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Associations between serum cytokine levels and postmenopausal depression in postmenopausal women with and without menopause hormone therapy

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Abstract

Background The etiology of depression involves many biological and environmental factors, among which the inflammatory process is an important contributor. However, the role of pro-inflammatory cytokines in postmenopausal depression is unclear. Therefore, we aimed to explore the association between the serum concentrations of four pro-inflammatory cytokines (IL-1β, IL-6, IL-18, and TNF-α) and depressive symptoms in postmenopausal women who had been receiving menopause hormone therapy (MHT) for at least 6 months and postmenopausal women who had not received MHT.

Methods This study included a total of 136 Chinese postmenopausal women aged 40 to 65 years who visited the gynecology outpatient department between June 2020 and December 2022. They were divided into the POST group ($n=94$) and the POST + MHT ($n=42$) group. Demographic information was collected, and the Hamilton Rating Scale for Depression (HAMD) was used to assess depression. The circulating levels of IL-1β, IL-6, IL-18, and TNF-α were determined using ELISA kits.

Results According to the HAMD score, 39.36% of the participants in the POST group and 14.29% in the POST + MHT group were considered to have depression. The POST + MHT group had significantly lower serum concentrations of IL-18 and TNF-α than the POST group. Multiple linear regression analysis showed that the serum IL-18 (β = 3.996, 95% CI = 0.508–7.484), and TNF-α levels (β = 4.784, 95% CI = 0.939–8.629) were significant predictors of the HAMD-24 scores in women in the POST group. In addition, age was found to be positively related with the level of depression (β = 0.531, 95% CI = 0.063–0.999).

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Conclusions Postmenopausal women who received MHT had a lower HAMD-24 score as well as lower serum TNF-α and IL-18 levels than women who did not receive MHT. Further, the TNF-α and IL-18 level were positively associated with the HAMD-24 score in women who had not received MHT.

Keywords Depression, Cytokines, Postmenopausal women, Postmenopausal depression, TNF-α, IL-18, Estrogen therapy, Hormone therapy, Inflammation, Inflammatory cytokines

Background

Depression is one of the leading causes of disability and death [1]. Epidemiological studies have demonstrated that the risk of depressive disorders in women is two times higher than that in men; moreover, women were found to have a three-fold higher risk of developing major depression during their late perimenopausal or postmenopausal period [2]. According to World Health Organization, the number of postmenopausal women is expected to reach 1.2 billion by 2030 [3].

The etiology of depression involves many biological and environmental factors, among which the inflammatory process is an important contributor. There are several lines of evidence for the role of pro-inflammatory cytokines in the pathogenesis of depression. First, peripheral and cerebrospinal fluid concentrations of various cytokines, such as interleukin (IL)-1, tumor necrosis factor-alpha (TNF-α), IL-6, and IL-18, have been found to be significantly altered in patients with depression who are otherwise clinically healthy [4]. Second, long-term exposure to cytokines, for example, through interferon-alpha (IFN-α) therapy, has been shown to lead to marked depressive symptoms in humans [5]. Third, anti-inflammatory therapy has been observed to have an antidepressant effect. For example, a medicine named Etanercept, a TNF-α antagonist, relieved the depressive symptoms of patients with psoriasis, and the antidepressant effect was independent of improvement in psoriasis [6]. Finally, anti-inflammatory effects have been observed with antidepressant treatments. For example, fluoxetine was reported to reduce the peripheral concentrations of IFN-γ and TNF-α in control volunteers, and other antidepressants have been found to decrease the expression of NLRP3 inflammasome components, as well as IL-1β and IL-18 levels, in mononuclear blood cells from patients with major depressive disorder [7–9]. Thus, the link between inflammatory pathways and depressive symptoms is well established in the literature.

Despite the ample literature on depressive symptoms and their association with cytokines, there is limited research focused specifically on postmenopausal women. In one of the few studies on this topic, elevated plasma IL-6 concentrations were observed in menopausal women with depressive symptoms [10]. Another study showed the role of IL-1β in acute stress experienced by post-menopausal women and predicted the occurrence of depressive symptoms during the following year [11]. However, some other studies have reported a negative association between postmenopausal depressive symptoms and cytokine concentrations [12, 13]. The association between serum IL-18 levels and depressive symptoms in postmenopausal women has not been previously reported. These findings show that the research on this topic is limited and controversial, and more researches efforts into this are required in the future.

Compared to general depression, the pathogenesis of perimenopausal depression is unique, and the sudden drop in sex hormone levels may be the main reason for depressive symptoms or the increased susceptibility to depression. However, because the mechanism underlying the anti-depressive effect of sex hormones is unclear, there are still doubts about the MHT for perimenopausal depression in clinical practice. Estrogen supplementation is only recommended as a second-line medication for the treatment of depression during menopausal transition. Therefore, it is necessary to investigate the anti-depressive effect of MHT and its mechanism. Some studies have demonstrated that MHT can reduce perimenopausal depression, but the mechanism has not been elucidated [14]. One study has reported the effects of MHT on immunity based on variations in the levels of some pro-inflammatory cytokines in women receiving MHT [15]. However, the mechanistic links between the effects of MHT on pro-inflammatory cytokines and depressive symptoms are not well studied in postmenopausal women. The present study seeks to fill in this research gap by exploring the association between pro-inflammatory cytokines and depressive symptoms in postmenopausal women. The study also examines whether the administration of MHT for at least 6 months has an effect on cytokine levels and depressive symptoms.

Methods

Participants

Participants were recruited from the gynecology outpatient department of the Women's Hospital, School of Medicine, Zhejiang University, between June 2020 and December 2022. Information on demographic variables, and medical history were obtained by gynecologists through interviews and physical examination. Participants were divided into the POST group and the POST + MHT group according to whether they were receiving MHT. All the participants provided their informed consent before the commencement of the

study. The inclusion criteria were age between 40 and 65 years and postmenopausal status according to the 2012 Stages of Reproductive Aging Workshop (STRAW) criteria [16]. Women who met any of the following criteria were excluded: (1) history of sex steroid or oral contraceptive use within the preceding 6 months for the POST group; (2) consecutive MHT for less than 6 months for the POST + MHT group; (3) history of mental illness (including premenopausal depression) or the use of antipsychotic drugs; (4) history of hysterectomy or oophorectomy; (5) history or evidence of uncontrolled hypertension, diabetes, cardiovascular disease, untreated thyroid disease, renal insufficiency, liver disease, autoimmune disease, life-threatening disease, history of thrombosis, and breast cancer; and (6) contraindication for MHT and inability to participate.

The ethical committee of the Women's Hospital, School of Medicine, Zhejiang University, has approved this study (Approval no. 20200053).

Treatment

The therapeutic regimen used in this study was in accordance with the guidelines for menopausal management and MHT in mainland China (2018) [17]. A personalized treatment plan was prescribed according to each patient's symptoms, age, and physical examination results. The dosage and type of estrogen applied used to treat the participants was based on their age and duration after menopause, in addition, because the uterus had not been removed in any of the participating women, they were all given progesterone. The specific therapeutic regimens used in this study are summarized in Supplementary Table 1. Oral estradiol was prescribed for 26 women: 11 women were treated with a cyclical regimen of 1-2 mg estradiol/ estradiol valerate tablets with 200 mg dydrogesterone for 14 days starting from the 14th day after bleeding, and 15 women were treated with 0.5-1 mg estradiol/ estradiol valerate tablets and 100 mg dydrogesterone every day.

Demographic and clinical data

Data on demographic and clinical variables, including age, residence, academic education, monthly income, age at menarche, and chronic health problems were collected by trained interviewers. The body mass index (BMI, kg/m^2) was calculated and classified according to the Chinese World Health Organization criteria: underweight, BMI < 18.5; normal, 18.5 ≤ BMI < 24; overweight, 24 ≤ BMI < 28; obesity, BMI ≥ 28.

Assessment of depression

The patients were assessed for depressive symptoms and severity using the 24-item Hamilton Rating Scale for Depression (HAMD), which comprises 10 items scored from 0 to 2 and 14 items scored from 0 to 4. A total score of 0–7 was considered to indicate no depression; 8–19, mild depression; 20–34, moderate depression; and ≥ 35, severe depression.

Assessment of circulating cytokine concentrations

The serum concentrations of four cytokines (IL-1β, IL-6, IL-18, and TNF-α) were measured using commercially available ELISA kits in accordance with the manufacturers' instructions. The IL-1β, IL-6, and TNF-α ELISA kits were purchased from Absin Bioscience Inc., China, and the IL-18 kit was from Jiangsu Meimian Industrial, China. Assays of cytokines were performed in duplicate, and average values were used for statistical analysis. The limits of detection (LODs) were 1.0 pg/ml for IL-1β, 1.56 pg/ml for IL-6, 5 pg/ml for IL-18, and 0.68 pg/ml for TNF-α.

Statistical analysis

Continuous variables with a normal distribution were presented as the mean ± standard deviation and analyzed with the independent sample *t*-test. Variables with non-normal distribution were presented as medians (10–90%), and inter-group differences in these variables were analyzed with the Mann-Whitney *U*-test. We used the χ^2 test/Fisher's exact test for comparisons of categorical variables, which were presented as frequency and proportions. Multiple linear regression analyses with the level of depression as the outcome were conducted. The estimates of regression were presented as β and 95% confidence intervals (CIs). The IL-1β, IL-6, and TNF-α values were below the LOD in more than one-third of the cases, which were categorized separately. The remaining women were divided into two groups based on the median values of each cytokine, with the lower serum concentration group considered as the reference group. For categorical analyses of IL-18, participants were divided into three groups according to the third percentile distribution of serum concentration, with the lowest third as the reference group.

SPSS 26.0 for Windows (IBM Corp., Armonk, NY, USA) was used for all statistical analyses, with $P < 0.05$ considered to indicate statistical significance.

Results

General characteristics of the participants

The general characteristics of the participants are summarized in Table 1. A total of 136 women who met the inclusion criteria were recruited: 94 in the POST group and 42 in the POST + MHT group. Only age was significantly different between the two groups ($p < 0.05$), with the POST + MHT group being older than the POST group (Table 1).

Table 1 General characteristics of participants

Variable	ALL($n=136$)	Post($n=94$)	Post + HRT($n=42$)	Statistics	*P*
Age (years, n, %)				χ^2=6.000	0.05
40–49	19(13.97)	16(17.02)	3(7.14)		
50–59	107(78.68)	74(78.72)	33(78.57)		
≥60	10(7.35)	4(4.26)	6(14.29)		
Age (years, mean ± SD)	53.54 ± 3.97	52.78 ± 3.78	55.21 ± 3.90	*t*=-3.425	0.001
Residence (n, %)				χ^2=0.003	0.959
Urban	104(76.47)	72(76.60)	32(76.19)		
Rural	32(23.53)	22(23.40)	10(23.81)		
Education level (n, %)				χ^2=0.561	0.905
Primary school	8(5.88)	6(6.38)	2(4.76)		
Middle school	80(58.82)	53(56.38)	25(59.52)		
College and above	39(28.68)	26(27.66)	13(30.95)		
Missing	9(6.62)	7(7.45)	2(4.76)		
Employment status (n, %)				χ^2= 1.609	0.657
Employed	63(46.32)	42(44.68)	21(50.00)		
Unemployed	24(17.65)	15(15.96)	9(21.43)		
Retired	41(30.15)	31(32.98)	10(23.81)		
Missing	8(5.88)	6(6.38)	2(4.76)		
Personal income per month (yuan, n, %)				χ^2=4.340	0.227
< 3000	41(29.41)	32(34.04)	9(21.43)		
3000–5000	32(23.53)	18(19.15)	14(33.33)		
> 5000	54(39.71)	37(39.36)	17(40.48)		
Missing	9(6.62)	7(7.45)	2(4.76)		
BMI (kg/m^2, n, %)				χ^2=3.026	0.388
Underweight (< 18.5)	5(3.67)	3(3.19)	2(4.76)		
Normal (18.5–24)	102(75.00)	73(77.66)	29(69.05)		
Overweight (24–28)	26(19.12)*	18(19.15)	11(26.91) *		
Age at menarche (years, mean ± SD)	14.63 ± 1.58	14.57 ± 1.58	14.75 ± 1.58	*t*=-0.603	0.548

Note: * One obese female (BMI > 28 kg/m^2) was included in the data

Table 2 Depression status and serum inflammatory markers concentration of participants

Variable	Post($n=94$)	Post + MHT($n=42$)	Statistics	*P*
Depression status (HAMD scores, n, %)			χ^2=8.815	0.032
Non-depression (<8)	57(60.58)	36(84.91)		
Mild depression (8–19)	25(25.96)	5(11.32)		
Moderate depression (20–34)	11(12.5)	1(1.88)		
Severe depression (≥35)	1(0.96)	0		
HAMD scores(mean ± SD)	8.90 ± 8.75	3.40 ± 4.43	*t* = 4.856	< 0.001
Inflammatory markers				
IL-1β(pg/ml)	0(0, 16.14)	0(0, 9.16)	*z*=-1.030	0.303
IL-6(pg/ml)	0(0, 29.88)	0(0, 8.53)	*z*=-0.827	0.408
TNF-α(pg/ml)	4.04(0, 181.06)	0(0, 11.20)	*z*=-2.089	0.037
IL-18(ng/L)	29.96 ± 29.24	20.23 ± 12.33	*t* = 2.728	0.007

Depression status

The mean HAMD score and the depression status of the participants are shown in Table 2. According to the HAMD score, 39.36% of the participants in the POST group and 14.29% participants in the POST + HRT group were considered to have depression (HAMD-24 more than 7). The HAMD score and the prevalence of depression were significantly higher in the POST group than in the POST + MHT group ($p < 0.05$) (Table 2).

Concentrations of inflammatory markers

The results of serum cytokine concentrations for the two groups are shown in Table 2. In many participants, the serum concentrations of IL-1β, IL-6, and TNF-α were below the LODs. Values below the LODs were considered to represent "true zero values," and the number of participants with these values in each group are shown in Supplementary Table 2. The concentrations of IL-1β and IL-6 in the POST group did not differ significantly from

Table 3 Differences in serum inflammatory levels among participants with different severity of depression

	Variable	Non-depression	Mild depression	Moderate depression	Severe depression	Statistics	*P*
	n	93	30	12	1		
Total(*n* = 236)	IL-1β(pg/ml)	0(0, 132.88)	0(0, 64.52)	2.95(0, 43.70)	58.4	h = 7.926	0.048
	IL-6(pg/ml)	1.58(0, 237.92)	0(0, 385.97)	0(0, 30.07)	0	h = 6.211	0.102
	TNF-α(pg/ml)	0(0, 361.77)	5.76(0, 543.46)	62.60(0, 440.37)	271.94	h = 8.392	< 0.001
	IL-18(ng/L)	20.82 ± 12.13	32.13 ± 33.88	56.78 ± 46.17	83.81	f = 11.398	< 0.001
	n	57	25	11	1		
POST (*n* = 94)	IL-1β(pg/ml)	0 (0, 132.88)	0(0, 64.52)	2.49(0, 43.70)	58.4	h = 4.263	0.234
	IL-6(pg/ml)	1.10 (0, 237.92)	0(0, 385.97)	0(0, 30.07)	0	h = 1.528	0.677
	TNF-α(pg/ml)	0(0, 361.77)	7.24 (0, 543.46)	71.67 (5.93, 440.37)	271.94	h = 26.240	< 0.001
	IL-18(ng/L)	27.63 ± 25.74	19.96 ± 13.93	59.82 ± 47.15	83.81	f = 7.247	< 0.001
	n	36	5	1	0		
POST + MHT (*n* = 42)	IL-1β(pg/ml)	0(0, 40.55)	0(0, 2.24)	12.9	-	h = 3.814	0.148
	IL-6(pg/ml)	0(0, 50.46)	0(0, 0)	3.35	-	h = 4.2	0.122
	TNF-α(pg/ml)	0(0, 120.04)	0(0, 8.77)	0	-	h = 0.785	0.675
	IL-18(ng/L)	21.09 ± 164.67	13.37 ± 49.25	23.32	-	f = 0.888	0.42

Table 4 Multiple linear regression analysis of inflammatory markers concentration and HAMD scores

Variable	Post			Post + MHT		
	β	95%CI	*P*	β	95%CI	*P*
IL-1β	4.085	-2.224, 10.394	0.201	1.834	-0.280, 3.948	0.087
IL-6	-3.395	-8.516, 1.726	0.191	-1.665	-3.668, 0.337	0.100
IL-18	3.777	0.265, 7.288	0.035	-1.519	-3.648, 0.610	0.156
TNF-α	4.277	0.222, 8.332	0.039	-1.105	-3.181, 0.971	0.286
Age	0.622	0.173, 1.070	0.007	0.353	-0.010,0.715	0.056
Residence	-3.651	-7.886, 0.585	0.090	-0.526	-3.960, 2.907	0.757
Education level	-1.727	-5.233, 1.781	0.330	1.248	-1.736, 4.304	0.392
Employment status	-0.822	-3.101, 1.458	0.476	-0750	-2.615, 1.116	0.419
Personal income	1.332	-1.122, 3.786	0.283	-1.620	-3.890, 0.649	0.155
BMI	2.465	-1.370, 6.301	0.205	-1.373	-3.805, 1.059	0.258

Note: Values are presented as β (95% CI). Adjusted for IL-1β, IL-6, IL-6, TNF-α, Age, place of residence, level of education, employment, income and BMI

those in the POST + MHT group. In contrast, the serum concentrations of IL-18 and TNF-α were significantly lower in the POST + MHT group (Table 2).

Association of serum cytokine concentrations with postmenopausal depression

Univariate analysis between depression severity and inflammatory cytokine levels were shown in Table 3. Differences in serum TNF and IL-18 levels were observed between individuals with varying degrees of depression within the general population and the post-group, while no significant differences were found in other comparisons.

Multiple linear regression analyses were performed to investigate the association between confounders (IL-1β, IL-6, IL-6, TNF-α, Age, place of residence, level of education, employment, income and BMI) and the HAMD-24 scores and the degree of influence that each confounder has on postmenopausal depression (Table 4). The result of this model showed in the POST group, age, the IL-18 and TNF-α levels were positively and significantly correlated with the level of depression, elevated TNF-α and IL-18 levels are more likely to influence the postmenopausal depressive symptoms (age: β = 0.622, 95% CI = 0.173–1.070; IL-18: β = 3.777, 95% CI = 0.265–7.288; TNF-α: β = 4.277, 95% CI = 0.222–8.332); while the other confounders including serum IL-1β and IL-6 concentrations, place of residence, level of education, employment, income and BMI were not significantly associated with the level of depression. In the POST + MHT group, no significant association was found between the serum cytokine concentrations and the level of depression (Table 4).

Discussion

The main finding of the current study is that the serum concentrations of IL-18 and TNF-α were related with the level of depression in postmenopausal women who did not receive MHT. This study is the first to report the link between IL-18 and postmenopausal depression, so these findings are expected to make an important contribution to the research on cytokines in postmenopausal depression. Another important finding of this study was that postmenopausal women who had been receiving MHT

for at least 6 months had a lower serum TNF-α and IL-18 levels as well as a lower HAMD-24 score than women who were not receiving MHT. These findings indicate that MHT might improve depressive symptoms by modulating immune function.

Increased plasma levels of IL-18 in patients with depression than in healthy controls had been reported by Du's study [18] and the IL-18 levels correlated with abnormal brain activity in patients with depression. The present study corroborated this association of IL-18 level with depressive symptoms in postmenopausal women, and is the few study to demonstrate this association. The underlying mechanism may involve cytosolic inflammasome-multiprotein complexes (NLRP) demonstrated in an animal study [19]. Thus, NLRP1 inflammasome-mediated IL-18 release may also lead to depression in the context of postmenopausal depression.

We also found that the TNF-α level was positively associated with the HAMD-24 score in postmenopausal woman who were not receiving MHT. Previously, changes in TNF-α levels have been found to affect the severity of psychiatric symptoms and the responses to treatment [20]. With regard to menopausal transition, only a small sample study by Karaoulanis et al. reported higher TNF-α levels in perimenopausal women with depression than in perimenopausal women without depression, but the differences were not significant [12]. This highlights the importance of conducting future studies with larger sample sizes.

Greater IL-6 responses in response to mental stress have been observed in postmenopausal women compared with older men [21], with another study on a small sample of 76 patients reporting significantly higher IL-6 concentrations in menopausal women with depressive symptoms [10] These findings contradict those of Karaoulanis et al.'s study. In addition, elevated IL-1β levels have been found to be related with chronic stress [22], postpartum depression [23] and the severity of depressive symptoms in elderly people [24]. In contrast to these findings, we did not find a significant association between serum IL-1β and IL-6 levels and the HAMD-24 score. This is probably because the IL-1β and IL-6 levels were below the LODs in most women, as previously reported in perimenopausal and adolescent females, and this may be related to the sensitivity and specificity of the ELISA kits used [12, 25, 26]. In the future, studies with large samples are needed to clarify the associations between IL-1β and IL-6 levels and postmenopausal depression.

Sex hormones have been proposed to play an important role in immunity and the regulation of inflammation. For example, estradiol was found to stimulate various cell adhesion molecules; inhibit cytokines such as IL-1, IL-6, and TNF-α; and also prevent bone loss, spinal cord inflammation and demyelination in mouse models [27–29]. Our results reveal that IL-18 and TNF-α were significantly decreased in women with MHT, thus supporting the anti-inflammatory effect of MHT and highlighting its potential contribution to the mood regulation as well.

Our study found that the group of women receiving MHT had less severe depression than those who did not receive MHT. Several studies have reported that MHT containing transdermal estradiol administration has beneficial mood effects on depression in perimenopausal women [30, 31]. With regard to postmenopausal depression, most studies included older postmenopausal women and did not find any anti-depressive effect of MHT [32, 33]. Only one study examined the antidepressant efficacy of estrogen therapy in 183 young women with an average age of 48 years who had been postmenopausal for at least 1 year; the study found that compared with the placebo, transdermal E2 (when used alone or in combination with norethisterone) led to a significant reduction in HAMD scores [34]. The majority of the postmenopausal women included in the present study were in their early postmenopausal stage, and the HAMD scores were significantly lower in women receiving MHT than those without MHT. These findings suggest that the perimenopausal and early postmenopausal stage might represent a critical window of menopausal transition associated with a high risk for depression, and it may therefore be an optimal time for administering MHT [35].

Additionally, in the previous study, we found that almost half of the postmenopausal women had depressive symptoms, further, the degree of depression increased with age [36]. The present results are in line with our previous study: that is, nearly 40% of the participants who were not receiving MHT had depressive symptoms that were mild to moderate. Moreover, in the present study, age also showed a positive correlation with the HAMD-24 score. Thus, early screening in the menopausal transition may help detect and treat menopausal depression before it becomes more severe.

There are several strengths and limitations in our present study. One of the strengths of our study is that it is one of the few studies to estimate the level of depression and serum cytokine levels in postmenopausal women with or without MHT. Besides that fact, there are some important new findings such as postmenopausal women who are receiving MHT has lower HAMD-24 score and lower levels serum IL-18, also the positive association between levels of serum IL-18 and the HAMD-24 score in postmenopausal women without receiving MHT, because of these findings, the involvement of IL-18 has significance in pathways like pyroptosis and cytosolic inflammasome which may provide valuable insights into the mechanisms underlying postmenopausal depression

and the antidepressant effects of MHT. However, the MHT regimens in our study were diversified, and the limited sample size made it impossible to estimate the effect of each type of MHT regimen separately on pro-inflammatory cytokines. The uneven distribution of the sample size between the two groups may lead to selection bias and the smaller sample size in the POST + MHT group risking an underestimation of the anti-depressive and anti-inflammatory effect, further cohort studies with bigger sample size should be conducted to confirm the findings. Despite adjusting for some common confounders, due to limited data, there are still meaningful confounders that have not been adjusted for, such as premenopausal depression. Another limitation is that the serum cytokine levels may not necessarily reflect the central production of cytokines in the women. Moreover, due to the cross-sectional design of our study, it was not possible to draw any causal inferences. Thus, in the future, the research should aim for larger, longitudinal studies with standardized MHT and additional biomarkers to clarify the complex relationship between hormones, cytokines, and mental health in postmenopausal women.

Conclusions

The present study showed that postmenopausal women who had been receiving MHT for at least 6 months had lower HAMD-24 score as well as lower level of serum TNF-α and IL-18 than women who were not receiving MHT. Furthermore, the TNF-α and IL-18 levels were positively associated with the HAMD-24 score in women without MHT. These findings indicate that the interaction between estrogen and cytokines may play a role in the complex pathophysiology of postmenopausal depression and warrant further exploration in future studies on larger patient samples.

Abbreviations

BMI	Body mass index
CI	Confidence interval
HAMD	Hamilton Rating Scale for Depression
IFN-α	Interferon-alpha
IL	Interleukin
LOD	Limit of detection
MHT	Menopausal hormone therapy
TNF-α	Tumor necrosis factor-alpha

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

J.Z. and Y.L designed the project and contributed to the paper writing, K.C. and X.L. performed data analysis, K.C. and NAG.C. write the paper, S.L. ,L.M and Y.H conducted the scale and the interviews, F.W. and M.S. collected the data.

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Data availability

The datasets supporting the conclusions of this article can be made available by the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The ethical committee of the Women's Hospital, School of Medicine, Zhejiang University, approved this study. All the participants provided their written informed consent for this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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