Comparison of serum cytokines levels in normal-weight and overweight patients with first-episode drug-naïve major depressive disorder

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Objective: Abnormal levels of blood cytokines have been demonstrated to be associated with both excess weight and major depressive disorder (MDD). However, few studies have addressed the direct effect of body mass index (BMI) on basal serum cytokines in individuals with first-episode drug-naïve MDD.

Methods: A total of 49 patients with first-episode drug-naïve MDD were categorized into normal weight (18.5 ≤ BMI < 25 kg/m²) and overweight (25 ≤ BMI < 30 kg/m²) groups according to WHO-criteria. The severity of depressive symptoms was assessed using the 24-items Hamilton Depression Scale (HAMD-24). A total of 37 cytokines were measured using Multiplex Luminex Assays. The scores of HAMD-24 and the levels of serum cytokines between normal weight group and overweight group were compared. Multiple linear regression analysis was performed to evaluate the association between abnormal serum cytokines levels and group after adjusting for HAMD-24 scores. The correlation between BMI and the scores of HAMD-24 and the levels of serum cytokines was evaluated using Pearson correlation analysis.

Results: The scores of HAMD-24 in overweight group were significantly higher than normal weight group (t = 2.930, P = 0.005). Moreover, the levels of IL-1α, IL-1RA, IL-3, CXCL10, TNF-α, and ICAM-1 in overweight patients with MDD were significantly higher than those in normal-weight patients with MDD (all P < 0.05). Furthermore, after adjustment for HAMD-24 scores, there was a significant correlation between abnormal serum cytokines levels (IL-1α, IL-1RA, IL-3, CXCL10, TNF-α, and ICAM-1) and group (all P < 0.05). Additionally, BMI was positively correlated to the serum levels of IL-1α (r = 0.428, P = 0.002), IL-3 (r =
Introduction

Depression and obesity often occur comorbidly, and their association has been reported repeatedly (1, 2). Several lines of evidence indicate a bidirectional relationship between depression and obesity. It has been reported that individuals with obesity are 32% more likely to experience depression compared with adults with normal weight (3) and vice versa, individuals with depression are 58% more likely to be obese compared with individuals without depression (4). Although the exact pathophysiological mechanism that links depression and obesity is yet to be fully elucidated, aberrant expression of cytokines in periphery is thought to be one of the comorbid mechanisms.

Many evidences confirmed a close relationship between cytokines and MDD. Recently, a cumulative meta-analysis reported higher levels of interleukin-6 (IL-6) and C-reactive protein (CRP) in patients with MDD compared to non-depressive individuals (5). Moreover, depressed patients who are resistant to conventional antidepressants had higher concentrations of peripheral blood levels of pro-inflammatory cytokines (6, 7). Furthermore, alterations in peripheral cytokine levels were reported to be associated with antidepressant treatment outcomes in MDD (8). These findings suggest that peripheral cytokines are implicated in the pathophysiology of depression and may hold significant promise as potential treatment target for depressive symptoms.

Adipose tissue is now recognized as an active endocrine organ expressing and secreting a variety of cytokines that play parts in the pathogenesis of many obesity-related diseases (9, 10). Obesity can be regarded as a state of chronic subclinical inflammation characterized by increased expression of proinflammatory cytokines, adipokines, and chemokines (11, 12). It has been demonstrated that plasma levels of pro-inflammatory cytokines such as IL-6, tumor necrosis factor-α (TNF-α), and IL-1β were significantly higher in overweight individuals than normal-weight individuals (13, 14). Considering the dysfunctional balance of cytokines in overweight or obesity, taken together the fact that abnormal level of blood cytokines may be both a causal mechanism and potential treatment target for depressive symptoms, it is crucial to understand to what extent weight gain contribute to the aberrant cytokine expression observed in patients with MDD.

In the present study, we examined the serum levels of multiple cytokines in patients with first-episode drug-naïve MDD, with the aim to analyze the direct effect of BMI on basal serum cytokines in patients with MDD. A total of 49 patients with MDD were categorized into normal weight (18.5 ≤ BMI < 25 kg/m²) and overweight (25 ≤ BMI < 30 kg/m²) groups. A total of 37 cytokines in patients with MDD were measured and the 24-items Hamilton Depression Scale (HAMD-24) was used to estimate the severity of depressive symptoms. The correlation between BMI and the scores of HAMD-24 and the levels of serum cytokines was evaluated using Pearson correlation analysis.

Materials and methods

Study design and participants

This study was conducted at Anhui Mental Health Center between August 2020 and June 2022. Fifty-three patients with first-episode drug-naïve MDD were diagnosed by trained psychiatrists according to the Diagnostic and Statistical Manual for Psychiatric Disorders-Fifth Version (DSM-V). Common criteria for patient inclusion and exclusion were shown in Table 1. A total of 49 patients with first-episode drug-naïve MDD were enrolled and categorized into normal weight (18.5 ≤ BMI < 25 kg/m²) and overweight (25 ≤ BMI < 30 kg/m²).
TABLE 1 Common criteria for patient inclusion and exclusion.

| Inclusion criteria                                                                 | Exclusion criteria                                                                                                                                 |
|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| (1) being between the ages of 18-65                                                | (1) current or lifetime history of major neurological disorders including Alzheimer’s disease, amyotrophic lateral sclerosis, ischemia, trauma, hepatic encephalopathy, Down’s syndrome, autism, multiple sclerosis, brain neoplasms, Parkinson’s disease and epilepsy |
| (2) meeting DSM-V criteria for depression                                            | (2) current or lifetime history of other psychiatric disorders including anxiety, schizophrenia, bipolar disorder, obsessive-compulsive disorder, alcohol and substance abuse, and attention-deficit hyperactivity disorder |
| (3) Hamilton Depression Rating Scale-24 (HAMD-24) scores higher than 20            | (3) current or lifetime history of chronic infections, inflammatory and immune disorders including rheumatoid arthritis, inflammatory bowel disease, and nephrotic syndrome, systemic lupus erythematosus, multiple sclerosis, autoimmune type 1 diabetes, asthma, sepsis, pulmonary fibrosis, primary biliary cirrhosis, autoimmune myasthenia gravis and stroke |
| (4) receiving no treatment with antidepressants, anti-inflammatory agents or other psychotropic drugs in the previous 3 months | (4) currently receiving anti-inflammatory treatment                                                                                                                                 |

kg/m²) groups according to WHO-criteria. Consecutive sampling technique was used to select the participants. All subjects were ethnic Han Chinese living in Anhui province. In the present study, 34 women and 15 men were enrolled, which is consistent with the gender difference in MDD incidence (15, 16). The Chinese version of HAMD-24, which has good reliability with Cronbach’s alpha value of 0.714 (17), was used to evaluate the severity of depressive symptoms in all participants. This procedure was approved by the ethics committee of the Anhui Mental Health Center (registration number HFSY-IRB-PJ-QXR-20200001) and was conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained from all the participants.

Blood sample collection and measurement of serum cytokines

The blood samples from the subjects was collected between 7:00 and 8:00 A.M., centrifuged at 1200 g for 10 min at 4°C. The supernatant was used as serum samples, which were maintained at -80°C until detection. The blood samples were collected at baseline before treatment. A total of 37 serum cytokines, including IL-1α (also called IL-1F1), IL-1β (also called IL-1F2), IL-1RA (also called IL-1F3), IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8 (also called C-X-C motif chemokine ligand 8, CXCL8), IL-10, IL-12 (also called IL-23 p40), IL-12 p70, IL-13, IL-15, IL-16, IL-17C, IL-27, IL-31, C-C motif chemokine ligand 3 (CCL3; also called macrophage inflammatory protein 1α, MIP-1α), CCL4 (also called MIP-1β), CCL11 (also called eotaxin), CCL17 (also called thymus and activation regulated chemokine, TRAC), CCL26 (also called eotaxin-3), CXCL10 (also called interferon-inducible Protein 10, IP-10; cytokine responsive gene-2, CRG-2), vascular endothelial growth factor (VEGF), VEGF-C, VEGFR1 (also called Flt1), TNF-α, TNF-β (also called lymphotoxin), Tie-2, interferon-γ (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF), fibroblast growth factor-basic (FGF basic, also called FGF2/ bFGF), thymic stromal lymphopoietin (TSLP), intercellular cell adhesion molecule-1 (ICAM-1), and placenta growth factor (PIGF) were measured by the multiplex bead immunoassay (LXSAHM-10 and LXSAHM-27, R&D system for antibody detection, Shanghai Universal Biotech Co., Ltd) according to the manufacturer’s instructions.

Statistical analysis

Statistical analysis was calculated using SPSS (version 17.0; IBM Corp., Armonk, NY, USA). The data are shown as mean ± standard error of the mean (SEM), and the statistical significance was set at P < 0.05. Student’s t-test for independent samples was used to compare the age, BMI, years of education, HAMD-24 scores, and serum cytokines levels and group after adjusting for HAMD-24 scores. Chi-squared test was used to determine the difference between the two groups with respect to sex and smoking status. The correlation between BMI and the scores of HAMD-24 and the levels of serum cytokines was evaluated using Pearson correlation analysis.

Results

Demographic and clinical characteristics of the participants

Table 2 summarizes the demographic and clinical characteristics of normal-weight patients with MDD (n = 34) and overweight patients with MDD (n = 15). There were no significant differences in age, sex, years of education, or smoking status between the two groups (all P > 0.05; Table 2). The scores of HAMD-24 in overweight group were significantly higher than normal weight group (t = -2.930, P = 0.005).
Differences of cytokine levels in serum between normal-weight patients with MDD and overweight patients with MDD

As shown in Table 3, the levels of IL-1α, IL-1RA, IL-3, CXCL10, TNF-α, and ICAM-1 in overweight patients with MDD were significantly higher than those in normal-weight patients with MDD (all \( P < 0.05 \)). There were no significant differences in other cytokines levels including IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-12 p70, IL-13, IL-15, IL-16, IL-17C, IL-27, IL-31, CCL3, CCL4, CCL11, CCL17, CCL26, VEGF, VEGF-C, VEGFR1, Tie-2, IFN-γ, GM-CSF, FGF basic, TSLP, and PI GF between the two groups (all \( P > 0.05 \); Table 3). Since the scores of HAMD-24 in overweight group were significantly higher than normal weight group, multiple linear regression analysis was performed to evaluate the association between abnormal serum cytokines levels and group after adjusting for HAMD-24 scores. As shown in Table 4, after adjustment for HAMD-24 scores, there was still a significant correlation between abnormal serum cytokines levels (IL-1α, IL-1RA, IL-3, CXCL10, TNF-α, and ICAM-1) and group (all \( P < 0.05 \)).

Correlation between BMI and HAMD-24 scores and the serum levels of cytokines

The relationships between BMI and HAMD-24 scores and the serum levels of cytokines in patients with MDD were analyzed by Pearson correlation tests (Figure 1). There was no significant relationship between BMI and HAMD-24 scores (\( r = 0.236, P = 0.102 \)). Among the serum cytokines, BMI was positively correlated to the serum levels of IL-1α (\( r = 0.428, P = 0.002 \)), IL-3 (\( r = 0.529, P < 0.001 \)), IL-6 (\( r = 0.285, P = 0.050 \)), IL-10 (\( r = 0.423, P = 0.003 \)), IL-12 (\( r = 0.367, P = 0.010 \)), IL-15 (\( r = 0.300, P = 0.036 \)), CXCL10 (\( r = 0.316, P = 0.030 \)), TNF-α (\( r = 0.338, P = 0.021 \)), and ICAM-1 (\( r = 0.440, P = 0.002 \)).

Discussion

To our knowledge, this is the first study to analyze the direct effect of BMI on basal serum cytokines in patients with first-episode drug-naïve MDD. Three main findings emerged from the present study. First, the scores of HAMD-24 in overweight group were significantly higher than normal weight group. Second, overweight patients with MDD showed higher serum levels of IL-1α, IL-1RA, IL-3, CXCL10, TNF-α, and ICAM-1. Third, BMI was positively correlated to the serum levels of IL-1α, IL-3, IL-6, IL-10, IL-12, IL-15, CXCL10, TNF-α, and ICAM-1 in MDD patients.

Several studies have evaluated the correlation between overweight or obesity and depression, and the results are conflicting. It has been reported that a positive relationship between overweight and depression scores was found in individuals from the United States and Europe (18–20). On the contrary, a negative correlation between BMI and depression scores were observed in individuals from Asia (21–23). In the present study, overweight patients with MDD showed higher scores of HAMD-24 compared to normal-weight patients with MDD, and no significant relationship between BMI and HAMD-24 scores in patients with first-episode drug-naïve MDD. The reasons for these conflicting relationships between BMI and depression scores remain unclear but might be due to the different races and variant designs (some for the general population and others for patients). Multicentric studies with larger sample sizes are required to validate these conflicting relationships.

IL-1α (a pro-inflammatory cytokine) and its inhibitor, IL-1RA (IL-1 receptor antagonist) belong to the IL-1 family. Previous studies have showed that increased IL-1α and IL-1RA concentrations in MDD patients compared to healthy controls (24, 25). Another study has indicated a positive correlation between increased BMI and elevated plasma level of IL-1α in obese women (26). IL-1RA can prevent the binding of IL-1α and IL-1β to IL-1R1, and is reported to be upregulated mainly in adipose cells in obese individuals (27). Consistently, the results of the present study showed that the serum levels of IL-1α and IL-1RA were increased in overweight patients with MDD compared to normal-weight patients with MDD. Moreover, BMI was found to be positively correlated to the serum levels of IL-1α in patients with MDD.

IL-3 is a glycoprotein cytokine involved in the hematopoietic response to infection, immune response and inflammatory stimulation. Recently, a meta-analysis including 107 studies regrouping 5,166 patients with depression and 5,083 controls
indicated that levels of IL-3 were significantly higher in patients with depression (28). Although IL-3 has been reported to be upregulated in obesity (29), few studies have reported differences in IL-3 levels in overweight and normal-weight patients with MDD. Our results firstly showed that the serum IL-3 levels were significantly elevated in overweight patients with MDD and were positively correlated with BMI.

CXCL10 is a member of the chemokine family secreted by various cell types, including monocytes, T cells, endothelial cells, and keratinocytes in response to secretion of IFN-γ and other proinflammatory cytokines (30). It has been reported that the serum levels of CXCL10 were elevated during depressive episodes, and this alteration correlated with increased depression severity (31, 32). More recent evidence indicated that peripheral blood levels of CXCL10 were significantly higher in obese subjects than in controls and significantly correlated with BMI (33). Combined with the results that the serum CXCL10 levels were significantly elevated in overweight patients with MDD and were positively correlated with BMI in patients with MDD in the present study, these findings provide more data linking peripheral CXCL10 to the obesity status in patients with MDD.

### TABLE 3 Comparison of serum cytokines between MDD patients without SI and MDD patients with SI.

| Variables (pg/ml) | MDD without SI | MDD with SI | t       | P     |
|------------------|----------------|-------------|---------|-------|
| IL-1α (IL-1F1)   | 3.29 ± 0.41    | 6.67 ± 1.38 | -2.342  | 0.032 |
| IL-1β (IL-1F2)   | 9.59 ± 1.45    | 10.08 ± 2.53| -0.176  | 0.861 |
| IL-1RA (IL-1F3)  | 957.06 ± 129.08| 1736.02 ± 453.57| -2.190  | 0.034 |
| IL-2             | 32.14 ± 5.18   | 38.28 ± 11.11| -0.574  | 0.569 |
| IL-3             | 25.97 ± 0.71   | 32.11 ± 1.93 | -3.727  | 0.001 |
| IL-4             | 30.74 ± 4.80   | 46.22 ± 9.66 | -1.605  | 0.115 |
| IL-5             | 2.05 ± 0.15    | 2.08 ± 0.17  | -0.109  | 0.914 |
| IL-6             | 9.77 ± 2.60    | 19.44 ± 6.41 | -1.676  | 0.101 |
| IL-7             | 10.63 ± 1.07   | 10.88 ± 1.48 | -0.131  | 0.897 |
| IL-8 (CXCL8)     | 531.98 ± 107.49| 672.35 ± 265.39| -0.589  | 0.558 |
| IL-10            | 2.76 ± 0.49    | 4.83 ± 1.06  | -1.787  | 0.090 |
| IL-12 (IL-23 p40)| 216.43 ± 10.20 | 252.71 ± 27.34| -1.534  | 0.132 |
| IL-12 p70        | 44.64 ± 10.35  | 27.46 ± 5.57 | 1.067   | 0.291 |
| IL-13            | 232.07 ± 7.78  | 258.86 ± 14.09| -1.788  | 0.081 |
| IL-15            | 3.68 ± 0.39    | 5.33 ± 0.96  | -1.602  | 0.126 |
| IL-16            | 170.54 ± 12.66 | 197.41 ± 17.74| -1.206  | 0.234 |
| IL-17C           | 11.19 ± 0.75   | 11.94 ± 1.45 | -0.503  | 0.617 |
| IL-27            | 307.96 ± 21.95 | 369.68 ± 53.88| -1.061  | 0.302 |
| IL-31            | 29.94 ± 1.46   | 28.67 ± 2.48 | 0.464   | 0.645 |
| CCL3 (MIP-1α)    | 595.29 ± 112.33| 732.10 ± 155.84| -0.678  | 0.501 |
| CCL4 (MIP-1β)    | 473.28 ± 78.81 | 527.31 ± 89.24| -0.398  | 0.693 |
| CCL11 (Eotaxin)  | 117.31 ± 9.25  | 120.52 ± 14.44| -0.189  | 0.851 |
| CCL17 (TRAC)     | 306.02 ± 21.04 | 393.72 ± 58.28| -1.415  | 0.174 |
| CCL26 (Eotaxin-3)| 14.29 ± 1.06   | 15.06 ± 2.18 | -0.356  | 0.723 |
| CXCL10 (IP-10/CRG-2) | 17.50 ± 0.91 | 21.54 ± 1.47 | -2.387  | 0.021 |
| VEGF            | 108.29 ± 10.95 | 144.82 ± 24.89| -1.343  | 0.195 |
| VEGF-C          | 1722.34 ± 105.82| 1898.45 ± 170.97| -0.901  | 0.372 |
| VEGFR1 (Fr1)    | 150.48 ± 8.56  | 174.36 ± 22.01| -1.011  | 0.325 |
| TNF-α            | 4.13 ± 0.47    | 6.34 ± 0.98  | -2.308  | 0.026 |
| TNF-β (Lymphotoxin) | 2.57 ± 0.14 | 2.90 ± 0.27  | -1.184  | 0.243 |
| Tie-2            | 16009.29 ± 1189.25| 18947.80 ± 3515.53| -1.005  | 0.320 |
| IFN-γ           | 15.58 ± 0.98   | 18.19 ± 1.59 | -1.418  | 0.163 |
| GM-CSF          | 3.37 ± 0.31    | 3.89 ± 0.47  | -0.927  | 0.359 |
| FGF basic (FGF2/bFGF) | 9.14 ± 1.03 | 12.22 ± 2.77 | -1.043  | 0.311 |
| TSLP            | 1.09 ± 0.05    | 1.14 ± 0.09  | -0.489  | 0.627 |
| ICAM-1 (CD54)   | 292954.01 ± 47435.41| 674661.53 ± 116416.43| -3.036  | 0.007 |
| PIGF            | 2.20 ± 0.12    | 2.46 ± 0.27  | -1.006  | 0.319 |
Elevated TNF-α levels are associated with a variety of conditions, including obesity and depression (34, 35). For example, recent meta-analyses have demonstrated very high concentrations of TNF-α in depressed patients as compared to healthy controls (36); elevated levels of TNF-α have been linked to poor antidepressant treatment response and (37, 38); and TNF-α inhibition can improve depressive-like behavior in clinical trials (39). As a cytokine largely expressed in adipose tissue, TNF-α is elevated in obesity and may contribute to obesity-associated metabolic disease (40). Consistently, our results showed that the serum TNF-α levels were significantly elevated in overweight patients with MDD and were positively correlated with BMI.

ICAM-1, a member of the immunoglobulin protein superfamily, is a cell-surface glycoprotein that is overexpressed on the endothelial lumen in many pathological states (41). A recently published meta-analysis including 9,203 people with depression, found an association between higher ICAM-1 levels and depression (42). Another study has indicated that the ICAM-1 levels in MDD patients after a 3-day wash-out of antidepressants were significantly higher compared to healthy controls (37). Moreover, ICAM-1 level was found to be correlated with BMI and waist circumference in Mexican Americans (43). Similarly, the serum ICAM-1 levels were significantly elevated in overweight patients with MDD and were positively correlated with BMI in the present study.

### TABLE 4 Multiple linear regression analysis to determine the independent predictors (HAMD-24 scores and group) of abnormal serum cytokines levels.

| Dependent variables | Independent variables | β   | t    | P     |
|--------------------|-----------------------|-----|------|-------|
| IL-1β              | Constant              | 2.254 | 1.094 | 0.280 |
|                    | HAMD-24 scores        | -0.097 | -1.666 | 0.103 |
|                    | Group                 | 4.155 | 3.530 | 0.001 |
| IL-1RA             | Constant              | 252.434 | 0.369 | 0.714 |
|                    | HAMD-24 scores        | -3.050 | -0.158 | 0.875 |
|                    | Group                 | 803.302 | 2.055 | 0.046 |
| IL-3               | Constant              | 24.761 | 8.706 | <     |
|                    | HAMD-24 scores        | -0.204 | -2.569 | 0.014 |
|                    | Group                 | 7.827 | 4.641 | <     |
| CXCL10             | Constant              | 11.599 | 3.643 | 0.001 |
|                    | HAMD-24 scores        | 0.050 | 0.544 | 0.589 |
|                    | Group                 | 4.305 | 2.293 | 0.027 |
| TNF-α              | Constant              | 1.082 | 0.602 | 0.550 |
|                    | HAMD-24 scores        | 0.024 | 0.449 | 0.656 |
|                    | Group                 | 2.276 | 2.042 | 0.048 |
| ICAM-1             | Constant              | 205.8486 | 0.102 | 0.919 |
|                    | HAMD-24 scores        | -4427.182 | -0.785 | 0.437 |
|                    | Group                 | 416320.036 | 3.645 | 0.001 |

FIGURE 1  
Correlation between BMI and HAMD-24 scores and the serum levels of cytokines in patients with MDD (Pearson correlation analysis).
It is noteworthy that IL-1β, IL-6, and IL-10 are the most frequently reported cytokines in depression and affective disorders. Several lines of evidence have demonstrated the involvement of IL-1β in MDD (44): (1) epidemiological data showed that levels of IL-1β in peripheral circulation and cerebrospinal fluid (CSF) of patients with MDD were increased; (2) antidepressants treatment could change the levels of IL-1β; (3) IL-1β administration could induce depression-like behaviors in rats. In the present study, there were no significant differences in serum IL-1β levels between normal-weight patients with MDD and overweight patients with MDD, suggesting that overweight may not be associated with serum IL-1β levels in patients with first-episode drug-naïve MDD. A updated meta-analysis based on 82 studies comprising 3212 participants with MDD and 2798 healthy controls has demonstrated that peripheral levels of IL-6 and IL-10 were elevated in patients with MDD compared to healthy controls while there was no significant change observed in the levels of IL-1β (25). In the present study, although there was no statistical difference, the serum IL-6 and IL-10 levels of overweight patients with MDD tended to be increased compared to normal-weight patients with MDD. Moreover, positive relationships were found between BMI and the serum levels of several interleukin family proteins including IL-6 and IL-10 in patients with first-episode drug-naïve MDD. Similarly, IL-6 levels were frequently elevated in obese subjects and positively correlated with obesity in human populations (45). Higher levels of IL-10 in overweight and obese subjects was correlated with BMI and the grade of abdominal obesity (13). Given that the sample size is relatively small, whether there are differences in the levels of IL-6 and IL-10 between normal-weight patients with MDD and overweight patients with MDD needs to be verified with large samples.

Additionally, positive relationships were also found between BMI and the serum levels of several interleukin family proteins including IL-12, and IL-15 in patients with first-episode drug-naïve MDD. Similarly, BMI was positively correlated to peripheral IL-12 and IL-15 in other studies. Specifically, overweight and obese subjects had higher levels of IL-12 than a normal-weight group, and this correlated with BMI and the grade of abdominal obesity (13). Another study revealed a positive relationship between circulating IL-15 concentration and fat mass in lean and obese participants (46). Taken together, these findings may link peripheral cytokines to the co-morbidity mechanism of depression and obesity. Given that this study is a cross-sectional study, the causal relationship between these cytokines and BMI needs further studies to explore.

There are some limitations that should be considered. Firstly, the present study is a single-center study with a relatively small sample size, which might represent sampling bias. Secondly, in the absence of a control group (healthy subjects with normal weight), we had no baseline data for serum cytokines levels in the healthy population. Thirdly, we only used HAMD-24 to assess the severity of depressive symptom. In order to make it certain that the diagnosis based on HAMD-24 is properly validated, other scales should be used to assess the severity of depressive symptom. Fourthly, this study is a cross-sectional study, the causal relationship between these cytokines and BMI needs further studies to explore. Fifthly, CRP was not measured in the present study. However, numerous studies have reported that CRP was consistently associated with obesity and depression (47, 48).

In conclusion, the present study reveals that overweight patients with MDD showed higher levels of IL-1α, IL-1RA, IL-3, CXCL10, TNF-α, and ICAM-1 compared to normal-weight patients with MDD, and BMI was positively correlated to the serum levels of IL-1α, IL-3, IL-6, IL-10, IL-12, IL-15, CXCL10, TNF-α, and ICAM-1 in MDD patients. These findings provide evidence that overweight may be associated with several serum cytokines in patients with first-episode drug-naïve MDD. Since this study is a cross-sectional study and the causal relationship between these cytokines and BMI could not be determined, whether these cytokines are involved in the co-morbidity mechanism of depression and obesity, and whether they can be potential targets for treatment still need further studies to investigate.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Anhui Mental Health Center. The patients/participants provided their written informed consent to participate in this study.

Author contributions

WG, YX, JG, and QX conceived the study. YX, JG, and QX wrote the protocol. WG, JL, YS, YZ, and FS performed the analyses. WG and YX wrote the first draft. All authors read and commented the manuscript and agreed on the final version.

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Conflict of interest

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

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