Women in
psychiatry mood disorders
2023

Edited by
Lisa Jones and Karen Tabb

Published in
Frontiers in Psychiatry

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Women in psychiatry 2023: Mood disorders

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Citation

Jones, L., Tabb, K., eds. (2024). *Women in psychiatry 2023: Mood disorders*.
Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5454-8

Table of
contents

Gender specific sexual dysfunction in patients with depression

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Background: This study aims to investigate the factors associated with sexual dysfunction (SD), with a particular focus on the influence of sex on the occurrence and severity of this condition in patients with major depressive disorder (MDD).

Method: Sociodemographic and clinical assessments were conducted on 273 patients with MDD (female=174, male=99), including the ASEX, QIDS-SR16, GAD-7, and PHQ-15. Univariate analyses, independent samples *t*-test, Chi-square test, and Fisher's exact test were used as appropriate, and logistic regression analysis was used to identify correlation factors for SD. Statistical analyses were performed using the Statistical Analysis System (SAS 9.4).

Result: SD was reported in 61.9% of the participants (ASEX score=19.6±5.5), and the prevalence of it in females (75.3%, ASEX score=21.1±5.4) was significantly higher than that in males (38.4%, ASEX score=17.1±4.6). Factors associated with SD included being female, being aged 45 years or above, having a low monthly income (≤750 USD), feeling more sluggish than usual (a QIDS-SR16 Item 15 score of 1 or above), and having somatic symptoms (evaluated with the total score of PHQ15).

Limitation: The use of antidepressants and antipsychotics might be a confounding factor affecting sexual function. Also, the lack of information in the clinical data regarding the number, duration, and time of onset of the episodes limits the richness of the results.

Conclusion: Our findings reveal the sex differences in the prevalence and severity of SD in patients with MDD. Evaluated with the ASEX score, female patients showed significantly worse sexual function than male patients. Being female, having a low monthly income, being aged 45 years or above, feeling sluggish, and having somatic symptoms may increase the risk of SD in patients with MDD.

KEYWORDS

major depressive disorder, sexual dysfunction, gender, ASEX, female

1. Introduction

The symptoms of major depressive disorder (MDD) include emotional, cognitive, and somatic symptoms (1, 2). In addition to the core symptoms, sexual dysfunction (SD) is reported by a majority of patients with MDD (3) and is associated with a low quality of life (4). Despite extensive research on MDD, SD has rarely been examined or considered as an associated factor

of MDD. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5™), SD is a clinically significant disturbance in a person's ability to respond sexually or to experience sexual pleasure, including delayed ejaculation, erectile disorder, female orgasmic disorder, female sexual interest/arousal disorder, genitopelvic pain/penetration disorder, and others (5).

In the general population, the prevalence of SD in the United States is 43% for women and 31% for men (6). According to an epidemiological summary of sexual dysfunction in Asia, 37% of men and 45% of women in China have at least one type of sexual dysfunction (7). Although there are some regional variations in the reported prevalence of SD, most of the literature shows a higher prevalence of sexual dysfunction in women than in men (7, 8). The most common sexual dysfunctions in men are erectile dysfunction and premature ejaculation; in women, those are low sexual desire and impaired sexual arousal (9). Recently, it has been reported that the prevalence of SD in patients with MDD ranges from 46.66 to 90% (4, 8, 10), much higher than that in the general population, and SD might have a great impact on the quality of life and prognosis of patients.

The pathogenesis and related factors of SD are complicated. Some researchers have surmised that SD may be associated with the patient's age, education level, physical health, emotional state, social and economic status, and cultural background (8, 11, 12). Moreover, the severity of MDD and the use of antidepressants have also been considered associated with the development of SD (13). Research has also found that SD occurred more frequently and was more severe in female patients with MDD than in male patients (8, 12), with symptoms including restricted sex drive and arousal, inability to reach orgasm, and decreased satisfaction from orgasm (14).

As sexual activity and functioning are sensitive topics in Asian cultural contexts, epidemiological studies published on sexual disorders in China are rare. Even fewer studies have taken patients with MDD as study subjects. Moreover, the impact of SD might be underestimated in Eastern cultures as patients with MDD may often be reluctant to talk about SD, even when they are in a hospital for the treatment of MDD. As there is limited evidence regarding the occurrence and severity of SD in patients with MDD, especially with regard to sex differences, this study aims to compare the sex differences in the aforementioned issue in a non-Western sample and, therefore, provide deeper insights into the biological and cultural pathogenesis.

2. Methods

2.1. Study design and participants

This study is a *post-hoc* data analysis of a Chinese nationwide naturalistic, prospective multi-center study conducted from May 2016 to October 2017 (15). It was approved by the Ethics Committee of Beijing Anding Hospital, Capital Medical University in 2016 and was approved by the ethics committees of all participating units (approval number: 2016-Science-Research-No.37). All patients participated in

the survey voluntarily and signed informed consent forms. The primary study included patients aged 18 years or older diagnosed with major depressive disorder (MDD) according to the International Classification of Diseases, Tenth Revision (ICD-10) criteria and treated with at least one antidepressant for 8–12 weeks at any of the 16 participating psychiatric outpatient centers. Patients with comorbid bipolar disorder, schizophrenia, schizoaffective disorder, or other mental disorders associated with medical conditions or substance use were excluded.

2.2. Assessments and outcomes

Sociodemographic and clinical characteristics were collected at baseline. We assessed the severity of depression and anxiety using the 16-item Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR16) and the Generalized Anxiety Disorder 7-Item (GAD-7) scale. The 15-item Patient Health Questionnaire (PHQ-15) was used to assess somatic symptoms. The Arizona Sexual Experience Scale (ASEX) was used to screen for sexual dysfunction (SD).

The QIDS-SR16 covers all the nine symptoms of MDD described in DSM-5. The items are measured on a 4-point scale ranging from 0 to 3, with a higher score indicating a higher severity of the measured symptom. The total score ranges from 0 to 27. The Chinese version of the scale has good reliability and validity (Cronbach's $\alpha = 0.86$) (16).

The GAD-7 scale consists of seven items. Each item is scored from 0 to 3 points, and the total score, as the sum of the scores of all items, ranges from 0 to 21 points. A higher score indicates a more severe symptom. The Chinese version of the GAD-7 scale has good psychometric properties (Cronbach's $\alpha = 0.92$) (17).

Different from the Patient Health Questionnaire-9 (PHQ-9), which focuses on depressive symptoms, the PHQ-15 measures somatic distress. It contains 15 items rated on a 3-point Likert scale ranging from 0 (not bothered at all) to 2 (bothered a lot). The Chinese version showed satisfactory internal consistency and test–retest reliability in a Hong Kong population (Cronbach's $\alpha = 0.89$) (18).

The ASEX is a five-item, easy-to-use rating scale for five domains of sexual function (sex drive, arousal, vaginal lubrication, ability to reach orgasm, and satisfaction from orgasm). The score of each item ranges from 1 to 6, and the total score ranges from 5 to 30. SD is defined as (i) a total ASEX score of 19 or above, (ii) any item with a score of 5 or above, or (iii) any three items with a score of 4 or above. The ASEX is a reliable, valid, and sensitive tool to measure SD in both males and females (19). The Chinese version of ASEX was used in this study because it has been shown to have good psychometric properties in Chinese patients with MDD (Cronbach's $\alpha = 0.85$) (20). All participants were instructed by a psychiatrist before completing the self-rating scale.

2.3. Statistical analysis

All statistical analyses were conducted using the Statistical Analysis System (SAS 9.4). In the univariate analyses, independent samples *t*-test, Chi-square test, and Fisher's exact test were used as appropriate. Logistic regression analysis was performed to explore the

TABLE 1 Demographic and clinical characteristics of all participants.

Male	Included (N=99)	Excluded (N=37)	t/χ²	p
Age	40.9±11.7	45.9±16.3	−1.73	0.0904
Marital status				**0.0202**
Married/partnered	74 (75.5%)	22 (59.5%)		
Divorced/separated	1 (1.0%)	3 (8.1%)		
Widowed	1 (1.0%)	3 (8.1%)		
Single	22 (22.5%)	9 (24.3%)		
Living				0.464
alone	8 (8.2%)	5 (13.5%)		
with family (parent, spouse, sibling)	83 (84.7%)	30 (81.1%)		
with friends	3 (3.1%)	2 (5.4%)		
other	4 (4.1%)	0 (0.0%)		
Years of education	13.1±4.0	11.4±4.1	1.78	0.078
Monthly average revenue, USD			2.58	0.4602
≤150	12 (12.1%)	7 (18.9%)		
150–750	47 (47.5%)	20 (54.1%)		
750–1,500	21 (21.2%)	6 (16.2%)		
≥1,500	19 (19.2%)	4 (10.8%)		
First depressive episode	62 (62.6%)	22 (59.5%)	0.11	0.7352
Duration of current episode	21.3±16.2	21.1±19.6	0.06	0.1433
Duration of antidepressant	9.6±1.6	9.4±1.6	0.5	0.6183
Antidepressant monotherapy	69 (69.7%)	22 (59.5%)	1.28	0.2588
Antipsychotic co-treatment	34 (34.3%)	20 (54.1%)	4.37	**0.0366**
QIDS-SR16	7.6±4.5	8.6±5.1	−1.14	0.2558
GAD-7	4.4±4.0	5.0±5.2	0.0071	0.9328
PHQ-15	5.6±4.2	6.9±4.7	−1.46	0.1463
Female	Include (N=174)	Exclude (N=118)	t/χ²	p
Age	41.4±11.6	51.7±16.4	−6.25	**<0.0001**
Marital status			22.11	**<0.0001**
Married/partnered	147 (84.5%)	74 (63.3%)		
Divorced/separated	2 (1.2%)	9 (7.7%)		
Widowed	3 (1.7%)	10 (8.6%)		
Single	22 (12.6%)	24 (20.5%)		

(Continued)

TABLE 1 (Continued)

Living				0.0803
alone	7 (4.0%)	13 (11.1%)		
with family (parent, spouse, sibling)	158 (90.8%)	97 (82.9%)		
with friends	7 (4.0%)	4 (3.4%)		
other	2 (1.2%)	3 (2.6%)		
Years of education	12.3±3.7	10.7±4.8	3.04	**0.0027**
Monthly average revenue, USD			4.65	0.1993
≤150	48 (27.6%)	32 (27.6%)		
150–750	90 (51.7%)	69 (59.5%)		
750–1,500	30 (17.2%)	10 (8.6%)		
≥1,500	6 (3.5%)	5 (4.3%)		
First depressive episode	101 (58.1%)	76 (64.4%)	1.19	0.275
Duration of current episode	20.6±14.7	21.8±16.7	0.51	0.4714
Duration of antidepressant	9.8±1.7	9.7±1.6	0.22	0.8237
Antidepressant monotherapy	129 (74.1%)	89 (75.4%)	0.06	0.8042
Antipsychotic co-treatment	54 (31.0%)	54 (45.8%)	6.54	**0.0105**
QIDS-SR16	7.4±4.7	6.5±4.1	1.61	0.1084
GAD-7	4.0±4.1	3.3±3.9	3.64	0.0564
PHQ-15	6.5±4.5	5.5±4.1	2.38	0.1227

QIDS-SR16, the 16-item quick inventory of depressive symptomatology-self-report; GAD-7, generalized anxiety disorder 7-item; PHQ-15, the 15-item patient health questionnaire; The bold are *p*-values that are less than 0.05 (indicating statistically significant differences).

correlation of SD with sex, age, years of education, monthly income, each item of QIDS-SR16, depressive symptoms (QIDS items), anxiety symptoms (GAD-7), somatic symptoms (PHQ-15), and antipsychotics co-treatment. The statistical significance was set at $p < 0.05$ (two-sided).

3. Results

3.1. Attrition bias

A total of 428 eligible patients were approached for the study. After excluding 155 patients who did not complete the ASEX questionnaire or indicated that it was "not applicable" due to sexual inactivity, 273 patients (174 females, 99 males) with a mean age of 41.2±11.6 (range=19–67) were included in the analysis. There were significant differences in marital status and antipsychotic co-treatment between included and excluded male patients, as well as in marriage status, antipsychotic co-treatment, age, and years of education between included and excluded female patients (see Table 1 for details).

TABLE 2 Sample characteristics (overall, males and females).

	Total (*N*=273)	Male (*N*=99)	Female (*n*=174)	*t*/χ²	*p*
Age	41.2 ± 11.6	40.9 ± 11.7	41.4 ± 11.6	−0.37	0.7100
Education, year	12.6 ± 3.8	13.1 ± 4.0	12.3 ± 3.7	1.84	0.0665
Current episode, week	20.9 ± 15.2	21.3 ± 16.2	20.6 ± 14.7	0.0864	0.7688
Symptom severity					
Depression (QIDS-SR total score)	7.5 ± 4.6	7.6 ± 4.5	7.4 ± 4.7	0.28	0.7799
Anxiety (GAD-7 total score)	4.2 ± 4.0	4.4 ± 4.0	4.0 ± 4.1	1.09	0.2975
Somatic symptoms (PHQ-15 total score)	6.2 ± 4.4	5.6 ± 4.2	6.5 ± 4.5	2.51	0.1132
Age				2.13	0.3455
18–30	60 (22.0%)	24 (24.2%)	36 (20.7%)		
30–45	115 (42.1%)	45 (45.5%)	70 (40.2%)		
≥45	98 (35.9%)	30 (30.3%)	68 (39.1%)		
Marital status				–	0.1626
Married/partnered	221 (81.3%)	74 (75.5%)	147 (84.5%)		
Divorced/separated	3 (1.1%)	1 (1.0%)	2 (1.2%)		
Widowed	4 (1.5%)	1 (1.0%)	3 (1.7%)		
Single	44 (16.2%)	22 (22.5%)	22 (12.6%)		
Living				–	0.1791
alone	15 (5.5%)	8 (8.2%)	7 (4.0%)		
with family (parent, spouse, sibling)	241 (88.6%)	83 (84.7%)	158 (90.8%)		
with friends	10 (3.7%)	3 (3.1%)	7 (4.0%)		
other	6 (2.2%)	4 (4.1%)	2 (1.2%)		
Monthly average revenue, USD				24.71	**<0.0001**
≤150	60 (22.0%)	12 (12.1%)	48 (27.6%)		
150–750	137 (50.2%)	47 (47.5%)	90 (51.7%)		
750–1,500	51 (18.7%)	21 (21.2%)	30 (17.2%)		
≥1,500	25 (9.2%)	19 (19.2%)	6 (3.5%)		
Antidepressant treatment					
Antidepressant monotherapy	198 (72.5%)	69 (69.7%)	129 (74.1%)	0.62	0.4294
Antidepressant polypharmacy (≥2 antidepressants)	75 (27.5%)	30 (30.3%)	45 (25.9%)	0.62	0.4294
Antipsychotic treatment					
Antipsychotic monotherapy without antidepressant					
Antipsychotic-antidepressant co-treatment					
Antipsychotics co-treatment	88 (32.2%)	34 (34.3%)	54 (31.0%)	0.32	0.5739

n, number of patients; QIDS-SR16, the 16-item quick inventory of depressive symptomatology-self-report; GAD-7, generalized anxiety disorder 7-item; PHQ-15, the 15-item patient health questionnaire; The bold are *p*-values that are less than 0.05 (indicating statistically significant differences).

3.2. Description of overall sample

The majority of the sample was married or partnered, lived with family, had a monthly average revenue of 150–750 USD (low and middle income), and had a high-school-level education. Mono-antidepressant treatment was used in 72.5% of the sample. Patient and illness characteristics did not significantly differ except for monthly income, which was higher in males with MDD (*p* < 0.0001) (Table 2).

3.3. Sexual dysfunction in males and females with MDD

Of the 273 patients, 169 (61.9%) reported sexual dysfunction with a mean ASEX score of 19.6 ± 5.5. Females had a significantly higher frequency of sexual dysfunction than males (75.3% vs. 38.4%, *p* < 0.001), with low sex drive reported in 44% of all female patients and difficulty in sexual arousal reported in 26.7% of them. Among male patients, 11.1% had difficulty in penile erection; among female patients, 25.9% had

difficulty in vaginal lubrication. Difficulty in reaching orgasm was reported in 29.7% of all patients, and unsatisfying orgasm was reported in 28.9% of them. Evaluated with the item scores and the total score of the ASEX, female patients experienced much more severe dysfunction in all sexual domains compared to male patients (all $p < 0.01$) (Table 3).

3.4. Factors associated with sexual dysfunction in patients with MDD

The logistic regression model for the overall sample showed that being female (OR = 4.5, 95%CI: 2.46, 8.24), being aged 45 years or above (OR = 2.33, 95%CI: 1.06, 5.10), low monthly income (≤750 USD, OR = 3.64, 95%CI: 1.91, 6.65), feeling more sluggish than usual (QIDS-SR16 Item 15 score ≥ 1, OR = 2.05, 95%CI: 1.11, 3.79), and having somatic symptoms (total score of PHQ15, OR = 1.09, 95%CI: 1.01, 1.17) were associated with sexual dysfunction (see Table 4).

4. Discussion

We observed a significant sex difference in sexual dysfunction among patients with MDD. The prevalence of sexual dysfunction was significantly higher in female patients than in male patients. Female patients demonstrated significantly more severe dysfunction in all sexual domains, as indicated by both item and total scores of ASEX, than male

patients. Our study suggests that sexual dysfunction in patients with MDD is likely associated with female sex, age above 45, low monthly income (≤ 750 USD), feeling more sluggish than usual (QIDS item 15 ≥ 1), and having somatic symptoms (evaluated with the total score of PHQ15).

An epidemiological summary of sexual dysfunction in Asia by Lewis et al. (7) reported that 37% of men and 45% of women in China have at least one type of sexual dysfunction. In the general population, women typically report more sexual functioning problems than men (21). The prevalence of sexual dysfunction is much higher in MDD patients than in the general population (8, 10, 22). A meta-analysis of 12 cross-sectional studies on depressive and persistent depressive disorders revealed that 82.75% of women (95% CI: 74.71–90.78) and 63.26% of men (95% CI: 52.83–73.69) experienced general sexual dysfunction (23). Our study found that, according to self-assessment results, 61.9% of patients with MDD experienced sexual dysfunction, with a significantly higher prevalence of sexual dysfunction in females (75.3%) than in males (38.4%). Our results are consistent with previous reports on the prevalence of sexual dysfunction, indicating a higher prevalence of sexual dysfunction in females with MDD than in males with MDD. Sex differences in sexual dysfunction in patients with MDD may be attributed to underlying neurobiological mechanisms (24). Patients with MDD exhibit decreased activation in various brain regions during visually evoked sexual arousal: males show decreased activation

TABLE 3 Sexual dysfunction (overall*, males and females).

	Total N=273	Male N=99	Female N=174	P
ASEX total score	19.6 ± 5.5	17.1 ± 4.6	21.1 ± 5.4	<0.0001
Positive item (≥5), n (%)				
quantify sex drive	120 (44.0%)	30 (30.3%)	90 (51.7%)	0.0006
arousal	73 (26.7%)	10 (10.1%)	63 (36.25%)	<0.0001
vaginal lubrication or penile erection	56 (20.5%)	11 (11.1%)	45 (25.9%)	0.0037
ability to reach orgasm	81 (29.7%)	16 (16.2%)	65 (37.4%)	0.0002
satisfaction from orgasm	79 (28.9%)	17 (17.2%)	62 (35.6%)	0.0012
Number of ASEX positive item	1.5 ± 1.9	0.8 ± 1.5	1.9 ± 2.0	<0.0001
Sexual dysfunction	169 (61.9%)	38 (38.4%)	131 (75.3%)	<0.0001

ASEX, Arizona Sexual Experience Scale; N, number of patients.
*Overall Sexual dysfunction was defined as (i) a total score ≥ 19, (ii) ≥ 5 in any item, or (iii) ≥ 4 in three items.

TABLE 4 Factors associated with sexual dysfunction.

	β	SE	χ^2	P	OR (95% CI)
Age strata					
40–45 vs. 18–30	−0.31	0.20	2.38	0.1229	0.95 (0.46, 2.00)
>45 vs. 18–30	0.58	0.22	7.12	0.0076	2.33 (1.06, 5.10)
Female	1.50	0.31	23.85	<0.0001	4.50 (2.46, 8.24)
Total score of PHQ15	0.08	0.038	4.65	0.0311	1.09 (1.01, 1.17)
Income level*: ≤ 750 vs. >750	0.65	0.16	15.42	<0.0001	3.64 (1.91, 6.95)
QIDS Item 15 (feeling more sluggish than usual) ≥ 1	0.36	0.16	5.32	0.0211	2.05 (1.11, 3.79)

*USD; n, number of patients; QIDS, the 16-item quick inventory of depressive symptomatology-self-report; PHQ-15, the 15-item patient health questionnaire.

in the hypothalamus, thalamus, caudate nucleus, and temporal gyrus, and females show decreased activation in the para-hippocampal gyrus and anterior cingulate cortex, which are vulnerable during MDD episodes (25, 26). Difficulty in communicating with life partners or the influences of East Asian cultures on the patients may also contribute to these results. The prevalence of sexual dysfunction in patients with MDD is associated with the severity of depression (27). Our results indicate that the severity of depression was similar between the male and female groups (there was no significant difference in the QIDS-SR total score between the male and female groups); therefore, the effect of sex on the prevalence of sexual dysfunction in patients with MDD was not substantially affected by the severity of depression.

In our study, female patients had higher scores across all domains of sexual dysfunction in the ASEX, including low sex drive, difficulty with sexual arousal, difficulty in achieving penile erection or vaginal lubrication, difficulty in achieving orgasm, and unsatisfying orgasm. Lai et al. ((14)) reported similar findings, with females (the mean ASEX score was 20.88) exhibiting significantly higher ASEX scores than males (the mean ASEX score was 16.93). Although some studies have suggested that ASEX scores are associated with the severity of depressive symptoms (10, 14), we found no significant correlation between the QIDS-SR16 total score and the ASEX score in our study. However, the occurrence of SD was indeed associated with one item of the QIDS-SR16 (the score of Item 15 feeling more sluggish than usual ≥1). In a 6-month follow-up study, we found no significant difference between the ASEX total scores of patients with or without remission, and sexual dysfunction did not improve with the alleviation of depressive symptoms (15). Therefore, our results suggest that sexual dysfunction in patients with MDD may be relatively independent of the severity of depressive symptoms, but may be affected by certain domains of MDD symptoms such as feeling sluggish. Nonetheless, it should be noted that some studies have suggested a strong association between SD and depressive symptoms evaluated with objective scales such as the HDRS (14, 28) or MADRS (29). The difference in evaluation tools may account for the varied conclusions.

Our results reveal that being female and feeling more sluggish than usual (a QIDS-SR16 Item 15 score ≥ 1) are associated with SD, along with being aged 45 years or above, having a low monthly income, and having somatic symptoms (evaluated with the total score of PHQ15). These factors may predict the likelihood of developing SD in patients with MDD, and we will discuss each factor individually below.

The mean age of our study population was 41 years for both male and female groups. Previous research suggests that sexual dysfunction may increase with age (3, 30). As women age, they experience a reduction in pelvic muscle tension, relaxation of the urethral meatus, a decrease in orgiastic rectal contractions, vaginal dryness associated with declining estrogen, and reduced libido (possibly linked to a decline in androgen levels (31)). In males, age-related changes in sexual response include a decrease in libido, the number and frequency of morning erections, penile sensitivity, and arousal, as well as a longer time needed to achieve and maintain an erection, prolonged plateau phase, reduced ejaculatory volume and force of expulsion, and prolonged refractory period (32). Being aged 45 years or above is a risk factor for sexual dysfunction in both male and female patients with MDD.

Low monthly income (≤ 750 USD) may result in high pressure regarding family responsibilities and a depressed sexual environment, leading to dissatisfaction with sexual function among patients, which could explain part of our results. Additionally, our study found that compared to men, a significantly higher proportion of women had low income, which may contribute to the high incidence of SD in women. Kim et al. (33) also suggested a correlation between female sexual dysfunction and lower economic income; moreover, lower socioeconomic status (measured by the poverty income ratio) and lower sexual frequency are directly correlated among female adults in the United States. A cross-sectional study on rural Iranian women found that financial stress and lack of support increased the likelihood of depression and the risk of sexual dysfunction (11).

One meta-analysis showed that poor physical condition was a significant predictor of SD (34), which is in line with our findings. A study on women in Hong Kong, China, also found that moderate or poor self-rated physical health, measured with a single item ("How would you evaluate your health status?") on a five-point Likert scale (ranging from "1 = very good" to "5 = very poor"), was associated with sexual dysfunction (35). There is a close correlation between physical discomfort and sexual dysfunction both in patients with MDD and the general population. It is worth noting that our study found that the total score of GAD-7 (indicating the severity of anxiety) was not a contributing factor to sexual dysfunction, which is consistent with some previous findings (4, 12).

This study has several limitations that should be considered. Firstly, we did not take into account the influence of attitudes toward sex activities and the mastery of sex-related knowledge, which have been shown to significantly affect the occurrence of sexual dysfunction (8). Secondly, the use of antidepressants and antipsychotics may affect sexual function (36), potentially contributing to the prevalence of sexual dysfunction in our results. However, as there was no significant difference in the use of these medications between the male and female groups, the possible impact of these confounding factors can be excluded. Thirdly, more detailed clinical information regarding the onset, number of episodes, and duration of sexual dysfunction would have strengthened the analysis and increased the generalizability of the results. Finally, the sample size was not calculated for the purpose of this study.

5. Conclusion

Our findings mainly revealed that there were sex differences in the prevalence and severity of SD in patients with MDD. Evaluated with the ASEX score, the sexual function of female patients was significantly worse than that of male patients. Being female, having a low monthly income, being older than 45 years old, feeling sluggish, and having somatic symptoms may increase the risk of SD in patients with MDD.

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.

Ethics statement

Author contributions

Funding

Acknowledgments

Conflict of interest

Publisher's note

References

1. Hursitoglu O, Kurutas EB, Strawbridge R, Oner E, Gungor M, Tuman TC. Uygur OF: serum NOX1 and Raftlin as new potential biomarkers of major depressive disorder: a study in treatment-naive first episode patients. *Prog Neuro-Psychopharmacol Biol Psychiatry*. (2023) 121:110670. doi: 10.1016/j.pnpbp.2022.110670

2. Zhang M. Major depressive disorder treatment guidelines in China. *J Clin Psychiatry*. (2010) 71:e06. doi: 10.4088/JCP.9058se1c.06gry

3. Seidman SN, Roose SP. Sexual dysfunction and depression. *Curr Psychiatry Rep*. (2001) 3:202–8. doi: 10.1007/s11920-001-0053-7

4. Zhao N, Wang X, Wu W, Hu Y, Niu Y, Wang X, et al. Gender differences in quality of life and functional disability for depression outpatients with or without residual symptoms after acute phase treatment in China. *J Affect Disord*. (2017) 219:141–8. doi: 10.1016/j.jad.2017.05.021

5. US APAD-TFAV. Diagnostic and statistical manual of mental disorders: DSM-5™. *Codas*. (2013) 25:191.

6. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States prevalence and predictors. *JAMA*. (1999) 281:537–44. doi: 10.1001/jama.281.6.537 %J JAMA

7. Lewis RW. Epidemiology of sexual dysfunction in Asia compared to the rest of the world. *Asian J Androl*. (2011) 13:152–8. doi: 10.1038/aja.2010.108

8. Lau JT, Kim JH, Tsui HY. Prevalence of male and female sexual problems, perceptions related to sex and association with quality of life in a Chinese population: a population-based study. *Int J Impot Res*. (2005) 17:494–505. doi: 10.1038/sj.ijir.3901342

9. McCabe MP, Sharlip ID, Lewis R, Atalla E, Balon R, Fisher AD, et al. Incidence and prevalence of sexual dysfunction in women and men: a consensus statement from the fourth international consultation on sexual medicine 2015. *J Sex Med*. (2016) 13:144–52. doi: 10.1016/j.jsxm.2015.12.034

10. Reddy RM, Saravanan RA, Praharaj SK, Thirunavukarasu M. Sexual dysfunction in women with depression: a hospital-based cross-sectional comparative study. *Indian J Psychol Med*. (2020) 42:46–51. doi: 10.4103/IJPSYM.IJPSYM_321_19

11. Khademi R, Hosseini SH, Nia HS, Khani S. Evaluating co-occurrence of depression and sexual dysfunction and related factors among Iranian rural women: a population-based study. *Biomedicine*. (2020) 10:33–9. doi: 10.37796/2211- 8039.1003

12. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA*. (1999) 281:537–44. doi: 10.1001/jama.281.6.537

13. Rappek N, Sidi H, Kumar J, Kamarazaman S, Das S, Masiran R, et al. Serotonin selective reuptake inhibitors (SSRIs) and female sexual dysfunction (FSD): hypothesis on its association and options of treatment. *Curr Drug Targets*. (2018) 19:1352–8. doi: 10.2174/1389450117666161227142947

14. Lai C. Major depressive disorder: gender differences in symptoms, life quality, and sexual function. *J Clin Psychopharmacol*. (2011) 31:39–44. doi: 10.1097/ JCP.0b013e318205a670

15. Xiao L, Zhu X, Feng L, Feng Y, Wu W, Wang G. Effects of treatment outcome on residual symptoms after acute phase treatment for MDD: a national, multicenter follow-up study. *Chin J Psychiatry*. (2021) 01:9–16. doi: 10.3760/ cma.j.cn113661-20200306-0009

16. Sung SC, Low CC, Fung DS, Chan YH. Screening for major and minor depression in a multiethnic sample of Asian primary care patients: a comparison of the nine-item patient health questionnaire (PHQ-9) and the 16-item quick inventory of depressive symptomatology – self-report (QIDS-SR16). *Asia Pac Psychiatry*. (2013) 5:249–58. doi: 10.1111/appy.12101

17. Sun J, Liang K, Chi X, Chen S. Psychometric properties of the generalized anxiety disorder Scale-7 item (GAD-7) in a large sample of Chinese adolescents. *Healthcare*. (2021) 9:1709. doi: 10.3390/healthcare9121709

18. Lee S, Ma YL, Tsang A. Psychometric properties of the Chinese 15-item patient health questionnaire in the general population of Hong Kong. *J Psychosom Res*. (2011) 71:69–73. doi: 10.1016/j.jpsychores.2011.01.016

19. McGahuey CA, Gelenberg AJ, Laukes CA, Moreno FA, Delgado PL, McKnight KM, et al. The Arizona sexual experience scale (ASEX): reliability and validity. *J Sex Marital Ther*. (2000) 26:25–40. doi: 10.1080/009262300278623

20. Lin CF, Juang YY, Wen JK, Liu CY, Hung CI. Correlations between sexual dysfunction, depression, anxiety, and somatic symptoms among patients with major depressive disorder. *Chang Gung Med J*. (2012) 35:323–31. doi: 10.4103/2319-4170.106138

21. Mercer C, Fenton K, Johnson A, Copas A, Macdowall W, Erens B, et al. Who reports sexual function problems? Empirical evidence from Britain's 2000 national survey of sexual attitudes and lifestyles. *Sex Transm Infect*. (2005) 81:394–9. doi: 10.1136/ sti.2005.015149

22. Nguyen HMT, Gabrielson AT, Hellstrom WJG. Erectile dysfunction in young men-a review of the prevalence and risk factors. *Sex Med Rev*. (2017) 5:508–20. doi: 10.1016/j. sxmr.2017.05.004

23. Gonçalves WS, Gherman BR, Abdo CHN, Coutinho ESF, Nardi AE, Appolinario JC. Prevalence of sexual dysfunction in depressive and persistent depressive disorders: a systematic review and meta-analysis. *Int J Impot Res*. (2022). doi: 10.1038/s41443-022-00539-7

24. Yang J. Functional neuroanatomy in depressed patients with sexual dysfunction: blood oxygenation level dependent functional MR imaging. *Korean J Radiol*. (2004) 5:87–95. doi: 10.3348/kjr.2004.5.2.87

25. Yang J, Park K, Eun S, Lee M, Yoon J, Shin I, et al. Jeong GJTjosm: assessment of cerebrocortical areas associated with sexual arousal in depressive women using functional MR imaging. *J Sex Med*. (2008) 5:602–9. doi: 10.1111/j.1743-6109.2007.00737.x

26. Bremner J, Vythilingam M, Vermetten E, Vaccarino V, Charney D. Deficits in hippocampal and anterior cingulate functioning during verbal declarative memory encoding in midlife major depression. *Am J Psychiatry*. (2004) 161:637–45. doi: 10.1176/ appi.ajp.161.4.637

27. Williams K, Reynolds MF. Sexual dysfunction in major depression. *CNS Spectr*. (2006) 11:19–23. doi: 10.1017/s1092852900026729

28. Roy P, Manohar S, Raman R, Sathyanarayana Rao TS, Darshan MS. Female sexual dysfunction: a comparative study in drug naive 1 (st) episode of depression in a general hospital of South Asia. *Indian J Psychiatry*. (2015) 57:242–8. doi: 10.4103/0019-5545.166623

29. Bonierbale M, Lançon C, Tignol J. The ELIXIR study: evaluation of sexual dysfunction in 4557 depressed patients in France. *Curr Med Res Opin*. (2003) 19:114–24. doi: 10.1185/030079902125001461

30. Meston CM, Levin RJ, Sipski ML, Hull EM, Heiman JR. Women's orgasm. *Annu Rev Sex Res*. (2004) 15:173–257.

31. Seidman SN. Hormonal aspects of sexual dysfunction: the therapeutic use of exogenous androgens in men and women. *Curr Psychiatry Rep*. (2000) 2:215–22. doi: 10.1007/s11920-996-0011-5

32. Schiavi RC, Segraves RT. The biology of sexual function. *Psychiatr Clin North Am*. (1995) 18:7–23. doi: 10.1016/S0193-953X(18)30067-4

33. Kim JI, Zhu D, Davila J, Lee J, Chubak BM, Melamed ML, et al. Female sexual dysfunction as measured by Low sexual frequency is associated with lower socioeconomic status: an analysis of the National Health and nutrition examination survey (NHANES), 2007-2016. *J Sex Med*. (2022) 19:90–7. doi: 10.1016/j.jsxm.2021.09.014

34. McCool-Myers M, Theurich M, Zuelke A, Knuettel H, Apfelbacher C. Predictors of female sexual dysfunction: a systematic review and qualitative analysis through gender inequality paradigms. *BMC Womens Health*. (2018) 18:108. doi: 10.1186/s12905-018-0602-4

35. Zhang H, Fan S, Yip PS. Sexual dysfunction among reproductive-aged Chinese married women in Hong Kong: prevalence, risk factors, and associated consequences. *J Sex Med*. (2015) 12:738–45. doi: 10.1111/jsm.12791

36. Montgomery SA, Baldwin DS, Riley A. Antidepressant medications: a review of the evidence for drug-induced sexual dysfunction. *J Affect Disord*. (2002) 69:119–40. doi: 10.1016/S0165-0327(01)00313-5

Effect of depressive symptoms on quality of work life in female nurses: a cross-sectional study using propensity score matching

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Background: Female nurses have been considered as a vulnerable population in the context of mental health, due to the nature of their work, which can be stressful and emotionally taxing. Understanding the relationship between depressive symptoms and quality of work life (QWL) can contribute to improving mental health and job performance. However, limited studies have focused on the effect of depressive symptoms on QWL in female nurses.

Objectives: The present study aimed to assess the effect of depressive symptoms on female nurses' QWL using propensity score matching (PSM).

Methods: A cross-sectional, online study using convenience sampling was conducted among 1,401 female nurses in China. PSM was used to minimize the impact of potential confounders between no depressive symptoms and depressive symptoms. Stepwise multiple linear regression analyses were performed on the PSM samples to explore the effects of depressive symptoms on the QWL.

Results: The results revealed there were 33.5% of the female nurses reported depressive symptoms before PSM. And female nurses in this study had a moderate level of QWL before PSM (122.11 ± 18.15), which remained steady after PSM (118.33 ± 18.04). After PSM, the final sample contained 864 female nurses. Stepwise multiple linear regression results indicated that depressive symptoms were the most strongly associated with QWL ($\beta = -0.454$, $p < 0.001$).

Conclusion: This study highlights the importance of developing mental health plans and psychological interventions for female nurses to maintain mental health and QWL, which is critical to the nursing workforce's sustainability.

KEYWORDS

depressive symptoms, female nurses, propensity score matching, quality of work life, cross-sectional study

1. Introduction

According to the World Health Organization's projections, depression is anticipated to become the leading contributor to the global disease burden by 2030 (1). Approximately 350 million people suffer from depression worldwide (2). Compared with the general population, nurses are particularly susceptible to developing depression due to exposure to emotional and traumatic situations (3). Female nurses are particularly vulnerable, with a higher likelihood of suffering from depression than males (4). Depression among nurses with a prevalence ranging from 22 to 35% (5–7). Depressive symptoms can limit nurses' psychosocial functioning, reduce their quality of life, and be unfavorable to their care work (8). Additionally, depressive symptoms in females may exhibit more intricate characteristics as a result of several contributing factors including physiological hormones and external stimuli (9). Therefore, female nurses' depressive symptoms should also be recognized and addressed as a significant public health concern, as it is vital to ensure the formation of an emotionally healthy nursing workforce.

Quality of work life (QWL) is a worker's satisfaction with the working life (10), which is characterized by the relationship between the worker and the working environment (11). Specifically, in the field of nursing, it pertains to the degree to which nurses can fulfill their personal needs (e.g., physical, emotional, and social) through their work environment experience and achieve organizational goals (12). Female nurses are consistently subjected to elevated expectations and take on a variety of dual roles at home and work (13). High QWL is relevant to alleviating the family-work conflict (14). Besides, enhancing the QWL for nurses is crucial for stabilizing the nursing workforce, especially in countries like China where the nurse-to-population ratio (per thousand population is 3.56) is relatively low compared to Western countries (15). Furthermore, given that female nurses constitute 97% of the over five million nursing workforce (16), healthcare managers have placed significant emphasis on improving their QWL, as poor QWL may lead to staff turnover, exacerbating the shortage of nursing human resources and cannot meet the growing demand for medical services (17, 18).

However, the effect of depressive symptoms on QWL among female nurses remains unclear. Unexplored associations between depressive symptoms and QWL may limit a variety of interventions targeting nurses' mental health and planning aimed at the long-term development of national nursing careers. Additionally, propensity score matching (PSM) is a valuable statistical method that minimizes selection bias and confounding variables in observational studies. This methodology strives to emulate the characteristics of a randomized controlled study, allowing for a more reasonable comparison between exposure group and the control group (19). Building upon our primary focus on the main effect, we have meticulously considered a comprehensive range of factors. These include participants' individual characteristics (such as age, BMI, educational level, etc.), work-related factors (such as employment type, weekly working hours, shift work schedules, etc.), as well as lifestyle and health-related factors (such as sleep quality, physical activity, menstruation status, etc.) which are well-known potential factors of depressive symptoms and QWL (20, 21). Therefore, this study aimed to explore the effect of depressive symptoms on QWL in female nurses through PSM adjusting for confounding variables, which would provide inspiration for managers to developing mental health plans and psychological interventions for female nurses to improve mental health and QWL, then maintaining the nursing workforce.

1.1. Theoretical framework

Job Demands–Resources theory (J-DR) guided this study (22). This model proposes that high job demand (e.g., emotional labor, physical demands, shift work, etc.) and low job resources (e.g., social support, team collaboration, training and development, etc.) can dampen worker motivation and exacerbate strain (23, 24), which can have negative effects on QWL. In this study, the main mechanism by which depressive symptoms may have an impact on the QWL is by depleting people's resources while adding additional demands. On one hand, depressive symptoms may impair concentration and judgment at work, further diminishing the individual's ability to cope with the demands of the job. On the other hand, individuals affected by depressive symptoms may lack behaviors such as actively seeking social support and increasing self-efficacy, which reduces their ability to access and utilize work resources. At the same time, depressive symptoms are closely linked to health risk behaviors, such as insufficient physical activity and sleep reduction (25, 26), which reduces an individual's access to psychological and physical resources. These behaviors play an important role in the onset of depressive symptoms and need to be evaluated as explaining or confounding factors. Based on this, the following hypothesis was posited: depressive symptoms have a negative impact on the QWL for female nurses.

2. Materials and methods

2.1. Study design, setting, and participants

This cross-sectional, descriptive study was conducted on 1,485 female nurses working in 4 hospitals in Fujian province, China from December 2022 to January 2023. To ensure uniformity, four investigators from each participating hospital underwent comprehensive training on the study protocol. Data collection was conducted online through WenJuanXing, a widely employed professional questionnaire survey platform in China. Participants who indicated their willingness to take part in the study were directed to an online informed consent form and the questionnaire through a Quick Response (QR) code provided by the four investigators. Subsequently, participants completed the informed consent process and responded to the questionnaire electronically. The survey was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (27).

The study employed inclusion and exclusion criteria. Eligible participants were required to meet the following inclusion criteria: (a) possession of professional qualification certificates; (b) female gender; and (c) voluntary agreement to participate in this study. The exclusion criteria were as follows: (a) retired nurses, refresher nurses, or student nurses; (b) work less than 6 months; and (c) absence due to illness, marriage, maternity, or other personal reasons for more than 1 month. The sample size was determined based on a previous study (28), where the standard deviation (S) for QWL equaled to σ was 0.6 and

permissible error δ was 0.06. Using the formula $N = \frac{(Z_{1-\alpha/2} \times \sigma)}{\delta^2}$ for a cross-sectional survey to calculate sample size ($\alpha = 0.05$; $Z_{1-\alpha/2} = 1.96$), it was determined that a minimum sample size of 385 was required.

2.2. Measures

2.2.1. Demographic characteristics

Data on participants' demographic information was collected, including age, body mass index (BMI), educational level, professional rank, employment type, personal monthly income, marital status, menstruation status, weekly working hours, and shift work schedule.

2.2.2. The short version of the international physical activity questionnaire

The IPAQ-SF is a 7-item instrument assessing physical activity. The Chinese version of IPAQ-SF has been validated among Chinese university students (29), measuring the intensity, frequency, and duration of physical activity over the last 7 days. Participants' physical activities were classified into three categories of physical activity (low, moderate, and high), which were calculated on the metabolic equivalent of tasks (METs). METs consider the type of activity, such as walking, moderate physical activity, and vigorous physical activity, along with the time spent on each activity. Following the IPAQ guidelines, researchers can determine the level of physical activity by calculating the MET score.

2.2.3. The Pittsburgh sleep quality index

The PSQI is a self-reported instrument that comprises 19 items, which measure an individual's sleep quality for the preceding month (30). The PSQI assesses seven components, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, hypnotic use, and daytime dysfunction. Each item is rated on a 4-point Likert scale ($0 =$ normal, $1 =$ mild dysfunction, $2 =$ moderate dysfunction, and $3 =$ severe dysfunction). The total scores of seven components are summed up to generate a global score, which ranges from 0 to 21, with a higher score indicating poorer sleep quality. The Chinese version of the PSQI has well-established overall reliability ($r = 0.82–0.83$) and test–retest reliability ($r = 0.85$) (31). Additionally, the critical value of seven points could better differentiate between good and poor sleepers among the Chinese population (32). In this study, Cronbach's α coefficient of this scale was 0.76.

2.2.4. Self-rating depression scale

The SDS is a 20-item instrument assessing the depressive symptoms of participants (33). The SDS is considered a reliable tool for assessing depressive symptoms in the Chinese population (34), with high internal consistency (Cronbach's $\alpha = 0.89$). Responses could range from 1 (never) to 4 (always), with 10 items on positive symptoms and 10 items on negative symptoms. The total score ranged from 25 to 100 and was obtained by multiplying the total original score by 1.25, with higher scores indicating more severe depressive symptoms. In China, a cut-off score of 53 is considered an indicator of risk for clinical depression, based on which the level of depressive symptoms was classified as mild (53–62 points), moderate (63–72 points), and severe (>72 points). In this study, Cronbach's α coefficient of this scale was 0.88.

2.2.5. The work-related quality of life-2 scale

The WRQOL-2 scale is a 34-item instrument evaluating respondents' QWL, which was developed by Van Laar et al. (35), and translated and revised by Shao et al. (36). The instrument measures 7 dimensions of the working conditions (WCS), stress at work (SAW), control at work (CAW), homework interface (HWI), employment evaluation of nurse (EEN), general well-being (GWB), and job and career satisfaction (JCS), using a 5-point scale scoring method to rate agreement levels for each dimension ($1 =$ "Strongly disagree" to $5 =$ "Strongly agree"). Before analysis, negatively worded items for SAW were reverse-scored. The Chinese version of WRQOL-2 scale consists of 32 scoring items, with a total score ranging from 32 to 160. Higher scores indicate higher QWL. The Chinese version of the instrument exhibited robust reliability and validity when utilized within the nursing profession in mainland China, as evidenced by a Cronbach's α coefficient of 0.94 (37). In this study, Cronbach's α coefficient of this scale was 0.96.

2.3. Statistical analyses

The statistical analyses were performed using IBM SPSS, version 27.0, and R, version 4.1.3. PSM was utilized to adjust for potential confounding variables between female nurses with no depressive symptoms and depressive symptoms. PSM draws more accurate conclusions about the association between depressive symptoms and QWL. The PSM matched age, BMI, educational level, professional rank, employment type, personal monthly income, marital status, menstruation status, weekly working hours, shift work schedule, sleep quality, and physical activity. PSM was performed at 1:1 nearest-neighbor with a caliper value of 0.05 using logistic regression.

The distributions of continuous variables such as QWL are described as means and standard deviations, and the distributions of categorical variables are expressed as frequencies and percentages. Baseline characteristics were compared across no depressive symptoms and depressive symptoms groups using Chi-squared tests for categorical variables and independent t-tests for continuous variables. Stepwise multiple linear regression analysis was conducted on the PSM samples to analyze the effect of depressive symptoms on QWL. All statistical tests were two-sided tests, and a p value of <0.05 was considered statistically significant.

2.4. Ethical considerations

The study was approved by the Ethical Committee of Fujian Maternity and Child Health Hospital (No. 2022YJ071). Regarding online survey consent, the initial section of the questionnaire mainly included informed consent. After reading the consent information, participants had to click on a response button "I agree to participate," indicating that they had read the consent information and agreed to participate before being allowed to complete the online questionnaire. The questionnaire survey was

anonymous and participants had the right to withdraw from the study at any time and for any reason. All methods in this study have been carried out following relevant guidelines and regulations. All data collected were confidential and used only in this study.

3. Results

3.1. Participant characteristics

A total of 1,485 questionnaires were distributed among female nurses, out of which 1,401 questionnaires were considered valid after eliminating inaccurate data or quality issues. The effective recovery rate was determined to be 94.3%. Among 1,401 female nurses, approximately two-thirds of participants were contract employees ($n = 932$). The age distribution of the participants showed that those aged 26–35 years accounted for the highest percentage ($n = 573$, 40.9%). In terms of marital status, the majority of participants were married ($n = 759$, 54.2%). A significant proportion of participants had an intermediate level of regular menstruation ($n = 889$, 63.5%) or held a senior nurse title ($n = 600$, 42.8%), while almost all had attained a junior college degree or higher qualification ($n = 1,325$, 94.6%). Additionally, 42.7% of participants

reported engaging in high levels of physical activity ($n = 598$), while over half of the participants reported having poor sleep quality ($n = 816$).

3.2. Comparison of no depressive symptoms and depressive symptoms groups before and after PSM

The study flowchart is depicted in Figure 1. After PSM, the sample size was reduced from 1,401 to 864, with an even distribution of 432 participants in each group. Depressive symptoms levels are shown in Figure 2, there were 33.5 and 50% of the female nurses reported depressive symptoms before and after PSM according to the SDS scale, respectively. Table 1 displays the data for no depressive symptoms and depressive symptoms groups before and after PSM. The PSM eliminated confounding bias, making the no depressive symptoms and depressive symptoms groups comparable. After PSM, there were no statistically significant differences between the two groups in age, BMI, educational level, professional rank, employment type, personal monthly income, marital status, menstruation status, weekly working hours, shift work schedule, and sleep quality ($p > 0.05$). Nevertheless, physical activity still shows a significant difference ($p < 0.05$).

FIGURE 1
Flowchart of this study. BMI, body mass index; PSM, propensity score matching.
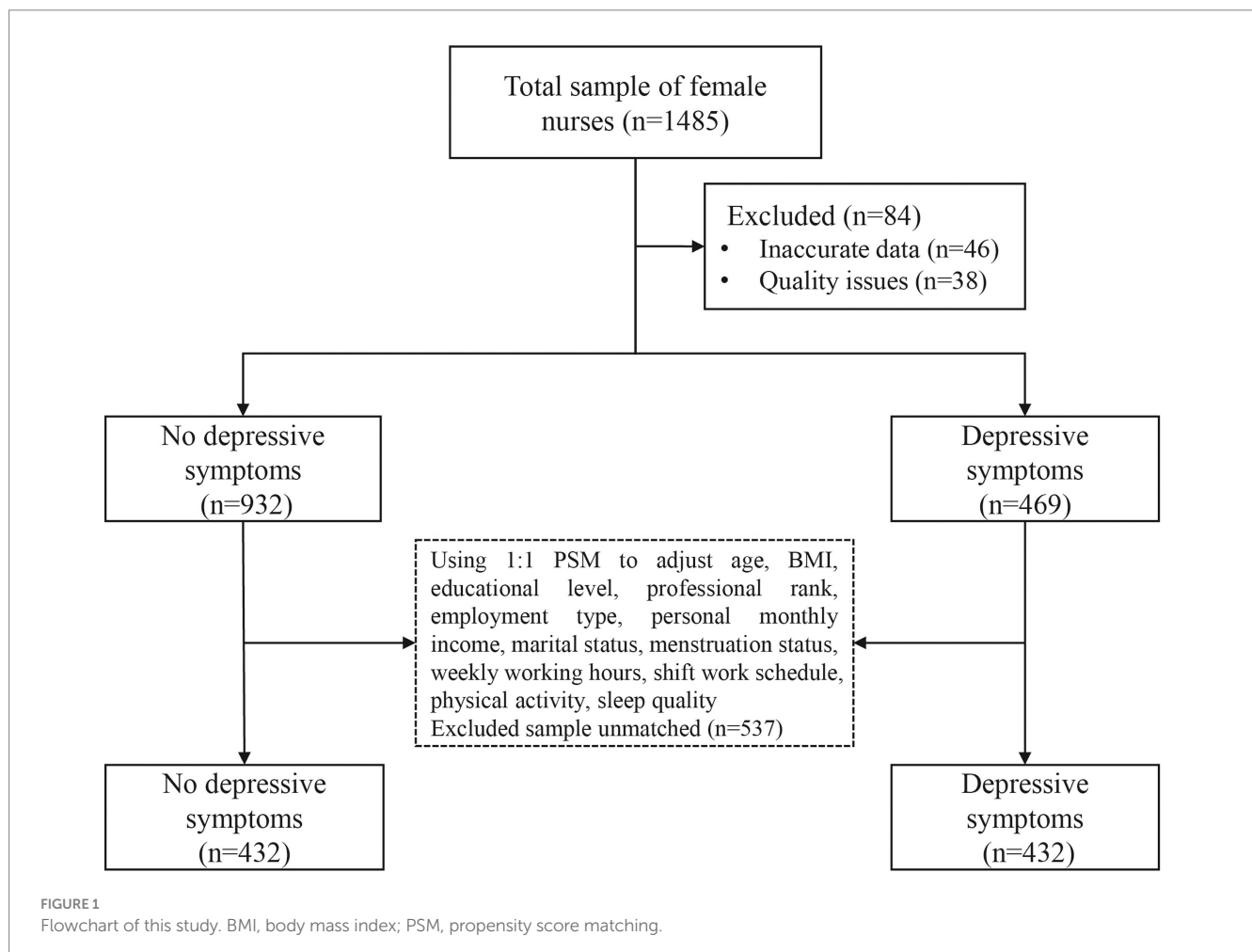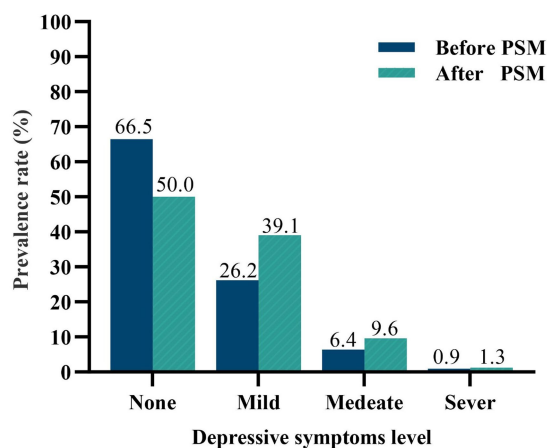
FIGURE 2
Comparison of depressive symptoms level before and after PSM.

3.3. Comparison of QWL between no depressive symptoms and depressive symptoms groups

The results indicated that the overall female nurses' QWL was at a moderate level before PSM (122.11 ± 18.15), which remained consistent after PSM (118.33 ± 18.04). Of the seven QWL dimensions, the "stress at work" dimension had the lowest levels before (15.84 ± 3.74) and after (15.14 ± 3.61) the PSM. Table 2 shows a comparison of QWL scores among female nurses before and after PSM in no depressive symptoms and depressive symptoms groups. However, there was a significant difference in the QWL and its dimensions scores between the no depressive symptoms and depressive symptoms groups. The use of PSM helped to ensure comparability between the two groups, thereby strengthening the validity of the results.

3.4. Stepwise multiple linear regression analysis for the factors of QWL

Table 3 presents the results of the stepwise multiple linear regression analyses, which largely confirmed the hypothetical model. Although different independent variables were included in each regression model, depressive symptoms consistently had the strongest association with QWL ($\beta = -0.454$, $p < 0.001$) and its seven dimensions, including WCS ($\beta = -0.379$, $p < 0.001$), SAW ($\beta = -0.364$, $p < 0.001$), CAW ($\beta = -0.346$, $p < 0.001$), HWI ($\beta = -0.345$, $p < 0.001$), EEN ($\beta = -0.371$, $p < 0.001$), GWB ($\beta = -0.374$, $p < 0.001$), and JCS ($\beta = -0.366$, $p < 0.001$).

4. Discussion

In this study, we compared the effect of depressive symptoms on QWL among female nurses through a large sample cross-sectional survey using PSM. To our knowledge, few studies focus on female nurses to explore potential gender-specific aspects of the relationship between depressive symptoms and QWL.

Our study found that the QWL of female nurses was at a moderate level, which is similar to previous studies in the UK (38), Iranian (20), and Canada (39), but higher than in Ghana (40). These similarities and differences across countries may be attributed to variations in cultural, social environments, healthcare systems, and nursing practices, which influence working conditions and subsequently affect nurses' QWL. It should be noted that international knowledge exchange and globalization standards might be contributing to a convergence in the nursing field, resulting in relatively similar QWL levels among nurses worldwide. Our results also indicated that the scores are slightly higher than those in China (41, 42). This may be due to all participants were from Fuzhou, an area with advanced medical technology and a standardized management system for nurses. Nurses in this region are highly competent and exhibit a high level of job satisfaction and fulfillment. However, it is noteworthy that female nurses had the lowest level in the "stress at work" dimension, meaning female nurses were under pressure. The primary reason may be the multidirectional character and intensity of occupational stressors experienced by nurses. Additionally, the intricate balance required to manage both family and work responsibilities might further amplify the perceived stress among female nurses (13). This phenomenon further underscores the importance of job demands and job resources to enhance mental health and effectively combat stress.

As hypothesized, the QWL of female nurses is negatively affected by their depressive symptoms. Previous studies have explored the impact of mental health on various aspects of nurses' well-being and reached similar conclusions (43, 44). According to the Job Demands–Resources theory, the depletion of critical job resources within nursing work, which can encompass factors like shift work, exposure to traumatic events, and high levels of stress, is posited to contribute to depressive symptoms (3). Additionally, the strong association between depressive symptoms and various adverse outcomes, including lack of energy, cognitive impairment, circadian variability, sluggishness, and sleep disturbance (45–48). These factors impair concentration and judgment, exacerbating the challenges female nurses face in effectively addressing job demands. Thus, female nurses with depressive symptoms face more social and cognitive demands at work but lack sufficient resources to cope with these demands. This ultimately leads to a decline in the QWL. Therefore, it is crucial to prioritize depressive symptoms of female nurses.

Our finding has identified a concerning trend where over one-third of female nurses are likely to be suffering from depressive symptoms, which exceeds previous study (6). Nurse managers must recognize the complexity of depressive symptoms in female nurses for effective strategies and improved mental health and QWL. To address Job Demands, it's important to ensure that workload distribution and scheduling take into account the potential impact of mental health issues. Prioritizing shift schedules aligned with circadian rhythms can alleviate strain caused by irregular hours. Nurturing a work-life balance culture assists female nurses in effectively managing their dual roles. To enhance Job Resources, provide female nurses with access to training and professional growth opportunities. Establish peer support groups to facilitate experience-sharing and camaraderie (49). Offer training programs for emotional resilience and stress management (50, 51). Cultivate supportive team environments with regular feedback and recognition systems, enhancing job satisfaction and fostering a sense of accomplishment. Implementing these strategies aligns with the principles of the Job Demands–Resources theory and significantly enhances mental health, job satisfaction, and overall work quality for female nurses.

TABLE 1 Comparison of no depressive symptoms and depressive symptoms groups before and after PSM.

Variables	Before PSM ($n = 1,401$)				After PSM ($n = 864$)			
	No depressive symptoms ($n = 932$)	Depressive symptoms ($n = 469$)	χ^2	p	No depressive symptoms ($n = 432$)	Depressive symptoms ($n = 432$)	χ^2	p
Age			6.744	0.081			6.610	0.085
≤25	355 (38.09)	166 (35.39)			174 (40.28)	154 (35.65)		
26–35	369 (39.59)	204 (43.5)			164 (37.96)	187 (43.29)		
36–45	166 (17.81)	89 (18.98)			75 (17.36)	82 (18.98)		
≥46	42 (4.51)	10 (2.13)			19 (4.4)	9 (2.08)		
Body mass index			1.870	0.393			1.019	0.601
Underweight	163 (17.49)	92 (19.62)			88 (20.37)	79 (18.29)		
Normal	644 (69.1)	324 (69.08)			301 (69.68)	303 (70.14)		
Overweight/obese	125 (13.41)	53 (11.3)			43 (9.95)	50 (11.57)		
Educational level			5.551	0.136			0.822	0.859[a]
Technical secondary school degree	42 (4.51)	34 (7.25)			21 (4.86)	26 (6.02)		
Junior college degree	490 (52.58)	251 (53.52)			232 (53.7)	229 (53.01)		
Bachelor degree	394 (42.27)	182 (38.81)			176 (40.74)	175 (40.51)		
Master degree and above	6 (0.64)	2 (0.43)			3 (0.69)	2 (0.46)		
Professional rank							5.969	0.113
Junior nurse	382 (40.99)	186 (39.66)	5.909	0.116	186 (43.06)	168 (38.89)		
Senior nurse	386 (41.42)	214 (45.63)			173 (40.05)	201 (46.53)		
Assistant advanced nurse	138 (14.81)	64 (13.65)			61 (14.12)	58 (13.43)		
Associate advanced nurse or advanced nurse	26 (2.79)	5 (1.07)			12 (2.78)	5 (1.16)		
Employment type			1.742	0.187			0.005	0.942
Formal employees	323 (34.66)	146 (31.13)			142 (32.87)	141 (32.64)		
Contract employees	609 (65.34)	323 (68.87)			290 (67.13)	291 (67.36)		
Personal monthly income (yuan)			27.227	**<0.001**			1.357	0.852
<3,000	17 (1.82)	21 (4.48)			11 (2.55)	14 (3.24)		
3,000–5,999	228 (24.46)	151 (32.2)			138 (31.94)	126 (29.17)		
6,000–8,999	350 (37.55)	172 (36.67)			168 (38.89)	167 (38.66)		
9,000–11,999	235 (25.21)	99 (21.11)			90 (20.83)	99 (22.92)		
≥12,000	102 (10.94)	26 (5.54)			25 (5.79)	26 (6.02)		
Marital status			0.215	0.643			0.042	0.838
Unmarried	423 (45.39)	219 (46.7)			199 (46.06)	202 (46.76)		
Married	509 (54.61)	250 (53.3)			233 (53.94)	230 (53.24)		
Menstruation status			35.391	**<0.001**			0.118	0.732
Irregular	290 (31.12)	222 (47.33)			187 (43.29)	192 (44.44)		
Regular	642 (68.88)	247 (52.67)			245 (56.71)	240 (55.56)		
Weekly working hours (hour)			11.989	**0.007**			3.605	0.307
≤35	231 (24.79)	100 (21.32)			90 (20.83)	95 (21.99)		
36–40	528 (56.65)	251 (53.52)			250 (57.87)	235 (54.4)		
41–45	151 (16.2)	94 (20.04)			83 (19.21)	84 (19.44)		
≥46	22 (2.36)	24 (5.12)			9 (2.08)	18 (4.17)		
Shift work schedule			6.651	0.084			3.093	0.378
Forward-rotating night shift	68 (7.3)	40 (8.53)			38 (8.8)	35 (8.1)		
Backward-rotating night shift	453 (48.61)	246 (52.45)			211 (48.84)	224 (51.85)		
12-hour rotating night shift	145 (15.56)	79 (16.84)			67 (15.51)	77 (17.82)		
Day shift	266 (28.54)	104 (22.17)			116 (26.85)	96 (22.22)		
Physical activity			10.034	**0.007**			9.187	**0.010**
Low	99 (10.62)	75 (15.99)			43 (9.95)	63 (14.58)		
Moderate	438 (47)	191 (40.72)			222 (51.39)	181 (41.9)		
High	395 (42.38)	203 (43.28)			167 (38.66)	188 (43.52)		
Sleep quality			106.358	**<0.001**			0.000	1.000
Good sleep	479 (51.39)	106 (22.6)			106 (24.54)	106 (24.54)		
Poor sleep	453 (48.61)	363 (77.4)			326 (75.46)	326 (75.46)		

Bold values were statistically significant. [a]Fisher exact test.

TABLE 2 Comparison of quality of work life between no depressive symptoms and depressive symptoms groups before and after PSM.

Variables	Before PSM ($n = 1,401$)				After PSM ($n = 864$)			
	No depressive symptoms ($n = 932$)	Depressive symptoms ($n = 469$)	t	p	No depressive symptoms ($n = 432$)	Depressive symptoms ($n = 432$)	t	p
Quality of work life (potential point: 32–160)	128.29 ± 14.89	109.82 ± 17.79	19.33	<0.001	126.51 ± 14.49	110.15 ± 17.53	14.95	<0.001
Working conditions (potential point: 6–30)	25.00 ± 3.23	21.49 ± 4.38	15.42	<0.001	24.67 ± 3.13	21.57 ± 4.33	12.04	<0.001
Stress at work (potential point: 5–25)	16.85 ± 3.47	13.84 ± 3.44	15.37	<0.001	16.46 ± 3.32	13.82 ± 3.4	11.57	<0.001
Control at work (potential point: 5–25)	20.45 ± 2.89	17.82 ± 3.79	13.19	<0.001	20.28 ± 2.77	17.88 ± 3.67	10.85	<0.001
Homework interface (potential point: 2–10)	8.52 ± 1.18	7.30 ± 1.72	13.74	<0.001	8.41 ± 1.17	7.33 ± 1.69	10.96	<0.001
Employment evaluation of nurse (potential point: 5–25)	20.90 ± 2.76	18.00 ± 3.79	14.72	<0.001	20.69 ± 2.69	18.10 ± 3.71	11.77	<0.001
General well-being (potential point: 5–25)	20.17 ± 2.89	16.99 ± 3.73	16.2	<0.001	19.70 ± 2.87	17.01 ± 3.72	11.93	<0.001
Job and career satisfaction (potential point: 4–20)	16.39 ± 2.15	14.38 ± 2.74	13.89	<0.001	16.29 ± 2.05	14.44 ± 2.71	11.34	<0.001

TABLE 3 Stepwise multiple linear regression analysis for the factors of quality of work life and its dimensions after PSM ($n = 864$).

Dependent variable	Independent variables	B	SE	β	t	p
Quality of work life[a]	Depressive symptoms	−16.356	1.081	−0.454	−15.132	<0.001
	Poor sleep quality	−5.117	1.258	−0.122	−4.068	<0.001
	Weekly working hours (41–45 h)	−3.256	1.371	−0.071	−2.376	0.018
Working conditions[b]	Depressive symptoms	−3.093	0.256	−0.379	−12.075	<0.001
	Poor sleep quality	−0.728	0.298	−0.077	−2.447	0.015
Stress at work[c]	Depressive symptoms	−2.626	0.222	−0.364	−11.847	<0.001
	Poor sleep quality	−1.515	0.260	−0.181	−5.832	<0.001
	Weekly working hours (41–45 h)	−0.947	0.282	−0.104	−3.361	0.001
	Personal monthly income (9,000–11,999 yuan)	−0.715	0.275	−0.082	−2.603	0.009
	Married	0.458	0.226	0.063	2.022	0.043
Control at work[d]	Depressive symptoms	−2.392	0.220	−0.346	−10.853	<0.001
	Regular menstruation	0.506	0.222	0.073	2.280	0.023
Homework interface[e]	Depressive symptoms	−1.067	0.098	−0.345	−10.850	<0.001
	Weekly working hours (41–45 h)	−0.273	0.125	−0.069	−2.181	0.029
	Weekly working hours (≥46 h)	−0.733	0.284	−0.082	−2.577	0.010
	Poor sleep quality	−0.241	0.115	−0.067	−2.102	0.036
Employment evaluation of nurse[f]	Depressive symptoms	−2.589	0.219	−0.371	−11.823	<0.001
	Poor sleep quality	−0.730	0.256	−0.090	−2.852	0.004
	Regular menstruation	0.477	0.222	0.068	2.150	0.032
General well-being[g]	Depressive symptoms	−2.677	0.222	−0.374	−12.060	<0.001
	Poor sleep quality	−1.160	0.262	−0.140	−4.422	<0.001
	Personal monthly income (3,000–5,999 yuan)	0.563	0.246	0.072	2.287	0.022
	Weekly working hours (41–45 h)	−0.605	0.283	−0.067	−2.137	0.033
Job and career satisfaction[h]	Depressive symptoms	−1.881	0.163	−0.366	−11.564	<0.001
	Age (26–35 years old)	0.337	0.168	0.064	2.004	0.045
	Poor sleep quality	−0.421	0.190	−0.070	−2.215	0.027
	Personal monthly income (9,000–11,999 yuan)	0.424	0.201	0.068	2.112	0.035

[a]$F = 223.652$, $p < 0.001$, $R^2 = 0.227$, Adjusted $R^2 = 0.224$.
[b]$F = 75.897$, $p < 0.001$, $R^2 = 0.150$, Adjusted $R^2 = 0.148$.
[c]$F = 40.543$, $p < 0.001$, $R^2 = 0.191$, Adjusted $R^2 = 0.186$.
[d]$F = 61.785$, $p < 0.001$, $R^2 = 0.126$, Adjusted $R^2 = 0.123$.
[e]$F = 34.109$, $p < 0.001$, $R^2 = 0.137$, Adjusted $R^2 = 0.133$.
[f]$F = 51.554$, $p < 0.001$, $R^2 = 0.152$, Adjusted $R^2 = 0.149$.
[g]$F = 45.353$, $p < 0.001$, $R^2 = 0.174$, Adjusted $R^2 = 0.171$.
[h]$F = 36.152$, $p < 0.001$, $R^2 = 0.144$, Adjusted $R^2 = 0.140$. SE, standard error.

This study suggests several directions for future research based on a few interesting findings. Firstly, multivariate analysis revealed poor sleep quality also considered a crucial indicator of QWL. Sleep quality and depressive symptoms are often intertwined, and their intricate interaction can exacerbate the adverse effects on QWL. Given that over half of the participants reporting poor sleep, addressing sleep problems is a timely topic for discussion. Hence, future researchers should perhaps also begin to examine the potential mediating mechanism of sleep quality in explaining the influence of depressive symptoms on QWL. Secondly, After PSM, physical activity was still showing a statistically significant difference between the no depressive symptoms and depressive symptoms groups. One explanation is that depressive symptoms may reduce people's motivation to

participate in physical activity. Another explanation is that the onset and development of depression may be related to the fact that physical activity promotes the release of neurotransmitters such as dopamine in the brain, which affects mental health. Further research is needed to better understand the relationship between physical activity and depression. Long-term longitudinal studies could help determine the role of physical activity as a predictor of depression risk, as well as the effect of depression on physical activity levels.

4.1. Strengths and limitations

The highlight of this study was focusing on female nurses to determine the effect of depressive symptoms on QWL using a large sample and propensity score matching. However, this study has some limitations that should be considered. Firstly, given the cross-sectional study design, it is challenging to infer causation based on the relationships between depressive symptoms and QWL. Future longitudinal studies are necessary to solve this critical issue. Secondly, the sample size was limited to four hospitals within a single province, which may restrict generalizability. Third, the investigation of female nurses diagnosed with major depression was inadequate since they could have left their jobs due to their illness. Finally, all variables were examined by self-report questionnaires, which may result in response bias.

5. Conclusion

This study has implications for better understanding the effect of depressive symptoms on QWL in female nurses using propensity score analysis. This study has demonstrated that depressive symptoms were prevalent among female nurses, and depressive symptoms adversely affect their QWL. These findings highlight the importance of developing mental health plans and implementing psychological interventions as a crucial investment in sustaining the mental health and quality performance of female nurses, thereby maintaining the nursing workforce.

Data availability statement

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

References

1. Malhi GS, Mann JJ. Depression. *Lancet*. (2018) 392:2299–312. doi: 10.1016/S0140-6736(18)31948-2

2. Depression and Other Common Mental Disorders [WWW Document], (2017). Available at: https://www.who.int/publications-detail-redirect/depression-global-health-estimates (Accessed March 3, 2023).

3. Wu Y, Yin X, Yan S, Jiang N, Tian M, Zhang J, et al. Prevalence of depressive symptoms in nurses compared to the general population based on Propensity Score

Ethics statement

Author contributions

J-NL and X-QC: writing—review and editing, conceptualization, methodology, and project administration. X-MJ: project administration and editing, conceptualization, and methodology. Q-QL: writing—original draft and methodology. Q-XZ: writing—review and editing and formal analysis. Y-QP and LH: writing—review and validation. YZ and R-LL: resources and investigation. All authors contributed to the article and approved the submitted version.

Funding

Acknowledgments

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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Matching: A nationwide cross-sectional study in China. *J Affect Disord*. (2022) 310:304–9. doi: 10.1016/j.jad.2022.05.012

4. Pachi A, Sikaras C, Ilias I, Panagiotou A, Zyga S, Tsironi M, et al. Burnout, depression and sense of coherence in nurses during the pandemic crisis. *Healthcare*. (2022) 10:134. doi: 10.3390/healthcare10010134

5. Al Maqbali M, Al Sinani M, Al-Lenjawi B. Prevalence of stress, depression, anxiety and sleep disturbance among nurses during the COVID-19 pandemic: A systematic

review and meta-analysis. *J Psychosom Res*. (2021) 141:110343. doi: 10.1016/j.jpsychores.2020.110343

6. Huang H, Xia Y, Zeng X, Lu A. Prevalence of depression and depressive symptoms among intensive care nurses: A meta-analysis. *Nurs Crit Care*. (2022) 27:739–46. doi: 10.1111/nicc.12734

7. Slusarska B, Nowicki GJ, Niedorys-Karczmarczyk B, Chrzan-Rodak A. Prevalence of depression and anxiety in nurses during the first eleven months of the COVID-19 pandemic: a systematic review and meta-analysis. *Int J Environ Res Public Health*. (2022) 19:1154. doi: 10.3390/ijerph19031154

8. Chen C, Meier ST. Burnout and depression in nurses: A systematic review and meta-analysis. *Int J Nurs Stud*. (2021) 124:104099. doi: 10.1016/j.ijnurstu.2021.104099

9. Kuehner C. Why is depression more common among women than among men? *Lancet Psychiatry*. (2017) 4:146–58. doi: 10.1016/S2215-0366(16)30263-2

10. Abdullah NAC, Zakaria N, Zahoor N. Developments in quality of work-life research and directions for future research. *SAGE Open*. (2021) 11:21582440211059176. doi: 10.1177/21582440211059177

11. Van Laar D, Edwards JA, Easton S. The Work-Related Quality of Life scale for healthcare workers. *J Adv Nurs*. (2007) 60:325–33. doi: 10.1111/j.1365-2648.2007.04409.x

12. Brooks BA, Storfjell J, Omoike O, Ohlson S, Stemler I, Shaver J, et al. Assessing the quality of nursing work life. *Nurs Adm Q*. (2007) 31:152–7. doi: 10.1097/01.NAQ.0000264864.94958.8e

13. Yuan L, Li Y, Yan H, Xiao C, Liu D, Liu X, et al. Effects of work-family conflict and anxiety in the relationship between work-related stress and job burnout in Chinese female nurses: A chained mediation modeling analysis. *J Affect Disord*. (2023) 324:309–16. doi: 10.1016/j.jad.2022.12.112

14. Al-Hammouri MM, Rababah JA. Work family conflict, family work conflicts and work-related quality of life: The effect of rotating versus fixed shifts. *J Clin Nurs*. (2023) 32:4887–93. doi: 10.1111/jocn.16581

15. www.gov.cn [WWW Document] (2022a). Available at: http://www.gov.cn/xinwen/2022-07/12/content_5700670.htm (Accessed April 3, 2023).

16. www.gov.cn [WWW Document] (2022b). Available at: http://www.gov.cn/xinwen/2022-05/13/content_5690090.htm (Accessed April 3, 2023).

17. Lee YW, Dai YT, Chang MY, Chang YC, Yao KG, Liu MC. Quality of Work Life, Nurses' Intention to Leave the Profession, and Nurses Leaving the Profession: A One-Year Prospective Survey. *J Nurs Scholarsh*. (2017) 49:438–44. doi: 10.1111/jnu.12301

18. Saygili M, Avci K, Sönmez S. Quality of work life and burnout in healthcare workers in Turkey. *J Health Manag*. (2020) 22:317–29. doi: 10.1177/0972063420938562

19. Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. *Stat Med*. (2008) 27:2037–49. doi: 10.1002/sim.3150

20. Babamohamadi H, Davari H, Safari A-A, Alaei S, Pordanjani SR. The association between workload and quality of work life of nurses taking care of patients with COVID-19. *BMC Nurs*. (2023) 22:234. doi: 10.1186/s12912-023-01395-6

21. Fond G, Fernandes S, Lucas G, Greenberg N, Boyer L. Depression in healthcare workers: Results from the nationwide AMADEUS survey. *Int J Nurs Stud*. (2022) 135:104328. doi: 10.1016/j.ijnurstu.2022.104328

22. Demerouti E, Bakker AB, Nachreiner F, Schaufeli WB. The job demands-resources model of burnout. *J Appl Psychol*. (2001) 86:499–512. doi: 10.1037/0021-9010.86.3.499

23. Bakker AB, Demerouti E. The job demands-resources model: state of the art. *J Manag Psychol*. (2007) 22:309–28. doi: 10.1108/02683940710733115

24. Demerouti E, Bakker AB. The job demands–resources model: challenges for future research. *SA J Ind Psychol*. (2011) 37:9. doi: 10.4102/sajip.v37i2.974

25. Pearce M, Garcia L, Abbas A, Strain T, Schuch FB, Golubic R, et al. Association between physical activity and risk of depression: a systematic review and meta-analysis. *JAMA Psychiat*. (2022) 79:550–9. doi: 10.1001/jamapsychiatry.2022.0609

26. Zhou Y, Wang S, Liu M, Gan G, Qin N, Luo X, et al. The role of sleep quality and perceived stress on depressive symptoms among tertiary hospital nurses: a cross-sectional study. *BMC Psychiatry*. (2023) 23:416. doi: 10.1186/s12888-023-04936-0

27. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Digit Diagnost*. (2021) 2:119–69. doi: 10.17816/DD70821

28. Lu R, Shao Y, Liao S. Analysis of quality of work and life of nurses and its influencing factors. *Chin Nurs Res*. (2015) 29:3221–4. doi: 10.3969/j.issn.1009-6493.2015.26.006

29. Qu NN, Li KJ. Reliability and validity of the Chinese version of the international physical activity questionnaire. *China J Epidemiol*. (2004) 25:87–90. doi: 10.3760/j.issn:0254-6450.2004.03.021

30. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4

31. Tsai P-S, Wang S-Y, Wang M-Y, Su C-T, Yang T-T, Huang C-J, et al. Psychometric evaluation of the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) in primary insomnia and control subjects. *Qual Life Res*. (2005) 14:1943–52. doi: 10.1007/s11136-005-4346-x

32. Liu X, Tang M, Hu L. Reliability and validity of the Pittsburgh sleep quality index. *Chin J Psychiatry*. (1996) 29:103–7.

33. Zung WW. A SELF-RATING DEPRESSION SCALE. *Arch Gen Psychiatry*. (1965) 12:63–70. doi: 10.1001/archpsyc.1965.01720310065008

34. Gong Y, Han T, Chen W, Dib HH, Yang G, Zhuang R, et al. Prevalence of anxiety and depressive symptoms and related risk factors among physicians in China: a cross-sectional study. *PLoS One*. (2014) 9:e103242. doi: 10.1371/journal.pone.0103242

35. Easton S, Van Laar D. User Manual for the Work-Related Quality of Life (WRQoL) Scale: A Measure of Quality of Working Life. 2nd Ed. Portsmouth, UK: University of Portsmouth. (2018)

36. Shao Y, Liao S, Zhong H, Bu S, Wen R. Work-related Quality of Life Scale among Chinese nurses: evaluation of the reliability and validity. *J Nurs Sci*. (2014) 29:1–3. doi: 10.3870/hlxzz.2014.13.001

37. Li P, Wang Y, Zhang M. Translation and validation of the Work-Related Quality of Life Scale (WRQoLS-2) in a nursing cohort. *Contemp Nurse*. (2022) 58:435–45. doi: 10.1080/10376178.2022.2147849

38. Gillen P, Neill RD, Mallett J, Moriarty J, Manthorpe J, Schroder H, et al. Wellbeing and coping of UK nurses, midwives and allied health professionals during COVID-19-a cross-sectional study. *PLoS One*. (2022) 17:e0274036. doi: 10.1371/journal.pone.0274036

39. Nowrouzi-Kia B, Nixon J, Ritchie SD, Wenghofer EF, VanderBurgh D, Sherman JE. Examining the quality of work-life of paramedics in northern Ontario, Canada: A cross-sectional study. *Work*. (2022) 72:135–47. doi: 10.3233/WOR-205025

40. Poku CA, Alem JN, Poku RO, Osei SA, Amoah EO, Ofei AMA. Quality of work-life and turnover intentions among the Ghanaian nursing workforce: A multicentre study. *PLoS One*. (2022) 17:e0272597. doi: 10.1371/journal.pone.0272597

41. Hu S, Liu J, Jiang P, Gu Y. Investigation on current status and analysis on influencing factors of quality of working life among obstetric nurses in Wuxi City. *Occupat Health*. (2021) 37:2634–2637+2642. doi: 10.13329/j.cnki.zyyjk.2021.0596

42. Tu S, Guan H, Zhu Y, Xie X. Impact of the sense of life meaning of nurses in oncology department on the quality of work life. *Chin Nurs Res*. (2022) 36:1395–9. doi: 10.12102/j.issn.1009-6493.2022.08.014

43. Hemsworth D, Baregheh A, Khorakian A, Muterera J, Plough JF, Garcia-Rivera BR, et al. The resource-based reflective risk assessment model for understanding the quality of work life of nurses. *Nurs Outlook*. (2020) 68:194–206. doi: 10.1016/j.outlook.2019.10.006

44. Martins V, Serrão C, Teixeira A, Castro L, Duarte I. The mediating role of life satisfaction in the relationship between depression, anxiety, stress and burnout among Portuguese nurses during COVID-19 pandemic. *BMC Nurs*. (2022) 21:188. doi: 10.1186/s12912-022-00958-3

45. Liu J, Xu X, Zhu C, Luo L, Wang Q, Xiao B, et al. Disrupted structural brain network organization behind depressive symptoms in major depressive disorder. *Front Psychiatry*. (2020) 11:565890. doi: 10.3389/fpsyt.2020.565890

46. Mirchandaney R, Asarnow LD, Kaplan KA. Recent advances in sleep and depression. *Curr Opin Psychiatry*. (2023) 36:34–40. doi: 10.1097/YCO.0000000000000837

47. Thapar A, Eyre O, Patel V, Brent D. Depression in young people. *Lancet*. (2022) 400:617–31. doi: 10.1016/S0140-6736(22)01012-1

48. Varghese S, Frey BN, Schneider MA, Kapczinski F, de Azevedo Cardoso T. Functional and cognitive impairment in the first episode of depression: A systematic review. *Acta Psychiatr Scand*. (2022) 145:156–85. doi: 10.1111/acps.13385

49. Finney RE, Torbenson VE, Riggan KA, Weaver AL, Long ME, Allyse MA, et al. Second victim experiences of nurses in obstetrics and gynecology: SVEST survey. *J Nurs Manag*. (2021) 29:642–52. doi: 10.1111/jonm.13198

50. Kunzler AM, Chmitorz A, Röthke N, Staginnus M, Schäfer SK, Stoffers-Winterling J, et al. Interventions to foster resilience in nursing staff: A systematic review and meta-analyses of pre-pandemic evidence. *Int J Nurs Stud*. (2022) 134:104312. doi: 10.1016/j.ijnurstu.2022.104312

51. Marotta M, Gorini F, Parlanti A, Berti S, Vassalle C. Effect of mindfulness-based stress reduction on the well-being, burnout and stress of Italian healthcare professionals during the COVID-19 pandemic. *J Clin Med*. (2022) 11:3136. doi: 10.3390/jcm11113136

Frontiers in Psychiatry

Risk analysis of depression among adult patients with epilepsy of different sex: a retrospective single-center study from China

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Objective: To determine sex differences in the prevalence of depression and assess the risk factors for depression among adult patients with epilepsy from the Dali area of China.

Methods: We retrospectively analyzed the clinical data of adult patients with epilepsy who visited the First Affiliated Hospital of Dali University from January 2017 to January 2022. Patient Health Questionnaire-9 was used to assess depressive symptoms in patients with epilepsy. The risk factors of depression were analyzed by binary logistic regression among different sex in patients with epilepsy.

Results: There were significant sex differences in depression in patients with epilepsy ($p < 0.001$), and females were 4.27 times more likely to suffer from depression than males (95% confidence interval: 3.70−4.92). The risk factors for depression among female patients with epilepsy included occupation ($p < 0.001$), years with epilepsy ($p < 0.001$), seizure frequency ($p < 0.001$), seizure type ($p < 0.001$), etiology ($p < 0.001$), number of antiseizure medications used ($p < 0.001$), antiseizure medications ($p < 0.001$), and electroencephalogram findings ($p < 0.001$). The risk factors for depression among male patients with epilepsy included age ($p < 0.001$), ethnicity ($p < 0.001$), occupation ($p < 0.001$), years with epilepsy ($p < 0.001$), seizure frequency ($p < 0.001$), seizure type ($p < 0.001$), etiology ($p < 0.001$), number of antiseizure medications used ($p < 0.001$), antiseizure medications ($p < 0.001$), and electroencephalogram findings ($p < 0.001$).

Conclusion: Adult female patients with epilepsy had a higher risk of depression than adult male patients with epilepsy. There were sex differences in the risk factors associated with depression among patients with epilepsy.

1 Introduction

Epilepsy is a prevalent neurological disorder, affecting approximately 70 million individuals worldwide (1). Epidemiological data has shown that the annual incidence rate of epilepsy is approximately 50.4–81.7/100,000 (2). A 2005 report from the World Health Organization showed that epilepsy accounted for 0.5% of the global health burden (3). Beyond the deleterious

effects of epilepsy itself, the presence of associated emotional and psychiatric disorders, including depression, anxiety, and autism spectrum disorder, is gaining growing attention. Patients with epilepsy may suffer heightened psychological stress because of the repetitive nature of epilepsy. This also leads to a higher prevalence of emotional disorders among patients with epilepsy than among the general population and patients with other chronic diseases (4). Moreover, depression, recognized as a mental disorder, is also considered as a common comorbidity linked with epilepsy (5). Depression is frequently seen as anxiety in patients with epilepsy (6). A threefold higher prevalence of depression among patients with epilepsy than among those without epilepsy has been reported (7). The prevalence of depression is approximately 55% in adults with temporal lobe epilepsy and drug-resistant epilepsy (8). In addition, the prevalence of the major depressive disorder is 17.4% (10.0–24.9%) in patients with epilepsy and as high as 20–60% in patients with drug-resistant epilepsy (9, 10). Major depressive disorder remains an important risk factor for suicide in patients with epilepsy (11). In the general population, a higher prevalence of depression has been shown among women than men (12). In patients with epilepsy, some studies have also observed that females exhibit a greater propensity for experiencing depressive symptoms than males (13, 14). In contrast, some studies from China and Ethiopia have found no significant sex differences in epilepsy comorbid depression (15–17). A meta-analysis encompassing diverse populations such as Asian, African, Caucasian, and others, further affirmed the lack of correlation between gender and depression in individuals diagnosed with epilepsy (18). Therefore, further extensive research is imperative to investigate potential sex discrepancies among epilepsy comorbid depression. The risk factors associated with depression in epilepsy patients may exhibit gender-specific variations. Nevertheless, there remains a lack of extensive large-scale studies investigating potential variations in the risk factors for depression among epilepsy patients of diverse genders. Hence, further studies on comorbid depression among patients with epilepsy are warranted, with a specific focus on risk factors for depression of diverse genders.

At present, the research on depression in patients with epilepsy is steadily growing. Lower literacy levels, head trauma, combination therapy with antiseizure medications (ASMs), and focal epilepsy are associated with high anxiety. However, these associations are shown to be not independent (19). A study conducted on risk factors for epilepsy comorbid depression residing in rural Sichuan in China revealed that annual income was associated with risk of depression (20). A cross-sectional study found that the level of education, place of residence, shame, and seizure frequency were significantly associated with depression (21). Many studies have shown that age, sex, marital status, medication dosage, and adverse medication events are also associated with depression in patients with epilepsy (22–26). A study has fund that level of education is a risk factor for depression in male patients with epilepsy, whereas the seizure frequency, epilepsy type, number of ASMs used, age, and settlement are not significantly correlated in females and males (16).

Currently, the risk analysis of depression in patients with epilepsy is gradually increasing, whereas studies on different sex are still lacking in international. Furthermore, the extant large-scale investigations into the association between epilepsy and the risk of depression predominantly emanate from the United Kingdom and the United States. The study from United Kingdom showed that depression was associated with an increased risk of epilepsy, but did

not delve into specific risk factors influencing the onset of depression (27). The study by Viguera et al. (28) found that black race and lower income were risk factors for depression among patients with epilepsy, but there was still a lack of more research on risk factors. Significantly, there is still a lack of large-sample studies from China, particularly with regard to comprehensive studies examining the risk to depression in patients with epilepsy across varying sex profiles. Thus, we herein determined sex differences in the prevalence of depression and assessed the risk factors for depression among adult patients with epilepsy from the Dali area of China.

2 Materials and methods

2.1 Study design

This study is a single-center retrospective study using data from the Epilepsy Center of the First Affiliated Hospital of Dali University. The First Affiliated Hospital of Dali University is a secondary epilepsy center and a teaching hospital of Dali University. This study enrolled patients who had received inpatient or outpatient treatments at our center during January 2017–2022. All patients had undergone psychological testing (Patient Health Questionnaire-9, PHQ-9) upon admission. Inclusion criteria: (1) the diagnosis of epilepsy consistent with the standard of the 2014 International League Against Epilepsy (29), (2) patients aged ≥18 years. Exclusion criteria: (1) patients with cognitive dysfunction (Assessment reliant upon the score obtained from the Mini-Mental State Examination at the time of admission) and psychiatric disorders (e.g., schizophrenia), (2) patients who had not undergone psychological tests at the time of admission. Reconfirmation of epilepsy diagnosis in the included patients was performed based on the clinical history and electroencephalogram (EEG) results. All data and diagnoses were confirmed by two neurologists. The following data were collected from the medical records: the score of PHQ-9, age, sex, ethnicity, occupation, level of educational, marital status, place of residence, years with epilepsy, seizure frequency (within the last 1 year), seizure type, etiology, number of ASMs used, ASMs (Statistical analysis was conducted for patients who used only one type of ASMs), and EEG findings.

PHQ-9 is a short and effective tool used for assessing depressive symptoms. It contains 9 items that reflect the mood of patients in the past 2 weeks (30). Each item contains a typical symptom of depressive disorder, and it is assessed by how often the symptoms have appeared in the past 2 weeks. Each item of this questionnaire consisted of the following 4 answers: "Not at all," "A few days," "More than half days," and "Nearly every day," which correspond to a score of "0," "1," "2," and "3." Past studies have shown that its specificity and sensitivity are high and that it has been widely used in the evaluation of epilepsy and depression. PHQ-9 is increasingly being used to evaluate depression in patients with epilepsy, with good applicability. Past studies have demonstrated that the PHQ-9 score of ≥10 best diagnoses depression (31). In this study, the Chinese versions of the PHQ-9 scales are used to evaluate depression in patients with epilepsy. Patients with PHQ-9 scores ≥10 are classified into the depression group. This study is retrospective in nature and do not necessitate the signing of informed consent forms by the patients. The research protocol received approval from the Ethics Committee of the First Affiliated Hospital of Dali University.

2.2 Statistical analysis

All patients were categorized by sex and their data were subjected to statistical analysis. Categorical variables were presented as percentages. The Chi-square test or Fisher's exact test was used to analyze the categorical variables in patients with epilepsy with or without depression. The binary logistic regression model was applied to analyze the risk factors (variables with $p < 0.05$ in univariate analysis) among the depression group in patients with epilepsy.

3 Results

3.1 Demographic characteristics

Overall, 3,620 eligible patients were included in the present study. Among them, 1,685 (46.55%) patients were female and 1,935 (53.45%) were male. The mean age of females was 36 (standard deviation: 15.05) years and that of males was 39 (standard deviation: 15.83) years. The ethnic distribution was as follows: 1620 (44.75%) Han, 1,113 (30.75%) Bai, 186 (5.14%) Yi, 184 (5.08%) Tibetan, 296 (8.18%) Lisu, and 221 (6.10%) others. Concerning occupation, there were 2,265 (62.57%) farmers, 520 (14.36%) employees, 602 (16.63%) students, and 233 (6.44%) with other jobs. A total of 1725 (47.65%) patients were married and 1895 (52.35%) were unmarried. There were 2048 (56.57%) patients from rural areas and 1,572 (43.43%) from urban areas. The detailed demographic characteristics of patients were shown in Table 1.

The chi-square test revealed a significant difference in sex ($p < 0.001$) between patients with epilepsy with and without depression. Females were more likely to be depressed than males (Table 2). Females were 4.27 times more likely to suffer from depression than males [odds ratio (OR) = 4.27, 95% confidence interval (CI): 3.70–4.92]. In univariate analysis, in order to observe whether a single ASM had an effect on depression, we selected subjects who were treated with only one ASM from the "number of ASMs used" group to conduct chi-square test and binary logistic regression analysis. These ASMs included sodium valproate, carbamazepine, lacosamide, lamotrigine, levetiracetam, topiramate, and oxcarbazepine. Univariate analysis revealed significant differences in age ($p = 0.012$), occupation ($p < 0.001$), years with epilepsy ($p < 0.001$), seizure frequency ($p < 0.001$), seizure type ($p < 0.001$), etiology ($p < 0.001$), number of ASMs used ($p < 0.001$), ASMs ($p < 0.001$), and EEG findings ($p < 0.001$) among female patients with epilepsy with and without comorbid depression. However, the ethnicity ($p = 0.072$), level of education ($p = 0.396$), marital status ($p = 0.408$), and place of residence ($p = 0.754$) were not significantly different between female patients with epilepsy with and without depression (Table 1). Univariate analysis revealed significant differences in age ($p < 0.001$), ethnicity ($p < 0.001$), occupation ($p < 0.001$), years with epilepsy ($p < 0.001$), seizure frequency ($p < 0.001$), seizure type ($p < 0.001$), etiology ($p < 0.001$), number of ASMs used ($p < 0.001$), ASMs ($p < 0.001$), and EEG findings ($p < 0.001$) among male patients with epilepsy with and without comorbid depression. However, the level of education ($p = 0.104$), marital status ($p = 0.086$), and place of residence ($p = 0.077$) did not show significant differences among male patients with epilepsy with and without comorbid depression (Table 1).

3.2 Prevalence and severity of depression symptoms in patients with epilepsy

In total, 1,433 (39.59%) patients were considered to have depression (PHQ-9 score ≥ 10), including 968 (26.74%) females and 465 (12.85%) males. A total of 537 patients (14.83%), including 287 females (7.93%) and 250 males (6.90%), appeared PHQ-9 score of ≥20 in our study (Table 3).

3.3 Factors influencing depression among adult female patients with epilepsy

Variables with $p < 0.05$ in the univariate analysis were included in the regression analysis, including age, occupation, years with epilepsy, seizure frequency, seizure type, etiology, number of ASMs used, ASMs, and EEG findings (Table 1). Occupation ($p < 0.001$), years with epilepsy ($p < 0.001$), seizure frequency ($p < 0.001$), seizure type ($p < 0.001$), etiology ($p < 0.001$), number of ASMs used ($p < 0.001$), ASMs ($p < 0.001$), and EEG findings ($p < 0.001$) had an independent effect on depression in female patients with epilepsy. Females with epilepsy for over 3 years (OR = 1.41, 95% CI: 1.13–1.78) were more likely to develop depression than those with epilepsy for less than 1 year. Focal epilepsy was more likely to cause depression than generalized epilepsy in females (OR = 2.22, 95% CI: 1.80–2.73). In the etiology analysis of epilepsy, those with structural (OR = 5.82, 95% CI: 3.92–8.64) and infectious (OR = 5.72, 95% CI: 3.93–8.32) epilepsy had a higher incidence of depression than those with epilepsy of unknown type. As the number of ASMs used increased, there was a tendency for the risk of depression to increase in female patients with epilepsy (≥ 2 ASMs: OR = 4.12, 95% CI: 2.11–8.05; 1 ASM: OR = 3.18, 95% CI: 1.65–6.13). Compared with oxcarbazepine, levetiracetam (OR = 2.47, 95% CI: 1.45–4.19) and topiramate (OR = 2.66, 95% CI: 1.34–5.30) increased the risk of depression, but sodium valproate (OR = 0.37, 95% CI: 0.21–0.65) reduced the risk of depression in females. Female patients with temporal area discharge (OR = 1.77, 95% CI: 1.37–2.30) were more likely to have depression than those without EEG discharge (Table 4).

3.4 Factors influencing depression among adult male patients with epilepsy

Variables with $p < 0.05$ in the univariate analysis were included in the regression analysis, including age, ethnicity, occupation, years with epilepsy, seizure frequency, seizure type, etiology, number of ASMs used, ASMs, and EEG findings (Table 1). Age ($p < 0.001$), ethnicity ($p < 0.001$), occupation ($p < 0.001$), years with epilepsy ($p < 0.001$), seizure frequency ($p < 0.001$), seizure type ($p < 0.001$), etiology ($p < 0.001$), number of ASMs used ($p < 0.001$), ASMs ($p < 0.001$), and EEG findings ($p < 0.001$) had an independent effect on depression in male patients with epilepsy. People with epilepsy between the ages of 27 and 45 have a higher risk of depression (OR = 1.27, 95% CI: 1.02–1.59). Males with epilepsy for 1–3 years (OR = 2.51, 95% CI: 1.93–3.26) were more likely to develop depression than those with epilepsy for less than 1 year. Male patients with epilepsy with one seizure in a month (OR = 4.10, 95% CI: 3.07–5.48) had a higher probability of depression than those with no seizures in a month. Focal epilepsy was

TABLE 1 Clinical and demographic characteristics among different sex in patients with epilepsy (n = 3,620).

Variable	Female				Male			
	With depression	Without depression	Statistical value	p	With depression	Without depression	Statistical value	p
Age			10.90	**0.012**			26.75	**<0.001**
18–26	311(32.13%)	207(28.87%)			143(30.75%)	430(29.25%)		
27–45	478(49.38%)	331(46.17%)			215(46.24%)	538(36.60%)		
46–64	143(14.77%)	148(20.64%)			73(15.70%)	394(26.80%)		
≥ 65	36(3.72%)	31(4.32%)			34(7.31%)	108(7.35%)		
Ethnicity			10.10	0.072			77.71	**<0.001**
Han Chinese	395(40.81%)	325(45.33%)			215(46.24%)	685(46.60%)		
Bai	334(34.50%)	251(35.01%)			70(15.05%)	458(31.15%)		
Yi	52(5.37%)	20(2.79%)			42(9.03%)	72(4.90%)		
Tibetan	56(5.79%)	36(5.02%)			26(5.59%)	66(4.49%)		
Lisu	107(11.05%)	72(10.04%)			36(7.74%)	81(5.51%)		
others	24(2.48%)	13(1.81%)			76(16.35%)	108(7.35%)		
Occupation			47.51	**<0.001**			87.37	**<0.001**
Farmer	645(66.63%)	416(58.02%)			365(78.49%)	839(57.07%)		
Employee	72(7.44%)	89(12.41%)			36(7.74%)	323(21.97%)		
Student	143(14.77%)	171(23.85%)			37(7.96%)	251(17.08%)		
Others	108(11.16%)	41(5.72%)			27(5.81%)	57(3.88%)		
Level of education			0.72	0.396			2.65	0.104
Below High School	681(70.35%)	518(72.25%)			358(76.99%)	1,076(73.20%)		
Bachelor degree or above	287(29.65%)	199(27.75%)			107(23.01%)	394(26.80%)		
Marital status			0.69	0.408			2.95	0.086
Married	430(44.42%)	304(42.40%)			222(47.74%)	769(52.31%)		
Unmarried	538(55.58%)	413(57.60%)			243(52.26%)	701(47.69%)		
Place of residence			0.10	0.754			3.13	0.077
Rural	603(62.29%)	452(63.04%)			222(47.74%)	771(52.45%)		
Urban	365(37.71%)	265(36.96%)			243(52.26%)	699(47.55%)		
Years with epilepsy			117.19	**<0.001**			62.00	**<0.001**
< 1 year	288(29.75%)	204(28.45%)			163(35.05%)	645(43.88%)		
1-3 years	107(11.06%)	226(31.52%)			159(34.20%)	251(17.07%)		
> 3 years	573(59.19%)	287(40.03%)			143(30.75%)	574(39.05%)		
Seizure frequency			59.35	**<0.001**			40.37	**<0.001**
Seizure-free	323(33.37%)	179(24.96%)			72(15.48%)	548(37.28%)		
< 1 time per month	137(14.15%)	210(29.29%)			251(53.98%)	466(31.70%)		
≥ 1 time per month	508(52.48%)	328(45.75%)			142(30.54%)	456(31.02%)		
Seizure type			56.90	**<0.001**			360.48	**<0.001**
Focal	430(44.42%)	190(26.50%)			393(84.52%)	502(34.15%)		

(Continued)

TABLE 1 (Continued)

Variable	Female				Male			
	With depression	Without depression	Statistical value	p	With depression	Without depression	Statistical value	p
Generalized	538(55.58%)	527(73.50%)			72(15.48%)	968(65.85%)		
Etiology			167.14	**<0.001**			220.53	**<0.001**
Unknown	538(55.58%)	589(82.15%)			143(30.75%)	753(51.22%)		
Structural	170(17.56%)	32(4.46%)			108(23.22%)	358(24.35%)		
Infectious	188(19.42%)	36(5.02%)			71(15.27%)	266(18.10%)		
Metabolic	56(5.79%)	47(6.56%)			132(28.39%)	72(4.90%)		
Immune	16(1.65%)	13(1.81%)			11(2.37%)	21(1.43%)		
Number of ASMs used			20.81	**<0.001**			40.36	**<0.001**
0	13(1.34%)	32(4.46%)			33(7.10%)	110(7.48%)		
1	649(67.05%)	502(70.01%)			324(69.68%)	789(53.67%)		
≥ 2	306(31.61%)	183(25.53%)			108(23.22%)	571(38.85%)		
ASMs			142.52	**<0.001**			247.86	**<0.001**
Sodium valproate	72(11.09%)	167(33.27%)			54(16.67%)	297(37.64%)		
Carbamazepine	77(11.86%)	115(22.91%)			43(13.27%)	208(26.36%)		
Lacosamide	52(8.01%)	29(5.78%)			39(12.04%)	69(8.74%)		
Lamotrigine	49(7.55%)	35(6.97%)			32(9.88%)	122(15.47%)		
Levetiracetam	298(45.92%)	104(20.72%)			120(37.04%)	31(3.93%)		
Topiramate	65(10.02%)	21(4.18%)			25(7.71%)	34(4.31%)		
Oxcarbazepine	36(5.55%)	31(6.17%)			11(3.39%)	28(3.55%)		
EEG findings			97.45	**<0.001**			127.74	**<0.001**
Temporal area discharge	341(39.36%)	129(23.57%)			110(23.66%)	387(31.77%)		
Others	139(18.49%)	221(36.40%)			262(56.34%)	354(26.80%)		
No discharge	368(42.15%)	247(40.03%)			93(20.00%)	529(41.43%)		

TABLE 2 The sex characteristics and multivariate logistic regression analysis for sex in patients with epilepsy.

Variable a	With depression	Without depression	χ^2	p
Sex			420.563	**< 0.001**
Female	968(67.55%)	717(32.78%)		
Male	465(32.45%)	1,470(67.22%)		

b			95% CI	
	OR	p	Lower limit	Upper limit
Sex		**< 0.001**		
Female	4.27	**< 0.001**	3.70	4.92
Male	1			

[a]Chi-square tests for sex between those with and without depression in patients with epilepsy. [b]Binary logistic regression analysis for sex of depression in patients with epilepsy.

more likely to cause depression than generalized epilepsy in males (OR = 10.53, 95% CI: 8.01–13.84). In the analysis of epilepsy etiology, the prevalence of metabolic epilepsy was 9.65 times greater than that of cases classified as epilepsy of unknown etiology (OR = 9.65, 95% CI: 6.88–13.54). Compared with oxcarbazepine, levetiracetam (OR = 9.85, 95% CI: 4.42–21.96) significantly increased the risk of depression, but sodium valproate (OR = 0.46, 95% CI: 0.22–0.98) reduced the risk of depression in males. Male patients with temporal area discharge were 1.61 times (95% CI, 1.19–2.19) more likely to have depression than those without EEG discharge (Table 4).

4 Discussion

This study is the first large-scale investigation about the risk factors for depression among adult patients with epilepsy in Western China. A total of 3,620 patients with epilepsy are included in the study. There are related studies from Northeast, Northwest, and Sichuan regions of China (16, 32, 33), but they have smaller sample sizes and lack comparisons between different ethnicity. In the present study, the overall prevalence of comorbid depression among adults with epilepsy was 39.59% (26.74% in females and 12.85% in males). A meta-analysis reported the prevalence of depression in patients with epilepsy ranged from 4.5 to 59% (34). Another study showed

Depression severity	PHQ-7 score	N (%)	
		Female	Male
Minimal or No depression	0–4	681(40.41%)	1,183(61.14%)
Mild depression	5–9	36(2.14%)	287(14.83%)
Moderate depression	10–14	430(25.52%)	179(9.25%)
Moderately severe depression	15–19	251(14.90%)	36(1.86%)
Severe depression	20–27	287(17.03%)	250(12.92%)

that the prevalence ranged from 20 to 55% (35). In the present study, 39.59% of patients with epilepsy had depression, which was consistent with the findings of these previous studies. This result was lower than the rural prevalence of 52.6% and higher than the urban prevalence of 26.7% reported in studies from western China (20, 36). However, studies from the United Arab Emirates and West China Hospitals showed prevalence rates of 25 and 26.9%, which were lower than the 39.59% we reported (35, 37). The present study results indicated that females were at a higher risk of having depression than males, which was similar to the findings of studies from Ethiopia and India (38, 39). Our study indicated that female patients with epilepsy who considered depression had significantly higher PHQ-9 scores than males, which also suggested that depressive symptoms might be more severe in females compared males. The psychological problems of female epilepsy patients need to be paid more attention. One prospective study found an 11.28% prevalence of depression among male patients with epilepsy, which was consistent with our results (32). However, the prevalence of depression in women in this study was 18.66%, which was significantly lower than that shown by our study. One possible explanation is the difference in the diagnosis of depression and sample sizes. Another possibility is the region included in the present study (Dali, Yunnan Province, China) has many ethnic minorities, a low level of economy and education, and a lack of awareness of the disease. The higher risk of depression in females than in males may be attributed to different personalities and income inequalities (40).

Patients with epilepsy with lower levels of education were more likely to suffer from depression (41). Another study reported the opposite result (21). However, the present study did not find a correlation between the level of education of men and women and depression, which was in line with the results of Wang et al. (20). Place of residence was also considered a risk factor for depression in patients with epilepsy, as reported by a study from Ethiopia (21). They found that patients with epilepsy living in rural areas tended to be more prone to depression than those living in urban areas. However, we found that they lacked correlation. Therefore, more samples are required to analyze the condition. In the relationship between marital status and depression, we found no effect in patients with epilepsy of different sex, which was consistent with the findings reported by some studies (17, 25). On the contrary, other studies identified that being unmarried was an independent risk factor for epilepsy comorbid depression (32, 38). This interpretation may be related to differences in different countries, ethnicities, and sample sizes. At present, there

was still a lack of research on the relationship between different ethnic groups and epilepsy comorbid depression. We found that male Bai people had a lower risk of depression, which might be related to the entertainment source of Bai people, such as dancing and singing. It was also conceivable that the Bai population might possess a reduced genetic predisposition to depression. However, the current body of research in this field remained insufficient. Nonetheless, in female epilepsy patients, susceptibility to depression showed no discernible association with ethnicity. Our analysis of different occupations revealed that office workers had the lowest risk of depression, and the trend was similar in females and males. This might be related to the higher income of office workers. However, there is still a lack of research on the occurrence of depression among different occupations in patients with epilepsy. More studies are needed on this topic. The relationship between age and depression in patients with epilepsy was controversial, some studies had suggested a relationship whereas others negated this view (42, 43). This study found that the relationship between age and depression was not obvious in female patients with epilepsy. Male patients with epilepsy aged 27–45 were 1.27 times more likely to suffer from depression than those aged over 65 years. However, male patients with epilepsy aged 46–64 years were less likely to develop depression than those aged over 65 years. A recent study had shown that patients with epilepsy aged 29–39 years show a higher tendency to depression (44). And this has similar results to our findings. A cross-sectional study of different ages and psychological stress showed that the PHQ-9 and PSS-10 scores were higher in the middle age group (26–44 years old) than high age group (>45 years old). It is possible that males between the ages of 27 and 45 may experience heightened psychological stress than others (45). This study also showed that patients with epilepsy were more likely to develop depression within 1–5 years, which was inversely correlated with the duration of the disease. Our results showed that males had the highest risk of depression within 3 years with epilepsy, whereas females were at risk after having epilepsy for more than 3 years, which was consistent with findings of the previous study. However, we did not study the condition over 5 years. Additional research is warranted to investigate the relationship between age and depression in patients with epilepsy.

One meta-analysis showed that more than 20 studies had reported that seizure frequency is a risk factor for depression (46). We also observed that seizure frequency was an independent risk factor for depression in both males and females. More frequent seizures might predict more severe depression (21). There may be a bidirectional relationship between depression and frequent seizures. One prospective study found that the occurrence of depressive symptoms was a predictor of epilepsy recurrence in adult patients with newly diagnosed epilepsy (47). Life-long mood disorders were also considered risk factors for seizure recurrence in adults (48). Moreover, focal seizures were more likely to present with depressive symptoms (49). Our findings also revealed that patients with focal epilepsy of both sexes were more prone to experiencing depression and significantly in males. This may be due to the existence of the same anatomical basis between depression and temporal lobe epilepsy. For example, patients with epilepsy and depression might have atrophy of the frontal lobe, hippocampus, and amygdala (50). Our study found a higher prevalence of depression in both females and males with temporal lobe discharge, which may explain the higher probability of depression in focal epilepsy.

TABLE 4 Binary logistic regression analysis for risk factors of depression among different sex in patients with epilepsy.

Variable	Female				Male			
			95%CI				95%CI	
	OR	P	Lower limit	Upper limit	OR	P	Lower limit	Upper limit
Age		<0.001				<0.001		
18–26	1.29	0.090	0.96	1.74	1.06	0.691	0.81	1.38
27–45	1.24	0.100	0.96	1.61	1.27	0.036	1.02	1.59
46–64	0.83	0.189	0.63	1.10	0.59	<0.001	0.46	0.75
≥ 65	1				1			
Ethnicity	–	–	–	–		<0.001		
Han Chinese	–	–	–	–	0.45	<0.001	0.32	0.62
Bai	–	–	–	–	0.22	<0.001	0.15	0.32
Yi	–	–	–	–	0.83	0.444	0.51	1.34
Tibetan	–	–	–	–	0.56	0.035	0.33	0.96
Lisu	–	–	–	–	0.63	0.066	0.39	1.03
others	–	–	–	–	1			
Occupation		<0.001				<0.001		
Farmer	0.59	0.006	0.40	0.86	0.92	0.725	0.57	1.48
Employee	0.31	<0.001	0.19	0.49	0.24	<0.001	0.13	0.42
Student	0.32	<0.001	0.21	0.48	0.31	<0.001	0.18	0.55
Others	1				1			
Years with epilepsy		<0.001				<0.001		
> 3 years	1.41	0.003	1.13	1.78	0.99	0.911	0.77	1.27
1-3 years	0.34	<0.001	0.25	0.45	2.51	<0.001	1.93	3.26
< 1 year	1				1			
Seizure frequency		<0.001				<0.001		
≥ 1 time per month	0.86	0.192	0.68	1.08	2.37	<0.001	1.74	3.23
< 1 time per month	0.36	<0.001	0.27	0.48	4.10	<0.001	3.07	5.48
Seizure-free	1				1			
Seizure type		<0.001				<0.001		
Focal	2.22	<0.001	1.80	2.73	10.53	<0.001	8.01	13.84
Generalized	1				1			
Etiology		<0.001				<0.001		
Structural	5.82	<0.001	3.92	8.64	1.59	0.001	1.20	2.10
Infectious	5.72	<0.001	3.93	8.32	1.41	0.035	1.02	1.93
Metabolic	1.30	0.198	0.87	1.96	9.65	<0.001	6.88	13.54
Immune	1.35	0.430	0.64	2.83	2.76	0.008	1.30	5.85
Unknown	1				1			
Number of ASMs used		<0.001				<0.001		
≥ 2	4.12	<0.001	2.11	8.05	0.63	0.040	0.41	0.98
1	3.18	0.001	1.65	6.13	1.37	0.133	0.91	2.06
0	1				1			
ASMs		<0.001				<0.001		
Sodium valproate	0.37	<0.001	0.21	0.65	0.46	0.046	0.22	0.98
Carbamazepine	0.58	0.054	0.33	1.01	0.53	0.103	0.24	1.14
Lacosamide	1.54	0.198	0.80	2.99	1.44	0.373	0.65	3.20

(Continued)

TABLE 4 (Continued)

Variable	Female				Male			
	OR	P	95%CI		OR	P	95%CI	
			Lower limit	Upper limit			Lower limit	Upper limit
Lamotrigine	1.21	**0.571**	0.63	2.30	0.67	0.322	0.30	1.48
Levetiracetam	2.47	**0.001**	1.45	4.19	9.85	**<0.001**	4.42	21.96
Topiramate	2.66	**0.005**	1.34	5.30	1.87	0.157	0.79	4.46
Oxcarbazepine	1				1			
EEG findings		**<0.001**				**<0.001**		
Temporal area discharge	1.77	**<0.001**	1.37	2.30	1.61	**<0.001**	1.19	2.19
Others	0.42	**<0.001**		0.55	4.22	**0.002**	3.20	5.52
No discharge	1				1			

In the analysis of the etiology of epilepsy, the prevalence of epilepsy of the unknown type was significantly higher other types. An epilepsy of unknown type was responsible for one-third of all etiologies (51), which could be attributed to the relatively less advanced diagnostic techniques for determining the underlying causes. Improving the diagnostic techniques remains pivotal for the categorization of epilepsy etiologies. This factor also contributed to the absence of genetic type data. Additionally, there was a higher proportion of female patients than male patients with epilepsy of an unknown type. This may potentially reflect sex discrimination within the diagnostic process. In the case of women, sex discrimination could lead to the development of depressive symptoms (52). The possibility of sex discrimination during the diagnostic process could also potentially contribute to the stigma experienced by women with epilepsy. However, there is a lack of research in this field. In the analysis of the relationship between the etiology of epilepsy and depression, we found that females with structural and infectious epilepsy and males with metabolic epilepsy had the greatest probability of depression, which might be potentially attributed to higher alcohol consumption among males. Infectious and structural etiologies were risk factors for suicidality in patients with epilepsy (53). Suicidal patients are often present with depressive symptoms. Our findings aligned with those of Lin et al. (53).

We also found that the number of ASMs used was an independent risk factor for depression in patients with epilepsy. A higher number of ASMs used often predicted a higher risk of depression. This was most pronounced in females, consistent with the findings of a previous study (54). It might also be related to the fact that some ASMs could cause mood disorders (55). Our study observed that sodium valproate decreased the risk of depression and levetiracetam increased the risk of depression in all patients with epilepsy. Topiramate increased the risk of depression in females, but not in male patients with epilepsy. Some studies indicated that sodium valproate, lamotrigine, and carbamazepine reduced the risk of depression in patients with epilepsy. Conversely, levetiracetam, benzodiazepines, and topiramate had been associated with an increased risk of depression in epilepsy patients, according to research findings (56–59). However, our results did not find an association between carbamazepine and depressive in patients with epilepsy. This may be due to the small sample size. Further research may be needed.

Nonetheless, our study has certain limitations. First, our study was a single-center, retrospective study; thus, there might be an under-representation of sample sizes. Second, we did not involve minors and only adult patients. Third, we did not exclude less common psychiatric disorders, such as bipolar disorder. Fourth, some patients had missing EEG findings (12.24%), which might have an impact on the analysis of EEG findings. Fifth, the diagnosis of depression was based on the patient's PHQ-9 score at admission over the past 5 years rather than on a clinical diagnostic assessment, which may have led to an overestimation of prevalence. Sixth, as a concise depression assessment tool, the PHQ-9 did possess limitations and it might not comprehensively distinguish among patients experiencing anxiety.

5 Conclusion

Adult female patients with epilepsy have a higher susceptibility to depression than male patients with epilepsy. Furthermore, female and male patients with epilepsy have distinct risk factors for depression. Occupation, years with epilepsy, seizure frequency, seizure type, etiology, number of ASMs used, ASMs, and EEG findings are independent risk factors for depression in female patients with epilepsy. In male patients with epilepsy, age, ethnicity, occupation, years with epilepsy, seizure frequency, seizure type, etiology, number of ASMs used, ASMs, and EEG findings are independent risk factors for depression. Early detection and timely management of these risk factors may help reduce the incidence of depression in patients with epilepsy.

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 research protocol received approval from the Ethics Committee of the First Affiliated Hospital of Dali University. This

study is retrospective in nature and hence did not necessitate the signing of informed consent forms by the patients.

References

1. Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. *Lancet*. (2019) 393:689–701. doi: 10.1016/S0140-6736(18)32596-0

2. Collaborators GBDE. Global, regional, and national burden of epilepsy, 1990-2016: a systematic analysis for the global burden of disease study 2016. *Lancet Neurol*. (2019) 18:357–75. doi: 10.1016/S1474-4422(18)30454-X

3. The Lancet. Wanted: a global campaign against epilepsy. *Lancet*. (2012) 380:1121. doi: 10.1016/S0140-6736(12)61646-8

4. Mula M, Kanner AM, Jette N, Sander JW. Psychiatric comorbidities in people with epilepsy. *Neurol Clin Pract*. (2021) 11:e112–20. doi: 10.1212/CPJ.0000000000000874

5. Kanner AM. Depression in epilepsy: prevalence, clinical semiology, pathogenic mechanisms, and treatment. *Biol Psychiatry*. (2003) 54:388–98. doi: 10.1016/s0006-3223(03)00469-4

6. Hingray C, McGonigal A, Kotwas I, Micoulaud-Franchi JA. The relationship between epilepsy and anxiety disorders. *Curr Psychiatry Rep*. (2019) 21:40. doi: 10.1007/s11920-019-1029-9

7. Fiest KM, Dykeman J, Patten SB, Wiebe S, Kaplan GG, Maxwell CJ, et al. Depression in epilepsy: a systematic review and meta-analysis. *Neurology*. (2013) 80:590–9. doi: 10.1212/WNL.0b013e31827b1ae0

8. Christian CA, Reddy DS, Maguire J, Forcelli PA. Sex differences in the epilepsies and associated comorbidities: implications for use and development of pharmacotherapies. *Pharmacol Rev*. (2020) 72:767–800. doi: 10.1124/pr.119.017392

9. Hermann B, Seidenberg M, Jones J. The neurobehavioural comorbidities of epilepsy: can a natural history be developed? *Lancet Neurol*. (2008) 7:151–60. doi: 10.1016/S1474-4422(08)70018-8

10. Singh T, Goel RK. Epilepsy associated depression: An update on current scenario, suggested mechanisms, and opportunities. *Neurochem Res*. (2021) 46:1305–21. doi: 10.1007/s11064-021-03274-5

11. Kanner AM, Saporta AS, Kim DH, Barry JJ, Altalib H, Omotola H, et al. Mood and anxiety disorders and suicidality in patients with newly diagnosed focal epilepsy: An analysis of a complex comorbidity. *Neurology*. (2023) 100:e1123–34. doi: 10.1212/WNL.0000000000201671

12. Altemus M, Sarvaiya N, Neill Epperson C. Sex differences in anxiety and depression clinical perspectives. *Front Neuroendocrinol*. (2014) 35:320–30. doi: 10.1016/j.yfrne.2014.05.004

13. Gaus V, Kiep H, Holtkamp M, Burkert S, Kendel F. Gender differences in depression, but not in anxiety in people with epilepsy. *Seizure*. (2015) 32:37–42. doi: 10.1016/j.seizure.2015.07.012

14. Zhu XR, Zhu ZR, Wang LX, Zhao T, Han X. Prevalence and risk factors for depression and anxiety in adult patients with epilepsy: Caregivers' anxiety and place of residence do mater. *Epilepsy Behav*. (2022) 129:108628. doi: 10.1016/j.yebeh.2022.108628

15. Bifftu BB, Dachew BA, Tiruneh BT, Birhan Tebeje N. Depression among people with epilepsy in Northwest Ethiopia: a cross-sectional institution based study. *BMC Res Notes*. (2015) 8:585. doi: 10.1186/s13104-015-1515-z

16. Liu Z, Yin R, Fan Z, Fan H, Wu H, Shen B, et al. Gender differences in associated and predictive factors of anxiety and depression in people with epilepsy. *Front Psych*. (2020) 11:670. doi: 10.3389/fpsyt.2020.00670

17. Tegegne MT, Mossie TB, Awoke AA, Assaye AM, Gebrie BT, Eshetu DA. Depression and anxiety disorder among epileptic people at Amanuel specialized mental hospital, Addis Ababa, Ethiopia. *BMC Psychiatry*. (2015) 15:210. doi: 10.1186/s12888-015-0589-4

18. Chu C. Association between epilepsy and risk of depression: a meta-analysis. *Psychiatry Res*. (2022) 312:114531. doi: 10.1016/j.psychres.2022.114531

19. Munger Clary HM, Snively BM, Hamberger MJ. Anxiety is common and independently associated with clinical features of epilepsy. *Epilepsy Behav*. (2018) 85:64–71. doi: 10.1016/j.yebeh.2018.05.024

20. Wang HJ, Tan G, Deng Y, He J, He YJ, Zhou D, et al. Prevalence and risk factors of depression and anxiety among patients with convulsive epilepsy in rural West China. *Acta Neurol Scand*. (2018) 138:541–7. doi: 10.1111/ane.13016

21. Addis B, Wolde M, Minyihun A, Aschalew AY. Prevalence of depression and associated factors among patients with epilepsy at the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia, 2019. *PloS One*. (2021) 16:e0257942. doi: 10.1371/journal.pone.0257942

22. Dessie G, Mulugeta H, Leshargie CT, Wagnew F, Burrowes S. Depression among epileptic patients and its association with drug therapy in sub-Saharan Africa: a systematic review and meta-analysis. *PloS One*. (2019) 14:e0202613. doi: 10.1371/journal.pone.0202613

23. Engidaw NA, Bacha L, Kenea A. Prevalence of depression and associated factors among epileptic patients at Ilu Ababore zone hospitals, south West Ethiopia, 2017: a cross-sectional study. *Ann Gen Psychiatry*. (2020) 19:19. doi: 10.1186/s12991-020-00268-5

24. Kwon OY, Park SP. Depression and anxiety in people with epilepsy. *J Clin Neurol*. (2014) 10:175–88. doi: 10.3988/jcn.2014.10.3.175

25. Onwuekwe I, Ekenze O, Bzeala A, Ejekwu J. Depression in patients with epilepsy: a study from Enugu, south East Nigeria. *Ann Med Health Sci Res*. (2012) 2:10–3. doi: 10.4103/2141-9248.96929

26. Yang Y, Yang M, Shi Q, Wang T, Jiang M. Risk factors for depression in patients with epilepsy: a meta-analysis. *Epilepsy Behav*. (2020) 106:107030. doi: 10.1016/j.yebeh.2020.107030

27. Josephson CB, Lowerison M, Vallerand I, Sajobi TT, Patten S, Jette N, et al. Association of Depression and Treated Depression with Epilepsy and seizure outcomes: a multicohort analysis. *JAMA Neurol*. (2017) 74:533–9. doi: 10.1001/jamaneurol.2016.5042

28. Viguera AC, Fan Y, Thompson NR, Lapin B, Chaitoff A, Griffith SD, et al. Prevalence and predictors of depression among patients with epilepsy, stroke, and multiple sclerosis using the Cleveland Clinic knowledge program within the neurological institute. *Psychosomatics*. (2018) 59:369–78. doi: 10.1016/j.psym.2017.12.003

29. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. (2014) 55:475–82. doi: 10.1111/epi.12550

30. Fiest KM, Patten SB, Jette N. Screening for depression and anxiety in epilepsy. *Neurol Clin*. (2016) 34:351–61. doi: 10.1016/j.ncl.2015.11.003

31. Fischer F, Levis B, Falk C, Sun Y, Ioannidis JPA, Cuijpers P, et al. Comparison of different scoring methods based on latent variable models of the PHQ-9: an individual participant data meta-analysis. *Psychol Med*. (2021) 52:3472–83. doi: 10.1017/S0033291721000131

32. Li Q, Chen D, Zhu LN, Wang HJ, Xu D, Tan G, et al. Depression in people with epilepsy in West China: status, risk factors and treatment gap. *Seizure*. (2019) 66:86–92. doi: 10.1016/j.seizure.2019.02.014

33. Zhong R, Chen Q, Li M, Li N, Zhang X, Lin W. Sex differences in anxiety in patients with epilepsy: status and risk factors analysis. *Epilepsy Behav*. (2021) 116:107801. doi: 10.1016/j.yebeh.2021.107801

34. Scott AJ, Sharpe L, Hunt C, Gandy M. Anxiety and depressive disorders in people with epilepsy: a meta-analysis. *Epilepsia*. (2017) 58:973–82. doi: 10.1111/epi.13769

35. Alsaadi T, El Hammasi K, Shahrour TM, Shakra M, Turkawi L, Almaskari B, et al. Prevalence of depression and anxiety among patients with epilepsy attending the epilepsy clinic at sheikh Khalifa Medical City, UAE: a cross-sectional study. *Epilepsy Behav*. (2015) 52:194–9. doi: 10.1016/j.yebeh.2015.09.008

36. Tong X, An D, Lan L, Zhou X, Zhang Q, Xiao F, et al. Validation of the Chinese version of the neurological disorders depression inventory for epilepsy (C-NDDI-E) in West China. *Epilepsy Behav*. (2015) 47:6–10. doi: 10.1016/j.yebeh.2015.03.012

37. Shen S, Dong Z, Zhang Q, Xiao J, Zhou D, Li J. The overlapping relationship among depression, anxiety, and somatic symptom disorder and its impact on the quality of life of people with epilepsy. *Ther Adv Neurol Disord*. (2022) 15:17562864221138147. doi: 10.1177/17562864221138147

38. Chaka A, Awoke T, Yohannis Z, Ayano G, Tareke M, Abate A, et al. Determinants of depression among people with epilepsy in Central Ethiopia. *Ann Gen Psychiatry*. (2018) 17:27. doi: 10.1186/s12991-018-0197-z

39. Rashid H, Katyal J, Sood M, Tripathi M. Depression in persons with epilepsy: a comparative study of different tools in Indian population. *Epilepsy Behav*. (2021) 115:107633. doi: 10.1016/j.yebeh.2020.107633

40. Zhong R, Chen Q, Li N, Zhang X, Lin W. Sex-based differences in the prevalence of and risk factors for depression in adult patients with epilepsy in Northeast China. *Epilepsy Behav*. (2021) 122:108201. doi: 10.1016/j.yebeh.2021.108201

41. Pham T, Sauro KM, Patten SB, Wiebe S, Fiest KM, Bulloch AGM, et al. The prevalence of anxiety and associated factors in persons with epilepsy. *Epilepsia*. (2017) 58:e107–10. doi: 10.1111/epi.13817

42. Ekinci O, Titus JB, Rodopman AA, Berkem M, Trevathan E. Depression and anxiety in children and adolescents with epilepsy: prevalence, risk factors, and treatment. *Epilepsy Behav*. (2009) 14:8–18. doi: 10.1016/j.yebeh.2008.08.015

43. Vujisic S, Vodopic S, Radulovic L, Injac-Stevovic L. Psychiatric comorbidities among patients with epilepsy in Montenegro. *Acta Clin Croat*. (2014) 53:411–6.

44. Bolling-Ladegaard E, Dreier JW, Kessing LV, Budtz-Jorgensen E, Lolk K, Christensen J. Directionality of the association between epilepsy and depression: a Nationwide register-based cohort study. *Neurology*. (2023) 100:e932–42. doi: 10.1212/WNL.0000000000201542

45. Zhang J, Pan Y, Hong J, Guo H, Wang M, Liu X, et al. Differences of medically unexplained symptoms among patients of different ages and sexes in the psychological clinic of a general hospital and the influencing factors of MUS: a cross-sectional study. *Front Psych*. (2022) 13:930212. doi: 10.3389/fpsyt.2022.930212

46. Qin SK, Yang ZX, Guan ZW, Zhang JH, Ping X, Lu Y, et al. Exploring the association between epilepsy and depression: a systematic review and meta-analysis. *PloS One*. (2022) 17:e0278907. doi: 10.1371/journal.pone.0278907

47. Zhong R, Chen Q, Zhang X, Li N, Lin W. Depressive and anxiety symptoms are predictors of seizure recurrence in adults with newly diagnosed epilepsy. *Front Psych*. (2021) 12:784737. doi: 10.3389/fpsyt.2021.784737

48. Baldin E, Hauser WA, Pack A, Hesdorffer DC. Stress is associated with an increased risk of recurrent seizures in adults. *Epilepsia*. (2017) 58:1037–46. doi: 10.1111/epi.13741

49. Peng WF, Ding J, Li X, Mao LY, Wang X. Clinical risk factors for depressive symptoms in patients with epilepsy. *Acta Neurol Scand*. (2014) 129:343–9. doi: 10.1111/ane.12191

50. Kanner AM. Depression in epilepsy: a complex relation with unexpected consequences. *Curr Opin Neurol*. (2008) 21:190–4. doi: 10.1097/WCO.0b013e3282f4e978

51. Dubey D, Alqallaf A, Hays R, Freeman M, Chen K, Ding K, et al. Neurological autoantibody prevalence in epilepsy of unknown etiology. *JAMA Neurol*. (2017) 74:397–402. doi: 10.1001/jamaneurol.2016.5429

52. Stepanikova I, Acharya S, Abdalla S, Baker E, Klanova J, Darmstadt GL. Gender discrimination and depressive symptoms among child-bearing women: ELSPAC-CZ cohort study. *EClinicalMedicine*. (2020) 20:100297. doi: 10.1016/j.eclinm.2020.100297

53. Lin M, Chen J, Li S, Qin Y, Wang X, Liu Y, et al. Risk factors for suicidal tendency in people with epilepsy in China: a case-control study. *Sci Rep*. (2021) 11:2742. doi: 10.1038/s41598-021-81870-9

54. Tombini M, Assenza G, Quintiliani L, Ricci L, Lanzone J, Ulivi M, et al. Depressive symptoms and difficulties in emotion regulation in adult patients with epilepsy: association with quality of life and stigma. *Epilepsy Behav*. (2020) 107:107073. doi: 10.1016/j.yebeh.2020.107073

55. Gangar K, Bhatt LK. Therapeutic targets for the treatment of comorbidities associated with epilepsy. *Curr Mol Pharmacol*. (2020) 13:85–93. doi: 10.2174/1874467212666191203101606

56. Hasegawa N, Tohyama J. Positive and negative effects of perampanel treatment on psychiatric and behavioral symptoms in adult patients with epilepsy. *Epilepsy Behav*. (2021) 117:107515. doi: 10.1016/j.yebeh.2020.107515

57. Ho PH, Leung WCY, Leung IYH, Chang RSK. Factors associated with depression in people with epilepsy: a retrospective case-control analysis. *Hong Kong Med J*. (2020) 26:311–7. doi: 10.12809/hkmj198310

58. Joshi R, Tripathi M, Gupta P, Goyal A, Gupta YK. Depression in patients receiving pharmacotherapy for epilepsy: An audit in a tertiary care Centre. *Pharmacol Rep*. (2019) 71:848–54. doi: 10.1016/j.pharep.2019.04.021

59. Liu J, Wang LN. Treatment of epilepsy for people with Alzheimer's disease. *Cochrane Database Syst Rev*. (2021) 2021:CD011922. doi: 10.1002/14651858.CD011922.pub4

Depression and anxiety in female refugees from East Africa and the Middle East displaced to Germany: cross-sectional results of the female refugee study, taking sociodemographic and migration-related factors into account

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At the end of 2022, 108.4 million people around the world were forcibly displaced, the highest number ever recorded. Of these, 50% were women. Despite this situation, little is known about the mental health of female refugees. The first aim of this study was to examine the prevalence of depression and anxiety symptoms among female refugees in Germany. The second aim was to examine which sociodemographic and migration-related variables have an impact on refugees' mental health, and the third aim was to assess the potential predictors of their mental health. A sample of 92 female refugees from East Africa and the Middle East living in Germany were interviewed. Symptoms of depression and anxiety were assessed using the Hopkins Symptom Checklist (HSCL-25). The experience of potentially traumatic events (PTEs) was assessed using the Posttraumatic Diagnostic Scale (PDS) and the Harvard Trauma Questionnaire (HTQ). In our sample of female refugees, 65.2% reported symptoms of depression, and 60.9% reported symptoms of anxiety. Symptoms of depression or anxiety were associated with being from the Middle East, having a higher level of education, and reporting more PTEs. The multiple regression model for anxiety was able to explain 32.4% of the variance in anxiety symptoms. The findings highlight the high burden of mental health problems that female refugees bear. The identified predictors of depressive and anxiety symptoms should sensitize medical and refugee professionals to identify vulnerable individuals and groups, refer them to appropriate psychological treatment, and, where possible, modify the identified predictors.

KEYWORDS

depression, anxiety, mental health, female refugee, traumatic event

Introduction

In 2022, the number of forcibly displaced persons in the world was the highest on record (1). The United Nations High Commissioner for Refugees (UNHCR) has estimated that there are 108.4 million forcibly displaced people worldwide, of whom 35.3 million are refugees (1). In 2016, when the interviews for this study began, more than 720,000 asylum applications were registered in Germany (2), the highest number ever recorded in Germany. Women accounted for 38% of all asylum applications in Germany in 2016 (2). The five most represented countries of origin that year were Syria, Afghanistan, Iraq, Iran, and Eritrea. At the time of the interviews for this study, the countries with the best prospects of obtaining a right of residence were Afghanistan, Iraq, Iran, Eritrea, Somalia, and Syria. It is important to know about the experiences of refugees and the measures taken in 2016 that can help people seeking protection in Germany today. However, the refugee population today is different in terms of country of origin, the circumstances of flight, and the reception conditions in Germany (2, 3). In 2022, Germany recorded the highest increase of people seeking protection[1] in the country since records have been kept (3). Approximately 1.1 million refugees from Ukraine have sought protection in Germany as a result of the international conflict between Russia and Ukraine (3, 4). In 2022 also, around 47.0% of people seeking protection in Germany were female, and among Ukrainian refugees, up to 64% were girls and women[2] (3). In response to the influx of refugees from Ukraine, the EU invoked the Temporary Protection Directive (5), according to which refugees from that country are granted a residence permit for one to three years without any bureaucratic application procedure (5). This grants them, for example, the right to stay in a private flat instead of a collective accommodation and access to statutory health insurance instead of emergency health insurance (6, 7). Therefore, a comparison between the refugee population in 2016 and today is only possible to a limited extent.

The UNHCR reports that women are a vulnerable group within the refugee population (8, 9). They experience more gender-based and sexual violence than men (10) and thus require special attention to address their needs (11). Research on refugees' mental health shows that female refugees have more mental health problems than male refugees (9, 10, 12, 13). Mental health disorders, such as depression and anxiety, are also more common among female refugees than among male refugees (13). A systematic review by Morina et al. (14) found that most studies in refugee populations focus on posttraumatic stress disorder (PTSD), depression and anxiety. There are few studies examining other mental health disorders. Morina et al. (14) point out, that the prevalence of all mental disorders must be higher in the refugee population due to the difficult circumstances during and after flight. Also chronic mental health problems may get worse under the lack of treatment (14). It is clear that the presence of mental health problems makes integration into the host country more difficult (15).

It remains to be seen, however, what impact mental health problems in refugee mothers have on the integration of their children.

At the same time, a review by Blackmore et al. found great heterogeneity in the reported prevalence of mental health problems, such as symptoms of depression and anxiety, in refugee populations and a lack of data on gender-specific mental health problems in these populations (16). Comparison with other studies shows that the prevalence of symptoms of depression or anxiety in the female refugee population is rarely reported (10, 17). Studies on the mental health of male and female refugees often consist mainly of male refugees, do not report their findings by gender, age, or ethnicity, and report heterogeneous prevalence rates for symptoms of depression and anxiety (10, 17).

More research is thus needed on the prevalence of symptoms of depression and anxiety in female refugee populations. The recent influx of Ukrainian refugees to Germany, most of whom are women (64.0%), underlines the importance and timeliness of this issue (3).

The refugee population in Germany and around the world is heterogeneous in terms of, for example, country of origin, route of flight, opportunities for residency in, and reception in the host country. It is therefore important to understand which sociodemographic and migration-related factors are associated with the mental health of refugees.

Reviews indicate that the association between mental health and sociodemographic and migration-related variables has not been well studied (10, 17–19). Only a few reviews have examined this association (10, 17–19), and the reported results are heterogeneous. Studies have shown that an older age (9, 10, 20–22) and having experienced more PTEs (21, 23–25) are associated with mental health problems. In their review, Mesa-Vieira et al. (10) reported that migrants with previous exposure to violence were likely to have poor mental health. Sundquist et al. (26) reported that economic difficulties in the host country appeared to be an even greater factor in poor mental health than exposure to violence prior to migration. Mesa-Vieira et al. (10) found that lower income levels in the host country and, in contrast to the above-mentioned studies, a younger age were associated with poor mental health (10). Lindert et al. (17) found in their review that a high level of income in the host country may be associated with better mental health in labor migrants, but not in refugees. Often, the reviews include refugees as well as migrants and labor migrants (10, 17); therefore, subgroup analyses by gender are not possible (17).

Regarding the relationship between the country of origin and mental health among refugees, the results are heterogeneous. Some studies have found significant differences in symptoms of depression and anxiety according to country of origin (23, 27, 28), while others have found no association between country of origin and mental health (24). Few studies have examined the association between the level of education and mental health in refugee populations. However, in those that do, the results are heterogeneous. A positive association between the level of education and symptoms of depression and anxiety (29), a negative association (9), and no association (22) have been reported. In addition, there is a lack of research on post-migration factors that may be associated with refugees' mental health, and current stressors in the lives of refugees should also be considered (18).

To address the above-mentioned research gaps, the first aim of this study was to investigate the prevalence of symptoms of depression and anxiety in female refugees. The second aim was to examine the

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1 Protection seekers are people applying for asylum, people with asylum, and refugees in Germany.

2 Since February 24, 2023, with the introduction of martial law, most Ukrainian men of draft age were banned from leaving Ukraine.

effects of sociodemographic and migration-related variables on mental health. Literature research was conducted to examine the sociodemographic and migration-related variables relevant to refugees' mental health. The third aim was to assess the potential predictors of mental health among female refugees.

Method

The present study was part of a larger research project, the Female Refugee Study (FRS) (30). This multicenter study was conducted in 2016 and 2017 in six German federal states and was funded by the State Commissioner for Migration, Refugees and Integration of the German government. The present study examines data from the Rhineland-Palatinate study center that we collected for the FRS. Ethics committee approval was obtained on September 19, 2016, and the study is registered in the Ethics Committee Register of the Rhineland-Palatinate Medical Association under the number 837.316.16 (10635). Inclusion criteria were female gender, age 18 years and older, cognitive capacity to be interviewed (verbally or in writing), ability to speak and understand one of the provided study languages (Arabic, Dari/Farsi, Somali, Tigrinya), living in a refugee reception center, and beingfrom Afghanistan, Eritrea, Iran, Somalia, and Syria. At that time, refugees from these countries had a high chance of being granted asylum in Germany. Recruitment took place in randomly selected refugee reception centers in Rhineland-Palatinate. The owner and operator of the reception centers for refugees, granted permission for the study. Female refugees were recruited through a 1.5-h information sessions at refugee reception centers. Each woman interested in participating in the study was interviewed privately after at least a 1-day interval. Informed consent was obtained either in writing or verbally. The interviews were conducted by trained bilingual female interviewers either as a guided questionnaire assessment or as a structured interview. Interviewers did not insist to answering to minimize the risk of retraumatizing. The questionnaire consisted of 71 questions, including psychometric instruments for trauma experience, quality of life, and symptoms of depression and anxiety. The questionnaire was translated (forward-backward translation) and adapted for ethical differences. Sociodemographic and migration-related data were assessed using investigator-related questions. As the dependent variables, the symptoms of depression and anxiety were assessed using the Hopkins Symptom Checklist (HSCL) (31–33), an instrument commonly used with refugee populations (34). The HSCL includes 25 symptoms of depression and anxiety, the presence and severity of which over the past 7 days are rated on a 4-point Likert scale (1 = not at all to 4 = very much). The HSCL symptom score is the mean of the responses. A cut-off value of ≥1.75 is commonly used to differentiate clinically relevant symptoms of depression and anxiety (35). The HSCL does not provide a clinical diagnosis; however, it does allow the severity of symptoms of depression and anxiety to be assessed and compared using symptom scores.

The independent variables are age in years, level of education as years of schooling, number of children, country of origin, stay in Germany (in months), marital status (single/partnership, cohabitation/partnership, separation), separation from children (yes/no), number of PTEs, experience of physical, psychological, or sexual violence (yes/no), distressing experiences in Germany (yes/no), and satisfaction with living conditions in Germany (rather satisfied/rather not satisfied). Regarding the assessment of the number of PTEs, the

Posttraumatic Diagnostic Scale (PDS) (36, 36) and the Harvard Trauma Questionnaire (HTQ) (37) were used.

Descriptive analyses of sociodemographic and migration-related variables were then performed. The prevalence of symptoms of depression and anxiety was calculated using the common cut-off (≥ 1.75) for the HSCL (35). Exploratory analyses of the data were then performed. Bivariate statistics were used to analyze the association between symptoms of depression and anxiety and sociodemographic and migration-related variables. For the bivariate analysis, the independent variables were transformed into categorical variables when necessary. Due to the non-parametric data, the Mann–Whitney U-test and the Kruskal-Wallis H-test were calculated, with a value of p of <0.05 considered significant. In the next step, the variables indicating an association with symptoms of either depression or anxiety in the bivariate analyses were entered into logistic regression models, with a value of p of <0.05 considered significant. Except for country of origin, the continuous version of the variables was used to calculate the regression models. The variables included in the logistic regression models were age (years), level of education (years), number of children, country of origin (Middle East/East Africa), and number of PTEs. Bivariate analysis indicated an association between the categorical variable of experience of physical, psychological, or sexual violence and symptoms of depression and anxiety. For precision and statistical reasons, instead of the categorical variable experience of physical, psychological, or sexual violence, we included the continuous variable number of PTEs in our regression models. Diagnosis of the calculated regression models was then performed. All statistics were performed using SPSS Statistics Version 23 (IBM, Armonk, NY).

Results

At the time of the study, 332 female refugees in Rhineland-Palatinate met the inclusion criteria. 92 female refugees participated in our study. Most of the female refugees interviewed were from Afghanistan (34.8%) and Syria (32.6%). They had been in Germany for between 2 and 27 months (median 12 months). The female refugees interviewed were mostly young women (median 29 years, mean 31.7 years). The study population differed according to their origin. Refugees from the Middle East were, on average, 5 years older than refugees from East Africa. Female refugees from Iran reported the highest level of education, followed by refugees from Eritrea and Syria. The lowest level of education was reported by female refugees from Somalia. Most female refugees interviewed reported being in a relationship (54.3%). Refugees from the Middle East were likelier to report having children (82.0%) than refugees from East Africa (56.0%). Of the women interviewed, 19.6% reported having been separated from their children.

The number of reported PTEs varied by country of origin. Refugees from Africa reported, on average, a higher median number of different PTEs (Eritrea: 12.0; Somalia: 12.5) than refugees from the Middle East (Afghanistan: 7.5; Iran: 6.0; Syria: 3.5). Female refugees in a partnership reported fewer PTEs than did women without a partnership. Female refugees without a partnership were likely to report six or more different PTEs (81.0%). Among the female refugees interviewed in a partnership, 46.0% reported having experienced six or more PTEs (see Table 1). The five most frequent reported PTEs were "forced separation from

TABLE 1 Sociodemographic and migration-related data of the study population (n = 92).

	Study population n = 92 (100%) n (%)	Middle East n = 67 (72.8%) n (%)	East Africa n = 25 (27.2%) n (%)
Age in years			
[*Median; IQR*]	[29.0; 12.0]	[32.0; 12.0]	[27.0; 8.0]
18–22	15 (16.3)	8 (11.9)	7 (28.0)
23–27	20 (21.7)	13 (19.4)	7 (28.0)
28–32	22 (23.9)	15 (22.4)	7 (28.0)
33–37	13 (14.1)	10 (14.9)	3 (12.0)
≥38	22 (22.9)	21 (31.3)	1 (4.0)
Level of education in years			
[*Median; IQR*]	[7.0; 9.8]	[7.0; 12.0]	[7.0; 7.0]
0	20 (21.7)	16 (23.9)	4 (16.0)
1–6	19 (20.7)	11 (16.4)	8 (32.0)
7–9	18 (19.6)	11 (16.4)	7 (28.0)
≥ 10	27 (29.3)	21 (31.3)	6 (24.0)
n.a.	8 (8.7)	8 (11.9)	–
Country of origin			
Afghanistan	32	32	
Eritrea	13		13
Iran	5	5	
Somalia	12		12
Syria	30	30	
Stay in Germany in months			
[*Median; IQR*]	[2.0; 6.0]	[12.0; 4.0]	[11.0; 12.5]
≤6	15 (16.3)	8 (11.9)	7 (28.0)
7–12	25 (27.2)	23 (34.3)	2 (8.0)
≥ 13	36 (39.1)	28 (41.8)	8 (32.0)
n.a.	16 (17.4)	8 (11.9)	8 (32.0)
Marital status			
Single	18 (19.6)	7 (10.4)	11 (44.0)
Partnership, cohabitation	50 (54.3)	45 (67.2)	5 (20.0)
Partnership, separated	24 (26.1)	15 (22.4)	9 (36.0)
Number of children			
[*Median; IQR*]	[2.00; 2.8]	[3.00; 3.0]	[1.00; 2.0]
0	23 (25.0)	12 (17.9)	11 (44.0)
1–3	48 (52.2)	34 (50.7)	14 (56.0)
≥4	21 (22.8)	21 (31.3)	–
Separation from children			
Separated	18 (19.6)	13 (19.4)	5 (20.0)
Not separated/no children	67 (72.8)	47 (70.1)	20 (80.0)
n.a.	7 (7.6)	7 (10.4)	–
Number of PTEs experienced			
[*Median; IQR*]	[8.0; 10.0]	[6.0; 8.0]	[12.0; 5.0]
0	9 (9.8)	9 (13.4)	–
1–5	24 (26.1)	23 (34.3)	1 (4.0)
6–10	27 (29.3)	19 (28.4)	8 (32.0)
≥ 11	30 (32.6)	15 (22.4)	15 (60.0)
n.a.	2 (2.2)	1 (1.5)	1 (4.0)

(Continued)

TABLE 1 (Continued)

	Study population n = 92 (100%) n (%)	Middle East n = 67 (72.8%) n (%)	East Africa n = 25 (27.2%) n (%)
Experience of physical, psychological, or sexual violence			
Yes	74 (80.4)	50 (74.6)	24 (96.0)
No	16 (17.4)	16 (23.9)	–
n.a.	2 (2.2)	1 (1.5)	1 (4.0)
Distressing experience in Germany			
Yes	27 (29.3)	15 (22.4)	12 (48.0)
No	54 (58.7)	45 (67.2)	9 (36.0)
n.a.	11 (12.0)	7 (10.4)	4 (16.0)
Satisfaction with living conditions in Germany			
Rather satisfied	40 (43.5)	25 (37.3)	15 (60.0)
Rather not satisfied	50 (54.4)	40 (59.7)	10 (40.0)
n.a.	2 (2.2)	2 (3.0)	–

n.a., not applicable; IQR, interquartile range.

TABLE 2 Symptoms of depression and anxiety.

	Depression Scale n = 88 (n/%)	Anxiety Scale n = 88 (n/%)
Median (IQR)	2.17 (1.02)	2.05 (1.30)
Range	1.00–3.87	1.00–3.80
Symptom score ≥ 1.75	60 (65.2)	56 (60.9)
Symptom score < 1.75	28 (30.4)	32 (34.8)
n.a.	4 (4.3)	4 (4.3)

Results of the HSCL. n.a., not applicable; IQR, interquartile range.

family members" (58.7%), "lack of shelter" (57.6%), "being close to death" (54.3%), "lack of food or water" (51.1%) and "ill-health without access to medical care" (46.7%).

Analyses of the HSCL revealed symptoms of depression in 65.2% of the female refugees interviewed and symptoms of anxiety in 60.9% (n = 88). Symptoms of depression and anxiety were more common in Middle Eastern female refugees than in East African female refugees. The HSCL symptom scores differed significantly according to country of origin (depression score median Middle East 2.26, median East Africa 1.86, $p = 0.018$; anxiety score median Middle East 2.40, East Africa 1.60, $p = 0.001$) (see Table 2).

Bivariate analyses showed that symptoms of depression were significantly associated with being from the Middle East (Mann–Whitney U-Test, value of $p < 0.05$), reported exposure to violence (Mann–Whitney U-Test, value of $p < 0.05$), and the number of children (Kruskal-Wallis H-Test, value of $p < 0.05$). Symptoms of anxiety were significantly associated with an older age (Kruskal-Wallis H-Test, value of $p < 0.05$), being from the Middle East (Mann–Whitney U-Test, value of $p < 0.01$), a high level of education (Kruskal-Wallis H-Test, value of $p < 0.05$), a high number of children (Kruskal-Wallis H-Test, value of $p < 0.05$), and reported exposure to violence (Mann–Whitney U-Test, value of $p < 0.05$) (see Table 3).

The regression model for anxiety symptoms, including the variables of age, level of education, number of children, country of origin, and number of PTEs, explained more than 32.4% ($p < 0.001$) of the variance in anxiety symptoms. Origin (standardized beta coefficient 0.301, $p = 0.007$) and the number of PTEs (standardized beta coefficient 0.397, $p = 0.002$) explained the most variance in anxiety symptoms. Besides country of origin and the number of PTEs, the variable of level of education added a significant explanation to the variance in symptoms of anxiety in the model.

The regression model for symptoms of depression, including the variables of age, education level, number of children, country of origin, and number of PTEs, showed no indication of a significant association (see Table 4).

Data were missing by 4.3% in the symptom scales and 0.0–8.7% in the sociodemographic and migration-related values. Missing data were excluded.

Discussion

As far as we know, the FRS was the first study of its kind in Germany. The cross-sectional data from the Rhineland-Palatinate discussed in the present study constitute a unique database of the

TABLE 3 Association between sociodemographic and migration-related data and symptoms of depression and anxiety, bivariate analyses.

Variables	Depression Scale n = 88 Median (IQR)	Anxiety Scale n = 88 Median (IQR)
Age in years (K-W)		*
18–22	1.87 (1.51)	1.60 (1.50)
23–27	2.03 (0.82)	1.80 (0.88)
28–32	2.21 (1.39)	2.10 (1.45)
33–37	2.14 (1.18)	2.56 (1.35)
≥38	2.35 (1.15)	2.75 (1.13)
Origin (M-W)	*	**
Middle East	2.26 (1.07)	2,40 (1,30)
East Africa	1.86 (0.74)	1,60 (0,68)
Level of education in years (K-W)		*
0	2.14 (1.08)	1.90 (1.62)
1–6	1.97 (0.95)	1.90 (1.00)
7–9	2.27 (1.14)	2.15 (1.58)
≥ 10	2.27 (1.20)	2.70 (1.23)
n.a.	1.73 (1.17)	2.20 (1.30)
Stay in Germany in months (K-W)		
≤6	2.33 (0.83)	2.00 (1.60)
7–12	2.37 (0.98)	2.27 (1.30)
≥ 13	1.87 (1.13)	2.00 (1.17)
n.a.	1.87 (1.47)	1.90 (1.49)
Marital status (K-W)		
Single	1.86 (0.65)	1.89 (1.14)
Partnership, cohabitation	2.20 (1.17)	2.10 (1.50)
Partnership, separated	2.30 (1.03)	2.25 (1.23)
Number of children (K-W)	*	*
0	1.87 (0.73)	1.89 (1.10)
1	1.60 (0.93)	1,80 (0.80)
2	1.70 (0.73)	1.63 (1.23)
3	2.47 (0.59)	2.70 (1.10)
4	2.63 (0.55)	2.80 (0.78)
5	1.27 (2.07)	1.60 (1.49)
6	2.33 (−)	2.33 (−)
7 (n = 1)	1.40 (−)	3.20 (−)
8 (n = 1)	1.80 (−)	1.50 (−)
Separation from children (M-W)		
Separated	2.33 (1.00)	2.50 (1.29)
Not separated/no children	2.10 (1.10)	2.00 (1.23)
n.a.	2.13 (0.91)	2.85 (1.40)
Number of PTEs experienced (K-W)		
0	1.87 (0.87)	1.56 (0.59)
1–5	2.21 (1.35)	2.15 (1.59)
6–10	1.93 (1.41)	2.00 (1.35)
≥ 11	2.30 (0.81)	2.50 (1.35)
n.a.	1.60 (−)	1.40 (−)
Experience of physical, psychological, or sexual violence (M-W)	*	*
Yes	2.24 (1.08)	2.27 (1.30)
No	1.80 (0.92)	1.58 (0.78)
n.a.	1.60 (−)	1.40 (−)

(Continued)

TABLE 3 (Continued)

Variables	Depression Scale $n = 88$ *Median (IQR)*	Anxiety Scale $n = 88$ *Median (IQR)*
Distressing experience in Germany *(M-W)*		
Yes	1.93 (1.33)	2.20 (1.32)
No	2.14 (1.03)	2.05 (1.28)
n.a.	2.55 (1.18)	2.30 (1.65)
Satisfaction with living conditions in Germany *(M-W)*		
Rather satisfied	2.10 (0.99)	2.05 (1.31)
Rather not satisfied	2.21 (1.16)	2.10 (1.35)
n.a.	1.69 (−)	1.56 (−)

*$p < 0.05$; **$p < 0.01$; IQR, interquartile range; n.a., not applicable. K-W, value of p computed with Kruskal–Wallis *H*-Test. M-W, value of p computed with Mann–Whitney *U*-Test.

TABLE 4 Multiple linear regression models of sociodemographic variables and number of PTEs and symptoms of depression and anxiety.

	Model depression	Model anxiety
	Standardized beta-coefficients (value of p)	
Age	0.053 (0.741)	0.254 (0.071)
Education	0.096 (0.412)	0.235 (0.023) *
Number of children	0.039 (0.824)	−0.054 (0.726)
Origin (Middle East/East Africa)	0.280 (0.054)	0.397 (0.002) **
Number of PTEs	0.187 (0.139)	0.301 (0.007) **
Fit of the model – R^2 (value of p)	0.110 (0.122)	0.324 (< 0.001) **

*$p < 0.05$; **$p < 0.01$.

mental health of female refugees. Our aim was to interview all female refugees in the Rhineland-Palatinate who met the inclusion criteria of the FRS. Almost one-third of this population was interviewed, so the data provided good insight into the mental health of female refugees in the Rhineland-Palatinate.

In our study population, the prevalence of symptoms of depression was 65.2%, and it was 60.9% for symptoms of anxiety. These prevalence rates are high, and given that they represent the burden of only two mental disorders among other possible disorders from which the female refugees interviewed may have suffered, the reported prevalence rates are worrying.

A comparison with the general population shows the expected higher burden of mental health disorders among female refugees (22, 38). The mean symptom score for depression (HSCL) in women in the general population without a clinical diagnosis is 1.30 (SD 0.42), and for anxiety, it is 1.29 (SD 0.34) (31). The median symptom score for depression and anxiety found in this study in the surveyed female refugee population is much higher, with a symptom score of 2.17 (IQR 1.02) for depression and 2.10 (IQR 1.34) for anxiety. These symptom scores in our sample are unexpectedly high compared with women in the general population diagnosed with a depressive or anxiety disorder. The mean symptom score for depression in women in the general population with a clinical diagnosis of a depressive disorder is 1.61 (SD 0.62), and for anxiety it is 1.60 (SD 0.47) (39). This highlights the exceptionally high burden of symptoms of depression and anxiety experienced by female refugees. In addition, it underscores the need for mental health treatment for this population. At the same time, medical care for refugees in Germany is limited in the first months after arrival to the treatment of acute illnesses or pain (40). And even

when medical care is available, there are many other barriers to adequate health care for refugees, such as language barriers, lack of knowledge of structures and where to go for help, lack of trust in the healthcare system, or inability to talk about intimate feelings (41). And even when refugees do receive medical care, there is a risk of under-diagnosis due to cultural differences in the presentation of symptoms (41). It is clear that mental disorders in female refugees make integration into Germany and learning the host language difficult, if not impossible, for them (15). The impact on their children must also be considered. Three-quarters of the surveyed refugees reported having children, and caring for children is surely even more difficult with the burden of mental illness.

Country of origin was associated with symptoms of depression or anxiety. The symptoms of both depression and anxiety were higher among female refugees from the Middle East. These findings are consistent with the results of a review by Blackmore et al. of populations of refugees and asylum seekers (16). The differences in the symptoms of depression and anxiety by country of origin may be explained by the loss of socioeconomic status following flight. Female refugees from the Middle East may experience a greater loss of socioeconomic status after their arrival in Germany than refugees from East Africa. Another reason may be culturally different strategies for coping with mental health problems. The presentation of symptoms of depression and anxiety is known to vary from culture to culture, which can lead to misdiagnosis (41).

The experience of physical, psychological, or sexual violence was associated with symptoms of depression and anxiety in our sample. The number of PTEs showed a significant association with the variance of anxiety symptoms, just below level of education. This is

consistent with other studies showing a strong association between the number of PTEs and the manifestation of mental disorders (21, 23–25). The experience of PTEs in refugees´ home country or during their flight, e.g., being close to death, lack of food, water and shelter, increases the risk for a wide spectrum of mental diseases, e.g., PTSD, depression, anxiety and somatization.

Unexpectedly, there was no evidence of an association between the symptoms of depression and anxiety and age in our sample. The multivariate regression model showed that age was not significantly associated with symptoms of depression and anxiety when controlling for level of education, number of PTEs, and country of origin. In contrast are the findings pertaining to the German general population and other refugee populations. In the general German population, a representative study from 2009 to 2012 showed that the prevalence of depression decreases with age: 15.6% of younger women, 11.0% of middle-aged women, and 5.0% of older women suffered from a depressive disorder (42). Other studies of refugee populations report that older age is associated with more symptoms of mental health disorders (9, 10, 20–22). Our sample of female refugees consisted mostly of young female refugees (median age 29 years), making it difficult to measure associations in higher age groups. Perhaps the lack of association between age and symptoms of depression and anxiety is due to our study population. On the other hand, our findings suggest that the number of PTEs experienced, the country of origin, and the level of education outweigh the influence of age on young female refugees.

Surprising in our results was the association between educational level and symptoms of depression and anxiety. A high level of education was significantly associated with high anxiety symptom scores. Symptoms of depression were likelier to be reported by female refugees with no or high levels of education than by female refugees with low to medium levels of education. These findings contrast with those of the general German population, where higher levels of education are associated with better mental health (43). Other studies of refugee populations have reported heterogeneous findings on the relationship between educational attainment and mental health (9, 22, 29). It should be kept in mind that higher levels of education may lead to a higher socioeconomic status in the home country and an even greater loss of socioeconomic status in the host country. This, in turn, is associated with symptoms of depression and anxiety, as Blackmore et al. found in their review (16).

Another unexpected finding was that the number of children was not associated with symptoms of depression or anxiety. In the regression models, no variance was explained by the number of children. Caring for children involves taking responsibility for others, a more difficult flight, and perhaps separation from one's children. There is less time to nurture oneself, to learn a new language, and to get to know the host culture. All of this should lead to more stress for women with children than for those without children. However, in our sample, other factors seemed to be more important. Another explanation could be that the positive effect of having children and the motivation to give them a better future outweigh the burden of parenthood.

Only the regression model for symptoms of anxiety showed a significant explained variance of 32.4% (value of p <0.001). The explained variance is small, as is common in models predicting human behavior (44). Nevertheless, our model could explain only 32.4% of the variance in the symptoms of anxiety. The variables of level of education, number of PTEs experienced, and country of origin (East Africa/Middle East) added a significant explanation to the variance of symptoms of anxiety in our sample. This suggests that other factors that were not analyzed could have played a more important role in the variance in symptoms of anxiety in our sample.

The main limitation of this study is the small sample size (n = 92), which included only female refugees from the Rhineland-Palatinate study center. Due to the small sample size, the variables examined and the associations found must be interpreted carefully. Another limitation is the relatively high number of variables analyzed compared to the small sample size. Therefore, all significant results should be interpreted with caution.

Regarding other limitations, it must be kept in mind that the instrument used to assess psychological symptoms, although often used in research with refugee populations, has not been validated for Middle Eastern and African cultures (33, 45, 46). It is possible that the burden of depression and anxiety symptoms was over- or underestimated in our analyses. Further research and validation studies are needed to accurately measure the symptoms of depression and anxiety across cultures. The additional assessment of symptoms of posttraumatic stress disorder, would have provided a better picture of the mental health problems experienced by refugee women with high levels of PTEs. Additional Fazel et al. (47) could show in their review about the prevalence of serious mental disorders in refugees a high comorbidity of PTSD and major depression and vice versa. The National Comorbidity Survey in the United States found that half of the women diagnosed with PTSD were also diagnosed with major depression (48). There are two important explanations, as suggested by Flory and Yehuda (49), either these two disorders have many overlapping symptoms, or the combination of PTSD and major depression is a subtype of one disorder. Flory and Yehuda therefore state that the question should not be, whether there is a comorbidity of PTSD, but which comorbidity is present (49). This underscores the urgent need to assess symptoms of PTSD and depression together. For future research, we recommend assessing symptoms of posttraumatic stress disorder in refugee populations.

Missing data were low in our sample, with 4.3% missing values on the symptom scales and 0.0–8.7% missing values on the sociodemographic and migration-related measures. Nevertheless, this may have led to an over- or underestimation of psychological symptoms, and some associations with the assessed factors may have remained hidden.

Female refugees from Ukraine are currently the largest group of female refugees coming to Germany (3). Like other refugees, they are likely to suffer from mental disorders (50, 51). A study of Ukrainian refugees in Germany found a high prevalence of mental health disorders which is comparable to the prevalence in other refugee populations, with almost half of the sample reporting symptoms of depression and more than half reporting symptoms of anxiety (50). This is a remarkably high prevalence, considering that Ukrainian refugees currently have easier access to residence permits in Germany without any bureaucratic procedures (5). In addition, they are allowed to stay in private apartments instead of collective accommodations and have access to statutory health insurance rather than emergency health insurance (6, 7). Buchcik et al. (50) suggest that the war in the home country and migration-related experiences, such as leaving male relatives behind and uncertainty about the future, outweigh the

easier reception conditions that Ukrainian refugees currently have in Germany.

Overall, refugee women are a vulnerable group. Female refugees from East Africa and the Middle East who were interviewed in this study had a high prevalence of symptoms of depression and anxiety. Experiencing symptoms of a mental disorder can lead to a high burden of disease and difficulties in integration into the host country. For healthy integration, it is necessary to identify the symptoms of mental disorders in female refugees as early as possible. Our findings show that the following factors are associated with symptoms of depression and anxiety: level of education, country of origin, and number of PTEs. Currently, many female refugees from Ukraine are arriving in Germany. Even though their country of origin is different from that of our sample, our findings can help estimate the prevalence of symptoms of depression and anxiety and associated factors in female Ukrainian refugees. Psychological support and psychotherapy must be made available as a low-threshold service for female refugees who need it. This is an important step in the integration of female refugees into their host countries. In addition, female refugees arriving in Germany should be screened for symptoms of mental disorders. The refugee population is always changing; therefore, ongoing research is needed to assess the mental health of female refugees in Germany.

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 Ethics Committee of the Rhineland-Palatinate Medical Association. The study is registered under the number 837.316.16 (10635). 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

HB: Writing – original draft. RK: Writing – review & editing. PK: Writing – review & editing. PD: Writing – review & editing. ClK: Writing – review & editing. SL: Writing – review & editing. ChK: Writing – review & editing. JJ: Writing – review & editing. MS-O: Writing – review & editing. UZ: Writing – review & editing.

Funding

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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References

1. Forced displacement in 2022 Copenhagen, Denmark (2023). United Nations High Commissioner for Refugees, editor. Available at: https://www.unhcr.org/global-trends-report-2022.

2. Das Bundesamt in Zahlen: Asyl 2016 (the Federal Office in Figures: Asylum 2016). Statistisches Bundesamt, editor. (Germany: Federal Statistical Office) (2017). Available at: https://www.bamf.de/SharedDocs/Anlagen/DE/Statistik/BundesamtinZahlen/bundesamt-in-zahlen-2016.pdf?__blob=publicationFile&v=16

3. Federal Statistical Office of Germany. Press release no. 125 of 30 march 2023: More than 3 million people seeking protection in Germany at the end of 2022. (2023). United Nations High Commissioner for Refugees (UNHCR), editor. Available at: https://www.destatis.de/DE/Presse/Pressemitteilungen/2023/03/PD23_125_125.html#:~:text=M%C3%A4rz%202023&text=WIESBADEN%20%E2%80%93%20Zum%20Jahresende%202022%20waren,um%201%2C14%20Millionen%20Personen.

4. European Parliament. UNHCR: Refugee data finder: Key indicators [internet]. (UNHCR). (2022). Available at: https://www.unhcr.org/refugee-statistics/.

5. Temporary protection: activation of the temporary protection directive. European Commission (2022). Available at: https://home-affairs.ec.europa.eu/policies/migration-and-asylum/common-european-asylum-system/temporary-protection_en.

6. Accommodation and housing for refugees from Ukraine [internet]. Federal Office for Migration and Refugees (2023). Available at: https://www.germany4ukraine.de/hilfeportal-en/accommodation-for-refugees-from-ukraine/accommodation-and-housing-for-refugees-from-ukraine

7. News: acceptance deadline for joining the statutory health insurance. Federal Office for Migration and Refugees (2023). United Nations High Commissioner for Refugees (UNHCR), editor. Available at: https://www.germany4ukraine.de/hilfeportal-en/news

8. UNHCR. Report warns refugee women on the move in Europe are at risk of sexual and gender-based violence. (2016). Available at: https://www.unhcr.org/news/news-releases/report-warns-refugee-women-move-europe-are-risk-sexual-and-gender-based-violence

9. Porter M, Haslam N. Predisplacement and postdisplacement factors associated with mental health of refugees and internally displaced persons: a meta-analysis. *JAMA*. (2005) 294:602–12. doi: 10.1001/jama.294.5.602

10. Mesa-Vieira C, Haas AD, Buitrago-Garcia D, Roa-Diaz ZM, Minder B, Gamba M, et al. Mental health of migrants with pre-migration exposure to armed conflict: a systematic review and meta-analysis. *Lancet Public Health*. (2022) 7:e469–81. doi: 10.1016/S2468-2667(22)00061-5

11. Bonewit A. Reception of female refugees and asylum seekers in the EU: Case study Germany. Policy Department C of the European Parliament. Research by Rosamund Shreeves. (2016). Available at: https://www.europarl.europa.eu/RegData/etudes/STUD/2016/536497/IPOL_STU(2016)536497_EN.pdf

12. Lindert J, Schouler-Ocak M, Heinz A, Priebe S. Mental health, health care utilisation of migrants in Europe. *Eur Psychiatry*. (2008) 23:s114–s20. doi: 10.1016/s0924-9338(08)70057-9

13. Keller A, Lhewa D, Rosenfeld B, Sachs E, Aladjem A, Cohen I, et al. Traumatic experiences and psychological distress in an urban refugee population seeking treatment services. *J Nerv Ment Dis*. (2006) 194:188–94. doi: 10.1097/01.nmd.0000202494.75723.83

14. Morina N, Akhtar A, Barth J, Schnyder U. Psychiatric disorders in refugees and internally displaced persons after forced displacement: a systematic review. *Front Psych*. (2018) 9:433. doi: 10.3389/fpsyt.2018.00433

15. Schick M, Zumwald A, Knopfli B, Nickerson A, Bryant RA, Schnyder U, et al. Challenging future, challenging past: the relationship of social integration and

psychological impairment in traumatized refugees. *Eur J Psychotraumatol*. (2016) 7:28057. doi: 10.3402/ejpt.v7.28057

16. Blackmore R, Boyle JA, Fazel M, Ranasinha S, Gray KM, Fitzgerald G, et al. The prevalence of mental illness in refugees and asylum seekers: a systematic review and meta-analysis. *PLoS Med*. (2020) 17:e1003337. doi: 10.1371/journal. pmed.1003337

17. Lindert J, von Ehrenstein OS, Priebe S, Mielck A, Brahler E. Depression and anxiety in labor migrants and refugees - a systematic review and meta-analysis. *Soc Sci Med*. (2009) 69:246–57. doi: 10.1016/j.socscimed.2009.04.032

18. Hynie M. The social determinants of refugee mental health in the post-migration context: a critical review. *Can J Psychiatr*. (2018) 63:297–303. doi: 10.1177/0706743717746666

19. Kien C, Sommer I, Faustmann A, Gibson L, Schneider M, Krczal E, et al. Prevalence of mental disorders in young refugees and asylum seekers in European countries: a systematic review. *Eur Child Adolesc Psychiatry*. (2018) 28:1295–310. doi: 10.1007/s00787-018-1215-z

20. Chaudhry N, Husain N, Tomenson B, Creed F. A prospective study of social difficulties, acculturation and persistent depression in Pakistani women living in the UK. *Psychol Med*. (2012) 42:1217–26. doi: 10.1017/S0033291711002388

21. Robertson CL, Halcon L, Savik K, Johnson D, Spring M, Butcher J, et al. Somali and Oromo refugee women: trauma and associated factors. *J Adv Nurs*. (2006) 56:577–87. doi: 10.1111/j.1365-2648.2006.04057.x

22. Sundquist K, Johansson LM, DeMarinis V, Johansson SE, Sundquist J. Posttraumatic stress disorder and psychiatric co-morbidity: symptoms in a random sample of female Bosnian refugees. *Eur Psychiatry*. (2005) 20:158–64. doi: 10.1016/j. eurpsy.2004.12.001

23. Gerritsen AAM, Bramsen I, Deville W, van Willigen LHM, Hovens JE, van der Ploeg HM. Physical and mental health of afghan, Iranian and Somali asylum seekers and refugees living in the Netherlands. *Soc Psych Psych Epid*. (2006) 41:18–26. doi: 10.1007/s00127-005-0003-5

24. Hocking DC, Kennedy GA, Sundram S. Social factors ameliorate psychiatric disorders in community-based asylum seekers independent of visa status. *Psychiatry Res*. (2015) 230:628–36. doi: 10.1016/j.psychres.2015.10.018

25. Heeren M, Wittmann L, Ehlert U, Schnyder U, Maier T, Muller J. Psychopathology and resident status - comparing asylum seekers, refugees, illegal migrants, labor migrants, and residents. *Compr Psychiatry*. (2014) 55:818–25. doi: 10.1016/j. comppsych.2014.02.003

26. Sundquist J, Bayard-Burfield L, Johansson LM, Johansson S-E. Impact of ethnicity, violence and acculturation on displaced migrants: psychological distress and psychosomatic complaints among refugees in Sweden. *J Nerv Ment Dis*. (2000) 188:357–65. doi: 10.1097/00005053-200006000-00006

27. De Jong JT, Komproe IH, Van Ommeren M. Common mental disorders in postconflict settings. *Lancet*. (2003) 361:2128–30. doi: 10.1016/S0140-6736(03)13692-6

28. Kröger C, Frantz I, Friel P, Heinrichs N. Posttraumatische und depressive Symptomatik Bei Asylsuchenden: screening in Einer Landesaufnahmestelle (posttraumatic stress and depressive symptoms amongst asylum seekers screening in a state refugee reception center). *Psychother Psychosom Med Psychol*. (2016) 66:377–84. doi: 10.1055/s-0042-114045

29. Bogic M, Ajdukovic D, Bremner S, Franciskovic T, Galeazzi GM, Kucukalic A, et al. Factors associated with mental disorders in long-settled war refugees: refugees from the former Yugoslavia in Germany, Italy and the UK. *Brit J Psychiat*. (2012) 200:216–23. doi: 10.1192/bjp.bp.110.084764

30. Shouler-Ocak M, Kurmeyer C, Jesuthasan J, Abels I, Sönmez E, Oertelt-Prigione S, et al. *Study on women refugees: Final report: Representative survey of female refugees in different federal states of Germany*. Schouler-Ocak M and Kurmeyer C, editor. (2017).

31. Glaesmer H, Braehler E, Grande G, Hinz A, Petermann F, Romppel M. The German version of the Hopkins symptoms Checklist-25 (Hscl-25)—factorial structure, psychometric properties, and population-based norms. *Compr Psychiatry*. (2014) 55:396–403. doi: 10.1016/j.comppsych.2013.08.020

32. Veijola J, Jokelainen J, Läksy K, Kantojärvi L, Kokkonen P, Järvelin M-R, et al. The Hopkins symptom Checklist-25 in screening Dsm-iii-R Axis-I disorders. *Nord J Psychiatry*. (2003) 57:119–23. doi: 10.1080/08039480310000941

33. Mollica R, Wyshak G, de Marnette D, Tu B, Yang T, Khuon F. Hopkins symptom checklist (HSCL-25): manual for Cambodian, Laotian and Vietnamese versions. *Torture*. (1996) 6:35–42.

34. Hollifield M, Warner TD, Lian N, Krakow B, Jenkins JH, Kesler J, et al. Measuring trauma and health status in refugees: a critical review. *JAMA*. (2002) 288:611–21. doi: 10.1001/jama.288.5.611

35. Petermann F, Brähler E. *HSCL-25: Hopkins-Symptom-Checkliste-25: Deutsche version (HSCL-25: Hopkins-Symptom-Checklist-25: German version)*. Hogrefe Group, editor. Göttingen: Hogrefe (2013).

36. Foa EB, McLean CP, Zang Y, Zhong J, Powers MB, Kauffman BY, et al. Psychometric properties of the posttraumatic diagnostic scale for Dsm-5 (Pds-5). *Psychol Assess*. (2016) 28:1166–71. doi: 10.1037/pas0000258

37. Mollica RF, Caspi-Yavin Y, Bollini P, Truong T, Tor S, Lavelle J. The Harvard trauma questionnaire: validating a cross-cultural instrument for measuring torture, trauma and post-traumatic stress disorders in Indochinese refugees. *J Nerv Ment Dis*. (1992) 180:111–6. doi: 10.1097/00005053-199202000-00008

38. Sundquist J, Behmen-Vincevic A, Johansson SE. Poor quality of life and health in young to middle-aged Bosnian female war refugees: a population-based study. *Public Health*. (1998) 112:21–6. doi: 10.1038/sj.ph.1900411

39. Mattisson C, Bogren M, Horstmann V. Correspondence between clinical diagnoses of depressive and anxiety disorders and diagnostic screening via the Hopkins symptom check List-25 in the Lundby study. *Nord J Psychiatry*. (2013) 67:204–13. doi: 10.3109/08039488.2012.711856

40. Asylbewerberleistungsgesetz in der Fassung der Bekanntmachung vom 5. (1997) Justizministerium, editor. (Germany: Federal of Justice). (Asylum seekers benefits act in the version of the publication of August 5, 1997).

41. Kirmayer LJ. Cultural variations in the clinical presentation of depression and anxiety: implications for diagnosis and treatment. *J Clin Psychiatry*. (2001) 62:22.

42. Cohrdes C, Hapke U, Nübel J, Thom J. Psychische Gesundheit in Deutschland (Mental Health in Germany) (2021). Robert-Koch-Institut, editor. Available at: https:// www.rki.de/DE/Content/GesundAZ/P/Psychische_Gesundheit/EBH_Bericht_ Psychiche_Gesundheit.pdf?__blob=publicationFile

43. Robert-Koch-Institut. Beiträge Zur Gesundheitsberichterstattung des Bundes - Daten und Fakten: Ergebnisse Der Studie "gesundheit in Deutschland Aktuell 2012" (contributions to the Federal Health Report - data and facts: Results of the study "current health in Germany 2012") Berlin (2012). Available at: https://www.rki.de/DE/Content/Gesundheitsmonitoring/ Gesundheitsberichterstattung/GBEDownloadsB/GEDA12.pdf?__blob=publicationFile

44. Minitab Blog. Regression analysis: How do I interpret R-squared and assess the goodness-of-fit? (2013). Available at: http://blog.minitab.com/blog/adventures-in-statistics-2/ regression-analysis-how-do-i-interpret-r-squared-and-assess-the-goodness-of-fit

45. Ventevogel P, De Vries G, Scholte WF, Shinwari NR, Faiz H, Nassery R, et al. Properties of the Hopkins symptom Checklist-25 (HSCL-25) and the self-reporting questionnaire (SRQ-20) as screening instruments used in primary care in Afghanistan. *Soc Psych Psych Epid*. (2007) 42:328–35. doi: 10.1007/s00127-007-0161-8

46. Lee B, Kaaya SF, Mbwambo JK, Smith-Fawzi MC, Leshabari MT. Detecting depressive disorder with the Hopkins symptom Checklist-25 in Tanzania. *Int J Soc Psychiatry*. (2008) 54:7–20. doi: 10.1177/0020764006074995

47. Fazel M, Wheeler J, Danesh J. Prevalence of serious mental disorder in 7000 refugees resettled in western countries: a systematic review. *Lancet*. (2005) 365:1309–14. doi: 10.1016/S0140-6736(05)61027-6

48. Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry*. (1995) 52:1048–60. doi: 10.1001/archpsyc.1995.03950240066012

49. Flory JD, Yehuda R. Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. *Dialogues Clin Neurosci*. (2015) 17:141–50. doi: 10.31887/DCNS.2015.17.2/jflory

50. Buchcik J, Kovach V, Adedeji A. Mental health outcomes and quality of life of Ukrainian refugees in Germany. *Health Qual Life Outcomes*. (2023) 21:23. doi: 10.1186/ s12955-023-02101-5

51. Rizzi D, Ciuffo G, Sandoli G, Mangiagalli M, de Angelis P, Scavuzzo G, et al. Running away from the war in Ukraine: the impact on mental health of internally displaced persons (IDPs) and refugees in transit in Poland. *Int J Environ Res Public Health*. (2022) 19:1–9. doi: 10.3390/ijerph192416439

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An examination of the psychometric properties of the Patient Health Questionnaire-9 (PHQ-9) in a Multiracial/ethnic population in the United States

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Depression and suicide are significant public health issues. The Patient Health Questionnaire-9 (PHQ-9) is commonly used to assess for symptoms of depression, but its psychometric properties within Multiracial/ethnic populations remains uncertain. In a study involving 1,012 English-speaking Multiracial/ethnic participants from the United States (US), the PHQ-9 showed strong internal consistency ($\alpha = 0.93$) and supported a one-factor structure. No measurement variance was observed between Non-White and White/Non-White Multiracial/ethic subgroups. PHQ-2, with a cutoff of ≥ 3, identified fewer depression cases than PHQ-9 (32% vs. 40%), with sensitivities of 75−99% and specificities of 74−96%; a cutoff of ≥ 2 missed fewer cases. Item performance of the ninth PHQ-9 question, addressing thoughts of death or self-harm, varied across generations with younger generations more likely to endorse thoughts of death or self-harm at any level of symptom severity. The findings suggest the PHQ-9 demonstrated adequate reliability within a population of Multiracial/ethnic adults in the US; however, the use of the 9th item of the PHQ-9 may not be adequate for identifying individuals at risk for suicidal thoughts and/or behaviors, particularly for older Multiracial/ethnic adults. The lower sensitivity of the PHQ-2 with a $\geq$ 3 cutoff suggests a cutoff of ≥ 2 may be preferable to miss fewer cases of depression.

KEYWORDS

depression, patient health questionnaire, factor analysis, statistical, psychometrics, racial groups, United States

1 Introduction

Depression and suicide are critical public health issues that impact individuals, families, and society at large. During and following the COVID-19 pandemic, the United States (US) experienced an increase in the prevalence of depressive symptoms for all racial and ethnic groups and an increase in suicide rates among adolescents and American Indian, Black, and Latino adults (1). As of June 2023, the US Preventive Services Task Force (USPSTF) recommends screening all adolescents and adults for depression (2).

The Patient Health Questionnaire-9 (PHQ-9) is an instrument used to assess for symptoms of depression consistent with Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria (3). The PHQ-9 has demonstrated robust psychometric properties in culturally, linguistically, and geographically diverse samples of adults, contributing to its widespread usage (4). Two questions from the PHQ-9, known as the PHQ-2, are often used

as a brief measure and is currently used by the CDC in their routine Household Pulse Survey (1). The ninth item of the PHQ-9 asks about "thoughts that you would be better off dead, or of hurting yourself." The ninth item of the PHQ-9 is used in primary care and other settings to identify individuals at risk for suicidal thoughts and behaviors; however, studies have indicated this to be an insufficient assessment tool for suicide risk (5–8).

In the US, Multiracial/ethnic populations are a rapidly growing demographic group that has been historically underrepresented in public health surveillance, research and practice (9, 10). Population growth appears to be increasing across generations: the 2021 American Community Survey estimates that 7.7% of Baby Boomers (born in or before 1964), 11.7% of Generation X (1965–1980), 12.9% of Millennials (1981–1996), and 16.6% of Generation Z (1997 or later) identify with two or more racial groups (11). Emerging research in the past decade suggests Multiracial/ethnic populations in the United States may have the highest prevalence of many mental health conditions, including depression and suicide (1, 12, 13). While studies have provided evidence to suggest the effectiveness of the PHQ-9 as a depression screener within White, Black, African American, Asian, Chinese American, Mexican American, and Latino populations in the US, partial measurement invariance was found for the one-factor model in a population of American Indian/Alaska Native adults, supporting efforts to continue examining the appropriateness of this tool within diverse populations (14–17). To the authors' knowledge, studies have yet to establish the psychometric properties of the PHQ-9 within Multiracial/ethnic populations in the US.

This study aims to investigate the psychometric properties of the PHQ-9 within a sample of Multiracial/ethnic adults in the United States. This study explored the following research questions: 1) Does the PHQ-9 have adequate psychometric performance in a Multiracial/ethnic adult population in the US? 2) Is psychometric performance comparable across generations and between White and non-White Multiracial/ethnic people? 3) How does the PHQ-2 compare with the PHQ-9 at identifying clinically meaningful depression in this population?.

2 Methods

A nonprobability-based convenience sample of English-speaking adults living in or from the United States that identify as multiracial and/or multiethnic and selected at least two distinct categories for racial/ethnic identity (White, Black or African American, American Indian or Alaska Native (AI/AN), Asian, Native Hawaiian or Pacific Islander, Middle Eastern or North African, Other) was obtained through an online anonymous survey collected from October–December 2022. Respondents were recruited from multiple market research panels facilitated by Qualtrics, which aims to mirror census representation, with compensation up to $9.50 (18). The Johns Hopkins Bloomberg School of Public Health Institutional Review Board (IRB) approved this study and informed consent was obtained.

2.1 Measures

Depressive symptoms and severity were assessed using the 9-item Patient Health Questionnaire (PHQ-9), a validated tool based on the DSM-5 criteria (3). On each item of the PHQ-9, participants were asked "Over the past 2 weeks, how often have you been bothered by

any of the following?" and provided responses on a 4-point Likert scale (0 = Not At All, 1: Several Days, 2: More than Half the Days, 3: Nearly Every Day). The PHQ-2 consists of the first two questions of the PHQ-9, "Little interest or pleasure in doing things," and "Feeling down, depressed, or hopeless." The survey collected demographic data on racial and ethnic identity, gender identity, sexual orientation, age, place of birth, educational attainment, and household income level. Participants were split into four age groups based on birth year: Gen Z was defined as born in 1997 or later, Millennial was born 1981–1996, Gen X was born 1965–1980, and Baby Boomers were born 1964 and earlier. To explore within-group differences, participants were split into two race groups: those who endorsed White as one of their racial/ethnic identities and those who did not.

2.2 Statistical analysis

The internal consistency of the PHQ-9 was measured using Cronbach's alpha and McDonald's omega. An exploratory factor analysis was conducted and scree plot examined to identify the number of latent factors. Measurement invariance was tested across two variables: age and race, defined above. In both cases, measurement invariance was tested by fitting a series of confirmatory factor analyses. In one model, factor loadings were constrained to be equal between groups and in another they were freely estimated. A chi-squared difference test was then used to compare models. In the event of a significant test, score tests were used to identify which questions differed between which groups. If the test was non-significant, the process was repeated constraining model intercepts and finally residuals (i.e., testing metric, scalar, and then strict invariance). If any of the tests were significant, further invariance testing was not done. The weighted least-squares estimator was used with robust standard errors calculated using the full weight matrix.

The PHQ-2 was compared to the PHQ-9 as a screening tool for depression. Using a threshold of ≥3 for the PHQ-2 and the PHQ-9 as the gold standard, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for moderate, moderately severe, and severe depression (PHQ-9 ≥ 10, 15, and 20, respectively). Performance measures were also calculated for PHQ-2 thresholds of ≥2, ≥3, and ≥ 4. Based on observed measurement variance of the PHQ-9 between generations, a *post-hoc* analysis was also conducted using a threshold of ≥3 stratified by generation.

All analyses were conducted using R Statistical Software version 4.2 (19) and the packages psych, lavaan, and semTools (20–22).

3 Results

3.1 Sample characteristics

The sample (*N = 1,012*) was majority female (67.5%, *n = 683*) and straight (80.1%, *n = 798*). More than half had attained less than a college degree (62.3%, *n = 627*), and about half reported a household income less than $60,000 (57.4%, *n = 552*). The mean birth year of the sample was 1981 (SD = 14.4). Almost half (43%, *n = 435*) of respondents were born between the years 1981–1996 and classified as Millennials; 27.4% (*n = 277*) between 1965 and 1980, classified as Gen-X; 15% (*n = 152*) after 1997, classified as Gen-Z; and 14% between 1946 and 1964, classified as Baby Boomers. Less than 1% of the sample were born before 1946. Over half of respondents (55%, *n = 557*)

reported identifying as part-White; 48.2% ($n=488$), Black or African American; 48.1% ($n=487$), Hispanic or Latino; 16.3% ($n=165$), Asian; 29.4% ($n=298$), American Indian or Alaska Native; 8.5% ($n=86$), Native Hawaiian or Pacific Islander; 8.1% ($n=82$), Middle Eastern or North African; 8.9% ($n=90$) identified with a racial or ethnic group not listed in these broad categories.

3.2 PHQ-9 psychometric properties

The Cronbach's alpha for the PHQ-9 in this sample was 0.93 (95% CI, 0.92–0.94) and McDonald's omega was also 0.93 (95% CI, 0.91–0.94). The factor analysis confirmed a one factor solution was the best supported; the scree plot is shown in Figure 1. The first factor had an eigenvalue of 5.76 and explained 59.7% of the variance. The factor loadings and uniqueness are shown in Table 1. When loadings were estimated separately by generation, the unconstrained model fit the data significantly better (chi-squared difference 55.226 on 24 degrees of freedom, $p=0.0003$). Score tests revealed that the loading of the 9th item differed significantly between all generations. Specifically, it decreased with increasing age, so the loadings were 0.900, 0.690, 0.471, and 0.361 for Gen Z, Millennials, Gen X, and Baby Boomers, respectively. When loadings, intercepts, and residuals were estimated separately by race group, the unconstrained model did not fit the data significantly better (chi-squared difference 30.4 on 25 degrees of freedom, $p=0.2097$), suggesting strict measurement invariance between race groups. The fit statistics for the final measurement model were: robust RMSEA 0.041, CFI 0.994, TLI 0.995, and SRMR 0.047.

3.3 PHQ-2 performance

The PHQ-2 identified significantly fewer people overall as depressed compared to the PHQ-9 (32% vs. 40%, $p<0.001$). Using a PHQ-2 score threshold of 3, the sensitivity for detecting PHQ-9 mild, moderate, and severe depression was 75, 95, and 99%, respectively. The specificity was 96, 85, and 74%, respectively. A threshold of 3 performed better overall than thresholds of 2 or 4; full details are shown in Table 2. PHQ-2 performance was generally comparable between generations. Using a threshold of 3, the sensitivity for mild

FIGURE 1
Scree plot for the PHQ-9. In this Multiracial/ethnic sample, the PHQ-9 appears to measure a single latent factor.

depression varied 72–76% between generations. The specificity was 90% for Gen Z and varied 96–97% for older generations.

4 Discussion

This study begins to fill a gap in the literature on the performance of mental health instruments within Multiracial/ethnic populations, a population underrepresented in public health research. To the author's knowledge, psychometric assessments of the PHQ-9 for this population have not been published. This study provides evidence to suggest the PHQ-9 demonstrates high reliability with a one-factor solution within Multiracial/ethnic adult populations in the US, suggests the PHQ-9 is an appropriate depression screening instrument for Multiracial/ethnic adult populations in the US, and joins prior studies demonstrating the utility of the PHQ-9 within some racially and ethnically diverse US populations (15, 17).

This study has several limitations. As a cross-sectional study conducted primarily among English-speaking Multiracial/ethnic adults with internet access and recruited via paid research panels, results may not generalize to all Multiracial/multiethnic people in the US. We included Hispanic and Latino Multiracial/ethnic people in our study population, so our results may have limited comparability to data that exclude Hispanic and Latino people from Multiracial categories. As few studies have been conducted among Multiracial/ethnic adult populations, there is no standardized or proposed approach for assessing within-group racial/ethnic differences, limiting the ability to analyze detailed racial/ethnic differences and comparability of results to future studies within Multiracial/ethnic populations (9). Finally, as the study lacks a formal clinical diagnostic element, we were unable to test the validity of the PHQ-9 within this sample.

4.1 Implications for Research and Practice

In an analysis across generations of adults, the study found variable measurement with respect to generation, with a particularly salient finding regarding the ninth question of the PHQ-9 which assesses for thoughts of death or self-harm. Specifically, the study found that the 9th item had progressively lower correlation with the underlying latent factor (i.e., depression) among older generations. A *post hoc* analysis suggested that older adults were less likely to report thoughts of death or self harm even when reporting high levels of other depressive symptoms. Additionally, Gen Z were more likely to report thoughts of death or self harm even at lower levels of other depressive symptoms than other generations. This finding aligns with a 2018 report by the American Psychological Association that found Gen-Z more open about reporting concerns related to mental health, and suggests the utility of a slightly tailored approach when using the PHQ-9 with different generations of Multiracial/ethnic adults (23). The use of the 9th item of the PHQ-9 may not be adequate for identifying individuals at risk for suicidal thoughts and/or behaviors, particularly for older Multiracial/ethnic adults, which may present an ethical challenge. The use of an additional tool to identify those at risk for suicide is recommended, as feasible. There is a need to conduct further research within diverse populations to explore for similar differences across age groups and explore the causes underlying this
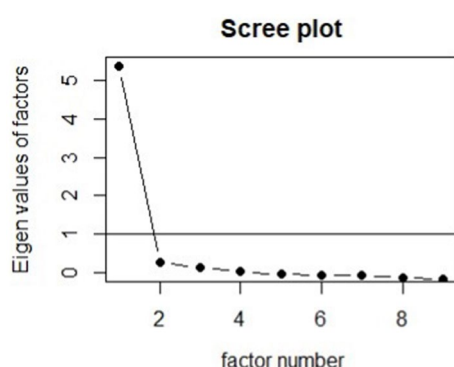
TABLE 1 Factor loading and uniqueness for items in the PHQ-9.

Item	Loading	Uniqueness
Question 1: Little interest or pleasure in doing things	0.830	0.311
Question 2: Feeling down, depressed, or hopeless	0.856	0.267
Question 3: Trouble falling or staying asleep, or sleeping too much	0.740	0.452
Question 4: Feeling tired or having little energy	0.782	0.388
Question 5: Poor appetite or overeating	0.793	0.371
Question 6: Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0.817	0.332
Question 7: Trouble concentrating on things, such as reading the newspaper or watching television	0.804	0.354
Question 8: Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0.669	0.552
Question 9: Thoughts that you would be better off dead or of hurting yourself in some way	0.633	0.600
Question 9 loading estimated separately for each generation		
Gen Z	0.900	–
Millennial	0.690	–
Gen X	0.471	–
Baby Boomer	0.361	–

TABLE 2 Comparing PHQ-2 score thresholds for detecting depression.

PHQ-2 threshold	PHQ-9 depression	Sensitivity	Specificity	PPV	NPV
2	Moderate	94%	70%	68%	95%
	Moderately Severe	99%	57%	39%	99%
	Severe	100%	49%	17%	100%
3	Moderate	73%	96%	92%	85%
	Moderately Severe	95%	85%	64%	98%
	Severe	99%	74%	28%	99%
4	Moderate	55%	99%	97%	77%
	Moderately Severe	78%	93%	75%	94%
	Severe	94%	85%	38%	99%

differential reporting of thoughts of death or self-harm to adequately inform public health research, surveillance, and clinical interventions.

This study found no evidence of measurement variance between Non-White and White/Non-White sub-populations. This study supports findings from a 2010 systematic review by Kroenke et al. that detailed the reliability of the PHQ-9 across populations and sample types, but was unable to support findings from prior research among and racially, ethnically, and linguistically diverse populations that preferred a two-factor solution (14, 17, 24). However, robust analyses of the psychometric properties of the tool by various Multiracial/ethnic constructs were not possible due to the limited sample of this exploratory study. Given the exploratory findings by generation and questions about the appropriateness of this tool within diverse samples, future research including a diagnostic element that can also examine results by different Multiracial/ethnic constructs (ie. White & Asian, White & Black, White & AI/AN, Black & Asian, Black and AI/AN, Black & White & Asian, etc.) are warranted. Future research conducted among international samples should also consider their local Multiracial/ethnic populations, and ensure psychometric assessments include these populations.

As the PHQ-2 is a widely adopted brief measure within the field of public health, this study explored the reliability and validity of the PHQ-2 at different cutoffs, using the PHQ-9 as the gold standard. Findings on the PHQ-2 align with prior evidence suggesting the adequacy of the commonly used cutoff of "3" to identify those endorsing symptoms of moderately severe or severe depression, with the recommendation of using the cutoff of "2" to miss fewer cases (25). These findings support a 2019 systematic review and meta-analysis and a 2016 diagnostic meta analysis that suggest reducing the cutoff to "2" to capture more potential cases, with the trade-off being the identification of a higher proportion of false positives (25, 26).

This study makes an important contribution to the literature by finding high internal consistency and support for measurement invariance of the one-factor PHQ-9 model within a sample of Multiracial/ethnic adults in the US. Additionally, this study provides critical information that questions the use of the 9th question alone as a suicide screener, particularly in mixed age populations. As many public health workers and health care providers seek to streamline screening and assessment processes, this study provides evidence to support the use of the PHQ-2 with Multiracial/ethnic adult

populations in the US with a recommended cutoff of 2 to capture the most potential cases. The PHQ is one of the most commonly used depression screening tools and Multiracial/multiethnic people are a diverse and growing population presently underrepresented in psychometric studies. It is important to have evidence that this common and important tool likely functions similarly for Multiracial/multiethnic people as for other clinical populations.

Data availability statement

The participants of this study did not give written consent for their data to be shared publicly. With permission by the Johns Hopkins University IRB, an anonymized dataset from the quantitative study can be made available upon written request to the corresponding author.

Ethics statement

The studies involving humans were approved by Johns Hopkins University Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their non-identifying written informed consent to participate in this study.

Author contributions

JS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. GK: Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. HW: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

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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References

1. Centers for Disease Control and Prevention. Mental Health - Household Pulse Survey - COVID-19. (2023). Available at: https://www.cdc.gov/nchs/covid19/pulse/mental-health.htm [Accessed January 21, 2023]

2. US Preventive Services Task Force, Barry MJ, Nicholson WK, Silverstein M, Chelmow D, Coker TR, et al. Screening for depression and suicide risk in adults: US preventive services task force recommendation statement. *JAMA*. (2023) 329:2057. doi: 10.1001/jama.2023.9297

3. Kroenke K, Spitzer RL. The PHQ-9: a new depression diagnostic and severity measure. *Psychiatr Ann*. (2002) 32:509–15. doi: 10.3928/0048-5713-20020901-06

4. Carroll HA, Hook K, Rojas Perez OF, Denckla C, Cooper Vince C, Ghebrehiwet S, et al. Establishing reliability and validity for mental health screening instruments in resource-constrained settings: systematic review of the PHQ-9 and key recommendations. *Psychiatry Res*. (2020) 291:113236. doi: 10.1016/j.psychres.2020.113236

5. Na PJ, Yaramala SR, Kim JA, Kim H, Goes FS, Zandi PP, et al. The PHQ-9 item 9 based screening for suicide risk: a validation study of the patient health questionnaire (PHQ)-9 item 9 with the Columbia suicide severity rating scale (C-SSRS). *J Affect Disord*. (2018) 232:34–40. doi: 10.1016/j.jad.2018.02.045

6. Penfold RB, Whiteside U, Johnson EE, Stewart CC, Oliver MM, Shortreed SM, et al. Utility of item 9 of the patient health questionnaire in the prospective identification of adolescents at risk of suicide attempt. *Suicide Life Threat Behav*. (2021) 51:854–63. doi: 10.1111/sltb.12751

7. Rossom RC, Coleman KJ, Ahmedani BK, Beck A, Johnson E, Oliver M, et al. Suicidal ideation reported on the PHQ9 and risk of suicidal behavior across age groups. *J Affect Disord*. (2017) 215:77–84. doi: 10.1016/j.jad.2017.03.037

8. Simon GE, Coleman KJ, Rossom RC, Beck A, Oliver M, Johnson E, et al. Risk of suicide attempt and suicide death following completion of the patient health questionnaire depression module in community practice. *J Clin Psychiatry*. (2016) 77:221–7. doi: 10.4088/JCP.15m09776

9. Charmaraman L, Woo M, Quach A, Erkut S. How have researchers studied multiracial populations: a content and methodological review of 20 years of research. *Cultur Divers Ethnic Minor Psychol*. (2014) 20:336–52. doi: 10.1037/a0035437

10. U.S. Census Bureau. (2020). Census illuminates racial and ethnic composition of the country. Census.gov (2021). Available at: https://www.census.gov/library/stories/2021/08/improved-race-ethnicity-measures-reveal-united-states-population-much-more-multiracial.html [Accessed January 18, 2023]

11. U.S Census Bureau. United States Census Bureau Microdata. ACS 1-Year Estim Public Use Microdata Sample 2021 (2021). Available at: https://data.census.gov/mdat/ [Accessed January 18, 2023]

12. Substance Abuse and Mental Health Services Administration. 2021 National Survey on drug use and health. (2022). Available at: https://www.samhsa.gov/data/data-we-collect/nsduh-national-survey-drug-use-and-health [Accessed January 18, 2023]

13. The Trevor Project. The mental health and well-being of multiracial LGBTQ youth. Trevor Proj. (2022). Available at: https://www.thetrevorproject.org/research-briefs/the-mental-health-and-well-being-of-multiracial-lgbtq-youth-aug-2022/ [Accessed January 18, 2023]

14. Harry ML, Coley RY, Waring SC, Simon GE. Evaluating the cross-cultural measurement invariance of the PHQ-9 between American Indian/Alaska native adults and diverse racial and ethnic groups. *J Affect Disord Rep*. (2021) 4:100121. doi: 10.1016/j.jadr.2021.100121

15. Huang FY, Chung H, Kroenke K, Delucchi KL, Spitzer RL. Using the patient health Questionnaire-9 to measure depression among racially and ethnically diverse primary care patients. *J Gen Intern Med*. (2006) 21:547–52. doi: 10.1111/j.1525-1497.2006.00409.x

16. Keum BT, Miller MJ, Inkelas KK. Testing the factor structure and measurement invariance of the PHQ-9 across racially diverse U.S. college students. *Psychol Assess*. (2018) 30:1096–106. doi: 10.1037/pas0000550

17. Patel JS, Oh Y, Rand KL, Wu W, Cyders MA, Kroenke K, et al. Measurement invariance of the patient health Questionnaire-9 (PHQ-9) depression screener in U.S. adults across sex, race/ethnicity, and education level: NHANES 2005-2016. *Depress Anxiety*. (2019) 36:813–23. doi: 10.1002/da.22940

18. Qualtrics Online Research Panels & Samples for Surveys. Qualtrics. (2023). Available at: https://www.qualtrics.com/research-services/online-sample/ [Accessed January 24, 2023]

19. R Core Team. R: A language and environment for statistical computing. (2023). Available at: https://www.R-project.org/

20. Revelle W. Procedures for psychological, psychometric, and personality research. (2023). Available at: https://CRAN.R-project.org/package=psych

21. Rosseel Y. Lavaan: an R package for structural equation modeling. *J Stat Softw*. (2012) 48:1–36. doi: 10.18637/jss.v048.i02

22. Jorgensen TD, Pornprasertmanit S, Schoemann AM, Rosseel Y. Semtools: Useful tools for structural equation modeling. (2022). Available at: https://CRAN.R-project.org/package=semTools

23. American Psychological Association. Stress in America™ generation Z. (2018). Available at: https://www.apa.org/news/press/releases/stress/2018/stress-gen-z.pdf

24. Kroenke K, Spitzer RL, Williams JBW, Löwe B. The patient health questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. *Gen Hosp Psychiatry*. (2010) 32:345–59. doi: 10.1016/j.genhosppsych.2010.03.006

25. Manea L, Gilbody S, Hewitt C, North A, Plummer F, Richardson R, et al. Identifying depression with the PHQ-2: a diagnostic meta-analysis. *J Affect Disord*. (2016) 203:382–95. doi: 10.1016/j.jad.2016.06.003

26. Levis B, Benedetti A, Thombs BDDEPRESsion Screening Data (DEPRESSD) Collaboration. Accuracy of patient health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. *BMJ*. (2019) 365:l1476. doi: 10.1136/bmj.l1476

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The magnitude of perinatal depression and associated factors among women in Kutaber woreda public health institution and Boru Meda general hospital, Ethiopia, 2022: a cross-sectional study

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Background: Perinatal depression, characterized by the presence of depressive symptoms during pregnancy and/or within the first 12 months postpartum, poses a significant global public health concern. It contributes to a multitude of health risks for mothers, their infants, and their families. Understanding of perinatal depression and its associated factors is crucial for effective prevention and intervention strategies. However, there is a lack of comprehensive research on this topic in Ethiopia. Therefore, this study aims to determine the prevalence and factors contributing to perinatal depression among Ethiopian women.

Methods: An institutional-based cross-sectional study was conducted, involving 552 women receiving perinatal services at Kutaber district health institution and Boru Meda General Hospital. Study participants were selected through systematic random sampling techniques. Perinatal depression was assessed using the Depression, Anxiety, and Stress Scale-21 (DASS-21). The associations between various determinants and perinatal depression were examined using binary logistic regression, and factors with a *p*-value of less than 0.2 were included in the multiple logistic regression analysis. A *p*-value less than 0.05 was considered statistically significant.

Results: The prevalence of perinatal depression was found to be 32.2%. The prevalence of perinatal depression was found to be 32.2%. Factors significantly associated with perinatal depression included being a student [adjusted odds ratio (AOR) = 4.364, 95% confidence interval (CI): 1.386, 13.744], experiencing excessive pregnancy-related concerns (AOR = 1.886, 95% CI: 1.176, 3.041), past substance use (AOR = 2.203, 95% CI: 1.149, 4.225), the presence of anxiety symptoms (AOR = 3.671, 95% CI: 2.122, 6.352), experiencing stress symptoms (AOR = 6.397, 95% CI: 3.394−12.055), and daytime sleepiness (AOR = 2.593, 95% CI: 1.558, 4.316).

Conclusion: The findings of this study indicate a relatively high prevalence and valuable factors associated with perinatal depression. It highlights the need for a comprehensive approach to perinatal mental health that takes into account not only the biological aspects of pregnancy but also the psychological, social,

and lifestyle factors that can impact a person's mental well-being during this critical period.

Introduction

Perinatal depression, a prevalent mental health issue, affects pregnant individuals and new mothers during the perinatal period, encompassing pregnancy and the postpartum period (1, 2). While extensively studied in developed countries, perinatal depression remains a significant concern in developing countries, where healthcare resources may be limited (3–17). Perinatal depression is characterized by the occurrence depressive symptoms during pregnancy and/or within 12 months following delivery (15–18). Globally, perinatal depression is a major public health concern due to its direct association with altered mother-to-child interaction, diminished outcomes in child development, and considerable personal, economic, as well as social costs (15, 19, 20). It is the most common mental health problems experienced by a woman during perinatal period (3, 4, 10–14) and is linked with increased risks of maternal & infant mortality and morbidity (5–9).

Due to physiological, psychological, hormonal, and social changes during pregnancy and the postpartum period, the likelihood of experiencing emotional disturbances such as depression may increase (21–23). Approximately 70% to 80% of all new mothers experience some negative psychological feelings or mood swings during pregnancy, delivery, and the first year after giving birth (24). Becoming a mother is a significant life transition that impacts a woman's sense of self and identity. It involves navigating various emotional, physical, and social changes. These changes often require women to reassess their roles, goals, and aspirations both within and outside of motherhood. This process of identity development is complex and can contribute to a mother's depression (25, 26). In the perinatal period, parents acquire new roles, responsibilities, and knowledge and respond to changes in personal identity, relationships, and family dynamics (27–31).

Depressive symptoms during the perinatal period may have devastating consequences not only for maternal health but also for mother-to-child interaction and their child's biological, physiological, social, and cognitive development (5, 7, 27, 32, 33).

Identity development before becoming a parent plays a crucial role in one's ability to cope with the responsibilities and challenges of parenthood. Developing a solid adult identity allows individuals to have a strong sense of self, a clear understanding of their values, and a firm grasp on their personal goals and aspirations (34). Transitioning to parenthood can be overwhelming in itself, and without a strong sense of self, individuals may find it challenging to navigate the changes and adjustments that come with this new role. They may feel a loss of personal freedom and struggle to find a balance between their own identity and the responsibilities of being a parent. When individuals enter parenthood without a well-established identity, they may face various challenges. Firstly, they

may struggle with a lack of self-confidence and uncertainty about their abilities as a parent. Secondly, they may experience difficulties in setting boundaries and establishing a sense of self within the parental role. They may struggle with balancing their own needs and desires with the demands of their child, leading to feelings of frustration, resentment, or guilt (35).

Regarding perinatal depression, neurobiological birth dynamics play a pivotal role. The perinatal period is characterized by significant hormonal fluctuations, especially during pregnancy and after childbirth, which can influence maternal mental health. Additionally, the neurobiological changes associated with pregnancy and childbirth can impact the mother's stress response and emotional regulation systems, contributing to the risk of perinatal mood disorders such as depression and anxiety (36–38).

In developing countries maternal mental health problems especially depression during perinatal period become the most challenging issue (39–41). According to WHO reports depression is the fourth leading cause of disability worldwide (42). Depression is also predicted to become the leading cause of disease burden by 2030, and it is already the leading cause of disease burden in women worldwide (42, 43). Perinatal depression rates vary globally, with studies reporting different prevalence rates. In the USA, rates ranged from 18.4% to 40.4% among women (44). In rural China, 13% exhibited symptoms of depression (14) while in Italy, 18.7% of perinatal caregiver professionals reported depression symptoms (45, 46). Low- and middle-income countries showed a wide range of 3%–50% prevalence (47). In Malaysia, depression rates during the perinatal period varied from 1.9% to 82.1% in developing countries and 5.2% to 74.0% in developed countries (48).

During the COVID-19 outbreak in Mexico, 39.2% of women developed depression symptoms (30), and in Portugal, 13%–16% experienced postnatal depression (32). Among Australian fathers, 10% experienced perinatal depression (49), and in Brazil, the prevalence was 24.3% during pregnancy and 10.8% postpartum (50). In Egypt, 40% of university students exhibited depressive symptoms (51). and in Ghana, 9.9% experienced antenatal depression (52). Various studies among pregnant women reported rates ranging from 24.94% to 58% for depressive symptoms (53–58). Several factors were associated with perinatal depression across these studies. Unemployment (45) and financial problems (13) were common determinants. Low social support, single status, lower education, unemployment, financial instability, and older age increased the risk (4, 59). Other systematic review and meta-analysis study in China shows that educational level and economic status of families were significantly correlated with perinatal depression (60). The absence of a partner (50), maternal age less than 30 years old, never being married (52), and low economic status and low economic status (50, 52) were also significant factors with perinatal depression.

Clinically, a history of depression, physical trauma (61), lack of physical activity (62), poor physical health (63), sleep disturbance (27), poor health status, and history of traumatic experiences (64), physical & sexual abuse (28), domestic violence (60), poor relationships with their parent (7), family conflict, lack of decision-making power and poor social support (14) were linked to perinatal depression. Lifetime stressful event exposure (7, 64, 65) perinatal smoking and/or the use of alcohol (50, 60, 66), and husband smoking status (57) were additional contributing factors.

Obstetric factors such as multiparity (50, 60), unintended pregnancy (52, 54, 55), and previous pregnancy loss (52, 67) having more than 4 living children (7, 57, 68), emotional detachment during childbirth (69), history of lifetime abortion (54), age at marriage (57), obstetric complications in previous and/or this pregnancy (57, 58), violence during pregnancy (70, 71) were also factors associated with perinatal depression. Generally, perinatal depression in developing countries particularly in Ethiopia poses a significant public health challenge, with potentially severe consequences for maternal and child well-being. Understanding the prevalence and associated factors in developing countries is crucial for effective prevention and intervention strategies. However, there is a lack of comprehensive research addressing the prevalence and the factors contributing to perinatal depression in Ethiopia. So, this study aimed to determine the prevalence and its associated factors of perinatal depression among women in Ethiopia.

Methods and materials

Study areas, design, and period

An Institution based cross-sectional quantitative study design was conducted to assess the prevalence and associated factors of perinatal depression among women attending perinatal services in Kutaber district public health facilities and Boru Meda general hospital from January to August 2022.

Population, sample size and sampling procedure

All women who attend antenatal care, postnatal care & child vaccination program in the last 12 months after delivery in the selected public health facilities of the district and Boru Meda general hospital. Women who attended perinatal health services in the selected public health of Kutaber district and Boru Meda General Hospital during the study period. Inclusion criteria for the enrolling women were the age of ≥18 years, having regular ANC & PNC follow up as well as women who came for delivery during the study period if they are volunteers. Women who are unable to communicate, severely ill and previous diagnosis of psychiatric disorder were excluded from the study. To study the associated risk factors with perinatal depression Epi. Info. Version 7, for double population proportion, was used with an assumption of; a two-sided confidence level (1-alpha) (95%), power (chance of detecting) (80%), the ratio of controls to cases (1), the hypothetical proportion of controls with exposure, and hypothetical proportion of cases with exposure from previous research findings of related

works (54, 57). Accordingly, the researcher gets the largest study participant in the second objectives sample size calculation which is 502 and takes it by adding 10% non-response rate. Finally, the population was also proportionally allocated. The study respondents were recruited using a systematic random sampling method. The total estimated number of women that visited the five public health centers and the one general hospital per day is 65 patients. Since the number of required test subjects were 552, a sampling interval of three were used as the constant difference between subjects. The first starting number of each study site was selected randomly using the lottery method from the registration counter. A structured interviewer-administered questionnaire was used to obtain socio-demographic and relevant associated information from the respondents.

Data collection tools and procedure

Perinatal depression was measured using the depression content of Depression Anxiety Stress Scale-21 (DASS-21). DASS-21 has been widely used in studying perinatal psychological health (72–76). Each item in DASS-21 is rated using a 4-point scale (0 for always false or not applicable to 3 for always true or totally applicable). Higher scores indicate greater distress levels. The internal consistency reliability of DASS-21 was very impressive in Ethiopia with Cronbach's alpha 0.75, 0.72, 0.86, and 0.95 for DASS depression, anxiety, stress, and total scales, respectively (77). These coefficients demonstrated good internal consistencies. The cut-off values for DASS depression, anxiety and stress were 9, 7, and 14, respectively (74, 75). Based on the will of the women those who had scores for depression, anxiety, and stress scale higher than the cut point were linked to the psychiatric ward for further diagnostic investigation.

The Epworth Sleepiness Scale was used as a subjective measure of a woman day time sleepiness. The test had a list of eight situations in which women were rated to become sleepy on a scale of 0, no chance of dozing, to 3, high chance of dozing (78, 79). The total score was based on a scale of 0 to 24. The scale estimates whether women were experiencing excessive sleepiness that possibly requires medical attention (78–82). Socio-demographic characteristics and obstetric variables: trimester, having previous pregnancy, previous pregnancy & labor complication, previous history of stillbirth, previous history of abortion, plan current pregnancy, previous ANC follow-up, current pregnancy complication and previous psychiatric history was collected by a structured and pre-tested questionnaire.

The Baby's father's support, partner's feeling on current pregnancy, community support, and substance use history was also collected by a structured questionnaire.

Operational definition

Perinatal period

The period starting from pregnancy (antenatal) until the end of the first year after a baby is born (postnatal) (6, 57, 83, 84).

Anxiety symptoms

Scoring above the cut-off scores (7) on DASS-21 scales used for assessing perinatal anxiety symptoms (11).

Stress symptoms

Scoring above the cut-off scores (14) on DASS-21 scales used for assessing perinatal stress symptoms (11).

Daytime sleepiness

Those women having ESS score of >10 (85–91).

Data quality assurance

To assure the data quality high emphasis was given in designing data collection instruments. The questionnaires were pretested Haroye health post on 10% of the sample size to check consistency and length of time each questioner took, sampling method and techniques.

Training was provided for data collectors, and supervisors and before data collection the questioners were checked its simplicity, clarity and understandability. Checking and re-checking of the data was employed to identify whether the data was completely filled or not by double data entry. Daily supervision of the data collection process was implemented. One day of training was given for data collectors and supervisors. To ensure the quality of data, a properly designed standardized data collection tool was used.

Data analysis procedure

Each completed questionnaire was coded. The data was checked and cleaned by entering into Epi data version 4.6 and was exported into Statistical Package for the Social Sciences SPSS window version 26, for analysis. Descriptive statistics were employed to estimate the prevalence of perinatal depression. Bivariate analyses (binary logistic regression) were carried out between the predictors and outcome variables.

Using significant variables ($p < 0.2$) from binary logistic regression models, a multivariable logistic regression model was fitted to identify the independent predictors of perinatal depression. The strength of association was measured by odds ratios with 95% confidence intervals. Statistical significance was declared at $p < 0.05$. To measure the fitness of the data to the model Hosmer–Lemeshow test was conducted. The small p-value <0.05 of the goodness of fit test means that the model is not good fit. And also apply to the binary logistics regression assumptions were conducted that were linearity of the independent variable, the inclusion of relevant variable, meaningful coding, independent observation, no multicollinearity and sufficiently large sample size.

Ethical consideration

The studies involving human participants were reviewed and approved by Ethical Committee of Wollo University College of Medicine and Health Science with an ethical review number (RCSPG-191/14). All procedures performed were in accordance with the ethical standards of the institutional and national research committee at which the studies were conducted and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. A written informed consent was obtained from each participant or their parents &/or legal guardians.

Results

Sociodemographic and husband-related characteristics of the study subject

A total of 552 women were recruited for the study, and all of them completed the questionnaire, resulting in a 100% response rate. The respondents were all aged between 18 and 45 years, with a mean age of 29.6 ± 5.385, a median of 29, and a mode of 30. Geographically, 295 (53.4%) lived in rural areas. The majority of the participants, 532 (96.4%), were of Amhara ethnicity, 363 (56.8%) were Muslim, 209 (37.9%) had completed primary school, 443 (80.3%) were married, 321 (58.2%) reported not knowing their monthly income, and 245 (44.4%) had medium levels of social support. Of the total 552 respondents, 333 (60.3%) had employed husbands (Table 1).

Description of respondents by obstetric & other psychosocial related factors

Out of the total respondents, 459 (83.2%) reported having happy feelings during pregnancy, 443 (80.3%) experienced pregnancy after marriage, 341 (61.8%) had 1–3 children, 391 (70.8%) had a history of normal vaginal delivery, and 485 (87.9%) had no history of sexual violence. Additionally, 199 (36.1%) had a history of substance use, and 153 (27.7%) were living with other chronic medical illnesses (Table 2).

Perinatal depression scores of the participants

The overall prevalence of perinatal depression was 32.2% (95% CI, 27.87–36.62). The cutoff point for depression on the DASS-21 scale was set at 9, and accordingly, 178 (32.2%) of study subjects met the criteria for depression symptoms. The depression scores on the DASS-21 scale ranged from 0 to 19, with a median score of 7 (Figure 1).

Distribution of perinatal depression among sociodemographic factors of the respondent

Among the respondents who developed perinatal depression, 125 (70.2%) were in the age group of 24–35 years, 92 (51.7%) lived in rural areas, 132 (74.2%) were married, 120 (67.4%) were employed, 94 (52.8%) did not have a known monthly income, and 85 (47.8%) reported having a moderate level of social support. Among the respondents who developed depression, 136 (76.4%) reported happy feelings during pregnancy, 133 (74.7%) reported that pregnancy was planned and wanted, 134 (80.3%) reported pregnancy occurring after marriage, 97 (54.4%) had a history of past obstetric pregnancy complications, 106 (59.6%) had 1–3 children, and 90 (50.6%) experienced adverse life events. Socially, 100 (56.2%) were exposed to financial conflicts. Clinically, among the women who developed depressive symptoms, 95 (53.4%) and 86 (48.3%) reported substance use in their lifetimes and in the past 3 months, respectively.

TABLE 1 Socio-demographic characteristics of study subject (n = 552).

	Variables	Frequency	Percentage
Age	<24	99	17.9
	24–35	392	71.0
	>35	61	11.1
Residency	Rural	295	53.4
	Urban	257	46.6
Ethnicity	Amhara	532	96.4
	Tigray	14	2.5
	Afar	4	0.7
	Oromo	2	0.4
Religion	Muslim	363	65.8
	Orthodox	172	31.2
	Catholic	6	1.1
	Protestant	9	1.6
	Others	2	0.4
Educational status	Unable to read and write	133	24.1
	Primary school	209	37.9
	Secondary school	115	20.8
	Diploma & above	95	17.2
Marital status	Single	64	11.6
	Married	443	80.3
	Divorced	28	5.1
	Widowed	17	3.1
Employment	Student	41	7.4
	Housewife	335	60.7
	Merchant	51	9.2
	Government	93	16.8
	Private	19	3.4
	Others	13	2.4
Monthly income	Do not know	321	58.2
	Up to 1,000	44	8.0
	>1,001	187	33.9
Husband employment status	Employed	364	65.9
	Not employed	183	33.2
	Has not husband	5	0.9
Marital conflict	Absent	231	41.8
	Present	316	57.2
	Has not husband	5	0.9
Support from her husband	Enough	437	79.2
	Not enough	110	19.9
	Has not husband	5	0.9

TABLE 2 Obstetric and other psychosocial characteristics of study subject (n = 552).

	Variables	Frequency	Percentage
Feeling on current pregnancy	Unhappy	93	16.8
	Happy	459	83.2
Is the current pregnancy planned?	Unplanned	119	21.6
	Planned	433	78.4
Premarital pregnancy	No	443	80.3
	Yes	109	19.7
Parity	Nulliparous	160	29.0
	1–4 previous live birth	334	60.5
	>previous live birth	58	10.5
Excessive pregnancy-related concern	Present	189	34.2
	Absent	363	65.8
Past history of obstetric complication	Present	204	37.0
	Absent	348	63.0
Bad attitude towards current pregnancy	Yes	115	20.8
	No	437	79.2
Number of children	No child	136	24.6
	1–3 Children	341	61.8
	4 and above children	75	13.6
Delivery outcome (last birth)	Stillbirth	88	15.9
	Live birth	423	76.6
	Still pregnant	41	7.4
Mode of delivery (last delivery)	Cs	108	19.6
	Other	12	2.2
	Still first pregnant	41	7.4
	Normal vaginal delivery	391	70.8
The presence of adverse life events?	No	399	72.3
	Yes	153	27.7
Illness in the family member?	Absent	434	78.6
	Present	118	21.4
Financial conflict?	Absent	310	56.2
	Present	242	43.8
History of domestic violence?	No	495	89.7
	Yes	57	10.3
History of sexual abuse?	No	485	87.9
	Yes	67	12.1
History of physical abuse?	No	484	87.7
	Yes	68	12.3

Factors associated with perinatal depression

Bivariate analyses were conducted between perinatal depression and independent variables (sociodemographic, obstetric and clinical factors). Finally, all individual factors with a *p*-value <0.20 in bivariate logistic regression analysis were entered into multivariate logistic regression for further analysis. According to the multivariate analysis, being a student (AOR = 4.364, 95% CI: 1.386, 13.744), excessive pregnancy-related concern (AOR = 1.886, 95% CI: 1.176, 3.041), ever substance use (AOR = 2.203, 95% CI: 1.149, 4.225), the presence of anxiety symptoms (AOR = 3.671, 95% CI: 2.122, 6.352), stress symptoms (AOR = 6.397, 95% CI: 3.394–12.055), and daytime sleepiness (AOR = 2.593, 95% CI: 1.558, 4.316) were significantly associated with perinatal depression (Table 3).
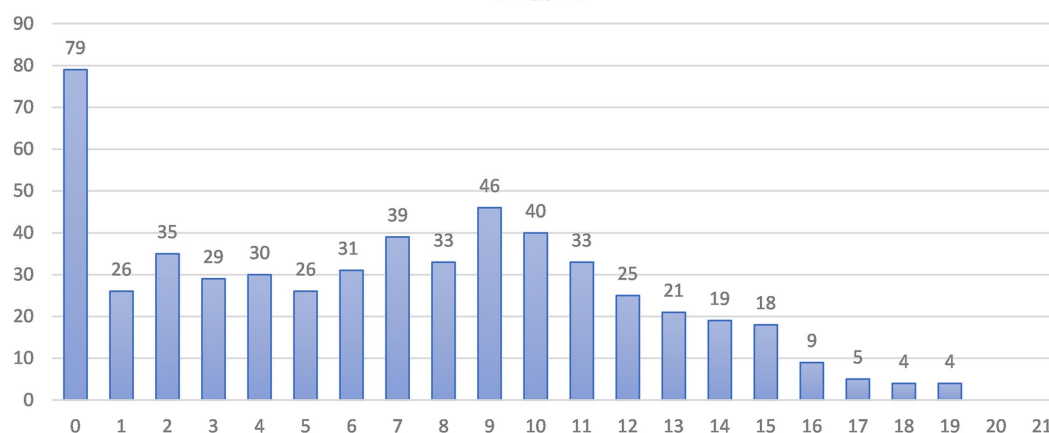
FIGURE 1
Graph of the total response of depression symptoms (from 0 up to 21) during perinatal period on the seven depression related items of DASS-21 scales. The X-axis indicates the sum scores (0–21) of depressions related symptoms assessment. Y-axis indicates the number of participants who score different level of depression related symptoms.

Discussion

The prevalence of perinatal depression in this study was 32.2%, which was consistent with findings from studies conducted in Nepal 36% (92), Brazil 25.9% (67), Latin America 28.2% (93), Vietnam 29.9% (94), South Africa 39% (71) Egypt 40% (51) and Ethiopia 35.9% (54). However, it was lower than the prevalence reported in studies conducted in the United States 40.4% (44), UK 47.3% (61), Mexico 39.2% (30), Rwanda 37.6% (7) and Ethiopia 58% (56). On the other hand, it was higher than the prevalence in studies conducted in Colombia 22.36% (9), Canada 17.9% (63), Norwegian 2% (28), China 13% (14), Malaysia 12.5% (95) Australia 19.8% (41), Asia 20% & 21.8% (96), Ghana 24.3% (50) and other parts of Ethiopia (24.9, 26.7, 25.8%) (53, 57, 58). Generally, the discrepancy of the prevalence of depression during the perinatal period might be a result of a difference in assessment tools, geographical areas, sample size, health status & cultures of the study subject and the study setting. Even though there is discrepancy, the result is supported by many other studies carried out elsewhere perinatal depression as a significant public health concern among women in the perinatal period (7, 28, 30, 44, 51, 61, 67, 70, 95, 97–99).

Being a student during the perinatal period was found to be a significant risk factor for perinatal depression (AOR = 4.364, 95% CI: 1.386, 13.744). This finding suggests that the unique challenges and stressors faced by student mothers may contribute to their vulnerability to depression. Early parenting presents numerous challenges, and these challenges are closely linked to the need for a mature and well-developed adult identity. Becoming a parent requires individuals to navigate significant changes in their roles, responsibilities, and priorities. They must also grapple with their own emotional and psychological development, as they transition from being a child or young adult to assuming the role of a caregiver (34).

These stressors might include academic demands, financial pressures, and social support deficits. Academically, student mothers may experience additional stress due to the demands of attending classes, completing assignments, and studying while also being pregnant or caring for a newborn (34). Financial pressures like balancing the costs of education, such as tuition fees, textbooks, and other expenses, with the financial responsibilities of pregnancy or caring for a child can be challenging for student mothers (100). Socially, student mothers may have limited social support networks due to being away from their families or lacking access to resources that could provide assistance during pregnancy and early motherhood (100–102) This lack of support can contribute to feelings of isolation and increased stress levels. It's important to note that these factors are not the sole causes of perinatal depression in student mothers, but they may contribute to their increased vulnerability. The combination of hormonal changes, sleep deprivation, and the demands of parenting can be particularly challenging for individuals who have not yet developed a strong sense of identity. They may struggle with feelings of isolation, inadequacy, and a sense of losing their own identity within the role of motherhood. These factors can contribute to the development or exacerbation of perinatal depression (35).

It's crucial for healthcare professionals, educational institutions, and support networks to be aware of these challenges and provide appropriate support and resources to help student mothers during this critical period (35).

Excessive worry or concern related to pregnancy was identified as another contributing factor (AOR = 1.886, 95% CI: 1.176, 3.041). This result indicates that heightened anxiety or preoccupation with pregnancy-related issues can increase the risk of perinatal depression. This might be due to the emotional toll of worrying about the health and well-being of both the mother and the baby. It's important to consider the possible mechanisms behind this relationship. Pregnancy can be a time of immense change and uncertainty, and concerns about the baby's health, the mother's well-being, and the impending responsibilities of parenthood may contribute to increased levels of concern/worry. This, in turn, can impact a woman's mental health during pregnancy and the postpartum period. Healthcare providers should be attuned to the psychological well-being of expectant mothers and offer appropriate support and resources to help them

TABLE 3 Factors associated with perinatal depression (*n* = 552) (bivariate & multivariate logistic regressions).

Variable	Depression			Bivariate analysis			Multivariate analysis		
	N_{Total}	Yes	No	*p*-value	COR	95% CI	*p*-value	AOR	95% CI
Educational status									
Unable to read and write	133	36	97	0.569	0.845	0.473–1.509	0.242		
Primary school	209	79	130	**0.220***	1.383	0.823–2.323	0.703		
Secondary school	115	34	81	0.880	0.955	0.528–1.728	0.607		
Diploma & above	95	29	66	1					
Marital status									
Married	443	132	311	1					
Single	64	23	41	**0.094***	0.393	0.132–1.171	0.493		
Divorced	28	13	15	0.421	0.607	0.179–2.052	0.649		
Widowed	17	10	7	**0.016***	0.297	0.111–0.797	0.361		
Employment									
Government	93	30	63	1					
Student	41	7	34	**0.115***	0.329	0.083–1.312	**0.012****	**4.364**	**1.386–13.744**
Housewife	335	120	215	0.846	0.893	0.286–2.791	0.412		
Merchant	51	15	36	0.531	0.667	0.187–2.372	0.274		
Private	19	1	18	**0.039***	0.089	0.009–0.889	0.358		
Others	13	5	8	0.657	0.762	0.230–2.527	0.210		
Monthly income									
Don't know	321	94	227	**0.127***	0.742	0.505–1.088	0.118		
Up to 1000	44	17	27	0.728	1.128	0.573–2.218	0.203		
>1,001	187	67	120	1					
Current pregnancy									
Unplanned	119	45	74	**0.143***	1.372	0.899–2.094	0.726		
Planned	433	133	300	1					
Excessive pregnancy-related concern									
Present	189	76	113	**0.004***	1.721	1.189–2.492	**0.009****	**1.886**	**1.170–3.041**
Absent	363	102	261	1					
Past history of obstetric complication									
Present	204	81	123	1					
Absent	348	97	251	**0.004***	1.704	1.182–2.456	0.280		
Bad attitude towards current pregnancy									
Yes	115	44	71	**0.122***	1.401	0.914–2.149	0.879		
No	437	134	303	1					
Number of children									
No child	136	36	100	1					
1–3 children	341	106	235	0.320	1.253	0.803–1.955	0.238		
4 and above children	75	36	39	**0.002***	2.564	1.419–4.634	0.494		
The presence of adverse life events?									
No	399	106	293	1					
Yes	153	72	81	**0.000***	2.457	1.668–3.620	0.119		
Illness in the family member									
Absent	434	120	314	1					
Present	118	58	60	**0.000***	2.529	1.666–3.841	0.214		
Financial conflict									
Absent	310	78	232	1					
Present	242	100	142	**0.000***	2.095	1.458–3.009	0.791		
History of domestic violence?									
No	495	147	349	1					
Yes	57	31	25	**0.000***	3.319	1.895–5.812	0.998		
History of sexual abuse?									
No	485	145	350	1					
Yes	67	33	24	**0.000***	3.467	2.053–5.854	0.115		

(Continued)

TABLE 3 (Continued)

Variable	Depression			Bivariate analysis			Multivariate analysis		
	N_{Total}	Yes	No	*p*-value	COR	95% CI	*p*-value	AOR	95% CI
Substances use in lifetime									
No	353	83	270	1					
Yes	199	95	104	**0.000***	2.972	2.050–4.308	**0.017****	**2.203**	**1.149–4.225**
Any substances in the past three months?									
No	366	92	274	1					
Yes	186	86	100	**0.000***	2.561	1.765–3.718	0.455		
Anxiety									
Have no anxiety	313	46	267	**1**					
Have anxiety	239	132	107	**0.000***	7.161	4.783–10.721	**0.000****	**3.671**	**2.122–6.352**
Stress symptoms									
Have no stress	439	94	345	**1**					
Have stress	113	84	29	**0.000***	10.631	6.580–17.177	**0.000****	**6.397**	**3.394–12.055**
Sleep problems									
Haven't day time over sleep	434	115	319	1					
Have day time oversleep	118	63	55	**0.000***	3.177	2.088–4.835	**0.000****	**2.593**	**1.558–4.316**
Chronic medical illness?									
No	399	104	295	1					
Yes	153	74	79	**0.000***	2.657	1.803–3.916	0.347		

p-value < 0.20, **Statically significant at p < 0.05 and p-value of Hosmer and Lemeshow goodness of fit test was = **0.616.*

navigate their anxieties. Additionally, interventions focused on stress reduction, coping strategies, and emotional support may be beneficial in reducing the risk of perinatal depression among individuals experiencing heightened pregnancy-related worries.

The study found that a history of substance use is associated with an increased risk of perinatal depression (AOR = 2.203, 95% CI: 1.149, 4.225). This result was supported by other studies conducted in China (40), in South Africa (19) and any other countries (50, 60, 66). Substance use can have adverse effects on mental health and can exacerbate depressive symptoms. It may also impair decision-making and coping mechanisms, making it harder for individuals to manage their emotional well-being during perinatal period.

Similar to other studies in China (99, 103), presence of anxiety symptoms was strongly associated with perinatal depression (AOR = 3.671, 95% CI: 2.122, 6.352). Anxiety and depression often cooccur, and this finding underscores the importance of assessing and addressing both conditions during the perinatal period. Understanding the relationship between anxiety and perinatal depression is crucial for healthcare professionals and researchers to effectively screen, diagnose, and provide appropriate interventions. It is well-known that anxiety and depression often cooccur, and this comorbidity can worsen the overall mental health of pregnant and postpartum women.

High levels of anxiety can directly contribute to the development or exacerbation of depressive symptoms. Anxiety increases stress levels, which can disrupt a woman's ability to cope with the challenges of pregnancy and early motherhood. Moreover, anxiety can interfere with sleep, appetite, and overall well-being, further exacerbating the risk of perinatal depression (99). Addressing both anxiety and depression during the perinatal period is crucial for optimal mental health outcomes. Early identification and intervention can help prevent the escalation of symptoms and improve overall maternal well-being. By recognizing and addressing the interconnected nature

of these mental health conditions, healthcare providers can provide holistic care to pregnant and postpartum women, promoting better outcomes for both the mother and the child.

Consistent with the results of previous studies (104), stress symptoms were found to have a substantial impact on perinatal depression (AOR = 6.397, 95% CI: 3.394–12.055). High levels of stress, whether related to personal life, relationships, or external factors, can overwhelm pregnant or postpartum individuals, making them more susceptible to depression. Stress, whether stemming from personal life, relationships, or external factors, can be particularly challenging during the perinatal period (105). Pregnancy and early parenthood can bring about various stressors, such as financial concerns, changes in identity, lack of support, and sleep deprivation. Additionally, hormonal changes and physical discomforts associated with pregnancy can further exacerbate stress levels.

When stress becomes overwhelming and persistent, it can disrupt an individual's emotional well-being and increase the likelihood of developing depression. The study highlights the importance of identifying and addressing stress symptoms during the perinatal period to mitigate the risk of depression. Interventions aimed at reducing stress and promoting emotional well-being during pregnancy and postpartum can be beneficial in preventing or minimizing the severity of perinatal depression (35). These interventions may include stress management techniques, social support networks, cognitive-behavioral therapy, and mindfulness-based approaches. Engaging in regular physical activity, practicing relaxation techniques, and seeking professional help when needed are also essential strategies for managing stress during this critical period.

Daytime sleepiness emerged as a significant factor associated with perinatal depression (AOR = 2.593, 95% CI: 1.558, 4.316). A similar finding was reported from the studies conducted in Sweden (106), and in USA (107). Disrupted sleep patterns are a common experience for many individuals during pregnancy and early parenthood. These

disruptions can be caused by a variety of factors, including physical discomfort, hormonal changes, anxiety, and the demands of caring for a new infant. Such disruptions can lead to significant daytime sleepiness, which may in turn contribute to mood disturbances and increase the risk of perinatal depression ([106]). Addressing sleep issues as part of perinatal care can involve a range of strategies, including providing education about sleep hygiene, offering guidance on managing discomfort and anxiety, and in some cases, considering the appropriate use of medication under the supervision of a healthcare professional. By understanding and addressing sleep issues as part of perinatal mental health care, healthcare providers can potentially reduce the risk of perinatal depression and improve the overall well-being of individuals during this critical life stage.

Limitation of the study

Recall and response biases might have occurred when completing the questionnaire. In addition, some of the independent variables like physical & sexual abuse, and the presence of suicidal wish was assessed by close-ended questions which may lead some patients to respond in an indecorous manner. Because of using a cross-sectional study design, we were not demonstrating any cause and effect association between the possible determinate factors and the outcome of interest.

Conclusion

Globally perinatal depression is a public health concern. It contributes to the high burden of health risks faced by mothers, their child and their family. This study underscores the complex interplay of various factors that contribute to perinatal depression. It highlights the need for a comprehensive approach to perinatal mental health that takes into account not only the biological aspects of pregnancy but also the psychological, social, and lifestyle factors that can impact a person's mental well-being during this critical period. Early identification, intervention, and support for individuals at risk for perinatal depression are crucial to improving maternal and child health outcomes. Additionally, public health campaigns and policies should focus on raising awareness about perinatal depression and promoting early detection and intervention to improve. Finally, further research and tailored interventions are warranted to address these associated factors effectively.

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.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of Wollo University College of Medicine and Health Science with an ethical review number (RCSPG-191/14). 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

JS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. EM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. NC: Data curation, Formal analysis, Methodology, Project administration, Validation, Writing – review & editing, Investigation, Software. HY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Visualization, Writing – review & editing. EA: Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – review & editing.

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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References

1. Luciano M, Di Vincenzo M, Brandi C, Tretola L, Toricco R, Perris F, et al. Does antenatal depression predict post-partum depression and obstetric complications? Results from a longitudinal, long-term, real-world study. *Front Psychiatry*. (2022) 13:1082762. doi: 10.3389/fpsyt.2022.1082762

2. Bm XL, Wang S, Wang G. Prevalence and risk factors of postpartum depression in women: a systematic review and meta-analysis. *J Clin Nurs*. (2021) 30:2665–77. doi: 10.1111/jocn.16121

3. Fernández-Ordoñez E, González-Cano-Caballero M, Guerra-Marmolejo C, Fernández-Fernández E, García-Gámez M. Perinatal grief and post-traumatic stress disorder in pregnancy after perinatal loss: a longitudinal study protocol. *Int J Environ Res Public Health*. (2021) 18:2874. doi: 10.3390/ijerph18062874

4. Sorsa MA, Kylmä J, Bondas TE. Contemplating help-seeking in perinatal psychological distress—a meta-ethnography. *Int J Environ Res Public Health*. (2021) 18:5226. doi: 10.3390/ijerph18105226

5. Hall SL, Hynan MT, Phillips R, Lassen S, Craig JW, Goyer E, et al. The neonatal intensive parenting unit: an introduction. *J Perinatol*. (2017) 37:1259–64. doi: 10.1038/jp.2017.108

6. Byrnes L. Perinatal mood and anxiety disorders. *J Nurse Pract*. (2018) 14:507–13. doi: 10.1016/j.nurpra.2018.03.010

7. Umuziga MP, Adejumo O, Hynie M. A cross-sectional study of the prevalence and factors associated with symptoms of perinatal depression and anxiety in Rwanda. *BMC Pregnancy Childbirth*. (2020) 20:68. doi: 10.1186/s12884-020-2747-z

8. Ganjekar S, Thekkethayyil AV, Chandra PS. Perinatal mental health around the world: priorities for research and service development in India. *BJPsych Int*. (2019) 17:2–5. doi: 10.1192/bji.2019.26

9. Gaviria SL, Duque M, Vergel J, Restrepo D. Perinatal depressive symptoms: prevalence and associated psychosocial factors. *Rev Colomb Psiquiatr*. (2019) 48:166–73. doi: 10.1016/j.rcpeng.2017.09.011

10. Iyengar U, Jaiprakash B, Haitsuka H, Kim S. One year into the pandemic: a systematic review of perinatal mental health outcomes during. *Front Psychiatry*. (2021) 12:674194. doi: 10.3389/fpsyt.2021.674194

11. Jonsdottir SS. Effects of perinatal distress, satisfaction in partner relationship and social support on pregnancy and outcome of childbirth. (2019). (Doctoral dissertation, Linnaeus University Press).

12. Antoniou E, Stamoulou P, Tzanoulinou MD, Orovou E. Perinatal mental health; the role and the effect of the partner: a systematic review. *Healthcare*. (2021) 9:1572. doi: 10.3390/healthcare9111572

13. Łojko D, Wszołek K, Suwalska J, Napierała M, Bogda P, Suchowiak S. Perinatal mental health during COVID-19 pandemic: an integrative review and implications for clinical practice. *J Clin Med*. (2021) 10:2406. doi: 10.3390/jcm10112406

14. Jiang Q, Guo Y, Zhang E, Cohen N, Ohtori M, Sun A, et al. Perinatal mental health problems in rural China: the role of social factors. *Front Psychiatry*. (2021) 12:636875. doi: 10.3389/fpsyt.2021.636875

15. Bao C, Jin D, Sun S, Xu L, Wang C, Tang W. Trajectories and depressive symptoms during the perinatal period: a longitudinal population-based study in China. *Front Psychiatry*. (2022) 13:762719. doi: 10.3389/fpsyt.2022.762719

16. Tefera TB, Erena AN, Kuti KA, Hussen MA. Perinatal depression and associated factors among reproductive aged group women at Goba and Robe Town of Bale Zone, Oromia Region, South East Ethiopia. *Matern Health Neonatol Perinatol*. (2015) 1:1–9. doi: 10.1186/s40748-015-0013-6

17. Nakku JEM, Okello ES, Kizza D, Honikman S, Ssebunnya J, Ndyanabangi S, et al. Perinatal mental health care in a rural African district, Uganda: a qualitative study of barriers, facilitators and needs. *BMC Health Serv Res*. (2016) 16:1–12. doi: 10.1186/s12913-016-1547-7

18. Lequertier B, Mclean MA, Kildea S, King S, Keedle H, Gao Y, et al. Perinatal depression in Australian women during the COVID-19 pandemic: the birth in the time of COVID-19 (BITTOC) study. *Int J Environ Res Public Health*. (2022) 19:5062. doi: 10.3390/ijerph19095062

19. Garman EC, Schneider M, Lund C. Perinatal depressive symptoms among low-income South African women at risk of depression: trajectories and predictors. *BMC Pregnancy Childbirth*. (2019) 19:202. doi: 10.1186/s12884-019-2355-y

20. Phoosuwan N. Perinatal depressive symptoms among women in north-eastern Thailand: risk factors, support and prevention. *Doctoral thesis*. (2020). (Doctoral dissertation, Acta Universitatis Upsaliensis).

21. Din Z, Ambreen S, Iqbal Z, Iqbal M, Ahmad S. Determinants of antenatal psychological distress in Pakistani women. *Arch Neuropsychiatr*. (2016) 53:152–7. doi: 10.5152/npa.2015.10235

22. Buist A. Perinatal mental health identifying problems and managing medications. *Aust Fam Physician*. (2014) 43:182–5. doi: 10.3316/informit.205997313865266

23. Ashford MT, Olander EK, Ayers S. Computer- or web-based interventions for perinatal mental health: a systematic review. *J Affect Disord*. (2016) 197:134–46. doi: 10.1016/j.jad.2016.02.057

24. Green SM, Inness B, Furtado M, Mccabe RE, Frey BN. Evaluation of an augmented cognitive behavioural group therapy for perinatal generalized anxiety disorder (GAD) during the COVID-19 pandemic. *J Clin Med*. (2022) 11:209. doi: 10.3390/jcm11010209

25. Bjelica A, Cetkovic N, Trninic-Pjevic A, Mladenovic-Segedi L. The phenomenon of pregnancy—a psychological view. *Ginekol Pol*. (2018) 89:102–6. doi: 10.5603/GP.a2018.0017

26. Meaney MJ. Perinatal maternal depressive symptoms as an issue for population health. *Am J Psychiatry*. (2018) 175:1084–93. doi: 10.1176/appi.ajp.2018.17091031

27. Cheng C, Chou Y, Chang C, Liou S. Trends of perinatal stress, anxiety, and depression and their prediction on postpartum depression. *Int J Environ Res Public Health*. (2021) 18:1–12. doi: 10.3390/ijerph18179307

28. Eid K, Torkildsen ØF, Aarseth J, Flemmen HØ, Holmøy T, Lorentzen ÅR, et al. Perinatal depression and anxiety in women with multiple sclerosis. *Neurology*. (2021) 96:e2789–800. doi: 10.1212/WNL.0000000000012062

29. Osman KM, Lara-cinisomo S, Anna-hernandez KLD. Associations between religiosity and perinatal anxiety symptoms among women of Mexican descent. *J Affect Disord*. (2022) 294:77–84. doi: 10.1016/j.jad.2021.06.066

30. Vianey B, Estrada-gutierrez G, Maribel S, Perichart-perera O, Rodr C, Gonz C, et al. Prevalence of depression, anxiety, and perceived stress in postpartum Mexican women during the COVID-19 lockdown. *Int J Environ Res Public Health*. (2021) 18:4627. doi: 10.3390/ijerph18094627

31. Noonan M, Jomeen J, Doody O. A review of the involvement of partners and family members in psychosocial interventions for supporting women at risk of or experiencing perinatal depression and anxiety. *Int J Environ Res Public Health*. (2021) 18:5396. doi: 10.3390/ijerph18105396

32. Costa J, Santos O, Virgolino A, Em M, Stefanovska-petkovska M, Silva H, et al. MAternal mental health in the WORKplace (MAMH @ WORK): a protocol for promoting perinatal maternal mental health and wellbeing. *Int J Environ Res Public Health*. (2021) 18:2558. doi: 10.3390/ijerph18052558

33. Nielsen-Scott M, Fellmeth G, Opondo C, Alderdice F. Prevalence of perinatal anxiety in low- and middle-income countries: a systematic review and meta-analysis. *J Affect Disord*. (2022) 306:71–9. doi: 10.1016/j.jad.2022.03.032

34. Goossens G, Kadji C, Delvenne V. Teenage pregnancy: a psychopathological risk for mothers and babies? *Psychiatr Danub*. (2015) 27:499–503.

35. Kristensen IH, Juul S, Kronborg H. What are the effects of supporting early parenting by newborn behavioral observations (NBO)? A cluster randomised trial. *BMC Psychol*. (2020) 8:1–9. doi: 10.1186/s40359-020-00467-5

36. Polese D, Riccio ML, Fagioli M, Mazzetta A, Fagioli F, Parisi P, et al. The newborn's reaction to light as the determinant of the brain's activation at human birth. *Front Integr Neurosci*. (2022) 16:933426. doi: 10.3389/fnint.2022.933426

37. Poletti M, Preti A, Raballo A. Focusing on modifiable early protective factors to prevent negative neurodevelopmental and psychiatric outcomes in at-risk infants. *Front Psychiatry*. (2023) 14:1302474. doi: 10.3389/fpsyt.2023.1302474

38. Highet N, Stevenson AL, Purtell C, Coo S. Qualitative insights into women's personal experiences of perinatal depression and anxiety. *Women and Birth*. (2014) 27:179–84. doi: 10.1016/j.wombi.2014.05.003

39. Elrassas H, Taha GR, El A, Muhammed D, Abd S, Kareem E, et al. Prevalence and related factors of perinatal depression in Egyptian mothers. *Middle East Curr Psychiatry*. (2022) 29:35. doi: 10.1186/s43045-022-00203-2

40. Hong L, Le T, Lu Y, Shi X, Xiang L, Liu M, et al. Distinct trajectories of perinatal depression in Chinese women: application of latent growth mixture modelling. *BMC Pregnancy Childbirth*. (2022) 22:1–11. doi: 10.1186/s12884-021-04316-0

41. Fisher J, De MC, Patel V, Rahman A, Tran T, Holmes W. Prevalence and determinants of common perinatal mental disorders in women in low- and lower-middle-income countries: a systematic review. *Bull World Health Organ*. (2012) 90:139–149H. doi: 10.2471/BLT.11.091850

42. Foundation WHO and CG. *Social determinants of mental health*. Geneva: World Health Organization (2014).

43. Cox J. Perinatal mental health around the world: a new thematic series. *BJPsych Int*. (2020) 17:1–2. doi: 10.1192/bji.2019.32

44. Mckee K, Admon LK, Winkelman TNA, Muzik M, Hall S, Dalton VK, et al. Perinatal mood and anxiety disorders, serious mental illness, and delivery-related health outcomes, United States, 2006–2015. *BMC Womens Health*. (2020) 20:150. doi: 10.1186/s12905-020-00996-6

45. Alfayumi-Zeadna S, Bina R, Levy D, Merzbach R, Zeadna A. Elevated perinatal depression during the COVID-19 pandemic: a national study among Jewish and Arab women in Israel. *J Clin Med*. (2022) 11:349. doi: 10.3390/jcm11020349

46. Luciano M, Sampogna G, Del Vecchio V, Giallonardo V, Perris F, Carfagno M, et al. The transition from maternity blues to full-blown perinatal depression: results from a longitudinal study. *Front Psychiatry*. (2021) 12:703180. doi: 10.3389/fpsyt.2021.703180

47. Baron EC, Hanlon C, Mall S, Honikman S, Breuer E, Kathree T, et al. Maternal mental health in primary care in five low- and middle-income countries: a situational analysis. *BMC Health Serv Res*. (2016) 16:53. doi: 10.1186/s12913-016-1291-z

48. Norhayati MN, Hazlina NHN, Asrenee AR, Emilin WMAW. Magnitude and risk factors for postpartum symptoms: a literature review. *J Affect Disord*. (2015) 175:34–52. doi: 10.1016/j.jad.2014.12.041

49. Rodrigues AL, Ericksen J, Watson B, Gemmill AW, Milgrom J. Interventions for perinatal depression and anxiety in fathers: a mini-review. *Front Psychol*. (2022) 12:744921. doi: 10.3389/fpsyg.2021.744921

50. Melo EF, Cecatti JG, Pacagnella RC, Leite DFB, Vulcani DE, Makuch MY. The prevalence of perinatal depression and its associated factors in two different settings in Brazil. *J Affect Disord*. (2012) 136:1204–8. doi: 10.1016/j.jad.2011.11.023

51. Salem GM, Allah MBA, Said RM. Prevalence and predictors of depression, anxiety and stress among Zagazig University students. *Med J Cairo Univ*. (2016) 84:325–34.

52. Weobong B, Soremekun S, Ha A, Amenga-etego S, Danso S, Owusu-agyei S, et al. Prevalence and determinants of antenatal depression among pregnant women in a predominantly rural population in Ghana: the DON population-based study. *J Affect Disord*. (2014) 165:1–7. doi: 10.1016/j.jad.2014.04.009

53. Biratu A, Haile D. Prevalence of antenatal depression and associated factors among pregnant women in Addis Ababa, Ethiopia: a cross-sectional study. *Reprod Health*. (2015) 12:99. doi: 10.1186/s12978-015-0092-x

54. Negewo AN. Prevalence of depression among pregnant women attending ANC follow up mother's at higher two health center, Jimma teaching health center, Shenen Gibe Hospital and JUSH, Jimma Town, Oromia Regional State, South West Ethiopia. *Clin Mother Child Health*. (2019) 16:315. doi: 10.4172/2090-7214.1000315

55. Bekele D. Prevalence and associated factors of mental distress during pregnancy among antenatal care attendees at Saint Paul's Hospital, Addis Ababa. *Obstet Gynecol Int J*. (2017) 7:00269. doi: 10.15406/ogij.2017.07.00269

56. Belayihun B, Mavhandu-Mudzuis AH. Psychological distress in women with obstetric fistula in Ethiopia: a multi-center, facility-based, cross-sectional study. *Ethiop J Health Dev*. (2018) 32:211–7.

57. Gebremichael G, Yihune M, Ajema D, Haftu D, Gedamu G. Perinatal depression and associated factors among mothers in southern Ethiopia: evidence from Arba Minch Zuria health and demographic surveillance site. *Psychiatry J*. (2018) 2018:1–12. doi: 10.1155/2018/7930684

58. Mersha AG, Abebe SA, Sori LM, Abegaz TM. Prevalence and associated factors of perinatal depression in Ethiopia: a systematic review and meta-analysis. *Depress Res Treat*. (2018) 2018:1813834. doi: 10.1155/2018/1813834

59. Glasheen C, Colpe L, Hoffman V, Warren LK. Prevalence of serious psychological distress and mental health treatment in a national sample of pregnant and postpartum women. *Child Health J*. (2015) 19:204–16. doi: 10.1007/s10995-014-1511-2

60. Yang K, Wu J, Chen X. Risk factors of perinatal depression in women: a systematic review and meta—analysis. *BMC Psychiatry*. (2022) 22:63. doi: 10.1186/s12888-021-03684-3

61. Fellmeth G, Plugge E, Fazel M, Nosten S, Oo MM, Pimanpanarak M, et al. Perinatal depression in migrant and refugee women on the Thai–Myanmar border: does social support matter? *Philos Trans R Soc B*. (2021) 376:20200030. doi: 10.1098/rstb.2020.0030

62. Susukida R, Usuda K, Hamazaki K, Tsuchida A. Association of prenatal psychological distress and postpartum depression with varying physical activity intensity: Japan Environment and Children's Study (JECS). *Sci Rep*. (2020) 10:1–9. doi: 10.1038/s41598-020-63268-1

63. Gheorghe M. Symptoms of postpartum anxiety and depression among women in Canada: findings from a national cross-sectional survey. *Can J Public Health*. (2021) 112:244–52. doi: 10.17269/s41997-020-00420-4

64. Vesga-López O, Blanco C, Keyes K, Olfson M, Bridget F, DSH G. Psychiatric disorders in pregnant and postpartum women in the United States. *Arch Gen Psychiatry*. (2008) 65:805–15. doi: 10.1001/archpsyc.65.7.805

65. Yim IS, Stapleton LRT, Guardino CM, Hahn-Holbrook J, Schetter CD. Biological and psychosocial predictors of postpartum depression: systematic review and call for integration. *Annu Rev Clin Psychol*. (2015) 11:99–137. doi: 10.1146/annurev-clinpsy-101414-020426

66. Soto-Balbuena C, De M, Rodríguez F, Isabel A, Gomis E, Javier F, et al. Incidence, prevalence and risk factors related to anxiety symptoms during pregnancy. *Psicothema*. (2018) 30:257–63. doi: 10.7334/psicothema2017.379

67. Nunes C, Brito DO, Alves SV, Ludermir AB. Postpartum depression among women with unintended pregnancy. *Rev Saúde Pública*. (2015) 49:33. doi: 10.1590/S0034-8910.2015049005257

68. Al-deen ALM. Assessment of psychological distress among pregnant women in Kirkuk City. *Mosul J Nurs*. (2014) 2:51–7. doi: 10.33899/mjn.2014.162921

69. Polachek IS, Harari LH, Baum M, Strous RD. Postpartum anxiety in a cohort of women from the general population: risk factors and association with depression during last week of pregnancy, postpartum depression and postpartum PTSD. *Isr J Psychiatry Relat Sci*. (2014) 51:128–34.

70. Nasreen HE, Kabir ZN, Forsell Y, Edhborg M. Prevalence and associated factors of depressive and anxiety symptoms during pregnancy: a population based study in rural Bangladesh. *BMC Womens Health*. (2011) 11:22. doi: 10.1186/1472-6874-11-22

71. Hartley M, Tomlinson M, Greco E, Comulada WS, Stewart J, Le Roux I, et al. Depressed mood in pregnancy: prevalence and correlates in two Cape Town Peri-urban settlements. *Reprod Health*. (2011) 8. doi: 10.1186/1742-4755-8-9

72. Lydon K, Fp D, Owens L, Avalos G, Km S, Connor OC, et al. Psychological stress associated with diabetes during pregnancy: a pilot study. *Irish Med J*. (2012) 105:26–8.

73. Bin NR, Kaur A, Soni T, Por LK, Miranda S. Construct validity and internal consistency reliability of the Malay version of the 21-item depression anxiety stress scale (Malay-DASS-21) among male outpatient clinic attendees in Johor. *Med J Malaysia*. (2017) 72:264–70.

74. Tran TD, Tran T, Fisher J. Validation of the depression anxiety stress scales (DASS) 21 as a screening instrument for depression and anxiety in a rural community-based cohort of northern Vietnamese women. *BMC Psychiatry*. (2013) 13:24. doi: 10.1186/1471-244X-13-24

75. Basha E, Kaya M. Depression, anxiety and stress scale (DASS): the study of validity and reliability. *Univ J Educ Res*. (2016) 4:2701–5. doi: 10.13189/ujer.2016.041202

76. Pezirkianidis C, Karakasidou E, Lakioti A, Stalikas A. Psychometric properties of the depression, anxiety, stress scales-21 (DASS-21) in a Greek sample. *Psychology*. (2018) 9:2933–50. doi: 10.4236/psych.2018.915170

77. Sileshi Bekele MDD. Depression, anxiety and stress among first year Addis Ababa university students: magnitude, and relationship with academic achievement. *J Health Med Nurs*. (2018) 56:53–9.

78. Fernández-Alonso AM, Trabalón-Pastor M, Chedraui P, Pérez-López FR. Factors related to insomnia and sleepiness in the late third trimester of pregnancy. *Arch Gynecol Obs*. (2012) 286:55–61. doi: 10.1007/s00404-012-2248-z

79. Bourjeily G, El Sabbagh R, Sawan P, Raker C, Wang C, Hott B. Epworth sleepiness scale scores and adverse pregnancy outcomes. *Sleep Breath*. (2013) 17:1179–86. doi: 10.1007/s11325-013-0820-9

80. Wilkerson AK, Uhde TW. Perinatal sleep problems. *Obstet Gynecol Clin North Am*. (2018) 45:483–94. doi: 10.1016/j.ogc.2018.04.003

81. Sharma SK, Nehra A, Sinha S, Soneja M, Sunesh K, Sreenivas V. Sleep disorders in pregnancy and their association with pregnancy outcomes: a prospective observational study. *Sleep Breath*. (2015) 20:87–93. doi: 10.1007/s11325-015-1188-9

82. Sarberg M, Bladh M, Josefsson A, Svanborg E. Sleepiness and sleep-disordered breathing during pregnancy. *Sleep Breath*. (2016) 20:1231–7. doi: 10.1007/s11325-016-1345-9

83. Leung BMY, Kaplan BJ. Perinatal depression: prevalence, risks, and the nutrition link—a review of the literature. *J Am Diet Assoc*. (2009) 109:1566–75. doi: 10.1016/j.jada.2009.06.368

84. Molenaar J, Hanlon C, Alem A, Wondimagegn D, Medhin G, Prince M, et al. Perinatal mental distress in a rural Ethiopian community: a critical examination of psychiatric labels. *BMC Psychiatry*. (2020) 20:1–10. doi: 10.1186/s12888-020-02646-5

85. Signal TL, Paine S, Sweeney B, Priston M, Muller D, Smith A, et al. Prevalence of abnormal sleep duration and excessive daytime sleepiness in pregnancy and the role of socio-demographic factors: comparing pregnant women with women in the general population. *Sleep Med*. (2014) 15:1477–83. doi: 10.1016/j.sleep.2014.07.007

86. Hein M, Lanquart J, Loas G, Hubain P, Linkowski P. Prevalence and risk factors of excessive daytime sleepiness in major depression: a study with 703 individuals referred for polysomnography. *J Affect Disord*. (2019) 243:23–32. doi: 10.1016/j.jad.2018.09.016

87. Hunskar GS, Bjorvatn B, Wensaas K, Hanevik K, Eide GE, Langeland N, et al. Excessive daytime sleepiness, sleep need and insomnia 3 years after Giardia infection: a cohort study. *Sleep Health*. (2016) 2:154–8. doi: 10.1016/j.sleh.2016.03.005

88. Boz S, Pol J, Anaïs L, Marie M, Gwenolé D. Risk of excessive daytime sleepiness associated to major depression in adolescents. *Psychiatr Q*. (2021) 92:1473–88. doi: 10.1007/s11126-021-09922-x

89. Prasad B, Steffen AD, HPA VD, Pack FM, Strakovsky I, Staley B, et al. Determinants of sleepiness in obstructive sleep apnea. *Sleep*. (2018) 41:1–9. doi: 10.1093/sleep/zsx199

90. Kawada T. Excessive daytime sleepiness, depression and sleep-disordered breathing in patients with cardiovascular disease. *Circ J*. (2018) 83:692. doi: 10.1253/circj.CJ-18-0941

91. Ohashi M, Kohno T, Kohsaka S, Fukuoka R, Hayashida K, Yuasa S, et al. Excessive daytime sleepiness is associated with depression scores, but not with sleep-disordered breathing in patients with cardiovascular diseases. *Circ J*. (2018) 82:2175–83. doi: 10.1253/circj.CJ-17-1395

92. Ho-Yen SD, Bondevik GT, Eberhard-Gran M, Bjorvatn B. Factors associated with depressive symptoms among postnatal women in Nepal. *Acta Obstet Gynecol Scand*. (2007) 86:291–7. doi: 10.1080/00016340601110812

93. Fonseca-Machado MDO, Alves LC, Cristina J, Jos V, Stefanello J, Ana M. Depressive disorder in pregnant Latin women: does intimate partner violence matter? *J Clin Nurs*. (2015) 24:1289–99. doi: 10.1111/jocn.12728

94. Fisher J, Tran T, Kriitmaa K, Tran T. Common perinatal mental disorders in northern Vietnam: community prevalence and health care use. *Bull World Health Organ*. (2010) 88:737–45. doi: 10.2471/BLT.09.067066

95. Lee KW, Ching SM, Hoo FK, Ramachandran V, Chong SC. Prevalence and factors associated with depressive, anxiety and stress symptoms among women with gestational diabetes mellitus in tertiary care centres in Malaysia: a cross-sectional study. *BMC Pregnancy Childbirth*. (2019) 19:367. doi: 10.1186/s12884-019-2519-9

96. Roomruangwong C, Epperson CN. Perinatal depression in Asian women: prevalence, associated factors, and cultural aspects. *Asian Biomed*. (2011) 5:179–93. doi: 10.5372/1905-7415.0502.024

97. George A, Luz RF, De Tychey C, Thilly N, Spitz E. Anxiety symptoms and coping strategies in the perinatal period. *BMC Pregnancy Childbirth*. (2013) 13:233. doi: 10.1186/1471-2393-13-233

98. Nagandla K, Nalliah S, Yin LK, Majeed ZA, Ismail M, Zubaidah S, et al. Prevalence and associated risk factors of depression, anxiety and stress in pregnancy. *Int J Reprod Contracept Obstet Gynecol*. (2016) 5:2380–8. doi: 10.18203/2320-1770.ijrcog20162132

99. Xian T, Zhuo L, Dihui H, Xiaoni Z. Influencing factors for prenatal stress, anxiety and depression in early pregnancy among women in Chongqing, China. *J Affect Disord*. (2019) 253:292–302. doi: 10.1016/j.jad.2019.05.003

100. Dadi AF, Wolde HF, Baraki AG, Akalu TY. Epidemiology of antenatal depression in Africa: a systematic review and meta-analysis. *BMC Pregnancy Childbirth*. (2020) 20:251. doi: 10.1186/s12884-020-02929-5

101. Adeponle A, Groleau D, Kola L, Kirmayer LJ, Gureje O. Perinatal depression in Nigeria: perspectives of women, family caregivers and health care providers. *Int J Ment Health Syst*. (2017) 11:27. doi: 10.1186/s13033-017-0134-6

102. Dadi AF, Yihunie T, Id A, Baraki AG, Wolde HF. Epidemiology of postnatal depression and its associated factors in Africa: a systematic review and meta-analysis. *PLoS One*. (2020) 15:e0231940. doi: 10.1371/journal.pone.0231940

103. Yu Y, Zhu X, Xu H, Hu Z, Zhou W, Zheng B. Prevalence of depression symptoms and its influencing factors among pregnant women in late pregnancy in urban areas of Hengyang City, Hunan Province, China: a cross-sectional study. *BMJ Open*. (2020) 10:e038511. doi: 10.1136/bmjopen-2020-038511

104. Richter-Levin G, Xu L. How could stress lead to major depressive disorder? *IBRO Rep*. (2018) 4:38–43. doi: 10.1016/j.ibror.2018.04.001

105. Gelaye B, Rondon M, Araya R, Williams MA. Epidemiology of maternal depression, risk factors, and child outcomes in low-income and middle-income countries. *Lancet Psychiatry*. (2016) 3:973–82. doi: 10.1016/S2215-0366 (16)30284-X

106. Sarberg M, Bladh M, Svanborg E, Josefsson A. Postpartum depressive symptoms and its association to daytime sleepiness and restless legs during pregnancy. *BMC Pregnancy Childbirth*. (2016) 16:137. doi: 10.1186/s12884-016-0917-9

107. Lewis BA, Gjerdingen D, Schuver K, Avery M, Marcus BH. The effect of sleep pattern changes on postpartum depressive symptoms. *BMC Womens Health*. (2018) 18:12. doi: 10.1186/s12905-017-0496-6

Prevalence of premenstrual syndrome and its associated factors in Africa: a systematic review and meta-analysis

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Background: Clinical research and epidemiological studies have shown that many women experience physical and behavioral symptoms that begin during the luteal phase of the menstrual cycle and terminate around the onset of menses; this is called premenstrual syndrome. The reviews stated that the pooled prevalence of premenstrual syndrome was around 50 percent. However, there has been no review done on premenstrual syndrome in Africa. Therefore, the aim of this systematic review and meta-analysis was to summarize the most recent data evidence on the pooled prevalence of premenstrual syndrome and its pooled effect of associated factors in Africa.

Method: We used an appropriate guideline for systematic reviews and meta-analyses reports, which is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). This review protocol was registered in PROSPERO (CRD42023414021). The publications were identified from PubMed/Medline, EMBASE, Scopus databases, and other grey searches. The included papers were the original data that reported the prevalence of premenstrual syndrome and associated factors published, in English, and papers available online from January 1, 2000, to May 30, 2023. The data was extracted in Microsoft Excel, and then it would be imported into STATA 11.0 for analysis.

Results: We have included 16 studies conducted in African countries with 6530 study participants. In this meta-analysis, the pooled prevalence of premenstrual syndrome among the reproductive-age participants in Africa was 46.98 (95% CI: 28.9−65.06%). Further, in subgroup analysis, the pooled prevalence of premenstrual syndrome was 57.32% in Nigeria, 43.8% in Ethiopia, and 38.6% among university students and 66.04% among secondary school students. Among associated factors, the early age of menarche was significantly related to premenstrual syndrome.

Conclusion: In this review, the pooled prevalence of premenstrual syndrome in Africa was high. Among factors, the early age of menarche was a risk factor for premenstrual syndrome. This finding might help the stakeholders (mental health policy makers, administrators, and mental health professionals) to address prevention, early screening, and management of PMS among reproductive-age women, and to give attention to more vulnerable bodies.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO, identifier CRD42023414021.

Introduction

Clinical research and epidemiological studies have shown that many women experience recurrent physical, behavioral, and/or psychological signs and symptoms that begin during the luteal phase of the menstrual cycle and terminate around the onset of menses or shortly thereafter; this is called premenstrual syndrome and/or premenstrual dysphoric disorder (1–3). These signs and symptoms are characterized as; Behavioural and/or psychological signs and symptoms: affective lability (feeling suddenly sad or tearful, or increased sensitivity to rejection), irritability or anger, depressed mood, feelings of hopelessness, anxiety, tension, restlessness, decreased interest in usual activities, lethargy, difficulty in concentration, changes in appetite, and hypersomnia or insomnia. Physical signs and symptoms include breast tenderness or swelling, joint or muscle pain, a sensation of "bloating" or weight gain, headaches or migraines, and abdominal cramps (2, 3).

The severe form of premenstrual syndrome is called premenstrual dysphoric disorder (PMDD) (4). Premenstrual dysphoric disorder was under depressive disorder not otherwise specified in the Diagnostic and Statistical Manual of Mental Disorder (DSM-IV) (5), but after careful scientific review of the evidence, PMDD is a new diagnosis in the Diagnostic and Statistical Manual of Mental Disorder-5 (DSM-5) (6). Almost 20 years of additional research on this condition has confirmed a specific and treatment-responsive form of depressive disorder that begins sometime following ovulation, remits within a few days of menses, and has a marked impact on functioning (6).

The scholars were also strengthened that PMS is a number of signs and symptoms that are characterized by physical symptoms and emotional and behavioral disturbances in the luteal phase of the menstrual cycle in the reproductive age women (7–10). Reproductive age in women (from menarche to menopause) has a different range, but mostly it falls between 15 and 49 years (11, 12). The study showed that an estimated 90% of women of reproductive age suffered from mild to acute premenstrual symptoms. Among them, about 20 to 40 percent encounter moderate to severe symptoms (PMS), while 2 to 8

percent experience severe PMS/PMDD (13). Another study revealed that 95% of women experience PMS; of them, 5% suffered severe PMS (14). In the United States of America (USA), the 12-month prevalence of PMDD is between 1.8% and 5.8% of menstruating women (15). And also, the systematic review and meta-analysis studies revealed that the prevalence of PMS was 47.8% (7) in the global population, PMS (43%), and PMDD (8%) (16) in India, whereas in Ethiopia, more than half (53%) (17) and (54.5%) (18) of the reproductive-age women had PMS and PMDD, respectively. However, there has been no review done on PMS and/or PMDD in Africa. Indeed, PMS and/or PMDD status has been the topic of a large number of studies, with a large variation in reported prevalence rates from 6.1% (19) to 94.8% (20).

The precise cause of PMS is unknown, but research has indicated that changing hormone levels such as those of oestrogen, progesterone, testosterone, prolactin, and serotonin synthesis in the brain also appear to play a major part in PMS (3, 15) (21). Stress, a history of interpersonal trauma, seasonal variations, and sociocultural features of female sexual behavior in general and female gender role in particular are environmental factors linked to the expression of premenstrual dysphoric disorder (6). Premenstrual dysphoric disorder's heritability in the United States is uncertain. Premenstrual symptoms, on the other hand, have heritability estimates ranging from 30% to 80%, with the most stable component considered to be roughly 50% heritable (6). And also, the review stated that alcohol intake was significantly associated with PMS (22). Whereas, other reviews showed that PMS/PMDD was associated with a higher risk of post-partum depression (PPD) (23), and suicidality (24, 25). Women with PMS or PMDD suffered distress and impairment in interpersonal or workplace functioning. These decreased productivity levels at work and school affect quality of life, increase health care utilization, and can lead to at least 2 days per month of absenteeism at work and an increase in medical appointments (26–28).

Identifying risk factors and the pooled prevalence of MPS could help health care professionals and policymakers plan health promotion, prevention, and early intervention programs.

However, per our search, there has been no systematic review or meta-analysis of the epidemiology of PMS in Africa. So, in response to this research gap, the aim of this study is to summarize the most recent data evidence from January 2000 to May 2023 for reproductive-age women in Africa. What is the pooled prevalence of PMS and the pooled effects of associated factors?

Materials and methods

Study design

In this study, we followed an appropriate guideline for systematic reviews and meta-analyses reports: of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (29) (Supplementary File 1). This review protocol was registered in PROSPERO (CRD42023414021).

Searching strategy

The publications were searched by PubMed/Medline, EMBASE, Cochrane Library, Scopus, HINARI, PsycINFO, African Journals Online (AJOL), and also the grey literature was searched by Google Scholar and World Health Organization (WHO) reports. We used the following search terms ("prevalence" OR "epidemiology" OR "magnitude" AND "premenstrual syndrome" OR "premenstrual dysphoric disorder" AND "associated factors" OR "risk factors" AND "women" AND "Africa") (Supplementary File 2).

Eligibility criteria

The studies had the following criteria: they were done in African countries and were all relevant observational studies (cross-sectional). And also, published in English, published and unpublished articles were considered. Searching was performed from 1 February 2023 to 30 May 2023, and articles available online from 1 January 2000 to 30 May 2023 were considered, but studies that could not be fully accessed (conference abstracts) were excluded. We looked over each study's abstract and title before adding those to our meta-analysis. Following the selection of pertinent research, the entire text was examined. As seen in Figure 1, we did not include any article with no interesting variables in our study.

Data extraction

MM and GN independently extracted all the necessary data from the articles using a standardized data extraction format. The data extraction format included the following items: the first author's name, publication year, country where the study was conducted, a screening tool used to examine PMS, number of participants, prevalence of PMS, and associated factors with PMS. The data extraction format was in the form of a two-by-two table. A

cross-check was done by MM and GM authors. If contrasting results occurred between the two authors during data extraction, they were discussing ways to achieve consensus and double extraction with other authors.

Tools and validity

Among the sixteen studies reporting estimates of the prevalence of PMS, six were assessed using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Three studies were assessed using the Premenstrual Syndrome Scale (PMSS), with an inter-rater reliability between 0.81 and 0.97 (30). The PMSS consists of 40 items on a 5-point Likert-type scale (as "never" was scored as "1", rarely as "2", sometimes as "3", very often as "4", and always as "5" points). The scale score is 40 to 200. A total score estimated at 80 points or above indicates PMS, and an increase in the scores indicates an increase in PMS severity (30, 31).

The American College of Obstetricians and Gynecologist diagnostic criteria (ACOG) were used to assess PMS in two studies (32), where the following criteria were followed:

1. The patient reports one or more of the following affective and somatic symptoms five days before menses in each of the three prior menstrual cycles: affective, depression, angry outbursts, anxiety, irritability, confusion, social withdrawal, somatic, Breast tenderness, abdominal bloating, headache, swelling of the extremities.
2. Symptoms are relieved within 4 days of menses onset without recurrence until at least cycle day 13.
3. Symptoms present in the absence of any pharmacologic therapy, hormone ingestion, or drug or alcohol abuse.
4. Symptoms occur reproducibly during two cycles of prospective recording.
5. The patient suffers from an identifiable dysfunction in social or economic performance.

Another two studies were assessed using the International Classification of Diseases, Tenth Edition (ICD-10). The remaining three studies were measured using a different tool, as shown here: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (6). The premenstrual symptoms screening tool (PSST) was used to assess PMDD, which includes a list of premenstrual psychiatric and physical symptoms and a measure of functional impairment in accordance with DSM-5 criteria (33). And the Calendar of Premenstrual Experiences (COPE) is a valid and reliable tool for the diagnosis of PMS (31, 34, 35). The COPE scoring for each symptom is a 3-point rating scale: absent = 0, present = 1, severe = 2 (31).

Quality appraisal

The quality of the research reports included in this review was assessed using the Joanna Briggs Institute (JBI) for cross-sectional study quality assessment (36). For this quality assessment tool, it
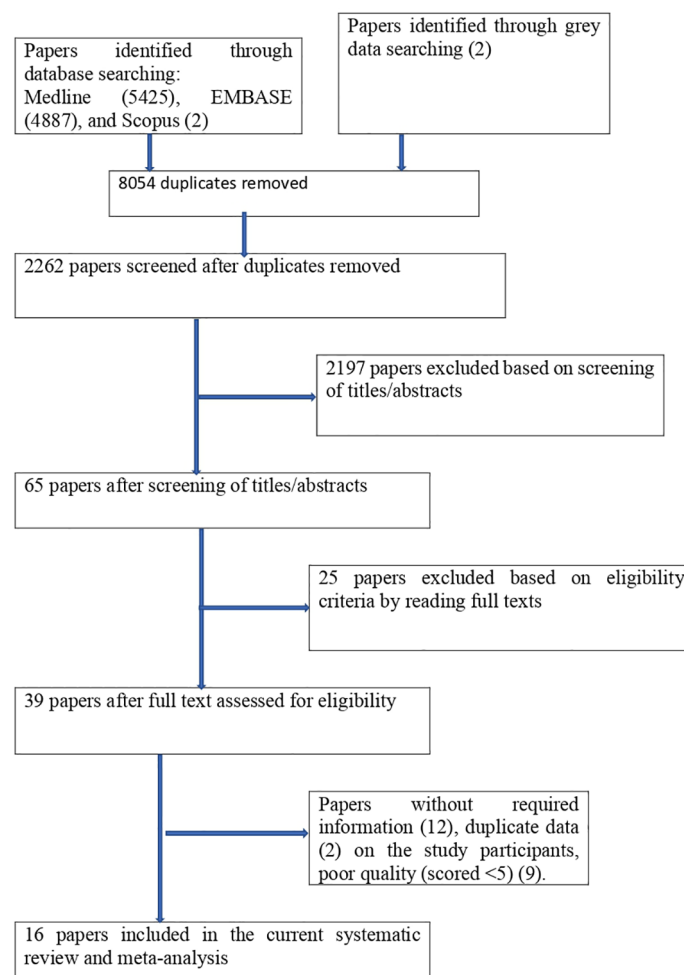
FIGURE 1
PRISMA flowchart of review search on the prevelance and associated factors of PMS.

included the following components: the methodological quality of the study, the comparability of the included studies, and the quality of the original articles with respect to statistical analysis. All authors independently evaluated the quality of the original research using JBI. The tool has a total of 9 scores, and articles with medium and high quality (articles that score 5 and above out of a 9-point scale) were included in this review for analysis. Also, some papers were excluded due to low quality scores (that scored less than 5). If there were any discrepancies between authors during the quality assessment of the included studies, they were solved by the involvement of other authors.

Data processing and analysis

The data was extracted in Microsoft Excel, and then it will be imported into STATA 11.0 for analysis. The extracted data were shown using texts, tables, and forest plots. The standard error of prevalence for each primary or original study was analyzed using the binomial distribution. The prevalence of the original studies was checked for heterogeneity using a heterogeneity I-squire (I^2) test

(37). We used a random-effects meta-analysis model to estimate Der Simonian and Laird's pooled effect of PMS. And we made a leave-one-out sensitivity analysis to identify the possible source of heterogeneity in the pooled meta-analysis of the prevalence of PMS among women in African countries. Publication bias was detected using funnel plot analysis (38) and Egger - weighted regression tests (39). A p value of less than 5% significance in the Egger test was considered to have statistically significant publication bias (39), Subgroup analysis was done to identify the impact of factors in a particular group for the prediction of the pooled prevalence of PMS.

Results

Study identification

There were 10314 publications identified in database searches, and another 2 records were added through grey searches. Among them, 8054 were removed due to duplicates; 2197 papers were excluded based on screening of titles/abstracts; 25 papers were excluded based on eligibility criteria by reading full texts; papers

were excluded due to (without required information (12), duplicate data (2), and poor quality (9). Finally, a total of 16 studies were involved in this systematic review and meta-analysis (Figure 1).

Characteristics of included studies

A total of 16 studies conducted in African countries, including 6530 study participants, were included in this review. Among the 16 studies included, nine were from Ethiopia (40–48), four from Nigeria (19, 20, 49, 50), and one from Uganda (51), Sudan (52) and Egypt (53). All of them were followed cross-sectional study designs. Regarding assessment tools, most of them were assessed by DSM-IV (six studies) and PMSS (three studies) (Table 1).

Study quality appraisals

To assess the quality of the studies we used the Joanna Briggs Institute (JBI) quality assessment criteria. All the studies involved in this review have good quality (JBI score >=5) (Supplementary File 3).

Meta- analysis

The pooled prevalence of PMS in Africa was 46.98 (95% CI: 28.9–65.06%) (Figure 2). Due to apparent heterogeneity across the studies, we have used a random effect model while conducting a meta-analysis ($I^2 = 99.7\%$, p < 0.000).

TABLE 1   Characteristics of studies included in the systematic review and meta-analysis on prevalence of premenstrual syndrome and associated in Africa.

First author name (year)	Country	Participants	Study design	Tool	SZ	P %	QS	AFW [AOR(95% CI)]
Elizabeth et al, (2022) (51)	Uganda	university students	Cross-sectional	ACOG	212	28.3	8	…
Tomader (2015) (52)	Sudan	university students	Cross-sectional	DSM-IV	401	9.5	5	…
Fikru et al, (2014) (40)	Ethiopia	university students	Cross-sectional	DSM-IV	258	37	8	…
Adiss et al, (2004) (41)	Ethiopia	university students	Cross-sectional	DSM-IV	242	27	8	…
Bolurin et al, (2009) (20)	Nigeria	university students	Cross-sectional	ICD-10	404	94.8	9	
Sisay et al, (2017) (42)	Ethiopia	university students	Cross-sectional	PSST	529	36.9	9	…
Balew et al, (2023) (43)	Ethiopia	university students	Cross-sectional	PMSS	408	41.2	9	Family history of MPS: [6.34(3.47, 11.56)]; Hormonal contraceptive: [10.3 (4.4, 24.1)]
Woredaw et al, (2020) (44)	Ethiopia	university students	Cross-sectional	DSM-5	386	34.7	9	Family history of PMS: [1.76 (1.05, 2.92)]
Kelechi et al, (2018) (49)	Nigeria	university students	Cross-sectional	COPE	480	42.9	6	…
Natnael et al, (2022) (45)	Ethiopia	university students	Cross-sectional	PMSS	591	37.9	9	Menarche (<13 years): [2.64 (1.34, 5.19)]
Abebaw et al, (2019) (46)	Ethiopia	Secoudary school students	Cross-sectional	ACOG	496	81.3	9	Menarche (<13 years): [2.68 (1.32, 5.47)]
Delelegn et al, (2019) (47)	Ethiopia	university students	Cross-sectional	DSM-IV	254	66.9	9	…
A. O. et al, (2008) (19)	Nigeria	university students	Cross-sectional	DSM-IV	410	6.1	8	…
Tilahun et al, (2015) (48)	Ethiopia	Secoudary school students	Cross-sectional	DSM-IV	181	30.9	8	
Dalia et al, (2021) (53)	Egypt	university students and staffs	Cross-sectional	PMSS	668	90.5	8	…
ANTAI et al, (2004) (50)	Nigeria	Secondary school students	Cross-sectional	ICD-10	200	85.5	6	…

SZ, sample size; P, prevalence; QS, quality score; AFW, Associated factors with; AOR, adjusted odd ratio; CI, confidence interval.
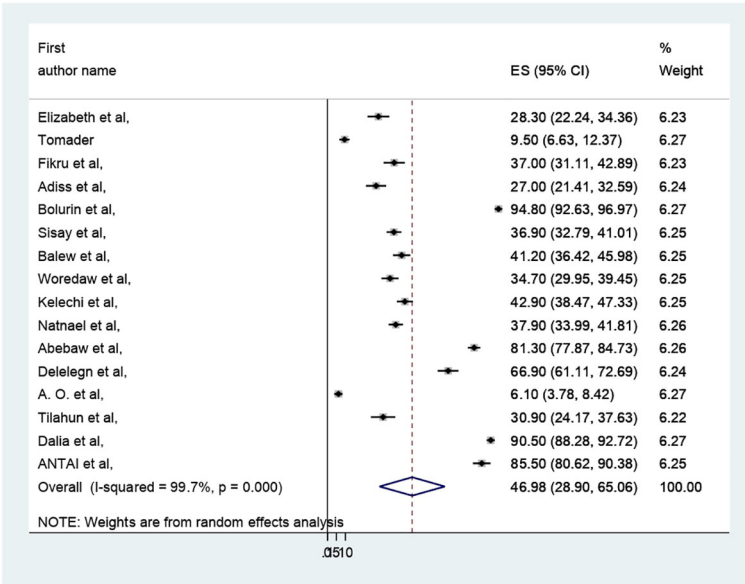
FIGURE 2
Forest plot of the pooled prevelance of PMS in Africa.

Publication bias

In this study, a funnel plot falls inside the triangle, which indicates the absence of publication bias (Figure 3), and Egger's regression test (P = 0.346) strengthened it (Table 2).

Subgroup analysis

The presence of heterogeneity was confirmed (I^2 = 99.7%, p < 0.000). So, subgroup analysis was conducted based on study country, type of participants, and assessment tool. A higher pooled prevalence of PMS was found in Nigeria (57.32%, I^2 = 99.9%, p = 0.000), followed by Ethiopia (43.8%) (I^2 = 99.6%, p = 0.000). The study participants' pooled prevalence of PMS among

university students and secondary school students was 38.6% (I2 = 99.7%, p = 0.000) and 66.04% (I^2 = 99%, p = 0.000), respectively. Regarding the assessment tool, the pooled prevalence of PMS was 29.44% by DSM-IV and 56.57% by PMSS. Therefore, this result showed there was high heterogeneity among subgroups, as indicated by I^2 (91.4 and above) and P = 0.001 (Figures 4–6), which indicate the need to conduct the sensitivity test.

A leave-out-one sensitivity analysis

The sensitivity analysis was done to check the heterogeneity of those studies by omitting one author or one study step by step to check the effect of each study on the overall prevalence of PMS in this systematic review and meta-analysis study. As evidenced by the
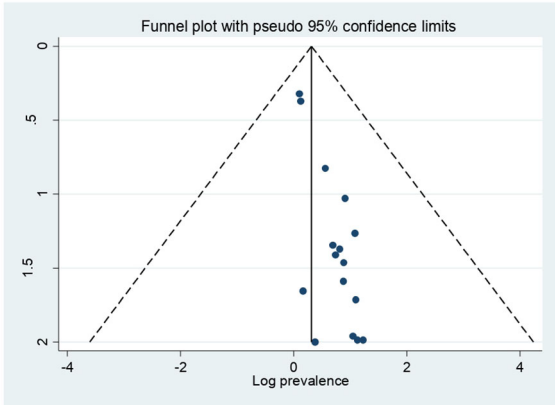
FIGURE 3
Funnel plot of PMS in Africa.

TABLE 2 Egger's test of premenstrual syndrome in Africa. A systematic review and meta-analysis.

Std_Eff	Coef.	Std. Err.	T	P>t	[95% Conf Interval]	
Slope	75.70633	24.63469	3.07	0.008	22.87018	128.5425
Bias	-13.18729	13.51646	-0.98	0.346	-42.17722	15.80264

results, all the values are within the estimated 95% confidence-interval (CI) ranged 43.78% to 49.52%, which indicates the omission of a single study had no significant difference in the prevalence of this systematic review and meta-analysis (Table 3).

Narrative analysis

The extracted important factors associated with PMS among participants of reproductive age, the individual study, in Africa were provided in Table 1 with reference to the studies analyzed in logistic regression with adjusted odd ratio. This section has narrated significant factors associated with PMS in Africa. The following results were obtained from the pooled analysis for these factors and in cases where two or more publications were present: age of menarche (<13 years) (adjusted odd ratio (AOR) = 2.66, 95% CI: 1.47–4.8) with two previous studies and within this review was significantly associated with PMS, whereas perceived family history of PMS (AOR = 2.96, 95% CI: 0.86–10.13) with two previous studies, was not significantly associated with PMS (Figure 7).

Discussion

In our systematic review and meta-analysis, we synthesized 16 studies investigating the prevalence and associated factors of PMS among 6530 reproductive age participants in Africa, of whom 3068 had been screened for PMS. In this review, the pooled prevalence of PMS in Africa was 46.98 (95% CI: 28.9–65.06%). This result was in line with the previous studies of systematic reviews and meta-analyses done in Ethiopia (17, 18), India (16) and Global (7). On the other hand, it was less than the Iranian study (54). This disparity may be attributed to the study participants' residency in Iran, but this review encompassed five nations; in Iran, 24 articles with a sample size of 9147 women of reproductive age were included. Additionally, additional assessment instruments (such as the American Psychiatric Association, Premenstrual Assessment Scale, Daily Record of Severity of Problems Chart, Researcher Made Questionnaire, Premenstrual Assessment Scale, and Hallbridge et al. questionnaire) were utilized in Iran, which were not included in this review. Further, in this analysis, DSM-IV was dominantly used for PMS assessment. This could result from differences in premenstrual syndrome screening and assessment methods' specificity and sensitivity.

In this review, regarding subgroup analysis, the pooled prevalence of PMS among participants of reproductive age was higher in Nigeria (57.32%) compared with Ethiopia (43.8%). This finding may vary depending on the number of studies and participant sample size. For example, four research with 1494 participants were conducted in Nigeria, while nine studies with 3345 participants were conducted in Ethiopia. It could also be due to variations in research regions and assessment tools along with sociocultural differences. Additionally, we used the study participant type; among secondary school and university
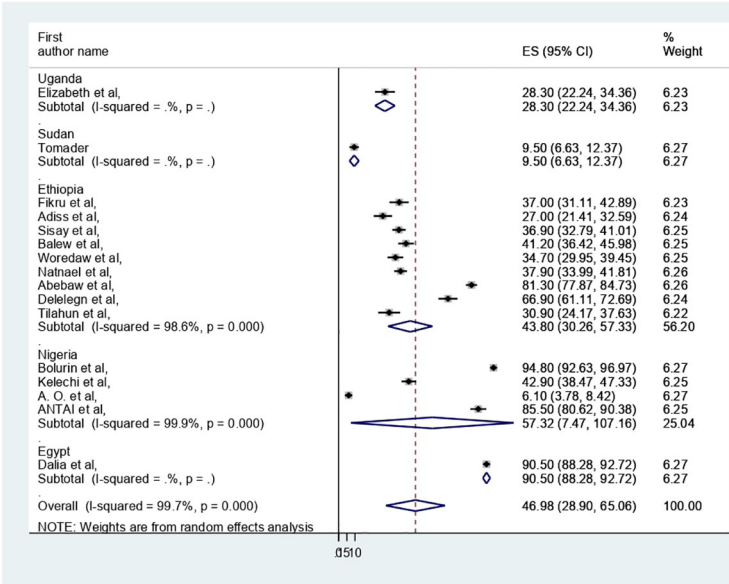
FIGURE 4
Forest plot on subgroup analysis of the pooled prevalence of PMS in Africa.

TABLE 3 Sensitivity analysis of PMS in Africa.

Study omitted	Estimated 95% CI	Heterogeneity	
		I^2 (%)	P-value
Elizabeth et al,	48.22(29.41-67.03)	99.8	0.001
Tomader	49.48(31.45-67.57)	99.7	0.001
Fikru et al,	47.64(28.75-66.53)	99.8	0.001
Adiss et al,	48.31(29.48-67.13)	99.8	0.001
Bolurin et al,	43.78(26.45-61.11)	99.7	0.001
Sisay et al,	47.65(28.54-66.76)	99.8	0.001
Balew et al,	47.36(28.33-66.39)	99.8	0.001
Woredaw et al,	47.8(28.82-66.77)	99.8	0.001
Kelechi et al,	47.25(28.15-66.35)	99.8	0.001
Natnael et al,	47.58(28.42-66.75)	99.8	0.001
Abebaw et al,	44.68(25.69-63.68)	99.7	0.001
Delelegn et al,	45.65(26.74-64.56)	99.8	0.001
A. O. et al,	49.52(32.94-66.49)	99.6	0.001
Tilahun et al,	48.04(29.24-66.85)	99.8	0.001
Dalia et al,	44.07(25.97-62.16)	99.7	0.001
ANTAI et al,	44.41(25.64-63.19)	99.8	0.001

students, the pooled prevalence of PMS was 66.04% and 38.6%, respectively. The menarche age and participant age may be the cause, as shown by the results of the earlier Iranian review (54).

In terms of factors associated with PMS, they were extracted in the individual study in Africa with reference to the studies analyzed in logistic regression with an adjusted odd ratio. However, most studies were analyzed by ANOVA, and some of them involved linear logistic regression.

The important variables linked to PMS have been discussed in this section, and in cases where two or more publications were present, our review identified that age at menarche and family history of PMS were positively and negatively associated with PMS. According to this finding, early menarche (<13 years) (AOR = 2.66, 95% CI: 1.47–4.8) was a risk factor for PMS. The results of this study could be explained by the earlier menarche age being linked to the early development of ovarian functions and ovulation with steroid hormone fluctuations at such a young age with less physical and psychological maturity, which may cause PMS manifestations; however, the earlier Ethiopian meta-analysis did not support this theory (17). In contrast, perceived family history of PMS (AOR = 2.96, 95% CI: 0.86–10.13) was not significantly associated with PMS in this analysis. The severe level of premenstrual dysphoric disorder's heritability in the United States is unknown. However, Premenstrual symptoms have heritability estimates ranging from 30% to 80% (6).

Regarding this study, all participants were secondary school and university students. This is a productive age group, so the ministry of education should incorporate the module into the curriculum and provide training about premenstrual symptoms and their management. We recommend more representative samples, or rather, a cross-sectional study design, be used in future research that concentrates on a more precise diagnosis.

Limitation

The limitation of this review is that it included only studies published in English that were cross-sectional studies since there
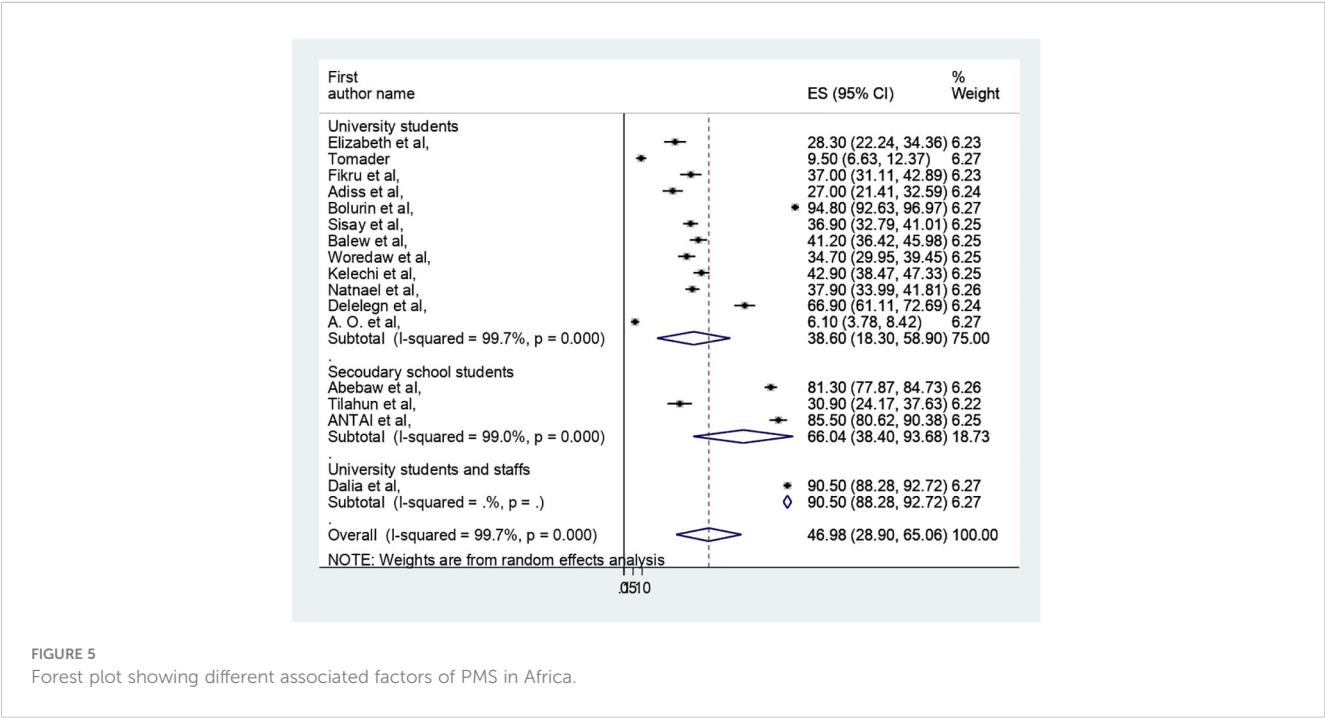
FIGURE 5
Forest plot showing different associated factors of PMS in Africa.
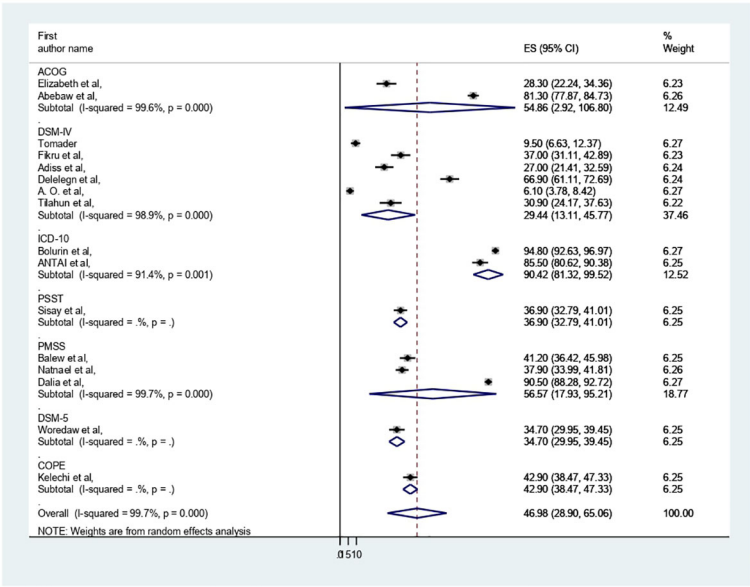
FIGURE 6
Forest plot on subgroup analysis based on the assessment tool used.
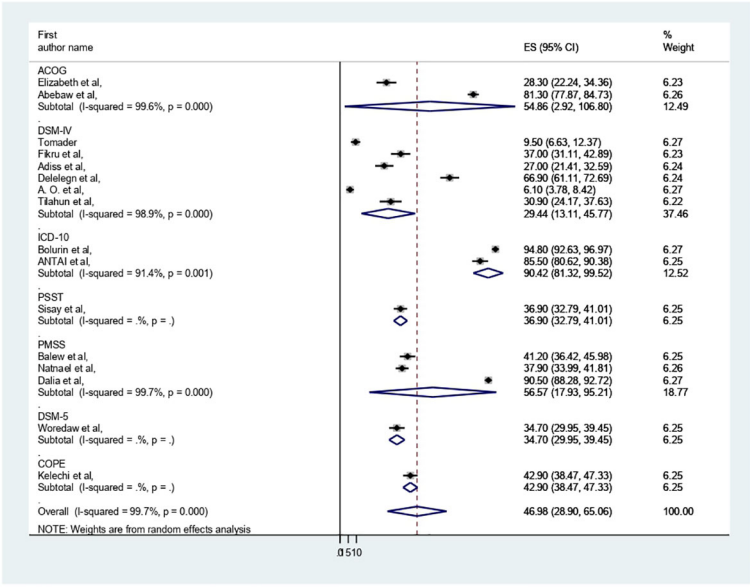
FIGURE 7
Forest plot showing different factors associated with PMS in Africa.

were no studies conducted with other study designs and a small number of articles were included.

Conclusion

In this review, the pooled prevalence of PMS in Africa was high. Among factors, the early age of menarche was a risk factor for PMS. This finding might help the stakeholders (mental health policy makers, administrators, and mental health professionals) to address

prevention, early screening, and management of PMS among reproductive-age women and to give attention to more vulnerable bodies.

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

FA: Conceptualization, Data curation, Methodology, Software, Validation, Writing – original draft, Writing – review & editing. MM: Data curation, Writing – review & editing. GiM: Data curation, Writing – review & editing. GN: Writing – review & editing. TT: Writing – review & editing. SF: Writing – review & editing. GR: Writing – review & editing. JS: Writing – review & editing. GeM: Writing – review & editing. DA: Writing – review & editing. TN: Writing – review & editing.

Funding

Acknowledgments

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

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1338304/full#supplementary-material

References

1. Cowen P, Harrison P, Burns T. *Shorter Oxford textbook of psychiatry*. USA: Oxford University Press (2012).

2. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, *5th* edn. Washington, DC: American American Psychiatric Association (2013).

3. Kwan I, Onwude JL. Premenstrual syndrome. *BMJ Clin Evid.* (2015) 2015:0806.

4. Steiner M, Peer M, Palova E, Freeman EW, Macdougall M, Soares CN. The Premenstrual Symptoms Screening Tool revised for adolescents (PSST-A): prevalence of severe PMS and premenstrual dysphoric disorder in adolescents. *Arch Womens Ment Health* (2011) 14:77–81. doi: 10.1007/s00737-010-0202-2

5. Sadock BJ. *Kaplan & Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry* (1998). Lippincott Williams & Wilkins. Copyright© 2007.

6. Guha M. Diagnostic and statistical manual of mental disorders: DSM-5 (5th edition). (2014) 28(3):36–7. doi: 10.1108/RR-10-2013-0256

7. Direkvand-Moghadam A, Sayehmiri K, Delpisheh A, Sattar KJ. Epidemiology of Premenstrual syndrome (PMS)-A systematic review and meta-analysis study. *J Clin Diagn Res* (2014) 8 (2):106–9. doi: 10.7860/JCDR/2014/8024.4021

8. Kleinstäuber M, Schmelzer K, Ditzen B, Andersson G, Hiller W, Weise C. Psychosocial profile of women with premenstrual syndrome and healthy controls: a comparative study. *Int J Behav Med* (2016) 23:752–63. doi: 10.1007/s12529-016-9564-9

9. Hofmeister S, Bodden S. Premenstrual syndrome and premenstrual dysphoric disorder. *Am Fam Physician* (2016) 94:236–40.

10. Gudipally PR, Sharma GK. Premenstrual syndrome. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing (2023).

11. Golshiri P, Akbari M, Abdollahzadeh MR. Age at natural menopause and related factors in Isfahan, Iran. *J Menopausal Med* (2016) 22:87–93. doi: 10.6118/jmm.2016.22.2.87

12. Bahrami N, Soleimani MA, Chan YH, Ghojazadeh M, Mirmiran P. Menarche age in Iran: A meta-analysis. *Iran J Nurs Midwifery Res* (2014) 19(5):444.

13. Matsumoto T, Asakura H, Hayashi T. Biopsychosocial aspects of premenstrual syndrome and premenstrual dysphoric disorder. *J Gynaecol Endocrinol* (2013) 29 (1):67–73. doi: 10.3109/09513590.2012.705383

14. O'Brien PM. Helping women with premenstrual syndrome. *BMJ: Brit Med J* (1993) 307(6917):1471. doi: 10.1136/bmj.307.6917.1471

15. Sadock BJ, Sadock VA, Ruiz P. *Kaplan & Sadock's synopsis of psychiatry: behavioral sciences/clinical psychiatry (Eleventh ed.)*. Philadelphia, PA: Wolters Kluwer (2015) p. 438.

16. Dutta A, Sharma A. Prevalence of premenstrual syndrome and premenstrual dysphoric disorder in India: A systematic review and meta-analysis. *Health Promot Perspect* (2021) 11(2):161. doi: 10.34172/hpp.2021.20

17. Geta TG, Woldeamanuel GG, Dassa TT. Prevalence and associated factors of premenstrual syndrome among women of the reproductive age group in Ethiopia: Systematic review and meta-analysis. *PLoS One* (2020) 15(11):e0241702. doi: 10.1371/journal.pone.0241702

18. Duko B, Mekuriaw B, Molla A, Ayano G. The prevalence of premenstrual dysphoric disorder among adolescents in Ethiopia: a systematic review and meta-analysis. *Ir J Med Sci (1971-)* (2021) 190:419–27. doi: 10.1007/s11845-020-02275-7

19. Adewuya AO, Loto OM, Adewumi TA. Premenstrual dysphoric disorder amongst Nigerian university students: prevalence, comorbid conditions, and correlates. *Arch Womens Ment Health* (2008) 11:13–8. doi: 10.1007/s00737-008-0213-4

20. Ehalaiye B, Eigbefoh J, Eifediyi RA, Omorogbe F, Isabu PA, Ugiagbe OA, et al. Premenstrual syndrome: prevalence, pattern and severity among female university students in Ekpoma, Nigeria. *Trop J Obstet Gynaecol* (2009) 26:142–50.

21. Wood SH, Mortola JF, Chan Y-F, Moossazadeh F, Yen SS. Treatment of premenstrual syndrome with fluoxetine: a double-blind, placebo-controlled, crossover study. *Obstet Gynecol* (1992) 80(3 Part 2):339–44.

22. del Mar Fernández M, Saulyte J, Inskip HM, Takkouche B. Premenstrual syndrome and alcohol consumption: a systematic review and meta-analysis. *BMJ Open* (2018) 8(3):e019490. doi: 10.1136/bmjopen-2017-019490

23. Cao S, Jones M, Tooth L, Mishra GD. History of premenstrual syndrome and development of postpartum depression: a systematic review and meta-analysis. *J Psychiatr Res* (2020) 121:82–90. doi: 10.1016/j.jpsychires.2019.11.010

24. Prasad D, Wollenhaupt-Aguiar B, Kidd KN, de Azevedo Cardoso T, Frey BN. Suicidal risk in women with premenstrual syndrome and premenstrual dysphoric disorder: a systematic review and meta-analysis. *J Womens Health* (2021) 30(12):1693–707. doi: 10.1089/jwh.2021.0185

25. Osborn E, Brooks J, O'Brien P, Wittkowski A. Suicidality in women with Premenstrual Dysphoric Disorder: a systematic literature review. *Arch Womens Ment Health* (2021) 24:173–84. doi: 10.1007/s00737-020-01054-8

26. Rapkin AJ, Winer SA. Premenstrual syndrome and premenstrual dysphoric disorder: quality of life and burden of illness. *Expert Rev Pharmacoecon Outcomes Res* (2009) 9(2):157–70. doi: 10.1586/erp.09.14

27. Borenstein JE, Dean BB, Endicott J, Wong J, Brown C, Dickerson V, et al. Health and economic impact of the premenstrual syndrome. *J Reprod Med* (2003) 48(7):515–24.

28. Bhuvaneswari K, Rabindran P, Bharadwaj B. Prevalence of premenstrual syndrome and its impact on quality of life among selected college students in Puducherry. *Natl Med J India* (2019) 32(1):17–9.

29. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Int J Surg* (2021) 88:105906. doi: 10.1016/j.ijsu.2021.105906

30. Padmavathi P, Sankar R, Kokilavani N, Dhanapal K, Ashok B. Validity and reliability study of premenstrual syndrome scale (PMSS). *Int J Adv Nurs Manag* (2014) 2(1):04–5.

31. Oo HH, Sein MT, Mar O, Aung AJ. Assessment of premenstrual syndrome among reproductive aged Myanmar women. *Asian J Med Sci* (2016) 7(4):39–43. doi: 10.3126/ajms.v7i4.13298

32. Yildirim N, Guzel D, Akdemir A. Prophylactic surgery for genetic predisposition of female organs. In: Dilek O.N., Uranues S., Latifi R. (eds) *Prophylactic surgery* (2021) Springer, Cham. doi: 10.1007/978-3-030-66853-2_27

33. Câmara R, Köhler CA, Frey BN, Hyphantis TN, Carvalho AF. Validation of the Brazilian Portuguese version of the premenstrual symptoms screening tool (PSST) and association of PSST scores with health-related quality of life. *Braz J Psychiatry* (2016) 39:140–6. doi: 10.1590/1516-4446-2016-1953

34. Steiner M. Premenstrual syndrome and premenstrual dysphoric disorder: guidelines for management. *J Psychiatry Neurosci* (2000) 25:459–68.

35. Feuerstein M, Shaw WS. Measurement properties of the calendar of premenstrual experience in patients with premenstrual syndrome. *J Reprod Med* (2002) 47:279–89.

36. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru CJ. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid-Based Healthc.* (2015) 13:147–53. doi: 10.1097/XEB.0000000000000054

37. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* (2002) 21:1539–58. doi: 10.1002/sim.1186

38. Sterne JA, Egger MJ. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* (2001) 54:1046–55. doi: 10.1016/S0895-4356(01)00377-8

39. Egger M, Smith GD, Schneider M, Minder CJB. Bias in meta-analysis detected by a simple. *graphical test* (1997) 315:629–34. doi: 10.1136/bmj.315.7109.629

40. Tolossa FW, Bekele ML. Prevalence, impacts and medical managements of premenstrual syndrome among female students: cross-sectional study in college of health sciences, Mekelle University, Mekelle, Northern Ethiopia. *BMC Women's Health* (2014) 14:1–9. doi: 10.1186/1472-6874-14-52

41. Tenkir A, Fisseha N, Ayele B. Premenstrual syndrom: prevalence and effect on academic and social performances of students in Jimma University, Ethiopia. *Ethiop J Health Dev* (2003) 17:181–8.

42. Alemu SM, Habtewold TD, Haile YG. Mental and reproductive health correlates of academic performance among Debre Berhan university female students, Ethiopia: the case of premenstrual dysphoric disorder. *Biomed Res Int* (2017) 2017:8. doi: 10.1155/2017/9348159

43. Zeleke B, Workineh Y, Melese A, Semachew A, Yigizaw M. Premenstrual syndrome, life style & behavioral coping mechanisms and associated factors among public high school regular female students at Bahir Dar City, Northwest, Ethiopia. *Research Square* [preprint] (2023). doi: 10.21203/rs.3.rs-2418487/v1

44. Minichil W, Eskindir E, Demilew D, Mirkena Y. Magnitude of premenstrual dysphoric disorder and its correlation with academic performance among female medical and health science students at University of Gondar, Ethiopia, 2019: a cross-sectional study. *BMJ Open* (2020) 10:e034166. doi: 10.1136/bmjopen-2019-034166

45. Eshetu N, Abebe H, Fikadu E, Getaye S, Jemal S, Geze S, et al. Premenstrual syndrome, coping mechanisms and associated factors among Wolkite university female regular students, Ethiopia. *BMC Womens Health* (2022) 22:22:88. doi: 10.1186/s12905-022-01658-5

46. Abeje A, Berhanu Z. Premenstrual syndrome and factors associated with it among secondary and preparatory school students in Debremarkos town, North-west Ethiopia. *BMC Res Notes* (2016) 2019:12:1–5.

47. Tsegaye D, Getachew Y. Premenstrual dysphoric disorder and associated factors among female health science students in Wollo University, Ethiopia, 2017/18. *Matern Health Neonatol Perinatol* (2019) 5:1–8. doi: 10.1186/s40748-019-0102-z

48. Mossie TB, Tesfaye YB, Metekiya WM, Tegegne MT. Magnitude of premenstrual dysphoric disorder and associated factors among high school girls, Mekelle, North Ethiopia. (2015) 29.

49. Nworie KM, Aluh DO, Onyekwum CA. Assessment of premenstrual syndrome among female students in Southeast Nigeria. *J Obstet Gynecol Investig* (2018) 1:55–61. doi: 10.5114/jogi.2018.79426

50. Antai AB, Udezi AW, Ekanem EE, Okon UJ, Umoiyoho AU. Premenstrual syndrome: prevalence in students of the University of Calabar, Nigeria. *Afr J Biomed Res* (2004) 7(2). doi: 10.4314/ajbr.v7i2.54067

51. Atim E, Okecho FN, Ndagire R, Nassozi CL. Prevalence and severity of premenstrual syndrome among female university students in central Uganda: A cross-sectional study. *Stud J Health Res Afr* (2022) 3:10–0.

52. Salih TBA. Prevalence of premenstrual dysphoric disorder. (2015) 3:961–71.

53. Kamel DM, Tantawy SA, Alsayed N, Bekhet AH, Elbkery N, Khairy A. The relationship between premenstrual syndrome and the quality of sleep among Egyptian women: An observational study. (2021) 56:172–8. doi: 10.31688/ABMU.2021.56.2.05

54. Ranjbaran M, Samani RO, Almasi-Hashiani A, Matourypour P, Moini A. Prevalence of premenstrual syndrome in Iran: A systematic review and meta-analysis. (2017) 15:679. doi: 10.29252/ijrm.15.11.679

Exploring gender differences in the relationship between gut microbiome and depression - a scoping review

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Background: Major depressive disorder (MDD) exhibits gender disparities, and emerging evidence suggests the involvement of the gut microbiome, necessitating exploration of sex-specific differences.

Methods: A review was conducted, encompassing a thorough examination of relevant studies available in Medline via Ovid, Embase via OvidSP, CINAHL, and PsycINFO databases from their inception to June 2023. The search strategy employed specific keywords and Medical Subject Headings (MeSH) terms tailored to major depressive disorder in women, encompassing unipolar depression, depressive symptoms, and dysbiosis.

Results: Five studies were included. Among the four studies, alterations in alpha (n=1) and beta diversity (n=3) in the gut microbiome of individuals with MDD were revealed compared to controls. Gender-specific differences were observed in four studies, demonstrating the abundance of specific bacterial taxa and highlighting potential sex-specific implications in MDD pathophysiology. Correlation analyses (n=4) indicated associations between certain bacterial taxa and the severity of depressive symptoms, with varying patterns between males and females. Studies (n=3) also highlighted promising findings regarding the potential utility of microbial markers in diagnosing MDD, emphasizing the crucial role of sex stratification in understanding the disease pathophysiology.

Conclusions: The findings underscore the importance of recognizing gender-specific differences in the composition of the gut microbiome and its relationship with MDD. Further comprehensive robust studies are required to unravel the intricate mechanisms underlying these disparities.

KEYWORDS

gut microbiome, depression, gender, biomarker, gut dysbiosis

Introduction

Major Depression, also known as major depressive disorder (MDD), is a prevalent mental and emotional ailment affecting an estimated 185 million people globally (1). The World Health Organization classified depression as the fourth-leading burden of disease globally in 2008, with projections indicating it could become the second-leading cause by 2030 (2). Women are disproportionately affected, experiencing nearly double the prevalence compared to men (1), a trend observed across both developed and developing countries (3).

Various theories such as the biopsychosocial model, have attempted to elucidate the underlying reasons for this gender disparity, pointing to differences in hormones (4, 5), neurotransmitters (5, 6), and brain structure (7, 8). Recent research has also explored the intricate relationship between the gut microbiome and depression, uncovering potential links through the gut-brain axis (9–31). While significant advancements have been made, there remains a dearth of evidence to precisely elucidate the mechanisms driving these disparities or the potential for sex-specific biomarkers.

The concept of 'gut dysbiosis' - an abnormal alteration in the composition and function of the gut microbiome - has gained traction as a potential player in the pathogenesis of MDD and other psychiatric disorders (9–31). The intricate communication between the gut microbiome and the brain through various pathways, including neural, immune, and metabolic mechanisms, presents a promising avenue for further exploration. Recent studies have highlighted differences in the gut microbiota composition between individuals with MDD and control groups, pointing to potential sex-specific differences that warrant further investigation (19, 32–35).

This scoping review aims to explore the existing evidence on the relationship between major depression and the gut microbiome, particularly in the context of women, while also summarizing the sex-specific differences in the gut microbiome profiles of male and female subjects with major depression.

Methods

A comprehensive literature search was conducted from database inception to June 2023 in Medline via Ovid (1946-present), Embase via OvidSP (1947-present), Cinahl Complete, and PsycINFO via Ovid (1806-present). The search used specific keywords and MeSH terms related to major depression in women, including unipolar depression, depressive symptoms, and dysbiosis.

Inclusion criteria encompassed studies with adult human participants of both sexes, focusing on female-specific outcomes. Studies investigating the relationship between major depression and gastrointestinal microbiota in adult humans were included, while those exclusively concerning other psychiatric disorders (e.g., schizophrenia, chronic stress, PTSD, bipolar disorder), subtypes of depression (e.g., postpartum, late-life depression), or other medical conditions were excluded. Additionally, studies involving females under 18 years old were not considered.

Results

From the initial database search, 784 studies were identified, and after removing 109 duplicates, 675 studies underwent phase one screening. Following this, 76 studies were subjected to full-text retrieval, resulting in 75 fully assessed articles. Ultimately, five articles were included in the literature review (Figure 1 for the PRISMA flow chart).

Characteristics of studies

The review included a total of (n=780) subjects from case-controlled studies in China and (n=1104) subjects from a retrospective cohort study in Germany. Among the case-control studies, (n=239) female and (n=125) male subjects with MDD were compared to (n=261) female and (n=155) male healthy controls. Notably, one study by Li et al. (33) involved subjects with Bipolar disorder (BD) (n=166) experiencing a depressive episode, whose data were excluded from this review's analysis (Table 1.1).

Gender-specific microbiome diversity alterations in subjects with major depression

Alpha diversity remained unchanged in MDD subjects across three studies (32–34), while one study (35) reported a reduction. Beta diversity analysis revealed significant differences in both male and female MDD groups compared to matched healthy controls (HCs) in studies by Chen and Li (32, 33). In the female-only study by Chen et al. (34), alterations in beta diversity were observed only at the species level in female MDD subjects. Notably, Li et al. (33) found that while alpha

FIGURE 1
Flow chart.
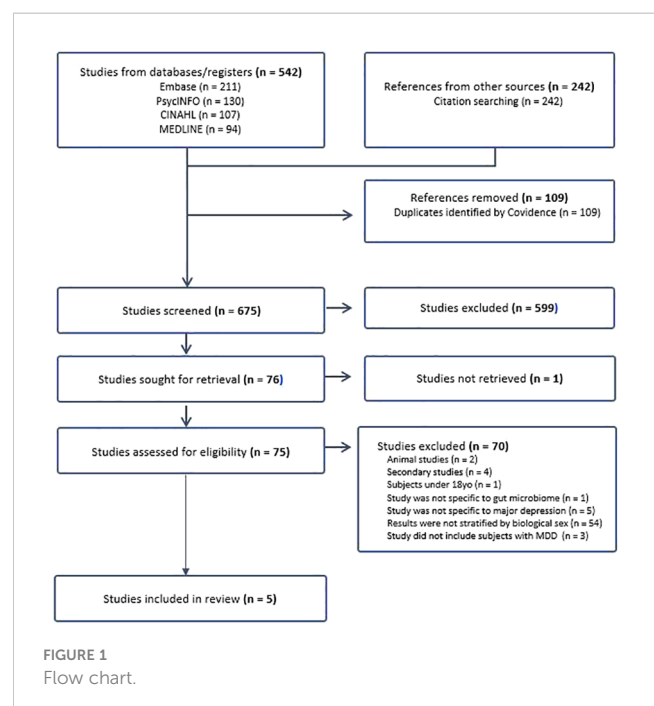
diversity was significantly higher in female healthy controls compared to male healthy controls, this difference was not evident in the context of depression. Table 1.2 provides an overview of the key findings.

Gender-specific microbiome profile alterations in subjects with major depression

All case-control studies (32–34), highlighted notable differences in gut microbiota between individuals with major depressive disorder (MDD) and the respective control groups. These distinctions were particularly pronounced when comparing male and female cohorts. Further details can be found in Table 1.3. Upon examining studies encompassing both male and female subjects, females with MDD exhibited a higher relative abundance of *Actinobacteria, Firmicutes, and Bacteroidetes* compared to the control group (32, 33). In male MDD patients, an increase and decrease in *Bacteroidetes* clusters, along with an increase in *Firmicutes* clusters, was observed. In the study conducted by Chen et al. (34) focusing on female MDD

patients, an increase in Bacteroidetes, Proteobacteria, Fusobacteria, and *Verruomicrobia*, and a decrease *in Firmicutes and Actinobacteria* was reported. Notably, only two studies (34, 35) investigated the microbiome at the species level, revealing significant changes at the family, genus, and species levels.

Correlation of bacterial taxa with severity of depression symptoms

Four studies examined the relationship between the severity of depression symptoms and specific bacterial taxa at the genus level (32–35). Among female MDD subjects, three genera (*Anaerotruncus, Parabacteroides, and Anaeroglobus*) exhibited associations with increased depressive symptoms, whereas five genera (*Clostridium XIVa, Erysipelotrichaceae incertae sedis, Streptococcus, Romboutsia, and Fusicatenibacter*) were linked to reduced depressive symptoms. In male MDD subjects, two distinct genera (*Collinsella, Veillonella*) were found to be correlated with depression symptoms (refer to Table 1.4).

TABLE 1.1 Characteristics of studies.

	Participant details					Recruitment location	Assessment tool	Sample analysis
	Female (n)	Male (n)	Average age	Subjects with MDD or DS	Medication status			
Chen et al 2018, China Case Control Study (32)	MDD (n=24) HC (n=24)	MDD (n=20) HC (n=20)	MDD (F, M) 42 yrs, 40 yrs HC (F, M) 44 yrs, 43 yrs	MDD patients undergoing first episode MDD	Drug naive	MDD in hospital HC in community	HDRS-17	16S rRNA
Li et al 2022, China Case Control Study (33)	MDD (n=77) HC (n=100) BD (n=83)	MDD (n=43) HC (n=71) BD (n=82)	MDD (F, M) 26 yrs, 26 yrs HC (F, M) 27 yrs, 26 yrs	MDD patients undergoing depressive episode	Unmedicated	MDD in hospital HC in community	DSM-IV HAMD	16S rRNA
Chen et al 2021, China Case Control Study (34)	MDD (n=62) HC (n=46)	Nil	MDD (F): 40 yrs HC (F): 37 yrs	MDD patients with HAMD-17 score ≥ 18	Medicated (n= 26) Unmedicated (n= 36)	MDD in hospital	DSM-IV HAMD-17	16S rRNA and shotgun metagenomic sequencing
Hu et al 2023, China Cross sectional study (35)	MDD (n=76) HC (n=91)	MDD (n=62) HC (n=64)	MDD: 29 yrs HC: 29 yrs	MDD patients	Unmedicated	MDD in hospital HC in community	DSM-IV HAMD-17	Shotgun metagenome sequencing
Chung et al 2022, Germany Retrospective Cohort Study (19)	DS (n=339) HC (n=339)	DS (n=213) HC (n=213)	DS:50 yrs HC:50 yrs	Adults in community with clinical diagnosis of dysbiosis	Unmedicated	DS in community HC in community	ICD-10	Clinical record of dysbiosis

MDD, Major depressive disorder; HC, Healthy Control; BD, Bipolar Disorder; DS, Dysbiosis; F, Female; M, Male; DSM, Diagnostic and Statistical Manual of Mental Disorders (-Text revision); HAMD or HDRS, Hamilton Depression Rating Scale (-Text revision); NR, Not reported; 26 patients had used antidepressants for less than 3 consecutive days in 2 weeks prior to faecal collection.[2] Adults (≥18 yrs) ≥ 1 visit to general practitioner; and ≥1 diagnosis of dysbiosis ≥ 3 months after initial diagnosis.

TABLE 1.2 Gender-Specific Microbiome Profile Alterations in Subjects with Major Depression.

Diversity	Alpha Diversity			Beta Diversity	
	MDD vs HC	MDD vs HC	MDD	MDD vs HC	
	Female	Male	Female vs Male	Female	Male
Chen et al., 2018 (32)	NS	NS	NS	*	*
Li et al., 2022 (33)	NS	NS	—	*	*
Chen et al 2021 (34)	NS	NS	N/A	NS (16SrRNA) *(SMG)	N/A
Hu et al., 2023 (35)	*↓	*↓	—	—	—

MDD, Major Depressive Disorder; HC, Healthy Controls; NS, No significant difference; *Significant difference; —, not reported; *↓Significantly decreased; N/A, not applicable; 16s, 16S rRNA gene sequencing; SMG, shotgun metagenomic sequencing.

Potential diagnostic role of microbial markers and dysbiosis in major depression

Two studies (33, 34) examined the accuracy of microbial markers in diagnosing MDD, identified sex-specific gut microbiota signatures, and evaluated diagnostic performance using the area under the receiver operating characteristic curve (AUC). Analysis of the diagnostic performance sensitivity of these microbial signatures showed area under the curve (AUC) values ranging from 0.79 to 0.92 for females and 0.79 for males with MDD. An additional study (19) investigated the risk of developing MDD within five years following an initial dysbiosis diagnosis and found a stronger association between dysbiosis and MDD diagnosis in males (HR:3.54, 95% CI: 1.75–7.14) compared to females HR:2.61 (95% CI: 1.74 – 3.92). (Refer to Table 1.5).

Discussion

Several recent studies have suggested that the gut microbiome profile is associated with Major Depressive Disorder (MDD), yet only a few have investigated the sex-specific link between MDD and the gut microbiome. This review represents the first comprehensive analysis examining the relationship between the gender-specific gut microbiome profile and MDD. To date, five primary studies have provided insights into the relationship between the gut microbiome and MDD in women (19, 32–35). These findings indicate a close association between the gut microbiome composition of females with MDD and the disorder itself, highlighting sex-specific differences in the gut microbiota of MDD patients. Certain genera were found to correlate with the severity of depression, and these correlations varied between males and females. Additionally, sex-specific differences were observed in the diagnostic performance of microbial markers and the risk of developing MDD following a dysbiosis diagnosis. While the underlying pathophysiological mechanism remains unclear, the distinct microbiome variability between sexes necessitates further investigation.

Regarding gender-specific microbiome diversity

Our review results are consistent with existing literature, emphasizing notable differences in the gut microbiota composition

between individuals diagnosed with MDD and controls (9–18). These differences primarily involve microbial diversity and the prevalence of specific bacterial taxa. Four separate studies highlighted discernible variations in microbial diversity in both male and female MDD patients compared to their healthy counterparts (32–35). Notably, one study observed no significant difference in microbial diversity between male and female MDD patients (32). Most case-control studies found no alterations in alpha diversity among female MDD subjects compared to female healthy controls, while one study (35) reported reduced alpha diversity in female MDD subjects relative to healthy controls, mirroring a similar trend observed in male MDD subjects.

All studies examining beta diversity identified significant differences between female MDD patients and healthy controls (32–34), with two studies also noting distinct variations in beta diversity between male MDD patients and healthy controls (32, 33). One study focusing solely on females revealed alterations in beta diversity at the species level in female MDD subjects (34). Despite observing higher alpha diversity in healthy females compared to healthy males, this distinction was not observed in the depressed state (33).

These findings suggest gender-specific differences in the gut microbiome that may be influenced by various factors, such as the menstrual cycle stage, diet, age, and environmental factors. Overall, the results emphasize distinct beta diversity in both female and male MDD patients compared to healthy controls (32–34), with potential discrepancies in alpha diversity stemming from methodological variations in assessing microbiome diversity and the influence of confounding factors. Further clinical studies are warranted to comprehensively investigate the role of the gut microbiome in both male and female MDD patients, considering the potential implications for other diseases prevalent in females. The studies used various techniques, including 16S rRNA gene sequencing and shotgun metagenomic sequencing (SMG), to assess the microbiome. However, discrepancies in the methodologies employed suggest the need for standardized approaches in future research.

In terms of gender-specific microbiome profiles

The current study reveals notable differences in the gut microbiome profiles of females with MDD in comparison to both

TABLE 1.3 Gender-Specific Microbiome Profile Alterations in Subjects with MDD compared to healthy controls.

	Phylum		Family		Genus		Species	
	Female	Male	Female	Male	Female	Male	Female	Male
Chen et al., 2018 (32)	Actinobacteria ↑ Actinobacteria ↑	Bacteroidetes ↓ Bacteroidetes ↑	Coriobacteriaceae ↑ Lachnospiraceae ↑ Ruminococcaceae ↑ Lachnospiraceae ↓ Ruminococcaceae ↓	Erysipelotrichaceae ↑ Lachnospiraceae ↑ Lachnospiraceae ↓ Ruminococcaceae ↓	*Actinomyces* ↑ *Bifidobacterium* ↑ *Asaccharobacter* ↑ *Atopobium* ↑ *Eggerthella* ↑ *Gordonibacter* ↑ *Olsenella* ↑ *Eubacterium* ↑ *Anaerostipes* ↑ *Blautia* ↑ *Roseburia* ↑ *Faecali-bacterium* ↑ *Desulfovibrio* ↑ *Howardella* ↓ *Sutterella* ↓ *Pyramidobacter* ↓	Bacteroides ↑ Erysipelotrichaceae incertae sedis ↑ Veillonella ↑ Atopobium ↑ *Anaerovorax* ↓ *Gordonibacter* ↓ *Pyramidobacter* ↓	NR	NR
Li et al., 2022 (33)	Firmicutes ↑ Bacteroidetes ↑	Firmicutes ↑	Lachnospiraceae ↑ Bacteroidaceae ↑ Bacteroidaceae ↑ Bacteroidaceae ↑ Bacteroidaceae ↑	Lachnospiraceae ↑	NR	NR	NR	NR
Chen et al 2021 (34)	16s: Bacteroidetes ↑ Proteobacteria ↑ Fusobacteria ↑ Firmicutes ↓ Actinobacteria ↓ SMG: Bacteroidetes ↑ Verrucomicrobia ↑ Fusobacteria ↑ Firmicutes ↓	NA	*Enterobacteriaceae* ↑ *Tannerellaceae* ↑ *Burkholderiaceae* ↑ *Campylobacteraceae* ↑ *Corynebacteriaceae* ↑ *Clostridia_unclassified* ↑ *Ruminococcaceae* ↓ *Lachnospiraceae* ↓ *Coriobacteriales_unclassified* ↓	NA	Escherichia-Shigella ↑ Prevotellaceae_NK3B31_group ↑ Hungatella ↑ Campylobacter ↑ Raoultella ↑ Barnesiella ↑ Coprobacillus ↑ Clostridium_innocuum_group ↑ Alistipes ↑ Enterobacteriaceae_unclassified ↑ Lachnoclostridium ↑ Prevotellaceae_unclassified ↑ Flavonifractor ↑ Eisenbergiella ↑ Anaerotruncus ↑ Anaeroglobus ↑ Mobiluncus ↑ Rodentibacter ↑ Fastidiosipila ↑ Finegoldia ↑ Aerococcus ↑ Ruminococcaceae_uncultured ↑ Turicibacter ↑ S5-A14a ↑ Parabacteroides ↑ GCA-900066755 ↑ Clostridia_unclassified ↑ Morganella ↑ Agathobacter ↓ Butyricicoccus ↓ Faecalibacterium ↓	NA	Clostridium_asparagiforme ↑ Alistipes_onderdonkii ↑ Clostridium_citroniae ↑ Barnesiella_intestinihominis ↑ Alistipes_finegoldii ↑ Oscillibacter_unclassified ↑ Clostridium_hathewayi ↑ Clostridiales_bacterium_1_7_47FAA ↑ Flavonifractor_plautii ↑ Clostridium_bolteae ↑ Akkermansia_muciniphila ↑ Porphyromonas_uenonis ↑ Campylobacter_hominis ↑ Adlercreutzia_equolifaciens ↑ Lachnospiraceae_bacterium_7_1_58FAA ↑ Murine_osteosarcoma_virus ↑ Anaerotruncus_unclassified ↑ Bilophila_wadsworthia ↑ Porphyromonas_asaccharolytica ↑ Erysipelotrichaceae_bacterium_2_2_44A ↑ Bacteroides_caccae ↑ Bilophila_unclassified ↑ Granulicella_unclassified ↑ Atopobium_vaginae ↑ Paraprevotella_unclassified ↑ Paraprevotella_xylaniphila ↑ Ruminococcaceae_bacterium_D16 ↑ Subdoligranulum_sp_4_3_54A2FAA ↑ Erysipelotrichaceae_bacterium_21_3 ↑	NR

(Continued)

TABLE 1.3 Continued

Phylum		Family		Genus		Species	
Female	Male	Female	Male	Female	Male	Female	Male
				Dorea ↓		Campylobacter_ureolyticus ↑	
				Coprococcus_3 ↓		Megamonas_unclassified ↓	
				Ruminococcaceae_UCG-013 ↓		Faecalibacterium_prausnitzii ↓	
				Eubacterium_ventriosum_group ↓		Eubacterium_rectale ↓	
				Lachnospiraceae_FCS020_group ↓		Haemophilus_parainfluenzae ↓	
				Eubacterium_hallii_group ↓		Dorea_longicatena ↓	
				Blautia ↓		Roseburia_hominis ↓	
				Anaerostipes ↓		Roseburia_inulinivorans ↓	
				Lachnospiraceae_NK4A136_group ↓		Megamonas_hypermegale ↓	
				Lachnospiraceae_UCG-001 ↓		Bacteroides_plebeius ↓	
				Erysipelotrichaceae_UCG-003 ↓		Streptococcus_australis ↓	
				Coprococcus_1 ↓		Weissella_cibaria ↓	
				Subdoligranulum ↓		Megamonas_funiformis ↓	
				Tyzzerella_3 ↓		Megasphaera_unclassified ↓	
				CAG-56 ↓		Bacteroides_xylanisolvens ↓	
				Lachnospiraceae_ND3007_group ↓		Streptococcus_salivarius ↓	
				Coriobacteriales_unclassified ↓			
				Moraxellaceae_unclassified ↓			
				Ruminococcus_1 ↓			
				Roseburia ↓			
				Ruminiclostridium ↓			
				Ruminococcus_2 ↓			
				Alcaligenes ↓			
				Fusicatenibacter ↓			
				Lachnospiraceae_UCG-006 ↓			
				Burkholderia-Caballeronia-Paraburkholderia ↓			
				Candidatus_Saccharimonas ↓			
				F0332 ↓			
				Bifidobacterium ↓			
				SMG:			
				Granulicella ↑			
				Adlercreutzia ↑			
				Barnesiella ↑			
				Parabacteroides ↑			
				Paraprevotella ↑			
				Alistipes ↑			
				Clostridiales_noname ↑			
				Flavonifractor ↑			
				Oscillibacter ↑			
				Anaerotruncus ↑			
				Ruminococcaceae_noname ↑			
				Bilophila ↑			
				Campylobacter ↑			
				Akkermansia ↑			
				Gammaretrovirus ↑			
				Lactobacillus ↓			
				Eubacterium ↓			
				Dorea ↓			
				Roseburia ↓			
				Faecalibacterium ↓			
				Megamonas ↓			

(Continued)

TABLE 1.3 Continued

	Phylum		Family		Genus		Species	
	Female	Male	Female	Male	Female	Male	Female	Male
					Megasphaera ↓ Haemophilus ↓			
Hu et al., 2023 (35)	NR	NR	Bacteroidaceae ↑ Prevotellaceae ↑ Bifidobacteriaceae ↑ *Ruminococcaceae* ↓ Lachnospiraceae ↓ Enterobacteriaceae ↓ Eubacteriaceae ↓	Bacteroidaceae ↑ Prevotellaceae ↑ Bifidobacteriaceae ↑ Ruminococcaceae ↓ Lachnospiraceae ↓ Enterobacteriaceae ↓ Eubacteriaceae ↓ Clostridiaceae ↓ Veillonellaceae ↓	Bacteroides ↑ Butyricimonas ↑ Faecalibacterium ↑ Clostridium ↑ Ruminiclostridium ↑ Parabacteroides ↑ Clostridium ↓ Roseburia ↓ Faecalibacterium ↓ Eubacterium ↓ Blautia ↓ Dorea ↓ Anaerostipes ↓ Akkermansia ↓ Ruminococcus ↓ Subdoligranulum ↓ Klebsiella ↓ unclassified_p:Firmicutes ↓	Bacteroides ↑ Blautia ↑ Bilophila ↑ Clostridium ↑ Eubacterium ↑ Parabacteroides ↑ Parasutterella ↑ Phascolarctobacterium ↑ unclassified_p: Proteobacteria ↑ Sutterella ↑ Eubacterium ↓ Faecalibacterium ↓ Adlercreutzia ↓ Anaerostipes ↓ Blautia ↓ Citrobacter↓ Clostridium ↓ Coprococcus ↓ Dialister ↓ Dorea ↓ Enterobacter ↓ Enterococcus ↓ unclassified_p:Firmicutes ↓ Klebsiella ↓ Lactococcus ↓ unclassified_f: Peptostreptococcaceae ↓ Ruminococcus ↓ Salmonella ↓ Subdoligranulum ↓	Bacteroides_vulgatus ↑ Bacteroides_salyersiae ↑ Bacteroides_stercoris ↑ Bacteroides_thetaiotaomicron ↑ Bacteroides_massiliensis ↑ Bacteroides_stercoris_CAG:120 ↑ Bacteroides_dorei ↑ Bacteroides_fragilis ↑ Bacteroides_sp._3_1_33FAA ↑ Bacteroides_sp._CAG:98 ↑ Bacteroides_ovatus ↑ Butyricimonas_virosa ↑ Eubacterium_siraeum ↑ Parabacteroides_distasonis ↑ Clostridium_sp._CAG:7 ↑ Clostridium_sp._CAG:217 ↓ Roseburia_intestinalis ↓ Faecalibacterium_prausnitzii ↓ Clostridium_sp._CAG:510 ↓ Faecalibacterium_sp._CAG:82 ↓ Eubacterium_ventriosum ↓ Blautia_obeum ↓ Blautia_wexlerae ↓ Blautia_sp._Marseille-P2398 ↓ Eubacterium_hallii ↓ Dorea_formicigenerans ↓ Anaerostipes_hadrus ↓ Eubacterium_hallii_CAG:12 ↓ Eubacterium_sp._CAG:202 ↓ Akkermansia_muciniphila_CAG:154 ↓ Ruminococcus_sp._5_1_39BFAA ↓ Eubacterium_sp._CAG:156 ↓ Clostridium_sp._CAG:417 ↓ Dorea_longicatena ↓ Subdoligranulum_variabile ↓ Klebsiella_pneumoniae ↓ Eubacterium_sp._CAG:115 ↓ Firmicutes_bacterium_CAG:41 ↓	Ruminococcus_gnavus ↑ Bacteroides_caccae ↑ Bacteroides_dorei ↑ Bacteroides_eggerthii ↑ Bacteroides_finegoldii ↑ Bacteroides_fragilis ↑ Bacteroides_massiliensis ↑ Bacteroides_ovatus ↑ Bacteroides_sp._3_1_33FAA ↑ Bacteroides_sp._3_1_40A ↑ Bacteroides_sp._4_3_47FAA ↑ Bacteroides_sp._9_1_42FAA ↑ Bacteroides_sp._CAG:98 ↑ Bacteroides_stercoris ↑ Bacteroides_thetaiotaomicron ↑ Bacteroides_uniformis ↑ Bacteroides_vulgatus ↑ Bacteroides_xylanisolvens ↑ Bilophila_wadsworthia ↑ Clostridium_sp._CAG:81 ↑ Coprobacillus_sp._CAG:235 ↑ Eubacterium_sp._CAG:146 ↑ Parabacteroides_distasonis ↑ Parabacteroides_merdae ↑ Parasutterella_excrementihominis ↑ Phascolarctobacterium_sp._CAG:207 ↑ Proteobacteria_bacterium_CAG:139 ↑ Sutterella_wadsworthensis ↑ Eubacterium_hallii ↓ Adlercreutzia_equolifaciens ↓ Anaerostipes_hadrus ↓ Blautia_obeum ↓ Blautia_sp._CAG:237 ↓ Blautia_sp._GD8 ↓ Blautia_sp._KLE_1732 ↓ Blautia_sp._Marseille-P2398 ↓ Blautia_wexlerae ↓ Citrobacter_freundii ↓ Clostridium_dakarense ↓ Clostridium_sp._CAG:62 ↓ Clostridium_sp._CAG:75 ↓ Coprococcus_eutactus ↓ Coprococcus_sp._ART55/1 ↓ Coprococcus_sp._CAG:131 ↓ Dialister_invisus ↓ Dialister_succinatiphilus ↓ Dorea_sp._CAG:105 ↓ Enterobacter_cloacae ↓ Enterobacter_sp._GN02315 ↓ Enterococcus_faecalis ↓ Eubacterium_hallii_CAG:12 ↓

(Continued)

TABLE 1.3 Continued

Phylum		Family		Genus		Species	
Female	Male	Female	Male	Female	Male	Female	Male
							Eubacterium_sp_CAG:115 ↓ Eubacterium_sp_CAG:180 ↓ Eubacterium_sp_CAG:202 ↓ Eubacterium_sp_CAG:251 ↓ Faecalibacterium_sp_CAG:74 ↓ Faecalibacterium_sp_CAG:82 ↓ Firmicutes_bacterium_CAG:227 ↓ Firmicutes_bacterium_CAG:341 ↓ Klebsiella_pneumoniae ↓ actococcus_garvieae ↓ Peptostreptococcaceae_bacterium_VA2 ↓ Ruminococcus_sp_5_1_39BFAA ↓ Ruminococcus_sp_CAG:17 ↓ Ruminococcus_sp_CAG:9 ↓ Ruminococcus_sp_IC304 ↓ Salmonella_enterica ↓ Subdoligranulum_variabile ↓

↑,relatively more abundant in subjects with MDD compared to HC; ↓, relatively less abundant in subjects with MDD compared to HC. NR, Not reported; NA, Not applicable.

healthy controls (HCs) and males with MDD. Analyzing data from four cross-sectional studies (32–35), we identified several differential abundances in bacterial clusters in both female and male MDD groups relative to HCs. These alterations primarily involved Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria, Fusobacteria, and Verrucomicrobia, which represent the dominant bacterial phyla in the human gut (29) Notably, despite previous literature suggesting Bacteroides as a signature gut microbe of MDD (17), our review unveiled inconsistent directions of compositional changes, which may be partly attributed to variations in the severity of depression. Hu et al. (35) also highlighted the influence of depression severity on gut microbiome alterations. Furthermore, a recent review on MDD and the gut microbiome by Knuesel and Mohajeri (22) identified disparities across studies, suggesting potential variations arising from different underlying causes and manifestations of depression across different age groups. Notably, the influence of confounding factors, such as the stage of the menstrual cycle, dietary patterns, physical activity, and environmental factors (28, 36) may contribute to the discrepancies observed in the findings. The current body of literature, however, lacks a sufficient number of studies investigating sex-specific differences in the gut microbiome concerning MDD.

In the correlation of bacterial taxa with the severity of depressive symptoms

Several studies have indicated associations between specific bacterial taxa and the severity of depressive symptoms in individuals with MDD, as observed in the works of recent studies (19, 32–35). Notably, certain genera, including Anaerotruncus, Parabacteroides, and Anaeroglobus, were linked to increased depressive symptoms, whereas the presence of Clostridium XIVa, Erysipelotrichaceae incertae sedis, Streptococcus, Romboutsia, and Fusicatenibacter was associated with reduced symptoms. Despite Chen et al. (32) documenting correlations in males with MDD, the literature remains relatively limited and heterogeneous. A comprehensive review by Knuesel and Mohajeri (22) emphasized a negative correlation between Faecalibacterium and depressive symptoms, coupled with a positive correlation in cases of remission and improved quality of life. Similarly, Jiang et al. (9) demonstrated a negative association between Faecalibacterium prausnitzii (FP) and the severity of depressive symptoms. Likewise, Hu et al. (35) utilized shotgun sequencing, revealing a negative correlation between Faecalibacterium and depressive symptoms in a mixed-sex group of MDD patients with moderate depression. However, this correlation was not observed in the subgroup with severe depression, suggesting the potential confounding impact of depression severity. While the reviewed studies did not definitively establish the specific link between Faecalibacterium and the severity of depressive symptoms in females with MDD, they reported varying levels of Faecalibacterium in females with MDD compared to HCs. Despite existing disparities, Faecalibacterium remains a critical bacterial taxon of interest, previously associated with gut health and overall host well-being (37). Further exploration through improved methodological approaches, including controlling for sex as a biological factor and considering depression severity, is warranted

TABLE 1.4 Correlation of Bacterial Taxa with Severity of Depression Symptoms.

	Positive Correlation			Negative Correlation		
	Females	Males	All	Females	Males	All
Chen et al., 2018 (32)		Collinsella	N/A	Clostridium XIVa, Erysipelotrichaceae incertae sedis, Streptococcus	Veillonella	NA
Li et al., 2022 (33)		NC	N/A	Romboutsia	NC	NA
Chen et al 2021 (34)	Anaerotruncus, Parabacteroides, Anaeroglobus	NA	N/A	Fusicatenibacter	NA	NA
Hu et al., 2023 (35)	N/A	NA	Moderate5: Bacteroides / Severe6: Bacteroides	NA	NA	Moderate5: Faecalibacterium Escherichia / Severe6: Ruminococcus Eubacterium

MDD, Major Depressive Disorder; NC, No correlation found; NA, Not assessed. [5]The severity of MDD was staged with the HAMD-17 scale, moderate depression (score, 17–23), [6] The severity of MDD was staged with the HAMD-17 scale, severe depression (score, ≥24).

to clarify the precise contribution of specific bacterial taxa to disease development or their status as a consequence of the disease.

As a potential diagnostic microbial marker in depression

The evaluation of the diagnostic efficacy of microbial markers in females with MDD is still in its preliminary stages. Two separate studies have identified sex-specific gut microbial markers capable of distinguishing between males with MDD, females with MDD, and HCs (33, 34). Examination of how well these microbial signatures perform diagnostically showed that the area under the curve (AUC) values ranged from 0.79 to 0.92 for females and 0.79 for males diagnosed with MDD. Although these findings are limited due to sparse data and disparate methodologies, the identification of sex-specific microbial panels with potential diagnostic capabilities highlights the significance of sex stratification in MDD case-control studies. Additionally, this discovery provides crucial insights into the divergent pathophysiological mechanisms and prognostic variances between male and female MDD patients. Moreover, a study by Chung et al. (19) observed sex-specific

disparities in the risk of developing MDD within five years following an initial dysbiosis diagnosis, with a notably stronger association among males compared to females. While specific microbial markers were not identified, this observation, in conjunction with existing evidence indicating the presence of sex-specific gut microbial profiles in MDD, emphasizes the potential for comprehensive characterization of sex-specific risk factors and the formulation of non-invasive gut microbial-based screening or diagnostic tools for MDD.

The limitations of the present study

Include the heterogeneity in measurement and reporting methods, as well as the use of limited sample sizes and study designs, which impose certain restrictions on the interpretability of the results. However, these findings provide critical insights into the potential role of the gut microbiome in the context of MDD, especially concerning sex-specific differences. Future research should emphasize the inclusion of sex as a biological factor, conduct longitudinal studies to understand microbiome changes in response to clinical variations better, and carefully control for

TABLE 1.5 Diagnostic performance of microbial markers and dysbiosis in diagnosis of MDD.

		Diagnostic Performance Sensitivity (AUC)		Microbial Makers			Hazard Ratio7	
				OTU (n)	OTU (n)	Species (n)		
		Female	Male	Female	Male	Female	Female	Male
Li et al., 2022 (33)	16S rRNA	0.795	0.798	11	50	NA	NA	NA
Chen et al 2021 (34)	16S rRNA & Shotgun metagenomic	0.92 (95% CI: 85.3% - 98.8%)	NA	18	NA	45	NA	NA
Chung et al., 2022 (19)	Clinical record 8	NA	NA	NA	NA	NA	2.61 (95% CI: 1.74 – 3.92)	3.54 (95% CI: 1.75–7.14)

AUC, Area under the curve; OTU, Operational taxonomic units; MDD, Major Depressive Disorder; HC, Healthy Controls; CI, Confidence Interval; NA, Not assessed; 7 Hazards Ratio, risk of being diagnosed with depression within five years of dysbiosis.
[8]Clinical Record: Diagnosis of Dysbiosis and MDD (ICD-10 code) recorded in patient clinical record.

confounding factors to establish a more comprehensive understanding of the complex interplay between the gut microbiome and MDD.

Conclusion

Despite the existing knowledge gaps and limitations, the findings underscore the significance of sex-specific differences in the gut microbiome of MDD patients. These insights hold important implications for potential advancements in the diagnosis, treatment, and understanding of the pathophysiology of MDD, emphasizing the necessity for further comprehensive investigations into the role of the gut microbiome in the context of sex-specific differences.

Author contributions

LN: Conceptualization, Validation, Writing – review & editing, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft. GL: Validation, Writing – review & editing. SC: Validation, Writing – review & editing. MM: Validation, Writing – review & editing. AY: Validation, Writing – review & editing. BO: Conceptualization, Supervision, Validation, Writing – review & editing.

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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References

1. Global Burden of Disease Collaborative Network. Global health data exchange (GHDx), in: *Global Burden of Disease Study 2019 (GBD 2019)* (2019). Seattle, United States: Institute for Health Metrics and Evaluation (IHME. Available online at: https://vizhub.healthdata.org/gbd-results/ (Accessed 2023 Nov 19).

2. World Health Organization. *Mental Health Gap Action Programme: Scaling up care for mental, neurological, and substance use disorders*. Geneva: World Health Organization (2008). Available at: https://www.who.int/publications/i/item/9789241596206.

3. Kessler R, Bromet E. The epidemiology of depression across cultures. *Annu Rev Public Health* (2014) 34:119–38. doi: 10.1146/annurev-publhealth-031912-114409

4. Noble RE. Depression in women. *Metabolism* (2005) 54:49–52. doi: 10.1016/j.metabol.2005.01.014

5. Labaka A, Goñi-Balentziaga O, Lebeña A, Pérez-Tejada J. Biological sex differences in depression: A systematic review. *Biol Res Nurs* (2018) 20:383–92. doi: 10.1177/1099800418776082

6. Eid RS, Gobinath AR, Galea LAM. Sex differences in depression: Insights from clinical and preclinical studies. *Prog Neurobiol* (2019) 176:86–102. doi: 10.1016/j.pneurobio.2019.01.006

7. Hoekzema E, Barba-Müller E, Pozzobon C, Picado M, Lucco F, García-García D, et al. Pregnancy leads to long-lasting changes in human brain structure. *Nat Neurosci* (2017) 20:287–96. doi: 10.1038/nn.4458

8. Mohammadi S, Seyedmirzaei H, Salehi MA, Jahanshahi A, Zakavi SS, Dehghani Firouzabadi F, et al. Brain-based sex differences in depression: A systematic review of neuroimaging studies. *Brain Imaging Behav* (2023) 17:541–69. doi: 10.1007/s11682-023-00772-8

9. Jiang H, Ling Z, Zhang Y, Mao H, Ma Z, Yin Y, et al. Altered fecal microbiota composition in patients with major depressive disorder. *Brain Behav Immun* (2015) 48:186–94. doi: 10.1016/j.bbi.2015.03.016

10. Naseribafrouei A, Hestad K, Avershina E, Sekelja M, Linløkken A, Wilson R, et al. Correlation between the human fecal microbiota and depression. *Neurogastroenterol Motility: Off J Eur Gastrointestinal Motil Soc* (2014) 26:1155–62. doi: 10.1111/nmo.12378

11. Szczesniak O, Hestad KA, Hanssen JF, Rudi K. Isovaleric acid in stool correlates with human depression. *Nutr Neurosci* (2016) 19:279–83. doi: 10.1179/1476830515y.0000000007

12. Foster JA, McVey Neufeld KA. Gut-brain axis: How the microbiome influences anxiety and depression. *Trends Neurosci* (2013) 36:305–12. doi: 10.1016/j.tins.2013.01.005

13. Sonali S, Ray B, Tousif HA, Rathipriya AG, Sunanda T, Mahalakshmi AM, et al. Mechanistic insights into the link between gut dysbiosis and major depression: an extensive review. *Cells* (2022) 11:1362. doi: 10.3390/cells11081362

14. Sasso JM, Ammar RM, Tenchov R, Lemmel S, Kelber O, Grieswelle M, et al. Gut microbiome-brain alliance: A landscape view into mental and gastrointestinal health and disorders. *ACS Chem Neurosci* (2023) 14:1717–63. doi: 10.1021/acschemneuro.3c00127

15. Sanada K, Nakajima S, Kurokawa S, Barceló-Soler A, Ikuse D, Hirata A, et al. Gut microbiota and major depressive disorder: A systematic review and meta-analysis. *J Affect Disdorders* (2020) 266:1–13. doi: 10.1016/j.jad.2020.01.102

16. Barandouzi ZA, Starkweather AR, Henderson WA, Gyamfi A, Cong XS. Altered composition of gut microbiota in depression: A systematic review. *Front Psychiatry* (2020) 11:541. doi: 10.3389/fpsyt.2020.00541

17. Yang J, Zheng P, Li Y, Wu J, Tan X, Zhou J, et al. Landscapes of bacterial and metabolic signatures and their interaction in major depressive disorders. *Sci Adv* (2020) 6:20201202. doi: 10.1126/sciadv.aba8555

18. Dinan TG, Cryan JF. Melancholic microbes: A link between gut microbiota and depression? *Neurogastroenterol Motil* (2013) 25:713–9. doi: 10.1111/nmo.12198

19. Chung SY, Kostev K, Tanislav C. Dysbiosis: A potential precursor to the development of a depressive disorder. *Healthcare (Basel)* (2022) 10:20220810. doi: 10.3390/healthcare10081503

20. Yao H, Zhang D, Yu H, Shen H, Liu H, Meng F, et al. The microbiota-gut-brain axis in pathogenesis of depression: A narrative review. *Physiol Behav* (2023) 260:114056. doi: 10.1016/j.physbeh.2022.114056

21. Kelly JR, Borre Y, O' Brien C, Patterson E, El Aidy S, Deane J, et al. Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. *J Psychiatr Res* (2016) 82:109–18. doi: 10.1016/j.jpsychires.2016.07.019

22. Knuesel T, Mohajeri MH. The role of the gut microbiota in the development and progression of major depressive and bipolar disorder. *Nutrients* (2021) 14:20211223. doi: 10.3390/nu14010037

23. Knudsen JK, Michaelsen TY, Bundgaard-Nielsen C, Nielsen RE, Hjerrild S, Leutscher P, et al. Faecal microbiota transplantation from patients with depression or

healthy individuals into rats modulates mood-related behaviour. *Sci Rep* (2021) 11:21869. doi: 10.1038/s41598-021-01248-9

24. Zheng P, Zeng B, Zhou C, Liu M, Fang Z, Xu X, et al. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. *Mol Psychiatry* (2016) 21:786–96. doi: 10.1038/mp.2016.44

25. Li N, Wang Q, Wang Y, Sun A, Lin Y, Jin Y, et al. Fecal microbiota transplantation from chronic unpredictable mild stress mice donors affects anxiety-like and depression-like behavior in recipient mice *via* the gut microbiota-inflammation-brain axis. *Stress (Amsterdam Netherlands)* (2019) 22:592–602. doi: 10.1080/10253890.2019.1617267

26. Łoniewski I, Misera A, Skonieczna-Żydecka K, Kaczmarczyk M, Kaźmierczak-Siedlecka K, Misiak B, et al. Major Depressive Disorder and gut microbiota – Association not causation. A scoping review. *Prog Neuropsychopharmacol Biol Psychiatry* (2021) 106:110111. doi: 10.1016/j.pnpbp.2020.110111

27. Audet MC. Stress-induced disturbances along the gut microbiota-immune-brain axis and implications for mental health: Does sex matter? *Front Neuroendocrinol* (2019) 54:100772. doi: 10.1016/j.yfrne.2019.100772

28. Manosso LM, Lin J, Carlessi AS, Recco KCC, Quevedo J, Gonçalves CL, et al. Sex-related patterns of the gut-microbiota-brain axis in the neuropsychiatric conditions. *Brain Res Bull* (2021) 171:196–208. doi: 10.1016/j.brainresbull.2021.04.001

29. Shobeiri P, Kalantari A, Teixeira AL, Rezaei N. Shedding light on biological sex differences and microbiota–gut–brain axis: a comprehensive review of its roles in neuropsychiatric disorders. *Biol Sex Differ* (2022) 13. doi: 10.1186/s13293-022-00422-6

30. Clarke G, Grenham S, Scully P, Fitzgerald P, Moloney RD, Shanahan F, et al. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Mol Psychiatry* (2013) 18:666–73. doi: 10.1038/mp.2012.77

31. Jašarević E, Morrison KE, Bale TL. Sex differences in the gut microbiome - Brain axis across the lifespan. *Philos Trans R Soc B: Biol Sci* (2016) 371. doi: 10.1098/rstb.2015.0122

32. Chen JJ, Zheng P, Liu YY, Zhong XG, Wang HY, Guo YJ, et al. Sex differences in gut microbiota in patients with major depressive disorder. *Neuropsychiatr Dis Treat* (2018) 14:647–55. doi: 10.2147/NDT.S159322

33. Li Y, Zhang H, Zheng P, Yang J, Wu J, Huang Y, et al. Perturbed gut microbiota is gender-segregated in unipolar and bipolar depression. *J Affect Disord* (2022) 317:166–75. doi: 10.1016/j.jad.2022.08.027

34. Chen YH, Xue F, Yu SF, Li XS, Liu L, Jia YY, et al. Gut microbiota dysbiosis in depressed women: The association of symptom severity and microbiota function. *J Affect Disord* (2021) 282:391–400. doi: 10.1016/j.jad.2020.12.143

35. Hu X, Li Y, Wu J, Zhang H, Huang Y, Tan X, et al. Changes of gut microbiota reflect the severity of major depressive disorder: a cross sectional study. *Trans Psychiatry* (2023) 13:137. doi: 10.1038/s41398-023-02436-z

36. Valeri F, Endres K. How biological sex of the host shapes its gut microbiota. *Front Neuroendocrinol* (2021) 61:100912. doi: 10.1016/j.yfrne.2021.100912

37. Lopez-Siles M, Duncan SH, Garcia-Gil LJ, Martinez-Medina M. Faecalibacterium prausnitzii: From microbiology to diagnostics and prognostics. *ISME J* (2017) 11:841–52. doi: 10.1038/ismej.2016.176

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"I am not the same as before": a mixed-methods study on depression in people with spinal injury in Qatar

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Incidence of spinal injury is high in the Middle East and North African region (MENA) due to the high incidence of road traffic crashes. A spinal injury may trigger mental health issues. Compared to the general population, people with spinal injury are at higher risk for developing major depression, anxiety, post-traumatic stress disorders, substance abuse, and suicide.

Objectives: The objectives of the study were to determine depression prevalence; identify relationships between depression and cause and site of spinal injury, sociodemographic factors, and social support; and explore the lived experiences of depression in people with spinal injury in Qatar.

Methods: A sequential cross-sectional mixed methods study was conducted. In the quantitative component, the universal sample consisted of 106 consenting individuals presenting with spinal injury at Hamad General Hospital, Doha, Qatar between January and December 2020. The Patient Health Questionnaire-9 was used to assess levels of depression and the Medical Outcomes Study Social Support Survey was used to assess perceived social support. The cause and site of injury were obtained from patient records. In the qualitative component, semi-structured in-depth interviews were conducted with 12 purposively selected participants from the quantitative component.

Results: Spinal injury had a negative impact on participants physical, mental, social, and spiritual wellbeing. In total, 69% of participants had some level of depression: 28% mild, 25.5% minimal, and 15% moderate to severe. Depression was not associated with socio-demographic factors, or the cause or site of spinal injury. Higher levels of emotional/informational support and positive social interaction were associated with milder depression. Social support and religious faith were critical in assisting participants to cope with their new situation.

Conclusions: Depression is prevalent among people with spinal injury attending health services. Early detection, referral, and treatment of depression are recommended. Strategies to enhance emotional/informational support and positive social interaction should be developed and tested with people with spinal injury.

1 Introduction

Spinal injury is a life-threatening traumatic event associated with significant health burden. The spinal vertebrae typically provide protection to the spinal cords soft tissues; however, they can be displaced causing harmful pressure on the spinal cord resulting in injury. Spinal injury refers to the damage done to either the spinal cord or the vertebrae, ligaments, and disks of the spinal column. The annual global incidence of spinal injury is approximately 40 to 80 cases per million population, with traumatic causes such as motor vehicle crashes, falls, violent acts, and sports-related injuries responsible for up to 90% of these cases (1). The incidence of spinal injury is higher in the Middle East and North African region (MENA) because of the high incidence of road traffic crashes. The proportion of traumatic spinal injuries due to road traffic crashes is 85% in Saudi Arabia (2) and 72% in Qatar (3), the highest rates in the world.

Spinal injury can cause severe physical disability, such as loss of motor, sensory, and other neurological functions (4). In addition, depending on the type of spinal cord injury, complications may include bowel dysfunction, impaired bladder control, sexual dysfunction, mobility restrictions and elevated risk of pressure ulcers (5). A spinal injury may significantly impact a persons daily routine, productivity, and quality of life (QoL) (6) and trigger mental health issues. Compared to the general population, individuals with spinal injury are at higher risk for developing major depression, anxiety, post-traumatic stress disorders, substance abuse, and suicide (7). In turn, depression has a significant negative influence on health and performance of daily living activities after spinal injury (7). Chronic pain due to spinal injury is also associated with depressive symptoms (8). Depression symptoms have been studied extensively among people with spinal injury. Depression is the most common psychological issue affecting approximately 30% of people with spinal injury (9–11) and the risk of depression is higher in those with spinal injury compared to those without (9). Up to 40% of people with spinal injury are clinically depressed during their initial rehabilitation (12, 13). Spinal injury and depression are correlated with longer stays at hospital, prolonged rehabilitation process, less functional improvements and independence as well as lower mobility at discharge (14, 15). If not addressed, depression may lead to

negative outcomes such as less independence, more complications, reduced community and social integration, and lower self-appraised health. Depression can also influence the individuals ability to cope with the physiological changes that occur after spinal injury and reduce their motivation to engage in rehabilitation (16). Early detection of depression in people with spinal injury improves quality of life and reduces associated comorbidities (17, 18).

Most research on spinal injury has been conducted in high income countries, with a small number of studies in the Middle Eastern region including Jordan (19), Turkey (20), Kuwait (21), Saudi Arabia (22), Iran (23), and United Arab Emirates (24). However, few studies assess the extent and/or experience of depression in people with spinal injury within the Arab Gulf region, and there have been no studies in Qatar. Such studies are necessary for developing strategies to reduce the risk of depression in people with spinal injury.

2 Methods

2.1 Study design and population

This cross-sectional mixed methods study aimed to determine the prevalence of depression in people with spinal injury; identify the association between the level of depression and cause and site of spinal injury, sociodemographic factors, and social support; and explore the experiences of depression in people with spinal injury attending health services in Doha, Qatar. The qualitative and quantitative methods were incorporated in all design aspects, conducted sequentially, and had equal value to the study (25). We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to comprehensively report the quantitative component of the study and its findings (26).

The study population and sample population for the quantitative component of the study consisted of all individuals attending Hamad General Hospital injury related services including Trauma and Neurological Inpatient Units, Trauma Intensive Care Unit, Trauma Stepdown, Trauma Outpatients Department, and Qatar Rehabilitation Institute Inpatient Unit and Outpatient Department between January and December 2020. Hamad General Hospital is the major

governmental healthcare institution in the State of Qatar, where most residents attend in case of emergency, hence it was selected for this study. The use of a universal or census sample enabled us to ensure that there was no selection bias, and that the diverse perspectives of all people with spinal injuries at that time would be included in the study. Eligible participants were: i) males and females; (ii) inpatient and outpatient; iii) aged 18-65 years; iv) recently acquired a spinal injury (spinal cord and spinal column injuries; both traumatic and non-traumatic); and v) conscious and able to communicate. Individuals unable to give informed consent, in a confused state or critical condition, with a history of depression or suicidal attempts, or injured because of a suicide attempt were excluded from the study. A total of 136 individuals met the inclusion criteria; 30 did not consent to participate, resulting in a final sample for the quantitative component of 106 participants. Purposive sampling was used to identify 20 individuals who had completed the quantitative component to approach for the qualitative component of the study, with 12 consenting to participate. Participants were selected to optimize the breadth of participant experiences, with consideration of age, sex, severity of injury, language spoken, and nationality. Purposive sampling is commonly used in the selection of participants that are most likely to result in useful insights. This serves the purpose of providing a credible understanding of the topic under study. Reasons for not participating in the quantitative or qualitative component related to individuals not feeling well enough or not interested in talking at the time.

2.2 Data collection

Individuals who met the inclusion criteria were approached at least two weeks after their admission to hospital with a spinal injury by BAS, the principal investigator. The information sheet and consent form were provided in English, Arabic, and Hindi, and explained to participants in the same language by BAS (Arabic and English), and a native Hindi speaking nurse. The data collection window closed in mid-January 2021 to accommodate any individuals that had been injured in late December 2020.

2.3 Study measures

2.3.1 Quantitative component

The quantitative component of the study consisted of an interviewer-administered questionnaire-based survey. All questionnaires were administered by BAS in Arabic or English. A native Hindi speaking nurse provided real time translation into and from English with participants who spoke Hindi. Having one questionnaire administrator and one translator reduced the potential for information bias arising from inter-interviewer or translator variability. The questionnaire included socio-demographic items for age, sex, nationality, education, marital status, and number of children. The questionnaire included two existing instruments for assessing depression and social support. Data on the cause and site of the injury were collected from participants medical records.

2.3.1.1 Patient health questionnaire

As there is no spinal injury-specific instrument for measuring depression, the Patient Health Questionnaire (PHQ-9) (27) was used to assess the severity of depression, consistent with other studies on the psychological effects of spinal cord injury (28). This questionnaire is the only instrument that aligns with the Diagnostic and Statistical Manual of Mental Disorders criterion that clinical diagnoses should be based on participants experiences in the past two weeks. PHQ-9 consists of nine items each rated from 0 (not occurring at all) to 3 (occurring nearly every day) with a total score ranging from 0 to 27. Results are categorized as minimal (1–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe depression (20–27). The English, Arabic, and Hindi versions of PHQ-9 were used in this study. The English version of the PHQ-9 version has been used extensively in people with spinal injury (11, 29, 30) and has high internal reliability (18). Internal reliability of PHQ-9 in this study was also high (Cronbachs α = .812.) The Arabic version of the PHQ-9 has been validated in a sample of individuals in Lebanon. The instrument had high internal reliability (Cronbachs α = .823) and reliability (31). No studies have validated the Hindi version of PHQ-9.

2.3.1.2 Medical outcomes study social support survey

The Medical Outcomes Study Social Support Survey (MOS-SSS) (32) identifies self-reported information regarding companionship, assistance, and other types of support including emotional and affectionate support. This instrument was originally created for individuals with chronic conditions; positive associations were observed between measures of social support and psychological health (32). The MOS-SSS is a 19-item questionnaire that yields an overall social support index and four subscale scores for emotional/informational support, tangible support, affectionate support, and positive social interaction. Emotional/informational support refers to perceived availability of someone to talk to about personal issues, the availability of advice or information when needed, and the expression of love and affection. Tangible support refers to the availability of practical assistance or material aid. It assesses the perceived availability of help with daily chores, financial assistance, or other forms of tangible support. Affectionate support refers to the perceived availability of love, affection, and expressions of care. It reflects the emotional aspects of support, emphasizing the importance of warmth and closeness in relationships. Positive social interaction refers to the perceived availability of someone to have fun with, to relax and enjoy time with, and to engage in recreational activities or social events. It focuses on the positive aspects of social interaction and companionship. Participants were asked to select the frequency of situations within each of these four domains of social support. Response scores are based on a five-point scale ranging from 1 (none of the time) to 5 (all the time). An overall social support index is determined by calculating average responses of the 19 items, yielding a score ranging from 15. Subscale scores are determined by calculating average responses for subscale items, yielding scores ranging from 15 for each subscale. Higher subscale and overall scores indicate more social support. The English version of the

MOS-SSS has been validated in numerous studies and found to have high internal validity and reliability (32, 33). The Arabic version of the MOS-SSS has been validated and found to have high validity and reliability (34). A psychometric review of various translations of MOS-SSS recommended that the Arabic version has potential use in future research and practice (33). In this study, the MOS-SSS had excellent internal reliability (Cronbachs α=.960), as did the subscales: emotional/informational support (α=.955), tangible support (α=.950), affectionate support (α=.922), and positive social interaction (α=.967). No studies have validated a Hindi version of the MOS-SSS.

2.3.2 Qualitative component
2.3.2.1 Semi-structured interview

A semi-structured interview was conducted to collect in-depth qualitative data on participants experiences with depression. Interviews were conducted by BAS in Arabic or English. A native Hindi speaking nurse provided real time translation into and from English with participants who spoke Hindi. As with the interviewer-administered questionnaire, having one interviewer and one translator reduced the potential for information bias arising from inter-interviewer or translator variability. Interview questions focused on participants feelings related to their injury over the past two weeks, how their injury contributed to such feelings, and how they were dealing with the consequences of their injury. Given the extent of participants medical condition, interviews were kept relatively short, lasting an average of 15 minutes. Interviews continued until data saturation was reached and no new information was emerging (35).

2.4 Data analysis

The mixed methods design included concurrent data analysis whereby quantitative and qualitative data analyses were completed separately, and results from analyses were then compared (36). Quantitative data analyses were completed using statistical software package IBM SPSS Statistics version 25.0 (SPSS Inc., Chicago, IL, USA). Initially, data were screened for outliers or data errors. There were no missing data due to the questionnaire being interviewer-administered. Descriptive statistics were calculated for all measures; continuous data are presented as mean ± Standard Deviation (SD), and categorical data are summarized as count (percentages). The proportion of participants in each depression category was calculated. A binary variable was then created by grouping mild, moderate, moderately severe, and severe categories of depression (labeled 'depression). Pearsons χ^2 test was used to test the association between depression and categorical independent variables. Pearson correlation coefficients (r) were calculated to evaluate the association between the continuous PHQ-9 score and MOS_SSS scores. The level of statistical significance was set at P<0.05.

Thematic analysis was used to analyze the interview data via the four-step method of data preparation, data reduction, displaying data, and verifying data (37). Data preparation involved verbatim transcription of interviews in English and Arabic. Arabic

transcriptions were translated into English. Interviews in Hindi were transcribed in English after real time translation. Data reduction included line by line coding, looking for similar concepts, categorizing concepts, and grouping them into larger themes. Data are displayed in the results section according to themes and categories, supported by direct quotations from participants. Quotes are short due to the medically required brevity of the interviews. Data verification was ensured by cross-checking results with the original transcripts (38). All data analysis took place in 2021.

2.5 Ethical considerations

The study was conducted in full compliance with the Declaration of Helsinki, Good Clinical Practice (GCP), and within the Ministry of Public Health laws and regulations in Qatar. Ethical approval was obtained from Medical Research Center of Hamad Medical Corporation and Qatar Universitys Institutional Review Board (QU-IRB 1341-E/20). To preserve the anonymity of participants, the specific nationality of participants is not reported, and instead, nationalities are grouped into regions. Pseudonyms are used for quotations when reporting qualitative data.

3 Results

3.1 Quantitative results

A total of 106 participants were included in the study. The average age was 36 years, and the majority were male, from Asia, married, had three or fewer children, and some level of education (Table 1). The two main causes of injury were motor vehicle crashes (38%) and falls (37%). Fewer injuries were caused by pedestrian accidents (10%), work-related accidents (9%), and back pain (4%). Most injuries affected the lumber spine (62%), followed by thoracic (39%), cervical (36%), and sacral spine (10%). Motor vehicle crashes were the most common cause of injury that resulted in thoracic neurological deficit (46.2%) and half of sacral spine injuries were caused by falls.

The mean PHQ-9 score was 4.82 ± 5.25 indicating mild depression. Overall, 31% of participants had no depression and 69% had some level of depression: 28% mild, 25.5% minimal, 7% moderate, 7% moderately severe, and 0.9% severe depression. There were no statistically significant relationships between depression and the cause of injury, site of injury, age, sex, nationality, education, marital status, or number of children (Table 2).

The overall mean MOS-SSS score was 4.12 ± 0.99. The subscale scores were affectionate support 4.25 ± 1.19, emotional/informational support 4.23 ± 1.03, positive social interaction 4.04 ± 1.26, and tangible support 3.9 ± 1.4. There was no significant association between PHQ-9 score and the overall social support index (r = -0.189; P = 0.053) (Table 3). Significant but weak inverse correlations were observed between PHQ-9 score and emotional/informational support (r = -0.202; P < 0.001), and positive social

TABLE 1 Demographic characteristics of study participants (N=106).

	Mean ± SD or N (%)
Age (years)	35.82 ± 10.00
≤35	59 (55.7)
>35	47 (44.3)
Sex	
Male	100 (94.3%)
Female	6 (5.7%)
Marital status	
Married	72 (67.9)
Single	34 (32.1)
Total number of children	
0	39 (36.8)
1-3	50 (47.2)
4-6	11 (10.4)
7-9	6 (5.7)
Nationality region	
Asia	72 (67.9)
Africa & Europe	10 (9.4)
Middle East	24 (22.6)
Education	
Uneducated	20 (18.9)
School	61 (57.5)
University	25 (23.6)

TABLE 2 Association between depression and cause of injury, site of injury, and sociodemographic factors (N=106).

	Depression n=73 (69%)	No depression n=33 (31%)	P value
	n (%)	n (%)	
Cause of injury			0.65
Fall	28 (71.8)	11 (33.3)	
Motor Vehicle	25 (62.5)	15 (37.5)	
Pedestrian	9 (81.8)	2 (18.2)	
Work Related	7 (9.6)	3 (9.1)	
Back Pain	2 (50)	2 (50)	
Other	2 (100)	0 (0)	
Site of injury			0.92
Cervical spine	25 (69)	11 (31)	
Thoracic spine	25 (64)	14 (36)	
Lumber spine	44 (71)	18 (29)	
Sacral spine	7 (70)	3 (30)	
Age			0.27
≤35	38 (64)	21 (36)	
>35	35 (75)	12 (25)	
Sex			0.09
Male	67 (67)	33 (33)	
Female	6 (100)	0	
Nationality			0.20
Asia	46 (64)	26 (36)	
Africa & Europe	7 (70)	3 (30)	
Middle East	20 (83)	4 (17)	
Education			0.99
School	42 (69)	19 (31)	
University	17 (68)	8 (32)	
Uneducated	14 (70)	6 (30)	
Marital status			0.79
Married	49 (68)	23 (32)	
Single	24 (71)	10 (29)	
Number of children			0.095
0	28 (72)	11 (28)	
1-3	33 (66)	17 (34)	
4-6	10 (91)	1 (9)	
7-9	2 (33)	4 (67)	

interaction (r = -0.210; P < 0.001). Participants with higher emotional/informational and positive social interaction had lower levels of depression.

3.2 Qualitative results

A total of 12 participants aged 20 to 46 years with eight different nationalities participated in the interviews. Nine participants had motor vehicle-related injuries, two had injuries caused by falls, and one had a pedestrian injury. Two thematic categories emerged relating to the impact of the spinal injury and coping with the injury. Themes related to the impact of injury were negative influence on lifestyle, less self-esteem and confidence, psychological challenges, reduced physical health functioning, interrupted sleeping patterns, and death thoughts. Themes on coping with injury were strong religion and faith, and social support (Figure 1).

TABLE 3 Association between Patient Health Questionnaire-9 (PHQ-9) score and Medical Outcomes Study Social Support Survey (MOS-SSS) scores (N=106).

	R	P value
Overall Social Support Index	-0.189	0.053
Emotional/Informational support	-0.202	0.001*
Tangible support	0.045	0.648
Affectionate support	-0.120	0.221
Positive social interaction	-0.210	0.001*

*Correlation significant at the 0.05 level (2-tailed).

3.2.1 Thematic category 1: Impact of the injury

3.2.1.1 Negative influence on lifestyle

Most participants struggled with their daily routines after injury, noting they were not the same person as prior to injury. One participant Zebiba mentioned she was unemployed after the injury, saying, "I stopped working for the time being. I dont even do anything at home, my husband and sister help me. My daughters stopped going to school because I am unemployed and going through financial problems." Yasser also noted the significant effect on him, saying "Injury had a great impact on my life, but I try not to think much about it." Another participant reported not being able to take care of her children. A few said that they are still fighting hard and struggling to overcome their situation. They mentioned that due to the pain, they are less active after the injury. Sara explained, "Before the accident, I was very active but now I can barely move because of the pain. I am not the same as before; I cant move and get out or take care of my children. These things affect me psychologically … Until now, I am still not allowed to carry my kids or any heavy things. I am even not allowed to move a lot." Muhanad said, "I try to fight this, and I try to look for ways to overcome my situation."

3.2.1.2 Psychological challenges

Most participants reported feeling sad and losing interest in everything. Some participants felt useless and helpless. Some participants also reported guilty feelings about the impact on their families due to their lack of ability to perform tasks independently. As Randa explained, "I sometimes feel sad and useless … not depressed, and not all times … I dont see myself as before … sometimes I feel that I lost interest in everything." Sara expressed similar ideas, saying, "I feel that I am useless; I was strong before but now I feel like I need people to help me. I cannot be independent like I was before." One participant stated that pain caused distress as well as mood swings which affected the performance of certain activities. Another reported that being away from family was the main cause of emotional and psychological stress. Muhanad explained, "A person feels distressed when not being able to move and perform family and social obligations Mood changes when in pain. If I need to do something but cannot … it affects my mental health." In contrast to these expressions of ongoing psychological distress, two participants reported being depressed only at injury time and then feeling normal with time. One participant mentioned that performing physical activity had a positive influence and improved their psychological wellbeing.

3.2.1.3 Reduced physical health functioning

Most participants reported difficulty in movement, pain, and tiredness, lacking energy and feeling weak. A few participants lost their appetite. Zenon said, "I cant walk, and I cant do any work now because of this back pain. … Even when someone is helping me, I cant walk." Jassim noted that "I cannot run like before."

3.2.1.4 Interrupted sleeping patterns

Some participants struggled with insomnia due to overthinking and distress or trouble breathing while sleeping due to pain. They were not getting enough sleep, and this impacted their recovery.

3.2.1.5 Reduced self-esteem and confidence

Some participants reported having lower self-esteem and confidence due to the trauma caused by the incident. Randa explained the situations in which she felt most affected, saying, "I feel afraid of going down the stairs and while going out of the house, even if I see a car; I am suffering from a trauma in my daily activities" and Zebiba also noted, "I feel afraid whenever I see a car."

FIGURE 1
Themes, subthemes, and number of participants reporting each sub-theme.
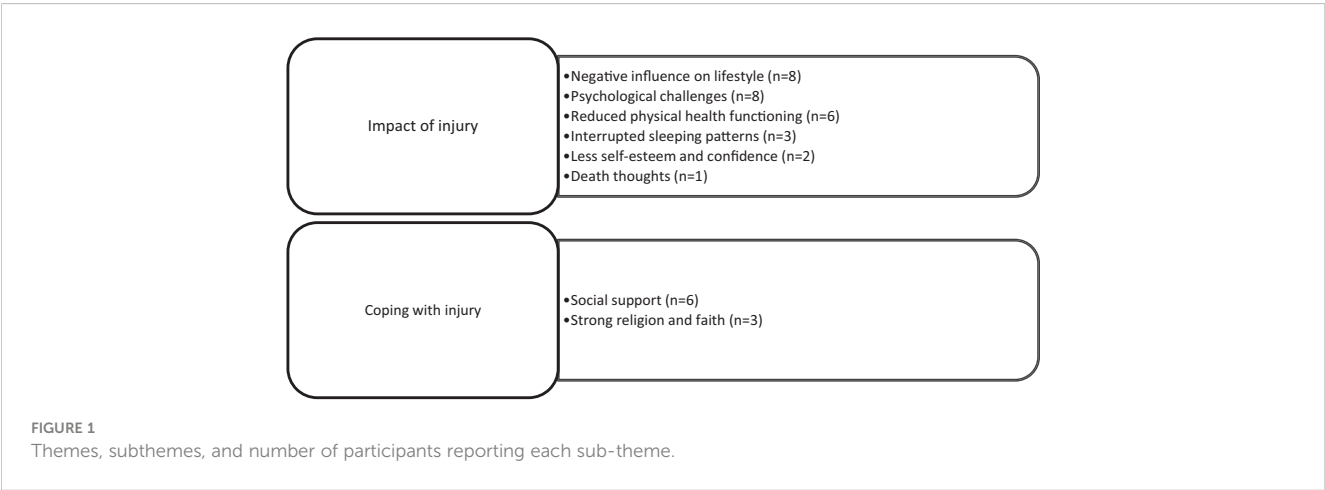
3.2.1.6 Death thoughts

One participant, Zebiba, reported having suicidal thoughts due to the unbearable pain. Death was perceived as a way to relieve sorrow and pain. She said, "In the beginning, I was thinking of death and saying Oh God relieve me. I was in so much pain, I just wanted to end everything."

3.2.2 Thematic category 2: Coping with the injury

3.2.2.1 Social support

Half the participants stated that social support, particularly from family, was the most important factor for coping with the injury. Family gatherings, quality time with their spouse and children, outings, and visits from friends were all found to ease the impact of the injury. They felt stronger because of the care offered by family members and friends. As Ibrahim said, "Everyone cares for me now … I feel a lot of happiness when a friend visits me." Hamad shared, "I got married after the injury and this is what helped me overcome my injury condition." Randa explained the impact of her familys support, saying "When I talk to my family, I feel much better, and I forget my sorrow. But when I am alone in my room or when going out alone, I feel sadder." One participant felt that social support from the medical staff was important, saying that conversations with the doctors provided relief.

3.2.2.2 Strong religion and faith

Three participants mentioned that religion and faith were the main factors for coping with their injuries. They reported that their belief and faith in God almighty were strong and ultimately helped them to cope with their situation. As Sara said, "I feel I am closer to God; I have a bigger faith and thankful I am alive … I accept my destiny and I have hope that I will recover." Muhanad said, "My strong belief in God almighty makes me more hopeful and accepting."

4 Discussion

This cross-sectional mixed methods study aimed to determine the prevalence of depression in people with spinal injury; identify the association between the level of depression and cause and site of spinal injury, sociodemographic factors, and social support; and explore the experiences of depression in individuals with spinal injury attending injury-related health services in Qatar. The questionnaire-based survey found that the prevalence of depression among the participants was high, with 69% of participants having some level of depression, including 15% with moderate to severe depression. Depression was not associated with socio-demographic factors, or cause or site of spinal injury. Interviews confirmed that spinal injury had a negative impact on participants lives, including their physical and mental health, as well as social and spiritual wellbeing. Participants struggled with their daily routines after the injury and had difficulties in their day-to-day activities, which had an impact on their self-worth and self-esteem. Some participants reported significant psychological challenges, including suicidal ideation. The highest levels of social support were affectionate support and emotional/informational support. Emotional/

informational support and positive social interaction were inversely correlated with depression. This was consistent with the findings of the interviews, which highlighted the important role of social support in improving participants ability to cope with their new situation. Social support, specifically family support, and participants spiritual support and religious faith were critical in assisting them to cope with their new situation.

Our findings on the high prevalence of depression in people with spinal injury are consistent with many other studies. A study across six countries found that for people with a physical injury, the odds of depression were 72% higher than people without injury, and the odds for those with an injury with a disability were 3.81 times higher than for those without injury (39). Another study found that for those hospitalized with traumatic injury, the severity of the injury was associated with the development of depression (40). Given that injury to the spine is likely to be severe and result in disability, the site of the injury is an important factor in the development of depression. Other research confirms that individuals with spinal injury are at higher risk for developing major depression, anxiety, and post-traumatic stress (41). The prevalence of depression in our study was slightly lower than in a study in Iraq, which found that 86% of study participants were depressed (42). Similar to other studies, this study found no significant associations between depression and sociodemographic factors (14, 18, 43, 44), which indicates that depression is not selective with respect to sociodemographic characteristics; it appears everyone is equally vulnerable. In contrast, other studies have found relationships between depression and sociodemographic factors, whereby females, less educated, and older age groups had a higher risk for depression (45). Such inconsistencies in results imply that the association between sociodemographic factors and depression is still not clearly identified and requires further investigation.

The finding from this study that spinal injury had a negative impact on participants daily routine, physical, mental, social and spiritual health is consistent with other studies in which people with spinal injury experienced confusion, tiredness, pain, stress, low self-efficacy, inadequate sleep, and reduced involvement in day-to-day activities and social integration (9, 46–48). Chronic pain conditions can increase suicide among people with spinal injury (49) with more than 50% of people with spinal injury having suicidal thoughts (49, 50). Although only one participant in this study had suicidal ideation in the early stages of injury, participants may have not been fully honest due to fear and the fact that suicide is forbidden from a religious perspective (51) or stigmatized from a cultural perspective (52); thus, it may have been underreported. In some religious and cultural communities, mental health issues, including suicidal thoughts, are highly stigmatized. Individuals may fear judgment, social exclusion, or shame, leading to underreporting or reluctance to seek help. Such stigma has been demonstrated in Asian (53) and Arab countries (54), the two largest groups of participants in our study. Cultural norms also play a role in shaping how emotions and mental health are expressed. Some cultures emphasize emotional restraint or discourage open discussion of personal struggles, which may hinder people from openly sharing their mental health concerns (52), including thoughts of suicide. Asian and Arab cultures emphasize collectivism and prioritizing the wellbeing of the family or community over individual concerns, which may have led to

participants being less inclined to disclose personal struggles, including mental health issues, to avoid burdening their loved ones.

Both quantitative and qualitative results demonstrated the importance of social support in coping with spinal injury. Likewise, the role of social support in coping with spinal injury has been highlighted in other studies (49, 55, 56). Social support is a crucial factor for reducing depression severity, improving coping ability, and injury recovery (57). In our study, emotional support, particularly from family was critical, and this is consistent with other studies (58). When family support is not available, peer support is effective (58). Given the large expatriate community in countries such as Qatar and the Gulf Cooperative Council (GCC), with many people not having family living with them, it is important for health institutions to facilitate peer support programs for people with spinal injury.

In this study, spiritual support played a significant role in helping participants to cope with their situation. Participants felt that having strong spiritual beliefs provided them with the strength required to address the needs arising from their new situation. This was consistent with other studies that also highlight the important role of spirituality in coping with spinal injury (56, 59, 60).One of the first studies conducted in a primarily Muslim country found that spiritual wellbeing was an important factor contributing to the capacity of individuals to cope with the physical, social, economic, and emotional issues arising from the injury (61).

Although we found no statistical association between depression and the cause or site of the spinal injury, we did not test whether these factors played a role in the relationship between depression and social support. Future studies should examine the potential mediating role of the nature of the spinal injury, as this may contribute to the type and intensity of social support required. The level and severity of the injury and the degree of physical independence will impact the level of practical and financial support required for mobility, daily activities, self-care, rehabilitation, and medical needs, as well as the degree of emotional support required (62).

This study had several strengths and limitations that must be considered in interpreting the results. A significant strength was the census sample whereby all individuals attending Hamad General Hospital injury-related services over one year were included. This enhances the generalizability of the results. The risk of variation in data collection was reduced by the principal investigator administering the questionnaire and conducting the interviews. The availability of instruments and interviews in three languages helped to optimize the number of participants from different nationalities, however Hindi versions of the PHQ-9 and MOS-SSS have not been validated, reducing the trustworthiness of results for participants speaking Hindi. Data collection was undertaken for a minimum of two weeks from injury onset, which may have impacted participants self-assessment of their mental state. The study did not determine how levels of depression may change over time. Most participants were migrant workers and may have feared deportation which might have caused underreporting. Conducting subgroup analyses with relatively small samples in this study may have resulted in type 2 errors. The methodological limitations and the specific context of Qatar with its high prevalence of migrant workers limit the generalizability of the findings to other countries.

This study provides a novel and important addition to research in Qatar and the region. Depression is prevalent among people with spinal injury and is associated with lower levels of social and spiritual support, but not sociodemographic factors or injury cause or site. Many of the poor outcomes associated with spinal injury arise from insufficient medical care and rehabilitation services, coupled with obstacles in physical, social, and policy environments (63). In addition to the direct impact of spinal injury on affective disorders, policy decisions that impact on care and support for people with spinal injury may also adversely affect neurological recovery, resulting in further increased levels of depression as well as other personal and economic burdens for both individuals and the health system (63). Delivering comprehensive care that includes depression diagnosis and treatment during acute and post-acute phases can mitigate the likelihood of depression and enhance overall quality of life by maximizing functional capabilities, promoting independence, ensuring overall wellbeing, and facilitating community integration to enable people with spinal injury to live full and meaningful lives (64). At a minimum, spinal injury care programs should include rehabilitation psychologists to facilitate the early detection of depression in people with spinal injury and timely referral to treatment (64). Beyond this, access to valid, reliable, and consistent data is required for policy makers to develop evidence-based actions, and a spinal injury registry could provide access to data to support evidence-based practice to optimize continuity of care, rehabilitation services, and social support for people with spinal injury (63).

All research creates the need for more research, and this study is no different. Knowing that people with spinal injury are at higher risk for depression is important. More research is now required on the impact of policies that enable culturally safe interprofessional collaborative practices for the early detection, referral, and treatment of depression in people with spinal injuries. Research is also required on the impact of programs developed by health services or within the social sector that provide more structured peer support for people with spinal injuries.

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 Qatar University Institutional 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

BS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Writing –

original draft, Writing – review & editing. LOH: Supervision, Methodology, Writing – review & editing.

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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References

1. World Health Organization and International Spinal Cord Society. *International perspectives on spinal cord injury*. World Health Organization (2013). Geneva, Switzerland.

2. Alshahri S, Cripps R, Lee B, Al-Jadid MS. Traumatic spinal cord injury in Saudi Arabia: an epidemiological estimate from Riyadh. *Spinal Cord*. (2012) 50:882–4. doi: 10.1038/sc.2012.65.

3. Quinones P, Nassal M, AlBader K, Al Muraikhi A, Al Kahlout S. Traumatic spinal cord injury in Qatar: an epidemiological study. *Middle East J Emergency Med*. (2002) 2:35–40.

4. Zurcher C, Tough H, Fekete C, Group SS. Mental health in individuals with spinal cord injury: The role of socioeconomic conditions and social relationships. *PloS One*. (2019) 14:e0206069. doi: 10.1371/journal.pone.0206069.

5. Ghazwin MY, Chaibakhsh S, Latifi S, Tavakoli AH, Koushki D. Quality of life in Iranian men with spinal cord injury in comparison with general population. *Archives of Neuroscience*. (2015) 2(2):e21529. doi: 10.5812/archneurosci.21529

6. Mousavi V-A. Quality of life in patients with spinal cord injury: the role of depressed mood. *Iranian J Neurosurg*. (2017) 2:9–14. doi: 10.29252/irjns.2.4.9.

7. van Leeuwen CM, Hoekstra T, van Koppenhagen CF, de Groot S, Post MW. Trajectories and predictors of the course of mental health after spinal cord injury. *Arch Phys Med Rehabilitation*. (2012) 93:2170–6. doi: 10.1016/j.apmr.2012.07.006.

8. Rintala DH, Loubser PG, Castro J, Hart KA, Fuhrer MJ. Chronic pain in a community-based sample of men with spinal cord injury: prevalence, severity, and relationship with impairment, disability, handicap, and subjective well-being. *Arch Phys Med Rehabilitation*. (1998) 79:604–14. doi: 10.1016/S0003-9993(98)90032-6.

9. Craig A, Tran Y, Middleton J. Psychological morbidity and spinal cord injury: a systematic review. *Spinal Cord*. (2009) 47:108–14. doi: 10.1038/sc.2008.115.

10. Fann JR, Bombardier CH, Richards JS, Tate DG, Wilson CS, Temkin N, et al. Depression after spinal cord injury: comorbidities, mental health service use, and adequacy of treatment. *Arch Phys Med Rehabilitation*. (2011) 92:352–60. doi: 10.1016/j.apmr.2010.05.016.

11. Williams R, Murray A. Prevalence of depression after spinal cord injury: a meta-analysis. *Arch Phys Med Rehabilitation*. (2015) 96:133–40. doi: 10.1016/j.apmr.2014.08.016.

12. Dezarnaulds A, Ilchef R. Psychological adjustment after spinal cord injury: Useful strategies for health professionals. *Agency Clin Innovation*. (2014). 2nd edition, place of publication Sydney, Australia. Agency for Clinical Innovation is the publisher of the report.

13. Kennedy P, Rogers BA. Anxiety and depression after spinal cord injury: a longitudinal analysis. *Arch Phys Med Rehabilitation*. (2000) 81:932–7. doi: 10.1053/apmr.2000.5580.

14. Arango-Lasprilla JC, Ketchum JM, Starkweather A, Nicholls E, Wilk AR. Factors predicting depression among persons with spinal cord injury 1 to 5 years post injury. *NeuroRehabilitation*. (2011) 29:9–21. doi: 10.3233/NRE-2011-0672.

15. Al-Owesie RM, Moussa NM, Robert AA. Anxiety and depression among traumatic spinal cord injured patients. *Neurosciences*. (2012) 17:145–50.

16. Davidoff G, Roth E, Thomas P, Doljanac R, Dijkers M, Berent S, et al. Depression and neuropsychological test performance in acute spinal cord injury patients: Lack of correlation. *Arch Clin Neuropsychology*. (1990) 5:77–88. doi: 10.1093/arclin/5.1.77.

17. Bombardier CH, Fann JR, Tate DG, Richards JS, Wilson CS, Warren AM, et al. An exploration of modifiable risk factors for depression after spinal cord injury: which factors should we target? *Arch Phys Med Rehabil*. (2012) 93:775–81. doi: 10.1016/j.apmr.2011.12.020.

18. Bombardier CH, Richards JS, Krause JS, Tulsky D, Tate DG. Symptoms of major depression in people with spinal cord injury: implications for screening. *Arch Phys Med Rehabilitation*. (2004) 85:1749–56. doi: 10.1016/j.apmr.2004.07.348.

19. Otom A, Doughan A, Kawar J, Hattar E. Traumatic spinal cord injuries in Jordanan epidemiological study. *Spinal Cord*. (1997) 35:253–5. doi: 10.1038/sj.sc.3100402.

20. Karacan I, Koyuncu H, Pekel O, Sumbuloglu G, Kjrnap M, Dursun H, et al. Traumatic spinal cord injuries in Turkey: a nation-wide epidemiological study. *Spinal Cord*. (2000) 38:697–701. doi: 10.1038/sj.sc.3101064.

21. Prasad L, Al Kandari S, Ramachandran U, Shehab D, Alghunaim S. Epidemiological profile of spinal cord injuries at a tertiary rehabilitation center in Kuwait. *Spinal Cord Ser Cases*. (2018) 4:1–5. doi: 10.1038/s41394-017-0036-5.

22. Robert AA, Zamzami MM. Traumatic spinal cord injury in Saudi Arabia: a review of the literature. *Pan Afr Med J*. (2013) 16:104. doi: 10.11604/pamj.2013.16.104.2902.

23. Rahimi-Movaghar V, Saadat S, Rasouli MR, Ganji S, Ghahramani M, Zarei M-R, et al. Prevalence of spinal cord injury in Tehran, Iran. *J spinal cord Med*. (2009) 32:428–31. doi: 10.1080/10790268.2009.11754572.

24. Grivna M, Eid HO, Abu-Zidan FM. Epidemiology of spinal injuries in the United Arab Emirates. *World J Emergency surgery*. (2015) 10:1–7. doi: 10.1186/s13017-015-0015-8.

25. Leech NL, Onwuegbuzie AJ. A typology of mixed methods research designs. *Qual Quantity*. (2009) 43:265–75. doi: 10.1007/s11135-007-9105-3

26. Vandenbroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the reporting of observational studies in epidemiology (STROBE). *Epidemiology*. (2007) 18:805–35. doi: 10.1097/ede.0b013e3181577511

27. Kroenke K, Spitzer RL. The PHQ-9: a new depression diagnostic and severity measure. *Psychiatr Annals*. (2002) 32:509–15. doi: 10.3928/0048-5713-20020901-06.

28. North N. The psychological effects of spinal cord injury: a review. *Spinal Cord*. (1999) 37:671–9. doi: 10.1038/sj.sc.3100913.

29. Williams RT, Heinemann AW, Bode RK, Wilson CS, Fann JR, Tate DG. Improving measurement properties of the Patient Health Questionnaire9 with rating scale analysis. *Rehabil Psychol*. (2009) 54:198. doi: 10.1037/a0015529.

30. Hoffman JM, Bombardier CH, Graves DE, Kalpakjian CZ, Krause JS. A longitudinal study of depression from 1 to 5 years after spinal cord injury. *Arch Phys Med Rehabilitation*. (2011) 92:411–8. doi: 10.1016/j.apmr.2010.10.036.

31. Al Jammal A. *Validity and reliability of the Arabic Version of the Patient Health Questionnaire-9 (PHQ-9) in Patients with Heart Failure (HF) in Lebanon*. Beirut, Lebanon: American University of Beirut (2023).

32. Sherbourne CD, Stewart AL. The MOS social support survey. *Soc Sci Med*. (1991) 32:705–14. doi: 10.1016/0277-9536(91)90150-B.

33. Dao-Tran T-H, Lam L-T, Balasooriya NN, Comans T. The Medical Outcome Study Social Support Survey (MOS-SSS): A psychometric systematic review. *J Advanced Nursing*. (2023) 79:4521–41. doi: 10.1111/jan.15786

34. Dafaalla M, Farah A, Bashir S, Khalil A, Abdulhamid R, Mokhtar M, et al. Validity and reliability of Arabic MOS social support survey. *SpringerPlus*. (2016) 5:1306. doi: 10.1186/s40064-016-2960-4

35. Morse JM. The significance of saturation. *Qual Health Res*. (1995) 5:147–9. doi: 10.1177/104973239500500201

36. Creswell JW, Creswell JD. *Research design: Qualitative, quantitative, and mixed methods approaches*. Sage publications 6th edition. (2020).

37. Folger JP, Scott Poole M. Relational coding schemes: The question of validity. *Ann Int Communication Assoc*. (1981) 5:235–47. doi: 10.1080/23808985.1981.11923847.

38. Wong L. Data analysis in qualitative research: a brief guide to using NVivo. *Malaysian Family Physician*. (2008) 3:14–20.

39. Jacob L, Pizzol D, Veronese N, Stubbs B, Koyanagi A. Physical injury and depression in six low- and middle-income countries: A nationally representative study. *J Affect Disord*. (2019) 248:99–107. doi: 10.1016/j.jad.2019.01.023

40. Wiseman TA, Curtis K, Lam M, Foster K. Incidence of depression, anxiety and stress following traumatic injury: a longitudinal study. *Scandinavian J Trauma Resuscitation Emergency Med*. (2015) 23:29. doi: 10.1186/s13049-015-0109-z

41. Bowen R, Peters E, Marwaha S, Baetz M, Balbuena L. Moods in clinical depression are more unstable than severe normal sadness. *Front Psychiatry*. (2017) 8:56. doi: 10.3389/fpsyt.2017.00056.

42. Hussain AA. Depression in spinal cord injured patients. *New Iraqi J Med*. (2007) 3:23–33.

43. Anderson CJ, Vogel LC, Chlan KM, Betz R, McDonald CM. Depression in adults who sustained spinal cord injuries as children or adolescents. *J Spinal Cord Med*. (2007) 30:S76–82. doi: 10.1080/10790268.2007.11754609.

44. Dryden DM, Saunders LD, Rowe BH, May LA, Yiannakoulias N, Svenson LW, et al. Depression following traumatic spinal cord injury. *Neuroepidemiology*. (2005) 25:55. doi: 10.1159/000086284.

45. Krause JS, Kemp B, Coker J. Depression after spinal cord injury: relation to gender, ethnicity, aging, and socioeconomic indicators. *Arch Phys Med Rehabilitation*. (2000) 81:1099–109. doi: 10.1053/apmr.2000.7167.

46. Rodrigues D, Tran Y, Wijesuriya N, Guest R, Middleton J, Craig A. Pain intensity and its association with negative mood states in patients with spinal cord injury. *Pain Ther*. (2013) 2:113–9. doi: 10.1007/s40122-013-0017-8.

47. Connolly FR, Aitken LM, Tower M. An integrative review of self-efficacy and patient recovery post acute injury. *J Advanced Nursing*. (2014) 70:714–28. doi: 10.1111/jan.12237.

48. Craig A, Tran Y, Siddall P, Wijesuriya N, Lovas J, Bartrop R, et al. Developing a model of associations between chronic pain, depressive mood, chronic fatigue, and self-efficacy in people with spinal cord injury. *J Pain*. (2013) 14:911–20. doi: 10.1016/j.jpain.2013.03.002.

49. Hartkopp A, Brønnum-Hansen H, Seidenschnur A-M, Biering-Sorensen F. Suicide in a spinal cord injured population: its relation to functional status. *Arch Phys Med Rehabilitation*. (1998) 79:1356–61. doi: 10.1016/S0003-9993(98)90227-1.

50. Pinkerton A, Griffin M. Rehabilitation outcomes in females with spinal cord injury: a follow-up study. *Spinal Cord*. (1983) 21:166–75. doi: 10.1038/sc.1983.27.

51. Hajiyousouf II, Bulut S. Mental health, religion and suicide. *Open J Med Psychol*. (2022) 11:12–27. doi: 10.4236/ojmp.2022.111002

52. Gopalkrishnan N. Cultural diversity and mental health: considerations for policy and practice. *Front Public Health*. (2018) 6:179. doi: 10.3389/fpubh.2018.00179

53. Vaishnav M, Javed A, Gupta S, Kumar V, Vaishnav P, Kumar A, et al. Stigma towards mental illness in Asian nations and low-and-middle-income countries, and comparison with high-income countries: A literature review and practice implications. *Indian J Psychiatry*. (2023) 65:995–1011. doi: 10.4103/Indianjpsychiatry.Indianjpsychiatry_667_23

54. Zolezzi M, Alamri M, Shaar S, Rainkie D. Stigma associated with mental illness and its treatment in the Arab culture: A systematic review. *Int J Soc Psychiatry*. (2018) 64:597–609. doi: 10.1177/0020764018789200

55. Beedie A, Kennedy P. Quality of social support predicts hopelessness and depression post spinal cord injury. *J Clin Psychol Med Settings*. (2002) 9:227–34. doi: 10.1023/A:1016003428370

56. Hall AG, Karabukayeva A, Rainey C, Kelly RJ, Patterson J, Wade J, et al. Perspectives on life following a traumatic spinal cord injury. *Disability Health J*. (2021) 14:101067. doi: 10.1016/j.dhjo.2021.101067

57. Khuong LQ, Vu T-VT, Huynh V-AN, Thai TT. Psychometric properties of the medical outcomes study: social support survey among methadone maintenance patients in Ho Chi Minh City, Vietnam: a validation study. *Subst Abuse Treatment Prevention Policy*. (2018) 13:1–8. doi: 10.1186/s13011-018-0147-4.

58. McLeod J, Davis CG. Community peer support among individuals living with spinal cord injury. *J Health Psychol*. (2023) 28:943–55. doi: 10.1177/13591053231159483

59. Wollaars MM, Post MW, van Asbeck FW, Brand N. Spinal cord injury pain: the influence of psychologic factors and impact on quality of life. *Clin J Pain*. (2007) 23:383–91. doi: 10.1097/AJP.0b013e31804463e5.

60. Rahnama P, Javidan A, Saberi H, Montazeri A, Tavakkoli S, Pakpour A, et al. Does religious coping and spirituality have a moderating role on depression and anxiety in patients with spinal cord injury? A study from Iran. *Spinal Cord*. (2015) 53:870–4. doi: 10.1038/sc.2015.102.

61. Akturk S, Akturk U. Determining the spiritual well-being of patients with spinal cord injury. *J Spinal Cord Med*. (2020) 43:69–76. doi: 10.1080/10790268.2018.1490875

62. Mohammadi F, Oshvandi K, Bijani M, Borzou SR, Khodaveisi M, Masoumi SZ. Perception of facing lifes challenges in patients with spinal cord injury in Iran: a qualitative study. *BMC Psychol*. (2022) 10:202. doi: 10.1186/s40359-022-00909-2

63. Arejan RH, Azadmanjir Z, Ghodsi Z, Dehghan HR, Sharif-Alhoseini M, Tabary M, et al. How can policymakers be encouraged to support people with spinal cord injury—Scoping review. *Global Spine J*. (2022) 12:732–41. doi: 10.1177/21925682211005406

64. Schultz KR, Mona LR, Cameron RP. Mental health and spinal cord injury: clinical considerations for rehabilitation providers. *Curr Phys Med Rehabil Rep*. (2022) 10:131–9. doi: 10.1007/s40141-022-00349-4

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Effectiveness of short sprint interval training in women with major depressive disorder: a proof-of-concept study

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Background: High-intensity intermittent training has emerged as an option for treating major depressive disorder (MDD). However, short sprint training (sSIT), an efficient HIIT modality, has not been tested yet for this purpose. The sSIT has been proven to induce the same metabolic adaptations, with the advantage of promoting lower muscle fatigue than other HIIT protocols.

Methods: Seventeen adult women diagnosed with moderate/severe MDD were randomly allocated into a sSIT group (n=9) or a control condition (n=8). The sSIT group completed, over two weeks, six 6-10-min sessions which consisted of 3-12 "all out" sprints of 5 s interspersed with low-intensity recovery of 30-45 s. The week before and after the intervention, both groups were evaluated with the Hamilton Depression Rating Scale of 21-itens (HAM-D21), and for physical fitness and incidental physical activity.

Results: The sSIT group exhibited significant improvements for HAM-D21 scores (24.6$\pm$8.2 vs. 16.8$\pm$10.1), maximum aerobic power (140$\pm$15 vs. 155$\pm$15 W), countermovement jump (13.0$\pm$3.4 vs. 14.9$\pm$3.1 cm), % of body fatness (32.4 $\pm$4.4 vs. 29.3$\pm$3.8%), and 4-days number of steps (13,626$\pm$11,309 vs. 16,643 $\pm$15,371) after the training period when compared to the control group.

Conclusion: Less than 1 hour of a sSIT protocol over two weeks have demonstrated to reduce depressive symptoms, while improving aerobic fitness and body composition, and increasing incidental physical activity in a sample of women diagnosed with MDD.

KEYWORDS

major depressive disorder, high-intensity interval training, physical activity, physical fitness, sprint interval training

1 Introduction

Depression, the leading cause of disability worldwide is at its maximum values of prevalence after the COVID pandemic, with women typically presenting 3-fold incidence than men (1). Currently, pharmacological interventions and psychotherapy are the first line therapeutic approaches for people with depression (2). However, besides their limited effectiveness (3), other well-known barriers for these dominant therapies in clinical practice are their financial costs, the low adherence (4) and side-effects (5). Meanwhile, an emerging body of evidence is supporting the effectiveness of physical exercise, a low-cost therapy without relevant side-effects which improve the quality of life of patients (6, 7). However, adherence to physical exercise for these patients can be also low (8). Therefore, finding physical exercise interventions that facilitate adherence for these patients is mandatory.

A recent review with meta-analysis and meta-regression (6) has suggested that the magnitude of the effects of physical exercise is not inferior to first-line treatments with moderate-to-high effect sizes on depressive symptoms after analyzing a pool of 41 RCTs. However, while the current evidence supports the effectiveness of either aerobic or resistance training (6), there are limited evidence about the most effective training protocols for patients with depression. In another recent review (9), it has been suggested that high-intensity intermittent training (HIIT) is an appealing physical exercise modality as it presents rapid effects on depressive symptoms but with a reduced training dose thus emerging as an efficient physical exercise treatment for these patients. Among the different HIIT protocols, short Sprint Interval Training (sSIT) may be a more suitable option than other HIIT and SIT protocols for the treatment of depression as it has been demonstrated to induce the same aerobic and anaerobic adaptations (10) but with a lower muscle fatigue (11) thus leading to a more positive affective response (12) because of the very short efforts (≤10 s) and session duration (~10 min). Further, the aerobic and anaerobic adaptations of these protocols can be evident after only 6 sessions in two weeks (13). These loading characteristics would favor the adherence of these patients who are typically sedentary (14). However, to the best of our knowledge, while some studies have confirmed the effectiveness of other SIT protocols with sprinting bouts of longer durations (30 s) in patients with depression (15, 16), no study have verified the effects of a sSIT protocol in this population.

Therefore, the aim of the current study was to verify the effects of a sSIT protocol on depressive symptoms, physical fitness components and incidental physical activity (PA) in a group of adult women diagnosed with Major Depressive Depression (MDD). Based on the current evidence with healthy adults, our hypothesis was that the physical exercise group would present lower depressive symptoms and improved physical fitness components after the short physical exercise intervention.

2 Methods

2.1 Participants

Sixty-four women volunteered for participation on this study after seeing advertisements in different media (Instagram, local TV,

etc.). Inclusion criteria were being an adult woman with diagnosis of moderate and severe major unipolar depressive disorder (MDD) following the DSM-5 and ICD-10 (F33.1 and F33.2). Exclusion criteria were being pregnant or with symptoms of menopause; be regularly exercising; having a BMI ≥ 35.0 kg/m^2; presenting a disease or condition that do not allowed participation in the exhaustive test and the physical exercise program or that interfered with the collected variables (e.g. use of a pacemaker; severe stenosis; severe heart failure, etc.); leaving the study at any stage, and not completing the required questionnaires. The patients maintained the use of their medication for the treatment of depression which included a variety of antidepressants and anxiolytics (i.e. Fluoxetine, Bupropion, Sertraline, Desvenlafaxine, Paroxetine, Clonazepam, Alprazolam, Diazepam, and Zolpidem). The Physical Activity Readiness Questionnaire (PAR-Q) was used to identify potential risks and contraindications to perform maximal incremental testing and participate in high-intensity physical exercise (17). Finally, participants were asked about comorbidities and the medication used. After inclusion, they were allocated by simple randomization (i.e. flipping a coin) into an physical exercise or a control group. Seventeen patients concluded the follow-up and were finally included in the control [n=8 (1 month-25 years of treatment)] and the experimental [n=9 (1 month-15 years of treatment)] groups (see Figure 1). This study protocol was approved by the Ethics Committee of the Federal University of Mato Grosso do Sul (36637420.5.0000.0021).

2.2 Study design

The completion of this randomized controlled trial included a 4-week period, with two weeks for clinical and physical evaluations (pre- and post-intervention) and two weeks for application of the experimental protocol (see Figure 2). During the application of the experimental protocol, the experimental and control groups were oriented to maintain their habitual lifestyle, including their nutritional habits. During week 1, there were three different evaluation sessions, with an interval of 24-48 hours between them. In the first sessions, questionnaires and interviews were applied by a psychiatrist for inclusion in the study and diagnosis of depressive symptoms. In the second session, participants were familiarized with all the physical fitness tests and were evaluated for body composition. In the third session, they completed all the physical tests. During the second and third weeks, the experimental protocol was applied. Finally, during the fourth week, the evaluations of the first week were repeated. The evaluators were blinded during the participants' evaluations in the first week, however this was not possible during the fourth week for the physical evaluations only.

2.3 Assessments and outcomes

2.3.1 Mental health

A psychiatrist applied the Portuguese version of the International Neuropsychiatric Interview - MINI, for the diagnosis of depression (18). The MINI is a short, structured diagnostic interview developed of
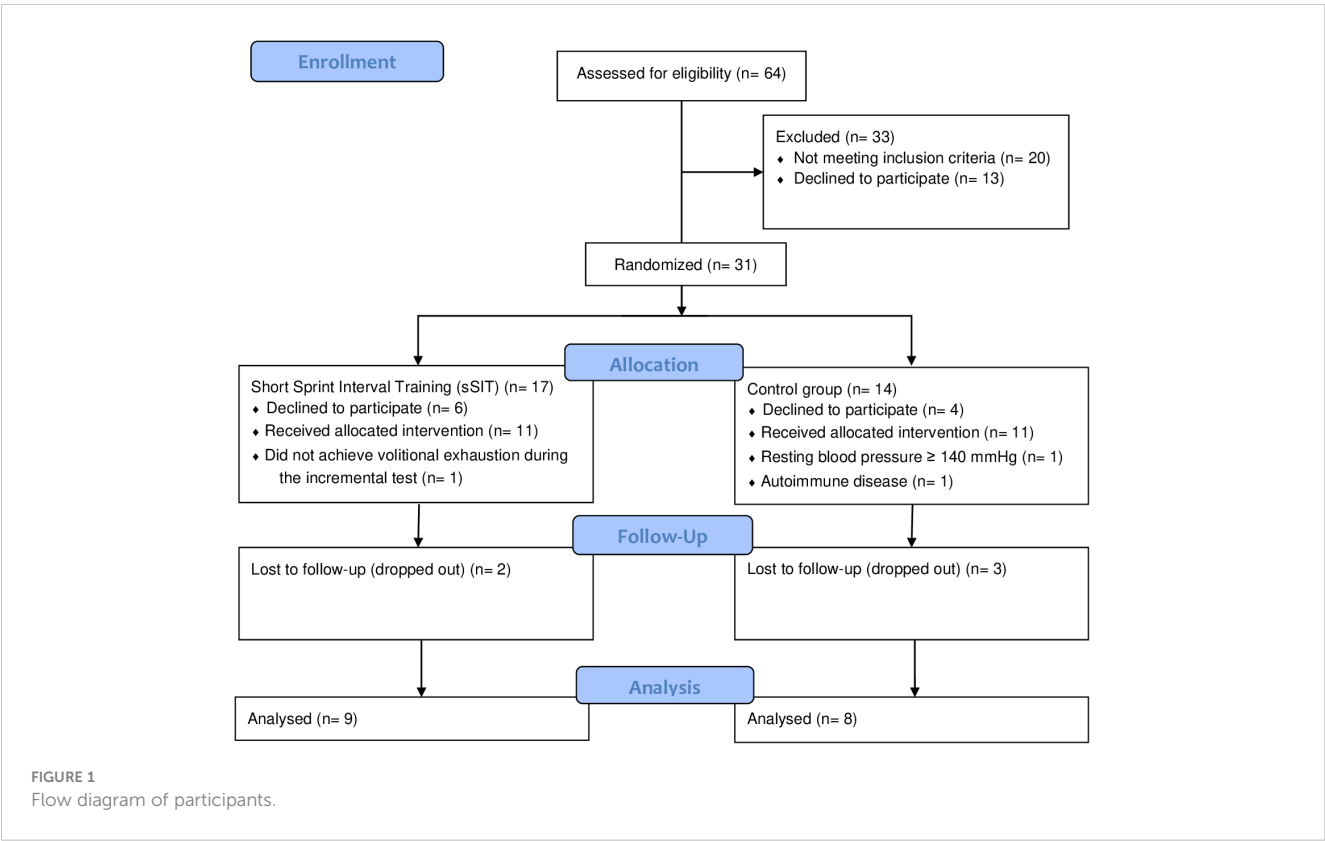
FIGURE 1
Flow diagram of participants.

choice for psychiatric evaluation and outcome tracking in clinical psychopharmacology trials and epidemiological studies. Permission for its use was formally granted.

The Portuguese version of the 21-item Hamilton Depression Scale (HAM-D21) was the main outcome for depressive symptom assessment (19). The HAM-D21 is a valid and reliable instrument and the most widely used clinician-administered depression assessment scale (20). The scale contains 21 items pertaining to symptoms of depression experienced over the past week to be applied as a structured interview. The cut-off points are: 0-3 normal; 4-7 borderline; 8-15 mild depression; 16-26 moderate depression; ≥27 points: severe depression (20).

2.3.2 Body composition

An anthropometric calibrated scale (LIDER 1050, Brazil) with a precision of 100g and 1cm was used to measure body mass and height. Subsequently, body mass index (BMI) was calculated (kg/m^2). Waist circumference (WC), abdominal circumference (AC) and hip circumference (HC) were measured with an anthropometric tape (Holtain Ltd., United Kingdom). A calibrated skinfold caliper (Holtain Ltd., United Kingdom) was used for measuring seven skinfolds (pectoral, middle axillary, subscapular, triceps, abdominal, suprailiac and thigh) following the guidelines of the American College of Sports Medicine (21). The % of body fat was subsequently calculated following previously

FIGURE 2
Study design. MINI: International Neuropsychiatric Interview; HAM-D21: 21-item Hamilton Depression Scale; PAR-Q: Physical Activity Readiness Questionnaire; IPAQ: International Physical Activity Questionnaire; PA: Physical activity; sSIT: short sprint interval training group.

described formulae (22). All these measures were recorded by the same experienced anthropometrist.

2.3.3 Aerobic fitness

The incremental test was performed on a cycle ergometer (INBRAMED – CG4, Brazil) connected to a computer with a custom software. The warm-up started with a load of 0 W for one min, and then the patients pedaled with 20 W of load for two min. After warming up, the patients completed the jump and handgrip evaluations. Subsequently, the incremental test started with 20 W with a progressive increase of 15 W every 2 min, maintaining a fixed cadence of ~60 rpm. During the test, heart rate, systolic and diastolic blood pressures, and rating of perceived exertion (BORG, 1982) were continuously monitored. All the patients were verbally encouraged to physical exercise until voluntary exhaustion (i.e. incapacity to maintain the cadence of ~60 rpm) which was validated with attainment of a maximum heart rate ≥90% of the estimated with a previously validated formula (23). Total time (s) and the maximum aerobic power (W) were recorded for further comparisons.

2.3.4 Countermovement jump

The jump evaluation, a surrogate of lower limbs power, was carried out with the countermovement jump test (CMJ) using the "My Jump2" App (Apple iPhone 12 PRO MAX, USA) which has been validated with the flight time method (24). The patient was asked to jump with maximum effort with the hands placed on their hips. The countermovement depth was freely chosen by the patients (25). The landing was performed with the tiptoes at the same place of take-off. Two jumps were collected with a rest interval ≥15 s and the highest jump was included for analyses (25).

2.3.5 Handgrip strength

Handgrip strength (HGS) was recorded with a calibrated dynamometer (Saehan®, Smedley-Type, Korea). The patient was asked to remain in an orthostatic position and to remain immobile throughout the test, without flexing the elbow and shoulder, and without performing shoulder girdle compensation (26). A verbal command was given to the patient who flexed only the finger joints, squeezing the instrument as hard as possible for ~3 s. Three consecutive measurements were collected with a one-minute interval in-between, and the mean value of the three attempts was used for subsequent analyses.

2.3.6 Incidental physical activity

The patients were required to fulfill the short version of the International Physical Activity Questionnaire (IPAQ) to confirm that they were physically inactive. To measure the level of incidental physical activity, a validated pedometer (Digi-Walker® - 700, Yamax, Japan) was used. This pedometer records vertical hip accelerations during gait cycles. The patients were instructed to use the pedometer 3 days a week and one day during the weekend. The placement of the pedometer was standardized by placing it on the waist (27, 28). They were also instructed to remove the pedometer while bathing and sleeping. During the days of recordings, the patients were asked by WhatsApp

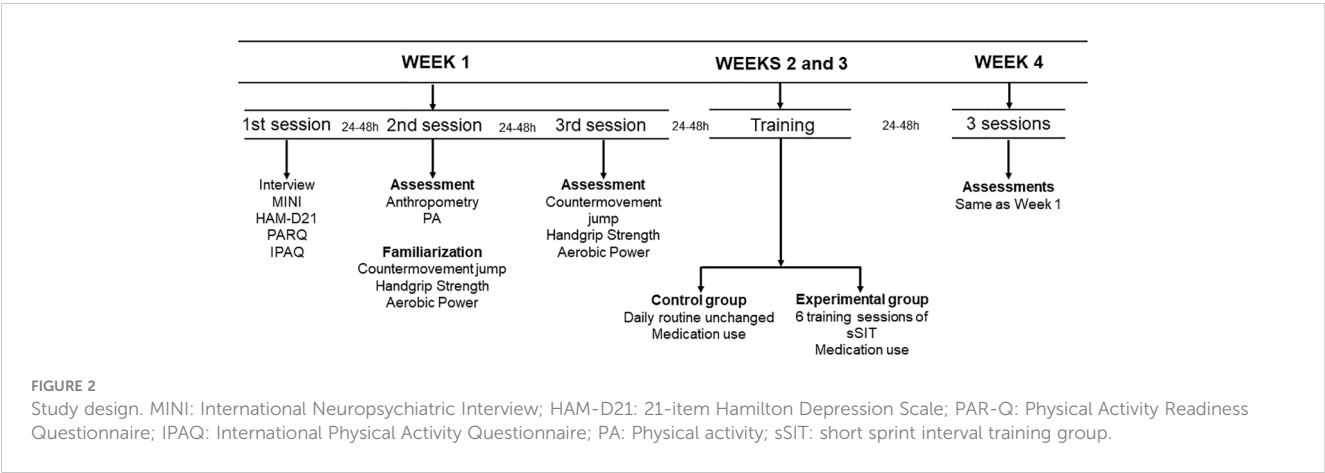to not forget these procedures. The total number of steps over the 4 days were included for comparisons between pre- and post-interventions.

2.4 Short sprint interval training

The training protocol was completed in the same cycle ergometer of the incremental testing (INBRAMED – CG4, Brazil) and lasted 6-10 min depending on the number of sprints. The warm-up consisted of a 2-min warm-up with 50W of load, at a cadence of ~60 rpm. During each sprint, the patients were instructed to pedal with the maximum possible cadence for 5 s, with strong verbal encouragement by the evaluator. The load imposed during the sprints was the maximum aerobic power (W) achieved during the maximum incremental test. The recovery between sprints lasted 30-45 s and was active with a load of 50W and a cadence of ~60 rpm. At the end of the last sprint, the patients were instructed to spend 2 minutes in active recovery with a load of 50 W.

The participants performed the sSIT three times a week with a rest of 24 to 48 h between sessions. The training periodization was linear (i.e., the number of sprints were progressively increased with a reduction in the last training session) but individualized as the patients were allowed to select the number of sprints in each session (see Figure 3). This protocol was adapted for clinical populations following the original protocol with physically active, young healthy individuals (13). It is expected that only 6 sessions, over two weeks, of this sSIT protocol can induce stable physical (i.e. aerobic and anaerobic performances) and physiological (e.g. VO_2max, redox status) adaptations (10).

2.5 Statistical analyses

Numerical variables were presented as mean and standard deviation (SD), or median and interval between 25th and 75th

WARM UP	2 min 60 rpm 50 W	
TRAINING PROTOCOL 5-s "all-out" sprints	**SESSION**	**SPRINTS NUMBER**
	1	3-4
	2	4-6
	3	6-8
	4	8-10
	5	10-12
	6	6-8
Recovery between sprints: ≥30 s pedaling at 60 rpm and 50 W		
COOL DOWN	2 min 60 rpm 50 W	

FIGURE 3
Training protocol with workload characteristics and number of sprints per session. Rpm: revolutions per minute; W: Watts.

percentiles, accompanied by 95% confidence intervals (CI 95%). Data normality assumptions were confirmed using the Shapiro-Wilk test (p>0.05). Percentage changes Δ (%) obtained between baseline and post-intervention values were compared using a Student t-test, and a Mann-Whitney test for parametric and non-parametric distributions, respectively. A Two-Way repeated measures (RM) of ANOVA was carried out to evaluate the effects of treatment (sSIT *vs.* control) and moment (week 1 *vs.* week 4). The Bonferroni *post hoc* test was used to make comparisons intra and intergroups. Partial eta squared (η_p^2) was calculated to determine the effect size (ES). Small, medium, and large effects correspond to η_p^2 values of 0.01, 0.06, and 0.14, respectively. All statistical analyses were performed using Sigma Stat for Windows (Version 3.5), and Jamovi® (Version 2.3, available at https://www.jamovi.org). Significance was set at 5% (P < 0.05).

3 Results

There were no statistically significant differences between groups (Control vs. sSIT) for age (47.0 ± 10.3 vs. 37.1 ± 12.1 yrs; p=0.091), height (161.6 ± 4.2 vs. 163.4 ± 4.8 cm; p=0.422), and body mass (81.0 ± 6.4 vs. 75.7 ± 13.2 kg; p=0.321) before the intervention. The HAM-D21 scores showed a statistically significant reduction in the sSIT group (Pre=24.67 ± 8.29, Post=16.89 ± 10.12; Δ% = -34.30 ± 32.26%) but not in the control group (Pre = 22.50 ± 6.97, Post = 24.00 ± 8.30; Δ% = 5.46 ± 24.66) (see Figure 4). There was a significant difference for factor time (F=6.562; p=0.022) and a group × time interaction (F=14.332; p=0.002). Effect sizes for these factors were 0.304 and 0.489, respectively, being classified as large. Pairwise comparisons with the Bonferroni correction revealed that there were pre- to post-changes in the sSIT group (p<0.001) only.

Body composition results are presented in Table 1. The sSIT intervention resulted in a lower % of body fatness after the intervention (p<0.05).

Physical fitness and PA measures are presented in Table 2. The sSIT intervention resulted in an increased aerobic fitness (i.e. Maximum aerobic power and total time) and incidental PA levels after the intervention (p<0.05). Of note, the CMJ showed a statistically significant change after the sSIT intervention (p<0.05).

4 Discussion

This is the first study exhibiting the positive effects of a sSIT program on symptoms of depression, physical fitness and PA in patients diagnosed with MDD. This study extends the previous evidence demonstrating the improvements in depressive symptoms after other HIIT protocols in people with mental illness (9). However, the current protocol has the advantage of being shorter than other HIIT protocols with only six 6-10-min sessions totalizing less than 1 hour of physical exercise over two weeks. Therefore, the results of the current study are very promising for the treatment of people with depression due to their effects on mental and physical health outcomes combined with a low time demand. This is important as one of the barriers to engaging in an physical exercise program is the lack of time.

Previous studies with other HIIT protocols have demonstrated a similar effectiveness to improve both depressive symptoms and aerobic fitness (9). The current evidence suggests that the neurobiological mechanisms relating depression and physical fitness are meditated by the adaptations of the aerobic metabolism as there is often a weak-to-moderate correlation between maximum oxygen consumption (VO_2max) and depressive symptoms across different studies (29, 30). Unfortunately, we were unable to evaluate VO_2max at follow up because of technical issues with the metabolic cart, and therefore cannot explore further whether changes on VO_2max are associated with changes on depressive symptoms. However, both maximum aerobic power (W) and total time (s) in the incremental test are well-recognized markers of aerobic fitness which are highly correlated to VO_2max. Furthermore,
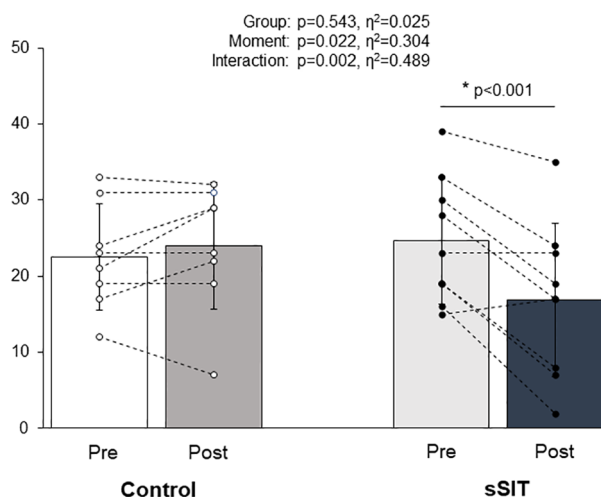

FIGURE 4
Changes in depression scores (HAM-D21) before (white bars) and after (black bars) the intervention period in the control and experimental groups. HAM-D21: 21-item Hamilton Depression Scale; sSIT: short sprint interval training group; *= p<0.05.

TABLE 1 Body composition parameters before and after the treatment in both groups.

Variable	Moment	Group				Factors		
		Control		sSIT		Group	Moment	Interaction
		Mean±SD	CI 95%	Mean±SD	CI 95%			
Body mass (kg)	Baseline	81.0 ± 6.4	68.4 – 93.6	75.7 ± 13.2	49.8 – 101.7	p=0.295 η_p^2=0.073	p=0.284 η_p^2=0.076	p=0.534 η_p^2=0.026
	Final	81.8 ± 7.0	67.9 – 95.6	75.9 ± 12.9	50.7 – 101.2			
	Δ (%)	0.89 ± 2.37	-3.8 – 5.5	0.38 ± 2.22	-4.0 – 4.7	p=0.649		
BMI (kg/m²)	Baseline	31.0 ± 1.4	28.2 – 33.8	28.3 ± 4.5	19.5 – 37.0	p=0.106 η_p^2=0.165	p=0.294 η_p^2=0.073	p=0.572 η_p^2=0.022
	Final	31.2 ± 1.4	28.6 – 33.9	28.4 ± 4.4	19.8 – 36.9			
	Δ (%)	0.89 ± 2.37	-3.7 – 5.5	0.38 ± 2.22	-4.1 – 4.8	p=0.651		
WC (cm)	Baseline	87.3 ± 5.6	76.3 – 98.2	81.3 ± 10.1	61.5 – 101.2	p=0.088 η_p^2=0.181	p=0.463 η_p^2=0.037	p=0.109 η_p^2=0.162
	Final	88.7 ± 4.6	79.6 – 97.7	80.8 ± 9.2	62.7 – 98.8			
	**Δ (%)	2.34 ± 2.18	-3.5 – 7.0	0.00 ± 2.62	-6.4 – 5.4	p=0.228		
AC (cm)	Baseline	94.1 ± 6.6	81.2 – 107.0	89.6 ± 11.7	66.7 – 112.5	p=0.175 η_p^2=0.119	p=0.464 η_p^2=0.036	p=0.104 η_p^2=0.167
	Final	96.4 ± 6.0	84.7 – 108.1	88.7 ± 10.1	68.8 – 108.6			
	Δ (%)	2.50 ± 3.87	-5.1 – 10.1	-0.73 ± 4.49	-9.5 – 8.1	p=0.136		
HC (cm)	Baseline	108.3 ± 6.8	95.0 – 121.5	104.2 ± 8.5	87.6 – 120.8	p=0.183 η_p^2=0.115	p=0.164 η_p^2=0.125	p=0.048 η_p^2=0.236
	Final	110.0 ± 6.7 *	96.8 – 123.2	103.9 ± 7.8	88.6 – 119.2			
	Δ (%)	1.63 ± 1.48	-1.3 – 4.5	-0.25 ± 2.17	-4.5 – 4.0	p=0.057		
Body fatness (%)	Baseline	34.7 ± 1.8	31.2 – 38.1	32.4 ± 4.5	23.7 – 41.2	p=0.025 η_p^2=0.293	p=0.068 η_p^2=0.205	p<0.001 η_p^2=0.558
	Final	35.6 ± 1.9	31.9 – 39.4	29.9 ± 4.1 *#	21.9 – 38.0			
	Δ (%)	2.80 ± 5.52	-8.0 – 13.6	-7.52 ± 3.87 #	-15.1 – 0.1	p<0.001		

Values are expressed as mean ± SD, and 95% confidence intervals (CI 95%). BMI, body mass index; WC, waist circumference; AC, abdominal circumference; HC, hip circumference; sSIT, short sprint interval training. Two-Way repeated measures of ANOVA and Bonferroni's test; * p<0.05 vs. Baseline (effect of moment within group); # p<0.05 vs. Control group (effect of group within moment); η_p^2, partial eta square. Δ (%) values obtained from the difference between baseline and post-intervention, and compared with Student t test; # p<0.05 vs. Control group. **Δ (%) WC values are expressed as median ± interval between 25th and 75th percentiles and analyzed with a Mann-Whitney test.

maximum aerobic power always presents a greater reliability than VO_2max itself because of the typically high technical error associated to metabolic measurements (31). Accordingly, the improvements in these working capacity parameters exhibited by our participants may be equivalent to ~1 MET following previous estimates (32). While we did not evaluate any metabolic parameter, the improvements in aerobic power experienced by our participants would be more related to peripheral adaptations associated to VO_2max than central adaptations which are more likely to occur with other HIIT protocols with longer physical exercise bouts (33). Therefore, further studies should explore the associations among metabolic and cardiovascular adaptations after HIIT and SIT protocols with changes of symptoms of depression. Meanwhile, clinicians and other health professionals should be aware of the possibility of evaluating aerobic fitness after physical exercise treatments with working capacity measures during direct and indirect protocols without the need for recording actual VO_2max values.

One alternative mechanism behind the antidepressive effects of the SIT protocols may be related to lactate. Recently, it has been suggested that lactate, a metabolite derived from glycolysis during anerobic efforts, can promote antidepressive-like effects and enhance resilience to stress via different signaling mechanisms after its administration in animal models (34, 35). While our sSIT

protocol has been designed to limit the glycolytic activation during sprinting bouts therefore reducing the associated metabolic fatigue and thus increasing the affective responses (10), it was expected that lactate levels were slightly elevated thus maybe promoting the positive effects observed in animal models. Future studies may test this hypothesis in humans while examining the increase of other hormonal mediators as Brain-Derived Neurotrophic Factor (BDNF) after SIT protocols differing in lactate levels (36, 37) and muscle contraction regimens (e.g. eccentric vs. concentric) (38).

Interestingly, the participants from the sSIT group slightly reduced their body fatness while importantly incrementing their incidental PA levels as recorded with their 4-days pedometer recordings. These results of a reduced adiposity after short-term HIIT interventions are not novel since a previous study (39) found a small reduction in body fatness after a Wingate-based SIT protocol of 30-s sprints of only 6 training sessions in a sample of young healthy adults. In addition, another recent study in patients with MDD (16) reported an increased, self-reported PA after a 4-week Wingate-based SIT intervention of 3 training sessions per week. Therefore, while these changes may be expected after SIT interventions, our protocol was more effective since the patients underwent less than 1 hour of physical exercise over two weeks. In

TABLE 2 Physical fitness and physical activity parameters before and after the treatment in both groups.

Variable	Moment	Group				Factors		
		Control		sSIT		Group	Moment	Interaction
		Mean±SD	CI 95%	Mean±SD	CI 95%			
CMJ (cm)	Baseline	10.2 ± 3.0	4.3 – 16.2	13.0 ± 3.4	6.3 – 19.6	p=0.036 η_p^2=0.260	p=0.003 η_p^2=0.446	p=0.075 η_p^2=0.196
	Final	10.8 ± 3.1	4.8 – 16.8	14.9 ± 3.1 *#	8.9 – 21.0			
	Δ (%)	6.35 ± 12.14	-17.4 – 30.1	17.64 ± 16.03	-13.8 – 49.1	p=0.126		
HGS (kgf)	Baseline	27.0 ± 3.4	20.3 – 33.7	26.5 ± 4.5	17.0 – 35.4	p=0.828 η_p^2=0.003	p=0.813 η_p^2=0.004	p=0.093 η_p^2=0.176
	Final	25.9 ± 4.0	18.0 – 33.8	27.4 ± 6.0	15.6 – 39.1			
	Δ (%)	-3.91 ± 9.27	-22.1 – 14.3	2.32 ± 7.97	-13.3 – 17.9	p=0.157		
AP (W)	Baseline	119 ± 16	88 – 151	141 ± 19 #	103 – 179	p=0.003 η_p^2=0.447	p=0.055 η_p^2=0.224	p=0.016 η_p^2=0.327
	Final	118 ± 16	86 – 149	155 ± 21 *#	113 – 197			
	** Δ (%)	0.00 ± 0.00	-9.82 – 6.82	9.68 ± 17.38 #	-15.21 – 37.17	p=0.015		
Total time (s)	Baseline	514 ± 51	415 – 612	569 ± 75	422 – 716	p=0.008 η_p^2=0.382	p=0.004 η_p^2=0.427	P<0.001 η_p^2=0.526
	Final	505 ± 46	415 – 595	653 ± 101*#	456 – 850			
	Δ (%)	-1.52 ± 3.52	-8.43 – 5.38	14.94 ± 11.42 #	-7.44 – 37.32	p=0.001		
Steps	Baseline	13,343±9,511	-5,299 – 31,984	18,843±8,781	1,632 – 36,053	p=0.038 η_p^2=0.258	p=0.484 η_p^2=0.033	p=0.009 η_p^2=0.371
	Final	10,181±6,905	-3,352 – 23,715	24,017 ±10,882*#	2,687 – 45,346			
	** Δ (%)	-14.1 ± 62.5	-243.7 – 303.6	26.7 ± 61.0	-66.8 – 134.4	p=0.136		

Values are expressed as mean ± SD, and 95% confidence interval (CI 95%). CMJ, countermovement jump; HGS, handgrip strength; AP, aerobic power; sSIT, short sprint interval training. Two-Way repeated measures of ANOVA and Bonferroni's test; * p<0.05 vs. Baseline (effect of moment within group); # p<0.05 vs. Control group (effect of group within moment); η_p^2, partial eta square. Δ (%) values obtained from the difference between basal and post-treatment values, and analyzed with a Student t test; **Δ (%) AP, and Steps values are expressed as median ± interval between 25th and 75th percentiles, and analyzed with a Mann-Whitney test; # p<0.05 vs. Control group.

this regard, it would be speculated that the changes in body composition would be related, not only to the physical exercise protocol, but also to the increase in PA levels following the physical exercise intervention. Previously, it has been suggested that post-exercise energy expenditure is not compromised after sSIT protocols when compared with protocols of longer sprinting bouts, but a reduced fat oxidation was reported (40). Therefore, it may be speculated that the increased PA levels, as a consequence of the improved mood in these patients, may be the main mechanism behind the reduced body fatness. Meanwhile, we cannot ignore the possibility that the patients changed their nutritional habits and energy intake despite being advised to maintain them during all the intervention. Future studies are warranted to better understand these physical adaptations and their related biological mechanisms.

Interestingly, CMJ, a simple and valid test for neuromuscular performance evaluation of the lower limbs' power, exhibited a significant change after the intervention. This is not somewhat surprising as a cross-training effect (41) may be expected as frequently exhibited by athletes training different physical exercise modalities. Further, this cross-training effect would be expected to be more evident in clinical populations with very low physical fitness levels as in the current study because of the strength required during sprinting bouts for the lower-limbs. Thus, it may be suggested that, despite using a non-specific method for strength development, the

anaerobic development after the sprinting bouts (13) may be potentially promoting strength-related adaptations which would likely become larger after a longer training period. This aspect is valid for this, and other clinical settings using diverse physical exercise interventions and should be considered in further studies.

This study is not without limitations. First, we did not control the energy intake of participants therefore future studies are required to explore the relative influence of physical exercise, PA and nutritional intakes in the changes associated with sSIT protocols. Second, we only included unipolar MDD patients therefore other psychiatric patients with symptoms of depression should be included in future studies. Third, we only recorded maximum aerobic power and total time in the incremental test as indices of aerobic fitness, thus future studies should report VO_2max, its specific central and peripheral adaptations, and lactate levels to better understand their link with symptoms of depression. Finally, this study presents a limited sample size and time of intervention. Therefore, future studies with greater sample sizes and longer interventions should confirm these important findings. However, it should be pointed out that most patients decided to regularly practice other forms of physical exercise after our sSIT intervention. Meanwhile, the effect sizes reported, the CIs, and their p-values are indicative of robust adaptations in accordance with previous studies using similar sSIT protocols with healthy young individuals (13, 42).

5 Conclusions

This study is the first to report significant changes in symptoms of depression after a sSIT protocol of only six 6-10-min sessions over two weeks in female patients diagnosed with MDD. These positive adaptations were associated to changes in aerobic fitness, body fatness and incidental PA levels. Future studies with greater sample sizes and follow-up should confirm the high effectiveness and efficiency of this protocol in this and other psychiatric populations dealing with symptoms of depression.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Ethics Committee of the Federal University of Mato Grosso do Sul (36637420.5.0000.0021). 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

JR: Writing – review & editing, Writing – original draft, Investigation, Data curation. FS: Writing – review & editing, Writing – original draft, Validation, Methodology. LT: Writing – review & editing, Writing – original draft, Methodology. KM: Writing – review & editing, Writing – original draft, Validation, Supervision. SO:

Writing – review & editing, Writing – original draft, Formal analysis, Data curation. PM: Writing – review & editing, Writing – original draft, Supervision, Investigation. DB: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

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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References

1. Santomauro DF, Mantilla Herrera AM, Shadid J, Zheng P, Ashbaugh C, Pigott DM, et al. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet*. (2021) 398:1700–12. doi: 10.1016/S0140-6736(21)02143-7

2. Gelenberg AJ, Marlene Freeman CP, Markowitz JC, Rosenbaum JF, Thase ME, Trivedi MH, et al. PRACTICE GUIDELINE FOR THE treatment of patients with major depressive disorder third edition WORK GROUP ON MAJOR DEPRESSIVE DISORDER(2010). Available at: http://www.psychiatryonline.com/pracGuide/ pracGuideTopic_7.aspx.

3. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet*. (2018) 391:1357–66. doi: 10.1016/S0140-6736(17)32802-7

4. Ostrow L, Jessell L, Hurd M, Darrow SM, Cohen D. Discontinuing psychiatric medications: A survey of long-term users. *Psychiatr Serv*. (2017) 68:1232–8. doi: 10.1176/appi.ps.201700070

5. Braund TA, Tillman G, Palmer DM, Gordon E, Rush AJ, Harris AWF. Antidepressant side effects and their impact on treatment outcome in people with

major depressive disorder: an iSPOT-D report. *Transl Psychiatry*. (2021) 11:417. doi: 10.1038/s41398-021-01533-1

6. Heissel A, Heinen D, Brokmeier LL, Skarabis N, Kangas M, Vancampfort D, et al. Exercise as medicine for depressive symptoms? A systematic review and meta-analysis with meta-regression. *Br J Sports Med*. (2023) 57(16):1049–57. doi: 10.1136/bjsports-2022-106282

7. Marx W, Manger SH, Blencowe M, Murray G, Ho FY-Y, Lawn S, et al. Clinical guidelines for the use of lifestyle-based mental health care in major depressive disorder: World Federation of Societies for Biological Psychiatry (WFSBP) and Australasian Society of Lifestyle Medicine (ASLM) taskforce. *World J Biol Psychiatry*. (2022) 24 (5):333–86. doi: 10.1080/15622975.2022.2112074

8. Kruisdijk F, Hopman-Rock M, Beekman ATF, Hendriksen IJM. Personality traits as predictors of exercise treatment adherence in major depressive disorder: lessons from a randomised clinical trial. *Int J Psychiatry Clin Pract*. (2020) 24:380–6. doi: 10.1080/13651501.2020.1787452

9. Ribeiro JA, Schuch FB, Vargas KFM, Müller PT, Boullosa D. A rapid review of randomized trials assessing the effects of high-intensity interval training on depressive symptoms in people with mental illness. *Int J Environ Res Public Health*. (2022) 19 (17):10581. doi: 10.3390/ijerph191710581

10. Boullosa D, Dragutinovic B, Feuerbacher JF, Benítez-Flores S, Coyle EF, Schumann M. Effects of short sprint interval training on aerobic and anaerobic indices: A systematic review and meta-analysis. *Scand J Med Sci Sports*. (2022) 32 (5):810–20. doi: 10.1111/sms.14133

11. Benítez-Flores S, de Sousa AFM, Totó ECDC, Rosa TS, del Rosso S, Foster C, et al. Shorter sprints elicit greater cardiorespiratory and mechanical responses with less fatigue during time-matched sprint interval training (SIT) sessions. *Kinesiology*. (2018) 50(2):137–48. doi: 10.26582/K.50.2.13

12. Metcalfe RS, Williams S, Fernandes GS, Astorino TA, Stork MJ, Phillips SM, et al. Affecting effects on affect: the impact of protocol permutations on affective responses to sprint interval exercise; A systematic review and meta-analysis of pooled individual participant data. *Front Sports Act Living*. (2022) 4:815555. doi: 10.3389/fspor.2022.815555

13. Benítez-Flores S, Medeiros AR, Voltarelli FA, Iglesias-Soler E, Doma K, Simões HG, et al. Combined effects of very short "all out" efforts during sprint and resistance training on physical and physiological adaptations after 2 weeks of training. *Eur J Appl Physiol*. (2019) 119:1337–51. doi: 10.1007/s00421-019-04125-6

14. Schuch F, Vancampfort D, Firth J, Rosenbaum S, Ward P, Reichert T, et al. Physical activity and sedentary behavior in people with major depressive disorder: A systematic review and meta-analysis. *J Affect Disord*. (2017) 210:139–50. doi: 10.1016/j.jad.2016.10.050

15. Minghetti A, Faude O, Hanssen H, Zahner L, Gerber M, Donath L. Sprint interval training (SIT) substantially reduces depressive symptoms in major depressive disorder (MDD): A randomized controlled trial. *Psychiatry Res*. (2018) 265:292–7. doi: 10.1016/j.psychres.2018.04.053

16. Gerber M, Minghetti A, Beck J, Zahner L, Donath L. Sprint interval training and continuous aerobic exercise training have similar effects on exercise motivation and affective responses to exercise in patients with major depressive disorders: A randomized controlled trial. *Front Psychiatry*. (2018) 9:694. doi: 10.3389/fpsyt.2018.00694

17. Luz LG de O, Farinatti P de TV. Questionário de Prontidão para Atividade Física (PAR-Q). *Rev Bras Fisiologia do exercício cio*. (2009) 4:43–8. doi: 10.33233/rbfe.v4i1.3585

18. Amorim P. Mini International Neuropsychiatric Interview (MINI): validação de entrevista breve para diagnóstico de transtornos mentais. *Rev Bras Psiquiatria*. (2000) 22:106–15. doi: 10.1590/S1516-44462000000300003

19. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. (1967) 6:278–96. doi: 10.1111/j.2044-8260.1967.tb00530.x

20. Furukawa TA. Assessment of mood: Guides for clinicians. *J Psychosom Res*. (2010) 68:581–9. doi: 10.1016/j.jpsychores.2009.05.003

21. American College of Sports Medicine. *Guidelines for Exercise Testing and Prescription. 8th ed*. Philadelphia: Lippincott Williams and Williams (2000) p. 66–68 p.

22. Jackson AS, Pollock ML, Ward A. Generalized equations for predicting body density of women. *Med Sci Sports Exerc*. (1980) 12:175–81. doi: 10.1249/00005768-198023000-00009

23. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. *J Am Coll Cardiol*. (2001) 37:153–6. doi: 10.1016/S0735-1097(00)01054-8

24. Balsalobre-Fernández C, Glaister M, Lockey RA. The validity and reliability of an iPhone app for measuring vertical jump performance. *J Sports Sci*. (2015) 33:1574–9. doi: 10.1080/02640414.2014.996184

25. Boullosa DA, Tuimil JL, Alegre LM, Iglesias E, Lusquiños F. Concurrent fatigue and potentiation in endurance athletes. *Int J Sports Physiol Perform*. (2011) 6(1):82–93. doi: 10.1123/ijspp.6.1.82

26. Cronin J, Lawton T, Harris N, Kilding A, McMaster DT. A brief review of handgrip strength and sport performance. *J Strength Cond Res*. (2017) 31:3187–217. doi: 10.1519/JSC.0000000000002149

27. Schneider PL, Crouter SE, Bassett DR. Pedometer measures of free-living physical activity: comparison of 13 models. *Med Sci Sports Exerc*. (2004) 36:331–5. doi: 10.1249/01.MSS.0000113486.60548.E9

28. Crouter SE, Schneider PL, Karabulut M, Bassett DR. Validity of 10 electronic pedometers for measuring steps, distance, and energy cost. *Med Sci Sports Exerc*. (2003) 35:1455–60. doi: 10.1249/01.MSS.0000078932.61440.A2

29. Papasavvas T, Bonow RO, Alhashemi M, Micklewright D. Depression symptom severity and cardiorespiratory fitness in healthy and depressed adults: A systematic review and meta-analysis. *Sports Med*. (2016) 46:219–30. doi: 10.1007/s40279-015-0409-5

30. Tonello L, Oliveira-Silva I, Medeiros AR, Donato ANA, Schuch FB, Donath L, et al. Prediction of depression scores from aerobic fitness, body fatness, physical activity, and vagal indices in non-exercising, female workers. *Front Psychiatry*. (2019) 10:192. doi: 10.3389/fpsyt.2019.00192

31. Billat LV, Koralsztein JP. Significance of the Velocity at &OV0312;O2max and Time to Exhaustion at this Velocity. *Sports Med*. (1996) 22:90–108. doi: 10.2165/00007256-199622020-00004

32. Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol*. (1990) 13:555–65. doi: 10.1002/clc.4960130809

33. Rosenblat MA, Granata C, Thomas SG. Effect of interval training on the factors influencing maximal oxygen consumption: A systematic review and meta-analysis. *Sports Med*. (2022) 52:1329–52. doi: 10.1007/s40279-021-01624-5

34. Carrard A, Elsayed M, Margineanu M, Boury-Jamot B, Fragnière L, Meylan EM, et al. Peripheral administration of lactate produces antidepressant-like effects. *Mol Psychiatry*. (2018) 23:392–9. doi: 10.1038/mp.2016.179

35. Karnib N, El-Ghandour R, El Hayek L, Nasrallah P, Khalifeh M, Barmo N, et al. Lactate is an antidepressant that mediates resilience to stress by modulating the hippocampal levels and activity of histone deacetylases. *Neuropsychopharmacology*. (2019) 44:1152–62. doi: 10.1038/s41386-019-0313-z

36. Reycraft JT, Islam H, Townsend LK, Hayward GC, Hazell TJ. Macpherson REK. Exercise intensity and recovery on circulating brain-derived neurotrophic factor. *Med Sci Sports Exerc*. (2020) 52:1210–7. doi: 10.1249/MSS.0000000000002242

37. Kujach S, Olek RA, Byun K, Suwabe K, Sitek EJ, Ziemann E, et al. Acute sprint interval exercise increases both cognitive functions and peripheral neurotrophic factors in humans: the possible involvement of lactate. *Front Neurosci*. (2020) 13:1455. doi: 10.3389/fnins.2019.01455

38. Boullosa D, Dragutinovic B, Deutsch JP, Held S, Donath L, Bloch W, et al. Acute and delayed effects of time-matched very short "all out" efforts in concentric vs. Eccentric cycling. *Int J Environ Res Public Health*. (2021) 18(15):7968. doi: 10.3390/ijerph18157968

39. de Sousa AFM, Medeiros AR, Benitez-Flores S, Del Rosso S, Stults-Kolehmainen M, Boullosa DA. Improvements in attention and cardiac autonomic modulation after a 2-weeks sprint interval training program: A fidelity approach. *Front Physiol*. (2018) 9:241. doi: 10.3389/fphys.2018.00241

40. Townsend LK, Islam H, Dunn E, Eys M, Robertson-Wilson J, Hazell TJ. Modified sprint interval training protocols. Part II. Psychological responses. *Appl Physiol Nutr Metab*. (2017) 42:347–53. doi: 10.1139/apnm-2016-0479

41. Foster C, Hector LL, Welsh R, Schrager M, Green MA, Snyder AC. Effects of specific versus cross-training on running performance. *Eur J Appl Physiol Occup Physiol*. (1995) 70:367–72. doi: 10.1007/BF00865035

42. McKie GL, Islam H, Townsend LK, Robertson-Wilson J, Eys M, Hazell TJ. Modified sprint interval training protocols: Physiological and psychological responses to 4 weeks of training. *Appl Physiol Nutr Metab*. (2018) 43:595–601. doi: 10.1139/apnm-2017-0595

Check for updates

State legislation and policies to improve perinatal mental health: a policy review and analysis of the state of Illinois

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Introduction: Maternal mental health problems, such as perinatal depression, are a major public health issue. In the U.S., several states have policies related to mental health during pregnancy and postpartum. The extent of these laws at the state level needs to be further explored and described.

Methods: We systematically searched the Illinois General Assembly to determine all existing legislation on the topic of perinatal mental health.

Results: This search uncovered two major Acts that 1) require universal perinatal depression screening and 2) raise awareness of the symptoms and treatment options related to maternal mental health. We also discovered provisions in the law that allow for untreated or undiagnosed postpartum depression or psychosis to be considered as a mitigating factor for women who commit forcible felonies.

Discussion: Through legislation, states can lead change at the systems-level to improve perinatal mental health outcomes.

KEYWORDS

perinatal mental health, depression, screening, public health policy, mitigating factor

1 Introduction

Mental health problems are a serious concern for women who experience a greater burden over the life course, especially during pregnancy and postpartum, the perinatal period. Mental health problems can onset during pregnancy and up to one year postpartum and are often defined as "perinatal mental illness" or "perinatal mood disorders" (1). Some perinatal mental health problems include perinatal depression, generalized anxiety, obsessive-compulsive disorders, panic, social anxiety disorder, and psychosis (2). Depression is common among perinatal women with an estimated one in eight affected by postpartum depression after childbirth (3). Along with perinatal depression, perinatal

anxiety disorders are also common among women (2). While not nearly as common, post-partum psychosis is a serious mental illness that affects 1-2 in every 1000 women and occurs rapidly after birth (2). Postpartum psychosis is categorized by symptoms such as hallucinations, mood fluctuation, confusion, delirium, and insomnia (2). Perinatal mental illness can be treated if identified early. If untreated, perinatal mental illness can have adverse effects on perinatal women, newborn infants, and their family members.

Perhaps the most serious result of perinatal mental health problems is the incidence of suicide and filicide among women with postpartum psychosis. Suicide is a leading cause of death among mothers up to one year of delivery. Women who experience postpartum psychosis use more violent means of committing suicide, which significantly differs from the common trend of women committing suicide nonviolently (4). The incidence of filicide after delivery is often, but not always, linked to maternal suicide (5). Neonaticide is a type of filicide in which the mother kills her baby within the first few days of life and infanticide is the killing of a baby within the first year of life (6). The rate of infant homicide was the highest in the United States, occurring in 8 out of 100,000 children (5, 7). Between the years 1976 to 2005, 38.2% of all homicides were children under the age of five that were killed by their mothers (7). While the rate of infanticide has decreased in recent years, infants are 5 times more likely to die by homicide when compared to any other point of the life course (CDC 2020). Accordingly, mental health problems of the mother can potentially present an imminent risk for the offspring.

Universal health screening is a public health approach to detecting mental health disorders for common mental health conditions such as depression or anxiety. Despite its importance, very few states mandate screening for depression or anxiety during pregnancy or the postpartum period. To date, only five states, New Jersey, West Virginia, Massachusetts, California, and Illinois have requirements or mandates for screening for maternal mental health conditions (8, 9). However, of these states, Illinois is the only state with language that involves other state agencies and references the American College of Obstetricians and Gynecology screening procedures as a guide (10). New Jersey and Illinois have the longest standing depression screening mandates and Illinois has continued to develop new policy approaches to improve perinatal mental health. Screening is essential at different points in the perinatal period as it provides insight into developing postpartum depression and/or other pregnancy complications. For many years, the focus of perinatal mental health problems was limited to the postpartum period, but recent trends to screen early and often now capture the antenatal period. People experiencing Antenatal Depression have frequently reported other stressors including conflict with family/partner, risk for miscarriage, and financial difficulties while pregnant (11). Additionally, a recent study found that the presence of maternal blues, which can present between 1 to 10 weeks postpartum, has a significant relationship to higher depressive symptomology scores and the development of depression and/or anxiety disorder (12, 13). Since antenatal mental health problems are often overlooked and represent such a great opportunity for interventions, we want to identify state specific policy levers to improve perinatal mental health. To date,

past policy reviews have examined perinatal depression policies broadly across states and have not looked closely at the laws within a particular state that address perinatal mental health (8). Therefore, this policy review conducts an in-depth analysis of Illinois, one of the states that mandates depression screening, to examine its perinatal mental health policies. In this review, we will identify relevant Illinois policies related to the treatment, detection, and handling of perinatal mental health disorders.

2 Methods

This policy review study utilizes a qualitative approach to the content analysis used by several qualitative legislative reviews (14). An *a priori* conceptual framework was used to guide the development of the legislative search criteria, the codebook of terms searched, and the analysis of legislation included in the policy review. A priori framework focused on the analysis of policies or programs that had already been passed and were implemented or being implemented. For the systematic search, we used the Illinois General Assembly website (www.ilga.gov), a database that contains a variety of material pertaining to Illinois law. It includes pending bills that have not yet been approved and passed by the legislature, recently enacted public acts (which have passed the legislature and have been signed by the Governor), and most important to this review, the Illinois Compiled Statutes. The Illinois Compiled Statutes is the grouping of all Illinois legislation into an organizational system by general subject and by topics within those subjects. The Legislative Reference Bureau of Illinois organizes all Illinois law into 9 major topic areas which are then divided into 67 separate chapters. Each of the approximately 2000 general Acts of Illinois are placed within one of the chapters in the Illinois Compiled Statutes (15). No Act appears in more than one chapter.

2.1 Identifying relevant legislation

We searched the Illinois Compiled Statutes with the goal of identifying all existing Illinois legislation related to perinatal mental health through the end of the 2022 legislative term. Based upon our framework we included the following 12 keywords as search terms: pregnancy, postpartum, antenatal, antepartum, perinatal, postnatal, prenatal, post-partum, puerperium, pregnant, neonatal, and natal. These terms were chosen because they are commonly used to reference the perinatal period. For each search term, we systematically entered the term into the Illinois Compiled Statutes keyword search. We did this separately for each of the 12 terms. When one of the 12 keywords appeared in the keyword search, the chapter in which it was placed, and the section number of the legislation were recorded.

2.2 Legislation selection

As of October 2023, the 12 search terms yielded 478 separate, initial results (see Figure 1). Of these 478 initial results, each was

FIGURE 1
Flow Diagram of Policy Selection and Inclusion in Content Analysis.
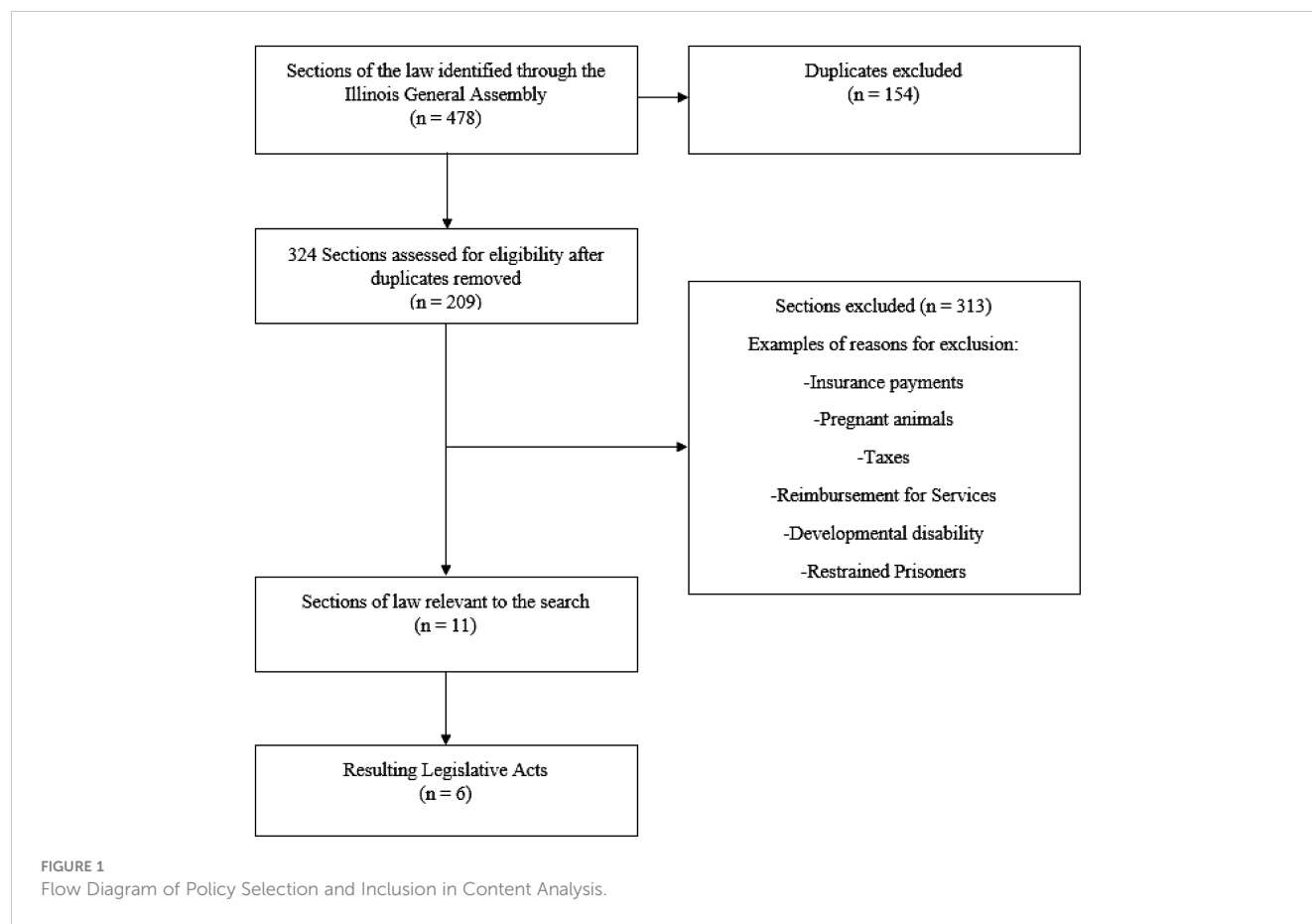
read to determine how the search terms were used. 154 results were deemed as duplicates and were removed. A duplicate occurred when more than one keyword appeared in the same section of legislation. For example, within Chapter 325 on early intervention services, the search terms "prenatal," "perinatal," and "neonatal" all appeared within the definition of "physical or mental condition which typically results in developmental delay." One of these results would be kept and the other two would be considered duplicate results and discarded. After the removal of the duplicates, 324 subsequent results were left. The remaining 324 results were examined to determine the subject matter of the legislation. Because the search terms were entered into the database simply as words without any context, the keyword search uncovered that the search terms were used in a variety of topics. Most of these topics were unrelated to the provision of perinatal mental health services. So, for example, the aforementioned result regarding early intervention services would then be removed because the content had no relationship to perinatal mental health. Instead, the result was simply part of the definition of the types of conditions eligible for early intervention services. As another example, the word "pregnant" led to sections on umbilical cord donation after pregnancy, foster care placement of children who were pregnant, graduation incentives for pregnant students, or even prohibitions on restraining pregnant prisoners. In these instances, the term "pregnant" was unrelated to perinatal

mental health and was eliminated. As a further example, the word "neonatal" led to provisions in the law regarding taxes for neonatal health services, costs of neonatal home therapy equipment, and data reporting on hospital discharges for neonatal infants. Since none of these cases were related to perinatal mental health, they, too, were eliminated. Therefore, after reading the legislation to ascertain the context for which the search terms appeared in the law, all instances where the search terms were unrelated to perinatal mental health screening and/or pregnant humans were excluded. For the purpose of this policy review, full-text versions of the laws were retrieved.

TABLE 1 Resulting Legislative Acts Related to Perinatal Mental Health Policy in Illinois in 2023.

Civil Administrative Code of Illinois, (2023). Department of Public Health Powers and Duties Law, 20 Illinois Compiled Statutes 2310/2310-223.
Code of Civil Procedure, (2023). 735 Illinois Compiled Statutes 5/2-1401(b-10).
Illinois Public Aid Code, (2023). 305 Illinois Compiled Statutes, 5/5-5.
Maternal Mental Health Conditions Education, Early Diagnosis, and Treatment Act, (MMHCEEDTA, 2023). 405 Illinois Compiled Statutes 120.
Perinatal Mental Health Disorders Prevention and Treatment Act, (PMHDPTA, 2023). 405 Illinois Compiled Statutes 95.
Unified Code of Corrections, (2023). Factors in Mitigation, 730 Illinois Compiled Statutes 5-5-3.1(17).

3 Results

The final sample consisted of 11 sections of legislation across six distinct Acts (Table 1). The majority of the results were located in two seminal Acts, the Perinatal Mental Health Disorders Prevention and Treatment Act (PMHDPTA) and the Maternal Mental Health Conditions Education, Early Diagnosis and Treatment Act, (MMHCEEDTA). Both Acts comprehensively deal with the prevention, treatment, education, and diagnosis of perinatal mental health conditions.

A smaller subset of results relevant to maternal mental health were also identified in discrete sections of other laws. One result was found in the Unified Code of Corrections, one result was found in the Code of Civil Procedure, one result was found in the powers and duties of the Department of Public Health, and one last result was found in the Illinois Public Aid Code. These results are presented as follows:

The Perinatal Mental Health Disorders Prevention and Treatment Act (PMHDPTA, 2023) was enacted in 2008 and amended in 2015 and 2018. The PMHDPTA contains 4 sections, which include the short title of the law, legislative findings regarding perinatal mental health disorders, definitions of terms, and requirements for perinatal mental health disorders prevention and treatment. In Section 5 of the Act, the Illinois General Assembly lists its findings and the purposes for the Act's passage. Among the legislative findings and purposes, the Illinois General Assembly found that perinatal mental health disorders include a wide range of emotional, psychological, and physiological reactions to childbirth that can challenge women's stamina during pregnancy and after birth and impair their ability to function and care for their children. The legislature also found that more than 500,000 women experience perinatal mental health disorders during pregnancy and into their children's first years of life, annually; women may experience perinatal depression regardless of their previous mental health diagnoses; women suffering from perinatal mental health disorders may require counseling and treatment yet be unaware of the need for or availability of such services; and that not only the women, but also their babies, the fathers, other children, and family members may be impacted by perinatal mental health disorders (PMHDPTA, 2023). Accordingly, the PMHDPTA's purpose is to provide information to women and their families about perinatal mental health disorders, to develop procedures to assess women for perinatal mental health disorders during prenatal and postnatal visits, and to promote the early detection of perinatal mental health disorders.

Section 10 of the PMHDPTA provides definitions for certain terms used in this law. Interestingly, the word "perinatal" which appears 19 times in this Act, is not defined. The closest the legislature comes to defining "perinatal" is by including the word as part of the term "perinatal mental health disorders" which it refers to as "postpartum depression," and is also undefined.

Section 15 of the PMHDPTA directs Illinois healthcare agencies to work with hospitals and healthcare providers to develop policies, procedures, information, and educational materials to meet certain requirements. Hospitals that provide labor and delivery services are required to inform mothers, after childbirth and before discharge, and fathers and family members, if possible, about the symptoms of perinatal mental health disorders, coping methods, and resources for treatment. Healthcare professionals who provide prenatal services must provide education to women, and their families, if possible, about perinatal mental health disorders. At prenatal visits, healthcare professionals must invite patients to complete questionnaires and review them following the recommendations of the American College of Obstetricians and Gynecologists (Patient Screening, n.d.). When the professional judgment of the healthcare professional indicates that a woman may be experiencing a perinatal mental health disorder, the healthcare professional must complete additional assessments. When healthcare professionals provide postnatal services, they must also invite women to complete questionnaires. Additionally, healthcare professionals who provide pediatric care to infants shall invite mothers to complete questionnaires at well-baby check-ups before the infants' first birthday to ensure that the infants are not compromised by the mothers' undiagnosed perinatal mental health disorders.

The Maternal Mental Health Conditions Education, Early Diagnosis, and Treatment Act (MMHCEEDTA, 2023) became law in Illinois in 2020. This Act includes the short title of the law; legislative findings regarding maternal mental health conditions; definitions; and educational material about maternal mental health conditions. In Section 10 of this law, maternal mental health conditions are defined as mental health conditions that occur during pregnancy or during the postpartum period, including, but not limited to postpartum depression. In Section 5 of the law, the legislature found that maternal depression is a common complication of pregnancy and that maternal mental health disorders include depression, anxiety, and postpartum psychosis. The Illinois General Assembly noted that maternal mental health conditions affect one in 5 women during or after pregnancy but that all women are at risk of suffering from these conditions. The legislature also found that untreated maternal mental health conditions have short-and long-term negative impacts on the health and well-being of affected women and their children: these impacts cause adverse birth outcomes, and emotional and behavioral problems in childhood and have significant medical and economic costs. The legislature estimated these costs to be $22,500 per mother. By passing this Act, the legislature stated its intention to raise awareness of the risk factors, signs, symptoms, and treatment options for maternal mental health conditions.

In Section 15 of the MMHCEEDTA legislation, the Illinois Department of Human Services (IDHS) will develop educational materials both for health care professionals and patients. Obstetric units will take the educational materials and provide them to their employees who regularly work in patient care for pregnant and/or postpartum women. Additionally, hospitals will incorporate the information into employee training and augment the information with relevant local resources. The information IDHS develops for postpartum women and their families will educate them about maternal mental health conditions, treatment options post-hospitalization, and community resources.

Four other results relevant to maternal mental health were also identified in discrete sections of other legislation. Illinois allows

maternal mental health to be considered as a factor in sentencing for crimes or in seeking relief after already being convicted of a crime. In the Unified Code of Corrections, post-partum depression or post-partum psychosis are factors in mitigation that may be considered when withholding or minimizing a defendant's prison sentence (Unified Code of Corrections, 2023). To be used as a mitigating factor, the post-partum depression or post-partum psychosis must be undiagnosed and/or untreated at the time of the offense; the condition would tend to excuse or justify the defendant's criminal conduct; a qualified medical person has since diagnosed the defendant as having suffered from these conditions; and the diagnosis or testimony about the illness was not used at the trial. In this law, post-partum depression is defined as a mood disorder that occurs during pregnancy and up to 12 months after delivery and can include anxiety disorders. Post-partum psychosis is defined as an extreme form of post-partum depression that can include "losing touch with reality, distorted thinking, delusions, auditory and visual hallucinations, paranoia, hyperactivity and rapid speech, or mania" (Unified Code of Corrections, 2023).

Similarly, the Code of Civil Procedure, (2023), allows a defendant to file a petition for post-judgment relief if she can establish that her participation in a forcible felony was a direct result of suffering from post-partum depression or post-partum psychosis. A defendant needs to demonstrate that there was no evidence of post-partum depression or post-partum psychosis presented by a qualified medical person at trial and/or sentencing. A defendant must demonstrate that she was unaware of the mitigating nature of her post-partum depression or post-partum psychosis or that if she was aware, she was unable to present this defense. Her inability to present the defense must stem from her suffering from these conditions at the time of her trial or sentencing. Alternatively, a defendant can establish that the post-partum depression or post-partum psychosis were not recognized mental illnesses at the time of the trial or sentencing and because of that, she was unable to receive proper treatment. She must also show that the evidence is of such a conclusive character that it would likely change the sentence that was imposed by the original court. In this law, post-partum depression and post-partum psychosis are defined exactly as they are in the Unified Code of Corrections.

New Illinois legislation directs the Illinois Department of Public Health (IDPH) to establish a classification system for levels of maternal care, including basic, specialty, subspecialty, and regional prenatal health care (Civil Administrative Code, 2023). One of the legislative directives requires IDPH to engage the Illinois Chapter of the American Academy of Pediatrics to expand efforts so that physicians conduct postpartum depression screenings at well-baby visits during the child's first year of life.

The final result of the content analysis uncovered a provision in the Illinois Public Aid Code. The Medical Assistance Program provides essential medical care and rehabilitative services to persons who are financially unable to meet their basic medical needs. As of July 2022, coverage for perinatal depression screenings for the 12-month period after pregnant persons give birth is an eligible and covered service (Illinois Public Aid Code, 2023).

4 Discussion

This policy review sought to identify relevant policies to address maternal mental health in Illinois. Eleven unique sections of legislation were uncovered concerning perinatal mental health within six different Acts enacted since 2008. This policy review of a single state finds that there is an increase in perinatal mental health legislation which aligns with previous reviews of legislation across the United States. In their 2013 review of legislation on perinatal mental health, Rhodes and Segre documented Illinois as one state with at least one Act related to perinatal mental health (10). As a contribution, this study provides specificity by systematically reviewing all legislation in one state and conducting a deep level policy content analysis. From this review, we were able to identify the many sections across statutes that relate to perinatal mental health. Of the six Acts, there are exceptional examples that capture Illinois' effort to address perinatal mental health. The first example is from the PMHDPTA which is similar to other states, that mandates universal depression assessments during pregnancy and postpartum. Perinatal mood disorders such as perinatal depression and anxiety are largely undetected in obstetric care. Even when they are detected, they are left untreated, as only 22% of women who screen positive for depression receive mental health services (13–15). Early detection of untreated mental health problems could be an essential step in preventing serious acts of harm to oneself or others. While it is difficult to assess the rates of perinatal anxiety and psychosis by state, among the 27 states that collected Pregnancy Risk Assessment Monitoring System data in 2012, Illinois had the second lowest rate of postpartum depressive symptoms at 8.1% (16). Within Illinois, past studies found that the rates of depressive symptoms and suicidal ideation detected on depression screens can be higher for low-income populations and racially minoritized populations (17, 18). Mandates for depression screening can be effective to motivate clinicians and health care systems to adopt screening practices (19, 20). Screening remains an essential approach to identify those in need of mental health care (21). Early detection of untreated mental health problems could be essential in preventing serious acts of harm to oneself and/or others.

The second example is the Maternal Mental Health Conditions Education, Early Diagnosis, and Treatment Act. Illinois' recognition that untreated mental health conditions negatively impact the short-and long-term health and well-being of pregnant persons and their children and require awareness and education regarding these conditions. Often providers are unaware of how to identify and treat mental health problems widening the gap of untreated mental health needs. Untreated perinatal mental health problems are common and costly. Policy level interventions offer unparalleled opportunity to create systems level approaches to identifying those in need of care along the perinatal mental health treatment pathway (22, 23). In some states, legislative decisions have resulted in psychiatry access programs to assist providers in treating mental health problems. Access programs have been used with children and adults and offer promises to address unmet patient needs to achieve equity in perinatal mental health outcomes (24). Access

programs are relatively new with the number of states adopting these programs at a swift pace (24). Now that nearly half of the states have perinatal psychiatry access programs, data collection efforts are needed to identify the effectiveness of these programs and any improved access to treatment (24).

The final example is the Unified Code of Corrections. Illinois is the first state to pass a law that allows postpartum depression and psychosis to be used as a mitigating factor in the sentencing of crimes. The Act allows postpartum depression or postpartum psychosis to be considered as a mitigating factor in forcible felonies committed by women who were neither treated for nor provided evidence of postpartum depression or postpartum psychosis at their trials or sentencing. Much earlier papers, such as Kendell et al. (1987), found women in the postpartum period were 30 times more likely to have a psychiatric admission than in any point in life (25). However, many women are undiagnosed and do not receive the treatment that they need (17, 18). This legislation takes the possibility of a misdiagnosis or underdiagnosis into account. This law recognizes that women may have undiagnosed or untreated mental health conditions related to their pregnancy and childbirth, which, in turn, may have contributed to their criminal behavior. Accordingly, the passage of the act creates a need for forensic review of previous cases to establish if undiagnosed or misdiagnosed mental health problems were related (26). Significantly, the law provides definitions of post-partum depression and post-partum psychosis and defines these conditions as occurring during pregnancy and up to 12 months after delivery. Following the passage of the act, over 20 women were among those who could possibly have a reduced sentence (27). Advocates from Illinois are working to use the example of Illinois to shift national policy and to bring awareness of maternal mental illness into law and corrections (28).

In addition to influencing state-level policy, legislators from Illinois also have been responsible for introducing several pieces of significant legislation to address perinatal disorders at the federal level. For example, U.S. Representative Bobby Rush and U.S. Senator Dick Durbin co-sponsored the Moms Opportunity to Access Help, Education, Research and Support for Postpartum Depression Act, or MOTHERS Act. Language from the MOTHERS Act can now be found in Section 2952 of the Patient Protection and Affordable Care Act, which expanded funding for research and programs on perinatal depression and psychosis. Additionally, Illinois was the first state to expand the provision of Medicaid from 60 days to the first year after giving birth (*Pritzker Administration Announces Illinois Is First State to Extend Full Medicaid Benefits to Mothers 12 Months Postpartum*, n.d.). The expansion of Medicaid should increase opportunities for access to providers and reduce risks of complications due to untreated mental health problems. However, data is needed to support the impact of Medicaid expansion. This study presents a strength of closely examining legislation in a single state to determine the state's efforts to address perinatal mental health, while past studies have broadly compared all states in the US. However, not one study, including ours, has compared legislative acts within and across states. Examining specific policies within states and

comparative analyses across states are needed to determine policy implementation effectiveness (24). Future studies are needed to carefully contrast legislation relevant to perinatal mental health at the level of state policy making.

5 Conclusion

From this policy review, Illinois has emerged as a leader in passing legislation to address the detection of perinatal mental health problems and the ramifications of untreated mental health problems. Foremost, the PMHDPTA mandates universal depression screening during pregnancy and postpartum and the MMHCEEDTA raises awareness of risk factors, signs, and treatment options related to maternal mental health conditions. More recently, legislation allows untreated or undiagnosed postpartum depression or psychosis to be used in the defense of criminal cases. This significant legislation provides a pathway for mental health to be considered in cases of infanticide and is the first of its kind to pass in the United States. It will be important to review the impact of these policies on national adoption of legislation to address maternal mental illness (28). While Illinois is a leader in advancing perinatal mental health legislation in its state, there remains a need for further reform in all states. From this policy review it is clear that one state in a high-income country is making strides to intervene in untreated mental health problems through legislation, but comparisons are needed across low- and middle-income country settings as well. Future policy reforms are still necessary to improve barriers in health services delivery and to improve perinatal mental health outcomes in high income countries.

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.

Author contributions

KT: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. W-JH: Data curation, Formal analysis, Methodology, Writing – review & editing. XR: Methodology, Writing – review & editing. SK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Funding

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.

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References

1. Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. *Obstetrics Gynecology*. (2005) 106:1071–83. doi: 10.1097/01.AOG.0000183597.31630.db

2. O'Hara MW, Wisner KL. Perinatal mental illness: definition, description and aetiology. *Best Pract Res Clin Obstetrics Gynaecology*. (2014) 28:3–12. doi: 10.1016/j.bpobgyn.2013.09.002

3. Woody CA, Ferrari AJ, Siskind DJ, Whiteford HA, Harris MG. A systematic review and meta-regression of the prevalence and incidence of perinatal depression. *J Affect Disord*. (2017) 219:86–92. doi: 10.1016/j.jad.2017.05.003

4. Sit D, Rothschild AJ, Wisner KL. A review of postpartum psychosis. *J women's Health*. (2006) 15:352–68. doi: 10.1089/jwh.2006.15.352

5. Resnick PJ. Child murder by parents: a psychiatric review of filicide. *Am J Psychiatry*. (1969) 126:325–34. doi: 10.1176/ajp.126.3.325

6. Ostler T, Kopels S. Schizophrenia and filicide. *Curr Women's Health Rev*. (2010) 6:58–62. doi: 10.2174/157340410790979761

7. West SG. An overview of filicide. *Psychiatry (Edgmont)*. (2007) 4:48.

8. Rowan PJ, Duckett SA, Wang JE. State mandates regarding postpartum depression. *Psychiatr Serv*. (2015) 66:324–8. doi: 10.1176/appi.ps.201300505

9. (2022). Maternal, Child, and Adolescent Health, Article 6, Maternal Mental Health, 123640, in California Health and Safety Code.

10. Rhodes AM, Segre LS. Perinatal depression: a review of US legislation and law. *Arch women's Ment Health*. (2013) 16:259–70. doi: 10.1007/s00737-013-0359-6

11. Luciano M, Di Vincenzo M, Brandi C, Tretola L, Toricco R, Perris F, et al. Does antenatal depression predict post-partum depression and obstetric complications? Results from a longitudinal, long-term, real-world study. *Front Psychiatry*. (2022) 13. doi: 10.3389/fpsyt.2022.1082762

12. Reck C, Stehle E, Reinig K, Mundt C. Maternity blues as a predictor of DSM-IV depression and anxiety disorders in the first three months postpartum. *J Affect Disord*. (2009). doi: 10.1016/j.jad.2008.05.003

13. Luciano M, Sampogna G, Del Vecchio V, Giallonardo V, Perris F, Carfagno M, et al. The transition from maternity blues to full-blown perinatal depression: results from a longitudinal study. *Front Psychiatry*. (2021) 12. doi: 10.3389/fpsyt.2021.703180

14. Loomis A, Davis A, Cruden G, Padilla C, Drazen Y. Early childhood suspension and expulsion: A content analysis of state legislation. *Early childhood Educ J*. (2021) 50 (2):1–18. doi: 10.1007/s10643-021-01159-4

15. Organization of the Illinois Compiles Statutes (ILCS). (2023). Available online at: https://ilga.gov/commission/lrb/lrbnew.htm.

16. Ko JY, et al. Trends in postpartum depressive symptoms—27 states, 2004, 2008, and 2012. *MMWR Morbidity mortality weekly Rep*. (2017) 66:153. doi: 10.15585/mmwr.mm6606a1

17. Tabb KM, Tabb KM, Amelia RG, Alexandre F-C, Nichole N, et al. Prevalence of antenatal suicidal ideation among racially and ethnically diverse WIC enrolled women receiving care in a Midwestern public health clinic. *J Affect Disord*. (2019) 256:278–81. doi: 10.1016/j.jad.2019.06.012

18. Tabb KM, Hsieh WJ, Gavin AR, Eigbike M, Faisal-Cury A, et al. Racial differences in immediate postpartum depression and suicidal ideation among women in a Midwestern delivery hospital. *J Affect Disord Rep*. (2020) 1:100008. doi: 10.1016/j.jadr.2020.100008

19. Tabb KM, Choi S, Pineros-Leano M, Meline B, McDonald HG, et al. Perinatal depression screening in a Women, Infants, and Children (WIC) program: perception of feasibility and acceptability among a multidisciplinary staff. *Gen Hosp Psychiatry*. (2015) 37:305–9. doi: 10.1016/j.genhosppsych.2015.03.008

20. Tabb KM, Samara P, Choi S, Hudson A, Donovan L, Huang H. Motivated by a mandate: A university-clinic partnership to develop a perinatal depression registry at a community based hospital in the Midwest. *Soc Work Soc Welfare*. (2019) 1:7–12. doi: 10.25082/SWSW.2019.01.001

21. Byatt N, Xu W, Levin LL, Moore Simas TA. *Position Statement on Screening and Treatment of Mood and Anxiety Disorders During Pregnancy and Postpartum, in APA Official Actions*. A.P. Association (2019).

22. Byatt N, Levin LL, Ziedonis D, Simas TAM, Allison, J. Enhancing participation in depression care in outpatient perinatal care settings: a systematic review. *Obstetrics gynecology*. (2015) 126:1048. doi: 10.1097/AOG.0000000000001067

23. Moore JE, McLemore MR, Glenn N, Zivin K. Policy Opportunities To Improve Prevention, Diagnosis, And Treatment Of Perinatal Mental Health Conditions: Study examines policy opportunities to improve prevention, diagnosis, and treatment of perinatal mental health. *Health Affairs*. (2021) 40:1534–42. doi: 10.1377/hlthaff.2021.00779

24. Hansen MED, Tobón AL, Haider UK, Simas TAM, Newsome M, Finelli J, et al. The role of perinatal psychiatry access programs in advancing mental health equity. *Gen Hosp Psychiatry*. (2023). doi: 10.1016/j.genhosppsych.2023.03.001

25. Buist A. Mood disorders in pregnancy: How do they affect mother and baby? *Med Today*. (2015) 16:42–46.

26. Wong G, Parnham G. *Infanticide and Filicide Foundations in Maternal Mental Health Forensics*. Washington, DC USA: American Psychiatric Pub (2020).

27. Feingold SB. A Groundbreaking Illinois Postpartum Law Brings Hope for Change in the UNITED STATES.", Chapter 3. In: Wong, editor. *Infanticide and Filicide: Foundations in Maternal Mental Health Forensics* (2020). p. 39.

28. Feingold SB, Lewis BM. *Advocating for women with postpartum mental illness: A guide to changing the law and the national climate*. Washington, DC USA: Rowman & Littlefield Publishers (2020).

Hyperhomocysteinemia is associated with the risk of venous thromboembolism in patients with mental illness: a case-control study

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Objective: The risk of venous thromboembolism in patients with mental illness has been insufficiently addressed. This study aimed to assess the correlation between hyperhomocysteinemia and venous thromboembolism prevalence among this population.

Methods: Patients with a diagnosis of mental illness and concurrent venous thromboembolism, admitted to Sir Run Run Shaw Hospital at Zhejiang University School of Medicine between January 2014 and December 2021, were included in the venous thromboembolism group. The control group, approximately twice the size, comprised individuals with mental illness but without venous thromboembolism. Basic clinical data were gathered for both cohorts.

Results: In psychiatric patients, elevated D-dimer levels(OR=5.60,95% CI 3.28−10.00), hyperhomocysteinemia (OR=2.37,95% CI 1.10−5.14), and hyperprolactinemia(OR= 2.68,95% CI 1.12−6.42)were significant risk factors for venous thromboembolism. According to further subgroup analyses, hyperhomocysteinemia is a significant risk factor associated with pulmonary embolism, with an OR of 5.08 (95% CI 1.20−21.48). An interaction effect between gender and homocysteine level was found, with a p-interaction of 0.022. A subsequent analysis confirmed the association between hyperhomocysteinemia and venous thromboembolism in female psychiatric patients, with an OR of 3.34 (95% CI 1.68−6.65), indicating that hyperhomocysteinemia is a significant risk factor for venous thromboembolism in women.

Conclusion: Patients with psychiatric disorders were found to have an elevated risk of venous thromboembolism, which was associated with increased levels of D-dimer, hyperprolactinemia, and hyperhomocysteinemia. A strong correlation between hyperhomocysteinemia and pulmonary embolism was identified in patients with mental illnesses. Furthermore, the study revealed that female psychiatric patients with hyperhomocysteinemia constituted a high-risk group

for venous thromboembolism. This finding holds significant clinical implications, suggesting that early preventative measures could be implemented for this high-risk population to reduce the incidence of thromboembolic events during hospitalization for psychiatric patients.

Introduction

Venous thromboembolism (VTE) is a common thromboembolic disease in the population, mainly including Deep Venous Thrombosis (DVT) and Pulmonary Thromboembolism (PTE) (1). The incidence of VTE is high all over the world, some studies had found that the annual incidence of VTE could be as high as 2 ‰ (1), A study found that the hospitalization rate of venous thromboembolism in China increased about five times between 2007 and 2016, and the mortality rate of VTE was seen to rise with age over time (2). Due to the high morbidity and mortality of VTE, it has become a public social health problem.

Patients with mental illness often suffer from social withdrawal and reduced physical activity due to their illness, and most patients with obvious psychiatric symptoms need to take antipsychotic drugs to control clinical symptoms, all of which can lead to blood hypercoagulation and promote the formation of venous thrombosis (3, 4). Previous research (5, 6) has found that the overall prevalence of venous thrombosis in hospitalized patients with mental illness was as high as 1–2%. However, concerning the incidence of venous thromboembolism (VTE) in individuals with mental disorders, the current body of research is scant, and no consensus on incidence rates has been established. Consequently, to ascertain the actual incidence rates of VTE among this patient population, future studies necessitate a more comprehensive and profound investigation. Nevertheless, the fact that mental patients are easy to be complicated with VTE has not attracted enough attention in clinics, which often leads to missed diagnosis and adverse clinical outcomes.

Homocysteine is an amino acid that relies on the vitamin B6 and vitamin B12 pathways for synthesis during methionine metabolism. Homocysteine can cause oxidative stress and promote vascular inflammation through the activation of various signaling pathways, which in turn causes vascular damage (7) and induces thrombus formation. It has been found that the increase of plasma homocysteine concentration is a risk factor for many cardiovascular diseases, which significantly increases the risk of atherosclerosis and contributes to the formation of arterial thrombosis (7–9). Additional research revealed that hyperhomocysteinemia is a stand-alone risk factor for VTE (10), However, studies on the correlation between homocysteine and VTE were mostly retrospective analyses (11, 12).

Several studies have found that the concentration of serum homocysteine in patients with mental disorders such as schizophrenia, depression and Alzheimer's disease was higher than that in the general population (13–15). Additionally, hyperhomocysteinemia may contribute to the onset and progression of certain mental illnesses.

At present, the attention caused by mental illness patients with VTE is still low, and there are few studies on the risk factors of mental illness patients with VTE. Referring to the previous literature, it is found that the incidence of HHcy in mental illness patients is much higher than that of the general population. It is speculated that HHcy may be a related risk factor for mental illness patients with VTE. Therefore, this paper intends to study the correlation between HHcy and VTE in patients with mental illness.

Material and methods

Study population

This is a single-center retrospective case-control study. From January 2014 to December 2021, we continuously enrolled 91 consecutive patients diagnosed with mental illness combined with VTE in Sir Run Run Shaw Hospital, Zhejiang University School of Medicine. Inclusion criteria for the case group: Patients with a diagnosis of both mental illness and VTE, with a diagnosis of mental illness that meets the diagnostic criteria of the International Classification of Diseases, 10th edition (ICD-10) or the American Manual of Mental Disorders and Statistics, 5th edition (DSM-V) (16). The diagnosis of deep vein thrombosis was dependent on Doppler ultrasound. And the diagnosis of pulmonary embolism was confirmed by CT pulmonary angiography. Any patients who fit one of the following descriptions were disqualified: 1. Patients diagnosed with venous thromboembolism prior to admission; 2. Patients who had taken contraceptives, folic acid, vitamin B12 and glucocorticoids within the last 6 months; 3. Patients were recently pregnant or breastfeeding; 4. Patient had a history of major surgery or trauma within the last 6 months. The appropriate subjects were selected from the psychiatric patients without VTE in the same period as the control group, the proportion was about 1:2. The study was approved by the Ethics Committee (Figure 1).

FIGURE 1
Flowchart of the study population.
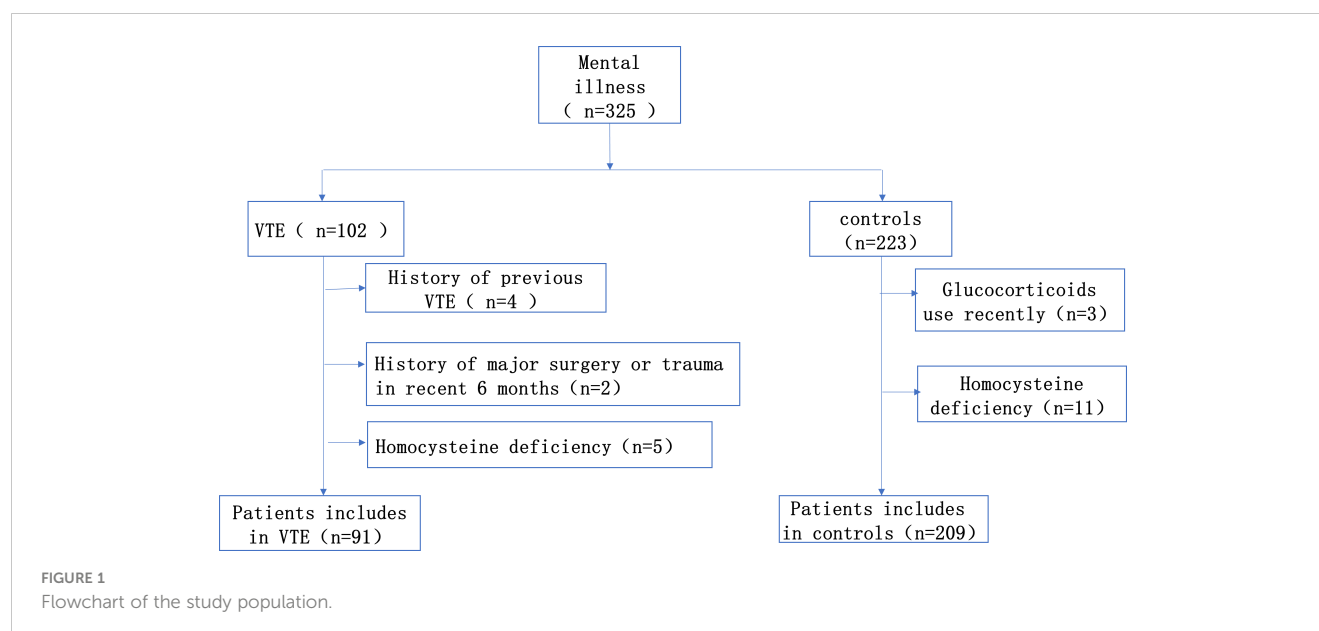
Clinical data collection and definitions

The patient's sex, age, body mass index (BMI), smoking history, antipsychotic use, olanzapine use, antidepressant use, Complications (hypertension, diabetes, chronic kidney disease, malignant tumor, coronary heart disease, cerebral infarction) were obtained and collected from the hospital medical record system. Routine blood tests and blood biochemistry were performed upon admission to obtain the following laboratory results such as neutrophils, lymphocytes, fibrinogen, platelets, D-dimer, CRP, homocysteine, prolactin and so on. Hyperhomocysteinemia is defined as plasma homocysteine levels >15 umol/L (17). Fasting blood samples were collected on admission. Hyperprolactinemia is defined as a single plasma prolactin level above the upper limit of normal (18), the upper limit of normal prolactin for men and postmenopausal women in our hospital was set at 20 µg/L.

Statistical analysis

Statistical analysis was conducted using SPSS 26.0 and R 4.2.2 software. Categorical data were presented as frequencies and analyzed by chi-squared test or Fisher's exact test as appropriate. Continuous data were expressed as mean ± SD or median with interquartile range according to the normality of the distributions. To test the differences between the groups, t-test was applied to continuous data that conform to a regular distribution, the Mann–Whitney U-test was used for continuous data that did not conform to a regular distribution. The concentration of plasma homocysteine was analyzed by categorical variables with 15 umol/L as the boundary. Logistic regressions were used to assess the relationship between homocysteine and VTE. On the basis of univariate analysis followed by Multivariate logistic regression analysis (including independent

variables with P values <0.1 and sex) to explore the independent risk factors for VTE in patients with mental illness. We then explored the effect of hyperhomocysteinemia on VTE according to the VTE subtype typing. It has been shown that there is a difference between elevated plasma homocysteine levels and the occurrence of VTE in different genders (19, 20). Then the interaction between gender and Hcy is analyzed by R4.2.2 software, the p value of the interaction is calculated, and the bar chart of the interaction between Hcy and gender is drawn by using the cat_plot function in R package to visualize, and then stratified analysis is carried out according to gender. Lastly, we computed the prediction probability of combined D-dimer, homocysteine and prolactin by logistic regression model, and plotted the predictive probability value and ROC curve of VTE to evaluate the predictive performance of combined three indicators in patients with mental illness complicated with VTE. In this study, the definition of P < 0.05 is statistically significant.

Results

As shown in Table 1, A total of 91 patients were included in VTE group, 27 (29.7%) males and 64 (70.3%) females, with a mean age of 66 years. The control group included a total of 209 cases, 63 (30.1%) males and 146 (69.9) females, with a mean age of 61 (55–68) years. There were no significant differences in BMI, Antidepressant, Lymphocyte, Platelet, TG, LDL, HDL and Physical restraint between the 2 groups. However, age, smoking history, antipsychotic use, olanzapine use, DDI, hsCRP, neutrophils, fibrinogen, homocysteine and prolactin were found to be statistically significant in the cases and control groups (p < 0.05).

Table 2 showed the multifactorial regression analysis of the occurrence of VTE in patients with mental illness. With the occurrence of VTE event as the dependent variable, independent

TABLE 1 Baseline characteristics of venous thrombosis cases and controls.

		VTE cases(n=91)	controls(n=209)	P value
Sex				
	male	27(29.7)	63(30.1)	
	female	64(70.3)	146(69.9)	0.934
Age(year)*		66(62–72)	61(55–68)	0.000
Smoking*				
	no smoking	81(89.0)	188(90.0)	
	previous smoking	8(8.8)	7(3.3)	
	current smoking	2(2.2)	14(6.7)	0.045
BMI(kg/m2)				
	< 18.5	6(6.6)	25(12.0)	
	18.5- 24.9	64(70.3)	139(66.5)	
	25.0- 29.9	21(23.1)	41(19.6)	
	≥30	0	4(1.9)	0.326
Antipsychotic*				
	none	29(31.9)	111(53.1)	
	first generation	0	0	
	Second generation	62(68.1)	98(46.9)	
	both	0	0	0.001
Olanzapine*		50(54.9)	72(34.4)	0.001
Mental illness				
	Depression	72(79.1)	164(78.5)	
	Non-depressive	19(20.9)	45(21.5)	0.899
Antidepressant		76(83.5)	170(81.3)	0.652
DDI(ug/mL) *		1.47(0.89–2.32)	0.29(0.23–0.44)	0.000
hsCRP(mg/L)*				
	≥6	12(13.2)	4(1.9)	0.000
Neutrophil (/L) *				
	<1.8*10^9	3(3.3)	15(7.2)	
	1.8–6.3*10^9	79(86.8)	189(90.4)	0.009
	>6.3*10^9	9(9.9)	5(2.4)	
Lymphocyte (/L)				
	<1.1*10^9	14(15.4)	26(12.4)	0.860
	1.1–3.2*10^9	76(83.5)	179(85.6)	
	>3.2*10^9	1(1.1)	4(1.9)	
Fibrinogen (g/L) *				
	<2	4(4.4)	8(3.8)	
	2–4	80(87.9)	198(94.7)	0.023
	>4	7(7.7)	3(1.4)	

(Continued)

TABLE 1 Continued

		VTE cases(n=91)	controls(n=209)	P value
Platelet (/L)				
	<125 *10^9	9(9.9)	10(4.8)	
	125–350*10^9	81(89.0)	197(94.3)	0.180
	>350 *10^9	1(1.1)	2(1.0)	
Homocysteine(umol/L)*				
	≤15	55(60.4)	158(75.6)	
	>15	37(40.7)	51(24.4)	0.004
Prolactin(μg/L)*				
	≤20	65(71.4)	175(83.7)	
	>20	27(29.7)	34(16.3)	0.008
TG(mmol/L)				
	>1.7	39(42.9)	67(32.1)	0.072
HDL(mmol/L)				
	<1.03	18(19.8)	49(23.4)	
	1.03–1.55	66(72.5)	131(62.7)	0.188
	>1.55	7(7.7)	29(13.9)	
LDL(mmol/L)				
	<1.89	3(3.3)	14(6.7)	
	1.89–4.21	84(92.3)	182(87.1)	0.394
	>4.21	4(4.4)	13(6.2)	
Physical restraint		3(3.3)	2(1.0)	0.166
Complication				
	Hypertension	45(49.5)	85(40.7)	0.158
	Diabetes	11(12.1)	26(12.4)	0.932
	CKD	2(2.2)	4(1.9)	1.000
	Cancer	6(6.6)	19(9.1)	0.472
	CHD*	15(16.5)	13(6.2)	0.005
	CI*	19(20.9)	15(7.2)	0.001

Continuous variables are shown as median (25th percentile– 75th percentile). Categorical variables are shown as percentages with numbers in brackets. P Value for continuous variables were obtained from Mann-Whitney U Test(age and DDI).P Value for categorical variables were obtained using $\chi2$ test or Fisher's Exact Test.
VTE, venous thromboembolism; BMI, body mass index; DDI, D-Dimer; hsCRP, high- sensitivity C- reactive protein; TG, Triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CKD, Chronic kidney disease; CHD, Coronary heart disease; CI, Cerebral infarction.
*indicates a statistical difference between the two groups, P value<0.05.

variables with P value<0.1 in the univariate analysis (age, smoking history, antipsychotic use, olanzapine use, D-dimer, CRP, neutrophils, fibrinogen, homocysteine, prolactin, triglycerides, coronary artery disease, cerebral infarction) and sex were included in the multifactorial regression model. The results showed that DDI (OR=5.60, 95%CI3.28–10.00), hyperhomocysteinemia (OR=2.37, 95%CI1.10–5.14) and hyperprolactinemia were statistically different between the cases and controls groups.

In this study, the interaction between homocysteine and sex was further analyzed, the p value of the interaction was calculated by R4.2.2 software, and the bar chart of the interaction between homocysteine and sex was drawn by using the cat_plot function in R packet, showing the interaction effects between homocysteine and sex. The y-axis denotes the VTE incidence rates. At plasma homocysteine concentrations ≤15 μmol/L, both male (0.28) and female (0.25) patients exhibited comparable rates of venous thromboembolism. Contrastingly, at levels >15 μmol/L, a

TABLE 2 Logistic regression analysis for risk factors attributing to VTE presence in the study.

		OR(95%CI)	P value
Sex		0.56(0.22–1.38)	0.206
Age(year)		1.05(0.999–1.09)	0.057
Smoking			
	No smoking	Reference	0.301
	Previous smoking	2.40(0.44–13.07)	
	Current smoking	0.35(0.05–2.67)	
Antipsychotic		1.58(0.90–2.77)	0.114
Olanzapine		1.31(0.44–3.84)	0.627
DDI(ug/mL) *		5.60(3.28–10.00)	0.000
hsCRP(mg/L)		3.43(0.61–19.23)	0.161
Neutrophil (/L)			
	<1.8*10^9	0.75(0.15–3.81)	
	1.8–6.3*10^9	Reference	0.788
	>6.3*10^9	1.68(0.29–9.73)	
Fibrinogen (g/L)			
	<2	0.92(0.15–5.62)	
	2–4	Reference	0.849
	>4	1.97(0.19–20.66)	
Homocysteine(umol/L)*		2.37(1.10–5.14)	0.028
Prolactin(μg/L)*		2.68(1.12–6.42)	0.027
TG(mmol/L)		1.51(0.71–3.20)	0.276
CHD		1.78(0.50–6.28)	0.371
CI		1.97(0.71–5.50)	0.195

DDI, D-Dimer; hsCRP, high- sensitivity C- reactive protein; TG, Triglyceride; CHD, Coronary heart disease; CI, Cerebral infarction.

*indicates a statistical difference between the two groups, P value<0.05.

In multivariable-adjusted regression models, homocysteine was the biomarker that was positively related with incident VTE, we further analyzed the association between hyperhomocysteinemia and the various subtypes of VTE (DVT group, PE group, DVT+PE group) (Table 3). In the unadjusted model, hyperhomocysteinemia was associated with DVT (OR 1.86, 95% CI 1.02– 3.38) and PE (OR 2.82, 95% CI 1.13–7.02). Both Model 1 (adjusted for age, prolactin and DDI) and Model 2 (adjusted for sex, age, TG, hsCRP, antipsychotic, prolactin and DDI.)showed a trend of increasing ORs among groups with DVT, PE, and DVT +PE. Model 2 showed a strong correlation between hyperhomocysteinemia and PE, with an OR of 5.08 (95%CI,1.20–21.48). In the DVT+PE group, the odds ratio (OR) was 39.31 with a 95% confidence interval (CI) of 0.63–2437, which was statistically indistinguishable. This indistinction may be attributed to the subgroup's limited sample size. Consequently, the findings do not conclusively negate the involvement of hyperhomocysteinemia in DVT+PE. Future studies will aim to substantiate this correlation by enlarging the DVT+PE group's sample size.

pronounced divergence in incidence rates was observed between genders. Notably, the rate for female patients escalated to 0.52, a stark increase, whereas the rate for male patients remained constant at 0.31, similar to prior data. Statistical analysis revealed the p-interaction was 0.022, thereby confirming a statistically significant interaction between gender and homocysteine levels. Considering the significant interaction observed between gender and

homocysteine levels, a subgroup analysis was performed. It was found that hyperhomocysteinemia was significantly correlated with VTE in female patients with mental disorders, which was a risk factor for VTE in female patients with mental disorders, and after adjusting multiple confounding factors (age, prolactin, D-dimer, triglyceride, CRP, antipsychotics). It still has a strong correlation, OR=3.34 (95%CI=1.68–6.65). On the contrary, hyperhomocysteinemia was not associated with the occurrence of VTE in male patients with mental illness, OR=1.19 (95%CI=0.48–2.92). Figures 2, 3

Model 1 adjusted for age, prolactin and DDI.

Model 2 adjusted for age, TG, hsCRP, antipsychotic prolactin and DDI.

Through the binary Logistic regression model in SPSS26.0, the prediction probability of VTE was calculated by combining the three laboratory indexes of D-dimer, homocysteine and prolactin, and then the ROC curve of prediction probability and VTE was drawn (Figure 4). The AUC area was 0.912 (95%CI:0.873–0.951), and the sensitivity and specificity of the best cutoff value was 0.934 and 0.828 respectively. It is suggested that the combination of D-dimer, homocysteine and prolactin has high diagnostic value for VTE in patients with mental disorders.

Discussion

In this study, it was found that hyperhomocysteinemia, hyperprolactinemia and elevated D-dimer were the risk factors of VTE in patients with mental illness, and after adjusting for a variety of confounding factors, the above three indexes were still strongly associated with the occurrence of VTE in patients with mental illness. Subsequently, the correlation of hyperhomocysteinemia among VTE subgroups was further studied, and it was found that hyperhomocysteinemia was a risk factor for DVT and PE in patients with mental illness in the model with unadjusted confounding factors. After adjusting for confounding factors, the correlation of hyperhomocysteinemia increased in DVT group, PE group and DVT+PE group, but only the p value of PE group was < 0.05. However, due to the relatively small number of cases in the subgroup analysis, there may be some bias, which leads to the underestimation of the relationship between HHcy and DVT+PE group and DVT group, so a larger sample is needed in the future. In addition, this study also found that there was an interaction between homocysteine and gender. Hyperhomocysteinemia significantly increased the risk of VTE in female patients with mental illness, and after adjusting for confounding factors, the interaction still existed. The follow-up stratified analysis gives more accurate results, suggesting that female mental patients with hyperhomocysteinemia are at high risk for VTE. The three factors of hyperhomocysteinemia, hyperprolactinemia and D-dimer were included in the ROC curve, and the AUC area was 0.912, suggesting that it has important reference value for the diagnosis of VTE in patients with mental disorders.

In recent years, more and more researchers were concerned that patients with mental illness were prone to co-occurring VTE with atypical clinical symptoms, which were easily missed. The reduction
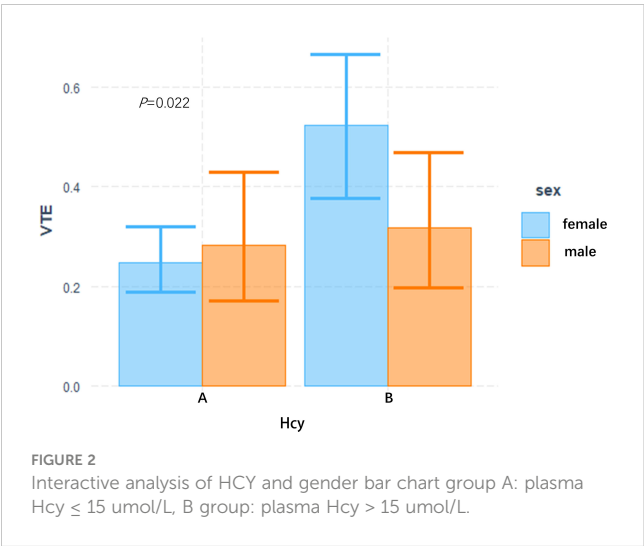
of activity caused by mental illness itself and the use of antipsychotic drugs during treatment can greatly increase the risk of venous thrombosis in patients with mental illness (21–23). However, in terms of clinical diagnosis and treatment, the attention to mental illness complicated with VTE is still low, and there is a high rate of missed diagnosis, which can easily lead to poor prognosis of patients.

However, the risk factors for the occurrence of venous thrombosis in patients with mental illness remain unclear and may be associated with the mental illness itself and the administration of antipsychotic drugs.
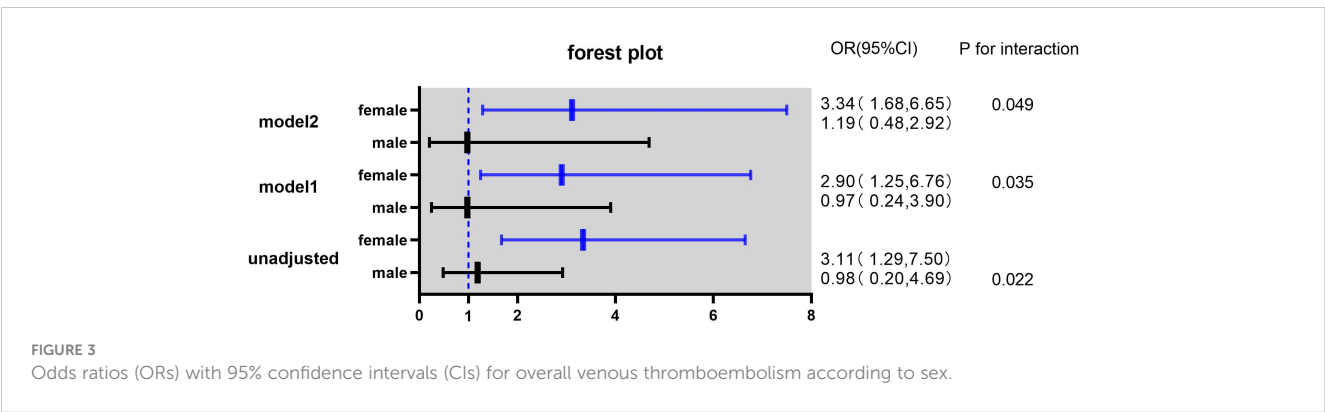
Homocysteine is an important enzyme in the regulation of methionine and cysteine metabolism. On the one hand, homocysteine levels are strongly correlated with psychiatric symptoms and patient prognosis, and they play a crucial role in the development of mental illness, particularly schizophrenia (24, 25). On the other hand, hyperhomocysteinemia is a risk factor for cardiovascular diseases, which can induce endothelial cell injury and apoptosis by inhibiting the synthesis and repair of DNA through multiple pathways (26). It can also interfere with NO metabolism of endothelial cells, lead to the imbalance of NO metabolism (27) and induce endothelial cell dysfunction. At the same time, homocysteine can directly or indirectly activate platelets, promote platelet adhesion and aggregation with a variety of blood
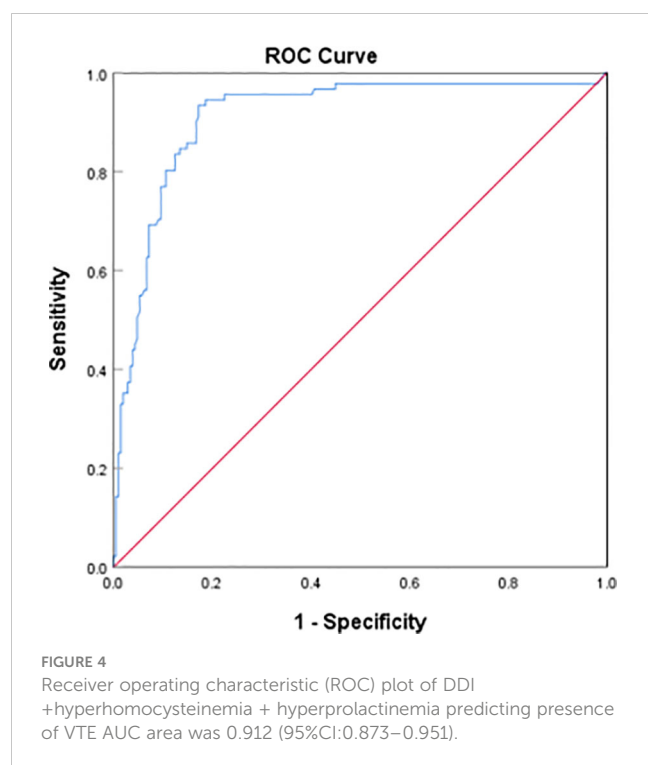
cells and endothelial cells, and regulate the contraction of blood clots (28). In general, hyperhomocysteinemia may affect coagulation and fibrinolysis in the body from multiple pathways.

A review of previous studies shows that most studies believe that hyperhomocysteinemia is an independent risk factor for VTE and increases the risk of venous thrombosis. Multiple meta-analyses (11, 29) suggested that hyperhomocysteinemia increased the incidence of venous thrombosis in patients. The latest meta-analysis found that the increase of plasma total homocysteine level was closely related to venous thrombosis. The incidence of VTE increased by 60% for every 5 mol/L increase in plasma homocysteine(OR=1.6, 95% CI, 1.10–2.34), which might be associated with the methylenetetrahydrofolate reductase gene 677TT (MTHFR 677TT) mutation (11). MTHFR is a key enzyme in homocysteine metabolism, When its gene mutation occurs, it will lead to the weakening of related enzyme activity and the continuous accumulation of homocysteine in the blood, resulting in hyperhomocysteinemia (30). However, the above studies do not adjust the influence of common confounding factors such as age, sex, smoking history and BMI, so the conclusions may be biased. A cohort study (31) found that elevated plasma homocysteine levels were significantly associated with the future occurrence of VTE. Patients with homocysteine level ≥ 12.9 μ mol/L had a 0.3-fold increased risk compared with patients with homocysteine level ≤ 8.6 μ mol/L, with a HR of 1.31 (95%CI:1.06–1.63). Further classification of PE and DVT revealed that elevated homocysteine levels were associated with unprovoked PE (HR=2.13 (95% CI, 1.30–3.51) and unprovoked DVT (HR=1.59 (95% CI, 1.05–2.40).

However, some studies have come to the opposite conclusion. A case-control study in the Netherlands included 1,689 cases with two separate control groups, one for general population controls and the other for partner-matched controls. The case group was compared with the two groups respectively. After adjusting the common confounding factors by logistic regression, the level of homocysteine had nothing to do with VTE. Further stratification was carried out according to sex, DVT, PE, inductive VTE and non-inductive VTE. It was still found that the increase of homocysteine concentration did not increase the incidence of thrombosis in patients (32).

There is a paucity of related research in patients with mental illness complicated with VTE. A variety of mental illness can cause an increase in the concentration of plasma homocysteine in patients (13,

FIGURE 4
Receiver operating characteristic (ROC) plot of DDI +hyperhomocysteinemia + hyperprolactinemia predicting presence of VTE AUC area was 0.912 (95%CI:0.873−0.951).

14). An observational study focusing on psychiatric disorders with VTE found that the most common laboratory risk factors for patients were elevated FVIII levels and hyperhomocysteinemia, with approximately 33% of patients having hyperhomocysteinemia (33). A meta-analysis (34) shows that about 30% of patients with depression have HHcy, accompanied by a decrease in folic acid levels, which is much higher than the proportion of hyperhomocysteinemia in the general population. A case-control (35) study included 93 patients with schizophrenia and 60 healthy volunteers found that patients with schizophrenia had lower concentrations of tetrahydrobiopterin and folic acid and higher levels of Hcy than healthy volunteers. Some studies have found that the prevalence of HHcy in patients with schizophrenia can reach 30–50% (13, 36). A population screening program in China, which included 110551 subjects from 31 provinces across the

country, found that only about 8 per cent of patients had HHcy (37). In conclusion, the prevalence of HHcy in patients with mental illness is substantially higher than that in the general population.

Therefore, this study explored the relationship between hyperhomocysteinemia and VTE in patients with mental illness. In this study, the proportion of hyperhomocysteinemia in the case group and the control group was 40% and 24% respectively, which was much higher than that in the normal population (8%). This is consistent with the conclusion that the incidence of hyperhomocysteinemia in patients with mental illness is higher than that in the general population.

It was also found that hyperhomocysteinemia was indeed a risk factor for VTE in patients with mental illness, and it still had a high risk ratio after adjusting confounding factors. Further analysis found that there was a strong correlation between hyperhomocysteinemia and the occurrence of PE in patients with mental illness. To investigate the correlation between homocysteine levels and DVT + PE group, a larger sample study is needed in the future.

In addition, there may be gender differences in the risk of VTE in hyperhomocysteinemia. The HUNT2 study from Norwegian (38) found that the risk of VTE was approximately doubled in male patients with plasma homocysteine concentrations above the 95th percentile, OR= 2.17 (95% CI 1.20–3.91), whereas no association was observed in female patients, OR=1.00. However, the stratified analysis of Tsai et al. (12) found that hyperhomocysteinemia was strongly correlated with the incidence of VTE in younger patients (<65 years old), female, Caucasian, and non-diabetic patients.

In this paper, we examined the interaction between homocysteine levels and gender, which showed that an interaction was present between homocysteine levels and gender with a p-interaction value of less than 0.05. This confirmed the statistical significance of the gender-based interaction analysis outlined in the article. Further, subgroup analyses substantiated these findings. The study indicated that female patients suffering from mental disorders with elevated levels of homocysteine faced a significantly high risk of developing venous thromboembolism (VTE). The OR value calculated in the model after adjusting for

TABLE 3 Associations Between hyperhomocysteinemia and VTE(DVT、PE、DVT+PE).

VTE	cases	controls	Unadjusted OR(95%CI)	Model 1 OR(95%CI)	Model 2 OR(95%CI)
DVT(n=64)					
Hyperhomocysteinemia	24(37.5)	51(24.4)	1.86(1.02–3.38)	1.97(0.93–4.15)	2.09(0.96–4.56)
PE(n=21)					
Hyperhomocysteinemia	10(47.6)	51(24.4)	2.82(1.13–7.02)	3.68(0.99–13.69)	5.08(1.20–21.48)
DVT+PE(n=6)					
Hyperhomocysteinemia	3(50.0)	51(24.4)	3.01(0.61–15.83)	13.19(1.28–135.83)	39.31 (0.63–2437.51)

VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism.
Model 1 adjusted for sex, age, prolactin and DDI.
Model 2 adjusted for sex, age, TG, hsCRP, antipsychotic, prolactin and DDI.

confounding factors was 3.34 (95%CI=1.68–6.65). There were some differences between this study and previous studies, the reasons may be as follows: 1. In the gender stratification analysis of hyperhomocysteinemia, the Norwegian study only explored the situation where the level of homocysteine was higher than 95 percentile (above 25.9 μ mol/l), which was different from the 15 μmol/L set in this study. 2. Different studies were aimed at different races and people, most of the previous research subjects are Caucasians, while the subjects of this study were Asians, and all of them were patients with mental illness. 3. There were certain selection bias and mixed bias in different studies.

Although a number of studies have shown that hyperhomocysteinemia is associated with the occurrence of VTE, clinical trials have found that reducing homocysteine therapy can not reduce the incidence of VTE in patients. The VITRO study (39) aimed to examine the effects of vitamin B supplementation on the reduction of DVT and PE by reducing homocysteine. The study recruited 701 patients with confirmed VTE (including 360 patients with hyperhomocysteinemia and 341 patients with normal homocysteine). Patients were randomized to the vitamin treatment and placebo treatment groups, and after 2.5 years of treatment and follow-up, vitamin treatment was found to reduce homocysteine levels in the hyperhomocysteine and normal homocysteine groups by 46% and 33%, but did not reduce the risk of recurrent venous thrombosis in the patients.

However, there are no randomized clinical trials on VTE in patients with mental disorders, and it is impossible to determine the correlation between lowering homocysteine levels with B vitamins and VTE in patients with mental disorders.

In this study, we plotted the ROC curve by combining DDI with homocysteine and prolactin for the first time. The value of DDI in the prediction of VTE had been unequivocally confirmed. A review of the previous literature found that a variety of antipsychotic drugs can lead to increased prolactin levels in patients (40, 41). It was found that the level of serum prolactin increased significantly in patients with mental illness treated with antipsychotics, and the increase of prolactin was positively correlated with the levels of DDI and fibrin/fibrinogen degradation products, which would increase the concentration of coagulation markers in patients (42). Some scholars had proposed that prolactin can bind to specific receptors on the surface of platelets to enhance platelet activity (43, 44). And prolactin can induce inflammatory response in the body, lead to the activation of a variety of inflammatory mediators and inflammatory cells, and affect endothelial function, thus directly or indirectly promote the formation of thrombus (45, 46). Therefore, we plotted the ROC curve combined with these three indicators for the first time. The results indicate that the combination of DDI, homocysteine and prolactin has a good predictive performance for the incidence of VTE in patients with mental illness.

Referring to the literature, this is the first clinical study to explore the relationship between hyperhomocysteinemia and VTE in patients with mental illness. as mentioned above, previous studies focused on the relationship between hyperhomocysteinemia and VTE in the general population, and the conclusions were different, which may be related to the selection bias of the included population, the different definition of hyperhomocysteinemia and the influence of confounding

factors. Secondly, the blood samples in this study were collected before the VTE event, so it can further substantiate the causal relationship between hyperhomocysteinemia and VTE in patients with mental illness. This paper also performed a subgroup analysis according to the thrombus site, and further analyzed the interaction between sex and homocysteine, and then conducted stratified analysis by sex. Based on the study of this paper, we discovered that female mental patients with hyperhomocysteinemia were at high risk of VTE. This study is beneficial for clinicians to detect high-risk patients early and initiate thrombus prevention measures for high-risk patients as soon as possible, so as to effectively reduce poor prognosis.

However, this study also had some limitations, in the subgroup analysis according to the thrombus site, the number of cases in some subgroups was small, especially in the DVT+PE group, so the conclusion may be biased, resulting in underestimating the association between hyperhomocysteinemia and DVT+PE group. Secondly, most of the patients included in this study were over 50 years old, so the conclusions may not be applicable to young patients with mental illness. Additionally, this investigation was a single-center study involving Chinese patients with mental disorders, predominantly those suffering from depression, and owing to the lack of severity assessment in the initial case data, a classification of disease severity was not incorporated into the statistical model. Moreover, in the process of data collection, it was observed that antipsychotic medications varied significantly in their varieties and dosages, so they couldn't be included in the statistical model. As a result, a binary classification approach was used without dosage information. Due to considerable variability in patient heterogeneity concerning the temporal relationship between fasting blood samples and thrombotic events, this section was not further analyzed in this paper. Finally, the predictors of this paper can not quantitatively evaluate the thrombus risk of patients with mental illness, and larger samples and further studies are needed in the future to develop a unique predictor of thrombus risk for patients with mental illness.

Patients with mental illness are at risk of VTE. Because of their diseases and the influence of taking antipsychotic drugs, they will increase the risk of metabolic syndrome. Therefore, the risk factors of VTE in patients with mental illness may be different from the general population. More studies are needed to explore the risk factors of VTE in patients with mental illness in the future. Further research will help to develop a unique thrombus risk assessment form for patients with mental illness in the future, so that high-risk patients can be identified early and accurate risk stratification can be carried out for patients. For high-risk patients, we should be vigilant, start physical prevention as early as possible (encourage more drinking water, more activities and the use of double lower extremity DVT pumps, etc.), and use drugs when necessary, so as to reduce the occurrence of VTE and improve the clinical prognosis of patients.

Conclusion

In patients with psychiatric disorders, a strong correlation was found between hyperhomocysteinemia and Pulmonary Embolism

(PE). An interaction between homocysteine levels and gender was observed. Hyperhomocysteinemia significantly increases the risk of Venous Thromboembolism (VTE) in female psychiatric patients. Therefore, the conclusion of this article is that female psychiatric patients with hyperhomocysteinemia constitute a high-risk group for VTE. This discovery has important clinical implications, indicating that early preventive measures can be taken for this high-risk group. This will reduce the risk of thromboembolic events during hospitalization for patients with psychiatric disorders, thereby improving their clinical 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.

Ethics statement

The study passed ethical review by the Ethics Committee of Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University (Study Approval No.0433). The ethics committee waived the requirement of written informed consent for participation due to the retrospective design. The studies were conducted in accordance with the local legislation and institutional requirements.

Author contributions

JW: Data curation, Investigation, Methodology, Software, Writing – original draft. YZ: Data curation, Investigation, Methodology, Writing – review & editing. KR: Data curation, Investigation, Writing – review & editing. YL: Data curation,

Methodology, Writing – review & editing. KY: Supervision, Writing – review & editing.

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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References

1. Khan F, Tritschler T, Kahn SR, Rodger MA. Venous thromboembolism. *Lancet*. (2021) 398:64–77. doi: 10.1016/S0140-6736(20)32658-1

2. Zhang Z, Lei J, Shao X, Dong F, Wang J, Wang D, et al. Trends in hospitalization and in-hospital mortality from VTE, 2007 to 2016, in China. *Chest*. (2019) 155:342–53. doi: 10.1016/j.chest.2018.10.040

3. Kowal C, Peyre H, Amad A, Pelissolo A, Leboyer M, Schürhoff F, et al. Psychotic, mood, and anxiety disorders and venous thromboembolism: A systematic review and meta-analysis. *Psychosom Med*. (2020) 82:838–49. doi: 10.1097/PSY.0000000000000863

4. Hoirisch-Clapauch S. Anxiety-related bleeding and thrombosis. *Semin Thromb Hemost*. (2018) 44:656–61. doi: 10.1055/s-0038-1639501

5. Takeshima M, Ishikawa H, Shimizu K, Kanbayashi T, Shimizu T. Incidence of venous thromboembolism in psychiatric inpatients: a chart review. *Neuropsychiatr Dis Treat*. (2018) 14:1363–70. doi: 10.2147/NDT

6. Wang Z, Yang Y, He X, Jiang X, Gao X, Liu P, et al. Incidence and clinical features of venous thromboembolism in inpatients with mental illness. *Clin Appl Thromb Hemost*. (2023) 29:10760296231160753. doi: 10.1177/10760296231160753

7. Fu Y, Wang X, Kong W. Hyperhomocysteinaemia and vascular injury: advances in mechanisms and drug targets. *Br J Pharmacol*. (2018) 175:1173–89. doi: 10.1111/bph.13988

8. Zhang N, Zhu L, Wu X, Yan R, Yang S, Jiang X, et al. The regulation of Ero1-alpha in homocysteine-induced macrophage apoptosis and vulnerable plaque formation in atherosclerosis. *Atherosclerosis*. (2021) 334:39–47. doi: 10.1016/j.atherosclerosis.2021.08.015

9. Škovierová H, Vidomanová E, Mahmood S, Sopková J, Drgová A, Červeňová T, et al. The molecular and cellular effect of homocysteine metabolism imbalance on human health. *Int J Mol Sci*. (2016) 17(10):1733. doi: 10.3390/ijms17101733

10. Köktürk N, Kanbay A, Aydoğdu M, Özyılmaz E, Bukan N, Ekim N. Hyperhomocysteinemia prevalence among patients with venous thromboembolism. *Clin Appl Thromb Hemost*. (2011) 17:487–93. doi: 10.1177/1076029610378499

11. Den Heijer M, Lewington S, Clarke R. Homocysteine, MTHFR and risk of venous thrombosis: a meta-analysis of published epidemiological studies. *J Thromb Haemost*. (2005) 3:292–9. doi: 10.1111/j.1538-7836.2005.01141.x

12. Tsai AW, Cushman M, Tsai MY, Heckbert SR, Rosamond WD, Aleksic N, et al. Serum homocysteine, thermolabile variant of methylene tetrahydrofolate reductase (MTHFR), and venous thromboembolism: Longitudinal Investigation of Thromboembolism Etiology (LITE). *Am J Hematol*. (2003) 72:192–200. doi: 10.1002/ajh.10287

13. Yang Y, Wang J, Xiong Z, Yao X, Zhang Y, Ning X, et al. Prevalence and clinical demography of hyperhomocysteinemia in Han Chinese patients with schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. (2021) 271:759–65. doi: 10.1007/s00406-020-01150-x

14. Smith AD, Refsum H. Homocysteine B. Vitamins, and cognitive impairment. *Annu Rev Nutr*. (2016) 36:211–39. doi: 10.1146/annurev-nutr-071715-050947

15. Obeid R, McCaddon A, Herrmann W. The role of hyperhomocysteinemia and B-vitamin deficiency in neurological and psychiatric diseases. *Clin Chem Lab Med*. (2007) 45:1590–606. doi: 10.1515/CCLM.2007.356

16. Kupfer DJ, Kuhl EA, Regier DA. DSM-5–the future arrived. *JAMA* (2013) 309 (16):1691–2. doi: 10.1001/jama.2013.2298

17. Finkelstein JD, Martin JJ. Homocysteine. *Int J Biochem Cell Biol*. (2000) 32:385–9. doi: 10.1016/S1357-2725(99)00138-7

18. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. (2011) 96:273–88. doi: 10.1210/jc.2010-1692

19. Rozemeijer K, le Cessie S, van Hylckama Vlieg A, Rosendaal FR, Vandenbroucke JP, Poole C, et al. Exposure opportunity: the advantages of including men in analyses of female-related risk factors. *Am J Epidemiol*. (2017) 185:965–73. doi: 10.1093/aje/kww193

20. Roach RE, Lijfering WM, Rosendaal FR, Cannegieter SC, le Cessie S. Sex difference in risk of second but not of first venous thrombosis: paradox explained. *Circulation*. (2014) 129:51–6. doi: 10.1161/CIRCULATIONAHA.113.004768

21. Arasteh O, Nomani H, Baharara H, Sadjadi SA, Mohammadpour AH, Ghavami V, et al. Antipsychotic drugs and risk of developing venous thromboembolism and pulmonary embolism: A systematic review and meta-analysis. *Curr Vasc Pharmacol*. (2020) 18:632–43. doi: 10.2174/1570161118666200211114656

22. Conti V, Venegoni M, Cocci A, Fortino I, Lora A, Barbui C. Antipsychotic drug exposure and risk of pulmonary embolism: a population-based, nested case-control study. *BMC Psychiatry*. (2015) 15:92. doi: 10.1186/s12888-015-0479-9

23. Barbui C, Conti V, Cipriani A. Antipsychotic drug exposure and risk of venous thromboembolism: a systematic review and meta-analysis of observational studies. *Drug Saf*. (2014) 37:79–90. doi: 10.1007/s40264-013-0127-6

24. Misiak B, Frydecka D, Slezak R, Piotrowski P, Kiejna A. Elevated homocysteine level in first-episode schizophrenia patients–the relevance of family history of schizophrenia and lifetime diagnosis of cannabis abuse. *Metab Brain Dis*. (2014) 29:661–70. doi: 10.1007/s11011-014-9534-3

25. Akanji AO, Ohaeri JU, Al-Shammri SA, Fatania HR. Associations of blood homocysteine concentrations in Arab schizophrenic patients. *Clin Biochem*. (2007) 40:1026–31. doi: 10.1016/j.clinbiochem.2007.06.001

26. Lehotsky J, Petras M, Kovalska M, Tothova B, Drgova A, Kaplan P. Mechanisms involved in the ischemic tolerance in brain: effect of the homocysteine. *Cell Mol Neurobiol*. (2015) 35:7–15. doi: 10.1007/s10571-014-0112-3

27. Lai WK, Kan MY. Homocysteine-induced endothelial dysfunction. *Ann Nutr Metab*. (2015) 67:1–12. doi: 10.1159/000437098

28. Litvinov RI, Peshkova AD, Le Minh G, Khaertdinov NN, Evtugina NG, Sitdikova GF, et al. Effects of hyperhomocysteinemia on the platelet-driven contraction of blood clots. *Metabolites*. (2021) 11(6):354. doi: 10.3390/metabo11060354

29. den Heijer M, Rosendaal FR, Blom HJ, Gerrits WB, Bos GM. Hyperhomocysteinemia and venous thrombosis: a meta-analysis. *Thromb Haemost*. (1998) 80:874–7.

30. Zaric BL, Obradovic M, Bajic V, Haidara MA, Jovanovic M, Isenovic ER. Homocysteine and hyperhomocysteinaemia. *Curr Med Chem*. (2019) 26:2948–61. doi: 10.2174/0929867325666180313105949

31. Aday AW, Duran EK, Van Denburgh M, Kim E, Christen WG, Manson JE, et al. Homocysteine is associated with future venous thromboembolism in 2 prospective cohorts of women. *Arterioscler Thromb Vasc Biol*. (2021) 41:2215–24. doi: 10.1161/ATVBAHA.121.316397

32. Ospina-Romero M, Cannegieter SC, den Heijer M, Doggen CJM, Rosendaal FR, Lijfering WM. Hyperhomocysteinemia and risk of first venous thrombosis: the influence of (Unmeasured) confounding factors. *Am J Epidemiol*. (2018) 187:1392–400. doi: 10.1093/aje/kwy004

33. Masopust J, Bazantova V, Kuca K, Klimova B, Valis M. Venous thromboembolism as an adverse effect during treatment with olanzapine: A case series. *Front Psychiatry*. (2019) 10:330doi: 10.3389/fpsyt.2019.00330

34. Stanger O, Fowler B, Piertzik K, Huemer M, Haschke-Becher E, Semmler A, et al. Homocysteine, folate and vitamin B12 in neuropsychiatric diseases: review and treatment recommendations. *Expert Rev Neurother*. (2009) 9:1393–412. doi: 10.1586/ern.09.75

35. Zhilyaeva TV, Kasyanov ED, Semennov IV, Rukavishnikov GV, Piatoikina AS, Kostina OV, et al. Tetrahydrobiopterin deficiency in schizophrenia: Biochemical and clinical aspects. *J Psychiatr Res*. (2022) 153:141–8. doi: 10.1016/j.jpsychires.2022.07.020

36. Geller V, Friger M, Sela BA, Levine J. Elevated homocysteine level in siblings of patients with schizophrenia. *Psychiatry Res*. (2013) 210:769–72. doi: 10.1016/j.psychres.2013.08.016

37. Tu W, Yan F, Chao B, Ji X, Wang L. Status of hyperhomocysteinemia in China: results from the China Stroke High-risk Population Screening Program, 2018. *Front Med*. (2021) 15:903–12. doi: 10.1007/s11684-021-0871-4

38. Naess IA, Christiansen SC, Romundstad PR, Cannegieter SC, Blom HJ, Rosendaal FR, et al. Prospective study of homocysteine and MTHFR 677TT genotype and risk for venous thrombosis in a general population–results from the HUNT 2 study. *Br J Haematol*. (2008) 141:529–35. doi: 10.1111/j.1365-2141.2008.07073.x

39. den Heijer M, Willems HP, Blom HJ, Gerrits WB, Cattaneo M, Eichinger S, et al. Homocysteine lowering by B vitamins and the secondary prevention of deep vein thrombosis and pulmonary embolism: A randomized, placebo-controlled, double-blind trial. *Blood*. (2007) 109:139–44. doi: 10.1182/blood-2006-04-014654

40. Krøigaard SM, Clemmensen L, Tarp S, Pagsberg AK. A meta-analysis of antipsychotic-induced hypo- and hyperprolactinemia in children and adolescents. *J Child Adolesc Psychopharmacol*. (2022) 32:374–89. doi: 10.1089/cap.2021.0140

41. Burghardt KJ, Mando W, Seyoum B, Yi Z, Burghardt PR. The effect of antipsychotic treatment on hormonal, inflammatory, and metabolic biomarkers in healthy volunteers: A systematic review and meta-analysis. *Pharmacotherapy*. (2022) 42:504–13. doi: 10.1002/phar.2689

42. Ishioka M, Yasui-Furukori N, Sugawara N, Furukori H, Kudo S, Nakamura K. Hyperprolactinemia during antipsychotics treatment increases the level of coagulation markers. *Neuropsychiatr Dis Treat*. (2015) 11:477–84. doi: 10.2147/NDT.S75176

43. Atmaca A, Gurlek A, Dagdelen S, Erarslan N, Buyukasik Y, Gultekin M, et al. Hyperprolactinemia of pregnancy is not associated with increased in *vivo* platelet activity and shortened in *vitro* bleeding times. *Exp Clin Endocrinol Diabetes*. (2006) 114:188–91. doi: 10.1055/s-2006-924064

44. Wallaschofski H, Kobsar A, Sokolova O, Siegemund A, Stepan H, Faber R, et al. Differences in platelet activation by prolactin and leptin. *Horm Metab Res*. (2004) 36:453–7. doi: 10.1055/s-2004-825727

45. van Zaane B, Squizzato A, Reuwer AQ, van Zanten AP, Twickler MT, Dekkers OM, et al. Prolactin and venous thrombosis: indications for a novel risk factor? *Arterioscler Thromb Vasc Biol*. (2011) 31:672–7. doi: 10.1161/ATVBAHA.110.209569

46. Montes de Oca P, Macotela Y, Nava G, López-Barrera F, de la Escalera GM, Clapp C. Prolactin stimulates integrin-mediated adhesion of circulating mononuclear cells to endothelial cells. *Lab Invest*. (2005) 85:633–42. doi: 10.1038/labinvest.3700256

Prevalence and associated factors of premenstrual dysphoric disorder among high school students in Finote Selam town, northwest Ethiopia

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Background: Premenstrual dysphoric disorder (PMDD) is the most prevalent but neglected psychiatric disorder, with somatic symptoms that are severe enough to markedly affect usual daily activities and have a negative impact on mental health and quality of life by affecting female patients' behavior and cognition. Studies regarding premenstrual dysphoric disorder and associated factors among high school students in low- and middle-income countries are limited. Therefore, the aim of this study was to assess the prevalence and associated factors of PMDD among high school students, and this is pivotal in further investigation.

Methods: A school-based cross-sectional study was conducted from March 25 to April 17, 2023 using a simple random-sampling technique to select a sample of 564 participants. Premenstrual dysphoric disorder was assessed using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Self-administered standardized questionnaires were used to collect data.

Result: A total of 548 study participants participated, with a 97.2% response rate. The prevalence of premenstrual dysphoric disorder among high school students was found to be 33.03% (95%CI: 29.20−37.09). In a multivariable analysis, irregular menstruation cycle (AOR = 4.242, 95%CI = 2.182−8.246), depression (AOR = 5.272, 95%CI = 2.779−10.002), having greater than 4 days of menstruation bleeding duration (AOR = 2.138, 95%CI = 1.105−4.138), and high perceived stress (AOR = 3.468, 95%CL = 1.217−9.880) were the factors significantly associated with premenstrual dysphoric disorder.

Conclusion: The overall prevalence of PMDD which was one-third among high school students was high. Moreover, long duration of menstruation bleeding, depressive symptoms, irregular menstruation cycle, and high perceived stress were significant factors in PMDD. Therefore, it needs early screening and

intervention in primary healthcare settings, especially for those who have high perceived stress, having depression, having a long duration of menstruation bleeding, and having an irregular menstruation cycle, so as to have good academic achievement and psychological wellbeing.

Introduction

Premenstrual dysphoric disorder (PMDD) is a combination of physical pain and emotional or behavioral abnormalities that start around a week before the start of menstruation (1). Around the world, 3% to 8% of women of reproductive age experience premenstrual dysphoric disorder (PMDD) (2). Prevalence data from around the world reveals that up to 75% of all women of reproductive age may suffer premenstrual syndrome (PMS), with 5% to 20% of women of reproductive age reporting moderate to severe premenstrual complaints. About 94.8% of women of reproductive age had PMS, characterized by one or more physical, emotional, or behavioral symptoms in the days leading up to menstruation (15 to 49 years) (3). In Africa, including Ethiopia, the magnitude of premenstrual dysphoric disorder is between 10.2% and 66.9% (4–7).

Premenstrual dysphoric disorder (PMDD) is a serious condition that seriously impairs a woman's functionality and quality of life. It affects female behavior, cognitive capacities, mental health status (like being seven times more likely to have suicidal thoughts and nearly four times more likely to attempt suicide), academic performance, interpersonal relationships, daily activities, and work productivity. A woman's general physical health can all be negatively impacted by PMDD (8–11). Even though the majority of women with PMS can carry out their daily tasks when in its extreme form, this condition has been linked to increased absenteeism from work and school, poor academic performance, high suicide ideation and attempt rates, and significant mental health issues (5, 12).

Students struggle to get out of bed and be at class on time, and unexpected mood changes make it challenging to deal with the fallout. When PMS is not treated and women experience additional personal or environmental stress, the symptoms become more severe, eventually developing into PMDD, a mental disease (13–15).

Different factors affect PMDD, including age, body mass index (BMI <30 kg), monthly pain, amount of menstrual blood loss, history of physical and mental illness, treatment-seeking behavior, history of traumatic events, sleeping hours, physical activity, not using the family planning method, and maternal history of PMS (16–18). Blood loss during periods, the existence of dysmenorrhea, a mother or sister with a positive premenstrual syndrome, and low agreeableness and extroversion as well as high neuroticism were significant risk factors for PMDD in terms of personality traits (10, 19, 20).

A family history of PMS and dysmenorrhea increases the risk. Other menstrual characteristics, such as age at menarche, irregular menstruation, a longer average menstrual cycle, menorrhagia, consuming tea, coffee, sweets or sweetened beverages, and junk food, food intake, and stress were significant predictors of PMDD (4, 10, 21).

While PMDD among high school students has been relatively well researched in developed countries, more premenstrual syndrome studies are available in developing countries, including Ethiopia. Nevertheless, in Africa, including Ethiopia, some premenstrual dysphoric disorder studies are available among university students. According to my research engine, a few studies were conducted among high school students in developing countries. Even though premenstrual disorders (PMDD) have a significant impact on academic performance, yet, in Ethiopia, premenstrual difficulties still receive insufficient attention (19). Those few studies were done without including factors like perceived stress and clinical factors like a history of mental illness (suicide and major depression). Therefore, this study assessed the prevalence of PMDD and various factors that might lead to early interventions for further obstacles among high school students.

Methods and materials

Study area, design, and period

The study was conducted in west Gojjam. Finote Selam town is one of the zones in the Amhara Region of Ethiopia. It is far by 171.2 km from Bahir Dar of Amhara Region town and 246 km from Addis Ababa, the capital city of Ethiopia. Based on the 2007 national census conducted by the Central Statistical Agency of Ethiopia (CSA), this town had a total population of 25,913, of whom 13,035 were men and 12,878 women. Most (97.92%) inhabitants practice Ethiopian Orthodox Christianity, and 2.08% are Muslim.

Moreover, 99.45% are members of the Amhara ethnic group. Three governmental high schools currently enroll 4,055 female students, but there are no private schools. There is one primary hospital and two health centers in the district which serve the community. A school-based cross-sectional study design was employed from March 25 to April 17, 2023 in Finote Selam town high school students. The source population was high school students who have been studying in Finote Selam town, and the study population comprised all high school students who were available during the data collection period in 2023.

Inclusion criteria

Students who have attended a class during the data collection time were included.

Exclusion criteria

High school students who were in serious conditions like illness at data collection time were excluded. Students who transferred from other schools to Finote Selam High School in the second semester of 2023 were also excluded.

Sample size determination and sampling techniques

The sample size was determined by assuming a single proportional formula. The prevalence of premenstrual dysphoric disorder was taken from a previously published study in Ethiopia at Ayder High School, Mekelle, and the magnitude of premenstrual dysphoric disorder was at 30.9% (22). The sample size (n) is calculated using a 95% confidence interval (CI) and a margin of error of 4% as follows:

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

where n = sample

z = critical value, 1.96

p = assumed prevalence of premenstrual dysphoric disorder from the previous study at Mekelle High School, 30.9%

d = precision (marginal error), 0.04

q = 1 - p

So, the minimum sample size was derived as follows:

$$n = \frac{(1.96)2 \times 0.309 \times 0.691 = 513}{(0.04)2}$$

Including 10% of the non-response rate, the final sample size was 513 + 51 = 564.

Associated factors, including severe menstrual pain, high perceived stress, and severe degree of dysmenorrhea, were highly associated with PMDD from previous studies at the University of Gondar and Wollo University (19, 22, 23). Therefore, using Epinfo version 7 software by double population formula, 95%CI and power 80% can be calculated, and high school students in the area of the study were stratified based on their schools in each grade, which are grade 9, grade 10, grade 11, and grade 12. Data from the Education Office indicated that the total number of high school students during data collection was 4,055 (grade 9 = 1,685, grade 10 = 1,070, grade 11 = 778, and grade 12 = 522). Then, the proportional allocation of study subjects for each school and each grade was calculated. Finally, a computer-generated method was used to select study participants from each stratum.

Data collection tool

Data was gathered using a comprehensive, well-organized questionnaire that was created after evaluating related literature and being adjusted for our situation.

An outcome variable prevalence of premenstrual dysphoric disorder was assessed by using DSM-5. The American Psychiatric Association produced the DSM-5, which is presently used in Ethiopia to diagnose clinical PMDD. Female students were deemed to have PMDD if they reported at least five DSM-5 diagnostic criteria symptoms in most of their menstrual cycles. These symptoms had to be present in the final week before the start of menstruation (1).

The Perceived Stress Scale-10 item (PSS-10), determined to be extremely reliable for assessing the role of stress in the etiology of psychiatric and behavioral illnesses, was used to measure individual stress levels. Scores on the PSS-10 ranging from 0 to 13 indicated low felt stress, scores 14 to 26 indicated moderately perceived stress, and scores 27 to 40 were thought to indicate highly perceived stress. In the evaluation of its dependability, a Cronbach's alpha of 0.88 was used (24).

Depression in high school was assessed using Patient Health Questioner (PHQ-9). It is a nine-item version, and each item response is rated as "0" (not at all) to "3" (nearly every day); the total score ranges from 0 to 27, with a cutoff ≥5 to indicate having depression symptoms. It has sensitivity of 88% and specificity of 88%. PHQ-9 has been translated and validated in Ethiopia and has been used extensively therein previously to assess depression (25).

The Oslo three-item social support scale, which had a cumulative score range of 3 to 14 and comprised three major categories, was used to evaluate social support. Respondents who scored between 3 and 8, 9 and 12, and 13 and 14 were classified as having weak, moderate, and strong social support, respectively, according to this category. Cronbach's alpha for the current study was 0.79, indicating acceptable reliability (26).

Structured yes/no questions were used to evaluate clinical factors such as family history of mental illness, history of other mental illnesses, suicidal ideation and attempt, and chronic medical illness.

The World Health Organization's (WHO) ASSIST (Alcohol, Smoking, and Substance Involvement Screening Test), a highly validated instrument, was utilized in the questionnaire's behavioral component sections, which include questions about substance use for its evaluation (current use and ever use) (27, 28).

The obstetric and gynecological variables menstrual cycle, menstrual pain, and age of menarche were evaluated using structured questions taken from the literature. The number of pads used per day during the menstrual period was used to calculate the amount of menstruation (22).

Menstrual pain was measured using a three-point verbal rating scale (VRS) with the adjectives mild, moderate, and severe rather than the four-point VRS with a "no pain" category. Only respondents who reported having dysmenorrhea were asked to rate their pain levels (29, 30).

Data collection

Data were collected using self-administered questionnaires. Three BSc nurses collected data using self-administered questionnaires. Two BSc psychiatry profession supervisors and the principal investigator were participating. For those data collectors and the supervisor, one training day was given before the data collection date. During the training, the objectives of the study were discussed. The data collection methods and tools, as well as how to handle ethical issues, were discussed with the data collectors. The structured questionnaire was also discussed in detail by going through each question with clarification for doubt.

Data quality assurance

To control the quality of the data, the questionnaire was translated appropriately into the local

Amharic language. At 1 week before the actual data collection, the questionnaire was pretested. Collection time was on 5% ($N = 28$) of Jiga High School students' studies, which was not be included in the primary survey. Therefore, the dependent variable tool assessment (DSM-5) Cronbach alpha was 0.83. The collected data was adequately handled, reviewed, and checked for completeness and consistency by the supervisor and principal investigator each day.

Data processing and analysis

The collected data were coded, cleaned, entered, and checked into the computer using EPI data version 4.6.02 and then imported into STATA version 14 to generate descriptive statistics: means, frequencies, percentages, and standard deviations. Logistic regression was used to determine an association between dependent and independent variables and to adjust odds ratios, and the significance level was determined. Using a confidence interval of 95%, univariable and multivariable logistic regressions were used to identify the independent predictors of premenstrual dysphoric disorder. This was done by entering each independent variable separately into the univariable analysis. The variables with a p-value of less than 0.2 on the univariable analysis were entered into the multivariable analysis. The statistically significant variables are then considered. An association with a p-value less than or equal to 0.05 on logistic regression was considered a predictor of premenstrual dysphoric disorder. Hosmer and Lemeshow test, with a p-value of 0.8026 for premenstrual dysphoric disorder, was applied to test the logistic regression model for the goodness of fit. Multicollinearity was performed for the model, and none of the variables scored above 10 (mean VIF = 1.27). For all statistical tests, a p-value less than 0.05 was considered significant.

Results

Sociodemographic characteristics of the respondents

Data were obtained from 548 female high school students with a response rate of 97.2%. The mean age of the participants was 17.312 ± 1.631, ranging from 15 to 22 years old, and 415 (75.73%) were between 15 to 18 years old. Almost three-fourths, 409 (74.64%), of students were originally from urban areas. The majority of students were single, 469 (85.58%), and more than half of the students lived with their two parents, 316 (57.66%) (Table 1).

Clinical characteristics of the respondents

Out of the total participants, 12 (2.19%) students had a known chronic medical illness, 19 (3.47%) had a history of mental illness, 47 (8.58%) had a family history of mental illness, 31 (5.66%) had lifetime suicide ideation, and 13 (2.32%) students had suicidal ideation within the last 12 months—from those students, seven (1.28%) had a suicide attempt within the last 3 months—and 209 (38.14%) students had depression symptoms (Table 2).

Substance-related factors of the respondents

Regarding substance use, out of out of 548 students, 86 (89.58%) had drunk alcohol at least once in their lifetime, whereas khat and cigarette lifetime users were seven (7.29%) and three (3.13%), respectively. Within the last 3 months, the total number of respondents who used alcohol was 26 (100%) (Table 3).

Psychosocial-related factors of the respondents

Regarding social support factors, among the total participants, 165 (30.11%) had poor social support, 308 (56.20%) had moderate social support, and 75 (13.69%) had strong social support (Figure 1).

Regarding perceived stress factors, from the total participants, 324 (59.12%) had low stress, 176 (32.12%) had moderate stress, and 48 (8.7%) had high stress (Figure 2).

Gynecological and obstetric characteristics of the respondents

Of the total participants, 386 (67.15%) had menses that started at the age of 13 to 16 years, and more than half of the respondents, 304 (55.47%), had irregular menstruation periodicity. There were

TABLE 1 Sociodemographic characteristics of the participants among high school students in Finote Selam town (n = 548), 2023.

Variables	Category	Frequency	Percent
Age	15–18	415	75.73
	>18	133	24.27
Residence	Rural	139	25.36
	Urban	409	74.64
Class of students	9	226	41.24
	10	143	26.09
	11	107	19.53
	12	72	13.14
Living arrangement	Mother and father	316	57.66
	One of the two	62	11.31
	Living alone	84	15.33
	Relatives	52	9.49
	Others	34	6.21
Mother education level	Unable to read and write	233	42.52
	Primary	150	27.37
	Secondary	75	13.69
	College and above	67	12.22
	Informal	23	4.20
Father education level	Unable to read and write	132	24.08
	Primary	153	27.92
	Secondary	84	15.33
	College and above	131	23.91
	Informal	48	8.76
Marital status	Single	462	84.30
	Married	62	11.33
	Divorce	13	2.36
	Widowed	11	2.010
Absenteeism	Yes	391	71.35
	No	157	28.65
Academic performance (score) first semester	A low score (<70)	266	48.54
	Average score (70–84.99)	179	32.65
	A good score (≥85)	103	18.81
Pocket money/months	Yes	109	19.89
	No	439	80.11

Others: home worker, friends, guardian.

TABLE 2 Clinical characteristics of the participants among high school students at Finote Selam town (n = 548), 2023.

Variables	Category	Frequency	Percent
Known chronic medical illness	Yes	12	2.19
	No	536	97.81
Diagnosis mental illness	Yes	19	3.47
	No	529	96.53
Ever thought of killing	Yes	31	5.66
	No	517	94.34
Thought of killing last 12 months	Yes	13	2.37
	No	535	97.53
Ever attempt killing self	Yes	7	1.28
	No	541	98.72
attempt killing yourself last 12 months	Yes	5	0.91
	No	543	99.09
Family history of mental illness	Yes	47	8.58
	No	501	91.42
Depressive symptoms	Yes	209	38.14
	No	339	61.86

447 (81.57%) students who reported to have menstrual pain from those, 172 (31.39%) had a long duration of menstruation bleeding, 158 (28.83%) had severe menstrual pain, 214 (39.05%) perceived that the menstrual pain had an impact on their academic performance, and 356 (64.96%) missed their class at least once in their school. A total of 115 (20.99%) respondents had a family history of menstrual-related problems. Of the total respondents, 217 (39.60) used greater than four pads during the menstrual period; those were high amounts of menstrual bleeding. Students who had menstrual pain used different pain management techniques: non-prescribed pain killer for 122 (22.26%), hot drinks for 362 (66.06%), massage for nine (1.64%), and consultation for 55 (10.04%) (Table 4).

TABLE 3 Substance-related description of the participants among high school students in Finote Selam town (n = 548), 2023.

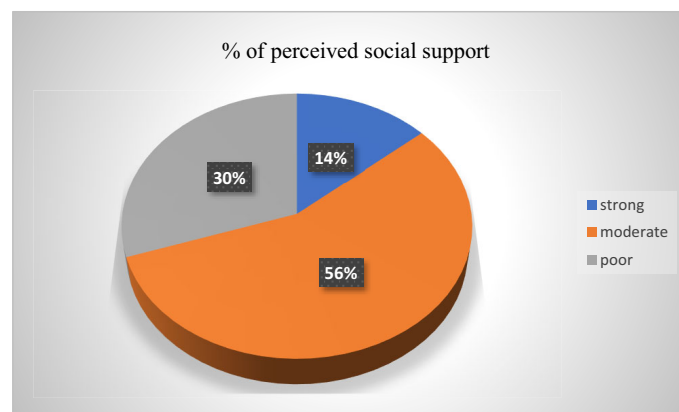| Variables	Category	Frequency	Percent
Ever use of a substance	Yes	96	17.52
	No	452	82.48
Which substance	Alcohol	86	89.58
	Chat	7	7.29
	Cigarette	3	3.13
Within 3 months of ever use of a substance	Yes	26	4.74
	No	522	95.26
Which substance	Alcohol	26	100

FIGURE 1
Psycho-social characteristics of participants among high school students in Finote Selam town (*n* = 548), 2023.

Prevalence of premenstrual dysphoric disorder

In this study, the overall prevalence of premenstrual dysphoric disorder among high school students was 33.03% (181) (95%CI: 29.20–37.09). The most commonly reported symptom was physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of "'bloating," and weight gain (55.39%), followed by being easily fatigued or a marked lack of energy (48.36%) (Table 5).

Factors associated with premenstrual dysphoric disorder

In a univariable logistic regression analysis, the factors that fulfilled a *p*-value less than 0.2 were starting age of menses at 13 to 16 years old, menstrual pain, amount of menstruation bleeding, duration of menstruation bleeding days, menstruation periodicity, family history menstruation related problem, perception impact of menstruation pain, perceived stress, having depression symptoms, and treatment seeking behavior. Finally, a multivariable analysis revealed that irregular menstrual cycle, having depressive symptoms, high perceived stress, and duration of menstruation bleeding greater than 4 days were found to be significantly associated with PMDD with 95% CI and at a *p*-value less than or equal to 0.05.

Those who had an irregular menstruation cycle were about (AOR = 4.242, 95%CI = 2.182–8.246) four times more likely to develop PMDD compared with those who had a regular menstruation cycle, and students who had depressive symptoms were about (AOR = 5.272, 95%CI = 2.779–10.002) five times to develop PMDD when compared to students who had no depression. Another associated factor with PMDD was having greater than 4 days of menstruation duration, which is (AOR = 2.138, 95%CI = 1.105, 4.138) two times more odds of having PMDD than those who had less than 4 days of menstruation duration. Students who had high perceived stress were about (AOR = 3.468, 95%CI = 1.217–9.880) 3.5 times to develop PMDD compared to those with low perceived stress (Table 6).
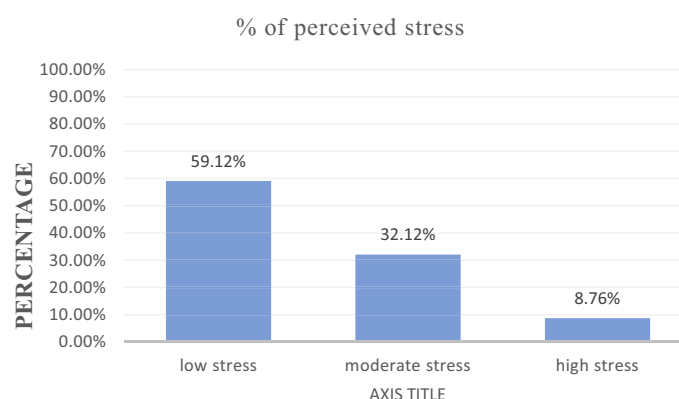

FIGURE 2
Perceived stress characteristics of low "felt" stress (0 to 13), moderate "felt" stress (14 to 26), and high "felt" stress (27 to 40) among high school in Finote Selam town (*n* = 548), 2023.

TABLE 4 Description of the gynecological and obstetric factors of the participants among high school students in Finote Selam town (*n* = 548), 2023.

Variable	Category	Frequency	Percent
Age when menses start	Before 13 years	99	18.07
	13 to 16 years	368	67.15
	After 16 years	81	14.78
Menstruation periodicity	Regular	244	44.53
	Irregular	304	55.47
Menstrual pain	No pain	101	18.43
	Mild pain	175	31.93
	Moderate pain	114	20.81
	Severe pain	158	28.83
Duration of menstrual bleeding	≤4 days	376	68.61
	>4 days	172	31.39
Amount of menstruation	Minimal (1 pad)	28	5.11
	Moderate (2–4 pads)	303	55.29
	Heavy (>4 pads)	217	39.60
Family history of menstrual-related problems	Yes	115	20.99
	No	433	79.01
Perception of impact on academic performance	Yes	214	39.05
	No	334	60.95
Impact of menstrual pain	Missing classes	356	64.96
	Missing tests	116	21.17
	Decreased score	60	10.95
	Dropped out	16	2.92
Actions taken for the menstruation pain	Non-prescribed painkiller	122	22.26
	Hot drinks	354	64.60
	Massage	17	3.10
	Consultation	55	10.04

TABLE 5 Frequency distribution of DSM-5 criteria to assess premenstrual dysphoric symptoms among high school students in Finote Selam town (*n* = 548), 2023.

Variable	Category	Frequency	Percent
Marked affective lability	Yes	186	33.94
	No	362	66.06
Marked irritability or anger or increased interpersonal conflicts	Yes	160	29.20
	No	388	70.80
Marked depressed mood, feelings of hopelessness or self-deprecating thoughts	Yes	167	30.47
	No	381	69.53
Marked anxiety, tension, feelings of being keyed up or on edge	Yes	221	40.33
	No	327	59.67
Decreased interest in usual activities (e.g., work, school, friends and hobbies	Yes	264	48.18
	No	284	51.82
Subjective difficulty in concentration	Yes	260	47.45
	No	288	52.55
Lethargy, easily fatigued, or a marked lack of energy	Yes	265	48.36
	No	283	51.64
A marked change in appetite, overeating, or specific food cravings	Yes	220	40.15
	No	328	59.85
Hypersomnia or insomnia	Yes	119	21.72
	No	429	78.28
Sense of being overwhelmed or out of control	Yes	154	28.10
	No	394	71.90
Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of "bloating," weight gain	Yes	303	55.29
	No	245	44.71

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition.

Discussion

Premenstrual dysphoric disorder has a negative impact on social interaction and educational achievement by increasing school absenteeism. Because of premenstrual symptoms, students prevent the participants from going to school due to their ignorance of menstruation, and women experience a range of feelings during menarche, including fear, embarrassment, and guilt (31). Those symptoms persist for days to a week: breast tenderness or swelling, joint or muscle pain, a sensation of "bloating," weight gain, easily fatigued or a marked lack of energy, and difficulty in concentrating. As a result, it is important to ascertain the prevalence of PMDD and identify the risk factors for it. Additionally, this would aid in problem prevention and the development of treatment plans that support female high school students' academic success.

This study found that the prevalence of PMDD among female high school students was 33.03% (95%CI: 29.20—37.09). This is consistent with other studies done in Ethiopia reported to be 30.9% in Mekelle High School (6) and 34.7% in the University of Gondar (19). Another study in Africa was consistent with this study at Nigeria University (36.1%) (5).

However, the prevalence of premenstrual dysphoric disorder in this study was higher than the previous research findings in Ethiopian students whose prevalence at Debr Berhan University was 13.8% (30) and at Assosa Technical Training College was 26.8% (32). The study's variation may be due to differences in the study population, with younger individuals more likely to experience

TABLE 6 Overall bivariable and multivariable logistic regression analysis of factors associated with premenstrual dysphoric disorder among high school students in Finote Selam town (*n* = 548), 2023.

Variable	Category	PMDD		COR and 95%CI	AOR and 95%CI	P-value
		Yes	No			
Amount of menstruation bleeding	Heavy (>4 pad)	151	66	4.829 (2.076, 11.234)	3.095 (0.951, 2.065)	0.060
	Moderate (2–4 pads)	21	282	0.157 (0.063, 1.016)	0.201 (0.059, 1.068)	0.781
	Minimal (1 pad)	9	19	1	1	
Perceived stress	High stress	26	22	4.709 (2.509, 8.837)	3.468 (1.217, 9.880)	**0.020***
	Moderate stress	90	86	4.169 (2.790, 6.230)	1.197 (0.609, 2.354)	0.601
	Low stress	65	259	1	1	
Menstruation pain	Severe pain	114	44	7.876 (4.453, 13.931)	2.259 (0.949, 5.376)	0.149
	Moderate pain	30	84	1.085 (0.587, 2.007)	0.378 (0.150, 1.009)	0.217
	Mild pain	12	163	0.223 (0.106, 1.070)	0.126 (0.045, 1.316)	0.215
	No pain	25	76	1	1	
Menstruation cycle	Irregular	148	156	6.066 (3.944, 9.328)	4.242 (2.182, 8.246)	**0.000*****
	Regular	33	211	1	1	
Age at menarche	Before 13 years	16	83	0.550 (0.265, 1.143)	0.403 (0.137, 1.186)	0.082
	13 to 16 years	144	224	1.836 (1.071, 3.149)	2.091 (0.870, 5.026)	0.099
	After 16 years	21	60	1	1	
Depression	Depressive	107	102	3.756 (2.584, 5.461)	5.272 (2.779, 10.002)	**0.002****
	Not depressive	74	265	1	1	
Duration of menstruation bleeding	>4 days	106	66	6.445 (4.329, 9.596)	2.138 (1.105, 4.138)	**0.024***
	≤4 days	75	301	1	1	
Perception impact of pain	Yes	104	110	3.155 (2.180, 4.567)	0.901 (0.480, 1.691)	0.747
	No	77	257	1	1	
Family history menstrual related problems	Yes	57	58	2.448 (1.607, 3.730)	0.996 (0.491, 2.023)	0.993
	No	124	309	1	1	
Treatment seeking behavior	Non-prescribed anti-pain	69	53	3.1733 (1.602, 6.283)	0.864 (0.259, 2.876)	0.812
	Hot drink	90	264	0.830 (0.463, 2.623)	0.640 (0.215, 1.901)	0.422
	Massage	6	11	1.329 (0.035, 2.638)	0.163 (0.008, 3.266)	0.236
	Consultation	16	39	1	1	

Hosmer–Lemeshow test = 0.8026, mean VIF = 1.27, Cronbach alpha = 0.725.
*p-value ≤ 0.05; **p-value ≤ 0.01; ***p-value ≤ 0.001.
The bold text indicated that these factors were significantly associated with PMDD.

premenstrual dysphoric disorder, while older students are less susceptible (33).

The current premenstrual dysphoric disorder prevalence was also higher in studies done in Egypt University (21.1%) (10) and South Africa University (10.2%) (34). The discrepancy might be the difference in the study population as well as sociocultural and socioeconomic characteristics. In Ethiopia, high school students reach puberty and start menstruating often without adequate information and have no psychological readiness to manage it, causing the onset of menstruation (menarche) to be shocking for girls. In high school, the lack of information is accompanied by a

lack of access to appropriate sanitary wear and proper facilities for managing menstruation (35).

The finding of the current study was also higher in studies conducted at Kuwait University (5.6%) (36), at Jordan University (7.7%) (37), in Vietnam high schools (1.0%) (38), in Korea (2.4%) (39), in India high schools (4.89%) (40), in Japan high schools (3.1%) (41), among Iran high school students (12.22%) (42), and in Germany (5.8%) (43) as well as with American rates of 6% and 4.7% PMDD, respectively (44, 45). The possible reason for the variation may be differences in socioeconomic determinants. This means that, in developed countries, there are good sanitary products,

adequate water supply, and privacy for changing sanitary pads, which continue to leave high school students unlimited options for safe and sufficient menstrual hygiene in high-income settings. Because of this reason, female students in menstruation will feel less shame, self-isolation, irritability, emotional liability, headaches, anxiety, depression, and traumatic experiences (46). Furthermore, the availability of health facilities between those countries and Ethiopia could be poor due to poor healthcare infrastructure and a shortage of trained health staff, which would lead to the delivery of inadequate healthcare services. In turn, premenstrual dysphoric disorder might not be identified and treated early.

In terms of sociocultural aspects, in Ethiopia, there is also a common belief (more commonly held by men) that menstruation does not start until a girl has a sexual intercourse for the first time (31). The existence of this false belief presents a potential hazard for girls approaching menarche if they live in families where this belief is held. The beginning of menses in girls is manifested when irritability, emotional liability, headaches, anxiety, depression, and traumatic experiences appear.

The other reason is that menstrual hygiene management is influenced by a variety of factors, including knowledge of reproductive biology, background beliefs about menstruation that are prevalent in societies, and the limitations that these beliefs place on female-related activities. Due to their confusion, embarrassment, and lack of preparation for the abrupt and unexpected onset of menstruation, adolescent girls may find it difficult to grow academically and socially due to menstrual hygiene management issues (47, 48). In terms of the type of study populations, between high school and university students, the latter have increased their knowledge about menstruation and experience of menses and thus have decreased behavioral changes due to menstruation.

On the other hand, the current study's finding is lower than the previous study done at Ethiopian Wollo University (66.9%) (21). The discrepancy may be the fact that the study at Wolo University surveyed first year to fourth year students, primarily first year students. As students transition into higher education, they face challenges like integrating into university culture, socioeconomic issues, interpersonal problems, demanding course loads, and insufficient institutional support, making them vulnerable to stress and depression (49), which might increase the prevalence of PMDD.

The current study's finding was also lower in studies conducted at Morocco University (55%) (50). The discrepancy might be due to the tools of assessment used in Morocco. The Moroccan high school students used the Daily Record of Severity of Problems (DRSP), but DRSP is a screening tool and not a diagnostic tool, and this might overestimate the prevalence of premenstrual dysphoric disorder among students (51). Moreover, the other discrepancy might be the sociocultural aspect since students in Ethiopia do not express their actual feelings related to premenstrual symptoms such as depressed mood, irritability, emotional, and somatic symptoms because of the culture of silence and associated stigma around menstruation; thus, this topic is not openly discussed at the family level. The abovementioned reason might be the reason for the lower prevalence of PMDD in this study (33).

Regarding factors affecting premenstrual dysphoric disorder, the duration of menstruation bleeding was significantly associated with a higher rate of premenstrual dysphoric disorder. The odds of premenstrual dysphoric disorder were two times among those students having longer durations of menstruation bleeding than students with shorter durations (<4 days). These findings were supported by other studies done among Mekelle high school students, Ethiopia (6), and among university students from Egypt (10) and Nigeria (5). The possible reason might be that having a long duration of menstruation bleeding days could cause fluctuations ranging from hormone-related issues like estrogen and progesterone that can increase the vulnerability to premenstrual dysphoric disorder because a drop in estrogen and progesterone may lead to a reduced level of serotonin, which can result in increased levels of sadness, anxiety, and irritability when women are on menses. Other reasons might be that, with a long duration of menstruation bleeding, students become absent from school and have decreased social interaction, which can increase the academic burden on students and which, in turn, can lead them to have low self-confidence and poor academic performance (31, 35, 52).

The present study also showed that premenstrual dysphoric disorder is significantly associated with high perceived stress among high school students. The odds of premenstrual dysphoric disorder were more than three times higher among students with high perceived stress than those without such stress. Similar findings were reported in the University of Gondar, Ethiopia, and Jordan (19, 53). The possible reason might be the development of anxiety and depressive symptoms like tension, a sense of difficulty in controlling one's self, a depressed mood, and irritability resulting from people becoming more stressed, thus impairing their ability to concentrate in school.

The aggravation of cardinal mood symptoms may be caused by premenstrual symptoms like anger and irritability which are linked to stress-related premenstrual severity. Others claim that students with low-income levels had a higher perceived stress, which can indirectly affect the prevalence of PMDD compared to those with higher incomes. Furthermore, this may be due to believing that having a low income is a very stressful situation in life, making premenstrual symptoms more severe and prevalent (54, 55).

Students with irregular menstrual cycles had about four times higher odds of premenstrual dysphoric disorder than students with regular menstrual cycles. This finding is consistent with other findings at Assosa Technical Training College, Ethiopia (32). Students who experience irregular menstrual cycles may develop a premenstrual dysphoric disorder for various reasons, i.e., students may experience high rates of absenteeism from class due to irregularities of menstruation each month, premenstrual symptoms, a lack of attention to their problems, and a lack of confidence during bleeding, all impacting their capacity to learn (56).

Students with depressive symptoms had about five times higher odds of premenstrual dysphoric disorder as compared with those who had no depressive symptoms. This finding is consistent with findings from Nigeria University (5) and among Korean women (57). The possible reason could be that women have more depressive symptoms, such as different somatic and affective symptoms that interrupt their function, which can aggravate

those somatic and affective symptoms like joint pain, irritability, lack of energy, depressed mood, and difficulty in concentrating during menstruation (58).

Strength and limitation of the study

We used an adequate sample for the study using an appropriate probability sampling technique and data collection procedure. However, there is recall bias—for example, age when menses started—, and the cross sectional study design by itself cannot assess the cause and effect relationship.

Conclusion

In this study, the magnitude of premenstrual dysphoric disorder was one-third among high school students, and it was higher compared to other studies. Long-duration menstruation periods, irregular menstruation cycles, high perceived stress, and depressive symptoms were factors significantly associated with PMDD among students. Therefore, it needs early screening and intervention in primary healthcare settings, especially for those who have high perceived stress, depressive symptoms, a long duration of menstruation bleeding, and an irregular menstruation cycle, so as for them to have good academic achievement and psychological wellbeing. Before menstrual symptoms can have an impact on students' academic performance, early diagnosis and intervention are required. Stress reduction programs could be a useful non-pharmaceutical treatment for relieving psychological and physical symptoms.

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 Ethical review committee of the University of Gondar. 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

Funding

Acknowledgments

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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References

1. Association AP. *Diagnostic and statistical manual of mental disorders*. Arlington: American Psychiatric Publishing (2013).

2. Dennerstein L, Lehert P, Heinemann K. Epidemiology of premenstrual symptoms and disorders. *Menopause Int*. (2012) 18:48–51. doi: 10.1258/mi.2012.012013

3. Ehalaiye B, Eigbefoh J, Eifediyi RA, Omorogbe F, Isabu PA, Ugiagbe OA, et al. Premenstrual syndrome: prevalence, pattern and severity among female university students in Ekpoma, Nigeria. *Trop J Obstetrics Gynaecology*. (2009) 26:142–50.

4. Adewuya A, Loto O, Adewumi T. Premenstrual dysphoric disorder amongst Nigerian university students: prevalence, comorbid conditions, and

correlates. *Arch Womens Ment Health*. (2008) 11:13–8. doi: 10.1007/s00737-008-0213-4

5. Issa BA, Yussuf AD, Olatinwo AWO, Ighodalo M. Premenstrual dysphoric disorder among medical students of a Nigerian university. *Ann Afr Med*. (2010) 9. doi: 10.4103/1596-3519.68354

6. Mossie TB, Tesfaye YB, Metekiya WM, Tegegne MT. Magnitude of premenstrual dysphoric disorder and associated factors among high school girls, Mekelle, North Ethiopia. *Ethiopian Journal of Health Development* (2015) 29(3):170-5.

7. Tadesse MG, Dire DD, Abraham YY. Prevalence of premenstrial disphoric disorder associated factors among students of tabor secondary and preparatory school in Hawassa City, Ethiopia cross sectional. (2020). doi: 10.21203/rs.3.rs-35797/v1

8. Branecka-Woźniak D, Cymbaluk-Płoska A, Kurzawa R. The impact of premenstrual syndrome on women's quality of life–a myth or a fact? *Eur Rev Med Pharmacol Sci*. (2022) 26:598–609.

9. Petersen N, London ED, Liang L, Ghahremani DG, Gerards R, Goldman L, et al. Emotion regulation in women with premenstrual dysphoric disorder. *Arch Women's Ment Health*. (2016) 19:891–8. doi: 10.1007/s00737-016-0634-4

10. Eldeeb SM, Eladl AM, Elshabrawy A, Youssef AM, Ibrahim MH. Prevalence, phenomenology and personality characteristics of premenstrual dysphoric disorder among female students at Zagazig University, Egypt. *Afr J Primary Health Care Family Med*. (2021) 13:2924. doi: 10.4102/phcfm.v13i1.2924

11. Prasad D, Wollenhaupt-Aguiar B, Kidd KN, de Azevedo Cardoso T, Frey BN. Suicidal risk in women with premenstrual syndrome and premenstrual dysphoric disorder: a systematic review and meta-analysis. *J Women's Health*. (2021) 30:1693–707. doi: 10.1089/jwh.2021.0185

12. Baca-García E, González AS, Diaz-Corralero PG, García IG, De Leon J. Menstrual cycle and profiles of suicidal behaviour. *Acta Psychiatrica Scandinavica*. (1998) 97:32–5. doi: 10.1111/j.1600-0447.1998.tb09959.x

13. Takeda T, Tasaka K, Sakata M, Murata Y. Prevalence of premenstrual syndrome and premenstrual dysphoric disorder in Japanese women. *Arch Women's Ment Health*. (2006) 9:209–12. doi: 10.1007/s00737-006-0137-9

14. Harrison WM, Endicott J, Nee J, Glick H, Rabkin JG. Characteristics of women seeking treatment for premenstrual syndrome. *Psychosomatics*. (1989) 30:405–11. doi: 10.1016/S0033-3182(89)72246-5

15. Wang M, Seippel L, Purdy RH, Bäckström T. Relationship between symptom severity and steroid variation in women with premenstrual syndrome: study on serum pregnenolone, pregnenolone sulfate, 5 alpha-pregnane-3, 20-dione and 3 alpha-hydroxy-5 alpha-pregnan-20-one. *J Clin Endocrinol Metab*. (1996) 81:1076–82. doi: 10.1210/jcem.81.3.8772579

16. Dutta A, Sharma A. Prevalence of premenstrual syndrome and premenstrual dysphoric disorder in India: A systematic review and meta-analysis. *Health promotion perspectives*. (2021) 11:161. doi: 10.34172/hpp.2021.20

17. Duko B, Mekuriaw B, Molla A, Ayano G. The prevalence of premenstrual dysphoric disorder among adolescents in Ethiopia: a systematic review and meta-analysis. *Irish J Med Sci (1971-)*. (2021) 190:419–27. doi: 10.1007/s11845-020-02275-7

18. Jember D, Duko B, Mihretie G. Premenstrual dysphoric disorder among assosa techinical premenstrual & Vocational education school students, assosa, Ethiopia. *J Psychiatry*. (2017) 20:2.

19. Minichil W, Eskindir E, Demilew D, Mirkena Y. Magnitude of premenstrual dysphoric disorder and its correlation with academic performance among female medical and health science students at University of Gondar, Ethiopia, 2019: a cross-sectional study. *BMJ Open*. (2020) 10:e034166. doi: 10.1136/bmjopen-2019-034166

20. Patil R, Patil T, Chaudhary A, Maldhure S, Gulhane R. Premenstrual dysphoric disorder-its prevalence and associated factors in nursing staff of medical college of central India. *NVEO-NATURAL VOLATILES ESSENTIAL OILS Journal| NVEO*. (2021) 24: 1359–64.

21. Tsegaye D, Getachew Y. Premenstrual dysphoric disorder and associated factors among female health science students in Wollo University, Ethiopia, 2017/18. *Maternal Health Neonatology Perinatology*. (2019) 5:1–8. doi: 10.1186/s40748-019-0102-z

22. Mossie TB, Tesfye YB, Metekiya WM, Tegegne MT. Magnitude of premenstrual dysphoric disorder and associated factors among high school girls, Mekelle, North Ethiopia. *Ethiopian J Health Dev*. (2009) 23.

23. Tsegaye D, Getachew Y. Premenstrual dysphoric disorder and associated factors among female health science students in Wollo University, Ethiopia, 2017/18. *Maternal Health, Neonatology and Perinatol*. (2019) 5(1):1–8. doi: 10.1186/s40748-019-0102-z

24. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. (1983) 24:385–96. doi: 10.2307/2136404

25. Padhy SK, Sarkar S, Beherre PB, Rathi R, Panigrahi M, Patil PS. Relationship of premenstrual syndrome and premenstrual dysphoric disorder with major depression: relevance to clinical practice. *Indian J psychol Med*. (2015) 37:159–64. doi: 10.4103/0253-7176.155614

26. Dowrick C, Shiels C, Page H, Ayuso-Mateos J, Casey P, Dalgard O, et al. Predicting long-term recovery from depression in community settings in Western Europe: evidence from ODIN. *Soc Psychiatry Psychiatr Epidemiol*. (2011) 46:119–26. doi: 10.1007/s00127-009-0179-1

27. Newcombe D, Tanielu-Stowers H, McDermott R, Stephen J, Nosa V. The validation of the alcohol, smoking and substance involvement screening test (ASSIST) amongst Pacific people in New Zealand. *NZJ Psychol*. (2016) 45. doi: 10.1037/t57104-000

28. Humeniuk R, Ali R, Babor TF, Farrell M, Formigoni ML, Jittiwutikarn J, et al. Validation of the alcohol, smoking and substance involvement screening test (ASSIST). *Addiction*. (2008) 103:1039–47. doi: 10.1111/j.1360-0443.2007.02114.x

29. Ameade EK, Mohammed BS. Menstrual pain assessment: comparing verbal rating scale (VRS) with numerical rating scales (NRS) as pain measurement tools. (2016). doi: 10.23937/2474-1353

30. Alemu SM, Habtewold TD, Haile YG. Mental and reproductive health correlates of academic performance among Debre Berhan university female students, Ethiopia: the case of premenstrual dysphoric disorder. *BioMed Res Int*. (2017) 2017. doi: 10.1155/2017/9348159

31. Tegegne TK, Sisay MM. Menstrual hygiene management and school absenteeism among female adolescent students in Northeast Ethiopia. *BMC Public Health*. (2014) 14(1):1–14. doi: 10.1186/1471-2458-14-1118

32. Jember D, Duko B, Mihretie G. Premenstrual dysphoric disorder among female students at assosa techinical & Vocational education training school, assosa, Ethiopia. *Prevalence*. (2017) 16:17.

33. Wash U. Menstrual hygiene management in Ethiopia. (2017).

34. Roomaney R, Lourens A. Correlates of premenstrual dysphoric disorder among female university students. *Cogent Psychol*. (2020) 7:1823608. doi: 10.1080/23311908.2020.1823608

35. Bulto GA. Knowledge on menstruation and practice of menstrual hygiene management among school adolescent girls in Central Ethiopia: a cross-sectional study. *Risk Manag Healthc Policy*. (2021) 14:911–23. doi: 10.2147/RMHP.S296670

36. Omu FE, Al-Marzouk R, Delles H, Oranye NO, Omu AE. Premenstrual dysphoric disorder: prevalence and effects on nursing students' academic performance and clinical training in Kuwait. *J Clin Nurs*. (2011) 20:2915–23. doi: 10.1111/j.1365-2702.2011.03708.x

37. Shehadeh JH, Hamdan-Mansour AM. Prevalence and association of premenstrual syndrome and premenstrual dysphoric disorder with academic performance among female university students. *Perspect Psychiatr Care*. (2018) 54:176–84. doi: 10.1111/ppc.2018.54.issue-2

38. Dinh Trieu Ngo V, Bui LP, Hoang LB, Tran MTT, Nguyen HVQ, Tran LM, et al. Associated factors with Premenstrual syndrome and Premenstrual dysphoric disorder among female medical students: A cross-sectional study. *PloS One*. (2023) 18:e0278702. doi: 10.1371/journal.pone.0278702

39. Rapkin AJ, Korotkaya Y, Taylor KC. Contraception counseling for women with premenstrual dysphoric disorder (PMDD): current perspectives. *Open Access J Contraception*. (2019) 10:27–39. doi: 10.2147/OAJC

40. Pattanashetty NO, Mugali J, Niharika H. Prevalence of premenstrual dysphoric disorder among high school girls of Gadag district, Karnataka, India-a school-based cross-sectional study. *Kerala J Psychiatry*. (2021) 34:90–5. doi: 10.30834/KJP.34.2.2021.273

41. Tadakawa M, Takeda T, Monma Y, Koga S, Yaegashi N. The prevalence and risk factors of school absenteeism due to premenstrual disorders in Japanese high school students—a school-based cross-sectional study. *BioPsychoSocial Med*. (2016) 10:1–7. doi: 10.1186/s13030-016-0067-3

42. Boustani F, Ziagham S, Jahangirimehr A, Honarmandpour A. Prevalence of premenstrual syndrome, premenstrual dysphoric disorder and associated factors among female high school students. *J Inflammatory Diseases*. (2019) 23:332–41. doi: 10.32598/JQUMS

43. Wittchen H-U, Becker E, Lieb R, Krause P. Prevalence, incidence and stability of premenstrual dysphoric disorder in the community. *psychol Med*. (2002) 32:119–32. doi: 10.1017/S0033291701004925

44. Sveindóttir H, Bäckström T. Prevalence of menstrual cycle symptom cyclicity and premenstrual dysphoric disorder in a random sample of women using and not using oral contraceptives. *Acta obstetricia gynecologica Scandinavica*. (2000) 79:405–13. doi: 10.1080/j.1600-0412.2000.079005405.x

45. Chawla A, Swindle R, Long S, Kennedy S, Sternfeld B. Premenstrual dysphoric disorder: is there an economic burden of illness? *Med Care*. (2002) 40:1101–12. doi: 10.1097/00005650-200211000-00011

46. Bajracharya S, Baniya A. Awareness of menstrual hygiene among adolescent girls at a government school, Chitwan, Nepal. *J Chitwan Medical College*. (2022) 12(2):14–8. doi: 10.54530/jcmc.652

47. Alam M-U, Luby SP, Halder AK, Islam K, Opel A, Shoab AK, et al. Menstrual hygiene management among Bangladeshi adolescent schoolgirls and risk factors affecting school absence: results from a cross-sectional survey. *BMJ Open*. (2017) 7 (7):. doi: 10.1136/bmjopen-2016-015508

48. Biruk E, Tefera W, Tadesse N, Sisay AJB. Assessment of menstrual hygiene management and its determinants among adolescent girls: A cross-sectional study in school adolescent girls in Addis Ababa, Ethiopia. *bioRxiv*. (2018) 450007. doi: 10.1101/450007

49. Henok Shiferaw N, Anand S, Gugsa Nemera N. Stress and coping strategies among generic B. Sc. nursing students of Jimma University, South West Ethiopia. *Int J Recent Adv Multidiscip Res*. (2015) 2(7):511–7.

50. Belakbir O, Rhaouti A, Belbachir S, Ouanass A. Characteristics of premenstrual dysphoric disorder in moroccan women: A cross-sectional study. *Sch J Med Case Rep*. (2022) 11:1108–14. doi: 10.36347/sjmcr.2022.v10i11.011

51. Endicott J, Nee J, Harrison W. Daily Record of Severity of Problems (DRSP): reliability and validity. *Arch Womens Ment Health*. (2006) 9:41–9. doi: 10.1007/s00737-005-0103-y

52. Belayneh Z, Mekuriaw B. Knowledge and menstrual hygiene practice among adolescent school girls in southern Ethiopia: a cross-sectional study. *BMC Public Health*. (2019) 19:1–8. doi: 10.1186/s12889-019-7973-9

53. Hamaideh S, Al-Ashram S, Al-Modallal H. Premenstrual syndrome and premenstrual dysphoric disorder among J ordanian women. *J Psychiatr Ment Health nursing*. (2014) 21:60–8. doi: 10.1111/jpm.12047

54. Gupta M, Dua D, Kaur H, Grover S. Prevalence of premenstrual dysphoric disorder among school-going adolescent girls. *Ind Psychiatry J*. (2019) 28(2):198. doi: 10.4103/ipj.ipj_79_19

55. Gerrish W, Lustyk MKB. (2010).

56. West S, Lashen H, Bloigu A, Franks S, Puukka K, Ruokonen A, et al. Irregular menstruation and hyperandrogenaemia in adolescence are associated with polycystic ovary syndrome and infertility in later life: Northern Finland Birth Cohort 1986 study. *Hum. Reprod* (2014) 29(10):2339–51. doi: 10.1093/humrep/deu200

57. Hong JP, Park S, Wang H-R, Chang SM, Sohn JH, Jeon HJ, et al. Prevalence, correlates, comorbidities, and suicidal tendencies of premenstrual dysphoric disorder in a nationwide sample of Korean women. *Soc Psychiatry Psychiatr Epidemiol*. (2012) 47:1937–45. doi: 10.1007/s00127-012-0509-6

58. Eccles H, Sharma V. The association between premenstrual dysphoric disorder and depression: A systematic review. *J Affect Dis Rep*. (2023) 100504. doi: 10.1016/j.jadr.2023.100504

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