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Understanding vulnerability to major depressive disorder

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Understanding vulnerability to major depressive disorder

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Editorial: Understanding vulnerability to major depressive disorder

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Editorial on the Research Topic
Understanding vulnerability to major depressive disorder

Major depressive disorder (MDD) is a complex and multifactorial psychiatric condition that remains a leading cause of disability worldwide. Despite its high prevalence, our understanding of the mechanisms that underlie individual vulnerability to MDD remains incomplete.

This Research Topic, *Understanding Vulnerability to Major Depressive Disorder*, brings together a diverse collection of original research and reviews that deepen our insights into the biological, psychological, social, and behavioral factors contributing to the onset and course of MDD. These articles span multiple methodologies—from animal models to human clinical and observational studies—highlighting the multidimensional nature of vulnerability and offering valuable avenues for both prevention and intervention.

Biological and neuroendocrine risk factors

Several contributions explore biological mechanisms that may predispose individuals to depression. Yang et al. investigated the preventive and therapeutic effects of vitamin D in a mouse model of adolescent depression, revealing that vitamin D administration mitigated depression-like behaviors despite no significant change in BDNF expression—suggesting that alternative neurobiological pathways may be involved.

Similarly, Osnaya-Brizuela et al. offered a focused review of acquired hypothyroidism, identifying its role in increasing the risk of psychiatric conditions, including depression and anxiety, potentially via dysregulation of the HPA axis, serotonergic function, neuroinflammation, and impaired neurogenesis. Since hypothyroidism is one of the identifiable and potentially treatable biological contributors to depression, consistent monitoring of at-risk individuals and patients with depression may help reduce illness exacerbation and facilitate effective treatment.

The peripartum period has unique biological features that predispose women to depression, in addition to the profound psychosocial transitions it entails. To enhance the mother-infant relationship in depressed mothers, researchers have explored fast-acting

and effective treatment options. Raja et al. conducted a comprehensive meta-analysis evaluating zuranolone, one of the approved treatments for postpartum depression. Their study provides compelling evidence that zuranolone is a safe and effective antidepressant with rapid therapeutic benefits.

Cognitive and behavioral vulnerabilities

A significant portion of this Research Topic focuses on maladaptive cognitive processing and emotional regulation as key elements of vulnerability. Monéger et al. employed an eye-tracking paradigm to investigate depressive self-focus bias following failure. They found that only a subgroup of severely depressed individuals—specifically those with high levels of guilt and self-blame—exhibited this attentional bias, challenging the assumption that self-focus is a universal feature of depression.

Human cognition relies on emotional input for decision-making, as proposed by Damasio's somatic marker hypothesis (1). In line with this, Tian et al. examined the relationship between alexithymia and neurocognitive functioning—specifically immediate memory—in first-episode, drug-naïve individuals with MDD. They found a negative correlation between immediate memory performance and alexithymia, suggesting that impairments in emotional processing may be linked to early neurocognitive deficits in depression.

Fortuna and Golonka developed the Depersonalization Mechanism Scale (DMS) and demonstrated that depersonalization functions both as a predictor and consequence of depressive symptoms. It was highly associated with maladaptive emotion regulation strategies such as rumination, self-blame, and withdrawal. Their findings suggest that depersonalization may operate as a trait-like, risk-enhancing coping mechanism in emotionally overwhelming contexts—one that also exhibits sex differences. The study highlights the value of incorporating depersonalization assessment in depression screening protocols.

Adding further insight into cognitive-affective vulnerabilities in youth, Zhao examined the mechanisms underlying suicidal ideation among adolescents with depressive symptoms. Their study identified rumination and school adaptation as critical mediators between depressive symptoms and suicidal ideation, with psychological distress acting as a key driver. These findings underscore the importance of targeting emotion regulation and social functioning in school environments when designing early suicide prevention strategies for adolescents.

Psychosocial and environmental contexts

Preventive strategies and resilience-building are essential in reducing the burden of depression, just as they are in other health domains. Wang et al. present a meta-analysis on the effects of physical exercise on negative emotions, offering robust evidence of its preventive and therapeutic potential for depression.

General medical conditions exert both biological and psychosocial burdens, often increasing the risk of depression. Kubanek et al. provided evidence supporting the need for routine depression screening among patients receiving hemodialysis. Although it remains unclear whether the vulnerability stems more from the biological impact of chronic kidney disease and its treatment or the life-limiting psychosocial consequences, their findings underscore the importance of integrating mental health monitoring into chronic care settings.

Along the same lines, Ai et al. utilized machine learning algorithms in a large longitudinal study to develop a predictive model for depression among middle-aged and elderly individuals with hypertension. Their results revealed that psychosocial and functional variables—such as chronic pain, sleep problems, and social isolation—were as predictive as traditional medical factors. This work highlights the potential of AI-assisted risk models in public health surveillance and clinical screening.

Cultural perspectives

As mental health systems shift toward community-based care, informal caregivers increasingly bear the responsibility for long-term support. However, many countries lack sufficient psychosocial and financial resources for caregivers. Munie et al. shed light on the psychological burden experienced by caregivers of individuals with severe mental illness in Northwest Ethiopia, documenting high rates of depression, burnout, and social isolation. Their mixed-methods study identified poverty, perceived stigma, patient nonadherence, and lack of social support as key predictors of caregiver depression.

While this Research Topic does not directly address intergenerational or cross-national dynamics, the inclusion of research from diverse geographic and sociocultural contexts—including studies from Ethiopia, China, and Eastern Europe—underscores the global relevance of depressive vulnerability and the importance of culturally attuned mental health strategies.

Concluding remarks

Taken together, the articles in this Research Topic offer a multifaceted understanding of vulnerability to major depressive disorder, encompassing biological, cognitive, emotional, environmental, and sociocultural domains. The diversity of these studies reflects the heterogeneity of depression itself—an illness that seldom arises from a single cause and often persists due to complex, interacting vulnerabilities.

What emerges is a compelling case for integrative models of risk and resilience. Whether examining the neuroendocrine implications of hypothyroidism, attentional biases linked to guilt, or the psychological toll of caregiving in under-resourced contexts, each study contributes a crucial piece to the broader puzzle of depression. Importantly, many of these contributions go beyond risk identification to propose actionable tools—such as machine learning algorithms and psychometric instruments—that could support early detection and personalized prevention.

This Research Topic also underscores the need to contextualize vulnerability—not only through biological frameworks but also within family systems, social inequalities, and cultural landscapes. Depression is not merely a disruption of neurochemistry; it is a condition fundamentally shaped by how individuals relate to themselves, others, and the world. Accordingly, addressing vulnerability requires a coordinated effort spanning clinical care, research, public health, and policy.

By advancing our understanding of who is vulnerable to depression and why, the research presented here lends support to more personalized, equitable, and preventative mental health strategies. As editors, we hope that the insights offered in this Research Topic will encourage further interdisciplinary collaboration and contribute to a future in which depression is not only more effectively treated—but also more effectively anticipated and, where possible, prevented.

Author contributions

MCE: Conceptualization, Writing – review & editing, Writing – original draft. AG: Writing – original draft, Conceptualization, Writing – review & editing. TF: Writing – review & editing, Conceptualization, Writing – original draft.

Reference

1. Damasio AR. The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philos Trans R Soc Lond B Biol Sci*. (1996) 351:1413–20. doi: 10.1098/rstb.1996.0125

Conflict of interest

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Construction of a machine learning-based risk prediction model for depression in middle-aged and elderly hypertensive people in China: a longitudinal study

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Background: Hypertension is a common chronic disease that can trigger symptoms such as anxiety and depression. Therefore, it is essential to predict their risk of depression. The aim of this study is to find the best prediction model and provide effective intervention strategies for health professionals.

Methods: The study subjects were 2733 middle-aged and older adults who participated in the China Health and Retirement Longitudinal Study (CHARLS) between 2018 and 2020. R software was used for Lasso regression analysis to screen the best predictor variables, and logistic regression, random forest and XGBoost models were constructed. Finally, the prediction efficiency of the three models was compared.

Results: In this study, 18 variables were included, and LASSO regression screened out 10 variables that were important for the establishment of the model. Among the three models, Logistic Regression model showed the best performance in various evaluation indicators.

Conclusion: The prediction model based on machine learning can accurately assess the likelihood of depression in middle-aged and elderly patients with hypertension in the next three years. And by combining Logistic regression and nomograms, we were able to provide a clear interpretation of personalized risk predictions.

KEYWORDS

hypertension, depression, middle-aged and elderly, machine learning, prediction model

Introduction

The aging of the population is one of the major social problems in the world today (1). As the country with the largest elderly population in the world, China is faced with severe challenges and threats of population aging (2). One of the biggest challenges of aging is health-related issues, most notably chronic disease (3). Admittedly, chronic disease has become one of the biggest threats to human health, especially to the elderly (4). Among these chronic diseases, cardiovascular diseases are the most common and the leading cause of death in China. High blood pressure is widely recognized as a major risk factor for cardiovascular disease and has one of the highest disease burdens globally (5). According to the World Health Organization (WHO), about 1.13 billion people worldwide currently have high blood pressure, and the number of people with high blood pressure is expected to increase by more than 400 million by 2025 (6). Over the past few decades, the prevalence of hypertension has increased dramatically, and disability-adjusted life years associated with hypertension have also increased significantly (7). In addition, the prevalence of hypertension among the elderly in China is as high as 50% (8). This situation has become one of the chronic diseases that seriously threaten public health, especially in the middle-aged and elderly population, and has brought a heavy burden to the whole society (9).

The increase in hypertension is accompanied by various problems and challenges. Studies have shown that individuals with high blood pressures have a higher prevalence of mental health disorders, due to changes in physical symptoms of high blood pressure patients, which seriously affect physical and mental health, prone to depression, anxiety and loneliness and other problems (10–12). In addition, taking medication every day and worrying about serious complications may also increase the psychological burden on patients (13). A meta-analysis study showed that the prevalence of depression in people with high blood pressure was 26.8%, higher than in the general population (14). Several studies in China have also suggested that high blood pressure is a risk factor for depression (15, 16). Studies have also shown that symptoms of depression are associated with higher rates of high blood pressure (17, 18). Many studies have shown that depression has a significant impact on hypertensive patients (19, 20). In addition, when the same scale was used to screen populations in different regions, the depression detection rate among hypertensive patients in China was higher than 17.3% in American Indians (21) and 24.0% in Australia (22).

Depression is a mood disorder that can cause a variety of functional physical impairments and loss of interest in daily activities, which can reduce quality of life (23). At present, depression has become a major mental health problem in low-income, middle-income, and high-income countries, and its lifetime risk has risen steadily over the past few decades (24, 25). According to Whiteford H. A. et al., they used data from the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 to estimate the burden of disease associated with mental and substance use disorders (26). The findings show that mental and substance use disorders account for 7.4% of disability-adjusted life years globally. At the same time, mental and substance use disorders are also the main causes of global years of life lost due to disability, and depression contributes the most to the global years of life lost due to mental and substance use disorders, reaching 40.5%. The findings highlight the important impact of depression on global health. In addition, a 2013 systematic review of Gu L et al. showed that the lifetime prevalence of depression in China was 3.3% (27). In 2014, Smith K et al. showed the epidemiological status of depression in the world in Nature, among which the incidence of depression in China was 3.02% (28). Depression is expected to become the leading cause of the global burden of disease by 2030 and has become the leading cause of suicide in China. This series of data shows that depression has become a global public health problem that needs adequate attention and attention (28).

When older people suffer from both hypertension and depression, the double burden of physical and mental illness increases the risk of cardiovascular and cerebrovascular disease, non-compliance with medication, poor quality of life, and suicide (12, 29, 30). In addition, research has shown that depression can affect treatment, physical function, and health outcomes in people with high blood pressure (31). Patients with long-term hypertension often have emotional disorders, but few people can timely detect and correctly understand the severity of depression, thus delaying treatment, which will also affect the control of hypertension. There is a lot of research on high blood pressure and depression. In the early 1990s, some studies showed no clear correlation between high blood pressure and depression. However, recent studies have found that clinically significant depressive symptoms are independently associated with elevated blood pressure (32, 33). In addition, Chinese scholars have also studied the heterogeneity of depression in non-hospitalized elderly patients with hypertension and studied the influencing factors of various categories (34).

In summary, although there have been many studies on the association between high blood pressure and depression, there is still a lack of tools and practical applications for risk assessment in high-risk patients. Clinically, we can only rely on the summary of experience to promote the prevention of depression in hypertensive patients. However, with the continuous progress of artificial intelligence (AI) technology in recent years, it has become an important topic in the field of health care, and its application is also expanding. Machine learning (ML) is an in-depth study of how to extract valuable information from massive amounts of data. It is not only a theory but also a practical discipline, which is the core and one of AI (35, 36). ML was first proposed by Samuel in 1959 (37), through ML, we can extract the best objective function from a large amount of data and use these functions to achieve optimization. It can effectively help doctors predict diseases through ML, thus effectively supporting clinicians' diagnosis and treatment decisions. Algorithms such as logistic regression (LR), random forest (RF), lasso regression, and XGBoost are included for the construction and validation of disease prediction models. However, in the prediction model of depression in middle-aged and elderly people with hypertension, there is a lack of relevant research. Therefore, this study will take the hypertension population in the China Health and Retirement Longitudinal

Study database as the research object and use R studio software to organize and analyze the data. Three classical machine learning algorithms were used to scientifically construct a prediction model for depression risk in middle-aged and elderly hypertensive patients. By evaluating and screening the efficacy of the model, an optimal model algorithm is derived to better understand the patient's disease changes.

Materials and methods

Data source

This study used data from the China Health and Retirement Longitudinal Study (CHARLS) from 2018 to 2020. CHARLS is a large-scale interdisciplinary survey project hosted by the National School of Development at Peking University. The project uses household surveys to collect high-quality longitudinal survey data from a nationally representative sample of people aged 45 years and older and their spouses (38, 39). The CHARLS survey covers 150 counties and 450 communities (villages) in 28 provinces. The survey used a probability sampling method proportional to population size, sampling at the county, household, and individual levels in four phases. This method has strong advantages in scientificity, geographical coverage, representativeness, and authenticity of samples.

Study participants

According to the purpose of the survey, the inclusion criteria for this study included: (1) age 45 years or older; (2) Patients with clinical diagnosis of hypertension. Exclusion criteria included: (1) participants who already had depressive symptoms or had not completed the depression scale at baseline (2018); (2) Participants who are unable to provide additional survey information on their own or who lack reliable information; (3) Participants who did not participate in follow-up in 2020; (4) Participants who did not complete the depression scale in 2020. In the end, a total of 2733 middle-aged and elderly people were included in this study, and the detailed process of participant selection is shown in Figure 1. The sampling unit for this study was middle-aged and elderly hypertensive patients. And since the number of samples screened in this study was large enough, no sampling weights were performed.

Research variable

Outcome variable

In the CHARLS questionnaire, participants were screened for depressive symptoms using the CESD-10 scale. The scale has strong reliability and validity, especially in the measurement of depression symptoms in the elderly (40, 41). The scale consists of ten items and uses the Likert4 scoring method. Item 5 "I am hopeful for the future" and item 8 "I am happy" are positive items, and the rest are negative items. Negative entries are assigned according to "rarely or not at all (less than 1 day) =0", "not much (1-2 days) =1", "sometimes or half the time (3-4 days) =2" and "most of the time (5-7 days) =3", while positive entries are assigned in reverse. Finally, the score of each item is added to get the total score, which ranges from 0 to 30 points. A total score of ≥10 was defined as the presence of depressive symptoms; If the total score is less than 10, it is defined as no depressive symptoms. A higher score indicates more severe depressive symptoms (42).

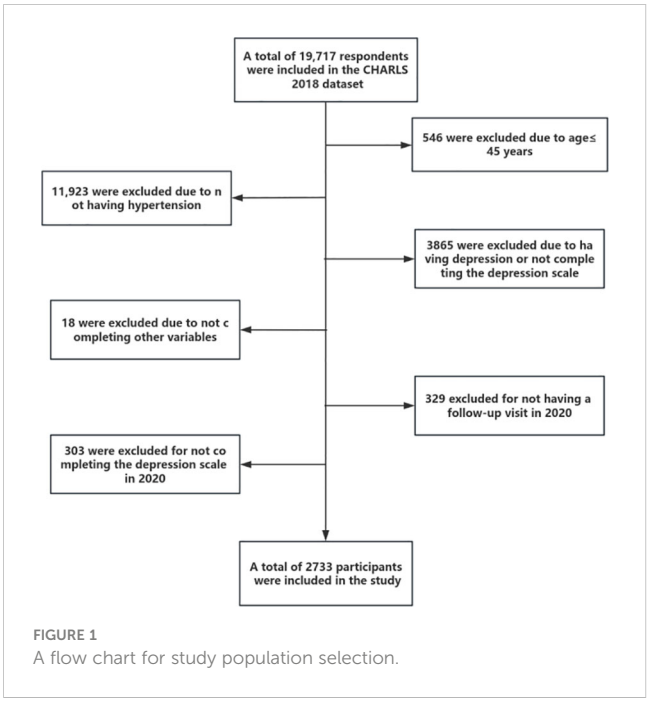

FIGURE 1
A flow chart for study population selection.

Socio-demographic factors

Sociodemographic factors include gender, hukou, education level, marital status, place of residence, and age. Among them, gender is divided into male and female; The level of education is classified as "none" and " ≥1 year"; Types of hukou include "agricultural hukou" and "non-agricultural hukou"; Marital status can be classified as "married" (including living with a spouse or temporarily separated for reasons such as work) and "unmarried" (including separated, divorced or widowed); Place of residence are divided into "urban", "urban-rural integration and special areas" and "rural"; Age is treated as a continuous variable.

Behavioral factors

Behavioral factors included exercise, social activities, smoke, drink, and sleep duration. Among them, exercise, social activities, smoke, and drink were classified as "yes" and "no". Sleep duration was measured by asking the question, "During the past month, how many hours per night did you sleep on average?". And was treated as a continuous variable in this study.

Health status

In this study, health status included disability, hearing difficulties, pain, and the number of chronic diseases. For the definition of disability, the following five questions were used: (1)

Do you have one of the following disabilities? (2) Do you have Brain damage/intellectual disability? (3) Do you have vision problems? (4) Do you have hearing problems? (5) Do you have a Speech impediment? Participants were defined as disabled if they answered "yes" to at least one of the above questions, otherwise, it is "no". For the definition of hearing difficulty, the following three questions were used: (1) Do you ever wear a hearing aid? (2)Is your hearing very good, good, fair, poor, or very poor(3)Do you have hearing problems? Hearing difficulties were defined if the answer to questions 1 or 3 was "yes" or if the answer to question 2 was "poor". In this study, chronic diseases included 13 types, namely: dyslipidemia, diabetes, cancer, cardiovascular disease, chronic lung disease, liver disease, psychiatric problems, stroke, psychiatric illness, arthritis or rheumatic disease, kidney disease, digestive system disease, or asthma. The number of chronic diseases was treated as a continuous variable in this study. In addition, the pain was defined as "yes" and "no".

Mental health factors

Mental health factors included life satisfaction, self-rated health, and self-rated memory, which were defined as "good", "fair" and "bad" in this study, and all three variables are categorical in this study.

Statistical analysis

In this study, R Studio software was used for data analysis with the aid of several R software packages, including rms, ROCR, Hmisc, random forest, glment, and caret, among others. Firstly, the general information table and scores of the patients were described. Because the measurement data in this study were not normally distributed, they were expressed as median and interquartile range, and the Mann-Whitney U test was used for comparison between groups and within groups. Count data were expressed as utilization rate, constituent ratio, or frequency, and the chi-square test was used for comparison between groups and within groups. The test level was set as α=0.05. Next, significant risk factors were screened using the Lasso regression method. Then, three machine learning algorithms, including logistic regression (LR), random forest (RF), and XGBoost, were used in the training set to construct depression risk prediction models for middle-aged and elderly hypertensive people.

Finally, the performance of the prediction models was evaluated by the area under the Receiver Operating Characteristic (ROC) curve, specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV).

Results

Analysis of the number of patients

We randomly divided all the screened patients into a training set and a calibration set in a 7:3 ratio. The training set served as the modeling group with 2050 cases, and the calibration set served as the testing group with 683 cases. For the flow chart of the study, see Figure 2.

Baseline data of training set and testing set

Except for hearing difficulty, social activities and age, there were no significant differences in baseline characteristics between the two groups (P >0.05), indicating that the two groups would not be biased due to the uneven distribution of dependent variables, as detailed in Table 1.

Identification of risk factors

In the training set, with the presence or absence of depression as the dependent variable (yes =1, no =0) and preselected risk factors for depression in middle-aged and elderly hypertensive patients as the independent variables, lasso Regression was used to screen risk factors. As can be seen from Figure 3A, the coefficients of the independent variables included in the model from the beginning will be gradually compressed, and the coefficients of the last part of the independent variables will be compressed to 0 to avoid overfitting the model. As can be seen from Figure 3B, by means of 10-fold cross-validation, λ+1 with the smallest error was selected as the optimal value, and finally, 10 risk factors including gender, household registration, education, pain, drinking, life satisfaction, self-rated memory, self-rated health, number of chronic diseases and age were screened out.

Construction of LR risk prediction model

After selection by lasso regression, we performed a multivariate logistic regression analysis in the training set, using forward stepwise and likelihood ratio tests to rule out confounding factors. The results are shown in Table 2, gender, hukou, pain, life satisfaction, self-reported health, self-reported memory, number of chronic diseases and age are independent risk factors for depression in middle-aged and elderly patients with hypertension. We plotted the nomogram for depression in middle-aged and elderly hypertensive patients as shown in Figure 4A, and the specific variable allocation is shown in Table 3. Finally, based on the risk factor scores in the nomogram, we can calculate the corresponding predicted probability, which is the probability of depression in middle-aged and elderly hypertensive patients. For example, female (score 31), agricultural hukou (score 50), pain (score 36.5), fair life satisfaction (score 25), poor self-rated memory (score 20.5), poor self-rated health (score 43), 5 chronic diseases (score 25), and age 80(score 54). These scores are added to give a total score of 285, corresponding to a risk of more than 50%. This means that patients may be at higher risk for depression and therefore require individualized preventive measures. The specific scoring criteria are shown in Figure 4B.

Construction of RF risk prediction model

A total of 2050 samples were used to establish the random forest model in the training group. Based on the value of mtry is 5, when ntree=500, the error basically tends to be stable, and the dynamic

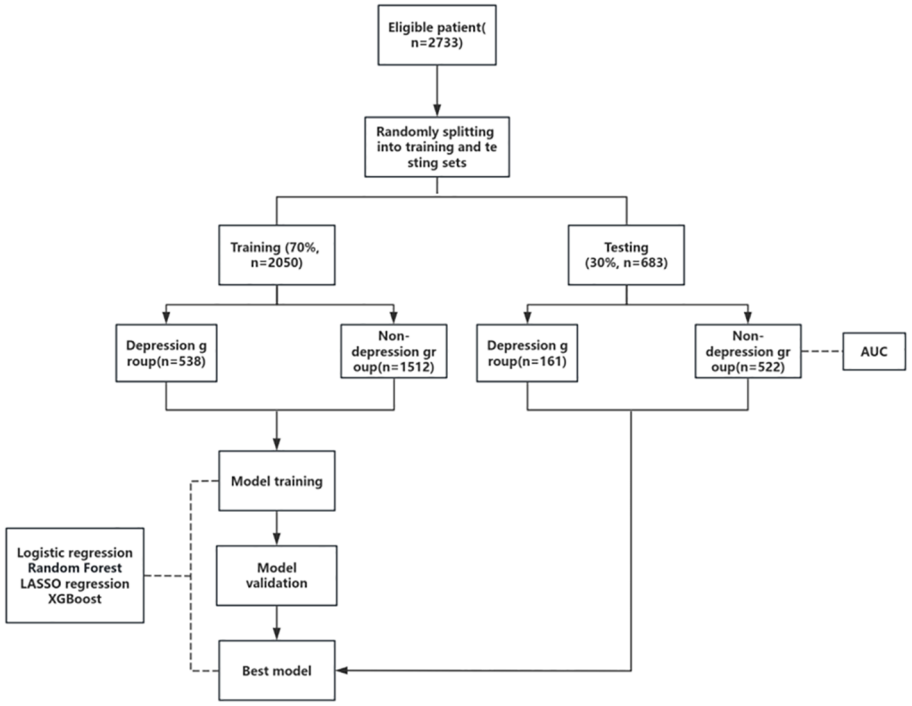

FIGURE 2
Flow chart of the study.

TABLE 1 Comparison of baseline data between the two groups.

	Traning set	Testing set	H/χ2	*p*-value
Gender			0.136	0.712
Male	1151(56.1%)	389(57%)		
Female	899(43.9%)	294(43%)		
Hukou				0.402
Non-agricultural	1472(71.8%)	479(70.1%)	0.702	
Agricultural	578(28.2%)	204(29.9%)		
Education level				0.386
None	310(15.1%)	94(13.8%)		
≥1	1740(84.9%)	589(86.2%)		
Marital Status			0.019	0.890
No spouse	223(10.9%)	73(10.7%)		
Have a spouse	1827(89.1%)	610(89.3%)		
Disabilities			1.091	0.296
No	1406(68.6%)	483(70.3%)		
Yes	644(31.4%)	200(29.3%)		
Hearing difficulty			3.976	0.046
No	1797(87.7%)	618(90.5%)		

(Continued)

TABLE 1 Continued

	Traning set	Testing set	H/χ2	*p*-value
Yes	253(12.3%)	65(9.5%)		
Pain			1.359	0.244
No	899(43.9%)	317(46.4%)		
Yes	1151(56.1%)	366(53.6%)		
Exercise			0.457	0.499
No	129(6.3%)	48(7%)		
Yes	1921(93.7%)	635(93%)		
Social activities			3.921	0.048
No	1110(54.1%)	340(49.8%)		
Yes	940(45.9%)	343(50.2%)		
Smoke			0.225	0.614
No	1503(73.3%)	494(72.3%)		
Yes	547(26.7%)	189(27.7%)		
Drink			0.648	0.421
No	1234(60.2%)	423(61.9%)		
Yes	816(39.8%)	260(38.1%)		
Resident			1.918	0.383
Urban	493(24%)	179(26.2%)		
Rural-Urban Integration and Special Areas	189(9.2%)	68(10%)		
Rural	1368(66.7%)	436(63.8%)		
Life satisfication			4.735	0.094
Good	861(42%)	256(37.5%)		
Fair	1112(54.2%)	403(59%)		
Bad	77(3.8%)	24(3.5%)		
Self reported memory			1.631	0.442
Good	303(14.8%)	88(12.9%)		
Fair	1267(61.8%)	436(63.8%)		
Bad	480(23.4%)	159(23.3%)		
Self reported health			0.472	0.790
Good	461(22.5%)	156(22.8%)		
Fair	1181(57.6%)	384(56.2%)		
Bad	408(19.9%)	143(20.9%)		
Sleep duration	6.5(2.5)	6.5(3)	1361.52	0.832
Number of chronic diseases	2(2)	2(2)	1360.37	0.438
Age	63(13)	62(13)	1299.68	0.010

relationship between the prediction error of random forest and the number of random trees is shown in Figure 5A. Therefore, it is the optimal model when mtry=6 and mtree=500. According to the mean value of Gini index reduction, the importance of the 10 variables was ranked. Age, number of chronic diseases, life satisfaction, self-rated health, and self-rated memory were the top 5 important indicators for predicting depression in middle-aged and elderly hypertensive people, as shown in Figure 5B.

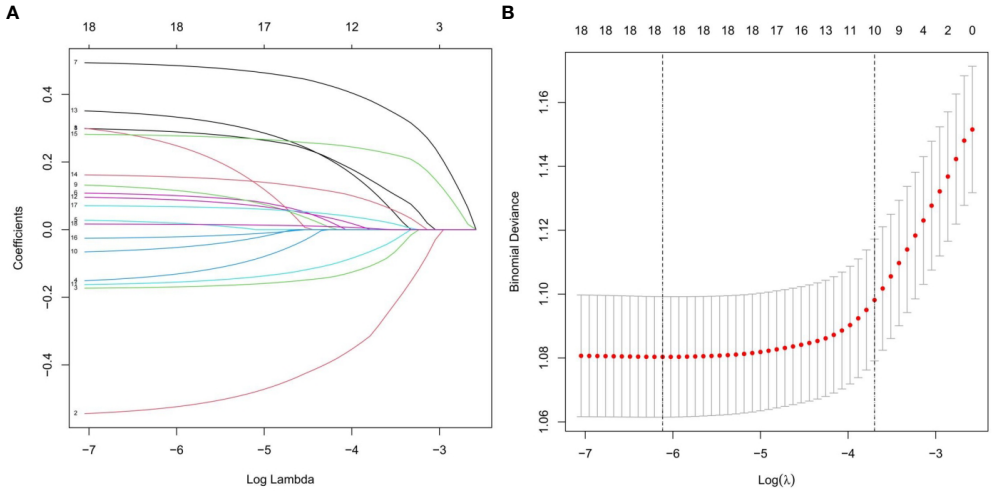

FIGURE 3
Lasso regression model was used to screen the risk factors. **(A)** Coefficient curves are generated according to the logarithmic (lambda) sequence, with nonzero coefficients generated by the optimal lambda. **(B)** Results of tenfold cross validation, partial likelihood deviation (binomial deviation) curves were plotted by validating the optimal lambda in the LASSO model, and virtual vertical lines were plotted according to the minimum lambda and standard error criteria.

Construction of XGBoost risk prediction model

In this study, risk factors were input into the XGBoost model for analysis. From the feature importance results in Figure 6, it can be seen that the top eight influencing factors are age, number of chronic diseases, pain, life satisfaction, self-rated health, gender, self-rated memory, and drink. Based on these results, the first eight factors were selected as input features for the model in this study.

Performance comparison results of three prediction models

In this study, we used the 683 participants in the testing set to compare the predictive effects of RF, LR and XGBoost three models on depression in middle-aged and elderly hypertensive people. As shown in Figure 7, the AUCs of the three models in the testing set ranged from 0.7 to 0.712. The AUC value of LR was the highest (AUC=0.712), and the AUC value of RF was the lowest (AUC=0.7). We also evaluated the accuracy, sensitivity, specificity, and other performance indicators of the model, as detailed in Table 4. The thresholds of the three models were 0.271, 0.191 and 0.198, respectively. The sensitivity of the LR model was the highest (0.789), followed by the XGBoost model (0.770), and the NPV of the LR model was the highest (0.716). In general, the LR model performed the best.

Discussion

Comparative model analysis

According to the 10 selected variables, this study used LR, RF and XGBoost machine learning algorithms to construct the risk prediction models for depression in middle-aged and elderly hypertensive patients and compared the models. The results showed that the LR-based model had the best performance in the

TABLE 2 Multivariate logistic analysis of depression in middle-aged and elderly patients with hypertension.

Variables	Coef	S.E.	Wald *Z*	*p*
Gender	0.439	0.108	4.08	<0.001
Hukou	-0.706	0.129	-5.47	<0.001
Pain	0.516	0.117	4.42	<0.001
Life satisfication	0.351	0.095	3.68	<0.001
Self-reported health	0.308	0.090	3.41	<0.001
Self-reported memory	0.181	0.089	2.03	0.043
Number of chronic diseases	0.072	0.033	2.16	0.031
Age	0.022	0.006	3.58	<0.001

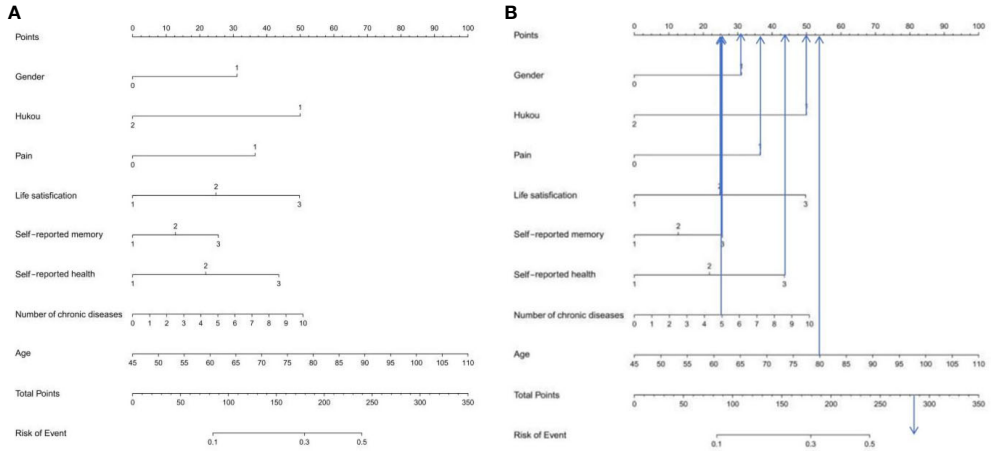

FIGURE 4
(A) Nomogram prediction model of logistic risk of depression in middle-aged and elderly patients with hypertension **(B)** Score explanation of the incidence of depression in middle-aged and elderly patients with hypertension. According to the risk factors in the Nomogram, the corresponding score of each variable can be known. After adding the scores of each variable, the prediction probability corresponding to the total score is the probability of depression in middle-aged and elderly hypertensive patients. Points is the individual score, Total Points is the total score, and Risk of Event is the incidence of depression corresponding to the total score.

area under the ROC curve, sensitivity and NPV, and was the best in general. In contrast, RF had the worst combined performance in several models. Several other machine learning algorithms are better able to deal with complex nonlinear relationships between variables, and using multiple algorithms can find the algorithm that performs best in this dataset, which is helpful to find models with good performance. In addition, we also constructed a nomogram model, which can be used to calculate the risk value of depression in middle-aged and elderly hypertensive patients. For example, female (score 31), agricultural hukou (score 50), pain (score 36.5), fair life satisfaction (score 25), poor self-rated memory (score 20.5), poor self-rated health (score 43), 5 chronic diseases (score 25), and age 80 (score 54). These scores are added to give a total score of 285, corresponding to a risk of more than 50%. This means that patients may be at higher risk for depression and therefore require individualized preventive measures.

TABLE 3 Case of variable assignment.

Variable	Assignment mode
Gender	Male=0; Female=1
Hukou	Agricultural hukou=1; Non-agricultural hukou=2
Pain	No=0; Yes=1
Life satisfication	Good=1; Fair=2; Bad=3
Self-reported health	Good=1; Fair=2; Bad=3
Self-reported memory	Good=1; Fair=2; Bad=3
Number of chronic diseases	Measured value
Age	Measured value

Influencing factors of depression in middle-aged and elderly patients with hypertension

This study found that depression in middle-aged and elderly patients with hypertension increased with age. This is consistent with the results of previous studies (43–46) and may be caused by factors such as the decline of physiological function and the weakening of psychological tolerance. Maatouk et al. interviewed 3,124 participants aged 57 to 84 years and used Logistic regression analysis to explore the relationship between high blood pressure and depressive symptoms (17). The findings show a significant link between depression and high blood pressure. In addition, individual perception is also influenced by many factors such as society, family, surrounding environment, economic income, culture, and customs (47). This suggests that we need to pay more attention to the mental health of middle-aged and elderly people, especially patients with hypertension. Therefore, in future work, more attention should be paid to the mental health of middle-aged and elderly people with hypertension to alleviate their negative emotions such as depression and anxiety. In addition, female patients were more likely to have depressive symptoms than men, which is consistent with the results of most studies (29, 48, 49). This may be due to the fact that women have a lower psychological tolerance to cope with stress, and are more sensitive to negative emotions, and a higher neuroticism score is also a factor (50). In addition, women often bear dual responsibilities and stress at home and at work, and women with chronic diseases may face difficulties in fulfilling gender-specific social roles, which also increases their risk of depressive and anxiety symptoms (48).

There is also a large difference in depressive symptoms between middle-aged and elderly hypertensive patients in urban and rural areas. Middle-aged and elderly hypertensive patients with agricultural hukou are more likely to have depressive symptoms, which is similar to the results of related studies (51). According to

FIGURE 5
(A) Dynamic relationship between prediction error of random forest and the number of random trees **(B)** Importance ranking of variable factors based on random forest.

this study, nearly half (40.6%) of the elderly hypertensive patients in rural areas of Jinzhong City of Shanxi Province, China were assessed using the CES-D (Center for Epidemiologic Studies Depression Scale), and nearly half (40.6%) of the patients had depressive symptoms (52). The reasons for this difference may be multifactorial. First of all, the economic level of middle-aged and elderly people in rural areas is much lower than that in towns and cities, which leads to the imperfect living environment, medical level and social security. Due to the limitation of economic conditions, the decrease of life status and satisfaction may increase the incidence of depression in middle-aged and elderly people in rural areas (53). Secondly, hypertensive patients in rural areas have lower awareness of disease, distance from medical institutions, and access to medical resources. This results in a lower sense of well-being for the patient, which in turn triggers depressive feelings.

Therefore, in addition to considering the disease factors of patients themselves, the government can start from the supply of public services and diagnosis and treatment services to formulate relevant policies (54). At the same time, according to the differences between urban and rural areas, different strategies can be taken to improve the mental health status of middle-aged and elderly patients with hypertension in rural areas. This may include better medical resources, better awareness of the disease, and a better social safety net. Through these measures, better support and help can be provided to middle-aged and elderly patients with hypertension and their quality of life can be improved (55).

Patients with hypertension often have other chronic diseases, and the results of this study suggest that those with coexisting chronic diseases are more likely to have depressive symptoms, and the more chronic diseases they have, the more likely they are to have depressive symptoms. This is consistent with other findings (48, 56) and may be due to limitations in daily functioning related to coexisting conditions (48). A similar conclusion was reached in the study by Gray et al. (57), who found that diabetes was an independent predictor of concurrent hypertension and depressive symptoms. In addition, cerebrovascular complications such as stroke and intracerebral hemorrhage were also more common in the depressed group, and many studies have shown that the occurrence of stroke is associated with an increased risk of

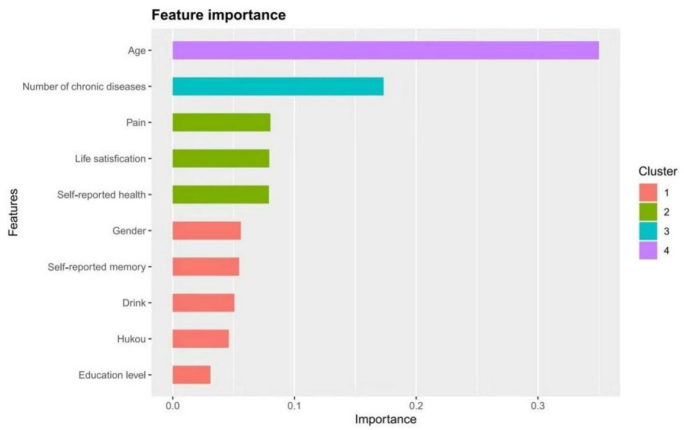

FIGURE 6
Importance ranking of variable factors based on XGBoost.

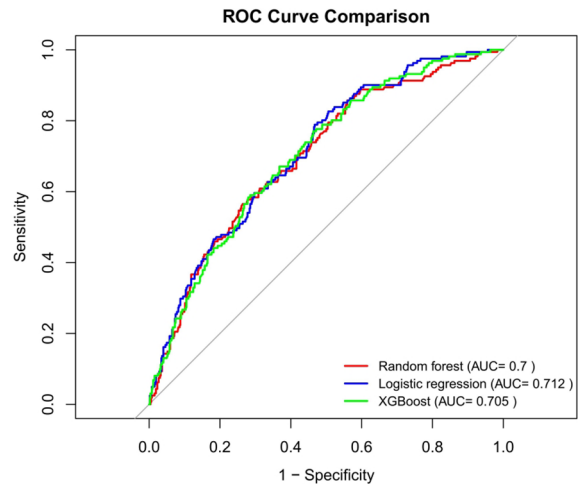

FIGURE 7
ROC curves for the three models.

depressive symptoms (58). Therefore, more attention should be paid to the emotional state of middle-aged and elderly hypertensive patients with multiple diseases in clinical practice.

The results of this study also showed that depressive symptoms were further aggravated if hypertensive patients also suffered from pain. This is similar to the findings of Chen et al (59) and Gerrits et al (60). In addition, a large number of cross-sectional studies have found that patients with pain have an increased risk of depression (61), and similarly, patients with depression have a higher risk of pain than those without depression (62). This may be because pain causes people to be limited in their physical activities, affecting their lives and reducing the frequency of contact with others. As pain and lack of social activities increase psychological distress, this leads to an increased incidence of depression. In conclusion, middle-aged and elderly patients with hypertension often have other chronic diseases, and the coexistence of these chronic diseases as well as pain symptoms may increase the risk of depression. Therefore, these complications should be paid attention to and actively managed in clinical practice to improve the mental health of patients.

Life satisfaction and depressive symptoms are two psychological constructs that are widely recognized and are often used in population health surveys to assess mental health (63). Europe and the United Kingdom and other countries have used life satisfaction as a relevant indicator to evaluate mental health (64). Although relatively few studies have examined the association between life satisfaction and blood pressure, the association has been found to be somewhat protective (65–68). The present study found that middle-aged and elderly hypertensive patients are more likely to have depressive symptoms, which is consistent with the results of previous studies (69). This may be due to the fact that middle-aged and elderly patients with low life satisfaction may experience many negative experiences and life stresses, which can exacerbate depressive moods. Therefore, when helping older people cope with depression, we need to focus on their life satisfaction and quality of life, provide positive support and help to help them cope with negative emotions and stress, and improve their quality of life and mental health.

The results of the present study also showed that patients with poorer self-rated memory had more severe depressive symptoms. Many previous studies have shown that people with high blood pressure have a decline in memory (70, 71). In addition, the results of a 12-year follow-up showed that middle-aged hypertensive people had worse cognitive function than healthy people without hypertension during the same period, and untreated hypertensive people had worse memory and information processing speed than those with stable blood pressure control (71). Subsequently, depressive symptoms occur due to memory loss in hypertensive patients, which has been demonstrated in previous studies (72, 73). Therefore, cognitive function training can be carried out in advance for middle-aged and elderly patients with hypertension in the future, which will contribute to the mental health of patients. In addition, poorer self-rated health was associated with a higher risk of depression. This is similar to the findings of Boima et al (43). On the one hand, it may be because when the self-rated health is poor, the ability of daily life is affected and the quality of life is decreased, resulting in heavier psychological burden, greater pressure, and more likely to produce depressive symptoms. On the other hand, it may be because the decline of health may lead to the limitation of people's communication and social activities with others. Lack of social support and a sense of isolation, which can also lead to the onset and exacerbation of depressive mood.

Limitations

There are some limitations in this study. First, we were unable to include all possible risk factors due to the structural limitations of the questionnaire. Second, the data relied heavily on respondents' self-reports, which may be subject to memory bias, subjective interpretation, and social expectations. Finally, although several methods were used to ensure the reliability and generalizability of the model, the results still need to be validated in external independent samples. Despite these limitations, we believe that these findings are instructive for the prevention and intervention of depressive symptoms in middle-aged and elderly patients with hypertension. Future research could further collect data on related factors to make the analysis of factors affecting depression more comprehensive and in-depth.

TABLE 4 Comparison of prediction performance of two kinds of models.

Model	AUC	Sensitivity	Specificity	PPV	NPV
Random forest	0.7	0.565	0.736	0.681	0.629
Logistic regression	0.712	0.789	0.533	0.628	0.716
Xgboost	0.705	0.770	0.536	0.624	0.700

Conclusion

In this study, a variety of machine learning algorithms were used to construct models for predicting the risk of depression in middle-aged and elderly patients with hypertension. After evaluation and comparison, the LR model was found to be the most predictive model. The results showed that gender, hukou, pain, life satisfaction, self-reported health, self-reported memory, number of chronic diseases, and age are risk factors for depression in middle-aged and elderly hypertensive patients. Medical staff can formulate intervention programs based on these related risk factors and implement them as early as possible to reduce the adverse effects of depression on middle-aged and elderly patients with hypertension.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: 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: The datasets generated for this study can be found in the China Health and Retirement Longitudinal Study (CHARLS) online datasets (https://charls.charlsdata.com/pages/data/111/zh-cn.html).

Ethics statement

The studies involving humans were approved by the Institutional Review Board of Peking University (IRB00001052-11015). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

FA: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. EL: Conceptualization, Writing – original draft, Writing – review & editing. HZ: Data curation, Writing – review & editing. QJ: Data curation, Writing – original draft.

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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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Evaluating the safety and efficacy of zuranolone in the management of major depressive disorder and postpartum depression, with or without concurrent insomnia: a rigorous systematic review and meta-analysis

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Introduction: Major depressive disorder (MDD), postpartum depression (PPD), and insomnia are neuropsychological conditions in which zuranolone is used to improve symptoms and prognosis of the disorder. This meta-analysis aimed to determine the efficacy of zuranolone in comparison to other drugs used for treating these conditions.

Methods: This meta-analysis included patients aged between 18 and 75 years who were diagnosed with major depressive disorder and postpartum depression with or without insomnia and were administered zuranolone for treatment. Only randomized controlled trials (RCTs) were included, and animal studies were excluded. The databases used were PubMed, Scopus, Cochrane, and Clinicaltrials.gov, with MeSH terms and relevant keywords for (Zuranolone) and (Depression). The Cochrane risk of bias tool was used for quality assessment.

Results: The meta-analysis included eight RCTs that analyzed data from 2031 patients. The meta-analysis revealed statistically significant changes in the Hamilton Depression Rating Scale (HAM-D), Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A), and treatment-emergent adverse effects (TEAE) scores in the PPD subgroup. HAM-D and TEAEs scores were also significant in the MDD subgroup, but the changes in the MADRS, HAM-A, and Bech-6 scores were insignificant. Serious adverse events were insignificant in all subgroups.

Conclusion: Meta-analysis found a significant improvement in depressive symptoms with zuranolone treatment, especially on day 15. This suggests that zuranolone is a promising therapeutic option for patients with MDD and PPD with or without insomnia.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=459554, identifier CRD42023459554.

KEYWORDS

zuranolone, major depressive disorder, postpartum depression, insomnia, meta-analysis

Introduction

Major Depressive Disorder (MDD) is a psychiatric condition characterized by persistent feelings of sadness and hopelessness, often accompanied by other symptoms such as changes in appetite, sleep disturbances, loss of interest in activities, and cognitive impairments. According to the World Health Organization, MDD is one of the most prevalent mental disorders worldwide, affecting over 300 million people of all ages (1). In the United States, it is estimated that 8.9 million adults had MDD in 2021, making it a leading cause of disability (1–3). The exact cause of MDD is not fully understood, but it is believed to be a result of complex interactions between various risk factors (4). Another mood disorder that can present with depressed mood is postpartum depression (PPD), which affects approximately 15% of new mothers after childbirth (5, 6). Factors that increase the risk of PPD include a history of depression, exposure to violence, obesity, and poor sleep quality after childbirth (7). Both MDD and PPD can also manifest as insomnia, defined as difficulty falling asleep or maintaining sleep (8). It is estimated that 10% of the global adult population suffers from chronic insomnia, while an additional 20% experience occasional symptoms (9, 10). Insomnia is closely associated with depression, and it is believed to exacerbate symptoms of depression and increase the risk of self-harm or suicide (11). Depression can also lead to insomnia by reducing the latency of REM sleep, which disrupts the body's natural sleep-wake cycle (12). There are several options for treating MDD, such as benzodiazepines, Selective Serotonin Reuptake Inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). Benzodiazepines promote the release of the neurotransmitter gamma-aminobutyric acid (GABA), which inhibits nerve activity in the brain. SSRIs decrease the reuptake of serotonin, resulting in the alleviation of MDD symptoms (13–15). SNRIs inhibit the uptake of monoamines within the synaptic cleft, which ultimately leads to improvement (16). Mirtazapine is beneficial in treating MDD by blocking presynaptic alpha 2 adrenergic receptors (17).

Another class of drugs, known as neuroactive steroids, has gained significant attention in addressing these conditions. Brexanolone, in its intravenous form, and allopregnanolone are essential in treating PPD by modulating gamma-aminobutyric acid (GABAa) receptors, resulting in reduced anxiety levels and improved sleep quality (18, 19). While these drugs have demonstrated promise in treating MDD, they also have numerous adverse effects. Benzodiazepines, for instance, can cause cognitive impairment, hyperexcitability, insomnia, anxiety, and seizures upon withdrawal. In contrast, approximately 30% of patients show no response to selective serotonin reuptake inhibitors (SSRIs) (20, 21). Zuranolone, a synthetic neuroactive steroid, increases GABA release by positive allosteric modulation of GABA receptors, showing potential for treating MDD and PPD (22–24). A study by Maximos et al. revealed that zuranolone improved PPD symptoms in adults and had beneficial effects on their insomnia symptoms (23). Another study demonstrated that zuranolone effectively relieved insomnia symptoms in females with anxiety and PPD (25).

Our systematic review and meta-analysis aim to determine whether zuranolone is a more effective treatment option for patients with PPD and MDD, with or without insomnia. This information can help physicians identify alternative treatment strategies for patients with MDD and PPD who may not respond to or experience severe side effects from conventional treatments. This study can prove beneficial for patients with MDD and PPD in assessing the efficacy of zuranolone in treating these disorders in individuals with concurrent insomnia symptoms.

Methods

Protocol and registration

This systematic review and meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (26). Prior to the initiation of the study, it was registered in the International Prospective Register of Systematic Reviews (PROSPERO) registry under the credentials CRD42023459554 (27).

Search strategy

An extensive search of electronic databases, including PubMed, Scopus, Clinicaltrials.gov, PsychINFO, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), was performed from inception until September 2023. No restrictions were imposed on time or sample size during the literature search. The following keywords were used in the search strategy along with relevant MeSH terms and Boolean operators: "Zuranolone" OR "SAGE-217" AND "depression" OR "major depressive disorder" AND "Postpartum depression." The detailed search strategy is presented in Supplementary Table 1. Furthermore, the bibliometrics of the published articles on related topics and conference proceedings were examined to ensure that no articles were overlooked.

Study selection

All articles retrieved from the search results were entered into Rayyan.ai, an online systematic review management platform (28). After removing duplicates, two investigators (S. A. and M.B.A. S.) independently screened the remaining studies in accordance with the specified inclusion and exclusion criteria. The initial screening process involved evaluating titles and abstracts to identify potentially eligible studies, which were then followed by a full-text assessment to ensure relevance based on our predetermined criteria. Any conflicts or disagreements were resolved through a consensus process or with the assistance of a third reviewer (L. M.). Studies were selected based on the following Population, Intervention, Control, and Outcomes (PICO) criteria: randomized clinical trials with parallel groups, population aged 18–75 years diagnosed with major depressive disorder (MDD) or postpartum depression (PPD) with or without insomnia, and intervention with zuranolone for treatment compared to a control group receiving placebo. We included studies reporting outcomes such as changes from baseline in the Hamilton Depression Rating Scale (HAM-D), Montgomery–Åsberg Depression Rating Scale (MADRS), and Hamilton Anxiety Rating Scale (HAM-A). Non-randomized trials, quasi-randomized trials, animal experiments, chemistry or cell line studies, conference abstracts, comments, editorials, review articles, meta-analyses, case reports, and case series were excluded, as were publications that reported duplicate data or were written in languages other than English.

Data extraction

Data extraction was performed by two authors: (A. R. and S.R.) In the event of disagreement, a third reviewer, M. A., was consulted to reach a consensus. Information on the title, author, year of publication, and demographics, including age, sex, and sample size in each group, was extracted meticulously. Moreover, relevant characteristics, such as the HAM-D score, dosage, length of treatment, status and degree of treatment-resistant depression, treatment strategy, adverse events, and general methodological details, including study arms and crossover trials, were also included. Data on treatment outcomes, including the post-HAM-D score, post Bech-6 score, MADRS, and post-HAM-A scores, were extracted from the included studies.

Quality assessment

Two independent authors, R. K. and A. R., assessed the risk of bias in the included studies using the Cochrane Risk of Bias (RoB 2.0) tool for randomized controlled trials (RCTs) (29). The RoB 2.0 addressed five specific domains: (1) Bias arising from the randomization process; (2) Bias due to deviations from the intended intervention; (3) Bias due to missing outcome data; (4) Bias in the measurement of the outcome; and (5) Bias in the selection of the reported results. This tool was applied to each included study, and the studies were classified as having a high, moderate, or low risk of bias based on the RoB classification. A third review author, H. A. U. R., was consulted to resolve any disagreements concerning the ROB assessment.

Statistical analysis

Statistical analysis was conducted using a random-effects model to pool the Mean Differences (MDs) and Risk Ratios (RRs) for continuous and dichotomous outcomes, respectively, with 95% Confidence Intervals (CIs). The pooled results were graphically represented in forest plots, and the I2 statistic was used to assess the heterogeneity across studies. An I2 statistic of > 50% was considered significant, indicating high heterogeneity, whereas a value of less than 50% indicated low heterogeneity. The I2 values were interpreted according to the guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions. Statistical significance was set at $P < 0.05$. Funnel plots were used to visually assess publication bias, and subgroup analyses were performed to identify sources of heterogeneity in clinical outcomes. The subgroups included patients with 1) major depressive disorder, 2) postpartum depression, and 3) Insomnia in patients with major depressive disorder or postpartum depression. Statistical analysis was conducted using Review Manager (RevMan, Version 5.4.1; The Cochrane Collaboration, Copenhagen, Denmark).

Results

A total of 624 studies were obtained, following which 8 RCTs were selected for inclusion in our review after excluding duplicates, reviews, and ineligible articles through Primary and Secondary screening (24, 25, 30–35). The PRISMA flowchart (Figure 1) provides a summary of the literature screening process. Our systematic review and meta-analysis included 8 studies that reported data on 2,031 patients. The characteristics of the included studies are presented in Table 1, which also indicates that all studies included had a low-to-moderate risk of bias. A detailed quality assessment of the included studies is illustrated in Figures 2A, B and detailed reasons are provided in Supplementary Table 2.

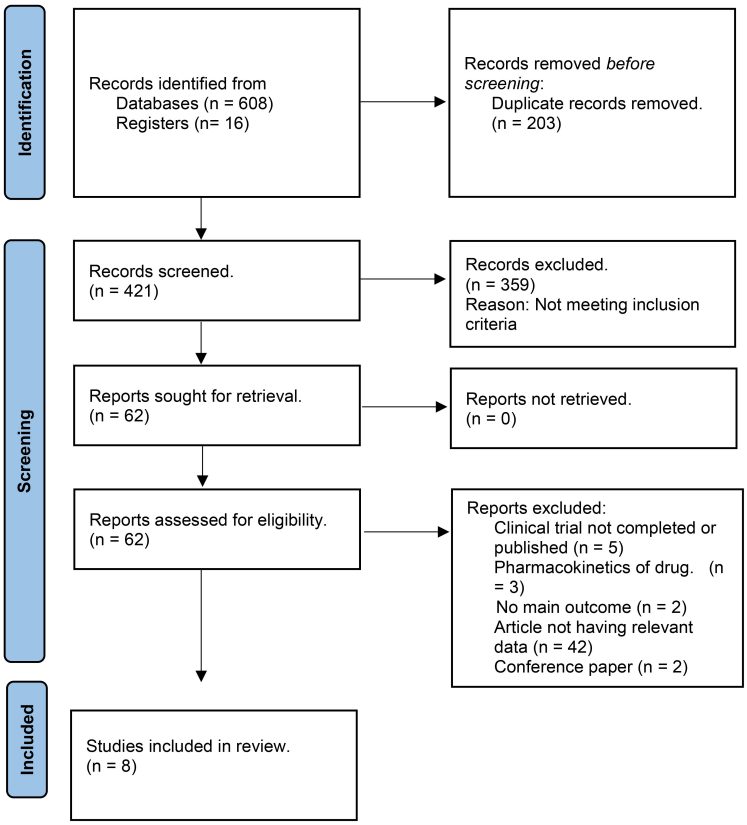

FIGURE 1
PRISMA Flowchart.

Primary outcome

Change from baseline in HAM-D score

Seven studies were assessed to determine the relationship between changes in HAM-D scores and the use of zuranolone. The results indicated a significant decrease in the HAM-D score in zuranolone consumers compared to the placebo group (MD: -1.71; 95% CI= [-2.47, -0.95]; p<0.00001; I2 = 38%). A consistent finding was observed in the subgroup analysis for the MDD (MD: -1.48; 95% CI [-2.21, -0.74]; p<0.0001; I2 = 0%) and PPD subgroup (MD: -4.08; 95% CI [-5.82, -2.35]; p<0.00001; I2 = 0%), except for patients with insomnia and MDD or PPD (MD: -0.79; 95% CI [-1.83, 0.26]; p=0.14; I2 = 0%) (Figure 3).

Secondary outcomes

Change from baseline in MADRS score

Five studies were evaluated to determine the impact of zuranolone on MADRS scores, which demonstrated a decrease in MADRS scores compared to placebo (MD=-0.82; 95% CI= [-1.52, -0.11]; p=0.02; I2 = 71%). A subgroup analysis revealed significant results within the PPD subgroups (MD=-4.86; 95% CI= [-7.35, -2.36]; p=0.0001; I2 = 0). However, no significant findings were observed in the MDD subgroup (MD= -0.27; 95% CI= [-0.69, 0.14]; p=0.12; I2 = 46%) (Figure 4).

Change from baseline in HAM-A score

Five studies were evaluated to determine the impact of zuranolone on HAM-A scores, which showed a significant overall reduction in HAM-A scores in patients administered zuranolone compared with placebo (MD=-2.23; 95% CI= [-4.19, -0.26]; p=0.03; I2 = 88%). A subgroup analysis showed significant results in the PPD subgroup (MD -2.75; 95% CI= [-4.33, -1.16]; p=0.0007; I2 = 0%). However, no significant reduction was observed in the MDD subgroup (MD=-1.73; 95% CI= [-4.50, 1.03]; p=0.22; I2 = 92%) (Figure 5).

The leave-one-out sensitivity analysis showed that the reduction in the HAM-A score was affected by a single study by Bruce et al. (12). Removing that study resulted in a significant reduction in I2 values (p = 0.09; I2 = 50%) and overall effect [MD = −1.65, 95% CI (−3.17, −0.14), p= 0.03] (Supplementary Figure 1).

Change from baseline in Bech-6 score

Two studies were analyzed for the impact of Zuranolone on the Bech-6 score. The results showed a non-significant difference between zuranolone and placebo in reducing the Bech-6 score (MD=-6.85; 95% CI= [-16.70, 3.01]; p=0.17; I2 = 96%). (Figure 6) The leave-one-out sensitivity analysis indicated that the Bech-6 score was influenced by a single study, i.e., Bruce et al. (12). When this study was removed, the I2 values showed a significant reduction in overall effect [MD = −2.50, 95% CI (−5.78, 0.78), p = 0.13] (Supplementary Figure S2).

TABLE 1 General characteristics of included studies and patients.

Studies	Drug Dose	Patients	Total Population		Age (Years)		Gender		BMI (kg/m2)		Baseline HAM-D score (mean and sd)		Antidepressants at baseline	
							Male; Female							
			Z group	Placebo	Z group	Placebo	Z group	Placebo	Z group	Placebo	Z group	Placebo	Z group	Placebo
Gunduz-Bruce et al., 2019 (31)	zuranolone (30mg)	Major Depressive Disorder	45	44	49.1 ± 13.6	38.3 ± 12.2	20;25	14;30	30.0 ± 6.3	29.9 ± 5.2	25.2 ± 2.6	25.7 ± 2.4	12	10
Kato et al., 2023 (33)	zuranolone (20-mg)	Major Depressive Disorder	85	83	39.3 ± 12.6	40.8 ± 10.6	36;49	35;47	23.9 (4.4)	23.6 (5.3)	24.8 ± 2.4	24.5 (2.1)	NA	NA
	zuranolone (30-mg)		82		38.8 ± 12.0		37;45		22.7 (4.0)		24.6 ± 2.2		NA	
Clayton et al., 2023 (24)	zuranolone (20-mg)	Major Depressive Disorder	188	190	41.9 ± 12.2	41.4 ± 12.2	47;112	51;106	NA	NA	25.8 ± 2.8	25.8 ± 3.1	46	49
	zuranolone (30-mg)		192		42.3 ± 11.8		45;121		NA		25.9 ± 2.9		47	
Clayton et al., 2023 (32)	zuranolone (50-mg)	Major Depressive Disorder	268	269	39.4 ± 12.3	40.1± 12.6	82;186	103;166	29.6 ± 6.3	30.3 ± 6.2	26.8 ± 2.6	26.9 ± 2.7	183	190
NCT03771664 et al., 2022	zuranolone (30-mg)	Insomnia and Major Depressive Disorder	43	43	44.6 ± 12.50	42.0 ± 11.60	15;28	12;31	NA	NA	NA	NA	NA	NA
							Female							
Deligiannidis et al., 2021 (30)	zuranolone (30-mg)	Postpartum Depression	76	74	29.3 ± 5.4	27.4 ± 5.3	76	74	31.1 ± 6	30.3 ± 8	28.4 ± 2	28.8 ± 2	16	18
Deligiannidis et al., 2023 (34)	zuranolone (50-mg)	Postpartum Depression	98	98	30.0 ± 5.9	31.0 ± 6.0	98	98	30.9 ± 6.3	29.6 ± 6.3	28.6 ± 2.5	28.8 ± 2.3	15	15
Deligiannidis et al., 2023 (25)	zuranolone (30-mg)	Insomnia and Postpartum Depression	77	76	16 ± 45	16 ± 45	77	76	NA	NA	26	26	16	13

mg, miligram; NA, not available.

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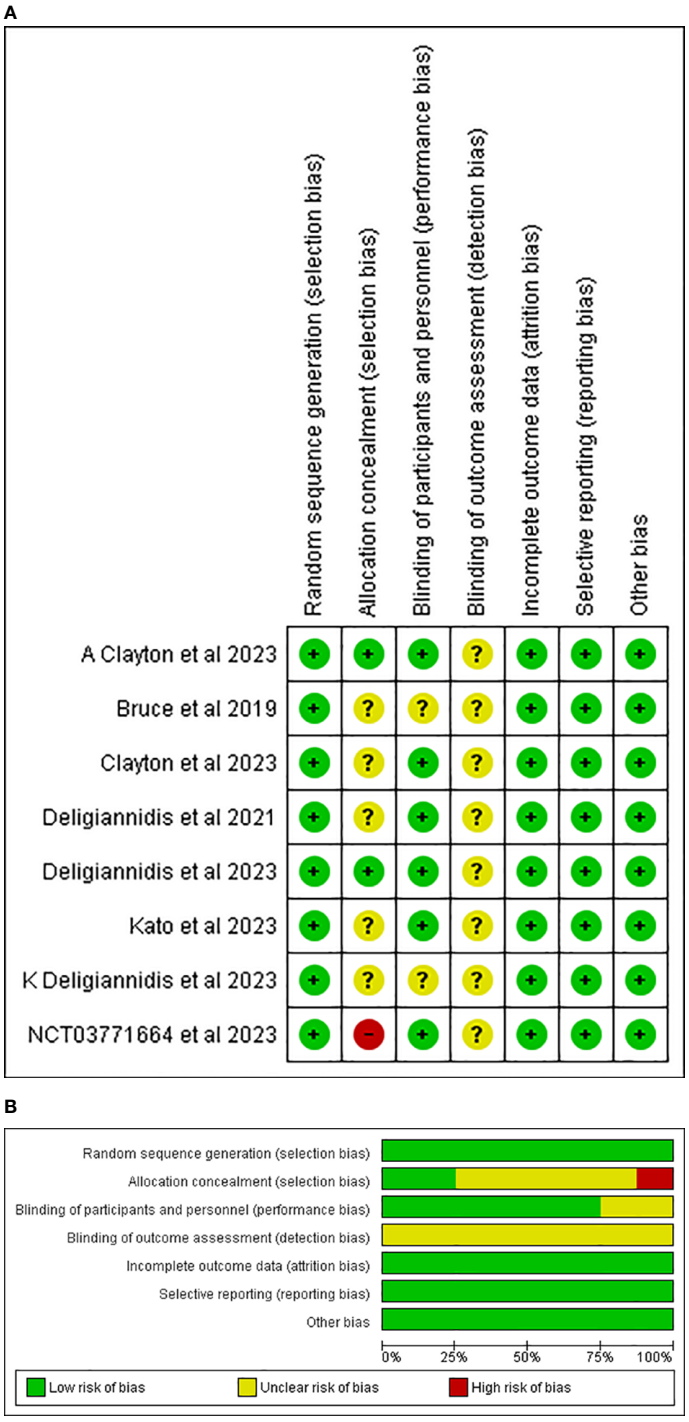

FIGURE 2
(A) Risk of bias summary. **(B)** Risk of bias graph.

Treatment-emergent adverse effects

Eight studies were included for the outcome of TEAEs, and the overall pooled result demonstrated that placebo was associated with fewer TEAEs than Zuranolone. (RR: 1.18, 95% CI [1.05, 1.32], p=0.007; I2 = 52%). After conducting a subgroup analysis, it was found that TEAEs were significantly higher in the Zuranolone group than in the placebo group for MDD and PPD. (RR: 1.16, 95% CI [1.16, 1.27]; p=0.0008, I2 = 0%) and (RR: 1.21, 95% CI [1.01, 1.45]; p=0.04; I2 = 0%) respectively. However, the insomnia subgroup and MDD or PPD did not show a significant association. (RR: 1.47, 95% CI [0.47, 4.58]; p=0.51; I2 = 52%) (Figure 7).

Serious adverse effects

Five studies were included in the analysis of serious adverse effects (AEs), and the overall pooled result showed no significant association between the groups (RR, 1.37; 95% CI [0.65, 2.90], p=0.41; I2 = 0%).

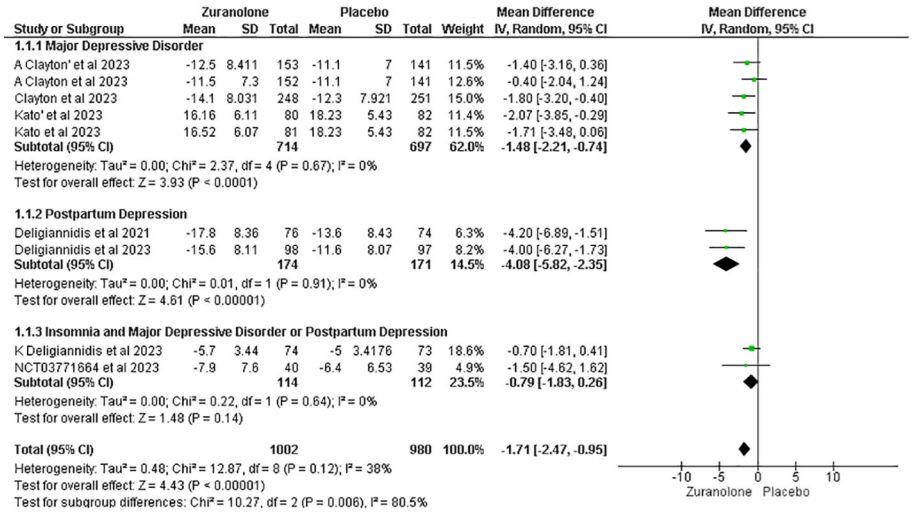

FIGURE 3
Forest plot of reduction in HAM-D score.

Following a subgroup analysis, insignificant findings were revealed for the MDD (RR: 1.32; 95% CI [0.45, 3.84]; p = 0.61; I2 = 0%), PD (RR: 1.76; 95% CI [0.35, 8.88]; p = 0.49; I2 = 43%), and insomnia with MDD or PD (RR: 1.00; 95% CI [0.06, 15.48]; p = 1.00) groups (Figure 8).

Meta-regression

We assessed mean age, female sex percentage, and body mass index (BMI) as potential covariates that could affect the effect size on our primary outcome and change from baseline in the HAM-D score. Female sex percentage and BMI showed a non-significant association; however, mean age was found to have a significant effect on the HAM-D score. The results are as follows: mean age, Coeff: 0.0270, p=0.0099; female sex percentage, Coeff: -0.0050, p=0.0563; BMI, Coeff: -0.0034, p=0.8616 (Supplementary Figures 3A–C).

Discussion

The purpose of this meta-analysis was to investigate the safety and efficacy of zuranolone in the treatment of postpartum depression, insomnia, and major depressive disorders. Our analysis included eight studies comparing zuranolone with a placebo and focused on six outcomes (24, 25, 30–35). The primary outcome measure was the change in the Hamilton Depression Rating Scale, while the secondary outcomes included the Montgomery Asberg Depression Rating Scale, Hamilton Anxiety Scale, Bech Scale, treatment-emergent side effects, and serious adverse effects. Although our primary outcome and some secondary outcomes showed significant improvements favoring zuranolone, these two outcomes did not reach statistical significance. However, the overall results favored drug use. However, due to the low certainty of the evidence, we approached the findings cautiously, emphasizing the need for additional studies to strengthen the reliability of the results. In summary, our meta-analysis suggests potential benefits of zuranolone in the treatment of postpartum depression, major depressive disorder, and insomnia. Specifically, we observed improvements in HAM-D scores on day 15 with zuranolone compared with placebo, along with reductions in HAM-A and

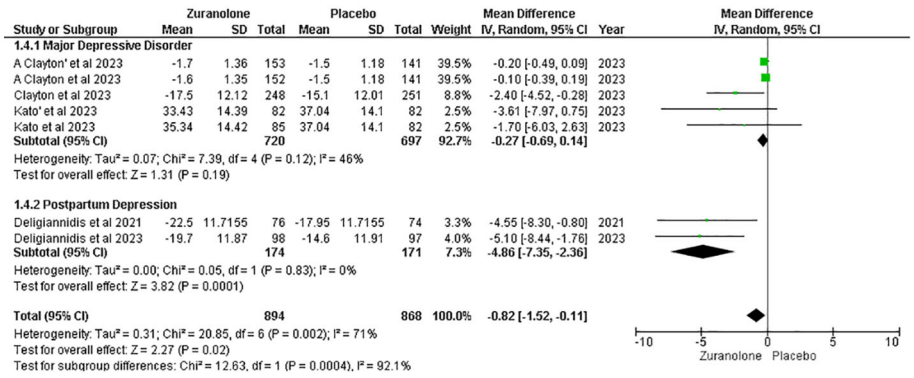

FIGURE 4
Forest plot of reduction in MADRS score.

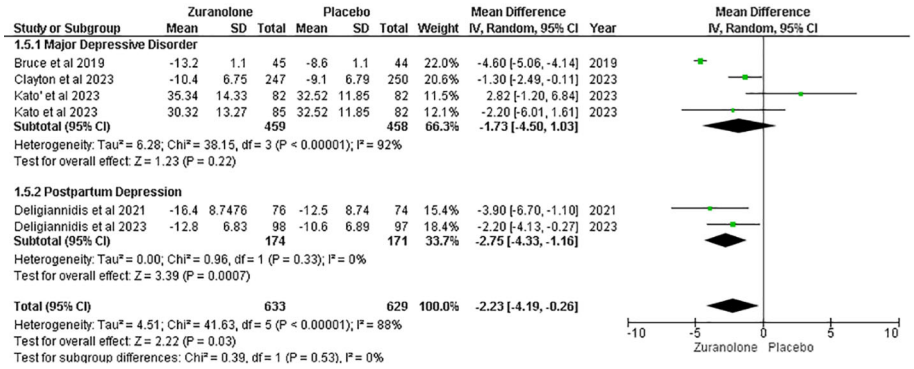

FIGURE 5
Forest plot of reduction in HAM-A score.

MADRS scores. Nevertheless, zuranolone users experienced mild treatment-related adverse effects.

Depression has been treated with a variety of medications, each presenting a unique balance between efficacy and safety considerations (20). These medications are among the most prescribed for depression, but their efficacy can be limited in certain cases. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are effective but have notable side effects and carry the risk of toxic reactions if overdosed (36). In contrast, newer drugs such as ketamine have shown promise in treating treatment-resistant depression and reducing suicidal behavior (37). However, concerns regarding its long-term use and potentially severe side effects have tempered enthusiasm. Psilocybin, another emerging option, appears promising for alleviating depression, anxiety, and insomnia (12). However, limited research has hampered broader acceptance (38). These concerns and the quest for more effective and safer treatments culminated in the development of zuranolone, which received FDA approval in 2023 (39). Zuranolone, which acts on GABA receptors, stands out for its rapid onset of action and efficacy in relieving depressive symptoms (6, 40). It helps in the orientation of neuronal circuits and organizes brain function, which is specifically linked to mood and behavior (41).

However, there are concerns regarding its long-term use and safety in the context of MDD; consequently, it has not been approved for use in treating MDD (42, 43). Studies have assessed the efficacy of zuranolone under various conditions. For example, in postpartum depression, significant improvements in the scores of the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Hamilton Rating Scale for Anxiety (HAM-A) were observed within a short treatment duration of 14 days, although accompanied by notable adverse effects (34, 44). Additionally, zuranolone has demonstrated benefits in individuals with major depressive disorder by enhancing neural circuits and overall brain function (45). It has also been effective in addressing insomnia in conjunction with postpartum depression, leading to improvements in sleep quality (46, 47). However, the use of zuranolone is associated with side effects, including a higher risk compared with a placebo, as indicated in certain studies (34, 46). Concerns regarding the potential suicide risk and impairment in daily activities have also been raised. Nevertheless, conflicting findings exist, with some studies reporting no significant increase in suicidal ideation, although noting other adverse effects (48). These complexities underscore the ongoing need for comprehensive research and cautious consideration of the benefits and risks of zuranolone in clinical practice.

The levels of zuranolone in the blood were dependent on the dose, with the highest levels observed in the 30 mg dosage group. These dosages were chosen based on safety and tolerability assessments from a prior phase 1 trial involving healthy Japanese individuals, including older adults, where the 30 mg dose showed promising results. Interestingly, both healthy Japanese and White adults had plasma exposure levels that were comparable to those of

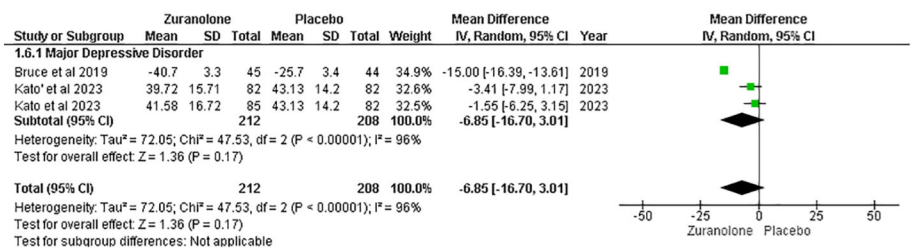

FIGURE 6
Forest plot of reduction in Bech-6 score.

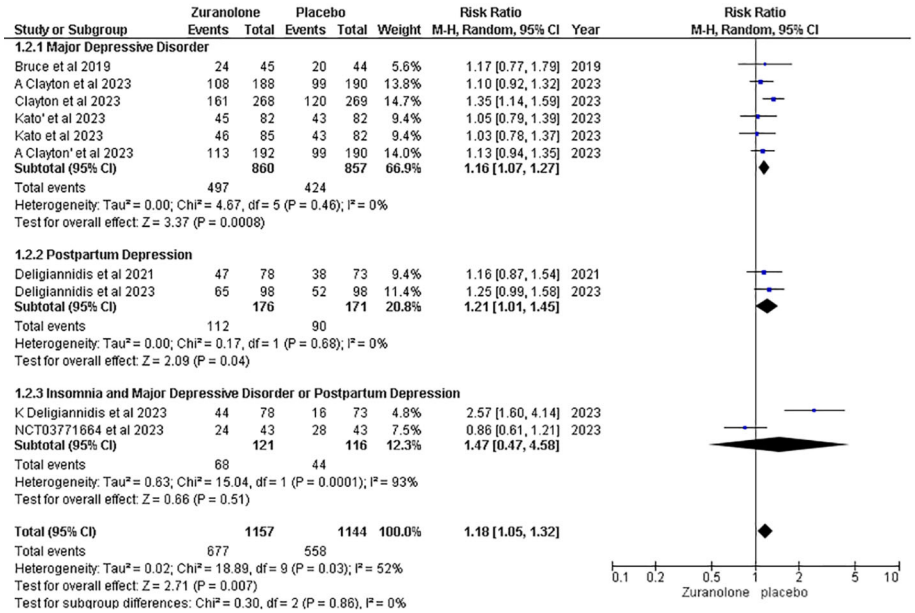

FIGURE 7
Forest plot of treatment emergent adverse effects.

zuranolone. Furthermore, a phase 2 study conducted in the US on individuals with MDD revealed a significant reduction in depressive symptoms with a 30 mg daily dose of zuranolone over 14 days without encountering any serious safety or tolerability concerns (33, 49). Additionally, a meta-analysis showed that increasing the dose of zuranolone correlated with symptom improvement, although this was accompanied by an increased risk of side effects (34). This finding was supported by another study that demonstrated the dose-dependent efficacy of zuranolone while noting a non-significant association between higher doses and severe adverse effects, consistent with our study's observations (50). These results were favorable when zuranolone was used for 14 days; however, when the drug was used for a similar duration throughout the year, it led to mild to moderate side effects, which were more common in patients who used 30 mg compared with those who took 50 mg (51).

Limitations

Despite the insights provided by our study, it has several limitations. First, the limited availability of recent studies resulted in small sample sizes, which could compromise the reliability and

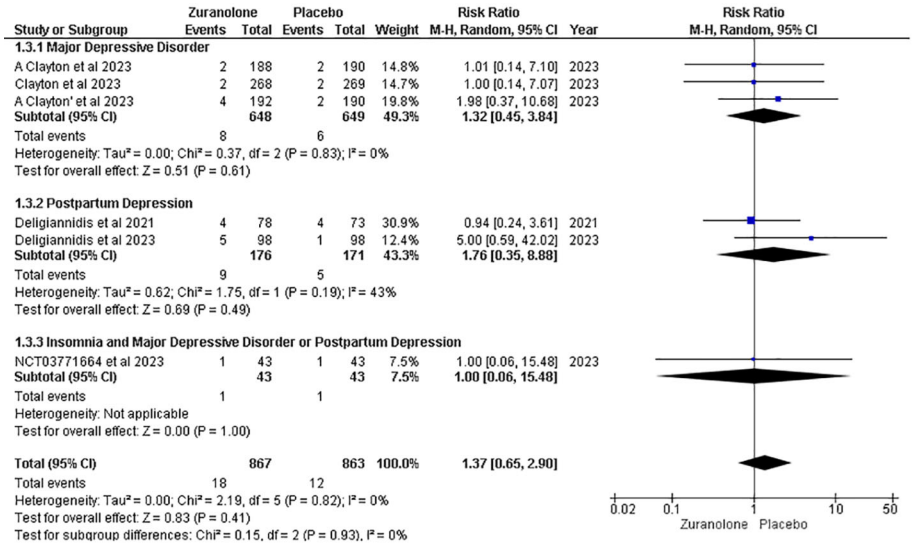

FIGURE 8
Forest plot of serious adverse effects.

accuracy of our findings. Second, insufficient data prevented us from considering preexisting medical conditions that may affect drug efficacy and safety. Lastly, we could not explore the potential interactions between the drug and pretreatment medications, which could influence its efficacy.

Conclusion

In summary, this meta-analysis was conducted to evaluate the effectiveness of zuranolone in treating MDD and PPD with or without insomnia. The results unequivocally showed a statistically significant improvement in depressive symptoms with the use of zuranolone, which was particularly pronounced on day 15. These findings underscore the potential of zuranolone as a promising therapeutic option for individuals with MDD and PPD with or without insomnia. However, further randomized controlled trials and observational studies are required to gain a deeper understanding of the efficacy of zuranolone in treating MDD and PPD with or without insomnia. It would be highly beneficial if future research included a larger sample size and information about new scales and outcomes.

Data availability statement

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

Author contributions

AR: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. SA: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Data curation, Conceptualization. MBAS: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Investigation. SLM: Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Conceptualization. RK: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Investigation. MA: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. SR: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. SBA: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Data curation, Conceptualization. HAUR: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization. FD: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Methodology, Investigation, Formal analysis. MA: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Project administration, Methodology, Investigation.

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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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Supplementary material

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Is the acquired hypothyroidism a risk factor for developing psychiatric disorders?

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Hypothyroidism is a prevalent thyroid condition in which the thyroid gland fails to secrete an adequate amount of thyroid hormone into the bloodstream. This condition may develop due to genetic or acquired factors. The most frequent cause of acquired hypothyroidism is chronic autoimmune thyroiditis, also known as Hashimoto's disease. Acquired hypothyroidism is diagnosed when patients present with overt hypothyroidism (also known as clinical hypothyroidism), as they exhibit increased TSH and decreased T_3 and T_4 serum levels. This article examines the prevalence of psychiatric disorders among patients diagnosed with acquired hypothyroidism with or without Levothyroxine treatment. We discuss the available evidence indicating that acquired hypothyroidism may be a risk factor for psychiatric disorders, and the effectiveness of thyroid treatment in relieving psychiatric symptoms. Additionally, we provide critical details on thyroid hormone cutoff values reported in the literature, their potential clinical importance, and their correlation with psychiatric symptoms. Finally, we

Abbreviations: 3-HAA, 3-hydroxyanthranilic acid; 3HKYN, 3-Hydroxy Kinurenine; 5-HT, serotonin; AA, anthranilic acid; BAI, Beck anxiety inventory; BDI, Beck depression inventory; BDI-II, Beck depression inventory-II; BDNF, Brain derived neurotrophic factor; CHS, Clalit health services; CI, confident interval; CRP, C-reactive protein; DSM-III-R, Diagnostic and statistical manual of mental disorders; eNOS, Endothelial NItric Oxide Synthase; FST, forced swimming test; HARS, Hamilton anxiety rating scale; HDRS, Hamilton depression rating scale; HPA-axis, Hypothalamic-Pituitary-Adrenal axis; HR, Hazard risk; IDO, Indolamine 2–3 Dioxygenase; IGNs, Immature granular neurons; IL, Interleukin; iNOS, Inducible Nitric Oxide Synthase; KP, Kynurenine Pathway; KYN, Kynurenine; KYNA, Kynurenic Acid; L-T_4, Levothyroxine; M-CIDI, Munich composite international diagnostic interview; MRI, magnetic resonance imaging; NAD, Nicotinamide Adenine Dinucleotide; NMDA, N-Methyl-D-Aspartate; nNOS, Neuronal Nitric Oxide Synthase; NO, Nitric Oxide; NOS, Nitric Oxide Synthase; PET, positron emission tomography; PHQ-9, Patient health questionnaire-9; PRIME-MD Test, Primary care evaluation of mental disorders; QUIN, Quinolinic Acid; ROS, Reactive Oxygen Species; SciELO, Scientific electronic library online; SSRIs, selective serotonin reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; STAI, state-trait anxiety inventory; T_3, triiodothyronine; T_4, thyroxine; Th17, T helper 17; THs, Thyroid hormones; ThyPRO, Thyroid-related quality-of-life patient-reported outcome; TNF, Tumor necrosis factor; TRP, Tryptophan; TRα1, Thyroid hormone receptor alpha 1; TSH, Thyroid stimulating hormone; TST, tail suspension test; WHO, World Health Organization.

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examined the various mechanisms by which acquired hypothyroidism can lead to depression. The high rate of comorbidity between hypothyroidism and psychiatric disorders deserves special attention, indicating the importance of consistent monitoring and timely identification of psychiatric symptoms to prevent disease exacerbation and facilitate therapeutic management. On the other hand, several mechanisms underlie the strong association between depression and acquired hypothyroidism. Deeper research into these mechanisms will allow knowledge of the pathophysiology of depression in patients with acquired hypothyroidism and will provide clues to design more precise therapeutic strategies for these patients.

KEYWORDS

acquired hypothyroidism, depression, anxiety, TSH, triiodothyronine (T3), thyroxine (T4), levothyroxine, L-T4

Highlights

- Acquired hypothyroidism increases the risk of depression and anxiety in adult patients with or without L-T4 treatment.
- Acquired hypothyroidism may lead to depression by multiple mechanisms, including alterations in serotonergic neurotransmission or the HPA axis, changes in adult hippocampal neurogenesis or brain region integrity, activation of systemic pro-inflammatory processes or neuroinflammation, or triggering of the kynurenine pathway.
- Several lines of research should be undertaken to investigate whether acquired hypothyroidism is a risk factor for the development of schizophrenia or bipolar disorder, or for the development of psychiatric disorders in children and adolescents.

1 Introduction

Hypothyroidism is a medical condition resulting from inadequate production of thyroid hormones (THs), often caused by thyroid gland dysfunction. According to Usman et al. (2023), hypothyroidism is diagnosed when thyroid stimulating hormone (TSH), triiodothyronine (T_3), and thyroxine (T_4) are >4.94 μIU/mL, <1.71 pg/mL, and <0.7 ng/dL, respectively (1). This condition results in clinical complications and disturbances in the physiological maintenance of bodily functions (2). Hypothyroidism can manifest because of either genetic or acquired factors. The latter can affect individuals during childhood, adolescence, or adulthood, and develops from sources other than genetic ones (2, 3). The most frequent cause of acquired hypothyroidism is chronic autoimmune thyroiditis, more commonly known as Hashimoto's disease. In addition to other causes, such as iodine deficiency, thyroidectomy, radioactive iodine therapy, radiation (4), viral infections (5), and drug use (6). In low-income countries, iodine deficiency is the leading cause of acquired hypothyroidism, whereas, in more developed countries (where foods are enriched and fortified with iodine), autoimmune thyroiditis is the predominant cause (6).

Acquired hypothyroidism is diagnosed when patients present with overt hypothyroidism (also known as clinical hypothyroidism), as they exhibit increased TSH and decreased T_3 and T_4 serum levels (TSH >4.94 μIU/mL; T_3 <1.71 pg/mL; T_4 <0.7 ng/dL). The prevalence of this disease may differ based on gender, age, or geographic location (7, 8). In the United States, in adolescent and adult populations, the prevalence of acquired hypothyroidism ranged between 2.1 to 6.1% depending on the criteria for defining hypothyroidism. Moreover, a higher occurrence in women was reported (8). In European countries, this prevalence was 0.37% with predominance in females (9). In Mexico, it was reported between 1.2–1.8% in the adult population (10, 11).

The close relationship between hypothyroidism and psychiatric symptoms has been the subject of extensive research. The evidence indicates an association between thyroid function and psychiatric disorders, including anxiety, depression, bipolar disorder, and schizophrenia (12, 13). Most clinical studies and previous reviews have focused on describing thyroid alterations in patients with psychiatric disorders, and the effects of psychiatric drugs on the thyroid endocrine system (12, 14, 15). In contrast, there are fewer scientific studies regarding the prevalence of psychiatric disorders in patients initially diagnosed with acquired hypothyroidism. Additionally, only a minority of investigations examine the effectiveness of Levothyroxine (L-T_4) treatment in mitigating or alleviating psychiatric disorders in these kinds of patients.

A pioneering study, published in the 60´s decade, showed that hypothyroidism could be causing psychiatric disorders. The study reported eight patients with both concurrent hypothyroidism and mental illness; six of them recovered with treatment consisting of consumption of thyroid gland or dried thyroid tissue and showed normal mental status in the medium term (from 2 to 12 years after the event) (16). It was suggested that hypothyroidism acts as an

inducer of mental changes and that thyroid medication could be relevant to the recovery of mental health. Recent evidence continues supporting this notion, the studies were compiled in this review to answer whether the acquired hypothyroidism acts as a risk factor for psychiatric disorders in patients with or without thyroid medication, and whether the L-T_4 treatment is successful in alleviating the psychiatric illness. In addition, we briefly address the possible mechanisms underlying the establishment of depression in patients with acquired hypothyroidism providing key points that should be considered for future research.

2 Methods

The search criteria, including the literature inclusion and exclusion criteria, as well as the limitations, are described in detail in the Supplementary Material.

3 Depression in patients with acquired hypothyroidism

Depression is classified as a mood disorder that presents with persistent sadness, emptiness or irritable mood, loss of interest in daily activities, hopelessness, difficulty experiencing pleasure, as well as disturbances in sleeping and eating (17, 18). According to the World Health Organization (WHO), one in eight people worldwide has a mental disorder, and depression affects 280 million people (19).

Depressive symptoms have a high prevalence in patients with hypothyroidism, and the study of this close relationship between the two conditions has aroused great interest in both the psychiatric and endocrinological fields. One of the greatest concerns in patients with acquired hypothyroidism is the imminent risk of developing depression, which will worsen the patient's condition and its therapeutic management. Based on different studies (8–11), the prevalence of acquired hypothyroidism is reported between 0.3 and 6.1%, whereas depression can afflict up to 18% of the population, according to Lee's findings (2023) (20). Even more interestingly, patients with acquired hypothyroidism have a high prevalence of depression reaching 79.2% in patients with hypothyroidism without treatment (21), between 12.1 and 36.7% in patients under L-T_4 treatment (1, 22, 23), and between 33.3 and 66.7% in patients who had developed an euthyroid state after L-T_4 treatment (See Table 1) (24, 25). This high prevalence of depression in patients with acquired hypothyroidism, with or without thyroid treatment, is in line with a higher risk of developing this psychiatric illness.

3.1 Depression in patients with acquired hypothyroidism without thyroid medication

Ittermann et al. (2015) showed that patients with acquired hypothyroidism, not taking medication, have 2.10 (95% CI, 0.86–5.11) or 2.32 (95% CI, 1.28–4.21) times higher risk of developing major depressive disorder according to data obtained by the Munich composite international diagnostic interview (M-CIDI) or Beck depression inventory II (BDI-II), respectively (26). Interestingly, this risk seems to be more if only women are evaluated. Guimaraes' research in women with overt hypothyroidism (TSH>4 μIU/mL and free T_4<0.7 ng/dL) found that they face 8.7 times (95% CI, 2.56–29.50) higher risk of experiencing depression than euthyroid women (21). The authors used Spitzer et al.'s (1994) PRIME-MD test (27) instead of the Beck depression inventory (BDI) for the assessment of depressive symptoms (21). Regarding the severity of depression, the literature shows that depressive symptoms were more severe in patients with overt hypothyroidism than control subjects or patients evaluated after receiving L-T_4 treatment, based on elevated scores in the Hamilton depression rating scale (HDRS) and BDI test (28, 29).

TABLE 1 Prevalence of depression in patients with acquired hypothyroidism without or with L-T_4 treatment.

Prevalence of depression in patients with acquired hypothyroidism	Population's characteristics	Psychiatric test	Reference
79.2%	Female patients with acquired hypothyroidism without thyroid medication.	Primary care evaluation of mental disorders (PRIME MD)	Guimaraes et al., 2009 (21)
12.1% (*)	Patients with diagnosis of acquired hypothyroidism under L-T_4 treatment.	Diagnostic and statistical manual of mental disorders (DSM-III-R)	Bunevicius et al., 1999 (23)
33.9%	Patients with diagnosis of acquired hypothyroidism under L-T_4 treatment.	Patient health questionnarie-9 (PHQ-9)	Mohammad et al., 2019 (22)
36.7%	Patients with diagnosis of acquired hypothyroidism under L-T_4 treatment.	PHQ-9	Usman et al., 2023 (1)
66.7% (*)	Patients with diagnosis of acquired hypothyroidism who had developed euthyroid state after treatment with L-T_4.	Beck depression inventory (BDI)	Talaei et al., 2017 (24)
54.5% (patients with 1 year of follow-up) 41.7% (patients with 5 year of follow-up) 33.3% (patients with 10 years of follow-up)	Patients with diagnosis of acquired hypothyroidism who had developed euthyroid state after treatment with L-T_4.	BDI	Gunes, 2020 (25)

*These values were calculated employing the article's data. In Bunevicius et al. (1999), the ratio was 4/33. In Talei et al. (2017), the ratio was 116/174.

3.2 Depression in patients with acquired hypothyroidism with thyroid medication

Regarding patients with acquired hypothyroidism under thyroid medication, Thvilum et al. (2014) found that, after the diagnosis of hypothyroidism, these patients were more likely to develop depression and require antidepressant treatment (HR: 1.30, 95% CI: 1.15–1.47) (30). The severity of their depressive stage was predominantly mild or moderate-severe. Mohammad et al. (2019) showed that depression was moderate in 10.7%, moderate-severe in 19.6%, and severe in 3.6% of these patients (22). In line, Usman et al. (2023) showed that such patients experienced mild, moderate, moderate-severe, and severe depressive symptoms in 44.4%, 33.3%, 16.7%, and 5.6% of cases, respectively (1). Both authors determined the severity of depression using the patient health questionnaire-9 (PHQ-9) (1, 22).

Clinical studies in patients receiving L-T_4 treatment have been also useful to study the relationship between TSH levels and depression severity, suggesting a positive correlation between elevated TSH levels and more severe depression (21, 24). Talaei et al. (2017) proposed a cut-off value of TSH for the evaluation and consideration of antidepressant treatment in patients with hypothyroidism treated with L-T_4 (24). They showed that a TSH cut-off point of ≥2.5 mIU/L is associated with a depression diagnosis, displaying 89.6% sensitivity (95% CI, 82.6–94.5) and 87.9% specificity (95% CI, 76.7–95.0). Additionally, the study found that a cut-off point of ≥4mIU/L indicated severe depression with 80.5% (95% CI, 64.0–91.8) and 95% (95.6% CI, 90.8–98.4) sensitivity and specificity, respectively. It's worth noting that the patients with hypothyroidism in Talaei et al.'s (2017) study were under treatment with L-T_4, with a mean age of 45.5 ± 11.7 years, and had mean T_3 and T_4 values of 1.2 ng/mL and 8.4 pg/dL, respectively. In addition, BDI score above 10 was used as a criterion for depression diagnosis (24). A study conducted by Guimaraes et al. (2009) revealed that 65% of women (mean age of 53.6 years) with TSH levels ≥10 μIU/mL exhibited depressive symptoms and had a 3-fold (95% CI, 1.21–7.79) higher likelihood of developing depression compared to those with normal TSH levels (>0.3 and ≤4 μIU/mL) (21).

Finally, it can be inferred that there is a close association between thyroid dysfunction and the onset of depressive symptoms. Some studies have even delved into the connection between the hypothyroid condition and a higher incidence of suicidal behavior. In a meta-analysis conducted by Toloza et al. (2021), it was reported that patients with suicidal behavior have significantly lower levels of free T_3 and total T_4 as compared to patients without suicidal behavior (31). The authors clarify that research on the correlation between thyroid disorders and suicidal behavior is limited, warranting further investigation for improved understanding.

Thus, individuals with acquired hypothyroidism, whether treated or not, are more susceptible to depression, according to current evidence. It is important to consistently screen these patients for depressive symptoms to manage this comorbid psychiatric condition and prevent further complications.

4 Anxiety disorder in patients with acquired hypothyroidism

Anxiety disorder is characterized by excessive fear, anxiety, and related behavioral disturbances. Fear is the emotional response to a real or perceived imminent threat, whereas anxiety is the anticipation of future threats. Such anxious responses are disproportionate to the context or triggering stimuli and can significantly hinder a person's daily life. Common symptoms of anxiety may comprise persistent worry, irritability, restlessness, difficulty concentrating, muscle tension, sleep disturbances, panic attacks, and avoidance of anxiety-provoking situations (18). Anxiety is a prevalent psychiatric disorder that affects 18.1% of people in the United States (32) and 301 million people worldwide (19). Interestingly, the presence of anxiety disorder has been reported in patients with acquired hypothyroidism, as evidenced by various studies in the adult population.

4.1 Anxiety in patients with acquired hypothyroidism without thyroid medication

Ittermann et al. (2015) found that individuals with a diagnosis of acquired hypothyroidism, with a mean age of 55 years and without L-T_4 treatment, have a 3.98 (95% CI, 1.48–10.72) higher risk of experiencing anxiety (test: M-CIDI) (26). In addition, these patients had significantly higher scores for anxiety, as well as decreased attention and executive task performance, in comparison with control subjects (test: state-trait anxiety inventory (STAI)) (29, 33). These elevated scores for anxiety were also reported when patients with overt hypothyroidism were compared with patients under L-T_4 treatment or with TSH values below 0.1 μIU/mL (test: Thyroid-related quality-of-life patient-reported outcome (ThyPRO)) (34).

4.2 Anxiety in patients with acquired hypothyroidism with thyroid medication

Thvilum et al. (2014) found that hypothyroid patients, even under L-T_4 treatment, had an increased risk of developing anxiety and requiring anxiolytic treatment after diagnosis of hypothyroidism (HR: 1.27; 95% CI, 1.10–1.47) (30). Interestingly, it has been reported that even after becoming euthyroid with thyroid medication, patients had higher anxiety scores than controls at 1, 5, and 10 years of follow-up (test: Beck anxiety inventory (BAI)) (25). The patients experienced several symptoms, including hot flushes, weakness, tremors in the legs and hands, dizziness or drowsiness, palpitations, a feeling of loss of balance, becoming terrified, and flushing of the face (25). Additionally, it has been demonstrated that discontinuing thyroid medication can result in increased anxiety levels (29, 33).

The relationship between serum TSH levels and anxiety disorders has not been extensively studied. One report found that

serum TSH levels and gender were the most significant predictive factors when anxiety was considered a dependent variable (34).

Overall, the literature suggests an association between hypothyroidism and anxiety, as supported by the higher risk of developing this disorder in patients with acquired hypothyroidism without or under L-T_4 treatment. Discontinuation of thyroid medication in hypothyroid patients appears to be a risk factor for the development of anxiety in patients with this condition, making appropriate and timely therapeutic management and psychiatric care highly relevant.

5 Negative evidence about the relationship between acquired hypothyroidism and depression or anxiety

In contrast to other authors, Grabe et al. (2005) showed that patients with overt hypothyroidism did not differ from euthyroid controls in scores for anxiety and depression employing Zerssen complaint scale (2005) (35). The authors explain that hypothyroid patients may have a differential susceptibility to low thyroid hormone levels, with not all of them developing a psychiatric disorder.

In line, Gulseren et al. (2006) found that patients with overt hypothyroidism had similar scores for anxiety that control subjects, employing the Hamilton anxiety rating scale (HARS) (28). The authors explain that the causal relationship between thyroid dysfunction and anxiety is still speculative and that their findings need to be interpreted with caution due to the small sample size and that studies in larger populations are needed.

6 Schizophrenia or affective bipolar disorder in patients with acquired hypothyroidism

Schizophrenia is a mental disorder that is primarily characterized by a progressive decline in cognitive function and a range of psychiatric symptoms, such as hallucinations, delusions, and disorganized thinking (speech) (18, 36). On the other hand, bipolar disorder is a chronic mood disorder mainly characterized by a mixture of manic (bipolar mania), hypomanic, and depressive (bipolar depression) episodes (37, 38). Schizophrenia and bipolar disorder affect 24 and 40 million people worldwide, respectively (19), and both have been associated with hypothyroidism since the 1960s (39, 40).

In 2018, Sharif and colleagues found that individuals with hypothyroidism exhibited a significantly higher prevalence of schizophrenia (2.01%) compared to controls (1.25%). Nevertheless, the study was unable to establish a causal relationship between hypothyroidism and schizophrenia. One limitation of this study was that the etiology and type of hypothyroidism were not determined (41). In a separate study, Benros and colleagues (2011) found that a previous autoimmune disease increased the risk of schizophrenia by 29%, However, only a small number of patients presented with autoimmune thyroiditis (n=3), suggesting that there was no evidence of an association between autoimmune thyroiditis and the development of schizophrenia (42).

On the other hand, Thomsen et al. (2005) analyzed data from a Danish patient registry to investigate whether hospitalization for hypothyroidism increases the risk of developing bipolar disorder. They found that only 0.17% of hypothyroid patients were later hospitalized for bipolar disorder, which is comparable to the hospitalization rate for patients with nontoxic goiter or osteoarthritis (43).

Thus, there is insufficient evidence to conclude whether hypothyroidism is a risk factor for the development of schizophrenia or bipolar disorder. Therefore, longitudinal studies are needed to determine the incidence of these two disorders in patients initially diagnosed with acquired hypothyroidism.

7 Effectiveness of thyroid hormones for mitigating or alleviating psychiatric comorbidities in patients with acquired hypothyroidism

The role and use of THs in the treatment of psychiatric disorders have been well documented. While THs are prescribed to patients with hypothyroidism, they are also known to accelerate or enhance the efficacy of some psychiatric drugs, particularly in refractory patients without thyroid disorders (44, 45). Some of these therapeutic effects have been reported in patients who do not respond to antidepressant treatment, as well as in patients who require an accelerated effect of antidepressants. Multiple studies indicate that the administration of T_3 hormone may benefit patients with depression (46–51). However, other reports suggest that the addition of L-T_4 to antidepressant treatment may result in a more effective response to treatment (52–54).

Although depression is a disorder that often accompanies hypothyroidism, few reports have been conducted to determine whether the thyroid treatment reverses the depressive state in patients initially diagnosed with hypothyroidism. It has been reported that treatment of hypothyroidism with T_4 alone does not improve mood (55). However, Gulseren et al. (2006) reported that hypothyroid patients with depression showed improvement after L-T_4 administration, which reversed the hypothyroid state, without the need for psychiatric medication (28). Consistent with this, Rack and Makela (2000) reported a clinical case in which a patient with a long history of hypothyroidism treated with T_4 maintained her depressed state, but when T_3 was added to her treatment, her mood improved markedly (56). Several reports support the idea that the combination of T_4+T_3 prevents depression, although in some cases they report only a trend toward improvement (23, 57). In contrast, reports indicate that the combination of T_4+T_3 does not significantly improve depressive states in hypothyroid patients (58, 59).

Controversial evidence exists regarding the potential advantages of thyroid medication in reducing anxiety symptoms. The literature reports a benefit of adding L-T_4 to anxiolytic treatment in hypothyroid patients with anxiety (28). Early initiation of L-T_4 treatment is suggested to avoid anxiolytic administration (60).

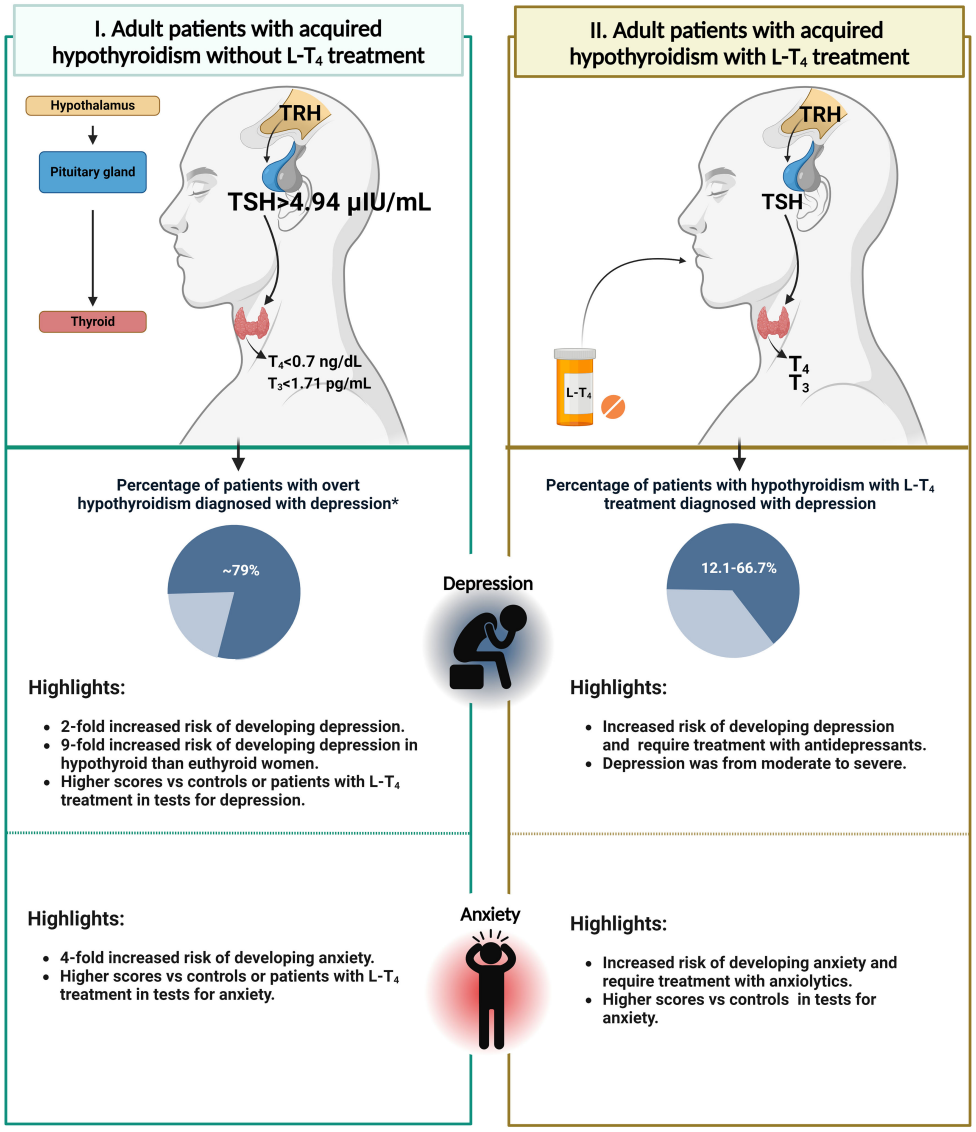

FIGURE 1
The association between acquired hypothyroidism and the subsequent development of depressive or anxiety disorders in adult patients. The figure on the left (I) depicts an adult patient with acquired hypothyroidism who has not received L-T_4 treatment and their thyroid hormone levels (Usman et al., 2023). It is evident that there is a correlation between overt-acquired hypothyroidism and an increased risk of developing depression or anxiety. The figure on the right (II) shows an adult patient with acquired hypothyroidism who is undergoing L-T_4 treatment. Furthermore, there is evidence indicating that depression or anxiety may be present despite the use of thyroid medication. The figure is based on clinical studies of the adult population (1, 21–26, 28–30, 33, 34). *Data obtained from the female population.

Monzani et al. (2023) reported that high doses of L-T_4 were required to reverse anxiety in thyroidectomized patients (34). In contrast, Gunes et al. (2020) reported that anxiety may persist in hypothyroid patients even after achieving euthyroid status through thyroid medication (25).

Schizophrenia's occurrence in hypothyroid patients, also known as myxedema psychosis, is rare. Thyroxine treatment's efficacy has been reported in various clinical cases of this condition. A report indicates that T_4 and T_3 combination therapy (61) as well as T_4 treatment alone improved symptoms in a woman with myxedema psychosis (62). Finally, there is no evidence indicating the effectiveness of L-T_4 in treating bipolar disorder in patients who have been initially diagnosed with hypothyroidism.

Determining the efficacy of THs in psychiatric disorders is challenging due to the varying results reported in studies. This variability can be attributed to differences in the severity of thyroid disease, pharmacological treatments, and the severity of their psychiatric conditions. Additionally, factors such as gender, age, disease onset, and duration may also affect results. It is important to note that the T_4 hormone must be converted to T_3 in various tissues, which can be a significant limitation in some patients, increasing the variability of reported results. However, because of the strength of

the reports indicating the benefit of THs in improving the symptoms of psychiatric illness present in hypothyroidism, consideration should be given to adjusting the treatment of hypothyroidism to improve psychiatric symptoms, even though the reports are scarce and conflicting. Figure 1; Table 1 summarize key information from this review.

8 Acquired hypothyroidism and depression: key points on mechanisms underlaying this relationship

Previous evidence has shown that acquired hypothyroidism is associated with the onset of depression. This finding has been confirmed by studies in rodents showing that adult-onset hypothyroidism induces depression-like behavior, as indicated by increased immobility time in the forced swimming test (FST) or tail suspension test (TST) (63–65). The literature from animal models and clinical studies indicates that acquired hypothyroidism may lead to depression through several mechanisms, including alterations in serotonergic neurotransmission or the hypothalamic-pituitary-adrenal axis (HPA axis), changes in adult hippocampal neurogenesis or brain region integrity, or by activation of systemic pro-inflammatory processes or neuroinflammation, or by the triggering of the kynurenine pathway. The following sections will provide a brief overview of the various mechanisms by which acquired hypothyroidism may lead to the development of depression.

8.1 Acquired hypothyroidism and serotoninergic neurotransmission

The monoamine hypothesis proposes that a reduced availability of monoamine neurotransmitters, such as serotonin (5-HT), dopamine and norepinephrine, results in decreased neurotransmission and impaired cognitive performance, which may lead to depression (66, 67). Preclinical and clinical evidence supports the notion that monoaminergic alterations could partially explain the presence of depression in patients with acquired hypothyroidism.

Although some studies have evaluated alterations in brain dopamine and norepinephrine levels in hypothyroid adult rodents, the results are controversial, and it is difficult to draw conclusions about them (63, 68–70). In contrast, the findings are consistent showing that serotoninergic neurotransmission is the most affected by hypothyroidism. Hassan et al. (2013) reported lower 5-HT levels in the blood plasma of hypothyroid rats in comparison to controls (68). Interestingly, serotonergic deficits are also observed in the brain. Yu et al. (2015) reported reduced 5-HT concentrations in the whole brain of hypothyroid rodents (71). More specific studies have shown that 5-HT is reduced in brain regions implicated in depression, such as the cerebral cortex (68), hippocampus (63, 69), prefrontal cortex (63, 69), and dorsal raphe nucleus (65), in adult rodents with hypothyroidism. Similarly, clinical evidence has demonstrated that patients with acquired hypothyroidism (without L-T_4 treatment) exhibit lower platelet 5-HT concentrations (72); this deficiency is also observed in serum samples from hypothyroid patients receiving L-T_4 treatment (73). Additionally, patients with acquired hypothyroidism have reduced central 5-HT activity, as evaluated by the response to dexfenfluramine (74, 75).

The expression of 5-HT_{2A} receptors in the prefrontal cortex (64, 76) and hippocampus (64) is lower in hypothyroid rats than in controls. Lee et al. (2017) reported that hypothyroidism provokes increased expression of 5-HT_{1A} receptors in the hippocampus (77), while Kulikov and Jeanningro (2001) did not observe changes in this receptor (76).

A recent study reported a significant inverse correlation between depression-like behavior (as measured by increased immobility time in the forced swim test or tail suspension test) and 5-HT levels or the expression of 5-HT_{2A} receptors in the prefrontal cortex and hippocampus of adult rodents with hypothyroidism (63, 64). At the clinical level, higher scores on the test for depression (test: HDRS) are correlated with reduced central 5-HT activity in patients with acquired hypothyroidism (75).

Thus, the evidence suggest that acquired hypothyroidism induces a deficit in serotoninergic neurotransmission by reducing the 5-HT concentration and the expression of postsynaptic $5HT_{2A}$ receptors. Consequently, these changes could lead to the development of depressive symptoms in patients. More studies should be carried out to elucidate the role of dopamine and norepinephrine in the relationship between hypothyroidism and depression.

8.2 Acquired hypothyroidism and kynurenine pathway

The kynurenine pathway (KP) plays a pivotal role in the pathophysiology of depression and has also been linked to hypothyroidism. KP metabolites play important roles in various tissues, either as a neuroprotective agent (kynurenic acid) or a neurotoxic agent (quinolinic acid). Additionally, KP modulates the immune system and provides energy in the form of nicotinamide adenine dinucleotide (NAD) for immune system responses. In the context of psychiatric disorders, numerous KP metabolites exhibit neuroactive properties, modulating neuroplasticity and exerting neurotoxic effects, at least in part, through their influence on NMDA receptor signaling and glutamatergic neurotransmission. In consequence, these metabolites have been demonstrated to have a significant association with psychiatric illness in the context of inflammation (78).

The KP is initiated by the metabolism of tryptophan (TRP). It is noteworthy that TRP is also the precursor of 5-HT and NAD, which is a cofactor involved in various metabolic pathways. In the TRP metabolism, the enzyme that represents the limiting step is indoleamine 2,3-dioxygenase (IDO). This enzyme determines whether the kynurenine or serotonin pathway or NAD synthesis occurs. IDO catalyzes the conversion of TRP into kynurenine (KYN), which is converted into two metabolites: 3-hydroxykynurenine (3-HKYN) or kynurenic acid (KYNA). Subsequently, 3-HKYN is transformed into 3-hydroxyanthranilic

acid (3-HAA), and it gives rise to quinolinic acid (QUIN), which acts as an agonist of NMDA receptors and may induce excitotoxicity and neuronal death (79).

A study of 57 young women with autoimmune thyroiditis revealed an abnormal activation of KP in these patients in comparison to healthy controls. The levels of KYN and anthranilic acid (AA) were elevated, while KYNA was reduced in autoimmune thyroiditis, resulting in an imbalance between AA and KYNA levels. In contrast, the other metabolites, including 3-HKYN and 3-HAA, remained unchanged, whereas QUIN exhibited a slight increase in patients with autoimmune thyroiditis (80).

The evidence from research in humans and animal models indicates that KYNA deficiency can result in neuronal loss (81, 82), while increased KYNA in the brain can induce cognitive dysfunction due to reduced signaling through NMDA receptors, which are critical for learning and memory (83, 84). Thyroid hormones modulate the synthesis of the tryptophan metabolite, KYNA. Experimental hypothyroidism is associated with an independent increase in cerebral KYNA levels. Some data indicates the existence of a new mechanism related to thyroid hormone deficiency. This suggests that high KYNA levels may play a role in cognitive impairment associated with hypothyroidism (85).

In pathological conditions, nitric oxide (NO) can cause oxidative damage through the formation of the highly reactive metabolite peroxynitrite. NO is synthesized from L-arginine by nitric oxide synthase (NOS). There are different isoforms of NOS, and both the endothelial (eNOS) and neuronal (nNOS) isoforms are calcium-dependent, while the inducible isoform (iNOS) is calcium-independent (86). It has been postulated that an elevation in reactive oxygen species (ROS) levels, resulting from the deficiency of thyroid hormones, may give rise to an oxidative stress condition in various organs, including the brain, with a subsequent lipid peroxidation response (85).

In a model of hypothyroidism induced by the administration of methimazole in adult rats, an increase in oxidative stress was found in the hippocampus and amygdala. This was accompanied by increased levels of free radicals, lipid peroxidation and nNOS activity (87). This oxidative stress was accompanied by the triggering of the apoptotic pathways and neuronal damage in all regions of the hippocampus (88), an effect that is mediated by the overactivation of NMDA receptors (89). These findings indicate that adult-onset hypothyroidism results in oxidative stress that leads to neuronal death in the hippocampus, where the nitrergic system is involved. This provides a potential explanation for the behavioral abnormalities observed during hypothyroidism.

The activation of the KP, the overproduction of NO, and the subsequent oxidative stress in hypothyroid subjects indicate that QUIN may be a potential mediator between acquired hypothyroidism, immunological and neurotransmitter alterations, and depression. This hypothesis is based on the observation that pro-inflammatory cytokines induce a change in 5-HT synthesis due to alterations in tryptophan metabolism by the activation of the kynurenine pathway in glial cells, which may ultimately lead to 5-HT depletion and increased production of the neurotoxic metabolite QUIN (90). Collectively, these processes may result in the onset of depression.

Based on the above, the potential causes of depressive symptoms in patients with acquired hypothyroidism include the triggering of the KP, induced oxidative stress, overstimulation of NMDA receptors, and neuronal apoptosis. It is possible that these events may be provoked by an overproduction of QUIN, although this hypothesis requires further investigation. Furthermore, the depletion of 5-HT caused by the activation of the kynurenine pathway also plays a significant role in the onset of depressive symptoms.

8.3 Acquired hypothyroidism and hypothalamic pituitary adrenal axis

The HPA axis is a vital neuroendocrine circuit responsible for regulating a variety of physiological processes and responses to stress (91). This axis coordinates the secretion of glucocorticoid hormones, such as cortisol, under normal conditions and in reaction to stressors (92). The HPA axis also facilitates the physiological adaptations that occur during stressful situations. Its activity is regulated through negative feedback mechanisms, which allow for self-regulation (93).

Dysregulation of the HPA axis has been documented in patients with acquired hypothyroidism, who have elevated serum cortisol levels (94, 95). Sinha et al. (2023) reported that patients with acquired hypothyroidism had significantly higher serum cortisol levels compared to healthy controls. They also found a positive correlation between raised serum cortisol and raised TSH levels; and a negative correlation between high serum cortisol and lower T_3 and T_4 levels. The authors explain that elevated cortisol levels in patients with hypothyroidism may be due to reduced cortisol elimination and negative cortisol feedback in the HPA axis. However, it could also be a possible compensatory mechanism triggered by the HPA axis with increased cortisol secretion to mitigate the metabolic consequences of thyroid hormone deficiency (94).

On the other hand, it has been reported that dysregulation of the HPA axis can lead to various physiological and psychological alterations, which in turn lead to the development of mood disorders (96). This is important because it shows that hypothyroidism affects the HPA axis and can cause depression. The HPA axis is implicated in the pathogenesis of conditions such as depression and post-traumatic stress disorder. Patients with both disorders exhibit abnormalities in the HPA axis regulation, including altered cortisol levels and a failure to suppress cortisol release in the dexamethasone suppression test (97). Hernandez et al. (2008) reported hypercortisolism (measured in urine) in patients with depression compared to healthy volunteers. Only after 52 weeks of treatment with selective serotonin reuptake inhibitors (SSRIs) did the patients achieve a significant reduction in their cortisol levels; however, the authors considered this reduction to be only a partial recovery of HPA axis function (98). Although patients improved clinically in terms of depressive symptoms, elevated cortisol levels resulting from HPA axis dysregulation kept potential relapse latent. Furthermore, in animal models, dysregulation of the HPA axis has been demonstrated to result in an increased depression-like behavior (99). In normal conditions, cortisol serves to reduce inflammation.

However, if an individual is chronically stressed or exhibits a dysregulation of the HPA axis, the subjects will present chronic hypercortisolism. This results in a diminished capacity of the HPA axis to regulate itself, which can lead to the release of pro-inflammatory cytokines by immune cells (100). Elevated pro-inflammatory cytokines have been demonstrated to play a significant role in the pathophysiology of depression (101).

Collectively, the evidence indicates that the development of depression in patients with acquired hypothyroidism appears to be significantly correlated with dysregulation of the HPA axis. This is consistent with the high prevalence of depression in hypothyroid patients and the reports of patients with depression with alterations in the HPA axis. Further research in patients with acquired hypothyroidism, with particular attention to HPA axis function and depressive symptoms, is essential to fully understand this complex relationship between thyroid function, the HPA axis, and depression. In conclusion, chronic hypercortisolism due to HPA axis dysregulation in hypothyroid patients appears to be key to the development of depression in these patients.

8.4 Acquired hypothyroidism and pro-inflammatory cytokines

Patients with hypothyroidism frequently present alterations in proinflammatory cytokines. Studies have demonstrated that individuals with hypothyroidism exhibit elevated levels of proinflammatory cytokines, including TNF-α, IL-6, and C-reactive protein (CRP), when compared to healthy individuals (102). It has been observed that levothyroxine treatment can reduce these cytokine levels, although it is not always possible to achieve normalization (102).

A study conducted in 2006 on patients with Hashimoto thyroiditis demonstrated a significant positive correlation between elevated serum IL-6 levels (a pro-inflammatory cytokine) and the required L-T_4 dose. Conversely, a significant negative correlation was observed between elevated IL-6 levels and serum T_3 and T_3/T_4 ratio (103). Another study in patients with autoimmune thyroiditis found that the serum levels of IL-2, IFN-γ, and TNF-α were elevated. This increase in these three pro-inflammatory cytokines may be explained by a higher number of activated T cells, resulting from the recognition of thyroid autoantibodies (104). Figueroa-Vega et al. (2010) demonstrated that patients with Hashimoto thyroiditis exhibit elevated circulatory levels of T-helper 17 (Th17) cells, a subpopulation of proinflammatory lymphocytes. Furthermore, elevated serum levels of IL-6 and IL-15 were observed in these patients. Both cytokines are involved in the differentiation of Th17 cells and possess pro-inflammatory properties (105).

The presented evidence highlights the pro-inflammatory state observed in hypothyroid patients. Indeed, Lai et al. (2024) propose a bidirectional relationship between elevated pro-inflammatory cytokines and the observed alterations in thyroid function (102).

Therefore, it is inevitable to associate depression in this context, a disorder characterized predominantly by a proinflammatory state. Liu et al. observed that patients with depression presented elevated serum levels of IL-1β, which correlated positively with the severity of depressive symptoms. In addition, TNF-α emerged as a promising biomarker for predicting the elevated risk of suicidal behavior (106). It is well established that systemic inflammation can affect the permeability and normal function of the blood-brain barrier (107), allowing peripheral cytokines to access the brain and producing neuroinflammation and alterations in neurotransmitter function (108). Furthermore, cytokines may influence monoamine synthesis through the degradation of tetrahydrobiopterin (BH4), a cofactor essential for 5-HT synthesis (108).

In 2017, Tayde et al. (2017) raised the question of whether proinflammatory cytokines are the link between hypothyroidism and depression (109). In this intriguing study, the researchers observed that individuals with primary autoimmune hypothyroidism exhibited elevated levels of IL-6, TNF-α, and CRP. The study included patients with antithyroid antibodies and TSH levels ≥10 μIU/mL. Following six months of treatment with levothyroxine, 42% of patients achieved remission of depression and an euthyroid state. Moreover, the administration of levothyroxine resulted in a significant reduction in the levels of the three pro-inflammatory markers, yet the reduction did not reach baseline levels (109). The findings of Tayde et al. (2017) provide compelling evidence that restoring thyroid function through L-T_4 treatment in hypothyroid patients can alleviate depressive symptoms while reducing the proinflammatory state in these patients. This study demonstrates that proinflammatory cytokines are crucial in the pathophysiology and mechanism of the development of depression.

It is crucial to acknowledge that most of the studies discussed in this section were conducted in patients with autoimmune thyroiditis. It would be valuable to ascertain whether the proinflammatory state observed in this form of hypothyroidism is also present in other types of hypothyroidism acquired through non-autoimmune causes.

8.5 Acquired hypothyroidism and adult hippocampal neurogenesis

Adult neurogenesis is the generation of new neurons in the mature brain (110). In the hippocampus, adult neurogenesis occurs in the subgranular zone of the dentate gyrus (111, 112) and is a complex process that involves the proliferation of neural stem cells and progenitor cells (Type 2a, 2b and 3 cells) (113–115), the differentiation of neuroblasts into granular neurons through the stadium of immature granular neurons (IGNs), and the integration of new neurons into preexisting circuits in the dentate gyrus (116, 117). It has been postulated that reduced adult hippocampal neurogenesis could be implicated in the pathophysiology of depression (118, 119), principally by leading to overactivation of the hypothalamus-pituitary-adrenal axis (120, 121) and by affecting the contextual encoding of emotions (119, 122).

Evidence from animal models has shown that adult-onset hypothyroidism provokes impaired neurogenesis, exerting a deleterious effect, particularly on postmitotic cells. Specifically, hypothyroidism significantly reduces the population of quiescent Type 2b and 3 cells, postmitotic neuroblasts and IGNs (123–126).

This reduced neurogenesis appears to be mediated by TRα1 aporeceptors (unlinked receptors), which could be predominant in hypothyroidism and be capable of repressing the expression of proneural and cell survival genes (127–129).

Interestingly, the neurogenic deficit in hypothyroid adult rats is accompanied by decreased expression of brain derived neurotrophic factor (BDNF) in the whole hippocampus (130) and, particularly, in the dentate gyrus (126). This phenomenon has also been reported in patients. Bilous et al. (2020, 2021) reported decreased expression of BDNF and neurogenesis-regulated genes in patients with primary hypothyroidism (131, 132). Alterations in the expression of BDNF are relevant because of three reasons: 1) the BDNF promoter is responsive to thyroid hormones (133), 2) this neurotrophic factor plays a key role in the postmitotic phase of the neurogenic process, promoting the survival of newborn neurons (134, 135), and 3) several studies have highlighted associations between low levels of BDNF and the development of behavioral symptoms of depression (136). Thus, BDNF could be the link between adult hypothyroidism, reduced neurogenesis and depression.

The relationship between adult neurogenesis and depression-like behavior in hypothyroidism condition was explored by Montero-Pedrazuela et al. (2006), who reported that reduced neurogenesis is accompanied by increased immobility time in the FST in hypothyroid rats (125). In contrast, increased hippocampal neurogenesis, provoked by simultaneous treatment with T_3 and fluoxetine, is associated with antidepressant behavior in rats (test: novelty suppressed feeding test) (137).

This evidence suggests that acquired hypothyroidism can induce depression by reducing adult neurogenesis and BDNF expression in the hippocampus. Deeper studies should be carried out to determine the causal relationships and molecular pathways involved in the associations between hypothyroidism, neurogenesis and depression.

8.6 Acquired hypothyroidism and structural changes in brain

Because thyroid hormones play an important role in the development of the nervous system, it is important to study whether structural changes are present in patients with acquired hypothyroidism. Although the adult brain has completed its development, thyroid hormones maintain different functions on neuronal physiology, so hypothyroidism may cause changes in the metabolism and structure of the nervous system, causing alterations in the functionality of different brain regions. Currently, with the development of various brain imaging techniques, it has been possible to study possible changes in brain structure in patients with untreated acquired hypothyroidism (138).

One structure that has received particular attention is the hippocampus, as this structure is associated with learning and memory functions as well as mood states, functions that are clearly altered in hypothyroid patients. There are reports in animal models of damage to the pyramidal neurons of the hippocampus as a result of decreased thyroid hormone levels (139, 140).

Using magnetic resonance imaging (MRI) in patients with untreated acquired hypothyroidism, a reduction in hippocampal volume has been observed (141), as well as a reduction specifically in the granular and molecular layers of the hippocampus (142). It has been proposed that the volume reduction correlates with a decrease in peripheral BDNF levels (143). In addition, using positron emission tomography (PET), it has been shown that hippocampal glucose utilization is reduced in hypothyroid patients (144).

Other structures associated with psychiatric disorders, such as the prefrontal cortex or the amygdala, have also been studied for changes due to the effects of acquired hypothyroidism. Although there are fewer studies on this topic, there is evidence of structural and metabolic changes, although the results are more variable.

Using voxel-based morphometry, a reduction in gray matter in the cerebellum as well as white matter in the cerebellum, frontal gyrus, temporal gyrus, and occipital gyrus has been reported (145), while using MRI, the group of Leyhe et al. (2014) observed decreased gray matter in the inferior frontal gyrus (146).

Regarding metabolic changes, decreased glucose utilization in the amygdala and anterior cingulate cortex has been reported (144), as well as decreased blood flow in the prefrontal, temporal and occipital lobes (147).

All these structural changes observed in hypothyroid patients could affect the proper functioning of the central nervous system and contribute to the development of psychiatric disorders.

9 Conclusion

Evidence supports that acquired hypothyroidism increases the risk of depression and anxiety in adult patients. Current data indicates that patients with acquired hypothyroidism without L-T_4 treatment face a 2-fold increased risk of depression and a 4-fold elevated risk of anxiety, with a notably higher risk for depression in women (about 9-fold more risk). The prevalence of depression in these patients is 79%, and they show elevated scores in depression or anxiety tests when compared to controls or patients receiving L-T_4 treatment. On the other hand, the literature shows that both depression and anxiety can be also present in patients with acquired hypothyroidism with L-T_4 treatment. These patients are at a higher risk of developing depression or anxiety and therefore require treatment with antidepressants or anxiolytics. Depression affects between 12.1% and 66.7% of these patients and is often classified as moderate to severe. Regarding anxiety, these patients exhibit higher scores on tests for anxiety versus controls.

The significant prevalence of depression in patients with acquired hypothyroidism, coupled with the high susceptibility to developing depression and anxiety, highlights the need for enhanced monitoring of psychiatric symptoms. Consistent monitoring and timely recognition of psychiatric symptoms, especially in patients with TSH serum levels >2.5 μIU/mL, will prevent disease aggravation, facilitating more effective therapeutic management. On the other hand, there is no strong evidence suggesting that acquired hypothyroidism could be a risk factor for schizophrenia or bipolar disorder; however, more scientific research is necessary to address

this matter. Finally, key points on the underlying mechanisms of the relationship between hypothyroidism and depression are presented. These evidence the different ways in which acquired hypothyroidism can lead to the onset of depression. These include disturbances in serotonergic neurotransmission or the HPA axis, alterations in adult hippocampal neurogenesis or brain region integrity, activation of systemic pro-inflammatory processes or neuroinflammation, or by the triggering of the kynurenine pathway.

Author contributions

NO-B: Writing – original draft. AV-P: Writing – original draft. DS: Writing – original draft. YG-M: Writing – original draft. JP-R: Writing – original draft. GP-S: Writing – review & editing, Supervision, Project administration, Conceptualization, Writing – original draft. KS-H: Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization, Writing – original draft.

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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.2024.1429255/full#supplementary-material

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Screening for depression in chronic haemodialysis patients as a part of care in dialysis setting: a cross-sectional study

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Background: Depressive disorder is common among haemodialysis patients. The purpose of this study was to explore approaches to diagnosing depression in the context of a real-life setting, with the view of creating practical recommendations. It also aimed to evaluate the prevalence of depression and dementia.

Methods: We conducted a cross-sectional study in two Dialysis Centres in Poland. Cognitive functions were evaluated using Mini–Mental State Examination (MMSE). The screening for depressive symptoms was assessed using Beck Depression Inventory II (BDI-II). The diagnosis of major depressive disorder was confirmed by a psychiatrist using Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5). Sociodemographic and clinical data were also collected.

Results: Initially, 136 patients agreed to participate in the study. Dementia was found in 13% of the study group. Sixty-two patients did not agree to perform all the proposed tests and were not included in the analysis, which eventually consisted of 70 patients. According to BDI-II, depressive symptoms were present in 35.7% of patients, while the diagnosis of major depressive disorder (MDD) was confirmed by the psychiatrist in 25.7%. According to the ROC analysis the optimal cut-off score for diagnosing MDD using BDI-II was ≥13 points.

Conclusions: This study suggests that the regular screening for depressive symptoms, followed by a psychiatric consultation in selected patients, might improve diagnosing depression with the goal of achieving a higher quality of life and a lower mortality rate. It may also be a cost-effective model for the management of depression among the haemodialysis population.

KEYWORDS

depression, screening, haemodialysis, compliance, dementia, BDI-II, MADRS

Introduction

Major depressive disorder (MDD) is a common psychiatric condition, with a twelve-month prevalence of around 5–10% and lifetime prevalence of around 20% (1–3). Among outpatients with general medical disorders the prevalence of depression largely exceeds that in the general population, reaching above 50% in groups with certain conditions (4). Given the burden of symptoms, high numbers of sufferers, and the fact that depression often goes undetected, the development of effective strategies for early identification and management of depression in such populations has become an important goal of clinical research (4).

Kidney diseases are among somatic disorders associated with high levels of depression, in particular in their more advanced chronic stages. Chronic kidney disease (CKD) has become a growing public health problem, with the number of individuals with all-stage CKD reaching almost 700 million and over 3 million patients requiring dialysis in 2017 (5). This number is expected to keep rising over the next decade to reach over 5.4 million by 2030, driven by the aging of population and increasing incidence of diabetes and hypertension (6). Among users of in-centre maintenance haemodialysis (MHD) - the most common form of renal replacement therapy (RRT) (7, 8)-depression is present in up to 40% of patients (9).

Estimates of depression prevalence among MHD users however vary between studies. One possible explanation is that depression may be not accurately diagnosed. This may be related to the presence of overlapping somatic symptoms, or differences in the diagnostic processes, such as assessment techniques, diagnostic tools, definitions and thresholds used (10, 11). It has been shown that the use of self- or clinician-administered questionnaires leads to higher estimations of depression compared with the interview-based diagnosis using Diagnostic and Statistical Manual of Mental Disorders 5 (DMS-5) criteria (12). Inaccurate diagnosing of depression has important clinical implications. Particularly noteworthy is the strong correlation between depression and all-cause mortality risk in patients receiving MHD (13, 14), with affective and cognitive symptoms of depression being a better predictor of long-term mortality than its somatic symptoms (15). Depressive symptoms are also independently associated with dialysis nonadherence, lower health resource utilisation (16) and decreased quality of life (17). Performing routine screening for depression has been recommended by Centres for Medicare and Medicaid Services in the United States (18) and in Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for cardiovascular disease in dialysis patients (19). Nevertheless, depression screening and integrated management of depression in the dialysis population remain insufficient (20, 21).

In the dialysis centres, where access to psychiatric care is often limited, diagnostic scales are frequently used to screen for depression in end-stage renal disease (ESRD). A number of screening tools have been used, including the Cognitive Depression Index (CDI) (22, 23),, the Center for Epidemiological Studies Depression Scale (CES-D) (24), the Hospital Anxiety and Depression Scale-Depressive Subscale (HADS-D) (25), Geriatric Depression Scale 15 (GDS-15) (26), and Initial Depression Inventory- Maintenance Haemodialysis (ID-MHD) (27). The most commonly used assessment tool has however been the self-administered Beck Depression Inventory, both in its original (BDI) and revised (BDI-second edition, BDI-II) versions (11, 28–31). Only few studies compared the consistency of diagnostic outcomes between different scales and clinical diagnosis made by a psychiatrist using DSM criteria (22, 23, 32, 33). Most of the studies performed in the elderly MHD population (26) suggested that in order for BDI and BDI-II to be valid tools comparable to the clinical interview, a traditional cut-off score of 14 points needed to be replaced by the threshold of 15 points or higher (22, 32, 33). This is mostly related to the impact of depressive somatic symptoms common in the MHD population. Establishing a threshold is crucial for promoting the use of BDI-II as a reliable screening tool. This should have important clinical value as on-dialysis assessments using BDI-II, thanks to the ease of using the scale, could constitute a convenient screenings procedure encouraging regular evaluation during the dialysis session, at a time when patients are easily accessible (22). There are some considerations when assessing patients for depression, especially in the elderly population. An important one is the presence of dementia. Approximately thirty percent of haemodialysis patients suffer from dementia (34, 35), with even higher rates among older patients and those with severe somatic conditions (36). The

limitations of the use of self-administered rating scales should be considered in this context. Excluding cognitive impairment before making the diagnosis of depression seems to be of significant importance (37). The purpose of this study was to explore commonly used approaches to diagnosing depression in the context of the real-life setting of the haemodialysis centre, with the view of contributing to the development of practical recommendations for depression assessment in haemodialysis patients. To achieve this, we compared recognition of depression using common approaches, specifically the self-rated questionnaire BDI-II, chosen because it remains an easy-to-administer, commonly used tool in the everyday clinical practice, with psychiatrist led assessment based on DSM-5 criteria. Additionally, individuals with and without depression were compared in terms of sociodemographic and clinical features. Dementia screening using Mini-Mental State Examination (MMSE) (38) and clinical evaluation was conducted in order to exclude its impact on depression screening. The study was designed to reflect the daily operating conditions of the haemodialysis centre.

Materials and methods

Study population

Adult ESRD patients from two Haemodialysis Centres were enrolled into the study. Individuals over 18 years old, with proper speaking abilities who had been receiving haemodialysis for at least 3 months were recruited consecutively by the medical staff of the dialysis centre. Patients with major psychiatric disorders other than depression, or those with visual or hearing impairments that prevented them performing the tests, were excluded. The study group received the high-flux haemodialysis or hemodiafiltration three times weekly. All participants gave their written informed consent for inclusion. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Independent Bioethics Committee for Scientific Research of Medical University of Gdansk.

Procedure and measures

The study was conducted in two Dialysis Centres in Poland (NZOZ Diaverum Gdańsk and Fresenius Nephrocare Ostróda). All the tests and interviews during the dialysis sessions were performed at least one hour after the initiation and one hour before the termination of the procedure, in order to reduce the risk of intradialysis hypotension impacting cognition. Before performing the depression screening, the MMSE was administered to all the patients by a trained researcher, in order to evaluate their cognitive function. Patients meeting the criteria of moderate or severe dementia (score <19 points) were excluded from the depression evaluation, to avoid the risk of dementia's impact on their ability to retrospectively assess their mental state. Individuals with mild cognitive impairment (MCI) (24–26 points) and mild dementia (19–23 points) remained in the study, due to the possibility of pseudodementia in the course of MDD. Depression was initially assessed with Beck Depression Inventory II (29). We used a validated version of BDI-II, the language used to collect the data was Polish. The BDI–II is a self-reported, 21-item inventory designed to assess the presence and severity of depressive symptoms. BDI-II assesses symptoms within cognitive, affective and somatic domains. Each item is rated from 0 to 3 points, and the total score ranges from 0 to 63. The score ≥14 points in BDI-II was interpreted as the presence of depressive symptoms. The original authors of the BDI-II recommended the following practical interpretation of their instrument: 0–13 points considered as none to minimal range depression, 14–19 mild depression, 20–28 moderate and 29–63 severe depression (29, 39, 40). All the patients, regardless of the BDI-II score, were subsequently invited for the clinical assessment performed by a senior psychiatrist, experienced in diagnosing MDD and assessing patients with chronic somatic illnesses. The psychiatrist was blind to BDI-II results. The psychiatrists conducted the diagnostic interview based on the DSM-5 criteria (41, 42), and subsequently applied the Montgomery-Asberg Depression Rating Scale (MADRS) to establish the severity of depression (43). MADRS is a standard in monitoring depressive symptoms and has been used in haemodialysis populations in previous studies (44, 45). The psychiatrists additionally used the Clinical Global Impression - Severity scale (CGI-S) to evaluate the severity of depression (46) and the Personal and Social Performance Scale (PSP) (47) to assess psychosocial functioning. The same procedure was followed by all three psychiatrists involved in the study. All the patients diagnosed with depression (regardless of the severity) were offered to remain under psychiatric care.

In one of the centres psychiatrists examined patients within the dialysis setting during the haemodialysis sessions. In the other the psychiatrist was only available in the ambulatory, which meant that patients had to attend a separate session that was scheduled independently of the dialysis treatment. In this centre, none of the patients who filled out the BDI-II questionnaire during their haemodialysis session agreed to the ambulatory clinical evaluation.

The demographic, clinical and laboratory data of the study group were obtained (Tables 1, 2). The severity of comorbidities was scored with the use of Charlson Comorbidity Index (CCI) (48), adjusted for age.

Statistical analysis

The statistical analysis was performed using the functions and procedures of the R package (49). Differences between both groups of quantitative variables were tested using the Wilcoxon test or Student's t-test. The appropriate tests (and additional options) were selected depending on the p value of the Shapiro-Wilk test and the homogeneity of the variance test. If the samples came from a normally distributed population, the basic features describing the

TABLE 1 Clinical data. Comparison between the non-depressed (MADRS < 10 or CGI < 3) and depressed (DSM-5 criteria, MADRS ≥ 10 and CGI ≥3) patients.

Parameter	Whole group *n*=70	Non-depressed *n*=52	Depressed *n*=18	p-value
BMI	26.9 (4.9)	27.3 (4.9)	25.8 (4.8)	0.294813[t]
Diabetes n, (%)				0.485198[c]
no yes	38 (54.2%) 32 (45.7%)	30 (57.7%) 22 (42.3%)	8 (44.4%) 10 (55.6%)	
CCI 1-2 mild 3-4 moderate >= 5 severe	6 (5; 8) 4 (5.7%) 9 (12.9%) 57 (81.5%)	6 (5; 8) 3 (5.8%) 6 (11.5%) 43 (82.7%)	6.5 (5; 8.5) 1 (5.6%) 3 (16.7%) 14 (77.8%)	0.684375[w]
Dialysis duration (years)	3 (2; 4.8)	3 (2; 4)	3.6 (2.2)	0.489249[w]
ESRD cause n, (%)				0.097571[f]
Diabetes GN Hypertension PKD Ischemic nephropathy Nephrolithiasis Reflux nephropathy Interstitial nephritis Other Unknown	19 (21.1%) 17 (24.3%) 4 (5.7%) 5 (7.1%) 5 (7.1%) 2 (2.8%) 3 (4.3%) 4 (5.7%) 6 (8.6%) 5 (7.1%)	12 (23.1%) 12 (23.1%) 3 (5.8%) 3 (5.8%) 4 (7.7%) 1 (1.9%) 3 (5.8%) 4 (7.7%) 6 (11.5%) 4 (7.7%)	7 (38.9%) 5 (27.8%) 1 (5.5%) 2 (11.1%) 1 (5.5%) 1 (5.5%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 1 (5.5%)	
Vascular access n, (%)				0.58603[f]
Arteriovenous fistula	25 (35.7%)	17 (32.7%)	8 (44.4%)	
Permanent catheter Temporary catheter	44 (62.9%) 1 (1.4%)	34 (65.4%) 1 (1.9%)	10 (55.6%) 0 (0.0%)	
Hb g/dl N: F 11.5-16.5, M 13.0-18.0	10.8 (1.3)	10.9 (1.4)	10.5 (1)	0.164954[t]
WBC G/l N: 4.0-11.0	6.8 (5.8; 8.1)	6.7 (5.8; 7.9)	7.3 (5.1; 8.2)	0.869732[w]
Albumin g/l N: 35-52	39.9 (3.8)	39.9 (3.6)	39.6 (4.4)	0.806852[t]
CaxPi	46.6 (13)	46.8 (11.7)	46.1 (16.4)	0.857303[t]
Kt/V >1,2	1.5 (1.2; 1.7)	1.5 (0.3)	1.5 (1.2; 1.7)	0.967294[w]
MMSE	28 (26; 29)	28 (25.5; 29)	27.5 (26.8; 29)	0.961678[w]
BDI-II	10 (7; 16.5)	10 (6; 14)	14.2 (8.2)	0.208242[w]
PSP	60 (46; 84)	67.5 (50; 86.2)	55 (45; 60.2)	0.013187[w]*

Samples from normally distributed populations are described using the mean and standard deviation. The remaining values of quantitative variables were described with the median and the first and third quartiles. n - the number of patients in the group, c - Pearson's $\chi 2$ test with Yates' continuity correction, w - Wilcoxon rank sum test with continuity correction, t - Student's t-Test, f - Fisher's exact test for count data, BMI- body mass index, CCI- Charlson Comorbidity Index, ESRD- end-stage renal disease, PKD- polycystic kidney disease, Hb- hemoglobin, N-normal range, CaxPi-calcium-phosphate index, Kt/V- dialysis adequacy, MMSE- Mini-Mental State Examination, BDI-II-Beck Depression Inventory II, PSP- Personal and Social Performance Scale
*- statistically significant

variables were mean values and standard deviations. In other cases, values are described using the median as well as the first and third quartiles. The Pearson's $\chi 2$ test with Yates' continuity correction and the Fisher's exact test for count data were used to test the independence of qualitative variables collected in tables presenting the size of individual groups. The research also used ROC analysis and logistic regression (50). For each of the tests used, the level of significance was set at $\alpha = 0.05$.

Results

Initially, 136 patients from two Dialysis Centres agreed to participate in the study. Four patients were diagnosed with moderate or severe dementia and were excluded from further evaluation. Patients diagnosed with MCI (14.2% of the whole group), mild dementia (12.9%), and those who did not agree to the MMSE screening (10%), remained in the study. Sixty-two

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TABLE 2 Sociodemographic data. Comparison between non-depressed (MADRS < 10 or CGI < 3) and depressed (DSM-5 criteria, MADRS ≥ 10 and CGI ≥3) individuals.

Parameter	Non-depressed	Depressed	p-value	
Gender (n=70)			0.733087[c]	
female	16 (30.8%)	7 (38.9%)		
male	36 (69.2)	11 (61.1%)		
Age (years) (n=70)			0.128411[w]	
Smoking (n=57)	70 (62.8; 76)	62.7 (12.5)	0.441555[f]	
no	34 (77.3%)	8 (61.5%)		
yes	6 (13.6%)	3 (23.1%)		
in the past	4 (9.1%)	2 (15.4%)		
Living (n=53)			1[f]	
alone	6 (16.7%)	3 (17.6%)		
with relatives	30 (83.3%)	14 (82.4%)		
Martial status (n=58)			0.257376[f]	
single	5 (11.9%)	3 (18.8%)		
married	29 (69.0%)	7 (43.8%)		
divorced	2 (4.8%)	2 (12.5%)		
widowed	6 (14.3%)	4 (25.0%)		
Residence (inhabitants) (n=52)			0.682529[f]	
<1.000	5 (13.5%)	1 (6.7%)		
1.000–10.000	5 (13.5%)	1 (6.7%)		
>10.000–100.000	3 (8.1%)	0 (0.0%)		
>100.000	24 (64.9%)	13 (86.7%)		
Work (n=66)			1[f]	
active	7 (14.6%)	2 (11.1%)		610
not active	41 (85.4%)	16 (88.9%)		611
Education (n=64)			0.097571[f]	612
primary school	3 (6.2%)	3 (18.8%)		613
vocational school	15 (31.2%)	3 (18.8%)		614
high school	21 (43.8%)	4 (25.0%)		
higher education (BA,MA,PhD)	9 (18.8%)	5 (31.2%)		615 616
no education	0 (0.0%)	1 (6.2%)		617

Percentages apply to the represented group (non-depressed or depressed); c - Pearson's $\chi 2$ test with Yates' continuity correction, w - Wilcoxon rank sum test with continuity correction, f - Fisher's exact test for count data, n – numbers for whom information was available, BA- Bachelor of arts, MA-Master of arts, PhD- Doctor, ESRD- end-stage renal disease, DM- diabetes mellitus, PKD- polycystic kidney disease.

patients (47%) did not agree to participate in some of the study procedures and were excluded from the analysis. Seventy patients (51.5%) who performed all depression evaluations were included in the final analysis. This group consisted of 23 females (32.8%) and 47 males (67.1%). The median age of participants was 69 years.

The numbers of patients with depression diagnosed using BDI-II only, differed from the numbers diagnosed by the psychiatrist using DSM-5 criteria and the scores of MADRS≥10 and CGI ≥3.

Forty-five patients (64.3% of the whole group) had BDI-II score of 0–13, which corresponded to no depression or minimal

symptoms. Out of this group, 9 (12.9% of the whole group) were diagnosed with depression by a psychiatrist using the DSM-5 criteria and the scores of MADRS≥10 and CGI ≥3.

Twenty-five patients (35.7% of the whole group) scored ≥14 points on BDI-II, consistent with the cut-off point for depression diagnosis. Of these patients, nine (12.9% of the whole group) were diagnosed with depression by a psychiatrist based on the DSM-5 criteria and scores of MADRS≥10 and CGI ≥3.

In more detail, 13 patients (18.6% of the whole group) had the BDI-II score of 14–19, which corresponded to mild depression. Of these, 4 (5.7% of the whole group) were diagnosed with depression by a psychiatrist based on the DSM-5 criteria and scores of MADRS≥10 and CGI ≥3.

BDI-II criteria for moderate (20–28) and severe (29–63) depression were met by, respectively, 8 patients (11.4% of the whole group) and 4 patients (5.7% of the whole group). Of these, respectively, 4 (5.7% of the whole group) and 1 (1.4% of the whole group) were diagnosed with depression by a psychiatrist based on the DSM-5 criteria and scores of MADRS≥10 and CGI ≥3.

Subsequently, we analysed the differences in qualitative and quantitative data between groups with and without depression based on the diagnosis made by the psychiatrist (depression: DSM-5 criteria, MADRS≥10 and CGI ≥3; no depression: remaining patients). The basic characteristics (sociodemographic and clinical data) for the whole group, as well as depressed and non-depressed subgroups, are presented in Tables 1 and 2.

In the whole group, the most common known primary cause of ESRD was diabetes mellitus (DM) (45.7% of all participants) and glomerulonephritis, followed by hypertension, policystic kidney disease and ischemia. The dominant vascular access was the permanent catheter. The CCI score interpreted as the severe comorbidity was found in 81.5% of participants, while mild comorbidity was found in in 5.7%.

The only statistically significant difference for quantitative variables was observed for the PSP score, which suggests that functioning of depressed and non-depressed patients differs across the dimensions assessed by the scale (socially useful activities, personal and social relationships, self-care, disturbing and aggressive behaviours). There were no statistically significant differences between depressed and non-depressed groups in terms of other quantitative variables, as well as qualitative variables, as shown in Tables 1 and 2 (all p-values >0.05). The number of patients with diabetes mellitus did not differ between groups. We also found no statistically significant differences in the albumin level, body mass index or comorbidity. However, in both groups the average CCI score met the criteria for severe comorbidity.

Using ROC analysis and logistic regression, the possibility of creating a potential tool to determine the absence of depression in dialysis patients based on the BDI-II score variable was examined. For this purpose, a logistic regression model was created, in which the dependent variable was membership of the group (with or without depression), determined using scores on the MADRS and CGI-S scales, as described above. The independent variable was the BDI-II score. Based on the model created in this way, an ROC curve was plotted and the cut-off point for the obtained model was calculated (Figure 1).

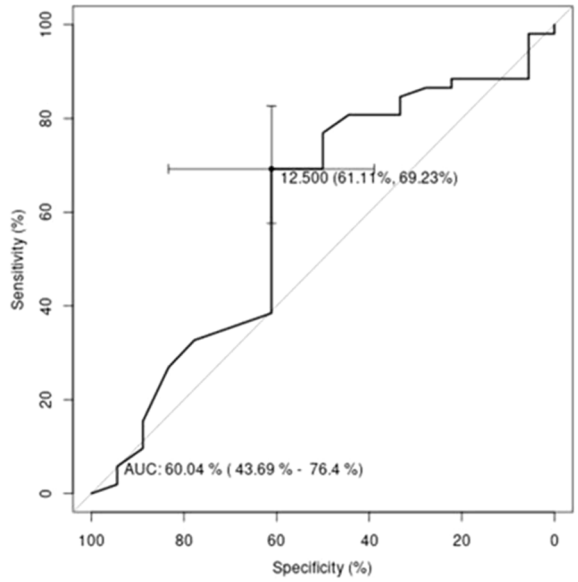

FIGURE 1
ROC curve for the logistic regression model. The independent variable is the BDI-II score and the dependent variable is membership of the group "no depression" or "depression".

The cut-off point established for BDI-II was the value dividing patients into two groups. Patients with predicted depression were those with a BDI-II score of 13 or greater and the remaining patients with scores of less than 13 were classified as 'predicted no depression'. Contingency tables were created on the basis of the groups defined in this way (Table 3).

The result of the independence test was statistically significant. It indicated that there is a relationship between the groups defined by BDI-II and the groups defined by the MADRS and CGI-S scales. The quality of the classification was assessed by determining values for parameters such as: TPR=69.2% (True Positive Rate - associated with the group "no depression"), TNR=61.1% (True Negative Rate - associated with the group "depression"), PPV=83.7% (Positive Predictive Value) and NPV=40.7% (Negative Predictive Value). In the created model for grouping the values of the BDI-II score variable, only the parameters assessing the classification into the "no depression" group could be considered satisfactory.

TABLE 3 Contingency table for the Beck variable.

Parameter	No depression (MADRS <10, CGI<3)	Depression (MADRS ≥10, CGI ≥3)	p-value
BDI-II			
nd d	36 16	7 11	0.045667[c]

nd, no depression; d, depression.

Discussion

In the studied population of patients with ESRD undergoing MHD, 35.7% had BDI-II scores corresponding to mild depression (the cut-off point of 14 points), with 17.1% with scores indicating moderate or severe depression (≥20 points). The number of patients diagnosed with MDD by the psychiatrist using DSM-5 criteria and scores of MADRS≥10 and CGI ≥3 however differed from this, with 25.8% diagnosed with depression. With the exception of PSP score, no statistically significant differences were found in terms of the sociodemographic and clinical features between the depressed and non-depressed patients. In our study, using ROC analysis and logistic regression, the suggested optimal cut-off point for BDI-II, which indicated patients without depression in the clinical evaluation, was 13 points. The compliance rate was low; 47% of the patients, that had agreed to participate in the study, refused to perform some of the proposed tests. MCI and mild dementia were observed in 27.1% of patients.

We used BDI-II as the screening tool as despite its limitations (11, 27), it remains a commonly used measure to explore depressive symptoms in the clinical settings, and this study was designed to reflect the common practices. Using the MADRS scale alone, applied by the psychiatrist, the percentage of individuals with depression reached 35.7%, equal to the number identified in BDI-II screening. These results are comparable with the prevalence of depressive symptoms observed in outpatient populations across different specialties [4]. Psychiatric evaluation attributed diagnosis of MDD based on DSM-5 criteria, with MADRS and CGI scores to assess severity, to 25.8% patients, hence lower than when the scales were used alone. This finding is consistent with previous reports of higher depression rates when self-reported questionnaires were used, compared to the clinical evaluation (12). Such discrepancy may be linked to a number of factors, specific to the researched population. Relevant to our studied population, somatic symptoms may get reported through questionnaires, while in fact they are related to the somatic condition, rather than depression. Indeed, numerous somatic comorbidities were seen in our tested population, and the CCI score indicated severe comorbidity in 81.5% of patients, consistent with the epidemiological data (7). Although the groups with and without depression did not differ in terms of clinical features, people with depression may be more sensitive to somatic problems (for example, it was shown that depression increases sensitivity to pain) (51), which may translate to allocating higher scores to somatic items, whereas a trained psychiatrist may have more clarity whether reported symptoms are related to depression or not. We noted that the number of patients meeting the criteria for depression according to MADRS alone, was equal to the number of patients whose scores on BDI-II indicated depression (35.7% in both cases). At the same time, only 27.8% of patients were diagnosed with depression by the psychiatrist using DSM-5 criteria. This suggests no superiority of clinician applied scales as compared with self-rated scales, and indicates that a full clinical assessment is warranted for a diagnosis. Importantly, this also suggests that some haemodialysis patients whose scores on depression assessment scales, whether self-rated or clinician applied, were indicative of depression, might not in fact have MDD. In such cases, starting depression treatment may be ineffective or even harmful, with the symptoms presented possibly reflecting mild depression, requiring psychological therapy rather than pharmacotherapy. Patients may also be suffering from dementia or yet another mental disorder requiring a different therapeutic approach altogether. The lack of precise diagnostics in the studies on the efficacy of antidepressant treatment in this group of patients may be one of the reasons for the ineffectiveness of therapy, giving false negative results (52).

An intriguing observation was that while BDI-II suggested depression (score ≥14) in a higher number of patients than later confirmed by a psychiatrist, some patients who had scores on BDI-II corresponding to no or minimal depression (≤13), were diagnosed with depression in a psychiatric assessment. This suggests that a psychiatrist may recognise depression based on DSM-5 criteria, when the key symptoms are present, which however may not reach the severity required for the diagnosis using BDI-II. Whether diagnosing patients with such low severity of symptoms is important, for example in the context of offering counselling, is an important questions, however beyond the scope of this study.

Unfortunately, in reality, availability of psychiatric support is low and regular psychiatric assessments in physical health settings are rare. Using a self-rated scale such as BDI-II would help identify patients who could potentially benefit most from a psychiatric assessment, hence focusing the resources available. Therefore, the regular screening using self-administered questionnaires is advisable. BDI-II is easy to perform and can be done while patients are having their haemodialysis session, with no additional burden on their time. The value of performing such a screening cannot be overappreciated. Depression has many adverse effects, from its intrinsic impact on well-being to the worsening of physical health and increased non-compliance with treatments. Therefore its recognition and management are crucial for regular clinical practice and the management of somatic health problems.

According to our results, the optimal cut-off point for BDI-II in diagnosing MDD in the haemodialysis population was equal to or greater than 13 points. It is similar to the one recommended in the general population (i.e. 14 points) (29, 39) and lower compared with cut-off points suggested in the previous studies (22, 32, 33).

Our studied group of patients had high average age and high rate of severe comorbidities. Population aging and increases in comorbidities, observed in patients receiving renal replacement therapy, is in line with changes in the general population. Both have been identified as risk factors for developing depression (7, 53, 54). In both groups the average CCI score suggested severe comorbidity, although with no statistical differences between depressed and non-depressed groups. One such comorbidity, present in the high percentage of patients in our group, was diabetes mellitus. DM is the most common cause of ESRD. Although our study did not identify statistical differences in any of the clinical factors between depressed and non-depressed groups, some of the aspects of somatic health warrant attention. For example, cardiovascular problems are a risk factor for depression, hence an assessment of their indices, especially modifiable ones, is potentially important (55). Phosphate retention is a risk factor for

cardiovascular mortality in patients with CKD, and can be potentially modified with diet (56, 57). Although this study did not allow for an assessment of the relationship between adherence to dietary recommendations, which influences phosphate levels, and the occurrence of depressive symptoms, this might be an important practical aspect of future studies. There were no significant between-group differences in other parameters suggested to be associated with future cardiovascular events, such as albumin and haemoglobin levels (57). We have not found statistically significant differences between depressed and non-depressed patients according to Kt/V, used to evaluate haemodialysis adequacy. However, its interpretation as a single parameter has many limitations (58).

One of the reasons for the lack of identification of between-group differences might be the small study sample. Almost half of the recruited patients were lost to the analysis as they refused to perform one or more of the required tests. Our observations of low compliance rate regarding diagnosing depression are consistent with the previous research (59, 60). In our studied population, almost half of the patients who initially gave their written consent to participate, did not agree to follow through with the further psychiatric evaluation. This seemed to be associated with the setup of the assessment. While 84% of patients agreed to a psychiatric assessment provided during their dialysis session, none of the patients followed up with a psychiatric assessment if it was offered in the ambulatory. One possible explanation may be the reluctance to use additional services, considering the time that patients already devote to the regular dialysis procedure. The attitudes to psychiatric assessments may also play a role. Interestingly, none of the patients from the dialysis centre which was in a small town – and incidentally where the assessment was offered in the ambulatory only – agreed to see the psychiatrist. Although not examined in the study, the stigma around psychiatric assessments is still an important issue, and may be more pronounced in particular social contexts. Even if the examination during a dialysis session is challenging given the lack of privacy in the setting where a number of patients share the dialysis room, as well as the noise of regular hospital activities, it seemed to be more acceptable for the patients in our study than when a separate appointment was required.

Therefore, on-dialysis consultations may be recommendable (22).

Our study included dementia screening using MMSE. The percentage of patients diagnosed with MCI or mild dementia was 27.1%. An assessment of cognitive impairments when assessing depression, especially in the elderly populations, is important, as dementia can distort the diagnosis of depression and influence the results of its treatment. At the same time, the results of MMSE have to be considered carefully as higher scores may be related to pseudo-dementia in the course of depression, as well as be related to the conditions of the examination itself. Previous research showed that dialysis patients with greater burdens of depressive symptoms performed worse in cognitive tests related to processing speed and executive function (61). Therefore, individuals who met the criteria of MCI and mild dementia in MMSE were not excluded.

In the real world, the access to a psychiatric assessment in the dialysis setting is very restricted. Employing a psychiatrist full-time is usually not considered cost-effective; examining all the patients would be associated with high costs and an additional pressure on scarce resources. However, given how common depression is in this population of patients, and how big its impact on general health is, an identification of depressed individuals is an important issue. One solution, supported by this study, could be the regular screening for depression using self-reported scales, applied during the dialysis session, in order to identify patients requiring a psychiatric consultation. Our results suggest that this consultation might be best offered during the dialysis session, as shown by differences in accepting an assessment depending on the setting during and outside of the dialysis session. Such models could be more beneficial both for patients and the service providers. Increasing the availability of psychiatric consultations in the dialysis settings for the selected patients, might improve the effectiveness of diagnosing and treating depression in this population, and in turn have an impact on physical health and treatment adherence. The proper screening algorithm might improve the treatment of depression and have an impact on patients' quality of life as well as compliance with the dialysis recommendations.

One of the study limitations was the small sample size, discussed above. The others were related to the differences between the two settings regarding the place and time of the psychiatric evaluation, which may be the reason why patients from one of the settings refused a psychiatric consultation. Performing the clinical evaluation during the dialysis session might be considered a limitation as well, given a relative lack of privacy and other factors discussed above. However, as our study suggested, in real life, even if such conditions are not ideal, this approach may still be more acceptable for patients than a separate appointment.

The future research on depression screening in the haemodialysis patients leading to the development of the practical recommendations regarding diagnosis and treatment, is an important clinical need. It might also be of importance to explore the correlation between depression and the compliance to the dialysis treatment itself.

Conclusions

This study suggests that, although the psychiatric assessment is considered superior to using depression rating scales, the regular use of self-rated questionnaires to assess depression during haemodialysis sessions may help to identify a subgroup of patients with suspected depression, who would benefit from a psychiatric assessment. This might be a cost-effective model for the management of depression among the haemodialysis population. Performing dementia screening should be taken into consideration before diagnosing depressive disorders. The regular screening for depressive symptoms, followed by a psychiatric consultation in selected patients as a part of regular care in Dialysis Centre, might improve diagnosing depression, with the

goal of achieving a higher quality of life, better treatment adherence, and a lower mortality rate.

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 humans were approved by Independent Bioethics Committee for Scientific Research of Medical University of Gdansk. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

AK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. MR: Formal analysis, Funding acquisition, Supervision, Writing – review & editing. BG: Data curation, Formal analysis, Methodology, Supervision, Validation, Writing – review & editing. PP: Data curation, Formal analysis, Investigation, Writing – review & editing. MP: Conceptualization, Data curation, Investigation, Writing – review & editing. ASK: Data curation, Investigation, Writing – original draft. PW: Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. MB: Data curation, Investigation, Writing – original draft. AM-S: Data curation, Investigation, Writing – original draft. PR: Data curation, Investigation, Supervision, Writing – review & editing. KC: Data curation, Investigation, Writing – review & editing. KB: Data curation, Investigation, Writing – review & editing. JG: Data curation, Formal Analysis, Investigation, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

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

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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Preventive and therapeutic effect of vitamin D on depression-like behavior in a mouse adolescent depression model and its association with BDNF protein expression

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Introduction: Previous studies in different populations have shown that vitamin D supplementation may reduce depression levels. In adolescents, vitamin D deficiency has been identified as a factor contributing to the onset of depression. This study aimed to establish a model of adolescent depression in mice by using the scientific unpredictable chronic mild stress (UCMS) model and to preliminarily evaluate the effect of vitamin D on the occurrence and development of depression and whether it is related to the protein expression of the BDNF pathway.

Methods: The UCMS method was used to establish a model of adolescent depression in 4-week-old C57BL/6 male mice, randomly divided into five groups: Control group, Stress group, Stress+ low-dose group, Stress+ medium-dose group, Stress+ high-dose group. At the same time as chronic stress, the administration groups were given intramuscular injections of different doses of vitamin D. After 8 weeks, behavioral tests, including the forced swimming test (FST) and open field test (OFT), were performed on each group of mice, along with recording of indicators, blood vitamin D level detection, and brain tissue western blot analysis.

Results: The results showed a significant difference in vitamin D levels among mice in different groups after 8 weeks ($P=0.012$). The results of behavioral testing showed a significant difference in the static time of forced swimming among the groups ($P<0.001$). Compared with the UCMS group, the static time of mice with vitamin D injection was significantly reduced ($P<0.001$). The total number of times mice entered the central area, the total distance of movement, and the time spent in the central area significantly increased after vitamin D injection compared with the UCMS-only group (all $P<0.001$). There was no significant difference in the expression of BDNF in the brain tissues of experimental mice ($P>0.05$).

Discussion: In conclusion, in the mouse adolescent depression model, appropriate vitamin D supplementation can reduce the occurrence of stress-induced depression. Furthermore, vitamin D deficiency may also serve as a potential risk factor for depression.

KEYWORDS

depression, vitamin D, BDNF, depression model, mouse

Background

Adolescence is an important period of psychological development, a stage of continuous growth and dynamic change. Physiological, psychosocial, and cognitive changes make adolescents susceptible to psychological disorders. Depression is a psychological disorder with a high incidence and is the leading cause of disability worldwide. A meta-analysis showed that the global point prevalence of depression was 34% between 2001 and 2020 based on self-reported depressive symptoms. The point prevalence of major depressive disorder (MDD) and dysthymia was 8% and 4%, respectively. Furthermore, depressive symptoms in adolescents increased from 24% between 2001 and 2010 to 37% between 2011 and 2020. The Middle East, Africa, and Asia have the highest prevalence of elevated depressive symptoms (1).

Since depression typically begins in adolescence, juvenile cases are more likely to be first cases, while adult cases may be relapses from earlier juvenile cases. Symptomatic characteristics differ between adults and adolescents. Autonomic dysregulation symptoms (insomnia, fatigue, and changes in appetite and weight) are more common in adolescents with MDD than in adults. Further, anhedonia/loss of interest and concentration problems are more common in adults with MDD. The differences in the presentation of depression in adolescents and adults may be related to different pathophysiological mechanisms. In addition to targeting those who already have clinical depression, research and policy should focus on education and supportive efforts to prevent adolescents from developing depression (2). It is important to study the psychological state of adolescence, and some factors and behaviors related to adolescence, such as poor school performance, may be associated with depression in adulthood, so early detection and management of externalizing disorders in children and adolescents is important (3). It is necessary to pay attention to early depressive symptoms, and more research data—especially on the influencing factors and mechanisms of depressive symptoms—are needed to support the prevention and treatment of depression in adolescents.

Research on factors related to depression has shown the benefits of vitamin D in the prevention and treatment of depression. Vitamin D deficiency (VDD) may be an associated risk factor for depression. VDD has a potential causative role in depression and suicide, while vitamin D supplementation has shown potential benefits in the adjunctive treatment of mood disorders, helping to reduce the risk of depression (4). Although some study results have been inconsistent, meta-analyses investigating the efficacy of vitamin D supplementation and the relationship between vitamin D and depression showed that vitamin D can significantly reduce depressive symptoms. People with lower serum vitamin D levels were found to have higher rates of depression, and vitamin D supplementation and increasing serum vitamin D levels had potential benefits in reducing the development and symptoms of depression (5). However, more extensive and detailed research on adolescent depression and vitamin D is needed.

To date, clinical studies on the therapeutic effect of vitamin D have paid more attention to the improvement of depressive symptoms in the elderly, among whom depressive symptoms and impaired physical function are very common. Studies have found that vitamin D supplementation can improve both of these conditions, especially for people with low vitamin D levels (6, 7). The cross-sectional data statistical analysis found that vitamin D level was inversely associated with depression, and both vitamin D deficiency and older age were associated with a higher risk of depression (8). Through double-blind randomized clinical trial, and serum vitamin D and depression severity evaluation, it was found indeed that the severity of depression of the intervention group (50000IU cholecalciferol/2 weeks) improved with an increased level of vitamin D for adult patients with depression, compared to the placebo-control group. However, the long-term effects of vitamin D on depression were not evaluated, and the way by which the vitamin D mediate depression was not explained (9). However, some studies have not found vitamin D to be therapeutic for depression in adults. In one outpatient multicenter study conducted between 2010 and 2013, patients aged 18–65 diagnosed with mild to severe depressive disorder were randomly assigned to receive either vitamin D supplements or placebo. However, there was no significant reduction in depressive symptoms on the Hamilton scale after vitamin D supplementation compared with placebo (10). However, long-term follow-up controlled clinical trial also found no significant difference in the risk of depression or clinically related depressive symptoms between the intervention and placebo groups after vitamin D supplementation, and the results did not support

preventing effect for depression (11). Therefore, the results of studies related to vitamin D and depression are not completely consistent.

In the adolescent population, it is thought that lower vitamin D levels may be associated with depression. Vitamin D deficiency has been found to play a role in the onset of depression (12). The results of a study based on the detection of blood 25(OH)D levels and self-reported depressive symptoms in Chinese adolescents explored the cross-sectional and longitudinal association between vitamin D and depression in early adolescence. Higher baseline serum 25(OH)D levels were found to be associated with a higher risk of depressive events, while baseline VDD was associated with an increased risk of depression. The results also support the potential beneficial role of vitamin D supplementation in reducing the risk of depression in early adolescence (13). Overall, there is growing evidence that vitamin D may affect mental health in addition to its association with calcium and phosphorus homeostasis and bone health. However, assessing vitamin D status in adolescents with depression or supplementing with vitamin D is not currently part of routine treatment.

Controlled intervention studies are essential to demonstrate whether vitamin D is associated with improving depressive symptoms in adolescents. A study on VDD patients with psychiatric disorders hospitalized in a psychiatric department confirmed that patients who received daily vitamin D supplementation showed improvements compared those who did not receive daily vitamin D supplementation (14). To prevent the risk of overdose, vitamin D supplements still need to be closely monitored, and safer ways are still needed for the population. However, for adolescent depression, due to the specificity of the population, relevant studies in animal models may still be a safer and more reliable research method, and vitamin D has shown a significant effect on the treatment of depression in successfully established animal models (15). It is clear that more human studies and animal models are needed to deepen understanding of the biological link between vitamin D and depression, to advance understanding of the various pathogeneses and pharmacological therapies of the disorder, and to increase the potential for new prevention and treatment options for adolescent depression.

The chronic mild stress (CMS) model is a widely used model for studies such as those on the effects of antidepressants. It was first developed nearly 40 years ago, based on the observation that long-term exposure to unpredictable/uncontrollable mild stressors in rodents can lead to reduced palatable fluid intake, behavioral hopelessness, motor inhibition, anxiety-like changes, and nutritional (somatic) abnormalities. Different studies have adapted this model to suit different needs (16). For animal models, positive effects of vitamin D on neuroprotection in the hippocampus, which plays a role in alleviating depression-like symptoms, have been found in adult mice (15).

The unpredictable chronic mild stress (UCMS) model is a commonly used depression model in depression-related research. Although originally designed for rats, the model is now also used in mice and is a very valuable model for gaining insight into the etiology and developmental components of major depressive disorder as well as identifying new therapies (17). The behavioral responses associated with different stress patterns are quite complex. The UCMS model has some advantages over the CMS model, and studies have examined the effects of two chronic stress regimens on anxiety-like and depressive behaviors. After 4 weeks of unpredictable chronic mild stress or chronic restraint stress, both models of chronic stress were found to produce anxiety-like behaviors, but only unpredictable chronic mild stress could induce depressive behaviors (18). However, there is still a lack of relevant research on the establishment of animal models of adolescent depression and the effect of vitamin D on the occurrence and development of depression in animal models.

Previous animal experiments have shown that different substances and pathways may improve or aggravate depressive symptoms, which may be related to the brain-derived neurotrophic factor (BDNF) pathway. As a result, BDNF has emerged as an important determinant of antidepressant efficacy (19). There is also considerable research on how depression-like behaviors can be produced by the BDNF signaling pathway, and some studies have shown that chronic stress exposure can induce the development of depression-like behavior though damaging the signaling between cyclic adenosine monophosphate-response element binding protein (CREB) and BDNF in the hippocampus, although the underlying mechanism remains largely unknown. Given the critical role of impaired CREB-BDNF signaling in depression, chronic unpredictable stress may significantly increase hippocampal NR6A1 protein expression levels, decreasing hippocampal CREB phosphorylation and BDNF protein expression. This leads to the occurrence of depression-like behaviors by impairing the CREB-BDNF signaling cascade (20). Therefore, the effect of VDD on the occurrence of depression or the improvement of depressive symptoms by vitamin D may also occur through the BDNF signaling pathway.

For the relevant animal studies of vitamin D, some studies have explored the antidepressant effects of vitamin D by using mouse animal studies. To discover the preventive and therapeutic effects of vitamin D on the depressive behaviors, control studies were manipulated by drug induction and depressive behaviors were evaluated by behavioral testing (21). Combined with the above studies, we hypothesized that vitamin D has some preventive effects on the development of depression, assuming the existence of factors that induce depression such as chronic mild stress. If the intervention is done by vitamin D supplementation, the depressive outcome may be altered even in the presence of stress factors. Details of vitamin D supplementation can be clarified further through the serum vitamin D detection, and the relationship between vitamin D and depression can be illustrated better (22). If vitamin D plays a preventive role on depression, it may be through the nerve loop. Therefore, in this study, we established a mouse model of adolescent depression through the scientific UCMS model and provided long-term supplementation of different doses of vitamin D in the form of experimental control in order to investigate the preventive and therapeutic effects of vitamin D in depression, preliminarily evaluate the role of vitamin D in the development of depression, determine whether this role is related to the protein expression of the BDNF pathway through western blot detection, and obtain corresponding data to lay the foundation and

provide support for in-depth research in larger samples in the future. Research method by non-oral administration-vitamin D injection and vitamin D detection in the blood was more accurate for vitamin D dose and related effects than previous studies.

Method

Materials

Animals

C57BL/6J mice, 4 weeks old, male, SPF-grade, were provided by Sipeifu Animal Company. All mice were randomly divided into five groups, 15 ones in each group. This study was approved by the animal ethics review board of China Medical University.

Main experimental agents

The main materials used were vitamin D3 (cholecalciferol, Solarbio), a mouse 1,25 dihydroxyvitamin D3 (1,25-(OH)2D3) enzyme-linked immunoassay kit (96T) (Jiangsu Enzyme Immunoassay Co., Ltd., MEIMIAN), antibody (target BDNF, working concentration 1:1,000; actin, working concentration 1:5,000), secondary antibody (goat anti-rabbit IgG[H+L]/HRP, final concentration 1:10,000) (Jackson), and sample diluent. Others included lotion, TBST, blocking solution, antibody diluent, electrophoresis solution, sample loading buffer, electroporation solution, a membrane (PVDF membrane pore size 0.45 μm, Millipore), filter paper (3 mm), and a chemiluminescence imaging system.

Main experimental equipment

The experimental equipment included a microplate reader (352 type, Labsystems Multiskan), plate washer (AC8 type, Thermo Labsystems), micro-high-speed centrifuge (instrument model: TG16W type, Xiangyi Group), water-isolated constant temperature incubator (GNP-9080 type, Shanghai Jinghong), electrophoresis instrument (Mini-PROTEAN Tetra Cell, Bio-Rad), wet transfer instrument (PowerPac Basic, Bio-Rad), chemiluminescence imaging system (FluorChem E ProteinSimple), multichannel pipette (300 μL Thermo), and vortex shaker (LP Vortex Mixer, Thermo).

Experimental methods

Establishment of animal models of adolescent depression and vitamin D3 administration

The UCMS method was used to establish an animal model of adolescent depression (17, 18), and various stimuli, such as tail clamping for 2 min, fasting for 24 h, water fasting for 24 h, wet bedding for 24 h, falling from heights, strange objects (multicolored building blocks/plastic cups), and odors (alcohol), were used. According to the experimental standard strictly, the experimental conditions and time were controlled strictly, ensuring that the stress and operation conditions of the groups were consistent. Male mice were randomly divided into five groups: Control group (normal saline injection alone), Stress group (UCMS and normal saline injection), Stress+ low-dose group, Stress+ medium-dose group, and Stress+ high-dose group (UCMS and injection of different doses of vitamin D3). All the stress groups were randomly modeled with two to three stimuli per day without recurrence for 8 weeks. Stress was performed at the beginning of the experiment. To observe the long-term effects of vitamin D on mice, it was started at an earlier time, and the duration of stress was 8 weeks instead of 4 weeks. At the same time, at the onset of stress, the stress + vitamin D groups received intramuscular injections of diluted vitamin D3, with 400 IU/week/mouse in the low-dose group, 800 IU/week/mouse in the medium-dose group, and 1,600 IU/week/mouse in the high-dose group, and normal saline injections were administered into the Control group and the Stress group simultaneously. Stress and the injection of vitamin D3 lasted for 8 weeks. Behavioral testing was performed one week after finishing injection.

Animal behavior testing

Forced swimming test

The principle of the forced swimming experiment is that the mouse is placed in a small container of water, and when, after repeated struggles, it cannot escape, the mouse will become stationary and keep itself floating on the surface of the water with a small limb movement, which is considered to be immobile time. The specific method employed involved filling a 2-L beaker with 22–25°C warm water to a 12-cm height. Subsequently, the mouse was placed in the beaker and a timer was set for 6 min. The behavior of the mouse was then tracked and analyzed using video tracking software (Smart 3.0), with the immobility time, which was within the last 4 minutes, being recorded.

Open field test

The open field test, also known as the open box test, is a method of evaluating spontaneous activity, exploratory behavior, and spontaneous anxiety in rodents. The open box is a 40-cm-long × 40-cm-wide × 40-cm-high observation box with an opening and white walls and surfaces, and the bottom of the box is divided into the central area and the surrounding area. A single mouse was placed in the central area of the open box, and each mouse was observed for 5 min. The experiment was carried out in a quiet room, and the top of the open box was equipped with a camera to observe and record the mouse's behavior. The behavioral video of the mice was tracked and analyzed using video tracking software (Smart 3.0). Before each mouse was tested, the inner walls and bottom surface of the open box were cleaned with 75% ethanol to prevent any residual information from the last animal (such as the animal's stool, urine, or smell) from affecting the results of the next test. The OFT recorded metrics were total distance of movement, total number of entries into the central area, and time spent in the central area.

Material acquisition

When the animals were grouped, apical blood from the tail tip was collected. After the behavioral experiment, the animals were sacrificed. Blood from the mouse eyeballs was taken in an EP tube, left at room temperature for 60 min, and centrifuged at 3,000 r/min

for 15 min at room temperature; the supernatant was stored in a −80°C refrigerator for later use. After the blood collection was completed, the experimental mice were decapitated, the brain was removed, and the hippocampus was separated on ice in an RNase-free EP tube and transferred to a −80°C freezer for later use.

Western blot BDNF protein level analysis

To analysis the BDNF protein level, hippocampus tissue was performed by Western blot. The main steps of the western blot analysis were as follows: (1) Loading: The processed tissue sample was directly loaded with a sample volume of 30 μg. (2) Electrophoresis: A constant voltage of 100 V was applied until the bottom of the glue plate of bromophenol blue was running. (3) Film transfer: A constant pressure of 110 V was applied for 90 min. (4) Closure: Closure was performed at 4°C overnight. (5) Primary antibody incubation: The antibody was diluted and incubated at room temperature for 2 h. (6) Elution: A destaining shaker was used to elute the membrane 3 times for 5 min each time. (7) Secondary antibody incubation: The secondary antibody was diluted and incubated at room temperature for 2 h. (8) Elution: A destaining shaker was used to elute the membrane 3 times for 5 min each time. (9) Color development: A chemiluminescence imaging system was used for color development. (10) BCA: This included the preparation of standards, preparation of analytical samples, spotting, color development, and reading.

BDNF protein level detection

Gel image analysis was performed, the film was scanned, and the net optical density value of the target band was analyzed using AlphaEaseFC and statistically analyzed.

Statistical analysis

SPSS 22.0 (version 22.0, SPSS Inc., Chicago, IL, USA) was used for statistical processing. All data were presented as mean ± standard deviation (mean ± SM). Single-factor ANOVA, *t*-tests, and Chi-square tests were used for between-group comparisons and multi-group comparisons, with $P<0.05$ indicating statistical significance.

Results

Changes in blood vitamin D levels in each group

As shown in Figures 1 and 2, at the baseline level, there was no significant difference in vitamin D levels among groups (K=0.068, P=0.999). After 8 weeks, there was a significant difference in vitamin

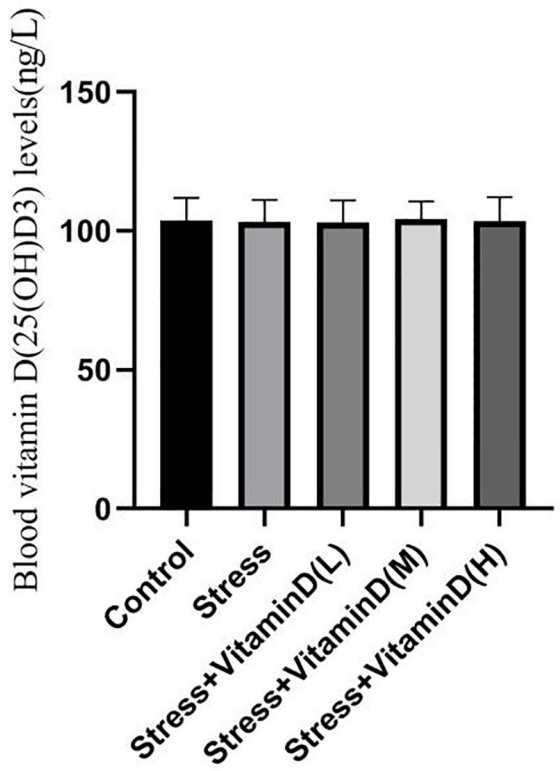

FIGURE 1
Comparison of the baseline blood vitamin D(25(OH)D3) levels in each group mice.

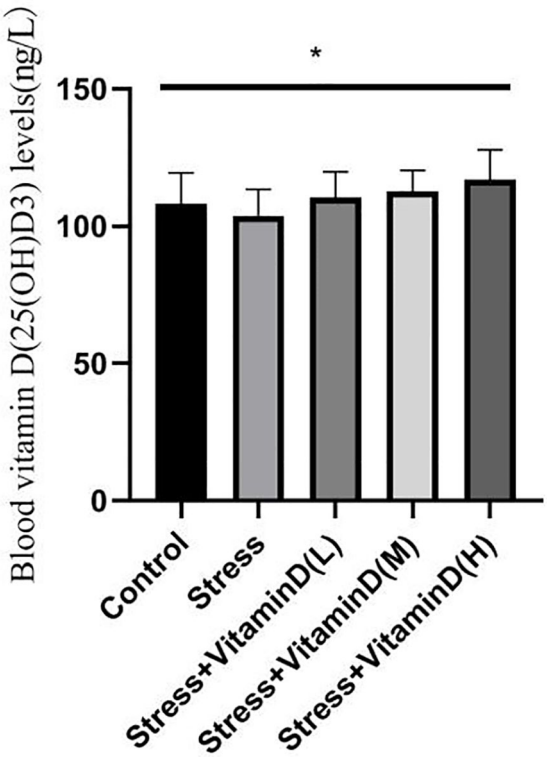

FIGURE 2
Comparison of the blood vitamin D(25(OH)D3) levels in each group mice after 8 weeks. *$p<0.05$.

D levels among groups (K=12.806, P=0.012). There was no significant difference between the control group and the UCMS alone group (K=1.389, P=0.239). There were, however, significant differences between the low-dose group and the control and UCMS alone groups (K=12.806, P=0.012), between the medium-dose group and the control and UCMS alone groups (K=6.781, P=0.034), and between the high-dose group and the control and UCMS alone groups (K=9.585, P=0.008). The results showed that the 1,25(OH)D3 blood levels in mice were indeed increased by vitamin D injection, but there was no significant difference among the three vitamin D injection groups (K=2.657, P=0.265).

Effect of vitamin D on forced swimming static time in a depressive model of UCMS mice

As shown in Figure 3, there were significant differences in forced swimming test results among the groups (K=45.703, P<0.001). The stationary time of the mice with UCMS alone was significantly higher than that of the control group (K=19.864, P<0.001), but the stationary time of UCMS mice after different doses of vitamin D injection was significantly lower than that of the mice with UCMS alone (K=39.836, P<0.001); the difference was extremely significant, and the reduction was the smallest in the low-dose vitamin D group.

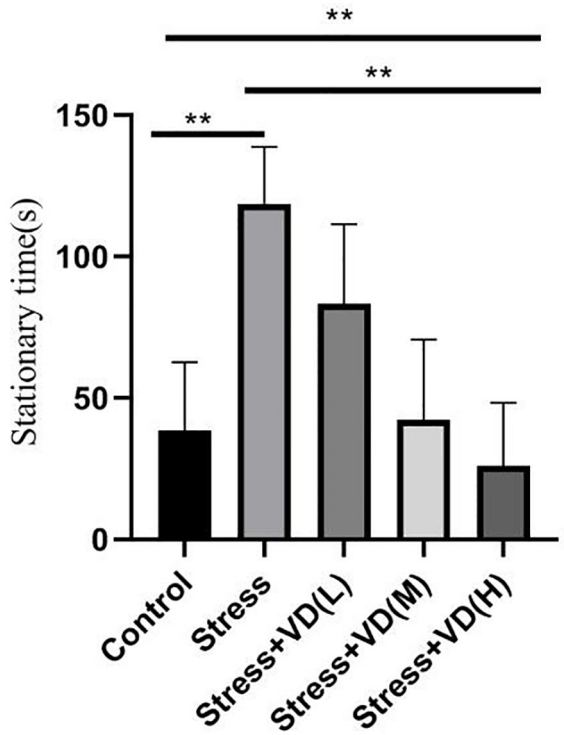

FIGURE 3
Comparison of the stationary time of the forced swimming test in each group mice. **p<0.01.

Effect of vitamin D on the total number of entries into the central zone by UCMS mice in the open field test

The results of the open field test showed a significant difference among groups (K=26.351, P<0.001), with the total number of entries into the central area being significantly lower for UCMS mice than for the control group (K=13.012, P<0.001), but the total number of entries of UCMS mice after different doses of vitamin D injection was significantly higher than that of mice with UCMS alone (K=23.610, P<0.001) (Figure 4). For the total moving distance of mice, the analysis results showed significant differences among the groups (K=14.623, P=0.006), and the total distance of mice with UCMS alone was significantly lower than that of the control group (K=5.709, P=0.017), but the total distance of UCMS mice after different doses of vitamin D injection was significantly higher than that of mice with UCMS alone (K=13.582, P=0.004) (Figure 5). For the time spent in the central area, there were also significant differences among groups (K=26.321, P<0.001). The time of UCMS mice with UCMS alone was significantly shorter than that of the control group (K=11.567, P=0.001), but the time of UCMS mice after different doses of vitamin D injection was significantly longer than that of mice with UCMS alone (K=23.890, P<0.001) (Figure 6). The behavioral testing indicated that UCMS alone and

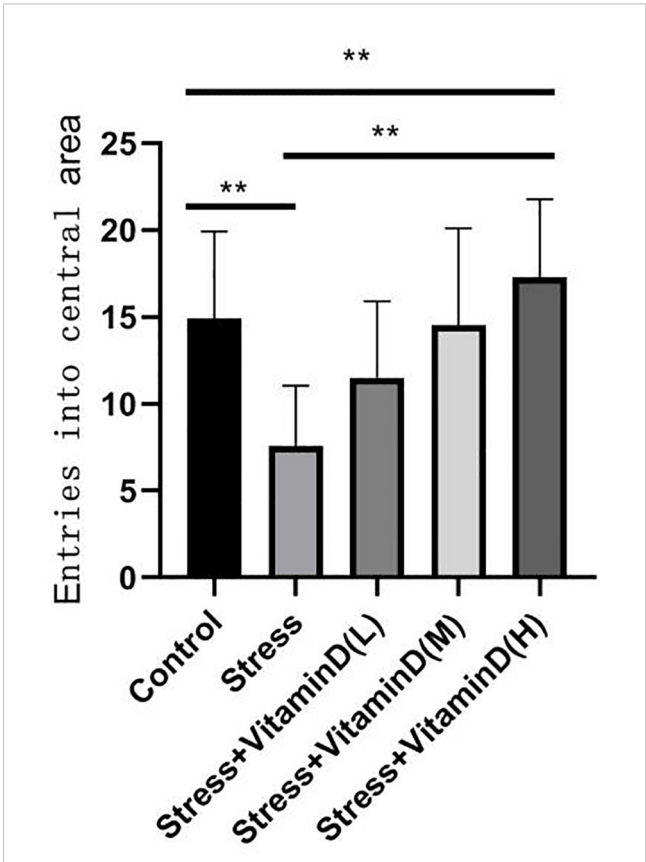

FIGURE 4
Comparison of the total number of entries into the central area by each group mice. **p<0.01.

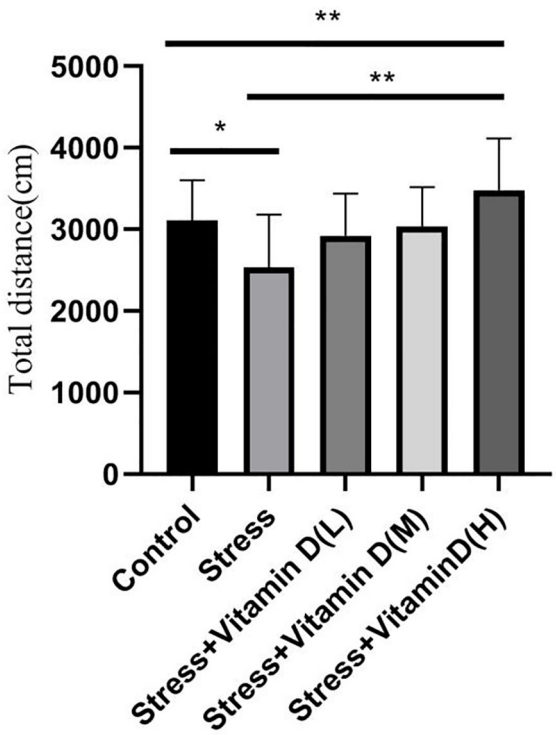

FIGURE 5
Comparison of the total moving distance of each group mice. *p<0.05, **p<0.01.

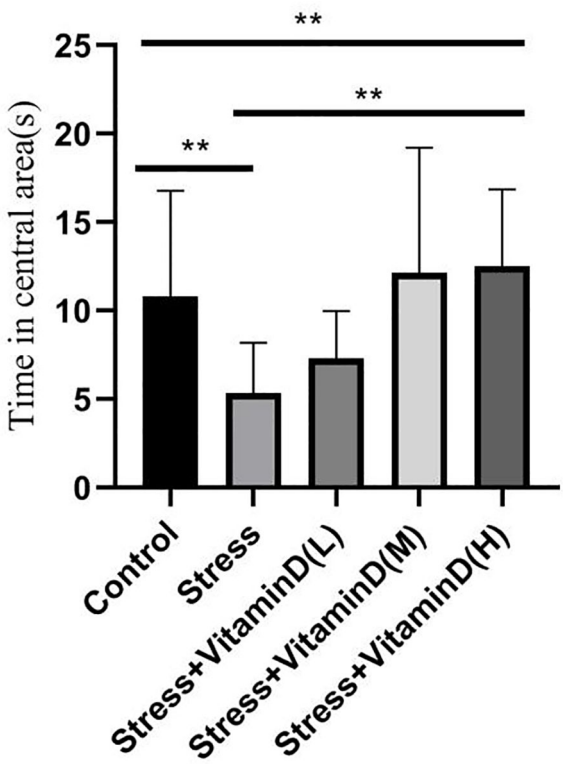

FIGURE 6
Comparison of the time spent in the central area by each group mice. **p<0.01.

the control group were significantly different (p<0.05), indicating that the depression model was successfully established.

Comparison of BDNF expression levels in the brain tissues of each group of mice

The comparison of BDNF expression among groups was carried out by analysis of the band results of the western blot of brain hippocampus tissue. The results showed that there was no significant difference in the ratio of BDNF to internal control actin among the groups (K=6.856, P=0.144) (P>0.05) (Figure 7).

Discussion

Many studies have been conducted on the relationship between vitamin D and depression, but the conclusions of the studies have not been consistent. For example, there have been human studies on vitamin D levels and the effect of vitamin D rs2228570 (FokI) polymorphism on the etiology and/or severity of diagnosed major depressive disorder, but the results showed no statistically significant differences in vitamin D levels or genotype distribution between groups (23). However, in another study involving a middle-aged group, a prospective association was explored by assessing baseline vitamin D status and depression as measured at follow-up assessment. It was found that, among participants without baseline depression, those with vitamin D insufficiency and VDD were more likely to have new-onset depression. VDD and vitamin D insufficiency may be risk factors of depression in middle-aged people, and VDD may also be a predictor of persistent depressive symptoms in people who are already depressed (24). It was also found that women with inadequate vitamin D levels (≤20 ng/L) were more likely to report elevated depressive symptoms at follow-up assessment, particularly in high-risk groups for depression, such as perinatal pregnant women, although these findings were not statistically significant. Sleep, anxiety, and underlying vitamin D disturbances in early pregnancy are associated with increased perinatal depression. Therefore, to reduce the risk of perinatal depression, studies have also pointed to interventions including ensuring adequate vitamin D levels during pregnancy as potential therapeutic targets (25). Another systematic review and meta-analysis synthesized evidence from randomized controlled trials comparing reductions in depression in patients treated with vitamin D and those treated with placebo. The findings showed that vitamin D supplementation is significantly better than placebo in reducing depression, adults respond significantly better to vitamin D than children and adolescents, and intermittent high doses of vitamin D orally or a single high dose intramuscularly appear to be more effective than daily oral doses. Studies have also shown that vitamin D supplements are effective and safe for people with depression (26). In sum, studies have shown that vitamin D levels are associated with depression, VDD is a risk factor for depression, and vitamin D

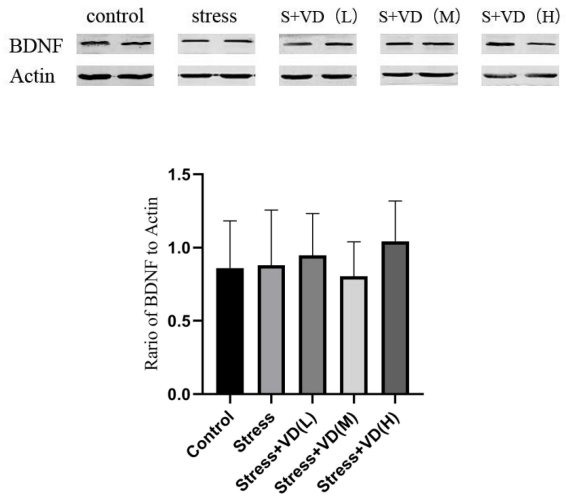

FIGURE 7
Comparison of BDNF expression levels in brain tissues of each group of mice.

supplementation is a potential protection against and treatment option for depression.

In this study, further research was conducted on the prevention of depression in adolescents though establishing an animal depression model. The results of animal behavior tests showed that the depressive behavior of mice was indeed reduced by vitamin D injections, with significant differences among groups ($P<0.05$). In the blood vitamin D level test, it was found that vitamin D injection did increase blood vitamin D levels. In addition, the blood vitamin D levels of mice decreased after UCMS alone. Whether this is related to stress itself and whether it indicates that a decrease in vitamin D levels may play a mediating role in the occurrence of depressive behavior after stress are questions worth further exploring. Regarding the dose of vitamin D injection, although the medium-dose and high-dose groups had clear advantages in increased vitamin D levels and reduced depressive behavior, whether the corresponding vitamin D dose is the safest and most suitable dose, and whether there are risks such as toxicity, also requires further study.

Some studies in adolescent populations have found that vitamin D status is not associated with depressive symptoms. However, research also highlights that adequate vitamin D levels during adolescence are necessary for a number of other health benefits (27). Therefore, it is possible that vitamin D does not play a substantial role in the occurrence of depression, but there are other influencing factors. In addition, these studies suggest that even if depression is not prevented, vitamin D has other benefits. The present study used an animal model, and there are potential differences between animal and human samples. It is therefore necessary to be cautious when drawing conclusions about how vitamin D affects depressive symptoms in humans and to also conduct relevant studies on humans.

Another question our study explored was whether the effect of vitamin D on depressive symptoms is related to the BDNF pathway. Previous studies, including animal studies such as mouse disease model studies, have confirmed the correlation between the antidepressant pathway of action and BNDF. For example, studies have shown that UCMS aggravated motor dysfunction and depression-like behavior compared to MCAO alone, while calcitriol injection enhanced vitamin D receptor and BDNF expression levels in the hippocampus and improved motor dysfunction and depression-like behavior in PSD model mice. Injection of BDNF-binding protein (TrkB-IgG) almost completely reversed the antidepressant and neuroprotective effects of vitamin D, strongly suggesting that vitamin D improved motor dysfunction and depression-like behavior in PSD model mice by promoting hippocampal BDNF signaling (28). However, the results of the present study showed that there was no significant difference in the ratio of BDNF to internal control actin among the groups. Thus, it was determined that there was no statistical association between depression levels and BDNF protein expression in mice.

Another study constructed an exposure model of other risk factors in mice by establishing a mouse model of pneumoconiosis with anxiety- and depression-like behaviors after 28 days of exposure to coal dust, with vitamin D3 treatment used from the first coal exposure. The results showed that coal dust could increase the expression of hippocampal fibrillary acid protein (GFAP) and the activation of astrocytes and decrease neurogenic differentiation factor 1 (NeuroD1) in the hippocampus, which may be the reason why patients with pneumoconiosis show more anxiety and depression than healthy people. The findings also showed that vitamin D3 significantly alleviated anxiety- and depression-like behaviors, reduced the expression level of GFAP, and increased BDNF and neuronal protection by inhibiting the overactivation of astrocytes. This is also the first evidence that vitamin D may be a new way to treat mood disorders caused by particulate matter (29). In these previous studies, the pathway of the protective effects of vitamin D against depression was seen in the involvement of BDNF. However, in the present study, vitamin D showed effects on preventing and improving depression, no evidence was found that these effects were related to the expression of BDNF protein levels.

However, some limitations of the present study should be acknowledged. First, for the study design, due to the young age of the mice, in order to reduce the sample loss caused by behavioral testing, the behavioral indicators were not tested at the beginning of the experiment, and the baseline of behavioral indicators was lacking, so there was no behavioral control before and after for the same group, which may affect the research conclusions. Second, there were significant differences in the behavioral indicators among the groups of mice, along with notable differences in blood vitamin D levels after the experiment. However, confirming an exact correlation between depressive behavior and vitamin D levels, as well as identifying potential related factors, requires further research. Additionally, it was found that the BDNF protein content across different groups was not as expected, and this conclusion also needs to be further confirmed, with further exploration of whether there are other ways vitamin D may affect depressive behavior.

Furthermore, in this research, only male mice were studied. Female mice and the effects of vitamin D on offspring depression

were not studied, and effects of other nutrients on depressive behaviors, previously investigated in other studies, were not explored in this research (30). At the same time, some studies have also investigated the effect of vitamin D supplementation before pregnancy on the cognitive function of the offspring of advanced maternal age (AMA) mice. Vitamin D supplementation was found to promote the development of offspring in AMA mice. Vitamin D supplementation could prevent impaired learning and memory ability in offspring born to AMA mice, with a significant impact on cognitive function in offspring (31). Therefore, the benefits of vitamin D for offspring have been well established in animal models. Although in this study, we conducted a controlled study on mice starting at 4 weeks of age, we did not study the offspring, did not examine cognition and other related functions, and did not investigate the effect of cognitive changes on depression. In order to get closer period to adolescence, 4 weeks old mice were selected. But due to the experimental operation, the death occurred in mice of individual groups, less than 2 ones, which may have an impact on the final result, although through a rigorous statistical analysis. These need to be studied in depth and on a larger scale in the future.

In addition, BDNF has been studied in the past as part of the mechanism of vitamin D's effect on depression, but the pathways of specific mechanisms, such as the specific signaling involved, have not been determined. For example, vitamin D3 has been found to be effective in producing an antidepressant-like response in mice, which may be related to BDNF/TrkB-related synaptic protein synapsin, and there may be some differential effects in different brain regions, with vitamin D3 increasing BDNF levels in the hippocampus and prefrontal cortex in mice (32). However, in this study, the results showed no significant difference among the groups, and no further in-depth study of BNDF-related pathways was conducted. Supplementary studies were carried out on other substance signaling pathways, which are also pending further in-depth research.

Finally, previous studies of other psychiatric disorders, such as attention deficit hyperactivity disorder and autism spectrum disorder (33), have found significant benefits of vitamin D in children with autism (34). Therefore, for children and adolescents, in order to ensure the safety of vitamin D, more studies on other mental disorders should be conducted to discover the different mechanism characteristics of vitamin D.

Conclusion

Vitamin D can affect the occurrence and severity of depressive symptoms, and in mouse animal models, vitamin D supplementation can reduce the occurrence of stress-induced depression. No significant association between the mechanism of vitamin D in depression and BDNF protein expression levels has been found.

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 author/s.

Ethics statement

The animal study was approved by the ethics committee of China Medical University. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

XY: Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Writing – original draft, Writing – review & editing, Investigation. JM: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. YH: Conceptualization, Investigation, Writing – original draft. LL: Conceptualization, Investigation, Methodology, Writing – review & editing. GZ: Data curation, Investigation, Software, Writing – review & editing.

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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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Predictors of depression among caregivers of patients with severe mental illness in Northwest Ethiopia, 2023: an explanatory sequential mixed-method study

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Background: Severe mental illness results in an enormous social and economic burden on affected individuals, their families, and communities, especially in developing countries, such as Ethiopia.

Objective: The aim of this study was to assess the level of depression among caregivers of patients with severe mental illness in Debre Tabor Town, Northwest Ethiopia in 2023.

Methods: This institution-based explanatory mixed study was conducted at Debre Tabor Compressive Specialized Hospitals between September 30 to October 30, 2023. A systematic random sampling technique was used to select 260 study participants, and a public health questionnaire was used to assess depression. Epicollect5 was used to collect data, which were then exported to the SPSS-25 for analysis. Variables with a *p*-value <0.25 were considered candidates for the multivariate logistic regression analysis. The odds ratios with a 95% confidence interval were used to determine the strength of the association. An in-depth interview was conducted with 11 participants, selected using purposive sampling.

Results: The prevalence of depression was 31.3% (95% CI = 29.7–38.6). The multivariate analysis showed that being female (AOD = 2.43, CI = 1.42–7.23), divorced/widowed (AOD = 1.8, CI = 1.32–6.34), poor social support (AOD = 2.2, CI = 1.9–5.87), and perceived stigma (AOD = 2.33, CI = 0.24–13.22) were positively associated with depression. The qualitative results suggest that being female, illiterate, severity of the illness, poor social support, and stigma were factors for depression.

Conclusions and recommendations: The prevalence of depression was high among caregivers of patients with severe mental illness. Female sex, being divorced or widowed, being illiterate, poor social support, and perceived stigma were the contributing factors. This implies that a greater focus on caregivers and the government increases mental health literacy and mental health community services.

KEYWORDS

caregiver, depression, Ethiopia, mental illness, severe mental illness

Introduction

According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*), the diagnosis of a major depressive episode (MDE) requires five or more symptoms to be present within a 2-week period. One of the symptoms should, at least, be either a depressed mood or anhedonia (loss of interest or pleasure). Supportive symptoms of MDE include appetite or weight changes, sleep difficulties (insomnia or hypersomnia), psychomotor agitation or retardation, fatigue or loss of energy, diminished ability to think or concentrate, feelings of worthlessness or excessive guilt, and suicidality (1).

Depression is a common psychiatric disorder and a significant public health problem with an estimated lifetime prevalence of 10% in the general population, and in clinical settings, it may reach 20%, and it is predominant in caregivers of patients with severe mental illness and chronic medical illness (2–4).

In 2008, the World Health Organization (WHO) ranked major depression as the third cause of disease burden worldwide and projected that the disease will rank first by 2030 (5).

In 2019, one in every eight people, or 970 million people around the world, was living with a mental disorder, with anxiety and depressive disorders being the most common. In 2019, 280 million people were living with depression, including 23 million children and adolescents (6).

Globally, 450 million people are estimated to be affected by mental disorders at any one time. These include 121 million people with depression, 24 million people with schizophrenia, and 37 million people with dementia (7).

Depression is the fourth most important contributor to the global burden of disease, and 4.4% of the total disability-adjusted life years (DALYs) is explained by depression (8, 9). Epidemiological evidence also shows that approximately 1.2% of the total burden in Africa to 8.9% in high-income countries is explained by depression (10). In sub-Saharan Africa (SSA), mental illness accounts for 19% of years lived with disabilities (YLDs) regionally. These estimates indicate that mental illness is one of the leading causes of ill health and disability (11).

Caregiving is a demanding and difficult task that may have a negative impact on the quality of life of caregivers. It has been reported that chronic caregiving becomes a burden for caregivers and leads to psychosocial distress and compromised quality of life in caregivers (12).

Studies have shown that caring for a mentally ill patient affects various aspects of caregivers' lives, including their quality of life and socioeconomic status (13). For instance, family caregivers of patients with severe mental illness are usually required to provide financial support and endure the burden of economic difficulties. They also provide physical and emotional support to the patient and bear the emotional and physical stress resulting from patients' disturbing behaviors that consequently affect daily routines and the ability to undertake the usual social activities that lead to psychological distress (14).

Severe mental illness results in an enormous social and economic burden on affected individuals, their families, and communities (15).

Caregivers experience psychological and emotional distress, reduction in social contact, and financial difficulties, and report lower life satisfaction and poor physical and mental health as a result of caregiving; this chronic stress and daily hassles cause profound objective and subjective burden for caregivers of relatives with severe mental illness (16, 17).

Caring for patients with severe mental illness demands a considerable amount of time and other resources from caregivers, who suffer twice as much as the general population (18).

However, stigma not only impacts the individual experiencing the severe mental illness but also affects those they are closely associated with (e.g., family members and primary caregivers), which directly or indirectly leads the individual to depression (19).

The prevalence of depression among caregivers of patients with severe mental illness is greater than that among the general population because of the burden of providing care to these patients with severe mental disease.

Abbreviations: AOD, adjusted odds ratio; CGI, clinical global impression; CI, confidence interval; DTCSH, Debre Tabor Comprehensive Specialized Hospital; MDE, major depression episode; OSSS, Oslo Social Support Scale; PHQ-9, public health questionnaire; QOL, quality of life; SMI, severe mental illness; SD, standard deviation; SPSS, Statistical Package for Social Sciences; WHOQOL-BREF, World Health Organization Quality of Life BREF; WHO, World Health Organization.

Studies in Ethiopia reported that among caregivers of patients with severe mental illness, the prevalence of depression was 19% (20) and 57.7% (21); this gap indicates the need for further investigation and focus on caregivers of patients with severe mental illness. Another study had a depression prevalence of 56.7%, which indicates that there is a high prevalence of mental distress among those who care for people with severe mental illness (22).

Depression among caregivers of patients with mental illness has been associated with many factors such as patient age, employment, income, ethnicity, educational level, perceived stigma, poor social support, and prolonged stays with the patient (23–25).

On the other hand, the patient's condition, caregiving burden, duration of caregiving, spouse caregiver, caregiver being unemployed, caregiver with chronic disease, caregiver's sleep quality, caregiver's avoidance, financial problems, and female sex were positively associated with depression, whereas the overall quality of life of the caregiver, pre-loss grief, caregiver's education level, caregiver's age, caregiver's sense of coherence, and caregiver's bond with patient were negatively associated with depression in caregivers of severe mental illness and among primary caregivers of severe mental illness who are female, mother, gave care for greater than five years, have no other caregiver (21, 26).

The impact of caregiving on the physical and mental health of caregivers is well documented. When compared to non-caregivers, caregivers experienced higher levels of depression, increased stress, more outpatient visits, and a lower quality of life (27).

Studies have shown that the status of caregivers of patients with mental disorders has been neglected in some countries, especially developing countries, including Ethiopia. Although some of the needs and challenges for caregivers and family members of patients may be common, they have unique needs and many uncertainties (28). However, many health professionals and healthcare providers, particularly psychiatric nurses, often focus their care on the patient and ignore the family and main caregivers of the patient. These professionals exclude them from the disease, treatment, and decision-making processes and do not consider their needs; hence, families do not have a chance to express their concerns and needs, and are at risk of serious psychological problems (29).

By identifying the problems and challenges of caregivers of patients admitted to the hospital, psychiatric nurses can plan their issues and problems.

Although numerous studies have been conducted on family caregivers of patients with mental illnesses in Ethiopia, a comprehensive exploration of their challenges has not been conducted. Therefore, mixed study evidence and other relevant evidence were explored to capture the challenges faced by caregivers of patients with mental health problems in the Ethiopian context and to reveal the problems of the caregivers. This study aimed to assess the predictors of depression and its associated factors among the primary caregivers of patients with mental illness.

Methods and materials

Study area and period

The study was conducted from 30 September to 30 October 2023 in Debre Tabor Comprehensive Specialized Hospital (DTCSH), Debre Tabor city, South Gondar zone, and Amhara region, which is located in the northwest part of Ethiopia. Debre Tabor Town is the capital city of the South Gondar zone, which is 666 km from Addis Ababa and 99 km from Bahir Dar (the capital city of the Amhara region). According to the 2007 population census report, the total population of South Gondar is estimated to be 2,051,738, and the zone has seven primary hospitals and one comprehensive specialized hospital.

The DTCSH has 30 inpatient beds; four outpatient department rooms and one substance rehabilitation unit are available in the psychiatry unit, and there are seven mental health specialists (MSc in integrated clinical and community mental health) and four BSc psychiatric nursing staff. The psychiatry section serves a total patient population of 7,000 persons per year, with approximately 530 patients with severe mental illness visiting their caregivers on a monthly basis.

Study design

An institutional-based explanatory sequential mixed study design was used.

Population

Source population: All caregivers of patients with severe mental illness in DTCSH.

Study population: All caregivers of patients with severe mental illness in DTCSH during the data collection period.

Eligibility criteria

Inclusion criteria

All adult caregivers of patients with severe mental illness at the DTCSH during the study period were included in the study.

Exclusion criteria

Caregivers who were unable to provide proper information (unconscious, severely ill, or unable to communicate) during the study period were excluded.

Caregivers who provided care for less than 6 months during the study period were likewise excluded.

Sample size determination

The sample size was determined by using a single population proportion formula by considering the rate of depressive disorders among caregivers of patients with severe mental illness to be 19%, as it was reported by a study conducted in Southwest Ethiopia (20) with 5% marginal error (d) and 95% confidence interval of certainty ($\alpha = 0.05$).

$$n = \frac{(z_{\alpha/2})^2 \, p(1-p)}{d^2}$$

$n = \frac{(1.96)^2 \, 0.19*(1-0.19)}{(0.05)^2} = 237$ for a possible non-response rate addition of 10%, which was the final sample size of 260. Eleven participants were purposively selected for the qualitative analysis.

Sampling procedure

For quantitative analysis, systematic random sampling was used to select study participants. The psychiatry clinic provides services to an average of 530 patients with SMI who visit their caregivers at the DTCSH per month. The sampling interval (*K*) was determined by dividing the expected number of caregivers of patients with SMI per month (530) by the sample size (260), which provided an approximate sampling interval of 2. Then, data were collected from each study participant with an interval of two until the desired sample size was reached, and the starting point was selected using the lottery method. For Part A, 11 study participants were selected using purposive sampling until information saturation was reached.

Study variables

Depression (yes or no) was used as the outcome variable. The independent variables included sociodemographic factors (age, sex, residence, educational status, occupational status, income, and marital status), psychosocial factors (duration of caregiving, social support, and stigma), clinical factors (having known medical illness and having a family history of mental illness), substance-related factors (alcohol use, khat use, and tobacco use), and patient-related factors (age, sex, educational status, comorbid medical illness, type of diagnosis, and severity of illness).

Operational definitions

Depression: Depression was measured as a PHQ-9 score > 10 on the depression scale (30).

Ever substance use: Those who had used substances in their lifetime (31).

Current substance use: Those who had used substances within the last 3 months (31).

Severe mental illness: The diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or major depressive disorder is thought to cause major morbidity and mortality (32).

Quality of life: Caregivers with scores less than 50 were categorized as having poor quality of life (33).

Caregiver: A family member/relative/any person who has the most frequent contact with the patient; who provides unpaid support to the patient financially, socially, psychologically, and physically; and who has mostly been vital in the patient's treatment visit.

Data collection procedure and instruments

Data were collected via the Epicollect5 software application on an Android phone and then uploaded to the creator. Four BSc psychiatric professional personnel from the study location and two supervisors collected data via face-to-face interviews. Subsequently, caregivers who met the eligibility criteria were given an informed consent form to sign after being informed about the study's goals, objectives, and purpose. The data collectors carry out the interview of qualified and willing caregivers of SMI patients at a convenient location while supervisors monitor the data collection procedure.

A semi-structured sociodemographic interviewer-administered questionnaire was used to obtain data such as age, sex, ethnicity, marital status, educational attainment, employment status, income, residence, type of diagnosis, duration of caregiving, and medical history of the patient and the caregiver.

A structured questionnaire, the Public Health Questionnaire (PHQ-9), was used to assess depression among primary caregivers. The PHQ-9 scores range from 0 to 27. Each of the nine items is scored from 0 ("not at all") to 3 ("nearly every day"). A PHQ-9 score of 10–14 indicates moderate depression and 15–19 indicates moderately severe depression. A score of 20–27 on PHQ-9 indicates severe type of depression that requires immediate initiation of therapy (30, 34). Moreover, PHQ-9 has been validated in an Ethiopian healthcare context, with a specificity and sensitivity of 67% and 86%, respectively. A cutoff point of ≥10 was used to screen for depression in this study (30).

Social support scale: Social support was measured using the Oslo Social Support Scale (OSSS-3) (35). The OSSS-3 total score ranged from 3 to 14. Scores from 3 to 8 indicate poor support, scores from 9 to 11 indicate intermediate support, and scores between 12 and 14 indicate strong social support. It has an acceptable internal consistency ($\alpha = 0.640$) and has been used in Ethiopian settings (36–38).

Severity of illness: The CGI severity scale responses of 1–3 are taken as mild, 4 as moderate, and 5–7 as severe illness for both subjective and objective severity assessments (39, 40).

Stigma: The Family Interview Schedule (FIS) questionnaire, which was developed as part of the World Health Organization, had good internal consistency (Cronbach's $\alpha = 0.92$). The FIS includes

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14 questions on families' experiences of stigma in the community. Each stigma item was rated on a four-point scale, not at all (0), sometimes (1), often (2), and many (3) with respect to stigma. To assess the distribution of stigma responses between groups, a stigma sum score was computed by summarizing all positive responses (≥1) for each of the 14 items. The presence of only one positive answer in the stigma questionnaire was sufficient to represent a form of perceived stigma (41).

Quality of life: The WHOQOL-BREF questionnaire is a 26-item, five-point Likert scale developed by the WHO to assess quality of life over the past 2 weeks in four domains (42–45).

Finally, the English version of the questionnaire was translated into Amharic (the local language) for easier comprehension by data collectors and respondents and then translated back into English by another individual to ensure semantic comparability.

Qualitative part: Data were gathered using an in-depth interview method. An interview guide was used as a data-gathering tool, which consisted of open-ended, semi-structured questions that could extract information in terms of the research aims and was created by the researcher after reviewing several studies. An audio tape record was used to avoid distraction from extensive note-taking. The interviews ranged from 30 to 90 min in length, using a tape recorder. Each individual was briefed about the study by the principal investigator, and the interviews were arranged between the principal investigator and the interviewee.

Data quality control

The questionnaire was first written in English, and then translated into Amharic by language experts for data-gathering purposes, and finally translated back to English to verify consistency. The quality of data was ensured through training for 1 day before data collection for data collectors and regular supervision, immediate feedback, and reviewing each of the completed questionnaires daily by the principal investigator.

Data processing, analysis, and interpretation

Data were checked for completeness, entered into the Epicollect5 software, downloaded to Microsoft Excel, and exported to SPSS-25. Descriptive statistics, such as mean, standard deviation, proportions, frequency, cross-tabulations, and percentages, were used to describe the dependent and independent variables in the study. The results are presented as charts, graphs, and tables. Bivariate and multivariate logistic regression analyses were used to identify depression and its related factors. Variables that were significant in the binary analysis ($p \leq 0.25$) were considered in the multivariable logistic regression analysis. Its strength is presented using odds ratios and 95% confidence intervals. The results are presented as words, tables, and figures.

Qualitative part: Data were obtained using in-depth interview and by transcribing the information to paper and grouping similar ideas, and then open code 4.03 software was used for thematic analysis.

Results

Sociodemographic characteristics of the respondents

A total of 260 participants participated in this study, with a response rate of 100%. The mean age of the respondents was 36.8 years with an SD of ±11.02 years, and the majority were between the ages of 30 and 40 years; 154 (59.3%) resided in urban areas. The majority of the respondents were men (139, 53.5%), married (180, 69.2%), Amhara by ethnicity (255, 98.1%), orthodox followers (187, 71.9%), and had an average monthly income of $78.2 (Table 1).

TABLE 1 Sociodemographic characteristics of study participants among caregivers of patients with severe mental illness at Debre Tabor, Northwest Ethiopia, 2023 (quantitative part, *n* = 260).

Characteristic	Category	Frequency	Percentage
Sex	Male	139	53.5
	Female	121	46.5
Age	20–30	75	28.8
	30–40	80	30.8
	40–50	69	26.6
	≥50	36	13.8
Residence	Rural	106	40.8
	Urban	154	59.2
Marital status	Married	180	69.2
	Single	50	19.2
	Divorced/ widowed	30	11.6
Religion	Orthodox	187	71.9
	Muslim	57	21.9
	Protestant	14	5.4
	Other	2	0.8
Ethnicity	Amhara	255	98.1
	Oromo	4	1.5
	Tigrawi	1	0.4
Educational status	Cannot read and write	68	26.2
	Primary education	79	30.3
	Secondary education	46	17.7
	College diploma	25	9.6
	Degree and above	42	16.2
Job	Governmental employee	75	28.8

(Continued)

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TABLE 1 Continued

Characteristic	Category	Frequency	Percentage
	Farmer	106	40.8
	Merchant	54	20.8
	Daily labor	6	2.3
	Job less	19	7.3
Estimated monthly income	Poor income (<$51.2)	67	25.8
	Medium income ($51.2–$87.2)	114	43.8
	Good income (>$87.2)	79	30.4
Kinship with the patients	Parents	114	43.8
	Spouse	56	21.5
	Children	35	13.5
	Sister/brother	43	16.5
	Other	12	4.6

Qualitative part

Eleven primary caregivers were selected, consented to participate, and interviewed. Most of the caregivers (7/11, 66.6%) were men, and 80% were between 30 and 45 years old. More than 90% (10/11) of the caregivers had diplomas, and above the majority had secured occupations (Table 2).

Patients-related characteristics

In addition to the study participants, the study investigated the patients' related characteristics; 150 (57.7%) participants were women, with a mean age of 35.67 years with an SD of ±11.845; 117 (45%) were single, and in terms of educational status, 97 (37.3%) attended primary education. Nearly half (123, 47.3%) of the patients were diagnosed with schizophrenia spectrum disorder with a mean duration of illness of 3.459 ± 2.19 years. A total of 51 (19.3%) patients had additional comorbid medical illnesses (Table 3).

Clinical, psychosocial, and substance characteristics of the study participants

A total of 33 (12.7%) caregivers had a history of mental illness, whereas 26 (10%) of the study participants had a chronic medical condition. Almost one-fourth of the individuals reported using substances within the previous 3 months, and nearly half reported having no social support. A total of 99 (38.1) participants had a poor quality of life, and 155 (59.6) participants were stigmatized (Table 4).

TABLE 2 Sociodemographic characteristics of study participants among caregivers of patients with severe mental illness at Debre Tabor, Northwest Ethiopia, 2023 (qualitative part, *n* = 11).

Characteristic	Category	Frequency	Percentage
Sex	Male	7	66.6
	Female	4	33.4
Age	<30	1	10
	30–45 years	10	90
Residence	Rural	2	20
	Urban	9	80
Marital status	Married	9	80
	Single	0	0
	Divorced/ widowed	2	20
Religion	Orthodox	11	100
Ethnicity	Amhara	11	100
Educational status	Primary education	1	10
	College diploma and above	10	90
Job	Governmental employee	8	70
	Farmer	1	10
	Merchant	2	20
Estimated monthly income	Poor income (<2,981)	1	10
	Medium income (2,982–5,020)	8	70
	Good income (>5,021)	2	20
Kinship with the patients	Parents	6	50
	Spouse	2	20
	Children	2	20
	Sister/brother	1	10

Prevalence of depression among caregivers of patients with severe mental illness

The overall prevalence of depression among primary caregivers of patients with severe mental illness was 33.1% (86).

Factors associated with depression

In the binary analysis of depression in relation to each explanatory variable, female sex, marital status, educational status, occupation, kinship with the patient, type of diagnosis, duration of providing care,

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TABLE 3 Patient-related characteristics of caregivers of patients with severe mental illness at Debre Tabor, Northwest Ethiopia, 2023 (n = 260).

Variables	Categories	Frequency	Percentage
Sex	Female	150	57.7
	Male	110	42.3
Age	<30	127	48.8
	30–40	77	29.8
	>50	56	21.4
Educational status	Cannot write and read	58	22.3
	Primary education	97	37.3
	Secondary education	65	25
	Diploma graduate	13	5.0
	Degree and above	27	10.4
Marital status	Single	117	45
	Married	95	36.5
	Divorced/widowed	48	18.5
Type of diagnosis	Schizophrenia spectrum disorder	123	47.3
	Bipolar-related disorder	87	33.5
	Major depression-related disorder	50	19.2
Duration of caregiving	6 months up to 1 year	124	47.7
	1–5 years	101	38.8
	>5 years	35	13.5
Comorbidity of medical illness	Yes	52	20.0
	No	208	80.0

TABLE 4 Clinical, psychosocial, and substance characteristics of caregivers of patients with severe mental illness at Debre Tabor, Northwest Ethiopia, 2023 (n = 260).

Variables	Categories	Frequency	Percentage
Chronic medical illness	Yes	26	10
	No	234	90
History of mental illness	Yes	55	21.2
	No	205	78.8
Social support	Strong social support	69	26.4
	Intermediate social support	67	25.8
	Poor social support	124	47.7
Ever used of substance	Yes	90	34.6
	No	170	65.4
Current use of substance	Yes	59	22.7
	No	201	77.3
Severity of the illness of the patients	Mild	140	53.8
	Moderate	69	26.4
	Severe	51	19.6
Perceived stigma	Yes	155	59.6
	No	105	40.4
Quality of life	Good	161	61.9
	Poor	99	38.1

chronic medical illness, poor social support, perceived stigma, and poor quality of life were found to be significant at a p-value of less than 0.25.

These factors were entered into multivariable binary logistic regression analysis to control for confounding effects. In the multivariate analysis, being female, being divorced or widowed, being unable to read and write and to attend primary education, providing care for patients with schizophrenia spectrum disorder and bipolar disorder, giving care for more than 5 years, having chronic medical illness, providing care for severely ill patients, having poor social support, and being stigmatized were significantly associated with depression ($p < 0.05$).

Female caregivers were 2.43 times more likely to develop depression than male caregivers (AOR: 2.43, CI = 1.42–7.23). The odds of developing depression were 1.8 times higher among respondents who were divorced or widowed than among married respondents (AOR: 1.8, CI = 1.32–9.90).

The likelihood of developing depression was 3.12 times higher among respondents who could not read and write (AOR: 3.12, CI = 1.22–9.90) and 1.93 times higher among respondents who attended primary school (AOR: 1.93, CI = 1.02–4.97) than among those who had a degree and above.

Being a caregiver of patients with schizophrenia spectrum disorders was 2.8 times more likely to develop depression than caregivers of patients with depression-related disorders (AOR: 2.8, CI = 1.09–7.55). Being a caregiver of patients with bipolar and related disorders was 1.69 times more likely to develop depression than being a caregiver of patients with depression-related disorders (AOR: 1.69, CI = 1.07–5.52).

The odds of developing depression were 1.98 times higher among those respondents who were giving care for more than 5 years than those who were giving care for less than 1 year (AOR: 1.98, CI = 1.05–5.56).

The likelihood of developing depression was 2.35 times more likely among respondents who had medical illnesses than among those who had no medical illnesses (AOR: 2.35, CI = 1.75–13.7). The odds of developing depression were 2.20 times higher among participants with poor social support than among those with strong social support (AOR: 2.20, CI = 1.90–5.87). The odds of developing depression were 2.33 times higher among participants who had perceived stigma than among those who did not perceive stigma (AOR: 2.33, CI = 0.24–13.22) (Table 5).

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TABLE 5 Bivariable and multivariable independent factors of depression among caregivers of patients with severe mental illness at Debre Tabor, Northwest Ethiopia, 2023 (n = 260).

Variable	Category	Depression		COR (95% CI)	AOD (95% CI)	p-value
		Yes	No			
Sex	Male	45	94	1.00	1.00	
	Female	47	74	2.38 (0.43–2.83)	2.43 (1.42–7.23)	**0.003***
Marital status of the caregiver	Married	61	119	1.00	1.00	
	Single	20	30	1.41 (0.43–2.94)	1.23 (1.06–3.23)	0.26
	Divorced/widowed	11	19	1.21 (0.39 - 1.96)	1.8 (1.32–6.34)	**0.001****
Educational status	Cannot read and write	30	38	3.56 (0.17–4.76)	3.12 (1.22–9.90)	**0.07***
	Primary education	20	59	1.78 (1.02–2.90)	1.93 (1.02–4,97)	**0.001****
	Secondary education	16	30	1.23 (1.16–2.56)	1.82 (0.82–6.04)	0.036
	College diploma	7	18	-0.14 (0.80–0.96)	1.43 (1.20, 4.92)	0.76
	Degree and above	13	28	1.00	1.00	
Occupational status	Government employee	20	55	1.00	1.00	
	Farmer	40	66	2.78 (1.79–4.67)	2.51 (1.54–5.67)	0.27
	Merchant	13	41	1.70 (1.02–3.21)	2.21 (1.05–4.21)	0.45
	Daily labor	4	2	2.50 (1.90–4.20)	2.30 (1.71–5.89)	0.67
	Jobless	9	10	3.56 (1.50–7.07)	3.87 (1.60–9.32)	0.75
Kinship with the patient	Parents	39	75	1.00	1.00	
	Spouse	16	40	2.66 (0.54–12.50)	2.36 (0.83, 4.24)	0.881
	Children	16	16	2.01 (0.44–10.15)	1.59 (0.30, 2.14)	0.535
	Sister/brother	13	30	4.21 (0.86–8.08)	2.01 (0.46, 2.99)	0.457
	Other	2	10	2.16 (0.42–11.30)	2.23 (1.87–12.45)	0.612
Type of diagnosis of the patient	Schizophrenia spectrum disorder	42	81	2.21 (0.62–2.46)	2.8 (1.09–7.55)	**0.001****
	Bipolar-related disorder	29	58	1.76 (0.55–2.52)	1.69 (1.07–5.52)	**0.024***
	Depression-related disorder	15	35	1.00	1.00	
Duration of giving care	6 months up to 1 year	35	89	1.00	1.00	
	1–5 years	35	66	1.26 (0.54–2.82)	1.33 (0.76–4.43)	0.256
	>5 years	15	20	1.33 (0.57–3.07)	1.98 (1.05–5.56)	**0.001****
Medical illness	Yes	10	16	2.78 (1.43–14.30)	2.35 (1.75–13.7)	**0.015***
	No	76	158	1.00	1.00	
Severity of illness	Mild	39	101	1.00	1.00	
	Moderate	26	43	1.50 (0.28–4.07)	1.87 (1.21–3.75)	0.456
	Severe	21	30	1.80 (0.42–6.81)	1.6 (1.02–7.45)	0.28
Social support	Poor	47	77	2.09 (1.57–3.98)	2.2 (1.9–5.87)	**0.001****
	Intermediate	20	47	1.85 (1.41–2.75)	1.5 (1.27–5.75)	0.457
	Strong	13	56	1.00	1.00	
Quality of life	Good	51	110	1.00	1.00	
	Poor	35	64	1.18 (0.69–4.02)	1.42 (0.87–3.90)	0.489

(Continued)

TABLE 5 Continued

Variable	Category	Depression		COR (95% CI)	AOD (95% CI)	*p*-value
		Yes	No			
Perceived stigma	Yes	74	81	2.82 (0.48–11.32)	2.33 (0.24–13.22)	**0.001****
	No	22	83	1.00	1.00	

*p < 0.05; **p < 0.01; Hosmer–Lemeshow test, 0.55.

Qualitative findings

To explore the prevalence of depression among caregivers of patients with severe mental illness, in-depth interviews were conducted with participants. In addition to the interview guide, preliminary quantitative results were used to frame the discussions. Throughout the analysis, three themes focused on sociodemographic characteristics and clinical and psychosocial themes.

Sociodemographic characteristic theme

Female caregivers were heavily burdened because they spent most of their time in the house and because they were physically weak. One participant stated: "It is very surprising that especially if a woman, we are subjected to a lot of pressure, that is, trying to sexual harassment, fights, and insults, punishment and saying that they will not go to health services, refuse to take the medications, refuse to eat and unable to care his personal hygiene I witness while her father asks he easily respond in every activity" (IDI008/42/F).

In addition, being illiterate also increased burden and psychosocial distress as one participant explained: "Not learning enough leads me a lot of problems For instance, I belief that the cause for the illness was evil spirit, magical ideas, spells, cruses and sometimes it's may be genetics due to this I was on traditional treatment (holy water, in magic house, Quran maskerat) for a long period of times due to the delay in visiting modern treatments the illness of my husband's illness is becoming more complicated, due to my poor knowledge I was discontinue for the follow up visit two times" (IDI 005/39/F).

Clinical themes

Caregivers described the significant challenges associated with their care recipients' severity of symptoms and behaviors related to physical problems.

"He is wary of people and feels as though they are always observing him. Every time we go out in public together, that is really annoying. He senses that he's being followed by people in helicopters. We therefore frequently have to go home before nightfall because there is a lot of air activity during the night" (IDI 007/27/F).

"I think too much … and I cannot fall asleep after that in the morning I suffer with headache, fatigability … which is affecting my health and I acquire depression and I was treated in last year due to over stressed about my mom illness" (IDI 004/31/M).

Psychosocial themes

Social interaction and participation in events were challenging for caregivers of individuals with SMI, both in the family and in the community. According to reports, a person's hostile behavior, lack of time for social gatherings, inability to perform expected social duties, and failure of children to establish their own ties outside the family, while parents failed to maintain their social relationships and may separate or become divorced, were the main causes of these challenges.

"Our social event participation is not the same to others. We used to take part in these events including neighbors' coffee ceremony, weeding … Now we do not take part in such events because we cannot do our part, she used to make coffee in our turn … not only surprisingly if I want help from the neighbors no one help me during emergency situations because of they are fear of her" (IDI00639/M).

Caregivers also reported many psychosocial problems, such as loneliness and sadness, while observing a family member in the street shouting and exhibiting odd behavior, and the fear of developing the same illness triggered such feelings. The level of stress was reported to be especially high when the patient ran away, when the patient had to be physically restrained, and during relapse. Stress and hopelessness made them wish that the individual with the illness would die, and some tried to harm themselves.

"I think we go out a little less because he is so hard to get out of the house … So we don't go out as much as I would like to. And we certainly don't go to as many public places that I would like to. I used to really enjoy going out and having friends. But it just became such an issue because when I got home, he didn't understand where I was and he would get so paranoid' (IDI 0011/47/M).

"I have no friends. My mom has no friends. I've always felt stigmatized … I was always ashamed, I never wanted anybody to know [mom had schizophrenia]. As a result, I had very little friends growing up because even if I tried to establish relationships, my mom would do something 'crazy,' then they would no longer want to be my friend" (Daughter of a woman with bipolar disorder) (IDI002/25/M).

Discussion

This study aimed to assess the level of depression among caregivers of patients with severe mental illness in Debre Tabor, Northwest Ethiopia. The results showed that the prevalence of depression among caregivers of individuals with severe mental illness was 33.1%, and different factors like sociodemographic (sex and educational status), clinical (severity of the illness), and psychosocial (social support and stigma) factors were explored by the study participants.

The results of this study are consistent with those studies conducted in Egypt, which were 34.1% (46) and 35.7% (47).

On the contrary, this result was lower than the study conducted in Ethiopia 56.7% (47) the variation may be in differences in the study participants in the previous study they were incorporate only child

caregivers so as the fact giving children with mental illness increase the burden of the caregivers, Ghana 66.2% (47) there is tool variation they use the Beck Depression Inventory (BDI) to measured depression among the caregivers and also had study population differences, Kenya 56.2% (47) this variation may be differences in study population, sample size and socio-cultural difference and in China 53.5% (47) the variation may be there is better social support than China and they used Center for Epidemiologic Studies Depression Scale (CES-D 10) to assess depression.

In contrast, the result was higher than the study conducted in Ethiopia (19%) (48); the possible reason for the difference may be the current relentless continuation of intense conflict and war in the study area, which may magnify the prevalence of the depression among caregivers in India (28.5%); this might be due to the difference in the screening tools: the current study used PHQ-9, but they used the Montgomery–Asberg Depression Rating Scale (MADRS) in India; in Saudi Arabia (18.3%) (24), the discrepancy could be attributed to the socio-cultural differences and the study participants.

Regarding associated factors for depression, this study showed that female caregivers were 2.43 times more likely to develop depression than male caregivers; this finding is in agreement with the study conducted in China (21). In Ethiopia (49), this may be attributed to the fact that women are more at risk for sexual violence or to poor copying mechanisms, low self-esteem, and sex hormonal differences, and the fact that women spend more time in providing care and carrying out personal-care tasks more often than men; time-intensive care among women is also more likely in societies and cultures that endorse the traditional value of women as the natural caregiver of patients (50–52). This finding is supported by the qualitative findings of the participants: "I witness that while my husband orders something he easily agreed but while I try to communicate and give his medication he refuse and insult me too …" (IDI 008, caregiver of a schizophrenic patient).

The results of this study revealed that being divorced or widowed is 1.8 times more likely to develop depression among married respondents (AOR: 1.8, CI, 1.32–9.90); this finding was supported by a study conducted in Ghana (53), which included divorce/widowed participants. Separation was associated with increased feelings of anxiety and loneliness, and no one shared the burden of care of the patients and increased risk of substance abuse (20). The study results showed that caregivers with a higher education level were less likely to be depressed, which was consistent with studies in Kenya and Tunisia (51, 54). This explains why educated caregivers share the responsibility of following up patients to ensure that they take their mediation and visit health facilities.

The most common related misconception concerns the causes of mental disorders, as the majority agreed that the Ethiopian society still associates the causes of mental disorders with magic, the evil eye, and possession, which complicate the illness and magnify the caregiver burden. "I feel like all the people think that the evil eye is the cause" (IDI 005). The other caregivers themselves believed that the main cause of her mother's sickness was possession: "My mom had fallen unwell, she was possessed by an evil spirit, and she was treated by a sheikh (a religious faith healer), and then she was diagnosed with schizophrenia. The caregivers believed that the first choice of treatment among many would involve seeking help from a sheikh, holy water who would usually treat a person with religious practices. To be honest with you, we also took him to a sheikh to read [Quran maskerat] over him" (IDI 004).

The results of this study showed that caregivers of patients with schizophrenia spectrum disorders and bipolar and related disorders were 2.8 times and 1.69 times more likely to develop depression, respectively, than caregivers of patients with depression-related disorders. This is because schizophrenia is a chronic, disabling disorder. Treatment is expensive, and the aggressive behavior of the illness also affects physical health (55). Symptoms of bipolar disorder, including violence, aggression, hyperactivity, and disinhibition, are major sources of distress for caregivers (56).

The odds of developing depression were 1.98 times higher among those respondents who gave care for more than 5 years than those who gave care for less than 1 year, which is in line with the study conducted in Ethiopia, Saudi Arabia, and Texas (49, 57, 58). One probable explanation could be that the patient requires constant and ongoing care for extended periods of time, and the caregiver's stressful role is highly correlated with the patient's duration of caregiving, trouble finding employment, and financial difficulties or increasing the care cost (50).

This finding suggests that caregivers were 2.20 times more likely to have depression among participants who had poor social support as compared with those who had strong social support, which is in agreement with the previous results in Ethiopia and China (21, 59, 60), possibly because inadequate social support has been associated with sadness and feelings of isolation. It has also been shown to modify brain activity and increase the likelihood of alcohol consumption, cardiovascular diseases, and suicide. Additionally, it provides a safeguard against unhealthy habits and negative health outcomes (17). Inadequate social support was the most powerful predictor of depressive symptom among caregivers of individuals with mental illness (53). This is supported by qualitative findings: "… yes … yes for sure no one is interested to help me because of the nature of the illness no one interested to give support informs of emotional, financial, in one occasion I can't brought the medication while ask the neighbor no one borrowed me" (IDI 008).

The results of this study showed that the odds of developing depression were 2.33 times higher among participants who had perceived stigma compared with those who did not, which is supported by a study conducted in Ethiopia (21, 61). A possible explanation is that high levels of personal or self-stigma are also correlated with high psychological distress, decreased social functioning, and impaired quality of life (51). This is in agreement with the qualitative findings of the participants: "one scenario what happened most of the society call me you are a father of crazy son so you may be the same to him and they are not interested to involve in social activity and they enforce to restrain him in the home" (IDI 0011).

Conclusion

The prevalence of depression among caregivers of patients with severe mental illnesses is high. Being female, illiterate, and divorced/widowed, providing care for patients with schizophrenia spectrum

disorder and bipolar disorder, giving care for more than 5 years, having chronic medical illness, providing care to severely ill patients, having poor social support, and being stigmatized were significantly associated with depression. Policymakers at all levels should design and implement policies to guarantee the inclusion of caregiver interventions in the mental health system.

Limitation of the study

The study findings might be prone to response bias due to the patients' self-reporting, and they do not provide an objective measure of depression. The questionnaire had some sensitive issues that may lead to social desirability.

Strength of the study

To minimize bias, we used a standardized and pre-tested questionnaire; the response rate in this study was high, which helped to reduce the probability of non-response.

This was an explanatory study that gave detailed insights into participants' experiences and impacts of caregiving for individuals with severe mental illness.

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 humans were approved by Debre Tabor University Institutional Ethical Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

BM: Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. ZB: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. GL: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. SA: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. AB: Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Investigation. GB: Writing – review & editing, Writing – original draft, Supervision, Software, Methodology, Investigation, Conceptualization. KS: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. ATM: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Data curation, Conceptualization. YK: Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Writing – review & editing, Writing – original draft, Software. TM: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. AT: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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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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Depressive self-focus bias following failure: an eye-tracking study among individuals with clinical depression

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Objective: Depression is often characterized by a persistent sense of failure. Cognitive theories of depression suggest that depressed individuals may exhibit a maladaptive cognitive style, characterized by increased self-focus following personal failure. The validity of this proposition, however, is yet to be fully examined. This study aimed to identify the relation between symptoms in major depressive disorder and increased self-focus in failure situations.

Methods: This clinical study involved a cohort of 30 patients diagnosed with and treated for depression. We used an eye-tracking paradigm to observe and analyze gaze direction – indicative of either self-focus or self-avoidance – after remembering a significant failure event.

Results: Contrary to the maladaptive cognitive style hypothesis, a majority of the depressed participants demonstrated an inclination towards self-avoidance following failure. Nevertheless, approximately 30% of the patient group – those with the highest scores of guilt, punishment, and self-blame – displayed a self-focused attentional bias post-failure.

Conclusions: The presence of a maladaptive self-focusing style may be confined to severely depressed patients with high levels of guilt, punishment, and self-blame. These findings could have substantial clinical implications, as attention bias modification interventions could be particularly beneficial for this subgroup of patients.

KEYWORDS

depression, eye-tracking, self-focus, failure, attentional bias

1 Introduction

Cognitive theories suggest that a variety of systematic cognitive biases are integral to the onset and the perpetuation of depressive symptoms (1–7). These cognitive biases in depression, such as the bias towards negative self-referential information, are well documented mechanisms reinforcing maladaptive negative self-schemas (8–11). This paper focuses on one specific bias: the depressive self-focus bias – a tendency to engage in prolonged self-focused attention after experiencing personal failure (12).

1.1 Failure-related cognitive bias in depression

Beck's (1) cognitive theory of depression suggests that, unlike non-clinical populations, individuals with depression harbor negative self-views (self-schemas) and might be especially inclined to process information that sustains these negative self-views. A considerable body of literature has demonstrated that individuals with depression tend to exhibit an attentional bias toward negative information, thus reinforcing the negative schemas outlined in Beck's theory of depression (see 13 for a review; although see 14). As an example, Hindash and Amir (15) asked participants to indicate whether sentences (e.g., "You get a new job") were related or not to a word presented afterward. Some words were negative ("Unqualified") while other where not ("Qualified"). They observed that dysphoric participants were faster to identify negative words as being related to the situations than non-dysphoric participants. This finding underlines a bias toward negative interpretations of situations, emphasizing that depressed individuals tend to favor evaluations consistent with negative self-views.

In this vein, several studies reported that when confronted with failure, depressed individuals produce dysfunctional attributions likely to foster self-blame, such as characterological (e.g., blaming one's self) rather than behavioral (blaming one's specific behavior) or circumstantial attributions (e.g., blaming specific circumstances; 16–18). Depression is also characterized by an attentional bias towards negative information, a pattern corroborated by eye-tracking studies (13, 19–26).

Importantly, depression is often associated with aversive self-awareness, which might exacerbate a sense of failure and cause biased self-perception (27–31). Accordingly, it was suggested that depressed individuals may display a maladaptive pattern of focusing their attention inwards in negative situations (12, 32). Specifically, Pyszczynski and Greenberg (12) showed that after false negative feedback on a task allegedly measuring intelligence, subclinically depressed participants, but not non-depressed individuals, preferred to be exposed to a mirror rather than avoid it, indicating a preference for self-focusing stimuli upon failure. This finding provides support for a depressive self-focus bias in individuals suffering from mild (subclinical) depressive symptoms. Understanding self-focus biases in failure context among depressed patient is critical for developing targeted interventions. Identifying such bias could inform more effective therapeutic approaches, such as cognitive-behavioral therapies specifically tailored to address these biases. Yet, there is a lack of empirical findings indicating how such self-focus bias in failure situations might characterize clinical samples, and to what extent depression severity might be associated to this bias. As such, it is crucial to extend previous findings from subclinical to clinical populations (see 33).

1.2 The present study

To further address the question of how depressive individuals deploy their attention upon failure, we relied on an eye-tracking paradigm. Eye-trackers are commonly employed to study how individuals direct their visual attention toward prominent elements in their surroundings (e.g., 34, 35). Consequently, they are useful tools for evaluating visual attention, particularly in relation to self-focused attention (36–39). In a recent study, Monéger et al. (40) have shown that participants focused less on their screen-reflected faces after a failure manipulation (indicating self-focus avoidance) than in a control condition. A similar paradigm was used here as it provides a precise, yet subtle and unobtrusive measure of whether individuals deploy their attention toward or away from the self upon failure. In the present study, this paradigm was applied for the first time in a sample of clinically depressed individuals. We would consider the maladaptive bias hypothesis to be supported if individuals with depression exhibit heightened self-focus following failure in comparison to their baseline (prior to the induction of failure).

2 Method

The study was conducted between December 2021 and June 2023. Ethical clearance was obtained from the Institutional Review Board of CPP Ouest I (number: 2021-A01098-33), and trial registration was completed at the Clinical Trial Registry before the study began (ClinicalTrials.gov Identifier: NCT0546550). All patients provided written informed consent after a full description of the study. Thirty participants (24 women and 6 men, M_{Age} = 38.72, SD_{Age} = 13.33) were recruited from the local University Hospital. All participants were diagnosed with severe major depression (based on an expert diagnosis and confirmed using the MINI-IV). With this sample size, an effect size of d_z = .53 can be detected with a statistical power of 80% in a paired sample t-test.

2.1 Patient selection

To participate to this study, participants' depression diagnosis had to be confirmed 24 hours before the experimental manipulation. The diagnosis was made by a professional clinician using the MINI-IV (see

Abbreviations: AOI, Area of Interest; MADRS, Montgomery-Åsberg Depression Rating Scale; BDI, Beck Depression Inventory; MINI, Mini international neuropsychiatric interview; OSF, Open Science Framework.

41). Ineligible participants for the study included individuals with mental deficiencies (IQ < 70), neurological impairments (epilepsy, encephalopathy, head trauma), those forced to stay in the hospital and/or not having healthcare. Eligible participants were required to be aged between 19 and 60 years old, be native French speakers, and have a normal or corrected-to-normal eyesight. Participants wearing rigid lenses were not included in the study to avoid difficulties with the eye-tracker task. All participants were diagnosed with major depression using the MINI-IV (see 41). Patients were diagnosed with unipolar depression (72.41%), bipolar depression (13.79%), or isolated depression (13.79%). As expected, both MADRS (M = 27.34, SD = 8.23) and BDI scores (M = 29, SD = 12.42) were high, indicating that participants were characterized with moderate (cut-of at 20 for the MADRS and 21 for the BDI) to severe depression (cut-off at 35 for the MADRS, and 31 for the BD1).

2.2 Material availability

Anonymized data, analysis codes, materials, and supplementary analyses are available on the OSF webpage of this study (https://osf.io/94y7v/).

2.3 Materials

2.3.1 Failure manipulation

In order to manipulate feelings of failure, we used an autobiographical task. Participants were asked to recall a significant personal failure. They were then instructed to describe the memory details in written, in a similar approach to an autobiographical Memory Tasks (42). To do that, they were guided with specific instructions designed to elicit a vivid memory (e.g., "*Describe in the most detailed manner how you felt and what you thought of during this episode*", "*How did you feel from a physiological standpoint during this episode*", etc., for similar tasks see, 43, 44, study 2; 45). After answering these questions, participants completed 4 Likert scale items used as controls (e.g., "The memory I recalled was clear in my mind", "The memory I described relates to a painful event in my life", "During this task, I felt in a failure situation", and "During this task, I was able to relive the emotions I felt during the episode I recalled"), using a 10 point scale ranging from 1 (Strongly Disagree) to 10 (Strongly Agree; the full material is available on the OSF webpage of the project, see anonymized OSF link).

2.3.2 Attentional bias measure

We measured attentional bias in self-focus by using an eye-tracker combined with a reflexive screen (iMac, 27", 44.5 cm × 65 cm or 17.5" × 25.6" or 1440 × 2560 pixels). The eye-tracker used was an Eye-Link Portable Duo with a sample rate of 500Hz. The experimenters were concealed from the participant (see Supplementary Online Material for a photograph of the experimental set-up). An Area Of Interest (AOI) was defined in the center of the screen as a large oval area covering 875,824.98 pixels (i.e., 23.76% of the total screen area). The size of the AOI was similar to the one used in Monéger et al. (40). The experimenter asked patients at the end of each session to gaze at the contour of their screen-reflected faces, thus ascertaining that their reflections were indeed captured in the defined AOI (see "AOI_def.docx" on the OSF webpage). Participants were instructed to complete a lexical decision task: strings of letters were displayed randomly in one of the four corners of the screen, and participants had to indicate as fast and as correctly as possible whether these targets were words (e.g., TABLE) or non-words (e.g., TEBLA). Target words were displayed until the participant provided a response using a button box. To indicate that the target was a word, they had to press a green button on the far right of the button box, and to indicate that the target was a non-word, they had to press a red button on the far left of the button box. During this task, we recorded gaze behavior occurring between the participant's response and the onset of the next target (i.e., during the inter-trial intervals). Inter-trial intervals durations were randomly selected in a sample of possible duration ranging from short (325 ms) to long (8485 ms, see Footnote 1). Each block of the study used the same inter-trial times so that they were balanced. This range of inter-trial intervals was the same as the one used by Monéger et al. (40). The rationale behind this range is that it promotes a sense of unpredictability that should foster participants' engagement in the task.

As in previous research, we assessed the total sum of the number of fixations in the AOI that were preceded by a fixation outside the AOI in all the inter-trial intervals for each block (hereafter, saccades in the AOI). Average time spent in the AOI during the inter-trial intervals (hereafter, dwell time) was also assessed, but previous studies using this protocol failed to detect an effect of failure on this measure (see 40). Dwell time and number of saccades in the AOI are negatively correlated: the more saccades toward the self, the less time we spent on average in the AOI (and vice-versa). Indeed, if an individual spent the whole task looking at oneself, this would result in a maximal dwell time, but a minimal number of saccades toward the self. Conversely, a large number of saccades toward the self implies that the participant was not consistently fixated on their reflection. Whereas dwell time reflects 'time spent looking at the self-reflected face', the number of saccades toward the self would reflect the 'number of time someone glanced toward the self after a period of non-focused state'. Given that previous research using the same paradigm identified the number of saccades in the AOI, but not the dwell time spent on the AOI, as a relevant indicator of self-focus bias (40), we report this variable as our criterion for identifying self-focus avoidance. Results regarding average dwell time are reported in the Supplementary Material, but should be interpreted cautiously given the negative relation that this indicator maintains with number of saccades into the AOI.

2.3.3 Montgomery-Asberg depression rating scale

The MADRS is a 10 items semi-structured interview scale administered by a trained professional. It assesses changes in core

depression symptoms severity such as sleep disturbances, sadness, or suicidal thoughts. In our sample, the internal consistency of the MADRS was acceptable (Cronbach alpha = .76).

2.3.4 Beck depression inventory

The BDI is a self-administered scale including 21-items measuring a broad range of depression symptoms. Each item measure a specific symptom and consists in a set of 4 propositions from which the participant must choose (e.g., Self-Hatred item: "I don't feel disappointed in myself", "I am disappointed in myself", "I am disgusted with myself", "I hate myself"). In our sample, the scale was associated to a very satisfying internal consistency (Cronbach alpha = .91).

2.4 Procedure

During the inclusion session, a professional clinician ensured that the inclusion criteria were met at least 24 hours before the experimental session. In addition to the MINI-IV that provided a diagnosis of depression (among other clinical diagnoses), depressive symptomatology was assessed using the MADRS (a clinician-rated 10 items scale with scores ranging from 0 to 60; 46) and the Beck Depression Inventory (A self-rated 21 items scale with scores ranging from 0 to 61; 47).

During the experimental session, participants were briefed about the eye-tracker and the procedure. Before the completion of the self-focus avoidance measure, participants completed measures of shame- and guilt-proneness. Because these measures are outside the scope of the current article, results relating to these measures in the Supplementary Material. They were then asked to stay steady on a chinrest while performing the cognitive task. After a training block of 12 trials, the participants performed a first block of 36 trials. Then, they were asked to complete the failure manipulation. After completing the failure manipulation, they performed a second block of 36 trials of the self-focus avoidance measure.

We conducted a paired sample t-test to investigate the self-focused attentional bias (i.e., more saccades toward the self after vs. before the manipulation), Pearson correlations to assess how depressive symptoms correlate with the self-focused attention after vs. before the manipulation, and subsample analyses comparing patients displaying a self-focused attentional bias (i.e., more saccades toward the self after vs. before the manipulation), and patients who did not. Analyses were performed using R (see OSF webpage for codes).

3 Results

3.1 Description of the current sample

Because the eye-tracker abruptly stopped functioning during one of the experimental sessions, data from one participant was lost, leaving a sample of 29 depressed patients (23 women and 6 men, M_{age} = 38.72, SD_{age} = 13.33).

In addition to a diagnosis of depression, the sample was additionally characterized by comorbid disorders, with some participants diagnosed with generalized anxiety (51.7%), bulimic disorders (13.8%), psychosis (6.9%), obsessive compulsive disorders (17.2%), social phobia (58.6%), panic disorders (during lifetime, 13.8%, and current 24.1%), alcohol (17.2%) and other substance addiction (6.9%), PTSD (20.7%), agoraphobia (58.62%), and mood disorder with psychotic characteristics (10.34%).

Importantly, most of the participants had pharmacological treatment. Thus, 86.21% of the total sample used antidepressants. Other pharmacological treatments included antipsychotics (37.93%) and thymoregulators (17.24%).

Most patients attempted to commit suicide in the past (69%) with a total average number of attempts of 1.76 (*Minimum* = 0, *Maximum* = 5, *SD* = 1.68).

3.2 Main results

Regarding the effectiveness of the failure manipulation, using 10-points scales, participants evaluated that their failure recall was clear and precise (M = 8.14, SD = 2.23), related to a painful event (M = 8.41, SD = 2.15), produced a sense of failure (M = 8.28, SD = 2.71) and that they felt they were able to relive the emotions of the situation (M = 7.07, SD = 2.90).

Figure 1 illustrates the density of saccades within the AOI (containing the participant's reflected self-image on the screen) before and after the failure manipulation. Overall, participants displayed fewer saccades within the AOI after recalling a failure memory, compared to before (M = 26.00, SD = 12.67 and M = 29.86, SD = 12.52, respectively). A paired-sample t-test has shown this difference to be significant, $t(28) = 2.42$, $p = .023$, Cohen's $d = 0.45$, 95% CI[0.06, 0.84]. This result contradicts the depressive self-focus attention bias hypothesis. However, it aligns with the pattern of self-focus avoidance observed in previous research involving non-depressed individuals (40).

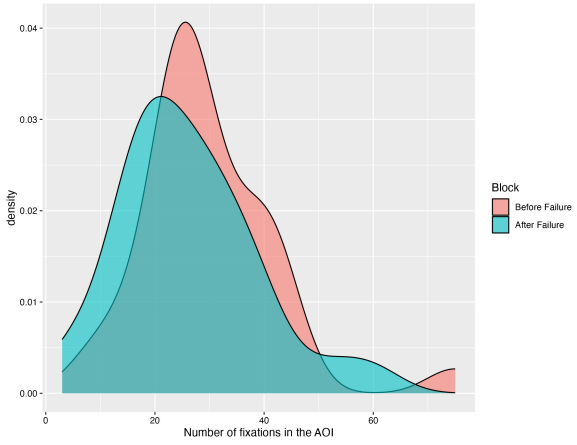

FIGURE 1
Density plot of saccades in the AOI before and after the failure manipulation.

To further understand the effects observed in this study, we conducted additional analyses. Specifically, we examined whether the increase in self-focus after the failure manipulation correlated with the severity of self-reported depressive symptoms (as indicated by BDI scores). The overall BDI score had a positive but non-significant correlation with increased self-focus after failure, as indicated by a Pearson's correlation between BDI scores and the difference in saccades toward the self after versus before failure recall, $r(27) = .31$, $p = .11$, 95%CI [-.068,.60] (but see footnote 2). Because the lack of significance may be due to the fact that some depressive symptoms assessed in the BDI are not directly relevant to the experience of failure (i.e., irritability, indecisiveness, loss of appetite, etc.), we conducted further correlation analyses on each BDI depressive symptoms to see whether specific symptoms predicted self-focus after failure (see 48). Moderate to strong correlations with self-focus after the failure manipulation and specific items of the BDI were observed. Specifically, self-focus bias was predicted by Feeling sad (Item 1), Hopelessness about the future (Item 2), Feeling guilty (Item 5), Feeling punished (Item 6), Self-hatred (Item 7), Self-blame (Item 8), Efforts (Item 15), Fatigue (Item 17, see Table 1). Importantly, self-focus bias after failure appeared to correlate with a pool of items related to failure and self-blame (i.e., Feeling guilty, Feeling punished, Self-hatred, and Self-blame).

TABLE 1 Correlations between self-focus attentional bias and specific depressive symptoms.

Self-focus attentional bias			
Depressive symptoms	*r*	*p*	*95% CI*
1. Feeling sad (*I am so sad and unhappy that I can't stand it*)	**.42**	.023	[0.062, 0.68]
2. Hopelessness about the future (*I feel the future is hopeless and that things cannot improve*)	*.36*	.051	[-0.0017, 0.65]
3. Feeling like a failure (*I feel I am a complete failure as a person*)	.15	.45	[-0.23, 0.49]
4. Dissatisfaction and Boredom (*I am dissatisfied or bored with everything*)	.31	.10	[-0.065, 0.61]
5. Feeling guilty (*I feel guilty all of the time*)	**.46**	.013	[0.11, 0.71]
6. Feeling punished (*I feel I am being punished*)	**.42**	.024	[0.060, 0.68]
7. Self-hatred (*I hate myself*)	**.46**	.012	[0.11, 0.71]
8. Self-blame (*I blame myself for everything bad that happens*)	*.34*	.068	[-0.026, 0.63]
9. Suicidal desires (*I would kill myself if I had the chance*)	.30	.11	[-0.075, 0.60]
10. Wanting to cry (*I used to be able to cry, but now I can't cry even though I want to*)	-.17	.38	[-0.50, 0.21]
11. Feeling irritated (*I feel irritated all the time*)	.034	.86	[-0.34, 0.40]
12. Interest for others (*I have lost all of my interest in other people*)	-.19	.34	[-0.52, 0.19]
13. Decision making (*I can't make decisions at all anymore*)	.018	.93	[-0.35, 0.38]
14. Feeling ugly (*I believe that I look ugly*)	.15	.43	[-0.23, 0.49]
15. Efforts (*I can't do any work at all.I can't do any work at all*)	*.32*	.09	[-0.053, 0.61]
16. Insomnia (*I wake up several hours earlier than I used to and cannot get back to sleep*)	-.11	.57	[-0.46, 0.27]
17. Fatigue (*I am too tired to do anything*)	**.50**	.0055	[0.17, 0.73]
18. Appetite (*I have no appetite at all anymore*)	.10	.61	[-0.28, 0.45]
19. Weight loss (*I have lost more than fifteen pounds*)	-.13	.49	[-0.48, 0.24]
20. Health concerns (*I am so worried about my physical problems that I cannot think of anything else*)	.28	.15	[-0.10, 0.58]
21. Libido (*I have lost interest in sex completely*)	-.18	.35	[-0.51, 0.20]

Bold values indicate significant correlations ($p < .05$).

3.3 Additional analyses

In additional analyses, we also investigated whether the group of patients exhibiting a self-focus attentional bias (i.e., focusing more on the self after vs. before recalling an episode of failure, n = 9) differed from those displaying self-focus avoidance (i.e., focusing less on the self after vs. before recalling an episode of failure, n = 20) in terms of demographic characteristics, psychiatric disorders, and pharmacological treatment (see Table 2). Overall, we found minimal differences between the two groups. It is noteworthy, however, that patients presenting a self-focus attentional bias after failure had significantly higher levels of depressive symptoms on the BDI scale (but not on the MADRS). Additionally, participants displaying the self-focus bias were marginally more likely to have a high suicide risk on the MINI (7/9 or 77%) compared to those presenting a self-focus avoidance bias (8/20 or 40%, p = .06).

4 Discussion

Depressed individuals typically demonstrate biased attention allocation toward negative stimuli, biased memory recall of negative stimuli, and biased negative interpretations of ambiguous situations (13, 34, 49–52). Depressive symptoms have been shown to correlate with higher self-focus (32, 53; see (54) for a meta-analysis). It has been postulated that depression might be characterized by a maladaptive self-focusing bias in failure situations (i.e., a tendency

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TABLE 2 Comparisons of patients displaying self-focus attentional bias and avoidance attentional bias.

Characteristics	Self-focus attentional bias	Self-focus avoidance bias	Chi-Squared	t-test
Demographics				
Age	M = 39.5 (SD = 13.53)	M = 37.0 (SD = 13.51)	*N/A*	$t(27) = -0.46$, $p = .65$
Gender	14 women, 6 men	9 women, 0 men	$\chi^2 = 3.40$, $p = .065$	*N/A*
Clinical Variables				
BDI	25.95 (SD = 11.45)	35.78 (SD = 12.38)	*N/A*	$t(27) = 2.09$, $p = .046$
MADRS	25.95 (SD = 6.57)	30.44 (SD = 6.84)	*N/A*	$t(27) = 1.38$, $p = .18$
Average number of attempted suicides	1.6 (SD = 1.63)	2.11 (SD = 1.83)	*N/A*	$t(27) = 0.75$, $p = .46$
Psychiatric Condition (MINI)				
Bipolar depression	2/20 = 10%	2/9 = 22.22%	$\chi^2 = 0.78$, $p = .38$	*N/A*
Unipolar depression	14/20 = 70%	7/9 = 77.78%	$\chi^2 = 0.19$, $p = .67$	*N/A*
Melancholic characteristics	11/20 = 55%	4/9 = 44.44%	$\chi^2 = 0.28$, $p = .60$	*N/A*
Previous Suicide attempts	13/20 = 65%	7/9 = 77.78%	$\chi^2 = 0.47$, $p = .49$	*N/A*
Previous depressive episodes	15/20 = 75%	7/9 = 77.78%	$\chi^2 = 0.026$, $p = .87$	*N/A*
Suicide risk	18/20 = 90%	9/9 = 100%	$\chi^2 = 0.97$, $p = .33$	*N/A*
Low suicide risk	8/20 = 40%	2/9 = 22.22%	$\chi^2 = 87$, $p = .35$	*N/A*
Medium suicide risk	2/20 = 10%	0/9 = 0%	$\chi^2 = 97$, $p = .33$	*N/A*
High suicide risk	8/20 = 40%	7/9 = 77.78%	$\chi^2 = 3.55$, $p = .06$	*N/A*
Previous maniac episode	5/20 = 25%	1/9 = 11.11%	$\chi^2 = 0.73$, $p = .39$	*N/A*
Panic attacks	3/20 = 15%	4/9 = 44.44%	$\chi^2 = 2.94$, $p = .086$	*N/A*
Agoraphobia	13/20 = 65%	4/9 = 44.44%	$\chi^2 = 1.081$, $p = .30$	*N/A*
Social phobia	4/20 = 20%	4/9 = 44.44%	$\chi^2 = 1.86$, $p = .17$	*N/A*
OCD	3/20 = 15%	2/9 = 22.22%	$\chi^2 = 0.23$, $p = .63$	*N/A*
PTSD	4/20 = 20%	2/9 = 22.22%	$\chi^2 = 0.019$, $p = .89$	*N/A*
Alcoholism	4/20 = 20%	1/9 = 11.11%	$\chi^2 = 0.34$, $p = .56$	*N/A*
Alcohol abuse	1/20 = 5%	1/9 = 11.11%	$\chi^2 = 0.36$, $p = .55$	*N/A*
Substance addiction	1/20 = 5%	1/9 = 11.11%	$\chi^2 = 0.36$, $p = .55$	*N/A*
Current psychotic syndrome	1/20 = 5%	1/9 = 11.11%	$\chi^2 = 0.36$, $p = .55$	*N/A*
Mood disorder with psychotic characteristics	1/20 = 5%	2/9 = 22.22%	$\chi^2 = 1.99$, $p = .16$	*N/A*
Bulimia	2/20 = 10%	2/9 = 22.22%	$\chi^2 = 0.78$, $p = .38$	*N/A*
Generalized Anxiety	10/20 = 50%	5/9 = 55.56%	$\chi^2 = 0.077$, $p = .78$	*N/A*
Pharmacological Treatment				
Antipsychotics	8/20 = 40%	3/9 = 33.33%	$\chi^2 = 0.12$, $p = .73$	*N/A*
Levothyrox	3/20 = 15%	1/9 = 11.11%	$\chi^2 = 0.079$, $p = .78$	*N/A*
Zopiclone	5/20 = 25%	1/9 = 11.11%	$\chi^2 = 0.73$, $p = .39$	*N/A*
Benzodiazepine	16/20 = 80%	8/9 = 88.89%	$\chi^2 = 0.34$, $p = .56$	*N/A*

to direct one's attention inward after experiencing failure; 12). In this study, we investigated whether clinical depression is linked to a self-focus pattern indicative of a maladaptive (as indicated by more self-focus following failure) self-focusing style and assessed how specific depressive symptoms might be associated to the bias.

Generally, our findings revealed fewer gazes directed towards the self after autobiographical recall of a failure experience, compared to before. Although this pattern contradicts the depressive self-focusing style hypothesis, it is largely consistent with self-focus avoidance observed in non-clinical samples (40, 55–57). This could suggest that the self-protective tendency to avoid self-awareness after failure is not entirely disrupted in depression, or that antidepressant medication effectively suppresses the debilitating self-focus attentional bias. Alternatively, this might provide evidence for a lack of attentional bias in depression, as emphasized in a study by Krings et al. (14).

However, approximately 30% of the patient group exhibited a self-focused attentional bias. Further analyses identified this maladaptive bias to be associated with specific depressive symptoms associated to failure sensitivity and self-blame: guilt, feelings of deserving punishment, self-hatred and self-blame. These findings suggest that a maladaptive self-focusing style might be confined to depressed patients presenting a certain profile regarding their relation to failure and the self. Moreover, patients who displayed a self-focused attentional bias post-failure, as compared to the remaining patients, also reported higher levels of depressive symptoms and a higher suicide risk, hence suggesting that the self-focus bias might be confined to severe forms of depression. These findings indicate that a self-focused attentional bias is linked to a more self-destructive pattern, which might have substantial clinical implications, as interventions targeting this cognitive bias could be particularly beneficial for this subgroup of patients.

The finding that only BDI scores, but not MADRS scores, predicted a higher self-focused attentional bias can be explained by the fundamental differences between these two scales. The BDI is a self-report inventory designed to capture a broad spectrum of depressive symptoms, including cognitive and affective components like guilt, self-dislike, and pessimism. These symptoms are intimately tied to the cognitive distortions and biases that characterize depression, making the BDI particularly sensitive to maladaptive thinking patterns such as a self-focused attentional bias. On the other hand, the MADRS is a clinician-administered scale that, while also assessing depression severity, places a greater emphasis on observable symptoms, including mood-related aspects like sadness and physical symptoms such as reduced appetite and lassitude. Although MADRS does include items related to pessimism and suicidal thoughts, it is less focused on the introspective, cognitive symptoms that are central to the BDI.

The current eye-tracking paradigm has limitations. First, gazing at the screen center may represent a strategy to minimize distance to the next target rather than self-directed attention, which could explain why dwell time is not a strong indicator of self-focus in this context (see 40). A pre- vs. post-test design, as used in this study, helps reduce such biases. However, including a control condition without a mirror surface could better differentiate between strategic gazing and self-directed attention. Using a within-participant design might increase participants' awareness of the study's true purpose, compromising its implicit nature. A between-participant design would preserve this implicit measure but reduce statistical power. For instance, while our paired t-test can detect an effect size of $dz = .53$, a between-participant design would require an effect size of $d = 1.06$ to achieve 80% power, making smaller effects harder to detect.

The relatively low sample size of this study already constitutes a limitation, which could have constrained our ability to detect significant effects. This could account for some of the marginally significant effects observed in this study. Unfortunately, small sample sizes are a common issue in clinical settings, limiting the generalizability of findings. Moreover, the sample was predominantly female. Although it was shown that depression was more prevalent among women, future studies might need to conduct replication in more balanced samples to assess the importance of gender on the observed findings. Regarding the task, although there were no feedbacks indicating "success" or "failure" for each trial, the nature of the lexical decision task might influence general feelings of failure. Future studies might integrate different task that would be less evaluative in order to avoid possible confounding effects from this aspect of the task. In addition, because we relied on a symptom-focused approach (i.e., computing correlations for each item of the BDI), false positive rates might have been inflated. Future replications are necessary to confirm the robustness of the present effects. Moreover, our sample was characterized by several comorbidities, such as anxiety, which could be confounding variables. It would be desirable to isolate the effect of each pathology, though this might pose a challenge, given the substantial comorbidity in depression. Lastly, it is possible that some effects were influenced by the pharmacological treatment patients were undergoing at the time of the study. Although it would be ideal, it is ethically unfeasible to replicate the present study in a sample of currently depressed patients not under treatment.

In conclusion, the present results suggest that, ceteris paribus, the self-focus attentional bias in depression might be weaker than expected based on existing literature. However, this particular bias might be indicative of the most severe forms of depression as indicated by a greater self-focus bias among patients characterized by a high suicide risk. In particular, high levels of symptoms reflecting self-blame and sensitivity to failure (guilt, punishment, self-hatred and self-blame symptoms) positively correlated with greater self-focus after vs. before recalling failure. Given the importance of aversive self-awareness, guilt and self-blame in suicide risk (55, 58), further investigations are warranted to understand the development of a depressive self-focusing style and strategies to mitigate it in clinical settings. Future research is needed to evaluate if targeting this bias could serve as an effective clinical intervention strategy.

5 Footnotes

(1) Inter-trial intervals used for the training block were: 490 ms, 566 ms, 677 ms, 754 ms, 1194 ms, 1480 ms, 3310 ms, 4237 ms, 4435 ms, 6531 ms, 7178 ms, 7281 ms. Inter-trial intervals used for each experimental block were: 325ms, 236 ms, 378 ms, 432 ms, 454 ms, 558 ms, 678 ms, 745 ms, 862 ms, 917 ms, 936 ms, 959 ms, 1040 ms, 1073 ms, 1117 ms, 1131 ms, 1235 ms, 1256 ms, 1310 ms, 1399 ms, 3197 ms, 3272 ms, 3277 ms, 3404 ms, 4079 ms, 4639 ms, 5527 ms, 5756 ms, 6195 ms, 6245 ms, 6352 ms, 6452 ms, 7204 ms, 7934 ms, 8480 ms, 8485 ms.

(2) As requested by an anonymous reviewer, a median split was performed to assess self-focus avoidance when comparing individuals with high BDI scores (i.e., BDI scores greater than the median score of the sample) and low BDI scores (i.e., BDI scores smaller than the median score of the sample). A student t-test revealed that patients with high BDI scores displayed higher self-focus after the manipulation of failure ($M = -0.53$, $SD = 8.04$) than participants with low BDI scores ($M = -7.43$, $SD = 7.98$), $t(27) = -2.32$, $p = .028$, $d = -0.86$, 95%CI[-1.62, -0.09]. We warmly thank the anonymous reviewer for their suggestion.

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: https://osf.io/94y7v/.

Ethics statement

The studies involving humans were approved by Comité de Protection des Personnes. TOURS - Région Centre - Ouest 1. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

JM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. GH-G: Methodology, Resources, Writing – review & editing. NJ: Resources, Writing – review & editing. DD: Investigation, Resources, Writing – review & editing. LW: Investigation, Writing – review & editing. LS: Writing – review & editing. AC: Conceptualization, Formal analysis, Methodology, Supervision, Writing – review & editing.

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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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Supplementary material

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When you avoid your feelings, you may feel even worse: how depersonalization puts you at risk of depression

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Background: The clinical form of depersonalization affects approximately 1%–2% of the adult population. This study aimed to describe the symptoms of depersonalization in a non-clinical sample and to operationalize depersonalization as a regulatory mechanism. This article introduces the Depersonalization Mechanism Scale, 41-item measure developed to assess one's tendency for depersonalization in response to overstimulation. The aim of the study is to explore how depersonalization mechanism is associated with cognitive and behavioral emotion regulation strategies, depression, and anxiety.

Method: The study included a sample of 300 Polish adults (149 men) from the general population, ranging in age from 18 to 60. Participants were administered the following questionnaires: Depersonalization Mechanism Scale (DMS), Behavioral Emotion Regulation Questionnaire (BERQ), Cognitive Emotion Regulation Questionnaire (CERQ), Occupational Depression Inventory (ODI), Patient Health Questionnaire (PHQ), and Trait Anxiety Scale (SL-C).

Results: An exploratory factor analysis revealed a two-factor structure of Depersonalization Mechanism Scale, with very high reliability coefficients for both subscales and full scale. A regression analysis revealed that depersonalization mechanism is a significant predictor of depressive symptoms. Depersonalization mechanism is strongly correlated with maladaptive regulation strategies such as withdrawal, ignoring, rumination, catastrophizing, self-blame, and blaming others. Weaker but significant connections were identified with certain adaptive strategies: acceptance, positive refocusing, putting into perspective, and seeking social support. Women were more prone to depersonalization than men.

Conclusions: Further research on depersonalization in non-clinical samples may improve understanding of this mechanism in the general population. This knowledge, combined with greater education about non-clinical forms of depersonalization, may support preventive programs against depression and professional assistance for people facing acute or chronic stressful life events.

KEYWORDS

depersonalization, depression, emotions, regulation strategies, non-clinical sample, measurement of depersonalization

Introduction

Difficulties in emotion regulation play an important role in the development and maintenance of psychopathology. Emotional dysregulation can be found in many mental health problems, including substance abuse, eating disorders, depression, or borderline personality disorder (1–4). Various definitions of emotion regulation can be found across literature, one of the most influential being the one proposed by Gross (5, 6). It is broadly defined as processes through which individuals monitor, evaluate, and modulate their emotions to adequately respond to environmental demands. Utilizing this framework, Folkman and Lazarus (7) introduced a distinction between problem- and emotion-focused coping, emphasizing the more adaptive value of problem-solving strategies. Gross's model is especially useful in investigating the relationship between specific strategies and symptoms of clinical disorders (1, 4, 8, 9). Maladaptive strategies (e.g., rumination, suppression, or avoidance) are consistently found to be more strongly associated with anxiety, depression, eating disorders, and substance abuse (10, 11). To specify more precisely the subtleties among strategies, Garnefski et al. (12) and Kraij and Garnefski (13) proposed a distinction between cognitive and behavioral strategies. While catastrophizing, rumination, self-blame, and other-blame are seen as less adaptive, positive reappraisal, planning, and putting into perspective are described as more adaptive (14) and useful in dealing with life difficulties, depression, anxiety, or anger (15). Behavioral strategies also can be divided in the same way—adaptive strategies are seeking distraction, actively approaching, and seeking social support, as opposite to less adaptive withdrawal and ignoring. While some strategies are well described and studied, some remain unclear in terms of definition, functions, and adaptive value. Another problem is associated with grouping strategies in complex mechanisms such as depersonalization. We propose a different understanding of this phenomenon and investigate its relationship to specific emotion regulation strategies, anxiety, and depression.

In its clinical form, depersonalization is characterized by persistent or recurrent episodes of experiences of unreality, detachment, or being an outside observer of one's thoughts, feelings, sensations, body, or actions (16). Two core components of depersonalization are detachment and hypoemotionality (emotional numbing or blunting) (17). An individual may feel as if in a dream or a game and may have a feeling of alienation from the reflection in the mirror. On a conscious level, a person recognizes themselves ("I know it is me") but lacks an emotional connection to their image ("It doesn't feel like me"), resulting in a profound sense of strangeness. Hypoemotionality refers to blunted affect: an individual remains capable of expressing emotions yet experiences them as strangely dampened.

This phenomenon can be described on a continuum, ranging from chronic, clinical form (depersonalization/derealization disorder), to transient episodes. Short-term experiences of depersonalization are mostly triggered by fatigue, anxiety, substance abuse, stress (18), or artificial induction (19) and are considered universal in the general population (20). Depersonalization appears in order to preserve adaptive behaviors (21) and allows to put off emotions and feelings that are too difficult to cope with and, therefore, tolerate the circumstances one is in (22).

We conceptualize depersonalization as an emotion regulation mechanism, broader than specific strategies. The use of word mechanism instead of strategy is not accidental—we suggest that a person can have at least some amount of control over which strategy to use in certain situation, while depersonalization is independent of the will. In the face of an overwhelming or demanding situation, depersonalization can "switch on" and provide a temporary relief. It distances an individual from their emotions and enables them to tolerate the challenges as long as needed. Despite short-term relief, it can exacerbate distress in the long run, potentially leading to emotional depletion, difficulties in maintaining relationships, and overall psychological distress. Regardless from clinical domain, we took inspiration from the burnout syndrome, where depersonalization is one of three core dimensions (23). In burnout, it is characterized as an increased mental distance to work, negativity, and work-related cynicism (24). On the one hand, clinical depersonalization withdraws a person from themselves; on the other, in burnout concept, it withdraws a person from other people and work-related context (25). We decided to merge these two ways of thinking and propose that trait-like depersonalization dampens emotional experiences and

interferes with the ability to maintain personal relationships. If an individual has a problem accessing their emotions, feels distanced, it is hard to be empathetic and attentive. As a result, they have very little energy to engage in relationships and provide support or reciprocation of any kind. We believe that this type of depersonalization could be placed in the middle of the abovementioned continuum, offering a more comprehensive understanding of this phenomenon. We conceptualize it as a trait-like tendency to "activate" depersonalization in order to regulate one's emotional state, which means certain individuals may be more prone to it than the others.

Since existing questionnaires focus on a clinical form of depersonalization, we decided to develop a new measurement tool (see *Materials and methods*). The aim of this paper is fourfold: (1) to propose a novel understanding of depersonalization as an emotion regulation mechanism; (2) to investigate relationships between depersonalization mechanism, cognitive and behavioral emotion regulation strategies, depression symptoms, and trait anxiety; (3) to explore behavioral and cognitive emotion regulation strategies as predictors of depersonalization mechanism; and 4) investigate whether depersonalization mechanism is a predictive factor for depression symptoms.

Materials and methods

Participants

The sample consisted of 300 Polish participants from the general population, meeting inclusion criteria: age 18–60. All participants were recruited by the Polish national research panel. Sample characteristics according to gender, age, and education are as follows: 151 women (50.3%) and 149 men (49.7%); 102 persons (34%) were between 46 and 60 years old, 86 persons (28.7%) between 36 and 45 years old, 70 persons (23.3%) were between 26 and 35 years old, and 42 persons (14%) were between 18 and 25 years old; 129 participants (43%) have received higher education, 167 persons (55.7%) finished high school or similar type of education, and four participants (1.3%) finished primary education. A total of 226 people (75.3%) were professionally active. Participants were asked to disclose any health problems; 151 participants (50.3%) had chronic illnesses (predominantly diabetes, high blood pressure, and asthma), and 146 participants (48.7%) were taking medication (mostly related to chronic illnesses). The sample was representative across all provinces of Poland.

Design and procedure

The research was carried out by the national research panel. At the beginning, respondents were asked about their gender, age, education, chronic illnesses, currently taken medication, and family risk factors. Then, they were provided with a set of questionnaires, described in detail in *Measures*. This study was carried out in accordance with the recommendations of the APA Ethics Code and Helsinki Declaration.

We constructed a new questionnaire that measures a tendency for depersonalization, named Depersonalization Mechanism Scale (DMS). During the developmental phase, we performed a pilot study, starting with an initial pool of 76 items. Items were inspired by already existing depersonalization scales, presenting satisfactory psychometric values: Dissociative Experiences Scale (26), Cambridge Depersonalization Scale (27), Depersonalization–Derealization Inventory (28), The Perceptual Alteration Scale (29), and The Dissociation Questionnaire (30). Moreover, some of the items were inspired by depersonalization subscales from burnout questionnaires: The Maslach Burnout Inventory–General Survey (MBI-GS) (23) (Cynicism subscale), Oldenburg Burnout Inventory (Disengagement subscale), and Link Burnout Questionnaire (25) (Deterioration of relations subscale). Initial 76 items were divided into three categories: 1) selected from the existing scales, for example, "I find my mind blank" from The Perceptual Alteration Scale (29); 2) items selected from the existing scales but with altered phrasing, for example, "I have the experience (…) instead of "Some people have the experience (…)" from Dissociative Experiences Scale (26); 3) created by the authors for example, "I feel that I have so little mental energy that I am able to do bare minimum when it comes to interacting with other people." After the pilot study, redundant and weak loading items were reviewed or discarded. The 50-item version remained and was utilized during research. This version has undergone another psychometric evaluation and factor analysis (described in detail below, in *Results*, *Factor analysis*). The final version of the scale consists of 41 items (described in detail in the *Measures*). The scale is designed as self-report and can be administered to adults. A whole version of the scale is presented in Supplementary Materials.

As the aim of this study was to explore the relationships between depersonalization mechanism, cognitive and behavioral emotion regulation strategies, depression symptoms, and trait anxiety, several instruments were used: Cognitive Emotion Regulation Questionnaire and Behavioral Emotion Regulation Questionnaire to analyze associations with different emotion regulation strategies; Patient Health Questionnaire and Occupational Depression Inventory for employees to assess links with depression; and Trait Anxiety Scale to investigate the relationship between depersonalization mechanism and anxiety.

Measures

Depersonalization Mechanism Scale (DMS)

This is a 41-item, self-report measure designed to assess a tendency to depersonalization. It consists of two subscales: emotional numbness and detachment. Items are rated on 5-point Likert scale, ranging from 0 never to 4 always. A general score ranges from 0 to 164 with a higher score, indicating a higher tendency to depersonalization. The scale was originally constructed in Polish and translated into English by the authors. Reliability scores are presented in Table 1.

TABLE 1 Reliability scores for the Depersonalization Mechanism Scale (DMS).

	Detachment	Emotional Numbness	Depersonalization
Cronbach's α	0.94	0.97	0.97
Average variance extracted (AVE)	0.46	0.44	0.45
McDonald's omega	0.97	0.94	0.97
Guttman's lambda-4	0.94	0.91	
Spearman–Brown correction	0.94	0.91	

Cognitive Emotion Regulation Questionnaire

Cognitive Emotion Regulation Questionnaire (CERQ) (31) is a 36-item, self-report measure designed to assess nine cognitive emotion regulation strategies used in response to threatening or stressful life events. It consists of nine, four-item scales: self-blame, blaming others, acceptance, refocusing on planning, positive refocusing, rumination, positive reappraisal, putting into perspective, and catastrophizing. Items are rated on a 5-point Likert scale, ranging from 1 (almost) never to 5 (almost) always. Subscale scores range from 4 to 20 with higher scores indicating greater tendency to particular strategy. The psychometric characteristics of the original version indicate good reliability, with Cronbach's α ranging from 0.75 to 0.86. In this study, Cronbach's α of the Polish version of CERQ ranges from 0.73 to 0.85.

Behavioral Emotion Regulation Questionnaire

Behavioral Emotion Regulation Questionnaire (BERQ) (13) is a 20-item, self-report measure to designed to describe five behavioral coping strategies: seeking distraction, withdrawal, actively approaching, seeking social support, and ignoring. Each scale consists of four items rated on 5-point scale, ranging from 1 (almost) never to 5 (almost) always. Each subscale is scored from 4 to 20—the higher the scores, the stronger the behavioral strategy. The psychometric characteristics of the original version indicate good reliability, with Cronbach α ranging from 0.86 to 0.93 (13). In this study, Cronbach's α of the Polish version of BERQ ranges from 0.80 to 0.94.

Occupational Depression Inventory

Occupational Depression Inventory (ODI) (32) is a nine-item, self-report measure designed to assess the severity of work-attributed depressive symptoms. It focuses on nine areas of depressive episodes (consistent with DSM-5 diagnostic criteria for major depressive disorder): anhedonia, depressed mood, sleep alterations, fatigue/loss of energy, appetite alterations, feelings of worthlessness, cognitive impairment, psychomotor alterations, and suicidal ideation. Additional question relates to work-related cause of depressive symptoms. Items are rated on a 4-point scale, ranging from 0 never or almost never to 3 nearly every day. In this study, Cronbach's α of the Polish version is 0.94.

Patient Health Questionnaire

Patient Health Questionnaire (PHQ-9) (33) is a nine-item self-report measure to assess the depressive symptoms. Participants are asked how often they experienced described states during the last 2 weeks. Items are rated on a 4-point scale, ranging from not at all to nearly every day, and are scored from 0 to 3, respectively. The general scores range from 0 to 27 and refer to different levels of depression severity (from minimal to severe). In previous studies, Cronbach's α revealed good reliability (e.g., 0.89) (34). In this study, Cronbach's α is 0.92.

Trait Anxiety Scale—SL-C

Trait Anxiety Scale—SL-C (35) is a 15-item measure assessing the intensity of anxiety as a personality trait. This is an English version of a Polish scale (Skala Lęku–Cecha, SL-C). Trait anxiety is understood as a tendency to perceive a situation as threatening or to anticipate future events in terms of the danger that manifests through characteristic cognitive, emotional, and behavioral symptoms. Items are rated on a 4-point scale, from 3 (often) to 0 (never). The SL-C is a one-factor tool; the score ranges from 0 (minimum trait anxiety intensity) to 45 (maximum trait anxiety intensity). The original Cronbach's α coefficient was 0.86. In this study, Cronbach's α is 0.89.

Results

The analysis was carried out with IBM SPSS Statistics 25. The following analysis was performed: descriptive statistics with Kolmogorov–Smirnov test, Pearson r correlations, Student's t-test for independent samples, Kruskal–Wallis test, and multiple regression analysis. Significance level was set at $\alpha = 0.05$.

Descriptive statistics

In the first step, descriptive statistics were calculated, along with Kołmogorov–Smirnov tests to determine distribution of variables. Apart from the emotional numbness subscale, all subscales significantly differed from normal distribution. Additional skewness tests were performed in order to verify whether they are between −/+2 standard deviations from the mean. In that case, it is safe to assume that the distribution is not significantly different from normal distribution (36). Based on the results presented in Table 2, it was decided to use parametric tests while fulfilling other assumptions.

TABLE 2 Descriptive statistics of the used methods.

Method	Subscale	M	Me	SD	Sk.	Kurt.	Min.	Max	W	*p*
DMS	Detachment	1.28	1.19	0.82	0.40	−0.63	0	3.52	0.07	<0.001
	Emotional numbness	1.78	1.79	0.82	0.15	−0.27	0	3.86	0.04	0.200
	Depersonalization	1.45	1.41	0.78	0.30	−0.49	0	3.54	0.06	0.011
BERQ	Seeking distraction	2.69	2.75	0.80	0.44	0.36	1	5	0.10	<0.001
	Withdrawal	2.30	2	1.11	0.86	−0.12	1	5	0.18	<0.001
	Actively approaching	2.79	2.75	1	0.48	−0.37	1	5	0.10	<0.001
	Seeking social support	2.45	2.25	0.95	0.75	0.21	1	5	0.13	<0.001
	Ignoring	2.31	2	0.92	0.75	0.27	1	5	0.13	<0.001
CERQ	Self-blame	2.56	2.50	0.79	0.71	0.30	1	5	0.14	<0.001
	Acceptance	2.66	2.50	0.78	0.63	0.53	1	5	0.14	<0.001
	Rumination	2.67	2.50	0.80	0.40	−0.12	1	5	0.10	<0.001
	Positive refocusing	2.52	2.50	0.80	0.63	0.35	1	5	0.12	<0.001
	Refocus on planning	2.91	2.75	0.92	0.46	−0.32	1	5	0.11	<0.001
	Positive reappraisal	2.63	2.50	0.90	0.39	−0.08	1	5	0.10	<0.001
	Putting into perspective	2.70	2.50	0.89	0.53	−0.02	1	5	0.13	<0.001
	Catastrophizing	2.41	2.25	0.86	0.78	0.71	1	5	0.13	<0.001
	Blaming others	2.23	2	0.82	0.97	1.39	1	5	0.15	<0.001
ODI	Occupational depression	0.71	0.44	0.76	1.07	0.34	0	3	0.18	<0.001
PHQ	Depression (PHQ)	0.89	0.67	0.76	0.72	−0.37	0	3	0.14	<0.001
	Difficulty with work, housework or relationships with other people	1.81	2	0.75	0.71	0.25	1	4	0.25	<0.001
SL-C	Anxiety-a trait	39.21	40	8.62	−0.21	−0.53	17	58	0.06	0.005

M, mean; Me, median; SD, standard deviation; Sk., skewness.; Kurt., kurtosis; Min and Max., minimum and maximum value; W, Kołmogorov–Smirnov test; p, significance level; DMS, Depersonalization Mechanism Scale; BERQ, Behavioral Emotion Regulation Questionnaire; CERQ, Cognitive Emotion Regulation Questionnaire; ODI, Occupational Depression Inventory; PHQ, Patient Health Questionnaire; SL-C, Trait Anxiety Scale.

Factor analysis

In order to determine psychometric values of the Depersonalization Mechanism Scale, principal component analysis with Oblimin rotation was performed. Sampling size was adequate—KMO = 0.96; Bartlett sphericity test [$\chi^2(1,225) = 11{,}091.21$; $p < 0.001$]. Seven factors had eigenvalue >1 (Table 3), but the scree plot showed three factors (Figure 1). Together, they explained 56.01% of variance.

Factors 1 and 2 were strongly, positively correlated ($r = 0.61$), and Factor 3 was not correlated either with Factor 1 ($r = -0.04$) or Factor

TABLE 3 Component's sum of squares after extraction and Oblimin rotation.

Component	All	% of variance	% cumulated	After rotation
1	22.66	45.33	45.33	20.53
2	2.88	5.75	51.08	16.74
3	2.47	4.93	56.01	2.64
4	1.34	2.68	58.69	
5	1.16	2.31	61.00	
6	1.07	2.14	63.13	
7	1.03	2.05	65.18	

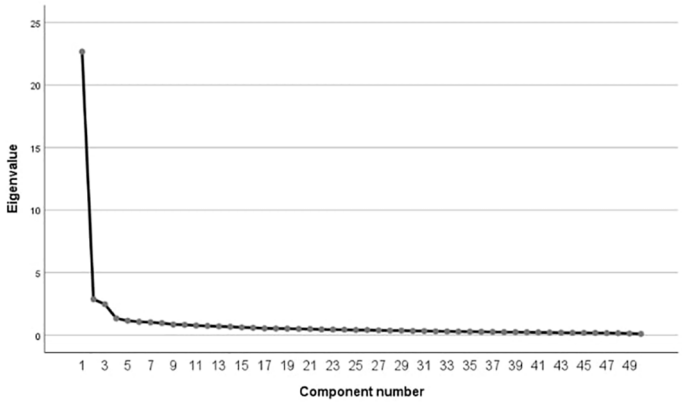

FIGURE 1
Scree plot for the exploratory factor analysis for the *Depersonalization Mechanism Scale*.

TABLE 4 Factor loadings for the Depersonalization Mechanism Scale items.

	Factor	
	1	2
1.45. Familiar voices appear strange and peculiar	.88	
1.16. I have trouble fully feeling my own body	.87	
1.37. I have the experience of not being fully connected to my body	.86	
1.19. My surroundings seem far away and unclear, as if I were looking at it through a fog	.83	
1.10. I have the experience of being out of touch with my body	.82	
1.36. When I look in the mirror it is like I am looking at a stranger—I know it is me, but I do not feel emotionally connected to my reflection	.82	
1.08. My body feels strange	.79	
1.04. I have the experience of being outside of my body/watching myself from the distance	.77	
1.20. I catch myself being so invested in daydreaming that it interferes with my day-to-day life	.76	
1.29. I am so invested in fantasies that I feel like I am experiencing them for real	.75	
1.17. I have an impression as if my emotions and thoughts were not coherent with myself	.74	
1.38. When I experience something difficult, everything seems so "flat" and "faded"	.69	
1.11. In difficult times, I have the experience of being detached from my emotions	.68	
1.41. I have the experience of watching my life from the distance	.65	
1.05. Smells do not evoke neither pleasant nor unpleasant feelings	.64	
1.13. My thoughts seem to float uncontrollably	.63	
1.39. I realize that I have no feelings in situations when I would normally feel something	.63	
1.15. I have the experience of being "spaced out"	.61	
1.06. It seems as if my thoughts are outside of my control, as if they are not consistent with the rest of my experiences	.58	
1.24. I find myself treating others in an impersonal and almost automatic manner	.53	.34
1.02. I have trouble recalling happy memories, even though I know I have them	.52	
1.32. I realize how disconnected I am	.51	.35
1.07. I go through my day as if I am on autopilot and at times, I catch myself that I don't remember what was happening	.50	
1.43. I have the experience of having a blank space in my head when I talk	.50	
1.44. When someone asks me a question, I feel as if I am answering automatically	.50	
1.42. The food has less distinct flavor	.48	
1.47. The fantasy world is a kind of escape from hard reality	.46	
1.26. I start distancing myself from everyone		.95
1.21. I do my business and I do not want to be bothered		.76
1.34. I feel emotionally distanced from others		.74
1.09. Other people seem unhelpful and ungrateful		.68
1.14. I try my best even though I am exhausted and yet nobody appreciates it		.67
1.28. It seems that people around me are particularly difficult		.65
1.18. I wish I had more control over my emotions		.64
1.49. When something particularly hard happens to me, I need a lot of time to gain balance again		.64
1.22. When things get hard, I become more and more cynical, relationships with others become less meaningful		.61

(Continued)

TABLE 4 Continued

	Factor	
	1	2
1.23. I only engage in what is necessary		.59
1.33. I have so little mental energy that I do the bare minimum when I interact with others		.58
1.50. I avoid contact with other people		.57
1.27. I feel emotionally detached from my surroundings	.32	.56
1.46. I start to distance myself and care very little about everything	.33	.54

2 (r = 0.03). We decided to remove items from Factor 3 along with five other items loading two factors at the same time. The final version of the scale consists of 41 items, organized into two subscales: detachment and emotional numbness (factor loadings are presented in Table 4). Discriminatory power of the items is presented in Table 5.

Average variance extracted (AVE) and composite reliability (CR)/McDonald's omega (37) scores were calculated for both subscales and the whole scale—are presented in Table 1. Average variance extracted in all of all three measures falls under the acceptable level of 0.50. However, according to Fornell and Larcker (38), AVE may be a more conservative estimate of the validity and "on the basis of p_n (composite reliability) alone, the researcher may conclude that the convergent validity of the construct is adequate, even though more than 50% of the variance is due to error" (p. 46). The composite reliability of all of the three constructs is above 0.90, so the internal reliability is deemed acceptable.

Correlations

Table 6 presents correlations between BERQ/CERQ and subscales of DMS (first and second column) and a whole scale (third column). Behavioral strategies positively correlated with depersonalization, except for actively approaching. Correlations ranged between 0.12 (seeking social support and depersonalization) and 0.70 (withdrawal and emotional numbness). The strongest correlations were found between all dimensions of depersonalization and withdrawal.

All relationships between depersonalization and cognitive strategies were significant, except the one between refocus on planning and detachment. Correlations ranged between 0.13 (positive reappraisal and emotional numbness) and 0.59 (rumination and emotional numbness). The strongest correlations were found between all dimensions of depersonalization and two subscales of CERQ—rumination and catastrophizing.

TABLE 5 Discriminatory power for the Depersonalization Mechanism Scale items.

	Discriminatory power		
	Detachment	Emotional numbness	Depersonalization
1.45. Familiar voices appear strange and peculiar	.71		.50
1.16. I have trouble fully feeling my own body	.80		.62
1.37. I have the experience of not being fully connected to my body	.77		.67
1.19. My surroundings seem far away and unclear, as if I were looking at it through a fog	.82		.59
1.10. I have the experience of being out of touch with my body	.80		.65
1.36. When I look in the mirror it is like I am looking at a stranger—I know it is me, but I do not feel emotionally connected to my reflection	.74		.69
1.08. My body feels strange	.70		.57
1.04. I have the experience of being outside of my body/watching myself from the distance	.71		.62
1.20. I catch myself being so invested in daydreaming that it interferes with my day-to-day life	.76		.72
1.29. I am so invested in fantasies that I feel like I am experiencing them for real	.66		.48
1.17. I have an impression as if my emotions and thoughts were not coherent with myself	.82		.73
1.38. When I experience something difficult, everything seems so "flat" and "faded"	.79		.69
1.11. In difficult times, I have the experience of being detached from my emotions	.74		.75
1.41. I have the experience of watching my life from the distance.	.75		.75
1.05. Smells do not evoke neither pleasant nor unpleasant feelings.	.48		.65
1.13. My thoughts seem to float uncontrollably	.77		.76
1.39. I realize that I have no feelings in situations when I would normally feel something	.74		.73

(Continued)

TABLE 5 Continued

	Discriminatory power		
	Detachment	Emotional numbness	Depersonalization
1.15. I have the experience of being "spaced out"	.77		.78
1.06. It seems as if my thoughts are outside of my control, as if they are not consistent with the rest of my experiences.	.74		.77
1.24. I find myself treating others in an impersonal and almost automatic manner	.75		.71
1.02. I have trouble recalling happy memories, even though I know I have them	.59		.66
1.32. I realize how disconnected I am	.73		.68
1.07. I go through my day as if I am on autopilot and at times, I catch myself that I do not remember what was happening	.68		.73
1.43. I have the experience of having a blank space in my head when I talk	.68		.62
1.44. When someone asks me a question, I feel as if I am answering automatically	.67		.80
1.42. The food has less distinct flavor	.53		.78
1.47. The fantasy world is a kind of escape from hard reality	.57		.72
1.26. I start distancing myself from everyone		.68	.74
1.21. I do my business, and I do not want to be bothered		.72	.45
1.34. I feel emotionally distanced from others		.74	.77
1.09. Other people seem unhelpful and ungrateful		.67	.73
1.14. I try my best even though I am exhausted and yet nobody appreciates it		.70	.78
1.28. It seems that people around me are particularly difficult		.74	.74
1.18. I wish I had more control over my emotions		.61	.77
1.49. When something particularly hard happens to me, I need a lot of time to gain balance again		.66	.59
1.22. When things get hard, I become more and more cynical, relationships with others become less meaningful		.74	.76
1.23. I only engage in what is necessary		.53	.69
1.33. I have so little mental energy that I do the bare minimum when I interact with others		.73	.69
1.50. I avoid contact with other people		.70	.68
1.27. I feel emotionally detached from my surroundings		.73	.53
1.46. I start to distance myself and care very little about everything		.73	.58

Table 7 presents correlations between depersonalization and occupational depression, depressive symptoms, and trait anxiety. Correlations ranged between 0.47 (detachment and anxiety—trait) and 0.69 (depressive symptoms and depersonalization). All the correlations were significant; the strongest relationship was found between all aspects of depersonalization and depressive symptoms.

Gender differences in depersonalization and emotion regulation strategies

Student's *t*-test was performed in order to determine whether men and women differ in severity of depersonalization and emotion regulation strategies. Differences in the aspect of emotional numbness (t = 3.12; p = 0.002) and depersonalization (t = 2.04; p = 0.043) were found to be significant, with women being more prone than men to both. However, the effect size was small (d = 0.36 and d = 0.24, respectively). There were no differences in the aspect of detachment.

Behavioral and cognitive emotion regulation strategies were also considered. In our sample, women were more likely than men to use the following behavioral strategies: withdrawal (t = 2.37; p = 0.019), actively approaching (t = 2.48; p = 0.014), and seeking social support (t = 2.72; p = 0.007); other differences were insignificant. However, the effect size was small (d = 0.27, d = 0.29, d = 0.31, respectively). Regarding cognitive strategies, in our sample, women were more likely to use the following strategies: self-blame (t = 2.36; p = 0.019), acceptance (t = 2.65; p = 0.009), rumination (t = 4.73; p< 0.001), and refocus on planning (t = 2.20; p = 0.029 and

TABLE 6 Pearson correlations between depersonalization and cognitive and behavioral emotion regulation strategies.

		Detachment	Emotional numbness	Depersonalization
BERQ	Seeking distraction	**.34****	**.38****	**.37****
	Withdrawal	**.62****	**.70****	**.68****
	Actively approaching	.00	.01	0
	Seeking social support	**.15***	.03	**.12***
	Ignoring	**.50****	**.41****	**.49****
CERQ	Self-blame	**.46****	**.53****	**.51****
	Acceptance	**.37****	**.45****	**.42****
	Rumination	**.48****	**.59****	**.54****
	Positive refocusing	**.26****	**.17***	**.24****
	Refocus on planning	.10	**.23****	**.15***
	Positive reappraisal	**.15***	**.13***	**.15***
	Putting into perspective	**.20****	**.23****	**.22****
	Catastrophizing	**.52****	**.56****	**.56****
	Blaming others	**.51****	**.46****	**.52****

*p< 0.05, **p< 0.001; BERQ, Behavioral Emotion Regulation Questionnaire; CERQ, Cognitive Emotion Regulation Questionnaire.
Statistically significant results are marked in bold.

catastrophizing (t = 3.33; p = 0.001); other differences were insignificant. Effect sizes were small (d = 0.27, d = 0.31, d = 0.25, d = 0.38, respectively), except for rumination, where the effect was medium (d = 0.50).

Multiple regression

Multiple regression analyses were conducted to test if behavioral and cognitive emotion regulation strategies significantly predicted depersonalization. The results of the regression indicated that behavioral emotion regulation strategies explained 52% of the variance in depersonalization [$R^{2\text{Adjusted}}$ = .52, $F(5,294)$ = 65.75, $p < 0.001$]. It was found that withdrawal (β = .38, $p < 0.001$), ignoring (β = .19, $p < 0.001$), and seeking distraction (β = .10, p = 0.038) significantly predicted depersonalization (Table 8).

Further analysis revealed that cognitive emotion regulation strategies are significant predictors of depersonalization and explained 42% of the variance [$R^{2\text{Adjusted}}$ = .42, $F(9,290)$ = 25.45, $p < 0.001$]. It was found that self-blame (β = .21, $p < 0.001$), blaming others (β = .25, $p < 0.001$), rumination (β = .23, p = 0.002), and refocus on planning (β = −.15, p = 0.009) were significant predictors of depersonalization (Table 9).

Subsequently, the two factors of depersonalization, i.e., detachment and emotional numbness, were tested to evaluate the extent to which depersonalization could predict symptoms of depression. The results of the regression analysis indicated that symptoms of depersonalization explained 48% of the variance [$R^{2\text{Adjusted}}$ = .48, $F(2,297)$ = 137.37, $p < 0.001$]. It was found that both detachment (β = .35, $p < 0.001$) and emotional numbness (β = .33, $p < 0.001$) significantly predicted depression (Table 10).

A significant regression was also found in the context of occupational depression [$R^{2\text{Adjusted}}$ = .33, $F(2,223)$ = 56.34, $p < 0.001$], indicating that depersonalization explained 33% of the variance (Table 11). In this analysis, only detachment was found as a significant predictor for occupational depression (β = .44, $p < 0.001$).

Discussion

The aim of this paper was to introduce our understanding of depersonalization mechanism and its relationship with selected emotion regulation depression and anxiety. Moreover, our purpose was to investigate whether depersonalization acts as a predictive factor for depressive symptoms.

This work proposes a new measure that offers a deeper understanding of this complex phenomenon. The constructed

TABLE 7 Pearson correlations between depersonalization and depression (measured by ODI and PHQ) and anxiety trait.

	Detachment	Emotional numbness	Depersonalization
Occupational depression (ODI)	**.57****	**.50****	**.58****
Depression (PHQ)	**.66****	**.65****	**.69****
Anxiety trait (SL-C)	**.47****	**.56****	**.53****

**p< 0.001; ODI, Occupational Depression Inventory; PHQ, Patient Health Questionnaire; SL-C, Trait Anxiety Scale.
Statistically significant results are marked in bold.

TABLE 8 Regression coefficients of behavioral emotion regulation strategies on depersonalization.

Variables	*B*	*SE*	*t*	*p*	95% CI
Constant	−.094	.135	−0.699	0.485	[−.359,.171]
Seeking distraction	.101	.048	2.089	0.038	[.006,.196]
Withdrawal	.381	.033	11.584	<0.001	[.316,.446]
Actively approaching	−.072	.039	−1.869	0.063	[−.148,.004]
Seeking social support	.067	.039	1.728	0.085	[−.009,.143]
Ignoring	.190	.039	4.865	<0.001	[.113,.267]
Seeking distraction	−.094	.135	−0.699	0.485	[−.359,.171]

CI, confidence interval.

method, the Depersonalization Mechanism Scale (DMS), comprises two subscales, namely, detachment and emotional numbness, both of high reliability ($\alpha = 0.97$ and $\alpha = 0.94$, respectively). The whole scale was also found to be highly reliable ($\alpha = 0.97$) and applicable to adults in non-clinical population.

We aimed to shed light on depersonalization outside of strictly clinical context and normalize it as one of the possible mechanisms of emotional regulation. We propose that depersonalization mechanism is a non-voluntary, complex reaction that entails specific cognitive and behavioral strategies. The maladaptive function of depersonalization may be suggested by stronger correlation with less functional cognitive strategies, namely, self-blame, blaming others, rumination, and catastrophizing, and behavioral ones, namely, withdrawal and ignoring. However, due to significant correlations with more adaptive strategies (acceptance, positive refocusing, putting into perspective, positive reappraisal, seeking distraction and seeking social support), we may conclude that there are some positive aspects of depersonalization indicating adaptive characteristics of this mechanism. Depersonalization may provide short-term relief, especially important when we do not have the ability to change the situation that we must endure. The most

TABLE 9 Regression coefficients of cognitive emotion regulation strategies on depersonalization.

Variables	*B*	*SE*	*t*	*p*	95% CI
Constant	−.304	.154	−1.980	0.049	[−.607, −.002]
Self-blame	.209	.062	3.373	<0.001	[.087,.330]
Acceptance	.061	.065	0.939	0.349	[−.067,.189]
Rumination	.226	.073	3.096	0.002	[.082,.370]
Positive refocusing	.013	.062	0.210	0.834	[−.109,.135]
Refocus on planning	−.145	.055	−2.626	0.009	[−.254, −.036]
Positive reappraisal	.014	.062	0.218	0.828	[−.109,.136]
Putting into perspective	.000	.063	−0.006	0.995	[−.124,.123]
Catastrophizing	.107	.066	1.610	0.108	[−.024,.237]
Blaming others	.250	.056	4.429	<0.001	[.139,.361]

CI, confidence interval.

TABLE 10 Regression coefficients of symptoms of depersonalization on depression (PHQ).

Variables	*B*	*SE*	*t*	*p*	95% CI
Constant	−.146	.077	−1.903	0.058	[−.297, −.005]
Detachment	.349	.061	5.692	<0.001	[.229,.470]
Emotional numbness	.331	.062	5.347	<0.001	[.209,.453]

CI, confidence interval; PHQ, Patient Health Questionnaire.

important aspect of determining the adaptability of a given mechanism is determined by flexibility and adequacy of use.

It is worth noting that depersonalization cannot be reduced to avoidance only, which is confirmed by correlations with various emotion regulation strategies. This leads us to the conclusion that depersonalization is a complex mechanism of emotional regulation. Additionally, causes and motivation distinguish depersonalization from avoidance. Avoidant personality disorder is driven by feelings of inadequacy and intense fear of rejection (16), avoidance-based emotion regulation strategies are used to escape from unpleasant experiences (13), while depersonalization could be understood as a kind of "energy conservation" mechanism. We believe that adaptivity of such strategies is dependable on flexibility of use, the amount of control over it, the severity of consequences, among others.

Such perspective on depersonalization may lead to normalization of this specific response and help to better understand seemingly inadequate behaviors and attitudes. Furthermore, it may influence support and psychoeducation in the therapeutic interventions in patients who experience acute or chronic stress. The need to raise awareness among practitioners and the general population is particularly important in the light of the apparent rise in depersonalization symptoms (39, 40). Alterations in the sense of self with all of its consequences may constrain people's ability to be more present and engaged in their lives. One of the possible results could be gradual drainage of social support network, essential for maintaining a sense of self (40).

Multiple regression analyses showed that behavioral and cognitive strategies play an important role in explaining depersonalization mechanism. The behavioral strategies explained a greater percentage of variance in depersonalization than cognitive ones. Among behavioral strategies, withdrawal, ignoring, and seeking distraction were significant predictors of depersonalization—the greater the level of these strategies, the stronger the symptoms of depersonalization. Cognitive strategies in regulating emotions revealed the similar pattern in relation to maladaptive strategies, namely, self-blame, blaming

TABLE 11 Regression coefficients of symptoms of depersonalization on occupational depression (ODI).

Variables	*B*	*SE*	*t*	*p*	95% CI
Constant	−.027	.097	−0.275	0.783	[−.218,.165]
Detachment	.439	.081	5.422	<0.001	[.280,.599]
Emotional numbness	.116	.080	1.437	0.152	[−.043,.274]

CI, confidence interval; ODI, Occupational Depression Inventory.

others, and rumination; the only one adaptive strategy that predicted the depersonalization was refocus on planning, which was negatively associated with depersonalization. It seems that planning may be more available in depersonalization than other adaptive cognitive strategies, like positive refocusing or positive reappraisal. This analysis helps to indicate specific emotion regulation strategies that may have a particular influence on strengthening depersonalization mechanism (i.e., withdrawal, ignoring, seeking distraction, self-blame, blaming others, and rumination), increasing the tendency to react in line with depersonalization characteristics and one cognitive strategy (i.e., refocus on planning) that may be crucial in limiting the tendency to depersonalization.

Another inspiring outcome of our analysis refers to the symptoms of depersonalization as predictors of depression. Gathered data indicate that, in a general context, both detachment and emotional numbness increase the symptoms of depression. Considering work-related context, it seems that detachment may play a crucial role in the development of occupational depression. Interestingly, "detachment" has stronger cognitive and behavioral connotations and is more prone to change than the "emotional numbness," which is related stronger to emotions and the states caused by them. Expanding research on depersonalization in non-clinical groups could be beneficial for our understanding of this phenomenon. Combining this knowledge with increased awareness of non-clinical depersonalization could help in the development of preventive actions against depression and provide better professional support for those experiencing acute or prolonged stressful life situations.

There are several limitations to our study. We focused primarily on the description and characteristics of depersonalization in non-clinical population. Further studies should incorporate clinical samples analyzing the problem of depersonalization mechanism in different disorders. It is very important to identify individual dispositions (e.g., temperament, personality, sensory processing sensitivity) and contextual factors (e.g., family ties, traumas, social support) as possible predictors of depersonalization mechanism. In this study, basic correlations with anxiety and depression are reported; however, cause-and-effect relationships need to be studied to describe possible functions and consequences. Finally, further research on neurophysiological correlates of depersonalization can bring insight into the fundamental brain mechanisms. It would be especially valuable to use an experimental model to study different aspects of the depersonalization mechanism, like information processing in different conditions and stimuli characteristics.

The results of this study may be used in intervening programs, which could focus on developing skills in reducing strategies such as withdrawal, ignoring, distraction, blaming oneself or others, rumination on the one hand, and intensifying planning strategies on the other. It seems that precise selection of these strategies may allow for more accurate therapeutic interventions to reduce the tendency to depersonalization. It is particularly important in the light of the strong association between depersonalization and depression symptoms, both in non-professional and occupational contexts. Understanding the mechanisms of depersonalization may benefit in weakening this tendency with regard to strength and duration of being detached and emotionally numbed. The consciousness of potential depressive consequences seems to be a sufficient reason to deepen knowledge about the mechanisms of depersonalization.

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 from the participants was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

DF: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. KG: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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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.2024.1481439/full#supplementary-material

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The influence of physical exercise on negative emotions in adolescents: a meta-analysis

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Background: Adolescence is also accompanied by ongoing mood changes (relative to childhood and adulthood), which can trigger more extreme negative emotional responses. Physical exercise alleviates negative emotions and reduces the risk of mental illness. However, the effect of physical exercise on negative emotions in adolescents is unclear, so it is valuable to synthesize previous studies with meta-analysis.

Objective: To examine the influence of physical exercise (PE) intervention on negative emotions in adolescents aged 10 to 19 years.

Methods: We retrieved the articles from PubMed, Web of Science, EBSCO, Cochrane, and Embase up to April 11, 2024. The main search terms were physical exercise, negative emotions, adolescents, randomized controlled trials. The meta-analysis was conducted using Review Manager 5.3. A random-effects model was employed to calculate the standardized mean difference (SMD) and 95% confidence interval (CI). Subgroups were analysed as the type of negative emotions, type of control group, intervention type, duration, time, frequency.

Results: The PE intervention group exhibited a significantly superior improvement in alleviating negative emotions compared to the control group (SMD = -0.59, 95% CI: -0.92 to -0.26, $p < 0.01$, $Z = 3.50$, $I^2 = 95\%$). PE was particularly effective in mitigating adolescent depression (SMD = -0.67, 95% CI = -1.07 to -0.28, $p < 0.01$, $I^2 = 96\%$) but did not yield significant results in reducing adolescent anxiety (SMD = -0.29, 95% CI = -0.63 to 0.05, $p = 0.10$, $I^2 = 95\%$).

Conclusion: PE intervention can ameliorate negative emotions in adolescents.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/, identifier CRD42024534375.

KEYWORDS

physical exercise, adolescents, negative emotions, mental health, meta-analysis

1 Introduction

Negative emotions are generally indicative of distress and are often conceptualized in varying intensities, such as anxiety, depression, sadness, and anger (1). Among these, depression and anxiety are frequently employed as predictors (2). Depression is often a chronic and recurring condition (3) associated with high levels of psychological distress, impairments in functioning, and poor physical health (4). Depression is the most predominant aspect of negative affect and a major contributor to the global burden of disease in young people under the age of 25 (5). It is estimated that one in five people will be affected by depression in their lifetime, and the majority of people with depression begin to experience the onset of the illness in adolescence to young adulthood (6, 7). Anxiety is the most common manifestation of psychopathology in youth, negatively affecting academic, social, and adaptive functioning and increasing risk for mental health problems into adulthood (8, 9). Approximately 1 in 4 adolescents exhibits increased levels of worry and anxiety. In addition, adolescent anxiety predicts ongoing mental health problems throughout life (10). Therefore, depression and anxiety are the most important aspects of negative emotions, and this study also focuses on these two aspects of negative emotions.

Adolescence, a period characterized by rapid growth and maturation, neuronal plasticity (11, 12), identity formation (13), and the establishment of behavioral tendencies, plays a crucial role in shaping mental well-being, potentially steering it in either positive or negative directions (14, 15). During this critical phase, individuals experience significant physical, psychological, and social development, which makes them particularly susceptible to negative emotional states influenced by various factors. Adolescence brings profound changes in the social environment, physical growth, and dramatic hormonal changes (16, 17). Behaviorally, adolescence is also accompanied by constant emotional changes (relative to childhood and adulthood), which can trigger more extreme emotional responses for at-risk individuals (18). Numerous studies have revealed that the incidence of negative emotions escalates considerably during adolescence, surpassed only by behavioral disorders (19–21). The predominant clinical manifestations of negative emotions in adolescents encompass apathy, somatic complaints, impaired concentration, indecision, overwhelming guilt, reckless behavior, disinterest in food or compulsive overeating, resulting in significant weight fluctuations, memory lapses, fear of death, defiance, pervasive sadness, anxiety, or despair, nocturnal insomnia, and excessive daytime drowsiness (22). It is therefore not surprising that adolescence is also a time when emotional symptoms such as anxiety and depression are often present. These emotional states not only exacerbate psychological suffering and impair the mental health of adolescents but are also closely associated with deliberate or inadvertent harmful behaviors (15, 23), such as smoking (24), drinking (25), and other detrimental activities. Hence, it is logical to conclude that an adolescent's environmental exposure could mitigate the development of negative emotions later in life (26).

Physical exercise (PE) encompasses aerobic activity, resistance training, as well as both physical and mental exercises (27). Numerous studies have revealed that engaging in physical activity not only bolsters mental health but also mitigates negative emotions and diminishes the risk of mental disorders (28, 29). For example, regular and appropriate PE has the potential to transform the brain's structure and function, thereby ameliorating negative emotional states by increasing levels of dopamine, serotonin, and norepinephrine (30). Scholars have also established a correlation between adhering to the three recommended 24-hour activity guidelines and a reduced risk of depression and anxiety (31). Research conducted among school-aged children in China indicated that those who adhered to the 24-hour activity standards exhibited the lowest risk of experiencing negative emotions (32). According to findings from Wang's study, a six-week regimen of PE has proven effective in alleviating symptoms of depression among adolescents aged 12 to 18 (27).

Research on negative emotions in adolescents is limited. Considering the influences noted in earlier studies and adolescents' natural emotional sensitivity, alongside the positive impacts of PE interventions on their emotional well-being, our study aimed to investigate negative emotions in individuals aged 10 to 19 years. We conducted a meta-analysis of existing literature to examine how the duration, time, and frequency of PE interventions affect study outcomes. Based on this, the hypothesis of this study was formulated: This study hypothesizes that physical exercise interventions will significantly reduce symptoms of anxiety and depression in adolescents.

2 Methods

Following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (33) and the Cochrane Handbook for Systematic Reviews and Meta-Analysis (34), this review was conducted. Moreover, the protocol for this review was duly registered on PROSPERO under the registration number CRD42024534375.

2.1 Search strategy

For this study, we searched PubMed, Web of Science, EBSCO, Cochrane, and Embase up to April 11, 2024. The main search terms were physical exercise, negative emotions, adolescents, randomized controlled trials, etc., and the search terms were connected by AND and the search terms were connected by OR. The search strategy was a Boolean logic search with the following search strategies: ("physical activity" or "physical exercise" or "sports activities" or "physical education" or "sport movement", sport or "athletic sports" or "aerobic exercise" or "aerobic training" or "resistance exercise", "muscle-strengthening exercise" or "strength training", "fitness game") AND ("negative emotion" or anxiety or anxious or depression or depressive or depress or pressure or stress or "psychological ill-being" or "mental disease") AND (adolescent or teenager or "junior high school students" or "senior high school students") AND ("randomized controlled trial" or RCT). The details of our search terms are outlined in Table 1, demonstrating the meticulousness and accuracy of our research approach. The study was conducted independently by two researchers (TW and

WCL), with a third researcher (YFL) consulted in case of disagreement. In this case, WCL performed the first stage of screening based on the title and abstract, and TW performed the second stage of screening by reading the full text. Finally, the data were analyzed by TW, WCL, and JXD and supervised and reviewed by QBZ and YFL.

2.2 Eligibility criteria

The relevant studies' inclusion criteria were established following the PICOS framework. For participants (P), studies involving adolescents aged 10 to 19 years were considered. Regarding Intervention (I), the experimental group received various forms of PE intervention. Comparison (C) groups encompassed no-exercise (NT), wait-list (WL), and attention/activity placebo (AP) conditions. Outcome (O) measurements are primarily focused on assessing negative emotions in adolescents. Lastly, Study Design (S) adhered to the randomized controlled trial methodology.

The following criteria were applied to exclude relevant studies: literature not in English, including unpublished materials, theses, and reviews; studies involving adults, animals, or special populations; literature lacking valid data extraction; duplicate publications; and full texts that were inaccessible.

2.3 Data extraction

The study followed the PRISMA statement guidelines when extracting data and selecting studies. Duplicate studies were eliminated using EndNote 20 software to consolidate articles from each source into a unified database. Data extraction was mainly carried out independently by two researchers (TW and WCL), with a third researcher (YFL) being consulted in case of disagreement. Data were analyzed by TW, WCL, and JXD and supervised and reviewed by QBZ and YFL. Investigations into the attrition of treatment during follow-up were conducted independently by two researchers (TW and QBZ), who examined the included literature and consulted a third researcher (YFL) in cases of discordance. When data cannot be extracted, we will contact the author of the article to resolve the issue. If we cannot get in touch, we will extract the data using WebPlotDigitizer software.

TABLE 1 Summary of search terms.

Category		Included search terms
Physical exercise		("physical activity" or "physical exercise" or "sports activities" or "physical education" or "sport movement", sport or "athletic sports" or "aerobic exercise" or "aerobic training" or "resistance exercise", "muscle-strengthening exercise" or "strength training", "fitness game")
	AND	
Negative emotion		("negative emotion" or anxiety or anxious or depression or depressive or depress or pressure or stress or "psychological ill-being" or "mental disease")
	AND	
Adolescent		(adolescent or teenager or "junior high school students" or "senior high school students")
	AND	
Randomized controlled trial		("randomized controlled trial" or RCT)

Utilizing Review Manager 5.3 (35), data were inputted for both intervention and control groups, encompassing mean values, standard deviations, and participant counts. To accommodate the anticipated heterogeneity between trials attributed to the implementation of diverse PE interventions, meta-analysis pooling was conducted using a random effects model. To facilitate the aggregation of data from various negative emotions symptom scales, the effect was evaluated as the standardized mean difference (SMD), calculated using Hedges' g, adjusted for small sample size bias, accompanied by 95% confidence intervals (CI) (36), and heterogeneity was evaluated through standard parameters of the I^2 statistic (34). In cases where the test indicated substantial heterogeneity (I^2 > 50%), we employed subgroup analysis and sensitivity analysis to elucidate the findings (37).

Subgroup analysis was utilized to investigate potential factors influencing the impact of PE on negative emotions. Pre-specified subgroup objectives were type of negative emotions (depression vs. anxiety), type of control group (WL/NT vs. AP), type of exercise intervention (aerobic vs. resistance vs. mixed), exercise intervention duration (<12 weeks vs. ≥12 weeks), exercise intervention time (<60min vs. ≥60min), exercise intervention frequency (≤3 times per week vs. >3 times per week).

2.4 Methodological quality assessment

The included studies were independently quality assessed using the Cochrane Risk of Bias Tool (38) by researchers TW and WCL, respectively. In this process, consensus is sought through in-depth discussion of any disagreements that arise in the assessment. If there were disagreements that could not be resolved through discussion, a third reviewer (CY) was consulted to ensure the objectivity and accuracy of the results. The methodological quality of the included studies was evaluated using the Cochrane risk of bias criteria, comprising seven items: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. Each item was assessed as "low risk", "uncertain risk", or "high risk" based on the responses to the signaling questions, contributing to an overall judgment of bias for each study assessed.

3 Results

3.1 Study selection

The literature search results and research selection process are shown in Figure 1. Initially, 3368 articles were retrieved from the

databases, of which 1156 were from Pumbed, 635 from Embase, 1063 from Cochrane, 406 from Web of Science, and 108 from EBSCO. Following the removal of duplicates, 2271 studies remained, while 2193 studies did not meet the eligibility criteria during the title and abstract screening phases. These ineligible papers covered reviews (n = 106); not relevant studies (n = 1882); animal experiments (n = 1); reports, cross-sectional studies, longitudinal studies, and other articles (n = 181); and alcohol/tobacco and other articles (n = 23). Out of 78 studies, 63 were excluded after reading their full texts: no data (n = 3); non-English (n = 3); unable to access original text (n = 6); experimental design discrepancy (n = 3); incorrect age (n = 20); intervention discrepancy (n = 9); and outcome index discrepancy (n = 19). A total of 15 articles were eventually included in the meta-analysis.

3.2 Study characteristics

As illustrated in Table 2, the sample sizes of the trials ranged from 24 to 1066 participants, with mean ages spanning from 12 to 18.8 years. Two studies included subjects with a healthy mental status, seven studies included subjects with an unhealthy mental status, and six studies did not report the mental status of the included subjects. A summary of the characteristics of the PE interventions implemented in each trial is provided in Tables 2 and 3. The majority of trials employed aerobic exercise, though there was significant variation in the types of PE. The duration of the interventions varied between 6 to 48 weeks, with sessions occurring 1 to 5 times per week. The time commitment per session ranged from 20 to 440 minutes. The control groups consisted of NT (n = 3), WL (n = 3), and AP (n = 8). Ten studies used per-protocol analysis, and five studies used intention-to-treat analysis.

3.3 Risk of bias

The methodological quality of the included literature was assessed using the Cochrane Risk Assessment Tool. For random sequence generation, 12 articles (39–50) were rated as low risk and 3 articles (51–53) as unclear risk. For allocation concealment, 13 articles (39–43, 45–52) were rated as low risk, 1 article (53) as unclear, and 1 article (44) as high risk. Regarding performance bias, 2 articles (46, 50) were rated as low risk, 3 articles (39, 41, 47) as unclear risk, and 10 articles (40, 42–45, 48, 49, 51–53) as high risk. Regarding detection bias, 4 articles (42, 43, 46, 50) were rated as low risk, 4 articles (39, 41, 47, 53) as unclear, and 7 articles (40, 44, 45, 48, 49, 51, 52) as high risk. For attrition bias, 11 articles (39, 42–47, 49–52) were rated as low risk and 4 articles (40, 41, 48, 53) as unclear risk. Regarding reporting bias, 10 articles (39, 40, 42–47, 50, 51) were rated as low risk, 4 articles (41, 48, 49, 53) as unclear risk, and 1 article (52) as high risk. Finally, with regard to other biases, 6 articles (39, 40, 43, 45, 47, 50) were rated as low risk, 8 articles (41, 42, 44, 46, 48, 49, 51, 53) as unclear risk, and 1 article (52) as high risk (Figure 2). The assessment of publication bias

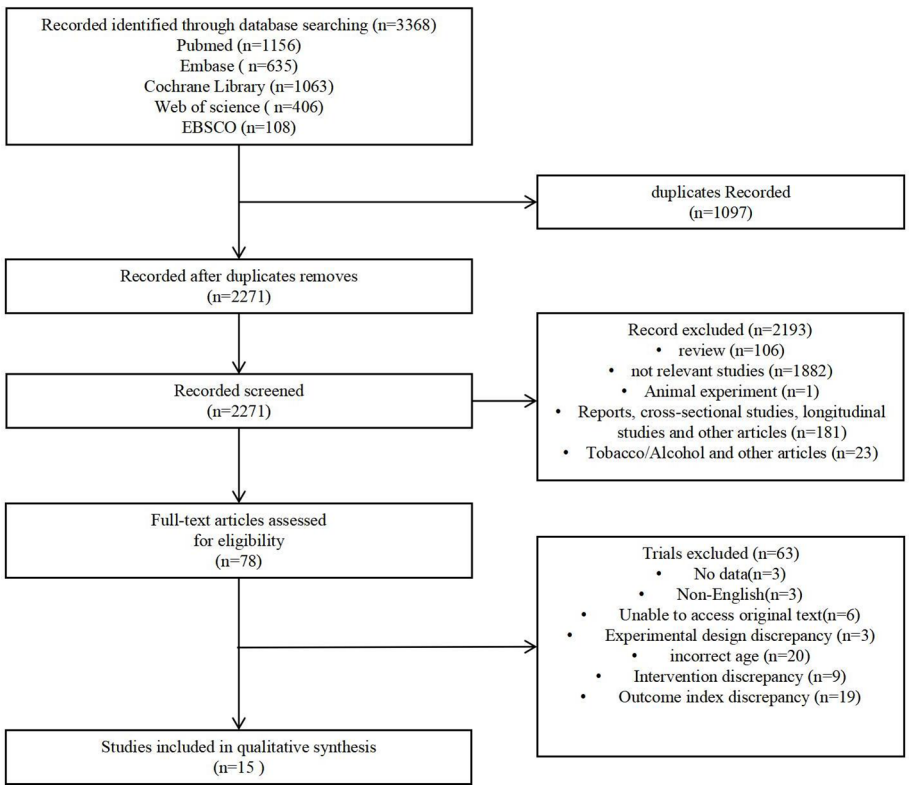

FIGURE 1
Flow chart of literature retrieval.

TABLE 2 Included trial characteristics.

Included studies	Sample size (Exp/Ctrl)	Age (Mean)	Mental state of the adolescents	Intervention	Duration (Weeks)	Time (Min)	Frequency (Times/Week)	Outcome	Outcome Measurement Tools	Control group	Mode of analysis
Ahmed, 2023 (39)	160/160	14.4	-	Aerobic	12	60	1	Depression	CESD-10	NT	Protocol
Carter, 2015 (40)	36/28	15.4	Unhealthy	Mixed	6	60	2	Depression	CDI-2	TAU	Intention-to-treat
Chung, 2021 (51)	115/113	12-16	Healthy	Adventure-based training	-	2-day/ 1-night	-	Depression	CES-DC	AP	Protocol
Crews, 2004 (41)	34/32	-	-	Aerobic	6	20	3	Anxiety Depression	STAIC BDI	AP	Protocol
Goldfield, 2015 (42)	73/78/72/75	15.6	Healthy	Aerobic Resistance Mixed	22	20-45	4	Depression	BRUMS	NT	Protocol
Hughes, 2013 (43)	14/12	17	Unhealthy	Aerobic	12	30-40	2-3	Depression	CDRS-R	AP	Intention-to-treat
Jeong, 2005 (52)	20/20	16	Unhealthy	Aerobic	12	45	3	Depression	SCL-90-R	WL	Intention-to-treat
Khalsa, 2012 (44)	67/34	16.8	-	Aerobic	11	30-40	2-3	Anxiety Depression	POMS-SF	AP	Protocol
Lima, 2022 (45)	308/251/289/218	17	-	Aerobic	24	200/ 240/ 440	4	Depression	CES-D	AP	Protocol
Melnyk, 2015 (46)	9/9	16	Unhealthy	Aerobic	48	20	1	Depression	BYI-II	WL	Protocol
Nabkasorn, 2006 (47)	21/28	18.8	Unhealthy	Aerobic	8	50	5	Depression	CES-D	WL	Intention-to-treat
Noggle, 2012 (48)	36/15	17	-	Aerobic	10	30-40	2-3	Anxiety Depression	POMS-SF	AP	Protocol
Norris, 1992 (49)	14/15/16	16.7	-	Aerobic	10	25-30	2	Anxiety Depression	MAACL	AP	Protocol
Philippot, 2022 (50)	20/20	15	Unhealthy	Mixed	6	-	4	Anxiety Depression	HADS-A HADS-D	AP	Intention-to-treat
Roshan, 2011 (53)	12	16.9	Unhealthy	Aerobic	6	-	3	Depression	HAM-D	NT	Protocol

Exp, Experiment group; Ctrl, Control group; CESD-10, Center for Epidemiologic Studies Depression Scale; CDI-2, Children's Depression Inventory-2; CES-DC, Depression Scale for Children; STAIC-Trait, Anxiety Inventory for Children; BDI, Beck Depression Inventory; ERICA, Emotion Regulation Index for Children and Adolescents; HBSC, Health Behavior in School-aged Children; BRUMS, 24-item Brunell Mood Scale; CDRS-R, Childs Depression Rating Scale–Revised; Symptom Check List-90-Revision; POMS-SF, The Profile of Mood States short form POMS-SF; PSS, The Perceived Stress Scale; CES-D, Centre for Epidemiological Studies Depression scale; BYI-II, The depression subscale of the Beck Youth Inventory II; HADS, The Hamilton Depression Rating Scale; HAM-D, Hamilton Depression Rating Scale; AP, Attention/Activity Placebo; NT, No-Treatment Control; WL, Wait-List control; TAU, Treatment as Usual; -: No report.

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TABLE 3 Subgroup analyses based on the primary meta-analysis.

Subgroup analysis	K	SMD	95%CI	*p* value	Heterogeneity	Test for subgroup difference
Primary meta-analysis	15	-0.59	-0.92 to -0.26	$p<0.01$	$X^2 = 458.54$, df = 25 ($p<0.00001$), Z = 3.50, $I^2 = 95\%$	
Type of Negative Emotions (2 sub-group analyses)						
Depression	15	-0.67	-1.07 to -0.28	$p<0.01$	$X^2 = 445.61$, df = 19 ($p<0.00001$), Z = 3.37, $I^2 = 96\%$	$X^2 = 2.10$, df = 1 (P = 0.15), Z = 3.50, $I^2 = 52.5\%$
Anxiety	4	-0.29	-0.63 to 0.05	*P = 0.10*	$X^2 = 10.39$, df = 5 ($p<0.00001$), Z = 1.66, $I^2 = 52\%$	
Type of Control Group (2 sub-group analyses)						
PE v. NT/WL	6	-1.37	-2.25 to -0.50	$p<0.01$	$X^2 = 193.78$, df = 7 ($p<0.00001$), Z = 3.08, $I^2 = 96\%$	$X^2 = 6.38$, df = 1 (P = 0.01), Z = 3.49, $I^2 = 84.3\%$
PE v. AP	8	-0.23	-0.38 to -0.08	$p<0.01$	$X^2 = 36.17$, df = 16 (P=0.003), Z = 3.04, $I^2 = 56\%$	
Type of Exercise Intervention (3 sub-group analyses)						
Aerobic	10	-0.45	-0.68 to -0.21	$p<0.01$	$X^2 = 95.22$, df = 17 ($p<0.00001$), Z = 3.77, $I^2 = 82\%$	$X^2 = 91.02$,df = 2 (P<0.00001), Z = 3.78, $I^2 = 97.8\%$
Resistance	1	-2.49	-2.91 to -2.06	$p<0.01$	-	
Mixed	3	-0.17	-0.40 to 0.06	$P = 0.15$	$X^2 = 0.94$, df = 3 (P = 0.81), Z = 1.43, $I^2 = 87\%$	
Duration (2 sub-group analyses)						
<12 weeks	8	-0.32	-0.54 to 0.10	$P = 0.004$	$X^2 = 424.31$, df = 9 (P = 0.01), Z = 2.90, $I^2 = 52\%$	$X^2 = 3.55$, df = 1 (P = 0.06), Z = 3.04, $I^2 = 71.8\%$
≥12 weeks	6	-0.97	-1.61 to 0.33	$P = 0.003$	$X^2 = 28.97$, df = 14 (P = 0.003), Z = 2.97, $I^2 = 98\%$	
Time (2 sub-group analyses)						
<60min	9	-0.59	-0.98 to -0.20	$P = 0.003$	$X^2 = 141.4$, df=16 ($p<0.00001$),Z=3.00, $I^2 = 89\%$	$X^2 = 0.05$,df=1(P=0.83), Z=3.20, $I^2 = 0\%$
≥60min	3	-0.70	-1.56 to 0.16	$P = 0.11$	$X^2 = 294.69$, df = 4 ($p<0.00001$), Z = 1.58, $I^2 = 99\%$	
Frequency (2 sub-group analyses)						
≤3times/week	11	-0.59	-1.10 to -0.08	$P = 0.02$	$X^2 = 256.98$, df = 16 ($p<0.00001$),Z = 2.28, $I^2 = 94\%$	$X^2 = 0.00$, df = 1 (P = 0.97), Z = 3.50, $I^2 = 0\%$
>3times/week	4	-0.58	-1.02 to -0.14	$P = 0.01$	$X^2 = 168.45$, df = 8 ($p<0.00001$), Z = 2.56, $I^2 = 95\%$	

K, Number of trials; SMD, Standardized Mean Difference; CI, Confidence Interval; PE, Physical Exercise; NT, No-Treatment; AP, Attention/Activity Placebo; WL, Wait-List.

in the included studies was performed visually through an analysis of the funnel plot (Figure 3, Supplementary Figure 1). The funnel plot analysis reveals notable asymmetry, indicating potential publication bias. This asymmetry suggests that smaller studies with non-significant results may be underrepresented, consequently inflating the true effect size in our meta-analysis. Beyond publication bias, discrepancies in study design, including variations in sample size, methodology, and population characteristics, may also contribute to the observed asymmetry. Smaller studies often exhibit more variable effect sizes, further compounding the asymmetry.

3.4 Meta-analysis results

In evaluating the effects of PE on negative emotions in adolescents, fifteen studies utilized negative emotions, such as depression or anxiety, as outcome measures. Initially, these studies were tested for heterogeneity, revealing substantial differences among them ($I^2 = 95\% > 50\%$, $p < 0.01$). A high degree of heterogeneity ($I^2 = 95\%$) in a meta-analysis indicates substantial variability across studies, likely due to differences in study populations, methodologies, contexts, or statistical issues. This variability can arise from factors like demographic differences, variations in interventions, study settings, and potential biases in publication. The implications are significant, as it suggests that the pooled results may not accurately reflect the true effect, limiting the generalizability of the findings. Therefore, we used a random-effects model and a way to minimize heterogeneity by dividing the subgroups. The meta-analysis, depicted in Supplementary Figure 2, demonstrated a significant improvement in negative affect in the PE intervention group compared to the control group (SMD = -0.59, 95% CI: -0.92 to -0.26, $p < 0.01$, Z = 3.50, $I^2 = 95\%$). This indicates a notable reduction in negative emotions among adolescents who engaged in PE.

3.5 Sensitivity analysis

Sensitivity analyses were conducted to further explore the sources of heterogeneity. The process involved systematically excluding individual studies from the analysis one at a time to assess their impact on the overall results. Factors such as study design, sample size, and quality scores were considered in these analyses to determine their potential influence on heterogeneity.

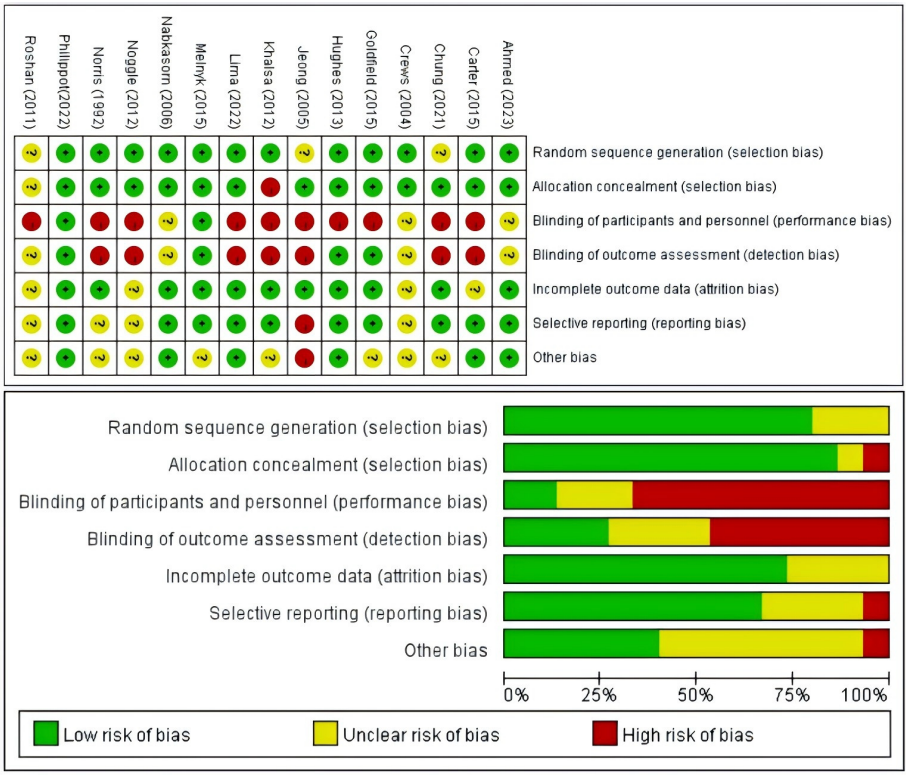

FIGURE 2
Results of the Cochrane risk of bias tool.

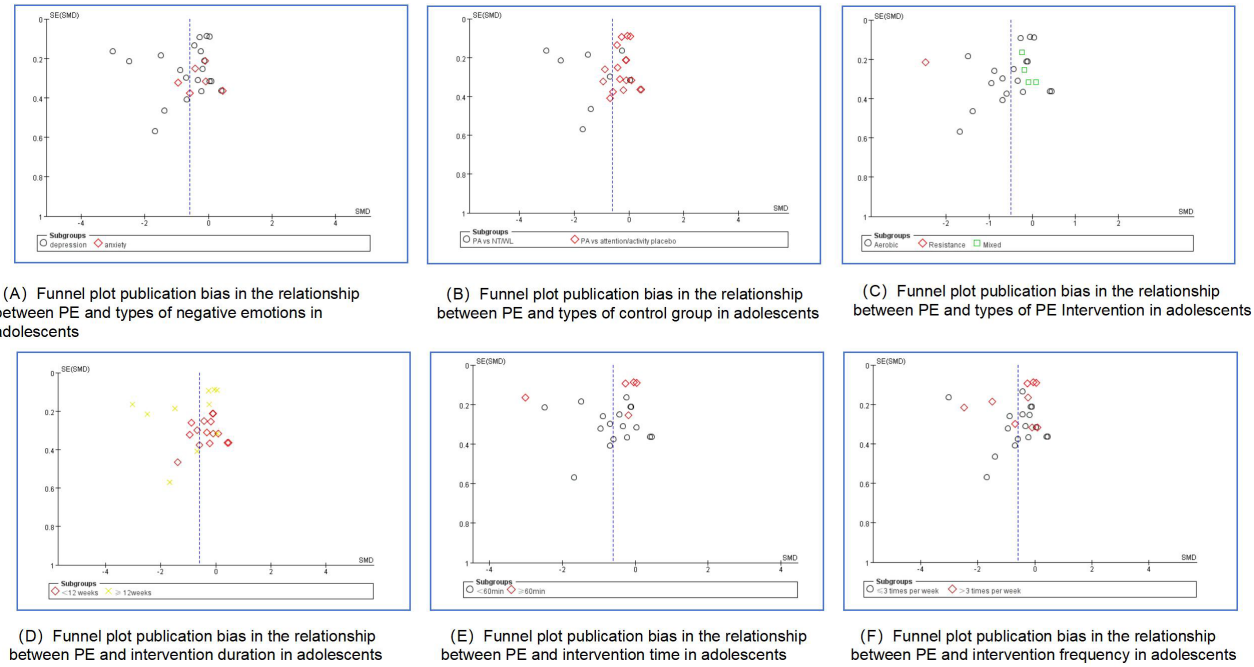

FIGURE 3
Funnel plot publication bias in the relationship between PE and negative emotions in adolescents (Subgroup analysis).

The results obtained after each exclusion were consistent with the initial analyses, indicating that no single study significantly affected the composite results. This consistency suggests that the composite effect size in this study is stable and robust.

3.6 Subgroup analysis

To explore potential modifications of PE effects on negative emotions, a subgroup analysis (Table 3) was conducted to assess the influence of specific factors. We divided the subgroups according to the Physical Activity Guidelines for Americans (54), a document that requires that the majority of the 60 minutes or more per day for children and adolescents should be moderate-intensity or vigorous-intensity aerobic exercise and should include vigorous-intensity physical activity at least 3 days per week. Therefore, the objectives of the subgroup analysis in this study were to determine the type of negative emotions (depression, anxiety), type of control group (WL/NT, AP), intervention type (aerobic, resistance, mixed), exercise intervention duration (<12 weeks, ≥12 weeks), intervention time (<60min, ≥60min), intervention frequency (≤3 times/week, >3 times/week).

3.6.1 Types of negative emotions

A total of 15 studies were included (Figure 4). 15 studies (39–53) provided data on the effect of PE intervention on adolescent depression; 4 studies (41, 44, 48–50) provided data on the effect of PE intervention on adolescent anxiety. A random-effects model was employed for the meta-analysis, revealing that the PE intervention had a pronounced impact on adolescent depression (SMD = -0.67, 95% CI = -1.07 to -0.28, $p < 0.01$, $I^2 = 96\%$), whereas its effect on adolescent anxiety (SMD = -0.29, 95% CI = -0.63 to 0.02, $p = 0.05$, $I^2 = 52\%$) was not statistically significant.

3.6.2 Types of control groups

A total of 14 studies were included (Figure 5). Six studies (39, 42, 46, 47, 52, 53) provided data on the type of control group that was the NT or WL group, and eight studies (41, 43–45, 48–51) provided data on the type of control group that was the placebo group. The results showed that PE improved negative emotions significantly in both the NT/WL (SMD = -1.37, 95% CI = -2.25 ~ -0.50, $p<0.01$, $I^2 = 96\%$) group and the AP group (SMD = -0.23, 95% CI = -0.38 ~ -0.08, $p<0.01$, $I^2 = 56\%$).

3.6.3 Types of PE Intervention

A total of fourteen studies were included (Figure 6). Ten studies (41–49, 53) provided data for aerobic exercise; one study (42) provided data for resistance exercise; and three studies (40, 42, 50) provided data for mixed exercise. Subgroup analyses showed that aerobic exercise (SMD = -0.45, 95% CI = -0.68 ~ -0.21, $p < 0.01$, $I^2 = 82\%$) and resistance exercise ($p < 0.01$) significantly improved negative mood. However,

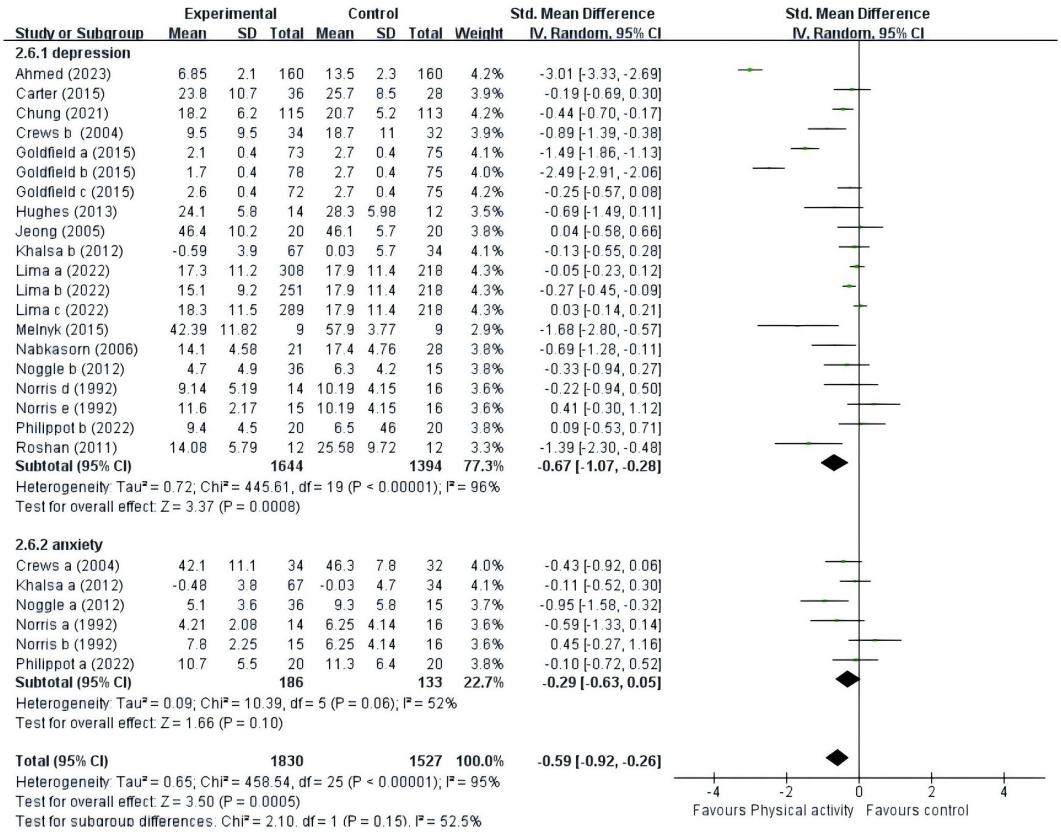

FIGURE 4
Forest plot of a meta-analysis of the relationship between PE and negative emotions after the intervention.

mixed exercise (SMD = -0.17, 95% CI = -0.40 ~ -0.06, p = 0.15, I^2 = 0%) was not significantly associated with negative mood in adolescents. Only one article on resistance exercise intervention was included, so the results should be interpreted with caution. Therefore, aerobic exercise had a significant effect on the improvement of negative mood in adolescents.

3.6.4 PE intervention duration

A total of fourteen studies were included (Figure 7). Eight studies (40, 41, 44, 47–50, 53) provided data for intervention duration of less than 12 weeks; six studies (39, 42, 43, 45, 46, 52) provided data for intervention duration of at least 12 weeks. The results showed that PE interventions of less than 12 weeks (SMD = -0.32, 95% CI = -0.54 ~ -0.10, p = 0.004, I^2 = 52%) or at least 12 weeks (SMD = -0.97, 95% CI = -1.61~-0.33, p = 0.003, I^2 = 98%) had a significant effect on adolescents' negative emotions. Overall, PE interventions lasting at least 12 weeks were significantly more effective in adolescents (p = 0.003) compared to those conducted for less than 12 weeks (p = 0.004).

3.6.5 PE intervention time

Twelve studies were encompassed in the analysis (Figure 8). Nine studies (41–44, 46–49, 52) provided data for intervention time less than 60 minutes; and three studies (39, 40, 45) provided data for intervention time greater than or equal to 60 minutes. The results showed that when the time was less than 60 minutes (SMD = -0.59, 95% CI = -0.98 ~ -0.20, p<0.01, I^2 = 89%), the PE intervention had a significant effect on the negative emotions of adolescents. When time was at least 60 minutes (SMD = -0.70, 95% CI = -1.56 ~ 0.16, p = 0.11, I^2 = 99%), PE intervention had no significant effect on adolescents' negative emotions. Therefore, the PE of adolescents can be controlled in under 60 minutes.

3.6.6 PE intervention frequency

A total of fifteen studies were included (Figure 9). Eleven studies (39–41, 43, 44, 46, 48, 49, 51–53) provided data at a frequency of three or fewer times per week; and four studies (42, 45, 47, 50) provided data at a frequency of more than three times per week. The results showed that adolescents were better able to improve negative affect with both PE interventions less than three times per week (SMD = -0.59, 95% CI = -1.10 ~ -0.08, P = 0.02, I^2 = 94%) and PE interventions more than three times per week (SMD = -0.58, 95% CI = -1.02 ~ -0.14, P = 0.01, I^2 = 95%). Overall, the PE interventions conducted with adolescents more than three times per week (p = 0.01) proved to be more efficacious than those administered fewer than three times per week (p = 0.02).

4 Discussion

This study aimed to explore the impact of PE on adolescents' experiences of negative emotions. From an initial pool of 3,368

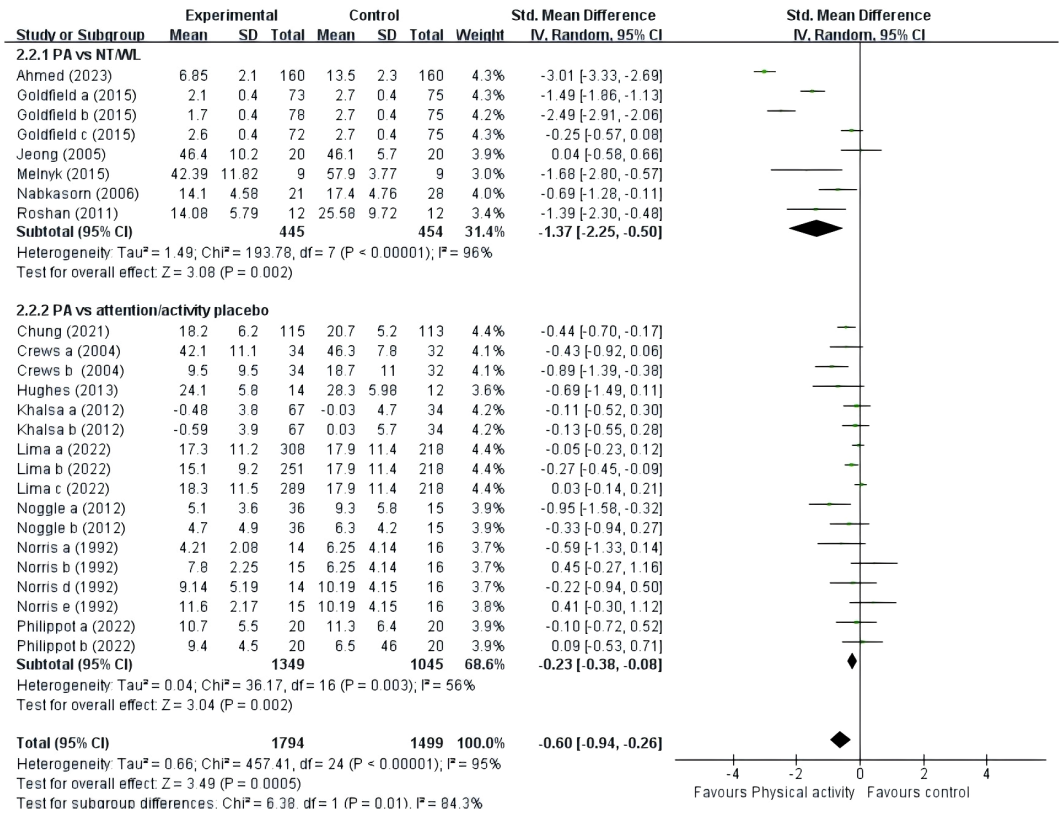

FIGURE 5
Forest plot of a meta-analysis of the relationship between PE and types of control group after the intervention.

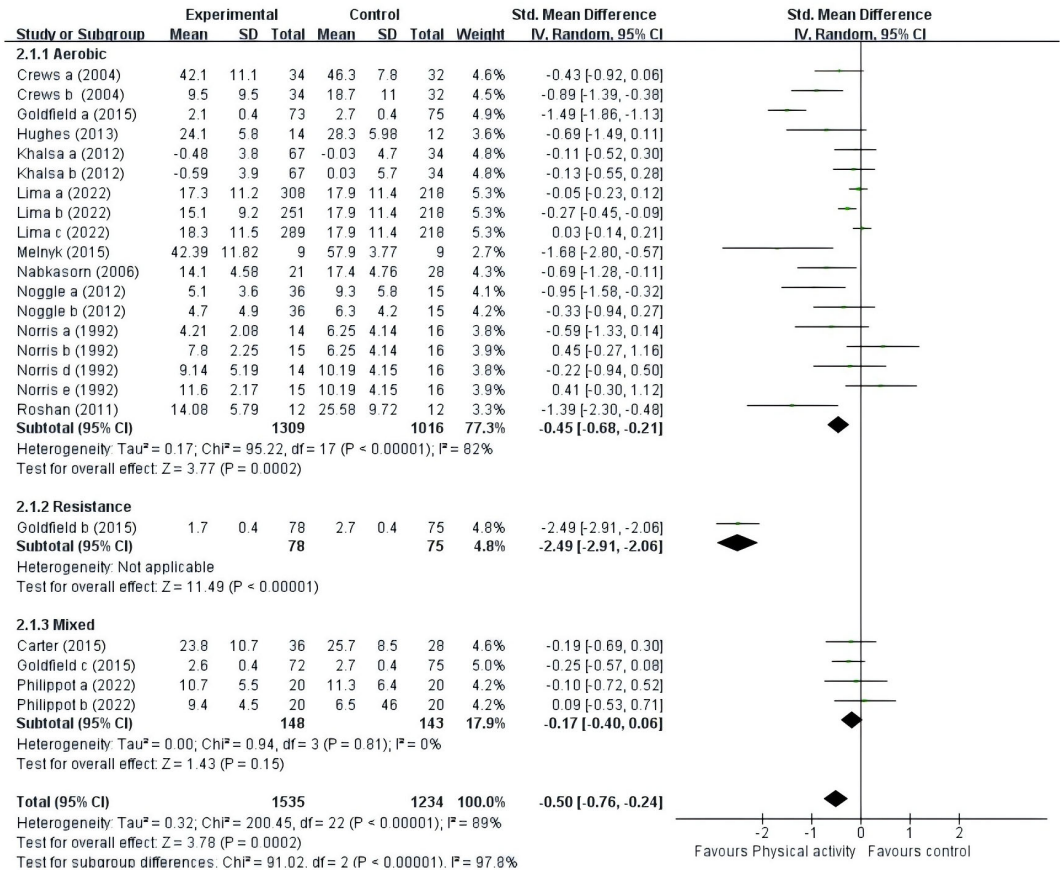

FIGURE 6
Forest plot of a meta-analysis of the relationship between type of PE intervention and negative emotions after the intervention.

search records, 15 studies were selected for inclusion in the meta-analysis. It was observed that since the included studies were randomized controlled trials focusing on PE interventions, the implementation of complete blinding was not feasible. Consequently, trials without blinding were not classified as low-quality during the literature quality assessment, as such a classification would be unjustified. The findings of this study indicate a significant reduction in adolescents' negative emotions as a result of engaging in PE. The conclusions from a 2022 review by Hale and colleagues on the correlation between exercise and mental well-being corroborate this outcome. Further subgroup analyses revealed that adolescents who participated in aerobic exercise sessions lasting at least 12 weeks, conducted more than three times per week, and with each session lasting less than 60 minutes, experienced substantial improvements in negative emotions.

4.1 The effect of PE intervention on different kinds of negative emotions in adolescents

The results of our meta-analysis indicated that participation in sports was effective in alleviating depression but not anxiety in adolescents. First, the aspect of physical activity in alleviating depressed mood in adolescents agrees with previous studies (55, 56). Participation in exercise enhances the synaptic transmission of monoamines from a physiological perspective, thereby stimulating the release of endorphins (57). These substances exert inhibitory effects on the central nervous system, effectively diminishing discomfort and elevating the brain's active state. Consequently, this process leads to a natural improvement in mood following physical exertion (58). In a comprehensive review conducted in 2001, Sallis examined 108 studies on PE and its effects on depression in children and adolescents. The review thoroughly documented the efficacy of PE in alleviating depressive symptoms in this demographic (55). A recent clinical study, notable for its integration of psychiatric and cardiological methodologies and compelling argumentation, conducted an exhaustive examination of 210 patients diagnosed with depression. The study's findings revealed a significant correlation between elevated depressive symptoms and decreased levels of PE among participants (56). Our meta-analysis further corroborated the effectiveness of PE in mitigating depressive symptoms among adolescents. However, our study did not confirm that physical activity was effective in reducing anxiety ($p = 0.10$), which is inconsistent with previous studies that have examined the ability of physical activity to reduce anxiety. A study by Tao (59) illuminates this issue, focusing on visually impaired children, revealing that continuous engagement in physical activities and the reduction of prolonged sedentary

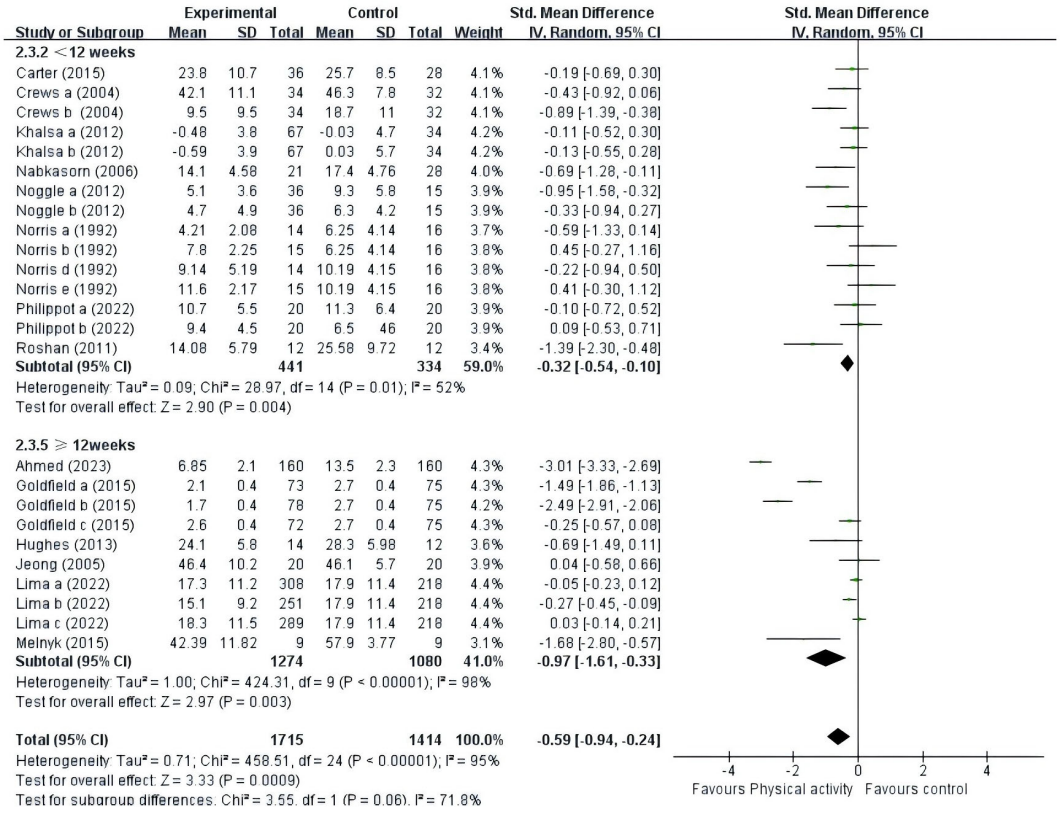

FIGURE 7
Forest plot of a meta-analysis of the relationship between PE intervention duration and negative emotions after the intervention.

behavior not only alleviated anxiety but also significantly contributed to its reduction (59). This discovery is supported by Gehricke's research, thus bolstering the evidence surrounding the beneficial impact of PE on reducing anxiety (60). This uncertainty was particularly evident in 7 of the 12 studies, which accounted for approximately 58.3% of the research in this area (61). From our analysis, the PE intervention did not reduce anxiety, which is more consistent with some studies. Related studies also lacked sufficient evidence that PE reduces anxiety (40, 44, 49, 50). There are several possible reasons for this situation: Critical factors encompass sample size and diversity, which significantly influence the generalizability of findings. The intervention's intensity, duration, and consistency are paramount, as low-intensity or short-duration exercises may fail to yield meaningful changes while inconsistent adherence can further attenuate the effects. The precision, reliability, and timing of measurement tools are also essential, as inadequately selected instruments or poorly timed assessments may overlook the intervention's true impact. Psychological elements, such as baseline anxiety levels and placebo effects, may additionally sway outcomes. Furthermore, statistical and external considerations, including the choice of control groups and environmental variables, add layers of complexity to the interpretation. Future research should incorporate larger, more heterogeneous samples and interventions that are meticulously tailored to the specific characteristics of the target population.

4.2 The effect of types of control groups on adolescents' negative emotions

This study investigated whether the type of control group affects the impact of physical exercise (PE) on adolescents' negative emotions. Our meta-analysis showed that physical activity resulted in a slight reduction in negative emotions compared to the AP group (SMD = -0.23). Physical activity significantly reduced negative affect compared to the NT/WL group. The smaller improvement in the placebo group suggests that the placebo itself can provide some psychological benefit, but not as much as the actual physical activity. This highlights the importance of considering the placebo effect in psychological and physical interventions. A narrative review indicates that the mental health benefits of acute exercise may be due to placebo effects, as the acute psychological outcomes of exercise are not shown to be mediated by stimulus characteristics such as exercise duration or intensity (62). Philippot's (50) longitudinal HADS-A scores showed a reduction in anxiety symptoms over time in both groups. Thus, we can infer that participants benefited from the anxiolytic effects of the general psychiatric environment but did not derive added value from physical activity or did not have a sufficient effect size to reach significance, perhaps because of the placebo group (50). However, further research is necessary to substantiate this finding due to the observational nature of the analysis, the limited number of trials, and their low quality.

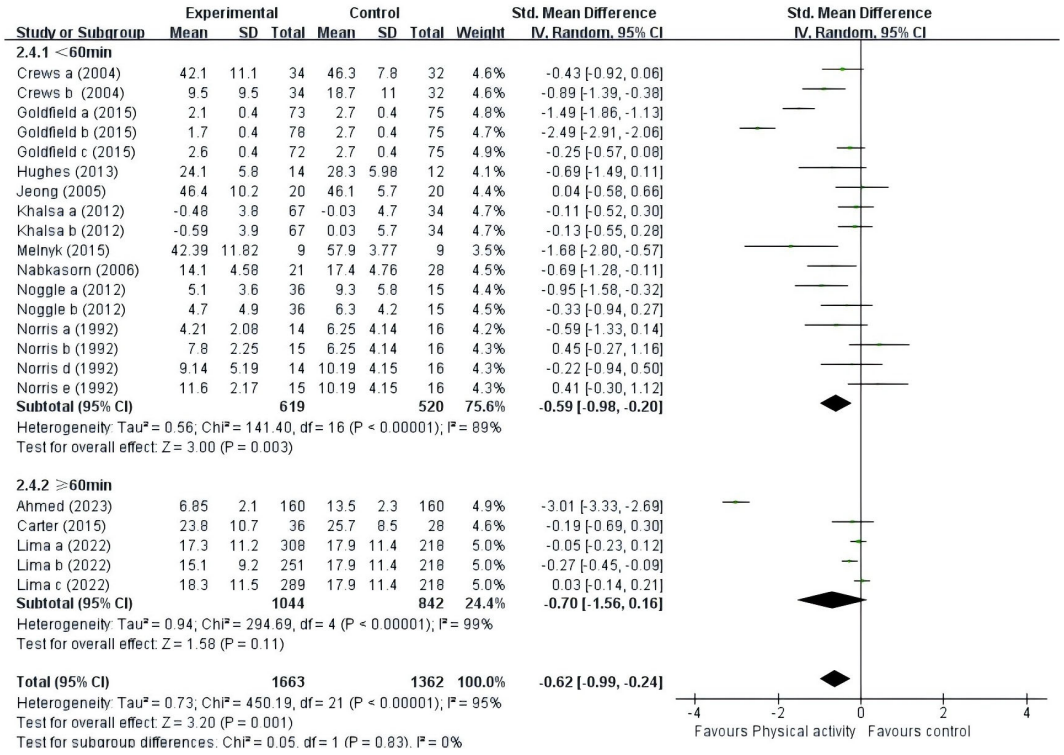

FIGURE 8
Forest plot of a meta-analysis of the relationship between PE intervention time and negative emotions after the intervention.

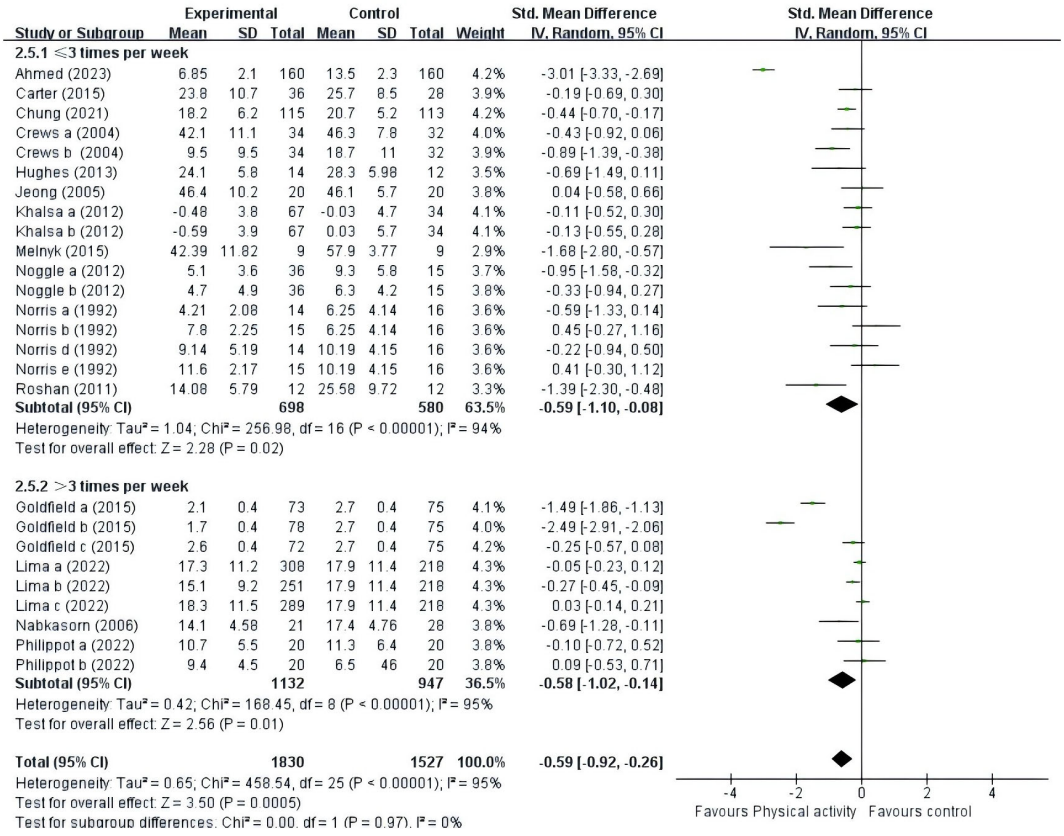

FIGURE 9
Forest plot of a meta-analysis of the relationship between PE intervention frequency and negative emotions after the intervention.

4.3 The effect of types of intervention on adolescents' negative emotions

The study examined whether the type of intervention affected the impact of PE on adolescents' negative emotions. Aerobic exercise emerged as the main focus in studies utilizing PE to alleviate adolescents' negative emotions, highlighting the widespread adoption of aerobic exercise as a preferred intervention method, consistent with previous research (54, 63, 64). Involving the voluntary movement of skeletal muscles, aerobic exercise surpasses basal metabolic rates. This form of exercise is intricately linked with various facets of well-being, encompassing physical health, mental well-being, and overall life satisfaction (63). The elevation in heart rate and oxygen consumption induced by aerobic exercise triggers the release of endorphins and various other neurotransmitters renowned for their mood-enhancing properties. In the domain of mental health and exercise physiology, the hypothesis regarding the role of endorphins enjoys substantial support. Many researchers commonly believe that endorphins play a crucial role in conserving energy during physical exertion, potentially resulting in psychological benefits such as improved mood and reduced anxiety levels (65). Direct evidence also suggests that PE has the capacity to elevate plasma endorphin levels (66). In a comprehensive review conducted in 2021, Song found that university students experienced substantial alleviation from symptoms of depression through the efficacy of both aerobic exercise and traditional Chinese exercises (64). Only one study in our meta-analysis explored the impact of resistance exercise on negative emotions in adolescents (42). This emphasizes the importance of embracing all forms of PE to optimize well-being and emotional health in this demographic. Furthermore, despite the potential for comprehensive exercise to provide a range of physical benefits, such as increased strength, flexibility, and coordination, its effect on negative emotions may not consistently demonstrate significance (40, 42, 50). These findings underscore the critical role of tailoring interventions to align with individual preferences and needs, taking into account factors such as adherence and enjoyment, which are known to influence the effectiveness of PE interventions in enhancing mental well-being and alleviating negative emotions. Additionally, the limited inclusion of only three studies may have contributed to the perception that the observed effect lacks significance.

4.4 The effect of PE intervention duration on adolescents' negative emotions

We assessed whether the duration of the intervention influenced the impact of PE on adolescents' negative emotions. For this study, we categorized the included studies into two subgroups based on intervention duration: fewer than 12 weeks and at least 12 weeks. Our subgroup analysis revealed that PE interventions lasting fewer than 12 weeks or at least 12 weeks significantly affected adolescents' negative emotions. Overall, interventions that lasted at least 12 weeks were more effective than those that lasted less than 12 weeks, which is consistent with previous studies (67–69). PE of a sustained and appropriate duration has the potential to induce significant changes in both the structure and function of the brain. These changes, in turn, have been associated with improvements in states of negative emotion. This improvement is attributed to heightened concentrations of dopamine, serotonin, and norepinephrine in the brain, known to positively influence mood regulation (30). However, long-term PE interventions may also lead to negative emotions not achieving that tan, possibly due to natural degradation processes, physical exhaustion, environmental monotony, or a combination of these factors (70, 71). Given the limited number of studies included, effect size statistics may be influenced, necessitating future large-scale studies to confirm the efficacy of PE intervention duration.

4.5 The effect of PE intervention time on adolescents' negative emotions

In our meta-analysis, we examined the influence of intervention duration on the correlation between PE and adolescent negative emotions. The studies included were divided into two categories based on duration: those lasting less than 60 minutes and those lasting 60 minutes or more. Our subgroup analyses indicated that PE interventions lasting less than 60 minutes significantly enhanced adolescents' negative emotions, whereas interventions lasting 60 minutes or more did not significantly affect these emotions, consistent with previous findings (54, 72, 73). Numerous studies have indicated that individuals with depression can alleviate negative emotions by engaging in aerobic exercises lasting 20 to 40 minutes (74). A separate retrospective analysis was conducted using data from a longitudinal study spanning a decade. This analysis revealed a significant correlation between regular PE, even for durations as short as 15 minutes, and reduced susceptibility to depression (73). The findings of this study align with the prevailing recommendations outlined in both the general health promotion guidelines of the Canadian government and those of the American Academy of Pediatrics. These guidelines emphasize the importance of engaging in at least 60 minutes of moderate-to-vigorous PE daily for children and adolescents to effectively maintain their physical and mental well-being. This highlights the critical role of consistent PE in promoting overall health and underscores the importance of adhering to such guidelines for optimal health outcomes in young individuals (75). However, based on the findings of this study, prolonged engagement may potentially lead to physical exhaustion, mental fatigue, or ennui among adolescents. Consequently, this could diminish the immediate mood-elevating effects commonly associated with PE and increase the likelihood of experiencing negative emotions. Extended periods of PE can stimulate androgen production akin to that observed with anabolic steroids, potentially resulting in a significant rise in irritability and aggression (76). Introducing novelty and variety into brief workout routines has been demonstrated to heighten enjoyment and intrinsic motivation. This enhancement of positive mood and emotion is reinforced by the diverse nature of these exercises, thereby aiding in the alleviation of negative emotions and contributing to overall emotional well-being.

4.6 The effect of PE intervention frequency on adolescents' negative emotions

The study aimed to evaluate how intervention frequency affects the relationship between PE and negative emotions in adolescents. This meta-analysis categorized the studies into two groups based on intervention frequency: less than three times per week and three times per week or more. The subgroup analysis revealed that adolescents experienced enhanced improvement in negative affect with both less frequent (less than 3 times per week) and more frequent (3 times per week or more) PE interventions. Overall, PE interventions more than three times per week were more effective than interventions less than three times per week, which is consistent with previous research (54, 73, 77). Current clinical recommendations propose that to alleviate negative emotions in children, engaging in exercise sessions lasting at least 45 minutes on a minimum of three days per week is advisable. These guidelines highlight the importance of exercise frequency in alleviating negative emotions among children (77). Adolescents should engage in PE sessions at least three times weekly, as recommended by current clinical guidelines. This structured regimen facilitates the establishment of consistent exercise habits among adolescents. Regular participation in PE over time promotes positive physical and mental adaptations, contributing significantly to overall well-being and long-term adherence to exercise routines. Integrating PE into their weekly schedule can lead to sustained improvements in mood and emotional well-being. Moreover, maintaining a high frequency of PE sessions helps sustain the mood-enhancing benefits of exercise throughout the week. By spacing out their PE sessions and consistently exposing themselves to the positive physical effects of PE, adolescents can experience more enduring improvements in mood, fostering emotional stability and long-term well-being. Therefore, increasing the frequency of PE sessions to three or more times weekly represents a potentially effective strategy to enhance mental health and emotional well-being in adolescents. Further research should explore optimizing PE interventions tailored to the specific needs and preferences of adolescents.

4.7 Proposed clinical interventions based on meta-analysis findings

To translate the findings of the meta-analysis into effective clinical practices for mitigating negative emotions in adolescents, several intervention strategies can be proposed, each meticulously tailored to address the unique needs of this population. Among the most impactful approaches is the introduction of structured physical activity programs, which could be implemented in schools or community centers specifically targeting adolescents who grapple with negative emotions. Ideally, these programs should be conducted three to five times per week, with sessions lasting between 30 and 60 minutes at a moderate to vigorous intensity, contingent upon the individual's fitness level and psychological state. The potential benefits of such programs are considerable, including the alleviation of symptoms associated with depression, anxiety, and stress, as well as enhancements in overall mood through the release of endorphins and the promotion of neuroplasticity. Moreover, group activities within these programs can provide essential social support, which is particularly advantageous for adolescents navigating negative emotions. However, challenges such as maintaining consistent participation, ensuring accessibility to facilities, and the necessity of individualized programming to accommodate varying fitness levels and emotional states must be carefully managed to optimize the success of these interventions.

Incorporating physical activity into existing therapeutic practices, such as cognitive-behavioral therapy (CBT), represents another promising intervention. This approach could involve the integration of brief exercise breaks—five to ten minutes of aerobic exercises—within therapy sessions or prescribing personalized exercise routines as part of therapy homework. The inclusion of physical activity in this context may enhance the overall efficacy of psychological treatments, empowering adolescents by equipping them with coping skills through movement. Nevertheless, this approach does pose challenges, including the need for additional training for therapists to integrate exercise effectively, as well as potential resistance from adolescents who may have low motivation or negative associations with physical activity.

Lastly, the development of school-based wellness programs that amalgamate physical education, mental health education, and mindfulness practices presents a holistic approach to addressing negative emotions in adolescents. These programs should incorporate curricula that educate students on the psychological benefits of exercise and stress management techniques, alongside peer support groups that encourage participation in physical activities and offer emotional support. The key advantages of this approach include the promotion of both physical and mental well-being and the cultivation of a culture that recognizes the interconnectedness of emotional health and physical activity. Nevertheless, the successful implementation of such programs necessitates coordination among educators, school counselors, and physical education instructors, and they must be designed to be sustainable and adaptable to the evolving needs of students.

In conclusion, the application of these meta-analysis findings offers a promising avenue for supporting adolescents with negative emotions through physical activity-based interventions. Whether through structured programs, integration into therapy, or comprehensive school-based initiatives, these strategies can be tailored to individual and group needs, though challenges such as adherence, accessibility, and the need for specialized training must be addressed. Future research should focus on further refining these interventions, identifying the most effective types and intensities of physical activity for different adolescent subgroups, and exploring innovative solutions to overcome the practical challenges in clinical applications.

5 Limitations of the review

Firstly, the limited sample size and the attrition of some participants during follow-up may not accurately represent all

groups, resulting in biased outcomes. Consequently, future research should increase the sample size to enhance the robustness of subgroup analyses. Secondly, regarding data analysis, some subgroup analyses failed to yield reliable conclusions or were not conducted (e.g., intervention intensity) due to constraints in the number and characteristics of included studies. This resulted in significant heterogeneity among subgroups, obscuring crucial implications and limiting the generalizability of the findings. Thirdly, negative affect extends beyond depression and anxiety to encompass emotions such as stress, distress, sadness, and anger. The focus of this meta-analysis on depression and anxiety underscores the necessity for future research to investigate and address other forms of negative emotions. Finally, some results rely heavily on participants' self-reported data. Self-reported behaviors may be subject to individual cognitive and memory biases, potentially affecting the accuracy of results and introducing reporting bias. Subsequent research efforts should explore the use of more objective measurement tools to minimize such biases.

6 Conclusion

The purpose of this study was to review the current literature on the relationship between negative emotions and physical activity in adolescents. The group engaged in physical activity exhibited significant improvement in ameliorating negative mood compared to the control group. Subgroup findings indicate that engaging in aerobic exercise for a minimum of 12 weeks, exceeding thrice weekly, with sessions not exceeding 60 minutes, proves highly efficacious. However, several limitations remain, such as smaller sample sizes, publication bias, the presence of heterogeneity in subgroup analyses, and the lack of objective measurements in measurement tools. Moreover, many of the studies in the meta-analysis were difficult to interpret because the study protocols were not standardized, especially not including the range of competence of the cohort, the duration of the study, the recommended exercise, and the monitoring of the control group. In addition, the variability of the results has to be considered, and the results of this study should be interpreted with caution. Considering the ability of physical activity to alleviate negative emotions among adolescents, there is a need to further explore the effects of physical interventions on alleviating adolescents' negative emotions. Follow-up studies should thoroughly examine differences in such interventions in terms of gender, age group, and exercise intensity. In addition, it would be desirable to incorporate local control variables into physical activity programs and to juxtapose the results with international studies to assess the impact of physical activity interventions on adolescents' negative affect in different cultural contexts.

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

TW: Writing – original draft. WL: Writing – original draft. JD: Writing – original draft. QZ: Writing – original draft. YL: Writing – review & editing.

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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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The prevalence and clinical correlation factors of cognitive impairment in patients with major depressive disorder hospitalized during the acute phase

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Objective: This study aimed to investigate the prevalence of cognitive impairment among patients with major depressive disorder (MDD) hospitalized during the acute phase and to analyze the in-depth association between this cognitive impairment and clinical correlation factors.

Methods: In this cross-sectional study, we recruited 126 patients aged between 18 and 65 years who were diagnosed with MDD. All these patients were inpatients from the Department of Psychiatry at the Second People's Hospital of Hunan Province. We employed a series of assessment tools, including the Pittsburgh Sleep Quality Index (PSQI), the 16-item Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS-16), the Pre-sleep Arousal Scale (PSAS), the Morningness-Eveningness Questionnaire (MEQ), the Hamilton Anxiety Rating Scale (HAMA), and the 17-item Hamilton Depression Rating Scale (HAMD-17). The patients were divided into a cognitive impairment group and a non-cognitive impairment group based on their scores on the Montreal Cognitive Assessment Scale (MoCA). Through Spearman's correlation analysis, we explored the correlation between the total MoCA score and the score of each factor. Additionally, we utilized binary logistic regression analysis to investigate the relationship between cognitive impairment and clinically relevant factors in MDD patients hospitalized during the acute phase and plotted ROC curves to evaluate their clinical efficacy.

Results: In this study, we found that the prevalence of cognitive impairment among MDD patients hospitalized during the acute phase was as high as 63.49%. Through statistical analysis, we observed significant differences between the cognitive impairment group and the non-cognitive impairment group in terms of age, place of residence, education level, and HAMD-17 scores. In the Spearman correlation analysis, we noted the following trends: visuospatial and executive abilities were negatively correlated with the HAMD-17 score ($P < 0.05$); naming ability was positively correlated with the PSAS score but negatively correlated with the MEQ score ($P < 0.05$); memory was also negatively correlated with the MEQ score ($P < 0.05$); attention was negatively correlated with the HAMA score; and abstract cognitive ability was negatively correlated with the MEQ score ($P <$

0.05). Through binary logistic regression analysis, we further revealed the relationship between cognitive impairment and factors such as living in a rural area (OR = 2.7, 95% CI = 1.083-6.731, $P < 0.05$), increased age (OR = 1.049, 95% CI = 1.013-1.087, $P < 0.01$), and the HAMD-17 score (OR = 1.10295, 95% CI = 1.031-11.79, $P < 0.01$). Additionally, ROC curve analysis demonstrated a significant correlation between the HAMD-17 score and the prediction of cognitive function in MDD patients hospitalized during the acute phase ($P < 0.001$). Specifically, the AUC for the HAMD-17 score was 0.73, with an optimal cut-off value of 19.5, sensitivity of 70.0%, and specificity of 63.0%. Furthermore, the AUC for age was 0.71, with an optimal cut-off value of 33.5, sensitivity of 59.0%, and specificity of 80.0%.

Conclusions: This study indicates that MDD patients hospitalized during the acute phase have a higher prevalence of cognitive impairment. This phenomenon reflects a significant correlation between clinical factors such as age, sleep-related characteristics, and the severity of depression with cognitive impairment. Therefore, regular assessment of cognitive function in MDD patients and early intervention may be crucial for the treatment and prognosis of the disease.

KEYWORDS

cognitive impairment, major depression disorder, acute phase, clinical correlation factors, hospitalized patients

1 Introduction

Major depressive disorder (MDD) is a psychiatric disease characterized by persistent depressive symptoms. Its clinical manifestations also include reduced interest, anhedonia, decreased appetite and libido, disinterest in sexual function, and cognitive impairment (1). In extremely severe cases, patients may develop suicidal thoughts or even engage in suicidal behavior, thereby constituting a serious mental disorder. A systematic review indicated that the global annual cumulative incidence of MDD and depressive symptoms ranged from 3.9% to 4.5% (2) In China, the overall prevalence of MDD among the elderly population aged 60 and above was 24.3%, while in the younger population, this proportion was slightly higher, reaching 28.4% (3, 4). This indicates a trend of earlier onset of MDD, which may impose significant economic pressure on families and society.

In addition to affective symptoms, patients with MDD often experience cognitive decline, manifested as impaired attention, memory, and executive function (5). MDD is not only a mental illness but also a significant risk factor for cognitive decline and dementia, with potentially long-lasting effects on patients. For example, a longitudinal study involving 22,789 participants with a 15-year follow-up showed that baseline depressive symptoms significantly elevated the incidence of dementia and cognitive impairment across the entire sample, especially in the younger population (6). Moreover, another long-term follow-up study found that the frequency of MDD episodes was positively correlated with the risk of dementia. A single depressive episode can increase the risk of dementia by 87%-92%, while two or more episodes almost double the risk (7). These findings have significantly heightened awareness of the profound impact MDD can have on cognitive function.

The incidence of cognitive impairment varies across different stages of MDD. In the prodromal and acute phases, the incidence of cognitive impairment is as high as 76.9% to 94.0%. During the remission period, the proportion decreases from 32.4% to 44.0% (8). Although fluctuations in depressive symptoms are closely related to cognitive function, studies have shown that improvements in cognitive function in patients with depression do not completely align with the relief of affective symptoms. Even with significant or partial relief of affective symptoms, the incidence of cognitive impairment can still reach as high as 44.0%. On the one hand, cognitive impairment during the acute phase may indicate the potential for long-term cognitive issues, making patients more likely to experience recurrent episodes of depression in the future. On the other hand, the suicide risk associated with MDD is significantly higher than that of other mental disorders. According to a review, MDD is a significant risk factor for suicide (9). Previous research has indicated that suicidal thoughts or behaviors in MDD patients may be related to cognitive impairment during the acute phase, and diminished cognitive function may further increase the risk of suicide (10). Among adolescents with MDD, cognitive impairment is particularly pronounced, especially in areas such as inhibitory control, verbal

fluency, switching ability, attention, and memory. These cognitive impairments contribute to adolescent impulsivity, poor classroom performance, low self-esteem, poor academic and social adjustment, and even an increased risk of suicidal behavior (11).

Early and effective identification and alleviation of cognitive impairment in patients with MDD are crucial for maximizing clinical recovery rates and significantly reducing the risk of suicide throughout the entire treatment process. Currently, although numerous studies have confirmed that some patients with acute MDD may experience varying degrees of decline in language, attention, working memory, verbal memory, processing speed, and executive function, there is still a lack of effective intervention methods in clinical practice (12). A meta-analysis suggested that most antidepressant drugs primarily target the affective symptoms of MDD, such as sadness, hopelessness, despair, and loss of interest, without demonstrating significant effects in improving cognitive functions such as attention, memory, and decision-making (13). Therefore, effectively identifying risk factors for cognitive decline during the acute phase of MDD treatment may become an important strategy for enhancing cognitive function in depressed patients.

Previous studies have demonstrated a strong correlation between depression, sleep disorders, and cognitive function (14). The primary sleep-related symptoms in patients with MDD include difficulty falling asleep, early morning awakening, frequent nighttime awakenings, and vivid dreaming (15). Polysomnography monitoring has revealed that, compared to healthy individuals, MDD patients exhibit abnormal sleep architecture, characterized by reduced slow-wave sleep (SWS), increased rapid eye movement (REM) sleep, and shortened REM sleep latency (16). The decrease in SWS may lead to the overactivation of central and peripheral immune-inflammatory factors, resulting in excessive phosphorylation of β-amyloid and tau proteins in the brain, which can exacerbate neuronal damage (17). Moreover, insufficient sleep in these patients may lead to decreased levels of brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) (18). BDNF, a protein crucial for neuronal survival, development, differentiation, and repair, plays a key role in regulating neuronal structure, plasticity, synaptic connections, and neurotransmitter transmission. Studies have shown that attention, working memory, and information processing speed in the brain are positively correlated with BDNF levels (19, 20). Another study that collected data on cerebrospinal fluid, cognitive abilities, and sleep quality from 1,168 Alzheimer's patients revealed that shorter sleep duration (< 7 hours) was significantly associated with higher levels of cerebrospinal fluid t-tau and p-tau (19). In summary, poor sleep quality and low sleep efficiency in MDD patients may be key contributors to cognitive impairment.

The circadian rhythm, commonly referred to as the biological clock, typically describes an endogenous 24-hour periodic rhythm that is prevalent in various biological processes (21). In the human body, this rhythm significantly influences sleep-wake cycles and metabolic processes. Research showed that compared to healthy individuals, patients with MDD experienced significant daytime functional impairments in both positive and negative emotions, with symptoms often being most severe in the early morning (22). In a circadian rhythm analysis involving 60 patients with MDD who were in remission, it was found that 35% of the patients identified as morning types, 58.3% as intermediate types, and 6.7% as evening types. These patients generally felt more fatigued in the morning and struggled to perform complex cognitive tasks (23). This suggests that disruptions to the circadian rhythm can negatively impact cognitive function. However, there is limited evidence to suggest a higher degree of excessive wakefulness and erroneous sleep-related cognitive beliefs in MDD patients. Increased bedtime activities, mental rumination, physical discomfort, and incorrect sleep cognitions may contribute to excessive wakefulness, resulting in circadian rhythm disturbances and sleep disorders, which ultimately exacerbate cognitive impairment (24).

There is currently no consensus on the cognitive function of patients with MDD, which is likely closely related to the characteristics of research objects and the inconsistency of research methods. Previous studies have compared the cognitive performance of MDD patients with different characteristics and identified several factors that may affect cognitive function, including increased levels of tumor necrosis factor, interleukin-8, and macrophage inflammatory protein (MIP)-1β in plasma, as well as an elevated body mass index (BMI). These factors may explain the deficits MDD patients experience in processing speed and working memory (25). Additionally, patients with late-onset MDD exhibited more significant deficiencies in memory, verbal fluency, and language and visuospatial abilities compared to those with early-onset MDD (26). However, there are only a few studies that have conducted in-depth evaluations of cognitive function and its associated factors during the acute phase of MDD, which provides us with further motivation for the exploration of this research area. Based on this, we planned to recruit patients with MDD with the aim of evaluating their cognitive function and examining clinically relevant characteristics such as sleep patterns and anxiety levels. The main objective of this study was to reveal the prevalence of cognitive impairment in MDD patients hospitalized during the acute phase and to analyze in detail the association between these impairments and clinically relevant factors.

2 Methods

2.1 Study design and participants

This cross-sectional investigation took place between December 2023 and June 2024. Psychiatric hospitalized patients in the Second People's Hospital in Hunan Province served as the participants.

The inclusion criteria are as follows (1): fulfills the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria for MDD; (2) being of Han nationality and aged between 18 and 65; (3) a 17-item Hamilton Depression Rating Scale (HAMD-17) score ≥17 points; (4) patients with first or recurrent depression in the acute phase who are not taking antidepressants or other treatments that affect cognitive function for nearly 2 weeks; (5) cooperating with the completion of questionnaires and psychological evaluation; and (6) signed informed consent.

The exclusion criteria are as follows: (1) having previously suffered from physical illnesses that caused cognitive impairment; (2) previously suffered from mental disorders that led to cognitive impairment; (3) unable to collaborate and communicate regularly; and (4) no signed informed consent form.

A total of 126 participants took part in the study out of the 143 patients who were initially enrolled as 17 patients were excluded for lack of data or other reasons. The questionnaire was administered by three well-trained clinical psychiatrists. The Ethics Review Committee of the Second People's Hospital of Hunan Province approved this study (No. 2023 (K) 018), and each participant signed a written informed consent form.

2.2 Sample size

The sample size was calculated as $N = z^2_{\alpha/2}\, P\frac{(1-p)}{\delta^2}$ in the study. According to the literature, the frequency of cognitive impairment in patients with MDD during the acute phase ranges from 85% to 94% (27), with $P = 0.94$. Assuming a tolerance error of 5%, we set $\alpha = 0.05$, which corresponds to $z_{\alpha/2} = 1.96$. Considering potential invalid responses at a rate of 10%, the final required sample size should be adjusted to reach at least 95 cases; thus, this study ultimately included a sample size of 126 cases.

2.3 Measurements

Three specially trained clinical psychiatrists conducted a detailed questionnaire survey with all participants to collect sociodemographic data and clinical characteristics. The data collected included information such as age, gender, height, weight, marital status, education level, comorbidities, place of residence, and bed partner. BMI was calculated by dividing body weight (in kg) by the square of height (in m). Based on the BMI values, we classified the patient into the following categories: underweight (BMI < 18.5 kg/m2), normal weight (BMI 18.5-24 kg/m2), overweight (24 ≤ BMI < 28 kg/m2), and obese (≥ 28 kg/m2) (28). After the participants completed the first part of the basic information collection, we proceeded to evaluate other clinically relevant factors.

2.3.1 The Pittsburgh Sleep Quality Index

This scale is suitable for patients with mental or sleep disorders and the general population with the goal of evaluating sleep quality (29). It consists of 19 self-rated items and 5 observer-rated items, primarily divided into seven components: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. Each section is scored from 0 to 3 points. The overall PSQI score ranges from 0 to 21 points, which is the sum of the scores for each section. A higher score indicates poorer sleep quality. The overall reliability coefficient for the Chinese version of the PSQI is 0.82 to 0.83 (30).

2.3.2 The 16-item Dysfunctional Beliefs and Attitudes about Sleep Scale

This scale aims to assess sleep-related misconceptions and beliefs, particularly self-perceived sleep misconceptions (31). It consists of 16 questions, rated on a scale from 1 to 5 points, resulting in a total score range of 16 to 80 points. The lower the score, the higher the incidence of erroneous beliefs. The total reliability coefficient for the Chinese version of the DBAS-16 is 0.765 (32).

2.3.3 The Pre-Sleep Arousal Scale

The PSAS comprises two dimensions, i.e., physical and cognitive arousal, specifically designed to assess a patient's level of wakefulness before bedtime (33). The scale consists of 16 test items, each scored on a 5-point scale ranging from 1 to 5 points. A higher score indicates an improvement in cognitive or physical arousal. The overall score ranges from 16 to 80 points. The overall reliability coefficient of the Chinese version of the PSAS is 0.91 (34).

2.3.4 The Morningness-Eveningness Questionnaire

The MEQ is primarily used to evaluate an individual's circadian rhythm type, consisting of 19 items (35). The total score ranges from 16 to 86 points. Specifically, a score below 41 indicates a tendency toward an evening type, a score above 59 indicates a tendency toward a morning type, and a score between 42 and 58 indicates an intermediate type. The overall reliability coefficient of the Chinese version of the MEQ exceeds 0.7 (36).

2.3.5 The 17-item Hamilton Depression Rating Scale

The HAMD-17 is an observer-rated scale specifically designed to measure the intensity of depressive symptoms (37). This scale primarily employs a 5-point scale, with most items scoring from 0 to 4 points. However, some items use a 3-point scale, with a scoring range of 0 to 2 points. A HAMD-17 score between 7 and 17 indicates that the patient may exhibit symptoms of depression; a score between 17 and 24 clearly indicates the presence of depressive symptoms in the patient. The higher the score, the more severe the depressive symptoms and affective disorders are. The overall reliability coefficient of the Chinese version of HAMD-17 is 0.714 (38).

2.3.6 The Hamilton Anxiety Rating Scale

The scale is designed to assess the level of anxiety symptoms in patients (39). It comprises a total of 14 questions, each rated on a 5-point scale ranging from 0 to 4 points. The overall score ranges from 0 to 54 points. A score of over 7 on the HAMA indicates the presence of anxiety symptoms; a score between 8 and 14 indicates that the patient may have mild anxiety symptoms; a score of 15 to 23 indicates the presence of moderate anxiety symptoms in the patient; and a score exceeding 24 points indicates severe anxiety symptoms. The total reliability coefficient of the Chinese version of HAMA ranges from 0.83 to 1.00 (40).

2.3.7 The Montreal Cognitive Assessment

The primary purpose of this scale is to evaluate cognitive impairment, covering seven key cognitive domains: visual construction skills, executive function, memory, language, attention-concentration, calculation, abstract thinking, and orientation (41). The range of the overall score is set from 0 to 30 points, and if the MoCA score is below 26 points, it indicates the presence of cognitive impairment. The overall reliability coefficient of the Chinese version of MoCA is 0.857 (42).

2.4 Statistical analysis

All the statistical analyses were conducted using IBM SPSS Statistics Version 25.0 software and GraphPad Prism software. Initially, the study examined the differences between the two variable groups (the group with cognitive impairment and the group without cognitive impairment). The chi-square ($\chi 2$) test was used to compare categorical variables, which were expressed in terms of counts (percentages). The study also applied the Kolmogorov–Smirnov (K–S) test to preliminarily assess the normal distribution of continuous variables. For variables that followed a normal distribution, the mean ± standard deviation was utilized to describe them, and the independent sample t-test was employed to compare the differences between the groups. For variables with a non-normal distribution, the median (interquartile range) was used for description, and the Mann–Whitney U test was used to analyze inter-group differences. Secondly, the study further utilized Spearman correlation analysis to explore the correlation between the MoCA scores and scores from other related scales. In the binary logistic regression analysis, the presence or absence of cognitive impairment was used as the dependent variable, and statistically significant related features were selected as independent variables to construct a binary logistic regression model. To evaluate the effectiveness of each factor, the study also plotted receiver operating characteristic (ROC) curves and calculated the area under the curve (AUC) to determine its diagnosis ability.

3 Results

3.1 Demographic differences between MDD patients with or without cognitive impairment hospitalized during the acute phase

According to the inclusion and exclusion criteria, a total of 126 patients were included in the study. Of these, 80 (63.49%) were diagnosed with MDD and cognitive impairment. The participants were divided into two groups: the cognitive impairment group consisted of 80 patients, including 56 men and 24 women; the group without cognitive impairment consisted of 46 patients, with 26 men and 20 women. The mean age of the cognitive impairment group was 37.5 years (22, 53.75), while the mean age of the non-cognitive impairment group was 26.5 years (19, 37.75). The age difference between the two groups was statistically significant ($P < 0.05$). Additionally, there were significant differences between the two groups in terms of education level and place of residence ($P < 0.05$). However, no significant differences were observed between the two groups in terms of sex, marital status, BMI, comorbidities, or bed partner ($P > 0.05$) (Table 1).

3.2 Clinical correlation factor differences between MDD patients with or without cognitive impairment hospitalized during the acute phase

In terms of sleep quality and sleep cognition, no significant differences were observed between the two groups. The PSQI ($P > 0.05$), PSAS ($P > 0.05$), HAMA ($P > 0.05$), and DBAS ($P > 0.05$) scores were all lower than normal values. When comparing the circadian rhythm types of the two groups, the results showed that the intermediate type was the most common, followed by the morning and evening types, but there was no significant difference between the two groups ($P > 0.05$). However, there was a statistically significant difference in the HAMD-17 scores between the two groups, with the cognitive impairment group having significantly higher HAMD-17 scores than the non-cognitive impairment group ($P < 0.05$) (Table 2).

3.3 Correlation analysis of cognitive function and other parameters in MDD patients hospitalized during the acute phase

To investigate the relationship between cognitive function and other variables, we conducted a correlation study. In this study, we employed Spearman correlation analysis on continuous numerical data. The Spearman correlation analysis revealed a significant positive correlation between the PSAS score and naming ability ($P < 0.05$). Concurrently, there was a significant negative correlation between the MEQ score and abilities in naming, memory, and abstraction ($P < 0.05$). The HAMD score showed a negative correlation with visuospatial and executive ability ($P < 0.05$). Additionally, the HAMA score was positively correlated with attention ($P < 0.05$) (Figure 1).

3.4 Correlation factors of cognitive impairment based on a binary logistic model in MDD patients hospitalized during the acute phase

After completing the correlation analysis, we further utilized a binary logistic regression model (backwards: Wald) with cognitive impairment as the outcome variable to identify different independent variables and their associations with the univariate analysis. The research results indicated that in the binary logistic regression model, a high HAMD-17 score (OR = 1.102, 95% CI =

TABLE 1 Demographics of MDD patients with or without cognitive impairment hospitalized during the acute phase.

Variable	With cognitive impairment (n=80)	Without cognitive impairment (n=46)	*t-value*	*P-value*
Age (years)	37.5 (22,53.75)	26.5 (19,37.75)	-3.193	<0.001
Sex				
Male, n (%)	56 (70)	26 (56.5)	2.335	0.127
Female, n (%)	24 (30)	20 (43.5)		
Education				
Middle school or less, n (%)	13 (16.3)	1 (2.2)	9.904	<0.05
Junior high school, n (%)	8 (10)	6 (13)		
High school, n (%)	30 (37.5)	12 (26.1)		
College or more, n (%)	29 (36.3)	27 (58.7)		
Marital status				
Unmarried, n (%)	26 (25.5)	27 (58.7)	5.429	0.066
Married, n (%)	30 (29.4)	18 (39.1)		
Divorced, n (%)	46 (45.1)	1 (2.2)		
BMI				
<18.5	12 (15)	8 (17.4)	1.095	0.798
18.5-24	43 (53.8)	27 (58.7)		
24-28	18 (22.5)	7 (15.2)		
>28	7 (8.8)	4 (8.7)		
Any other diseases				
No, n (%)	31 (38.8)	20 (56.5)	3.724	0.054
Yes, n (%)	49 (61.3)	26 (43.5)		
Rural/urban Residence				
Rural, n (%)	48 (60)	18 (39.1)	5.1	<0.05
Urban, n (%)	32 (40)	28 (60.9)		
Bed partner				
No, n (%)	21 (26.3)	24 (52.2)	8.549	0.057
Yes, n (%)	59 (73.8)	22 (47.8)		

BMI, body mass index.

1.03-11.79, $P < 0.01$), older age (OR = 1.049, 95% CI = 1.013-1.087, $P < 0.01$), and living in rural areas (OR = 2.7, 95% CI = 1.083-6.731, $P < 0.05$) were significantly associated with cognitive impairment in MDD patients (Table 3).

3.5 ROC analysis of the factors that influence cognitive impairment in MDD patients hospitalized during the acute phase

We conducted ROC analysis to evaluate the factors identified in the binary logistic regression analysis that were significantly associated with cognitive impairment in MDD patients (Table 4). The results of the ROC curve analysis revealed that age and the HAMD-17 score were significantly associated with cognitive impairment in MDD patients ($P < 0.001$). Specifically, the ROC analysis results for age revealed an AUC of 0.71, a cut-off value of 39.5, a sensitivity of 59%, and a specificity of 80%. For the HAMD-17 score, the ROC analysis showed an AUC of 0.73, a cut-off value of 19.5, a sensitivity of 70%, and a specificity of 63% (Figure 2).

4 Discussion

The aim of this study was to investigate the prevalence and clinical relevance of cognitive impairment in MDD patients hospitalized during the acute phase. The main findings of the

TABLE 2 Clinical correlation factors of MDD patients with or without cognitive impairment hospitalized during the acute phase.

Variable	With cognitive impairment (n=80)	Without cognitive impairment (n=46)	*t-value*	*P-value*
PSQI score	14 (11,17)	15 (11,17.25)	-0.419	0.675
Sleep quality	2 (2,3)	2 (1,3)	-0.108	0.914
Sleep latency	3 (2.25,3)	3 (2,3)	-0.348	0.728
Sleep time	2 (1,3)	2 (1,3)	-0.492	0.623
Sleep efficiency	3 (1,3)	3 (2,3)	-1.142	0.254
Sleep disturbances	1 (1,1)	1 (1,1)	-0.693	0.488
Sleep medications	2 (0,3)	3 (0,3)	1.103	0.270
Daytime dysfunction	3 (2,3)	3 (2,3)	0.811	0.417
PSAS score	41.36 ± 11.36	42.02 ± 12.05	-0.307	0.760
DBAS -16 score	37 (30.25,44.25)	36 (30.75,43.25)	-0.355	0.722
MEQ				
Morning type, n (%)	23 (28.7)	19 (41.3)	2.573	0.276
Intermediate type, n (%)	40 (50)	21 (45.7)		
Evening type, n (%)	17 (21.3)	6 (13)		
HAMD-17 score	22 (18,25.75)	19 (13,22.25)	-2.799	<0.01
HAMA score	20.16 ± 6.77	17.93 ± 7.25	1.733	0.086

PSQI, Pittsburgh Sleep Quality Index; PSAS, Pre-sleep Arousal Scale; DBAS-16, 16-item Dysfunctional Beliefs and Attitudes about Sleep Scale; MEQ, Morningness-Eveningness Questionnaire; HAMD-17, 17-item Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale.

study are as follows: (i) The prevalence of cognitive impairment among MDD patients hospitalized during the acute phase was 63.49%. (ii) Among MDD patients hospitalized during the acute phase, there were significant differences in age, education level, place of residence, and clinical symptoms (HAMD-17 score) between patients with cognitive impairment and those without cognitive impairment. (iii) The study also found that visuospatial and executive abilities were negatively correlated with the HAMD-

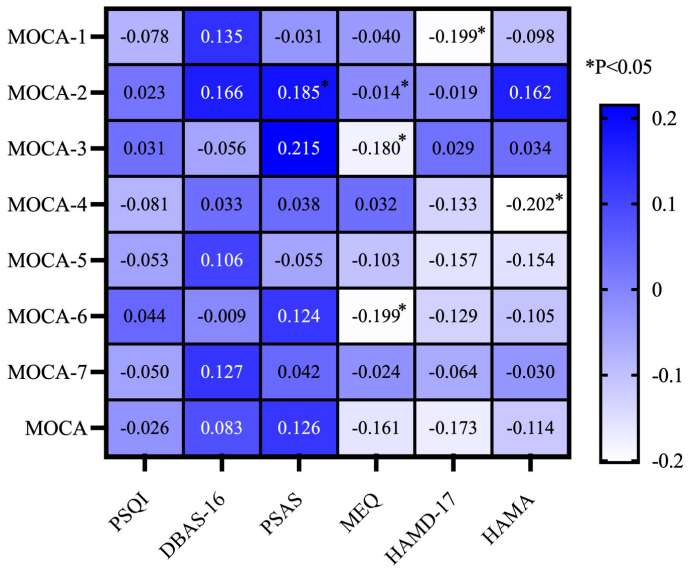

FIGURE 1
Correlation analysis of cognitive function and other parameters in MDD patients hospitalized during the acute phase. MOCA-1, Visuospatial and Executive; MOCA-2, Naming; MOCA-3, Memory; MOCA-4, Attention; MOCA-5, Language; MOCA-6, Abstraction; MOCA-7, Orientation; MoCA, Montreal Cognitive Assessment; PSQI, Pittsburgh Sleep Quality Index; HAMD-17, 17-item Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; PSAS, Pre-Sleep Arousal Scale; DBAS-16, 16-item Dysfunctional Beliefs and Attitudes about Sleep Scale; MEQ, Morningness-Eveningness Questionnaire.

TABLE 3 Correlation factors of cognitive impairment based on a binary logistic model in MDD patients hospitalized during the acute phase.

Variable	B	SE	Wald X^2	*P*	OR (95%CI)
HAMD-17 score	-0.98	0.034	8.074	<0.01	1.102 (1.031-1.179)
Education					
Middle school or less	1.234	1.187	1.080	0.299	3.434 (0.335-35.166)
Junior high school	-0.905	0.75	1.455	0.228	0.405 (0.093-1.760)
High school	0.515	0.482	1.142	0.285	0.726 (0.651-4.306)
College or more	-	-	-	-	-
Age (years)	0.048	0.018	7.140	<0.01	1.049 (1.013-1.087)
Rural/Urban Residence					
No	0.993	0.466	4.541	<0.05	2.7 (1.083-6.731)
Yes	-	-	-	-	-

HAMD-17, 17-item Hamilton Depression Rating Scale.

17 score; naming ability was positively correlated with pre-sleep arousal level; memory was negatively correlated with the MEQ score; attention was negatively correlated with the HAMA score; and abstraction was negatively correlated with the MEQ score. (iv) Further analysis showed that the HAMD-17 score, age, and place of residence were important clinically relevant factors for cognitive impairment in MDD patients hospitalized during the acute phase. (v) By plotting the ROC curve, it was found that the AUC of the HAMD-17 score was approximately 73%, while the AUC of age was approximately 71%. This study explored for the first time the correlation between sleep characteristics and cognitive function in MDD patients hospitalized during the acute phase and provided a detailed analysis of factors such as the degree of wakefulness before bedtime, sleep cognition, and circadian rhythm types. In addition, we conducted in-depth research on the accuracy of the HAMD-17 score and age in identifying cognitive impairment in MDD patients hospitalized during the acute phase.

First, we reported that the prevalence of cognitive impairment among MDD patients hospitalized during the acute phase was 63.49%. Compared to a cross-sectional study of the elderly population in China that found a prevalence of depression among the elderly to be 15.9%, with 36.4% of MDD patients suffering from mild cognitive impairment (MCI), our study identified a lower prevalence of cognitive impairment at 63.49% (43). However, most patients in our study had a history of antidepressant use and hospitalization, and the definition of MDD was stricter, which may have excluded more patients from the study. Another 3-year prospective study revealed that during the acute phase of MDD, the prevalence of cognitive impairment, energy deficiency, and sleep problems ranged from 85% to 94% (27). Although there are differences in the above research results, they all indicate that patients with depression have a higher incidence of cognitive impairment, consistent with the results of our study. The discrepancies in results may stem from the heterogeneity of the related research, which could be influenced by demographic characteristics, age, and socio-cultural features. Nevertheless, these studies largely support our findings, indicating a relatively high incidence of cognitive impairment in MDD patients hospitalized during the acute phase.

Second, this study revealed significant disparities in clinical characteristics (such as age, education level, and place of residence) between MDD patients with or without cognitive impairment who were hospitalized during the acute phase. Existing research suggests that MDD patients hospitalized for cognitive impairment during the acute phase are typically older and have lower levels of education compared to those without cognitive impairment. In addition, the majority of MDD patients with cognitive impairment who were hospitalized during the acute phase reside in rural areas. Previous studies have emphasized that age remains the most critical factor contributing to cognitive decline, while insufficient early education may increase the risk of cognitive deterioration in patients in their later years (44). A study employed magnetic resonance imaging technology to investigate variations in brain structure and cognitive function in different age groups, finding that both cross-sectional and longitudinal studies observed a significant non-linear 1% annual decrease in cerebral cortex thickness before the age of 14 and after the age of 60 (45). This trend was particularly evident in the frontal and parietal cortical regions, responsible for executive function and attention (46). However, current research exploring the influence of education level on cognitive impairment in MDD patients is limited. A study on the memory and processing speed of initial and untreated depression patients showed that education level had a more significant confounding effect compared to the severity of depression (47). Moreover, a large-scale cross-sectional study of the Chinese population revealed that the cognitive function of the elderly residing in eastern China or urban areas seemed to be better than that of the elderly living in central and western China or rural areas. This finding suggests that residential areas may also have subtle effects on cognitive function (48).

Third, the evaluation results of multiple clinically relevant scales (such as PSQI, PSAS, DBAS-16, MEQ, HAMD-17, and HAMA) indicate that among hospitalized MDD patients in the acute phase, those with cognitive impairment exhibited higher scores on the PSQI, PSAS, DBAS-16, HAMD-17, and HAMA compared to those without cognitive impairment. Additionally, according to the MEQ

TABLE 4 ROC analysis of the factors that influence cognitive impairment in MDD patients hospitalized during the acute phase.

	AUC	Cut-off	Youden index	Sensitivity	Specificity
HAMD-17 score	0.73	19.5	0.33	0.7	0.63
Age (Years)	0.71	33.5	0.392	0.59	0.80

HAMD-17, 17-item Hamilton Depression Rating Scale; AUC, Area Under the Curve

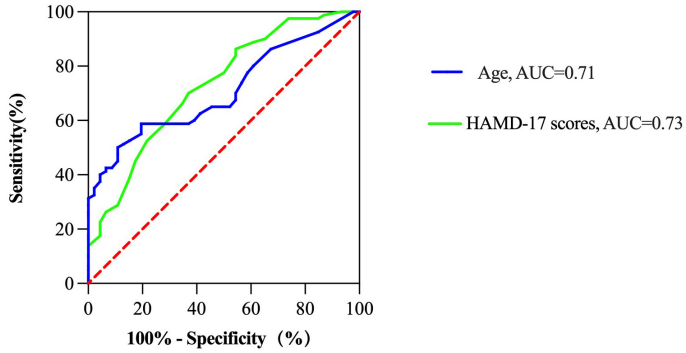

FIGURE 2
ROC analysis of the factors that influence cognitive impairment in MDD patients hospitalized during the acute phase.

results, individuals with cognitive impairment had a higher proportion of morning chronotypes, while among MDD patients with a late chronotype, the proportion with cognitive impairment was lower than that of those without cognitive impairment. We investigated the correlation between various sleep characteristics and cognitive impairment in MDD patients hospitalized during the acute phase. Using MoCA scoring, we observed significant but relatively weak correlations between certain cognitive functions and the PSAS, MEQ, HAMD-17, and HAMA scores. However, no significant correlation was observed between other scales, or the correlation was too weak to have practical significance. Previous studies have shown that sleep quality is a risk factor for depression and has an independent correlation (49). Factors such as high alertness before falling asleep, incorrect sleep cognition, and disrupted circadian rhythms can exacerbate the decline in sleep quality. For instance, a clinical study revealed that incorrect sleep cognitive concepts were more likely to lead to sleep disorders in patients with mental disorders. In this study, the authors proposed that addressing these incorrect sleep concepts was key to improving sleep problems (6). Another review showed that after adjusting for covariates such as demographics, there was still a significant correlation between sleep quality and cognitive impairment in MDD patients, but no such correlation was found in healthy participants (50). These research results show that a long-term decline in sleep quality may lead to cognitive impairment. Although this trend was not significant in our study, if it persists, it may impact patients' treatment plans and management.

Fourth, in this study, we reported three important related factors: HAMD score, age, and education level. The results indicated that all three factors might have an impact on cognitive function during acute hospitalization. This discovery was consistent with previous research findings. From a psychopathological perspective, in patients with MDD, the gray matter volume of the left amygdala, bilateral anterior cingulate cortex (PreC), and posterior cingulate cortex (PCC) increased, while the gray matter volume of the right lower parietal lobe decreased. The changes in these brain regions were closely related to cognitive control, maintenance of episodic memory, and attention, and the integration and conflict resolution of perceptual information (51). In addition, current research has not only focused on changes in a single brain region but also delved into the activation patterns of neural circuits between different regions of the brain. According to functional magnetic resonance imaging (fMRI) studies, the functional connectivity (FC) patterns between brain regions in patients with depression might have been related to cognitive function. For instance, the study by Zhang et al. found that compared to healthy individuals, patients with depression exhibited higher FC between the right dorsolateral prefrontal cortex (DLPFC) and regions such as the left inferior temporal gyrus, left cingulate cortex, and right inferior frontal gyrus (52). The frontal cortex plays a crucial role in the brain, involving language, cognition, executive function, and emotional regulation (53). Experts believe that the enhanced FC between the thalamus and DLPFC might be a cause of cognitive decline, as the thalamus plays a crucial role in cognitive processes (54). Additionally, another study found a positive correlation between the HAMD score and the resting state functional connectivity (rsFC) of the right DLPFC (55). This finding suggests a certain correlation between the severity of depression and the strength of functional connections between these critical brain regions.

Finally, the ROC curve was plotted. The AUC for age and the HAMD-17 score were approximately 71% and 73%, respectively. These results indicate that age and the severity of depressive symptoms had certain diagnostic value in evaluating whether MDD patients hospitalized during the acute phase exhibited cognitive impairment.

Our research had several limitations. First, as a cross-sectional study, we were unable to establish a causal relationship between cognitive impairment and other factors among hospitalized MDD patients during the acute phase. Second, since our sample was confined to Chinese individuals, the applicability of our findings to populations in other countries may be limited due to sociodemographic traits. Third, our sample predominantly consisted of hospitalized patients who were typically in the acute phase of the disease, implying that our findings may not be generalizable to MDD patients during the stable phase. Additionally, the PSQI score relies on a patient's subjective experiences, potentially introducing individual cognitive biases. Moreover, the research period extending over a month might result in recall bias. Consequently, it is essential to conduct in-depth cohort studies in the future to further validate our findings.

In summary, this study indicates that the prevalence of cognitive impairment is higher among MDD patients hospitalized during the acute phase. Factors such as a higher HAMD-17 score, older age, and lower education levels are associated with cognitive impairment in these patients. Additionally, the HAMD-17 score and age can also predict the severity of cognitive impairment. These findings suggest that swiftly improving the clinical condition of high-risk populations may help reduce their risk of cognitive impairment. Therefore, clinicians should conduct detailed evaluations based on the individual circumstances of each patient and closely monitor the cognitive function of those with depression. Given the mutual effect between depressive symptoms and cognitive function, the timely assessment of the cognitive status of patients with depression is crucial for early behavioral intervention during the acute phase.

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by The Second People's Hospital's ethical review board in Hunan Province, China, accepted this study (No. 2023 (K) 018).The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HZ: Writing – original draft. JC: Conceptualization, Writing – review & editing.

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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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Immediate memory is associated with alexithymia in Chinese Han first-episode, drug-naïve major depressive disorder

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Background: Alexithymia is defined as a difficulty in identifying and describing one's own emotions. It represents a risk factor for cognitive deficits and is frequently observed in individuals with depressive disorders. However, the relationship between alexithymia and neurocognitive function in major depressive disorder (MDD) is still unknown. This study aimed to explore the association between alexithymia and neurocognition in patients with MDD.

Methods: A total of 134 Chinese Han first-episode drug-naïve patients with MDD were recruited. The 20-item Toronto Alexithymia scale (TAS-20), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the 9-item Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety Disorder-7 items (GAD-7) was used to assess alexithymia, neurocognitive functioning, and emotion. Multivariable liner regression models were used to estimate the association between alexithymia and neurocognition. Interaction and stratified analyses were conducted according to age, gender, marital and education status.

Results: Among the 134 patients with MDD, 55 participants (41%) had alexithymia. In the fully adjusted model, TAS total score (TAS-T) (β: -0.34, 95% CI: -0.61~-0.07) and difficulty identifying feelings (DIF) (β: -0.8, 95% CI: -1.3~-0.31) were statistically significantly associated with immediate memory.

Conclusions: Higher level of alexithymia, particularly the difficulty identifying feelings facet, is associated with lower scores of immediate memory in patients with MDD.

KEYWORDS

alexithymia, difficulty identifying feelings, neurocognition, immediate memory, major depressive disorder

Introduction

Major depressive disorder (MDD) is a prevalent psychiatric disease with high rates of morbidity, disability, and mortality and has become a worldwide health concern (1). In addition to mood symptoms, individuals with depression often experience impaired cognitive functioning (2). Psychiatrists are increasingly focusing on the cognitive dysfunction of depression, preferring to view it as a stand-alone symptom rather than a secondary phenomenon to the mood symptoms of depression. The diagnostic criteria for MDD in both the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the International Classification of Diseases, Eleventh Revision (ICD-11) focus on changes in cognitive function (3, 4). Cognitive dysfunction, which is a common symptom of depressive disorders, not only restricts the patient's ability to perform in multiple areas, but also significantly degrades their overall quality of life. Additionally, it increases the risk of physical illnesses and serves as a factor that negatively impacts the prognosis of depression (5). Therefore, cognitive impairment in patients with depressive disorders is a noteworthy clinical target for attention.

Alexithymia is a deficit in the cognitive processing of emotions with three major facets, (1) difficulty in identifying one's feelings and distinguishing them from bodily sensations; (2) difficulty in describing one's feelings to others; and (3) an externally oriented cognitive style (6). Alexithymia frequently occurs in a variety of somatic and psychiatric disorders (7–12), however, individuals suffering from depression have a higher rate of alexithymia than people with other psychiatric disorders (13). Numerous studies have found that disturbances in neurocognitive functioning are related to the degree of alexithymia (11, 14). Studies in different populations, both healthy and clinical individuals, have found that alexithymia is associated with multiple dimensions of neurocognitive functioning, including language, executive and visuospatial abilities, attention and memory (15, 16). Neuroimaging studies further support the idea that alexithymia can have an impact on cognitive function (17).

Despite the association between alexithymia and depression, as well as cognitive functioning, to the best of our knowledge, no study has investigated the relationship between alexithymia and neurocognitive function in patients with depression. This study aimed to explore the association between alexithymia and neurocognitive function in patients with MDD. Given that neurocognitive function and alexithymia may be influenced by medication exposure and disease progression, only patients with the first episode, drug-naïve MDD were included in the study (18). Because both alexithymia and cognitive functioning were culturally influenced, only the Han Chinese, the largest population in China, were selected for this study (19, 20). Since there were a limited number of studies in this area, our study was exploratory and with no specific hypotheses on which particular domain of neurocognitive function was specifically associated with alexithymia in patients with MDD.

Materials and methods

Study design and study population

We conducted this cross-sectional study to explore the association between alexithymia and neurocognition in patients with MDD, following the guidelines of the STROBE statement. Data was collected between January 2021 and July 2022 in China. The study comprised of 134 drug-naïve patients with their first-episode depression. These participants were selected from Tianjin Anding Hospital. The inclusion criteria were as follows: (1) First diagnosed with MDD according to DSM-5; (2) All patients were first-episode without previous pharmacological treatment; (3) aged 18-60 years. Participants were excluded based on the following criteria: (1) ethnic background other than Han; (2) serious physical disease; (3) a history of any mental illnesses other than MDD; (4) pregnancy; and (5) substance abuse. The ethics committee of the Tianjin Anding Hospital approved the study, which was conducted in accordance with the Declaration of Helsinki. All participants signed a written informed consent before assessment.

Data collection

Alexithymia

The 20-item Toronto Alexithymia Scale (TAS-20) was used to measure alexithymia (21). It has demonstrated favorable internal consistency and test-retest reliability in the general population (22), with Cronbach α-coefficients ranging from 0.81 to 0.86 (21). It consists of three dimensions: difficulty in identifying feelings (DIF), difficulty in describing feelings (DDF), and externally oriented thinking (EOT). Each item on the TAS-20 is scored on a five-point Likert, with total scores ranging from 20 to 100. Higher total scores reflect greater alexithymia. Individuals who score 61 or above on the TAS total score (TAS-T) are classified as having alexithymia (23).

Neurocognition

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used to evaluate neurocognitive functions (24). The RBANS is a widely used neuropsychological battery which assesses different domains of cognitive function, including Attention, Language, Visuospatial/construction, Immediate memory, and Delayed memory. RBANS has good validity and reliability in Chinese people (25). The RBANS total score demonstrated strong internal consistency, with a reliability coefficient of 0.806. The Cronbach's α values for each of the RBANS subscales ranged from 0.142 to 0.727 (25).

Psychological assessment

The Patient Health Questionnaire-9 (PHQ-9) was used to assess the severity of depression in the last two weeks. It is a self-rated measure of depression consisting of nine items that align with the criteria for major depression in the Diagnostic and Statistical

Manual of Mental Disorders, Fourth Edition (DSM-IV) (26). PHQ-9 scores range from 0 to 27, with higher scores indicating more severe depression. Depressive symptoms were categorized by severity into five groups: minimal (scores of 0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27) (27). It has been demonstrated as a valid and reliable measure of depression among the Chinese population, with Cronbach α-coefficients ranging from 0.84 to 0.87 (27).

The Generalized Anxiety Disorder-7 items (GAD-7) was used to evaluate the severity of anxiety. GAD-7 is developed by Spitzer and his colleagues to evaluate the severity of anxiety in the last two weeks (28). It is a 7-item self-report scale with a range of scores from 0 to 21, with higher scores indicating greater anxiety severity. It has been discovered to be a reliable and valid tool for screening GAD, as demonstrated in a Chinese population (29). The Cronbach's α coefficient was 0.898, indicating excellent internal consistency (29).

Demographic characteristics (age, gender, marital status, and education) were recorded through a standardized questionnaire. Alexithymia and emotion were assessed by the patients themselves after a detailed explanation by the psychiatrist. Two experienced and trained psychiatrists assessed neurocognitive functions using the RBANS assessment manual. The inter-rater correlation coefficient for the RBANS total score was 0.86.

Statistical analysis

Continuous variables were presented as means and standard deviations (SD) for normal distribution, mediation and interquartile range (IQR) for non-normal distribution and categorical variables as frequencies and percentages. Differences between groups were analyzed using the student t-test for normally distributed variables, the Mann-Whitney test for skewed distribution variables, and the chi-square test for categorical variables. Multivariable liner regression models were used to assess the association of alexithymia and neurocognition. Unadjusted and adjusted β with 95% confidence intervals (CIs) were calculated. Model 1 was unadjusted. Model 2 was adjusted for age, gender, marital and education status. Model 3 was further adjusted for PHQ-9 and GAD-7. Given that 29 years was the mean age of the study population and that having ≥16 years of education is indicative of higher education, we conducted interaction and stratified analyses based on age grouping (above and below 29 years), gender, marital status (single and married), and education (above and below 16 years). The *P*-value reported was two-sided and statistical significance was defined as a value less than 0.05. All the analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and Free Statistics software versions 1.8 (Beijing Free Kelin Medical Technology Co, Ltd.).

Results

Basic characteristics of the study participants

This study screened 152 patients with first-episode, drug-naïve MDD, of whom 10 were not included for meeting one of the exclusion criteria. Participants who failed to complete the RBANS assessment (*n*=8) were also excluded. Ultimately, 134 participants were included in the study analysis. Figure 1 presents a flow diagram.

Finally, 134 patients were enrolled in this study, and 55 participants (41%) had alexithymia (TAS-T≥61). The average age of the participants was 29.1 (10.1) years. Of the participants, 54 (40.3%) were male, 84 (62.7%) were single, and 64 (47.8%) had higher education (years of education≥16). All participants had

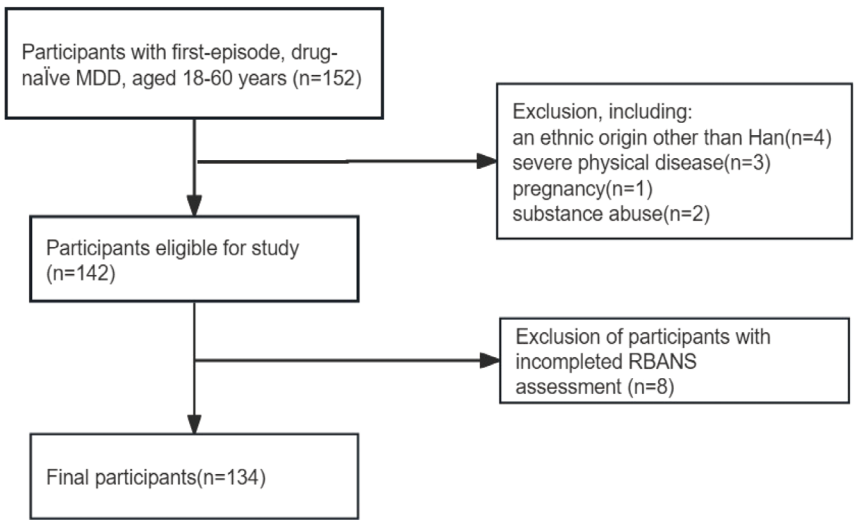

FIGURE 1
Flowchart of participant selection. MDD, major depressive disorder; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

PHQ-9 scores of ≥5 (The percentages of different severity levels are detailed in Supplementary Figure 1). Individuals with alexithymia were younger (mean age, 25.6 vs. 31.4 years), more inclined to be single (41 [74.5%] vs. 43 [54.4%]) and had higher PHQ-9 scores. Additionally, a higher proportion of individuals with alexithymia had more severe depression (48 [87.3%] vs. 57 [72.2%]). Table 1 shows the main characteristics of the study subjects.

Associations between alexithymia and neurocognition

The relationship between alexithymia and neurocognition is presented in Table 2. The univariate linear regression analysis showed significant negative associations between TAS-T and language (β: -0.25, 95% CI: -0.49~-0.02) as well as immediate memory function (β: -0.3, 95% CI: -0.57~ -0.04). Additionally, there were negative associations between the DIF subscale and language (β: -0.49, 95% CI: -0.93~-0.06) and immediate memory function (β: -0.64, 95% CI: -1.12~-0.16).

After adjusting for gender, age, marital status and education (Model 2), the associations between TAS-T (β: -0.2, 95% CI: -0.46~0.05) and language and between DIF (β: -0.4, 95% CI: -0.87~0.07) and language disappeared. Nevertheless, the negative association between TAS-T and immediate memory and between DIF and immediate memory were still significant in both Model 2 and Model 3. Model 3 was further adjusted for PHQ-9 and GAD-7. In fully adjusted Model 3, the immediate memory score decreased by 0.34 points for each 1-point increase in the total TAS score (Model 3, β: -0.34, 95% CI: -0.61~ -0.07) and decreased by 0.8 points for each 1-point increase in the DIF subscale score (Model 3, β: -0.8, 95% CI: -1.3~-0.31).

TABLE 1 Basic characteristics of the study participants.

Variables	Total (n = 134)	Non-alexithymic (n = 79)	Alexithymic (n = 55)	p
Gender, n (%)				0.31
Male	54 (40.3)	29 (36.7)	25 (45.5)	
Female	80 (59.7)	50 (63.3)	30 (54.5)	
Marital Status, n (%)				0.018
Single	84 (62.7)	43 (54.4)	41 (74.5)	
Married	50 (37.3)	36 (45.6)	14 (25.5)	
Education, year, n (%)				0.797
<16	70 (52.2)	42 (53.2)	28 (50.9)	
≥16	64 (47.8)	37 (46.8)	27 (49.1)	
Depression severity, n (%)				0.037
mild-moderate	29 (21.6)	22 (27.8)	7 (12.7)	
moderately severe- severe	105 (78.4)	57 (72.2)	48 (87.3)	
Age, year	29.1 ± 10.1	31.4 ± 10.9	25.6 ± 7.6	< 0.001
TAS total score	58.5 ± 9.9	51.8 ± 6.3	68.1 ± 5.2	< 0.001
DIF	22.0 ± 5.5	18.7 ± 3.7	26.7 ± 4.1	< 0.001
DDF	16.0 ± 3.3	14.2 ± 2.5	18.7 ± 2.3	< 0.001
EOT	20.5 ± 3.6	18.9 ± 3.3	22.7 ± 2.7	< 0.001
RBANS total score	91.9 ± 14.9	92.7 ± 15.3	90.8 ± 14.5	0.485
Attention	109.7 ± 14.5	110.9 ± 13.1	108.1 ± 16.3	0.285
Language	95.3 ± 14.0	96.2 ± 14.5	94.1 ± 13.2	0.388
Visuospatial	88.7 ± 17.7	88.4 ± 17.8	89.1 ± 17.8	0.817
Immediate Memory	85.9 ± 15.4	87.3 ± 16.3	84.0 ± 14.1	0.232
Delayed Memory	91.1 ± 14.1	91.3 ± 15.0	90.8 ± 12.9	0.867
PHQ-9	18.2 ± 5.0	17.3 ± 5.3	19.4 ± 4.4	0.017
GAD-7	13.0 ± 5.0	12.5 ± 5.2	13.7 ± 4.6	0.159

TAS, Toronto Alexithymia scale; DIF, difficulty identifying feelings; DDF, difficulty describing feelings; EOT, externally oriented thinking; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; PHQ-9, Patient Health Questionnaire-9 items; GAD-7, Generalized Anxiety Disorder-7 items.
The severity of depression was categorized based on PHQ-9 total scores:mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27).

TABLE 2 Multivariable liner analysis evaluating the association between alexithymia and cognitive score.

Variable	Attention		Language		Visuospatial		Immediate Memory		Delayed Memory	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
	Model 1		Model 1		Model 1		Model 1		Model 1	
TAS total	-0.16 (-0.41~0.1)	0.22	-0.25 (-0.49~-0.02)	0.04*	-0.1 (-0.41~0.21)	0.54	-0.3 (-0.57~-0.04)	0.03*	-0.14 (-0.39~0.1)	0.25
DIF	-0.36 (-0.82~0.1)	0.12	-0.49 (-0.93~-0.06)	0.03*	-0.25 (-0.82~0.31)	0.38	-0.64 (-1.12~-0.16)	0.01*	-0.29 (-0.74~0.16)	0.20
DDF	-0.35 (-1.12~0.43)	0.38	-0.57 (-1.31~0.17)	0.13	-0.3 (-1.25~0.64)	0.53	-0.64 (-1.46~0.17)	0.12	-0.09 (-0.85~0.66)	0.81
EOT	-0.08 (-0.78~0.62)	0.82	-0.34 (-1.01~0.33)	0.31	0.09 (-0.77~0.94)	0.84	-0.33 (-1.07~0.41)	0.38	-0.35 (-1.03~0.33)	0.31
	Model 2		Model 2		Model 2		Model 2		Model 2	
TAS total	-0.14 (-0.41~0.12)	0.29	-0.2 (-0.46~0.05)	0.12	-0.09 (-0.4~0.23)	0.59	-0.33 (-0.59~-0.07)	0.02*	-0.13 (-0.38~0.12)	0.30
DIF	-0.33 (-0.82~0.16)	0.19	-0.4 (-0.87~0.07)	0.10	-0.28 (-0.87~0.31)	0.35	-0.77 (-1.25~-0.29)	0.002*	-0.3 (-0.76~0.16)	0.21
DDF	-0.31 (-1.11~0.5)	0.46	-0.38 (-1.16~0.4)	0.34	-0.25 (-1.22~0.73)	0.62	-0.7 (-1.51~0.12)	0.10	-0.01 (-0.77~0.76)	0.98
EOT	-0.1 (-0.79~0.59)	0.78	-0.32 (-0.99~0.35)	0.35	0.14 (-0.69~0.98)	0.74	-0.24 (-0.94~0.46)	0.51	-0.3 (-0.95~0.35)	0.37
	Model 3		Model 3		Model 3		Model 3		Model 3	
TAS total	-0.13 (-0.4~0.14)	0.36	-0.23 (-0.49~0.03)	0.09	-0.13 (-0.45~0.2)	0.45	-0.34 (-0.61~-0.07)	0.01*	-0.11 (-0.37~0.14)	0.38
DIF	-0.31 (-0.82~0.2)	0.24	-0.47 (-0.96~0.02)	0.07	-0.38 (-1~0.23)	0.23	-0.8 (-1.3~-0.31)	0.002*	-0.26 (-0.73~0.22)	0.30
DDF	-0.28 (-1.1~0.54)	0.50	-0.4 (-1.19~0.39)	0.32	-0.29 (-1.28~0.69)	0.56	-0.7 (-1.52~0.12)	0.10	0.02 (-0.75~0.78)	0.96
EOT	-0.06 (-0.76~0.64)	0.87	-0.35 (-1.03~0.32)	0.31	0.09 (-0.76~0.93)	0.84	-0.26 (-0.96~0.45)	0.48	-0.3 (-0.95~0.36)	0.38

Modal 1: No adjustment.
Modal 2: Adjusted for gender, age, marital status and education.
Modal 3: Adjusted for gender, age, marital status, education, PHQ-9 and GAD-7.
TAS, Toronto Alexithymia scale; TAST, TAS total score; DIF, difficulty identifying feelings; DDF, difficulty describing feelings; EOT, externally oriented thinking; PHQ-9, Patient Health Questionnaire-9 items; GAD-7, Generalized Anxiety Disorder-7 items; CI, confidence interval.
*$P<0.05$.

Subgroup analyses

Figures 2A, B displays the results of the stratified and interaction analyses investigating the associations between the TAS total score and immediate memory, as well as between the DIF score and immediate memory. In the stratified analysis, results were consistent with those observed in the multivariable linear regression analysis. No significant interactions were found within any subgroups, including gender, age, marital status and education level (all P for interaction>0.05).

Discussion

This cross-sectional study examined the association between alexithymia and neurocognitive function in Chinese Han first-episode, drug-naïve MDD. The results revealed a negative association between alexithymia and immediate memory. This negative association remained significant after adjusting for covariates including age, gender, marital and education status and emotion and remained stable across subgroups. This suggests that level of alexithymia was negatively associated with immediate memory independent of demographic factors and emotions in first-episode, drug-naïve MDD. Interestingly, when comparing individuals with and without alexithymia, we did not observe a significant difference in immediate memory performance. The reasons may be as follows: First, the immediate memory performance of the alexithymia group was indeed lower than that of the non-alexithymia group. However, the relatively small sample size limited the ability to detect significant differences. Second, we observed a negative association between alexithymia as a continuous variable and immediate memory. This association may not be significant when alexithymia is treated as a categorical variable because it reduces statistical power. Third, the alexithymia group had a relatively younger age distribution and a higher proportion of participants with higher education. These demographic characteristics may have influenced memory performance, thereby masking the true relationship between alexithymia and immediate memory. In contrast, our regression and stratified analyses accounted for multiple covariates and potential confounders, which allowed us to more accurately identify the independent impact of alexithymia on memory performance.

Studies have shown that alexithymia is associated with impaired cognitive processing of emotional information and with deficits in learning and memory. This is particularly the case when it comes to emotional information and contexts (30). A small sample of older adults reported a negative correlation between story and figure recall and alexithymia (31). Similarly, in a study conducted on young adults, it was found that those with high levels of alexithymia had a decreased immediate recall ability but unimpaired long-term

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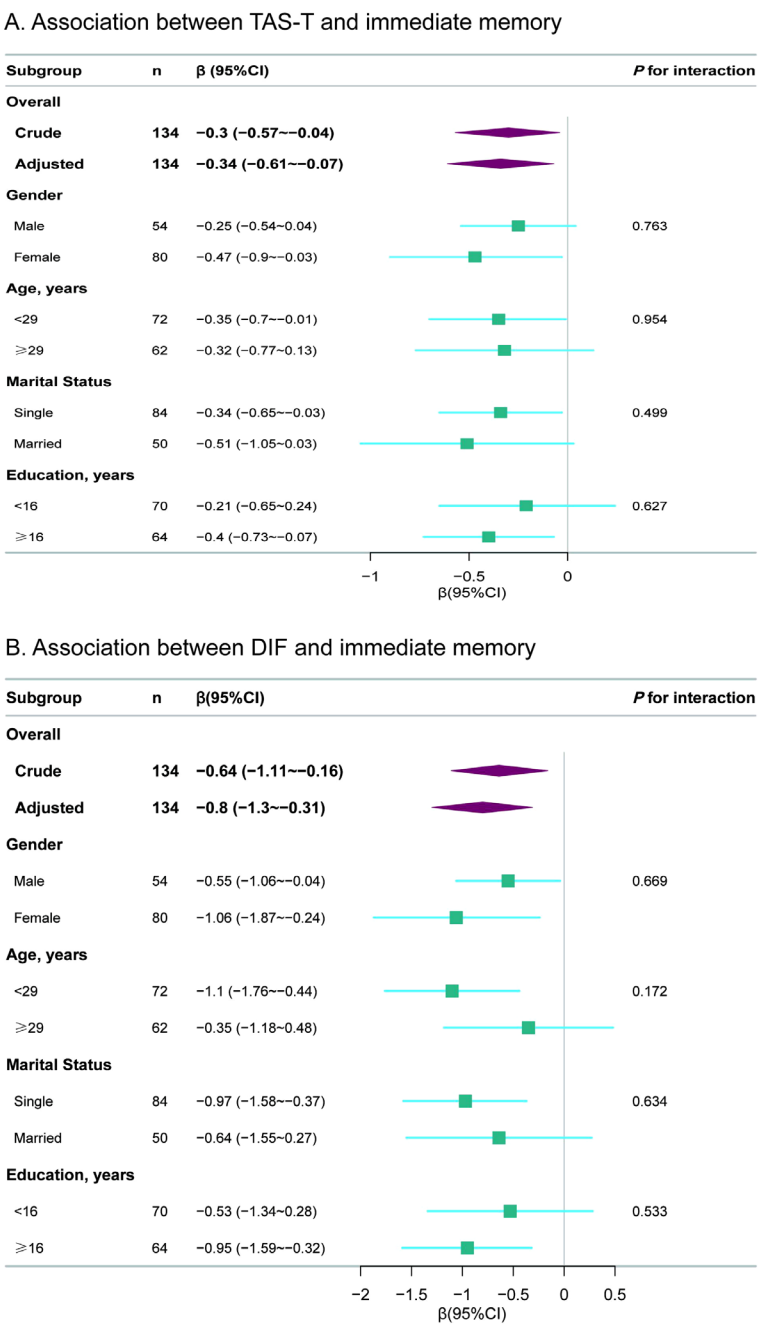

FIGURE 2
Subgroup analyses for the associations of TAS total and DIF subscale scores with immediate memory. **(A)** Association between TAS-T and immediate memory **(B)** Association between DIF and immediate memory. TAS, Toronto Alexithymia scale; TAS-T, TAS total score; DIF, difficulty identifying feelings; CI, confidence interval. The *p*-value for interaction represents the likelihood of interaction between the variable and the TAS total score or the DIF subscale score. Each stratification was adjusted for gender, age, education, marital status, PHQ-9 and GAD-7.

recognition of the words for neutral memoranda in a neutral context (32). Vermeulen found that alexithymia inhibited short-term memory but not long-term retrieval, regardless of whether the information was emotional or not (33). Conversely, some studies have found that individuals with higher levels of alexithymia may exhibit preserved or even improved memory for emotionally provocative words (34). Recent studies have explored the relationship between alexithymia and neurocognitive function across various patient populations. However, the specific associations between alexithymia and cognitive function vary across diseases, likely attributable to differences in disease pathology, heterogeneity of cognitive tests used, and sample characteristics. For instance, a recent meta-analysis found that the prevalence of alexithymia in Parkinson's disease (PD) is significantly higher than in the general population and is associated with cognitive impairment (35). Studies on PD have shown that alexithymia correlates with

deficits in the visuospatial domain and executive function, rather than memory functions (36). Similar findings were observed in HIV patients, where alexithymia correlated with deficits in visuospatial and executive functions but not memory impairments (37). A meta-analysis of eight studies revealed a moderate to large effect size for the association between alexithymia and schizophrenia (38). In schizophrenia, the EOT dimension of alexithymia has been linked to deficits in working memory (11, 39). In contrast, study on multiple sclerosis (MS) found that alexithymia correlated with depression and anxiety but not with cognition (40), suggesting that its primary impact on emotional regulation rather than cognition. Our study revealed a statistically significant negative association between level of alexithymia and immediate memory in patients with MDD. These findings underscore the significant role of population-specific factors in shaping the relationship between alexithymia and cognitive function. Further investigations across diverse populations are warranted to provide a more comprehensive understanding of this complex relationship.

Research has shown that alexithymia, which refers to the difficulty in identifying and describing one's own emotions, is related to decreased empathic behaviors (41, 42). Alexithymia appeared to underlie difficulties in key cognitive processes essential for empathy, specifically in sharing the emotional state of others (43). This lack of empathy results from difficulties in perceiving emotions, leading to misinterpretation of social cues and ultimately resulting in a lack of understanding of others' emotions (44). Studies have shown that individuals suffering from MDD experience diminished feelings of compassion (45). Furthermore, recent evidence has shown that the presence of alexithymia contributes to a deficit in empathy in depression (46). Previous literature has suggested that the motivation to empathize with others can guide attention and memory (47). Although the underlying mechanism cannot be tested in the present study, it is possible that the ability of empathy to raise emotional arousal can enhance the encoding of information (48). Consequently, "DIF", a core feature of alexithymia in patients with major depressive disorder (MDD), may be significantly associated with memory deficits, potentially mediated by reduced empathic ability.

Alexithymia, an impairment of affective and cognitive emotional processing, may reflect changes in brain regions important for cognitive function. A study on general population sample showed that the TAS-20 total score and DIF were both associated with less gray matter volumes of bilateral dorsal anterior cingulate cortex (ACC) (49). ACC is an essential area of the cerebral cortex for cognitive deficits production (5, 50). Recent evidence has shown that the human anterior cingulate and orbitofrontal cortex regions are linked to Meynert' septal nuclei and basal forebrain nucleus, which contain cholinergic neurons that project to the hippocampus and neocortex respectively (51). The impairment of the ACC system has been proposed as a cause for hippocampal episodic memory storage impairment (51). Additionally, volume reductions in the ACC have been observed in early-onset mood disorders with some specificity (52). Alexithymia is also strongly related to chronic stress, which is associated with brain structural and neuroendocrine alterations which may act as a mechanism for deficits in memory function (16). In particular, brain regions such as the hippocampus and prefrontal cortex, which are crucial for declarative memory functioning, especially short-term memory, have each been found to be affected by chronic stress (53, 54). Overall, further research is needed to understand the mechanisms underlying the association between alexithymia and memory impairment in patients with MDD, including neuroimaging and basic science research.

The expression and experience of emotions are inherently influenced by culture (19). For example, Western cultures encourage the expression of emotions more than Eastern cultures. Given that alexithymia is primarily characterized by difficulties in emotion identification and communication, it is influenced by culture (55). Previous research has shown that Asian groups exhibit higher levels of alexithymia compared to their European American counterparts (55). Moreover, different cultural backgrounds can exert a significant impact on specific neurocognitive processes (20), such as attention (56) and memory (57). Research in the field of neuroscience has also confirmed these findings (58, 59). Different cultural environments and diverse patterns of social interaction can profoundly influence memory development (60). Given the influence of culture on alexithymia and cognitive functioning, the present study chose a specific population, the Han Chinese, as the subject of the study and found negative associations between alexithymia and immediate memory in this population. Nevertheless, future studies with larger sample sizes and diverse populations are needed to further clarify the association between alexithymia and cognitive functioning in different cultural contexts.

In this study, we observed a negative association between alexithymia and verbal function in the unadjusted model. However, this association was no longer significant after adjusting for covariates. This finding aligns with the alexithymia–language hypothesis proposed by Hobson, which suggests that language deficits lead to impaired emotional awareness and, consequently, alexithymia (61). Studies in both clinical and healthy populations have supported this hypothesis, indicating that higher levels of alexithymia are associated with poorer verbal function (62, 63). The language difficulties observed in alexithymia may reflect a lack of early social language learning opportunities. Longitudinal studies have also demonstrated that language development in childhood can influence the manifestation of alexithymia in adolescence (64). However, some studies have reached the opposite conclusion (65). Given the considerable heterogeneity in sample characteristics, clinical presentations, and methodologies across studies, the relationship between alexithymia and language remains uncertain (66). According to the language hypothesis, individuals with language deficits are more likely to exhibit higher levels of alexithymia compared to those with normal language function. However, not all individuals with alexithymia exhibit significant language impairments (60). This may explain why the association between alexithymia and verbal function was attenuated after controlling for various demographic characteristics in our study.

Limitations

There are several limitations to our study that need to be acknowledged. Firstly, owing to the cross-sectional design of our study, it is impossible to establish any causality between the variables. Secondly, although our sample size is not small when compared to previous studies in this area, it still remains a limiting factor of our research. Thirdly, the emotion scales we used in our study, PHQ-9 and GAD-7, are self-assessment questionnaires. However, emotion evaluation was used as a covariate in this study to test the stability of the results. In future studies if emotion seen as an observed variable, including other assessment scales such as Hamilton Rating Scale for Depression (HAMD) and Hamilton Anxiety Rating Scale (HAMA) would provide a more comprehensive evaluation of emotions. Fourthly, despite the application of regression models and stratified analyses, complete elimination of residual confounding effects stemming from unmeasured or unknown factors cannot be guaranteed. For instance, there may be other psychological variables that might influence cognitive processes or the relationship between alexithymia and memory deficits. Fifthly, our study population included individuals with varying severities of depression, which may have influenced the association between alexithymia and cognitive function. Future studies should consider stratifying analyses by depression severity to better understand these complex relationships. Sixthly, it may be difficult to generalize the findings to the entire population of depressed patients because alexithymia is closely related to culture, and only Chinese Han patients were selected in this study. Furthermore, different subtypes of MDD may exert distinct impacts on cognitive function (67). Our study did not investigate the comorbid symptoms of depression to differentiate between subtypes. Therefore, it would be an interesting direction for future research to explore the relationship between alexithymia and cognitive function across different subtypes of MDD. Nevertheless, our study represents the first attempt to explore the relationship between alexithymia and neurocognition in patients with MDD, which could contribute to a deeper understanding of the cognitive impairment in MDD. Despite these limitations, future research should focus on well-designed and larger sample longitudinal studies to validate our findings.

Conclusions

In conclusion, higher level of alexithymia, particularly the difficulty identifying feelings facet, is associated with lower immediate memory scores among Chinese Han population with depression. More attention should be paid to altered cognitive functioning in patients with MDD who suffer from alexithymia, especially those with difficulty in identifying feelings. Future studies would further explore the mechanisms of the association between alexithymia and neurocognitive functioning.

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 humans were approved by the ethics committee of the Tianjin Anding Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

XT: Formal analysis, Writing – original draft. FB: Formal analysis, Investigation, Writing – original draft. YZ: Formal analysis, Investigation, Writing – original draft. YG: Investigation, Writing – original draft. YW: Investigation, Writing – original draft. YL: Investigation, Writing – original draft. CZ: Investigation, Writing – original draft. ML: Project administration, Writing – original draft. JL: Funding acquisition, Project administration, Writing – review & editing.

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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.2025.1473204/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Percentages of different depression severity levels according to PHQ-9 total score.

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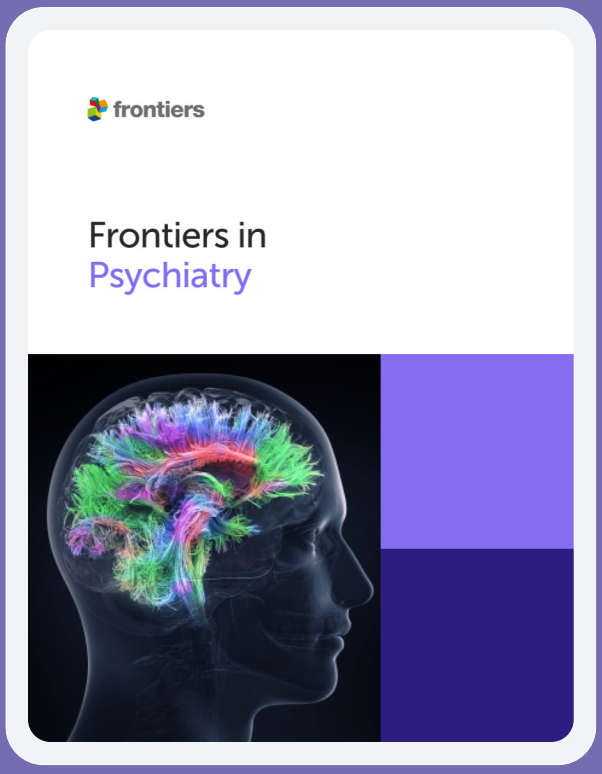

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