LA and SL were involved in the reviewing of the proposal, analysis, interpretation, and critical review of the drafted 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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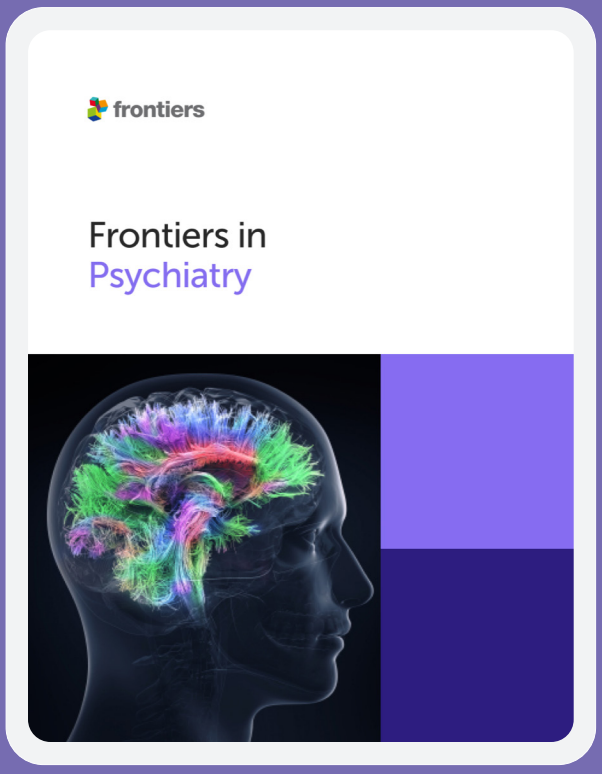


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