BMC Psychiatry

RESEARCH

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Associations of leptin levels with psychopathology, BDNF and inflammatory cytokines in patients with chronic schizophrenia as well as gender differences

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Abstract

Background Metabolic syndrome significantly contributes to mortality among individuals suffering from chronic schizophrenia (CS), and there is a strong correlation between this condition and plasma leptin (LEP) levels. However, there are relatively few studies on the factors affecting leptin levels in chronic schizophrenia, and findings are often inconsistent. The purpose of this study was to investigate the leptin levels and their association with psychopathology, BDNF and inflammatory cytokines in patients with chronic schizophrenia, as well as potential gender differences.

Methods The study enrolled 301 individuals diagnosed with chronic schizophrenia. Participants were assessed for psychotic symptoms, insomnia severity, and depressive symptoms using the Positive and Negative Syndrome Scale (PANSS), Insomnia Severity Index (ISI), and Calgary Depression Scale for Schizophrenia (CDSS), respectively. Leptin, BDNF and inflammatory cytokines levels were also detected.

Results Among the patients, Log LEP levels were positively correlated with females, body mass index (BMI), systolic and diastolic blood pressures, Log BDNF, Log IL-6, and Log IL-17 A levels, and negatively correlated with the total score on the PANSS, as well as scores on the positive, negative, and general psychopathology subscales (all $p < 0.05$). Multiple linear regression analyses revealed that Log LEP levels were independently correlated with gender ($\beta = 0.514$, $t = 15.601$, $p < 0.001$), BMI ($\beta = 0.053$, $t = 12.096$, $p < 0.001$), diastolic blood pressure ($\beta = 0.005$, $t = 2.334$, $p = 0.020$), and Log IL-17 A levels ($\beta = 0.062$, $t = 2.097$, $p = 0.037$). Notably, these associations between leptin and the above factors were only observed in the male patients.

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Conclusions A significant link was identified between leptin levels and the presence of psychotic symptoms, BDNF, and inflammatory cytokines (especially IL-6 and IL-17 A) in individuals suffering from chronic schizophrenia, with notable variations observed between genders. Future research, including more longitudinal studies and animal models, is necessary to delve deeper into these associations and uncover their underlying mechanisms.

Keywords Chronic schizophrenia, Leptin, BDNF, Inflammatory cytokines, Gender differences

Introduction

Schizophrenia is a long-term, debilitating psychiatric condition marked by impairments in cognitive function, emotional response, and behavioral patterns [1]. According to epidemiologic data, the prevalence of schizophrenia (14.2 to 23.6 million) increased by 65% from 1990 to 2019, thereby placing a heavy burden worldwide [2]. Compared to other mental disorders, schizophrenia has a higher degree of chronicity and symptom complexity [3]. In addition, schizophrenia has been strongly associated with premature mortality [4]. Barber et al. [5] found that cardiovascular disease, associated with metabolic syndrome, is a primary cause of mortality among individuals with schizophrenia.

Leptin is a hormone secreted by adipose tissue, and its main functions include appetite suppression, increased energy expenditure, regulation of fetal growth and the growth and development of individuals during childhood and adolescence, modulation of inflammatory response and immune function, and maintenance of normal lipid metabolism [6]. However, abnormally elevated leptin levels may increase the likelihood of developing cardiovascular and other metabolic disorders [7]. Recent investigations have suggested that individuals with schizophrenia may experience abnormally elevated leptin levels [8], which can have negative effects on overall health. For instance, studies have demonstrated a robust correlation between leptin and metabolic syndrome in schizophrenic patients [9–10], highlighting the importance of identifying determinants influencing elevated leptin levels in this population.

In recent years, there has been a growing interest in the link between leptin and the psychopathology of schizophrenia. Previous studies have found that leptin can send important signals to the limbic dopamine system in the midbrain and stimulate the lateral hypothalamic area, which in turn modulates the dopaminergic and serotonergic neurotransmitter systems, as well as key areas of the brain related to the regulation of behavior and mood [11]. These systems and areas are intimately connected to the development of psychiatric disorders, including schizophrenia [12]. In addition, several clinical studies have revealed that leptin levels in patients with schizophrenic are strongly associated with psychopathological symptoms. For example, Hönig et al. [13] discovered that in patients with schizophrenia, leptin levels are negatively correlated with the scores on the Positive and Negative Syndrome Scale (PANSS). A cross-sectional study also revealed that symptoms of insomnia were strongly linked to higher leptin levels among schizophrenic patients [14]. Furthermore, a study conducted in China demonstrated a robust correlation between the leptin levels of schizophrenic patients and the severity of their depressive symptoms [15]. However, there are also studies that have obtained conflicting results. Nurjono et al. [16], and Hendouei et al. [17], found that there was a positive association between leptin levels and the total scores on the PANSS, as well as scores on the positive symptom scale and the general psychopathology scale. Meanwhile, a controlled study showed limited effects of sleep deprivation on leptin levels [18]. Given the inconsistent findings in this area and the paucity of studies on the correlation of leptin with symptoms of insomnia and depression in schizophrenia patients, more research is needed to explore the relationship between leptin levels and these psychopathological symptoms.

It is worth noting that leptin, in addition to its possible association with the onset of schizophrenia and psychopathological symptoms, may also be associated with abnormal alterations in certain biological markers in individuals. Among these, there has been a surge of interest in brain-derived neurotrophic factor (BDNF) and inflammatory cytokines among these research areas. BDNF, a protein extensively present in the central nervous system and various other tissues, belongs to a family of neurotrophic factors that significantly contributes to the growth, function, and disease of the nervous system by promoting neuronal survival, supporting synaptic plasticity, and influencing the manifestation, development, course, and worsening of neurological disorders [19]. Previous research has indicated that fluctuations in BDNF levels could be associated with the underlying pathophysiological mechanisms in individuals with schizophrenia. In recent years, an association between BDNF levels and leptin has also been found [20–21]. For example, BDNF operates within the leptin-melatonin signaling cascade to regulate energy balance by modulating hypothalamic neurons involved in energy homeostasis [22]. Schizophrenia is often associated with metabolic disturbances, including weight gain and increased risk of obesity and type 2 diabetes, which may be partly due to disruptions in the leptin-melatonin signaling cascade modulated by BDNF [23]. Understanding this pathway is crucial for developing targeted interventions to improve

metabolic health in patients with schizophrenia. Additionally, many studies have demonstrated that blood pro-inflammatory cytokine levels are frequently elevated among chronic schizophrenia patients [24–25]. The link between schizophrenia and inflammatory cytokines may also involve changes in leptin levels. For example, Martorell et al. [26] discovered that there was a positive association between leptin levels and IL-6 levels in patients with schizophrenia. However, these associations between leptin and BDNF as well as inflammatory cytokines have been less studied in patients with schizophrenia and warrants further in-depth exploration.

Thus, our research endeavored to scrutinize the correlations between leptin and psychopathology, BDNF, and inflammatory cytokines in chronic schizophrenia, while also examining potential gender differences in these relationships.

Methods

Study design and participants

This is a cross-sectional study. From May to December 2018, we selected chronic schizophrenia patients who were hospitalized at Chaohu Hospital of Anhui Medical University, Hefei Fourth People's Hospital and Ma'anshan Fourth People's Hospital as the study subjects. Data collection was completed within 7 of admission for all patients. The inclusion criteria for participants were as follows: (1) aged 18–65 years old; (2) diagnosed with schizophrenia by at least two attending-level physicians, in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria; (3) having a disease duration exceeding 5 years; and (4) possessing certain comprehension to complete the whole research process successfully. Patients were excluded if they had any of the following: (1) co-existing infections, severe neuroendocrine or metabolic disorders, or other serious physical illnesses; (2) a current or previous diagnosis of depressive disorder, bipolar disorder, or other psychiatric disorders according to the DSM-5; (3) a history of alcohol or substance abuse; (4) being pregnant or lactating women; and (5) patients who are taking nonsteroidal anti-inflammatory drugs, corticosteroids, or other immune modulators. The study was approved by the Ethics Committee of Chaohu Hospital of Anhui Medical University (No. 201805-kyxm-03), and all subjects and their legal guardians signed an informed consent form.

Measures

Demographic characteristics

A self-administered questionnaire was used to investigate the general conditions of all enrolled subjects, such as gender, age, body mass index (BMI), blood pressure (systolic and diastolic), years of education, age at first onset of illness, duration of illness, and antipsychotic drug use. Resting systolic and diastolic blood pressure were measured by trained doctors using an automated oscillometric device (Yuwell YE680A, Jiangsu Yuyue Medical Equipment, China). Participants rested seated for 5 min before three consecutive measurements at 2-minute intervals, with the mean of the last two readings used for analysis. Cuff size was adjusted according to mid-arm circumference. The "years of education" reported in this study refer to the total number of years of formal education that participants have completed. This measure is calculated based on the highest level of education attained by the participants, according to the standard structure of the Chinese education system, using the following standard conversion: Elementary school: 6 years; Middle school: 9 years; High school (including vocational high school): 12 years; College degree or above: 16 years. This calculation method is consistent with the standards used by the National Bureau of Statistics and is widely applied in demographic and educational research [27]. In this study, chlorpromazine equivalents were used to express the dose of antipsychotic drugs in chronic schizophrenia patients [28].

The positive and negative syndrome scale (PANSS)

The Positive and Negative Symptom Scale (PANSS) was used to assess patients' psychotic symptoms [29]. This scale consists of 30 items, categorized into three sections: positive symptoms (16 items), negative symptoms (7 items), and general psychopathology (7 items). The total score of PANSS ranges from 30 to 210, with higher scores indicating greater symptom severity. The Chinese version of PANSS has been well adapted among Chinese patients with schizophrenia and has good reliability and validity [30].

The Calgary depression scale (CDSS)

The Calgary Depression Scale (CDSS) was employed to evaluate the severity of the subjects' depressive symptoms [31]. The scale consists of 9 items, each scored from 0 to 3, with a higher total score indicating a higher severity of depression. The CDSS has been widely used in Chinese patients with schizophrenia [32].

The insomnia severity index (ISI)

The Insomnia severity index (ISI) was used to assess the severity of insomnia and its impact on daily life of the patients over a 2-week period [33]. The scale consists of 7 items and the total score ranges from 0 to 28, with higher scores indicating more severe insomnia. The Chinese version of ISI has been shown to be highly reliable in patients with schizophrenia [34].

Biochemical assays

All patients with chronic schizophrenia had their blood samples completed within 7 days of admission. Fasting venous blood samples were collected from all subjects between 6:00 am and 8:00 am. The blood samples were then centrifuged in a centrifuge at 3000 rpm for 15 min at 4 °C within 30 min of collection. And the upper layer of plasma was collected in a sterile Eppendorf tube and stored at -80 °C until sent for examination. The plasma levels of inflammatory cytokines, including interleukin (IL)-1β, IL-6, IL-17 A, and tumor necrosis factor-alpha (TNF-α) (kit: Sangon Biotech, Shanghai, China), BDNF (kit: Meso Scale Discovery, Rockville, MD, USA) and leptin (kit: Cusabio Biotechnology Company, Wuhan, China) were measured by enzyme-linked immunosorbent assay (ELISA). Raw concentrations of BDNF and leptin levels are expressed as ng/mL. Raw concentrations of IL-1β, IL-6, IL-17 A and TNF-α levels are expressed as pg/mL.

Statistical analysis

Statistical analyses were performed using SPSS 23.0 software. For testing whether continuous variables conformed to normal distribution, we used the Kolmogorov-Smirnov test. "Mean ± standard deviation (M ± SD)" was used for normal distribution, and "median (quartiles) [Me (Q1-Q3)]" was used for non-normal distribution. And categorical variables were expressed as "frequency (%)". In univariate analyses, independent samples t-tests and Mann-Whitney U-tests were used to compare demographic and clinical variables between the male and female groups. Pearson's or Spearman correlation analyses were used to examine the correlation between leptin levels and other variables. Bonferroni correction was used to adjust for multiple testing. Subsequently, multivariate linear regression analyses with the "stepwise" method were used to examine which factors (variables with $p < 0.05$ in correlation analyses) were independently associated with the patients' leptin levels (dependent variable). This study rigorously tested the key assumptions of the regression models. The normality of the residuals was verified using the Shapiro-Wilk test and QQ plots. The homoscedasticity of the residuals was verified using the Breusch-Pagan test and residual plot analysis. Multicollinearity among variables was also assessed by calculating the variance inflation factor (VIF), with all VIF values in this study being less than 5.0. This indicates that multicollinearity was within an acceptable range. In these analyses, to ensure that the measurements of the blood indices conformed to a normal distribution, we referred to previous studies [35–36] and log-transformed the BDNF levels, leptin levels, IL-1β, IL-6, IL-17 A and TNF-α levels with base 10 to obtain Log (X) values for Log BDNF, Log LEP, Log IL-1β, Log IL-6, Log IL- 17 A and Log TNF-α. BDNF and leptin levels were expressed as log10 (ng/mL) after logarithmic processing. IL-1β, IL-6, IL-17 A and TNF-α levels were expressed as log10 (pg/mL) after logarithmic processing. For all statistical tests, $p < 0.05$ (two-tailed) was defined as statistically significant.

Results

Socio-demographic and clinical characteristics of patients with chronic schizophrenia

A total of 301 eligible patients with chronic schizophrenia participated in this study, including 173 males and 128 females. The socio-demographic and clinical characteristics were shown in Table 1. The mean age of the male patients was 44.22 ± 10.79 years, while the female patients had a mean age of 45.60 ± 11.20 years. The BMI and systolic blood pressure were higher in female patients than in males (all $p < 0.05$). In terms of clinical characteristics, male patients had significantly higher PANSS total scores and scores across its three subscales (all $p < 0.05$). Regarding biochemical parameters, female patients had higher levels of Log LEP (Fig. 1), Log IL-6 and Log IL-17 A (all $p < 0.05$). However, there were no statistical differences in ISI, CDSS scores, or levels of Log BDNF, Log IL-1β, and Log TNF-α between male and female patients (all $p > 0.05$). In addition, after Bonferroni correction ($\alpha = 0.05/25 = 0.002$), the differences in BMI, systolic blood pressure, Positive subscale score, General psychopathology subscale score, Log IL-6 and Log IL-17 A levels were no longer significant between male and female patients.

Correlations between leptin levels with socio-demographic and clinical variables in patients with chronic schizophrenia

As shown in Table 2, in the total sample, Spearman's correlation analyses showed that the mean Log LEP levels were higher in female patients than in males ($r = 0.651$, $p < 0.001$). And furthermore, Pearson's correlation analyses showed that Log LEP levels were moderately positively correlated with BMI ($r = 0.551$, $p < 0.001$), very weakly positively correlated with systolic blood pressure ($r = 0.199$, $p = 0.001$), diastolic blood pressure ($r = 0.224$, $p < 0.001$), Log BDNF ($r = 0.157$, $p = 0.006$), Log IL-6 ($r = 0.116$, $p = 0.045$), and Log IL-17 A levels ($r = 0.159$, $p = 0.006$), and very weakly negatively correlated with the PANSS total scores (r = -0.188, $p = 0.001$), Positive Symptom Scale scores (r = -0.120, $p = 0.038$), Negative Symptom Scale scores (r = -0.200, $p < 0.001$), and General Psychopathology Scale scores (r = -0.167, $p = 0.004$) (Fig. 2). In male patients, Pearson's correlation analysis showed that Log LEP levels were moderately positively correlated with BMI ($r = 0.674$, $p < 0.001$), weakly positively correlated with diastolic blood pressure ($r = 0.321$,

Table 1 Socio-demographic and clinical characteristics of patients with chronic schizophrenia

Variables	Total ($N=301$)	Male ($n=173$)	Female ($n=128$)	t/Z	*P*
Age (years), M ± SD	44.81 ± 10.97	44.22 ± 10.79	45.60 ± 11.20	−1.081[a]	0.281
BMI (kg/m^2), M ± SD	24.09 ± 3.77	23.57 ± 3.70	24.80 ± 3.75	−2.836[a]	**0.005**
Systolic blood pressure (mmHg), M ± SD	114.86 ± 12.26	113.50 ± 11.16	116.70 ± 13.43	−2.250[a]	**0.025**
Diastolic blood pressure (mmHg), M ± SD	75.99 ± 8.09	75.55 ± 8.29	76.59 ± 7.81	−1.093[a]	0.275
Age at onset (years), M ± SD	26.06 ± 8.28	25.86 ± 7.95	26.33 ± 8.74	−0.483[a]	0.630
Duration of illness (years), M ± SD	18.77 ± 10.11	18.55 ± 9.74	19.06 ± 10.61	−0.430[a]	0.667
Chlorpromazine Equivalents (mg), M ± SD	463.17 ± 263.49	435.50 ± 249.33	500.57 ± 278.12	−2.131[a]	**0.034**
ISI total score, Me (Q1-Q3)	2.00 (1.00–5.00)	2.00 (1.00–5.00)	2.00 (1.00–5.00)	−0.455[b]	0.649
CDSS total score, Me (Q1-Q3)	3.00 (0.00–5.00)	3.00 (1.00–5.00)	2.50 (0.00–4.00)	−0.855[b]	0.393
PANSS total score, M ± SD	78.11 ± 24.02	82.16 ± 23.88	72.63 ± 23.19	3.462[a]	**0.001**[*]
Positive subscale score, M ± SD	17.93 ± 7.40	18.72 ± 7.83	16.87 ± 6.66	2.210[a]	**0.028**
Negative subscale score, M ± SD	21.61 ± 7.63	23.01 ± 7.59	19.71 ± 7.30	3.791[a]	< **0.001**[*]
General psychopathology subscale score, M ± SD	38.59 ± 12.58	40.44 ± 12.63	36.10 ± 12.13	2.996[a]	**0.003**
BDNF (ng/ml), Me (Q1-Q3)	1.25 (0.68–2.46)	1.20 (0.61–2.51)	1.29 (0.76–2.44)	−1.211[b]	0.226
Log BDNF (ng/ml), M ± SD	0.13 ± 0.40	0.11 ± 0.43	0.16 ± 0.36	−1.059[a]	0.290
LEP (ng/ml), Me (Q1-Q3)	1.20 (0.46–2.81)	0.53 (0.33–1.19)	2.81 (1.65–4.23)	−11.277[b]	< **0.001**[*]
Log LEP (ng/ml), M ± SD	0.06 ± 0.45	−0.20 ± 0.36	0.40 ± 0.33	−14.853[a]	< **0.001**[*]
Inflammatory cytokines					
IL−1β (pg/mL), Me (Q1-Q3)	2.70 (1.69–4.18)	2.70 (1.85–3.91)	2.63 (1.55–4.91)	−0.021[b]	0.983
Log IL−1β (pg/mL), M ± SD	0.44 ± 0.43	0.42 ± 0.36	0.46 ± 0.51	−0.839[a]	0.402
IL−6 (pg/mL), Me (Q1-Q3)	0.64 (0.51–1.07)	0.63 (0.50–0.98)	0.64 (0.52–1.33)	−1.072[b]	0.284
Log IL−6 (pg/mL), M ± SD	−0.04 ± 0.47	−0.09 ± 0.38	0.03 ± 0.56	−2.068[a]	**0.040**
IL−17 A (pg/mL), Me (Q1-Q3)	3.53 (2.03–8.45)	3.27 (1.88–6.40)	3.73 (2.50-17.87)	−2.853[b]	**0.004**
Log IL−17 A (pg/mL), M ± SD	0.69 ± 0.55	0.61 ± 0.51	0.81 ± 0.58	−3.065[a]	**0.002**
TNF-α (pg/mL), Me (Q1-Q3)	19.12 (14.76–23.63)	19.12 (15.30-22.19)	18.83 (14.12–26.58)	−0.354[b]	0.724
Log TNF-α (pg/mL), M ± SD	1.30 ± 0.21	1.28 ± 0.14	1.32 ± 0.28	−1.687[a]	0.093

Notes: BMI, body mass index; ISI, Insomnia Severity Index; CDSS, Calgary Depression Scale for Schizophrenia; PANSS, The Positive and Negative Syndrome Scale; BDNF, brain-derived neurotrophic factor; LEP, leptin; IL−1β, interleukin−1β; IL−6, interleukin−6; IL−17 A, interleukin−17 A; TNF-α, tumour necrosis factor-α; M ± SD, Mean ± Standard Deviation; Me (Q1-Q3), Median with Interquartile Range; t, Independent Samples t-test; Z, Mann-Whitney U test statistic;

[a] Independent Samples t-test; [b] Mann-Whitney U-test;

Bold values mean $P<0.05$ (comparisons between males and females); [*] $P<0.05/25=0.002$(Bonferroni correction)

$p<0.001$), and very weakly positively correlated with systolic blood pressure ($r=0.231$, $p=0.002$), Log BDNF ($r=0.173$, $p=0.023$), Log IL-6 ($r=0.164$, $p=0.031$), and Log IL-17 A levels ($r=0.218$, $p=0.004$) (Fig. 3). In contrast, in female patients, Pearson's correlation analysis showed that Log LEP levels were only weakly positively correlated with BMI ($r=0.481$, $p<0.001$) (Fig. 4). In addition, in the total sample, after Bonferroni correction ($\alpha=0.05/19\approx0.0026$), the correlations between the Log LEP levels and Positive Symptom Scale scores, General Psychopathology Scale scores, Log BDNF, Log IL-6 and Log IL-17 A levels were no longer significant. In male patients, after Bonferroni correction ($\alpha=0.05/18\approx0.0028$), the correlations between the Log LEP levels and Log BDNF, Log IL-6 and Log IL-17 A levels were no longer significant.

Factors associated with leptin levels by multivariate linear regression analyses

The results of the multiple stepwise linear regression analyses were given in Table 3. In the total sample, Log LEP levels were independently correlated with gender (beta = 0.514, t = 15.601, $p<0.001$), BMI (beta = 0.053, t = 12.096, $p<0.001$), diastolic blood pressure (beta = 0.005, t = 2.334, $p=0.020$) and Log IL-17 A (beta = 0.062, t = 2.097, $p=0.037$). In male patients, Log LEP levels were independently correlated with BMI (beta = 0.063, t = 11.979, $p<0.001$), diastolic blood pressure (beta = 0.006, t = 2.480, $p=0.014$) and Log IL-17 A levels (beta = 0.187, t = 5.125, $p<0.001$). In female patients, Log LEP levels were independently correlated only with BMI (beta = 0.042, t = 6.153, $p<0.001$).

Discussion

For this study, we examined plasma leptin concentrations in chronic schizophrenia patients and explored their associations with psychopathology, BDNF, and inflammatory cytokines. Initially, we found that the leptin levels of patients correlated with their gender, BMI, and blood pressure. Consistent with previous studies [37], our data showed that female patients exhibited markedly higher leptin levels compared to males. Several factors might

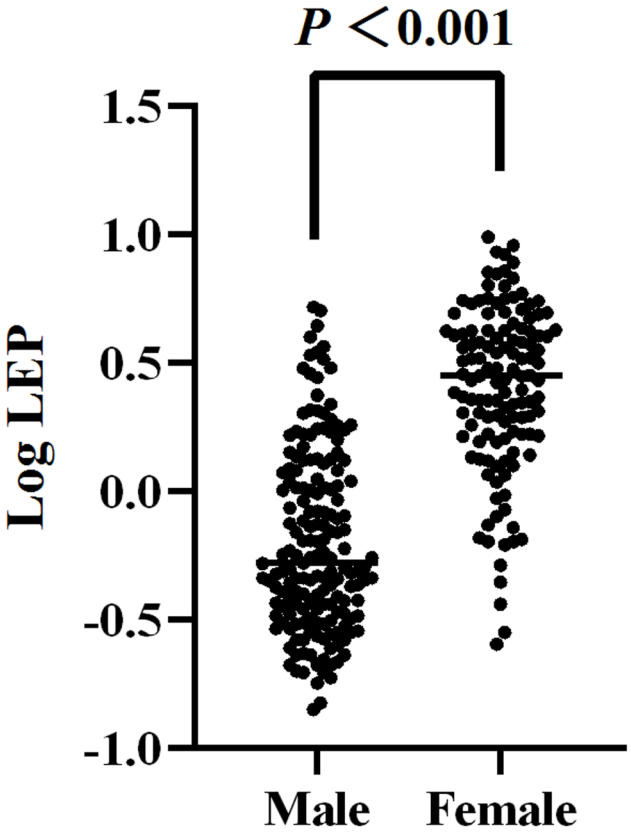

Fig. 1 Comparison of male and female Log LEP levels (t=-14.853, $p < 0.001$)

underpin this disparity. First, leptin is mainly secreted by adipose tissue, and its levels rise in correlation with the body's fat storage [38]. The percentage of subcutaneous fat is generally greater in females compared to males, and there is also a gender difference in fat distribution, with females having higher fat content in the lower limb region than males [39]. Thus, differences in body fat content and distribution result in higher leptin levels in females than in males. Secondly, engaging in resistance or strength exercises that increase muscle mass may lead to greater leptin suppression and a higher rate of fat loss, possibly due to an increase in leptin receptor expression [40]. In contrast, males typically possess greater muscle mass compared to females, which may account for the relatively lower leptin levels observed in males. Additionally, through our correlational and regression analyses, we identified a positive association between leptin levels and BMI among patients suffering from chronic schizophrenia, aligning with prior research outcomes [41]. This could be due to antipsychotic medication use. A longitudinal study revealed that after 4 weeks of olanzapine treatment, schizophrenia patients experienced notable rises in BMI and leptin levels compared to baseline [42]. A meta-analysis of longitudinal studies investigating the impact of antipsychotic drugs on leptin levels found that elevated leptin levels in schizophrenia patients could be a consequence of weight gain caused by antipsychotic medications [43]. The observed increase in leptin levels in association with higher BMI indicate that leptin functions as a negative feedback mechanism in the presence of increased adiposity. Our research corroborated the existing body of literature by establishing a positive correlation between leptin and blood pressure [44]. Fujita et al. [45] likewise observed a positive association between leptin and blood pressure and noted that leptin might play a mediating role between body fat and blood pressure. These outcomes indicate that elevated leptin levels could be linked to the onset and advancement of high blood pressure by mechanisms including decreased nitric oxide synthesis, increased sympathetic nerve activity, abnormal activation of the renin-angiotensin-aldosterone system (RAAS), and water and sodium retention [46]. Therefore, it is imperative to closely monitor the effects of leptin on blood pressure in schizophrenia patients to facilitate the timely prevention of detrimental cardiovascular complications.

Furthermore, our investigation discovered a number of relationships between leptin levels as well as the psychiatric symptoms in those diagnosed with chronic schizophrenia. Correlation analyses revealed a negative correlation between leptin levels and PANSS scores, including total, positive, negative, and general psychopathology. However, when these factors were incorporated into the multiple linear regression models, the above correlations were no longer significant, which diverged from the outcomes of certain earlier investigations [37, 47]. Zhang et al. [37] reported that leptin was inversely associated with all psychotic symptoms, and that the negative symptom scale score was an independent predictor of leptin levels. On the other hand, Liu et al. [47] determined that the PANSS total scores and the positive symptom scale scores were independent influences on patients' leptin levels. In fact, the subjects selected for this study were patients with long duration of illness and repeated multiple hospitalizations. A meta-analysis indicated that individuals with recurrent schizophrenia had notably elevated leptin levels compared to both healthy individuals and those experiencing their first episode of the illness [48]. This suggested that disease duration might play a moderating role. It could be hypothesized that the cumulative effect of influences such as prolonged treatment, psychotic symptoms, and prolonged living with unhealthy habits might be responsible for the elevated leptin levels in chronic patients. Concurrently, these inconsistent studies might also be due to the use of medications, methodological issues, and sample heterogeneity. Therefore, more large-sample studies are needed in the future to delve deeper into the correlation between leptin and psychotic symptoms among chronic schizophrenia patients.

Table 2 Correlations between log leptin with socio-demographic and clinical variables in patients with chronic schizophrenia

Variables	Total sample (*N* = 301)		Male (*n* = 173)		Female (*n* = 128)	
	r	*P*	*r*	*P*	*r*	*P*
Gender	0.651[b]	< **0.001**[*]	-	-	-	-
Age	0.007[a]	0.899	−0.009[a]	0.907	−0.094[a]	0.293
BMI	0.551[a]	< **0.001**[*]	0.674[a]	< **0.001**[**]	0.481[a]	< **0.001**[**]
Systolic blood pressure	0.199[a]	**0.001**[*]	0.231[a]	**0.002**[**]	0.059[a]	0.506
Diastolic blood pressure	0.224[a]	< **0.001**[*]	0.321[a]	< **0.001**[**]	0.120[a]	0.176
Age at onset	0.020[a]	0.735	−0.026[a]	0.734	0.039[a]	0.662
Duration of illness	−0.030[a]	0.600	0.005[a]	0.951	−0.151[a]	0.089
Chlorpromazine Equivalents	−0.005[a]	0.936	−0.070[a]	0.361	−0.169[a]	0.057
ISI total score	0.046[b]	0.429	0.017[b]	0.826	0.093[b]	0.298
CDSS total score	0.002[b]	0.974	−0.001[b]	0.986	0.101[b]	0.256
PANSS total score	−0.188[a]	**0.001**[*]	−0.109[a]	0.155	−0.039[a]	0.660
Positive subscale score	−0.120[a]	**0.038**	−0.033[a]	0.670	−0.085[a]	0.343
Negative subscale score	−0.200[a]	< **0.001**[*]	−0.137[a]	0.073	0.001[a]	0.992
General psychopathology subscale score	−0.167[a]	**0.004**	−0.103[a]	0.179	−0.031[a]	0.732
Log BDNF	0.157[a]	**0.006**	0.173[a]	**0.023**	0.125[a]	0.160
Inflammatory cytokines						
Log IL−1β	0.057[a]	0.323	0.004[a]	0.960	0.061[a]	0.493
Log IL−6	0.116[a]	**0.045**	0.164[a]	**0.031**	−0.070[a]	0.431
Log IL−17 A	0.159[a]	**0.006**	0.218[a]	**0.004**	−0.148[a]	0.095
Log TNF-α	0.077[a]	0.182	0.096[a]	0.208	−0.052[a]	0.558

Notes: BMI, body mass index; ISI, Insomnia Severity Index; CDSS, Calgary Depression Scale for Schizophrenia; PANSS, The Positive and Negative Syndrome Scale; BDNF, brain-derived neurotrophic factor; LEP, leptin; IL−1β, interleukin−1β; IL−6, interleukin−6; IL−17 A, interleukin−17 A; TNF-α, tumour necrosis factor-α;

[a] Pearson's correlation; [b] Spearman's correlation;

Bold values mean $P < 0.05$; [*] $P < 0.05/19 \approx 0.0026$(Bonferroni correction); [**] $P < 0.05/18 \approx 0.0028$(Bonferroni correction)

Unfortunately, we failed to detect a correlation between leptin and insomnia and depressive symptoms in schizophrenia patients. This finding contrasts with that of Miller et al. [14], who reported a positive association between insomnia and elevated leptin levels in this patient population. A meta-analysis of healthy populations revealed that individuals with short sleep duration and those experiencing sleep deprivation exhibited higher leptin levels [49]. However, a subsequent cross-sectional study demonstrated that acute sleep deprivation decreased blood leptin concentrations [50]. And similar to our findings, McHill et al. [18] found that prolonged sleep deprivation did not markedly affect alterations in leptin. In contrast to our results, a case-control study showed a significant negative correlation between leptin and depressive symptoms among schizophrenia patients [15]. There has been a scarcity of research on the association between leptin and depressive symptoms in individuals with schizophrenia, mostly focusing on depressed patients. And the available evidence suggested that there might be a potential link between leptin imbalance and depressive symptoms, but the findings obtained were somewhat different. For instance, Takekawa et al. [51] identified that elevated leptin levels correlated significantly with the presence of depressive symptoms. Conversely, Yang et al. [52] observed that individuals with depression had comparatively reduced leptin levels when compared to healthy controls. Meanwhile, Heinen et al. [53] determined that there was no significant difference in leptin levels between patients with major depressive disorder and healthy controls. Given these inconsistent results, further research is required to investigate the relationship between leptin levels and symptoms of insomnia and depression in schizophrenia patients.

In addition, our study revealed a positive association between leptin and BDNF, implying that BDNF might partially influence leptin levels. Cao et al. [54] discovered that hypothalamic BDNF could down-regulate leptin production in adipocytes through sympathetic β-adrenergic signaling, indicating that BDNF could directly influence leptin expression. Moreover, Wang et al. [22] demonstrated that BDNF expression in the paraventricular nucleus (PVN) of the hypothalamus was critical for leptin regulation of sympathetic innervation in adipose tissue. The lack of BDNF PVH neurons diminishes the effect of leptin on innervation, suggesting that the BDNF signaling pathway is essential in leptin signaling. BDNF is likely to be crucial in the signaling of leptin by influencing the leptin signaling pathway and by regulating the impact of leptin on the sympathetic innervation of adipose tissue, thereby participating in the regulation of energy balance and body weight. BDNF modulates the leptin signaling

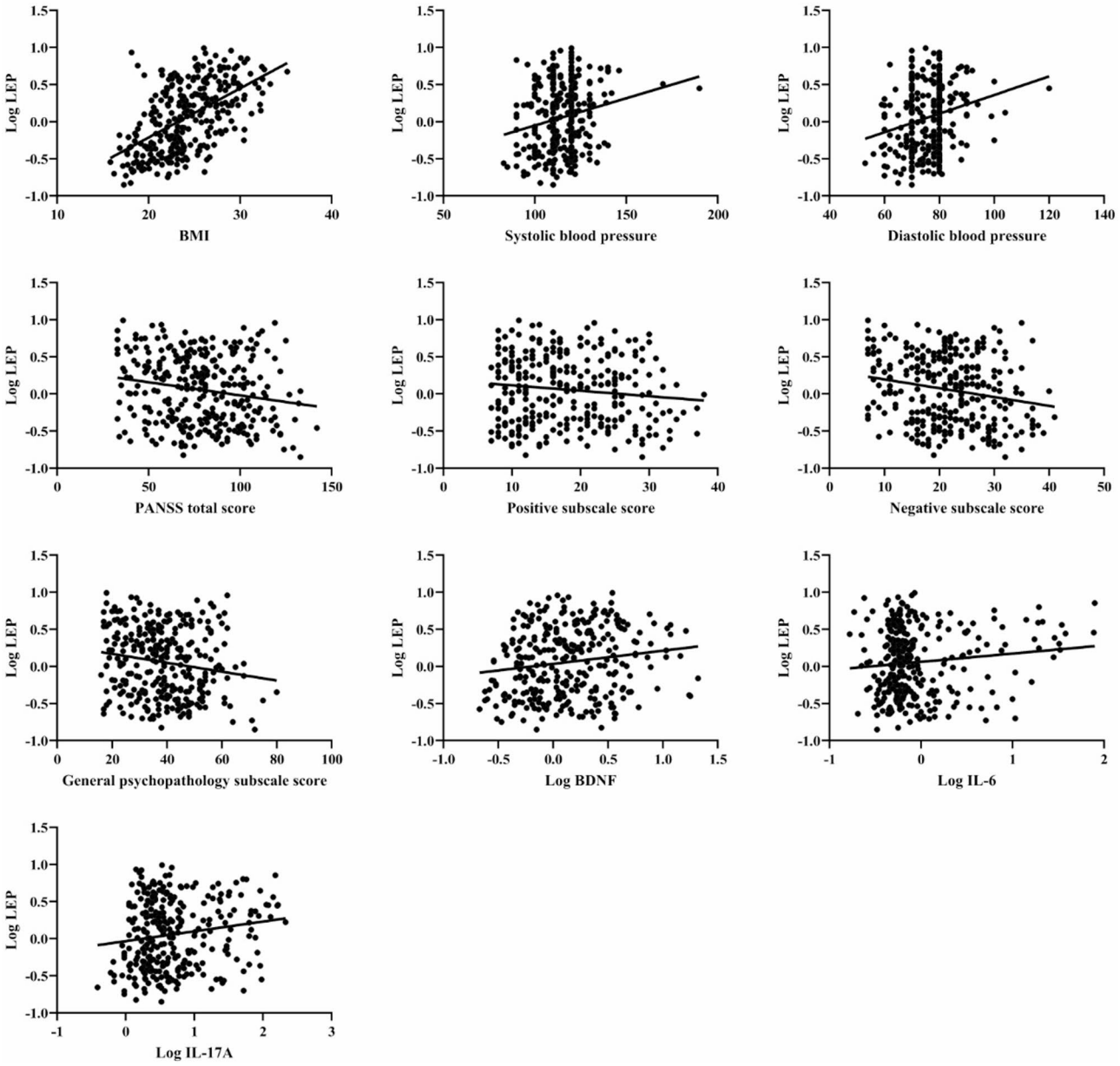

Fig. 2 Pearson's correlation of Log LEP with the BMI ($r = 0.551$, $p < 0.001$), Systolic blood pressure ($r = 0.199$, $p = 0.001$), Diastolic blood pressure ($r = 0.224$, $p < 0.001$), PANSS total score (r=-0.188, $p = 0.001$), Positive subscale score (r=-0.120, $p = 0.038$), Negative subscale score (r=-0.200, $p < 0.001$), General psychopathology subscale score (r=-0.167, $p = 0.004$), Log BDNF ($r = 0.157$, $p = 0.006$), Log IL–6 ($r = 0.116$, $p = 0.045$) and Log IL–17 A ($r = 0.159$, $p = 0.006$) in total sample

pathway in key hypothalamic nuclei (such as the PVN), thereby controlling appetite, promoting lipolysis and energy expenditure to maintain energy balance by influencing sympathetic innervation of adipose tissue and regulating synaptic plasticity and neuronal function [22, 55]. Nevertheless, in patients with schizophrenia, antipsychotic medication use is associated with significant weight gain and metabolic disturbances [56], which may alter leptin levels and increase obesity [57]. However, the association between leptin and BDNF was no longer significant when we included it in the regression analysis, which might be attributed to the fact that other factors had a more important influence on leptin levels.

Finally, we also observed some links between leptin and inflammatory cytokines (especially IL-6 and IL-17 A) in patients. Previous studies had partially explored these interactions in patients with schizophrenia. Leptin levels were found to be positively correlated with IL-6 levels in individuals with schizophrenia, as demonstrated by Martorell et al. [26]. Furthermore, the findings from an animal study indicated that IL-17 A significantly increased leptin expression in mouse adipocytes [58]. Leptin

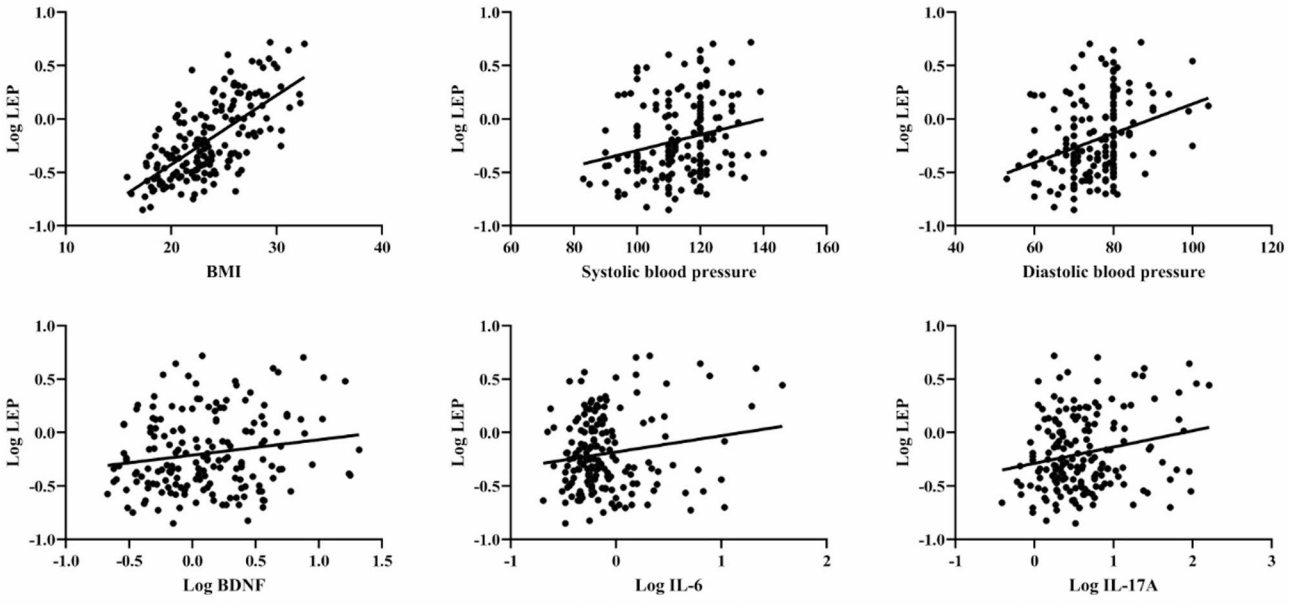

Fig. 3 Pearson's correlation of Log LEP with the BMI ($r=0.674$, $p<0.001$), Systolic blood pressure ($r=0.231$, $p=0.002$), Diastolic blood pressure ($r=0.321$, $p<0.001$), Log BDNF ($r=0.173$, $p=0.023$), Log IL–6 ($r=0.164$, $p=0.031$) and Log IL–17 A ($r=0.218$, $p=0.004$) in male patients

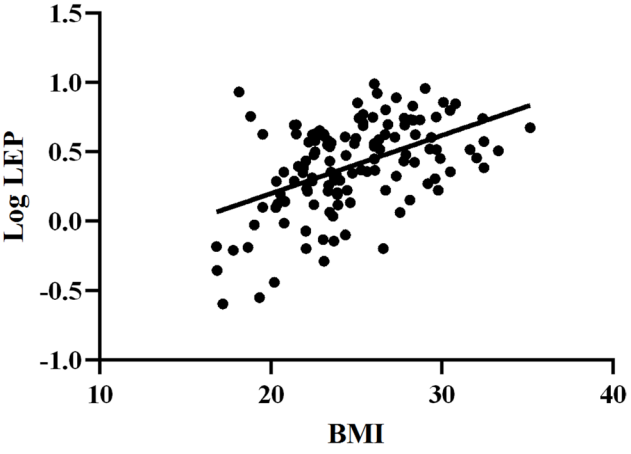

Fig. 4 Pearson's correlation of Log LEP with the BMI ($r=0.481$, $p<0.001$) in female patients

Table 3 Independent correlates of log LEP in patients

Variables	Beta	t	*P*
Total sample			
Gender	0.514	15.601	< **0.001**
BMI	0.053	12.096	< **0.001**
Diastolic blood pressure	0.005	2.334	**0.020**
Log IL–17 A	0.062	2.097	**0.037**
Males			
BMI	0.063	11.979	< **0.001**
Diastolic blood pressure	0.006	2.480	**0.014**
Log IL–17 A	0.187	5.125	< **0.001**
Females			
BMI	0.042	6.153	< **0.001**

Notes: BMI, body mass index; IL–17 A, interleukin–17 A;

Bold values mean $P<0.05$

itself is an adipocytokine and belongs to the same cytokine superfamily as IL-6 [59]. It is well-established that leptin plays a crucial role in modulating the inflammatory response and immune function [60]. In fact, leptin can act as a pro-inflammatory cytokine, influencing the expression and activity of other cytokines, including IL-6 and IL-17 A [61]. Inflammation is essential for preserving tissue equilibrium and is involved in the processes of metabolic diseases [59]. Abella et al. [60] found that circulating leptin levels and leptin expression within adipose tissue increased after exposure to inflammatory stimuli. These findings suggested that pro-inflammatory mediators might be able to upregulate leptin expression, thereby promoting an inflammatory response and creating a mutually reinforcing inflammatory cycle. In summary, the relationship between leptin and inflammatory cytokines is complex and bidirectional. Leptin not only responds to inflammatory stimuli but also actively participates in the regulation of the inflammatory response. This interplay is critical in understanding the pathophysiology of metabolic and inflammatory diseases.

Interestingly, the correlations mentioned earlier were observed solely among the male patients in our study. This finding could be attributed to disparities and variations in sex hormones [62]. In females, elevated estrogen levels stimulate leptin production, with leptin levels peaking in the middle of the menstrual cycle, synchronized with the nocturnal luteinizing hormone pulse. In contrast, in males, elevated androgens levels inhibit leptin secretion. Additionally, there are differences in metabolic and immune responses between males and females. Cossins et al. [1] found that there were associations between

leptin and inflammatory cytokines only in males. Males may be more sensitive to the effects of leptin because of differences in metabolic and immune responses. We speculated that the interplay of these factors may have contributed to our observation of an association between leptin and the aforementioned factors in male patients. Additional research is needed to explore potential gender differences between leptin levels and psychopathology, BDNF, and inflammatory cytokines in schizophrenic patients.

In this research, we provided a relatively comprehensive discussion of the psychopathology, BDNF, and inflammatory markers associated with leptin levels and compare the differences in these associations between males and females with schizophrenia. However, the present study had a few constraints. First, the cross-sectional nature of our study precluded the drawing of causal conclusions, and thus, the findings require further validation through longitudinal studies. Second, our study was conducted on chronic schizophrenic patients with a long duration of illness, some of whom were repeatedly hospitalized multiple times, which may have more confounding factors. Third, we did not perform power analyses to determine the sample size. This may have implications for the statistical power of our results and the ability to detect significant effects. Future research should consider conducting power analyses to ensure that sample sizes are sufficient to detect meaningful differences or associations. Fourth, one significant limitation of our study is the absence of a control group of healthy individuals. Without a control group, it is challenging to determine whether the observed associations between leptin levels and sociodemographic and clinical characteristics are specific to schizophrenia or are characteristic of the general population. Due to the lack of a control group from a healthy population, the results in this study regarding the association of schizophrenia should be interpreted with caution, future studies should include a control group to validate the specificity of these conclusions. Finally, our study did not control for the type of antipsychotic medication in patients with chronic schizophrenia; therefore, we could not explain the effect of antipsychotic medication on the study results. It is possible that patients receiving different types of antipsychotic medication and duration of treatment may have produced different results. Future research, including more longitudinal studies and animal models, is necessary to delve deeper into these associations and uncover their underlying mechanisms.

Conclusion

In conclusion, our findings suggested that there was correlations between leptin levels and psychotic symptoms, BDNF, and inflammatory cytokines (especially IL-6 and IL-17 A) in chronic schizophrenia patients, with significant gender differences. These findings helped us to further understand the relationship between leptin levels and psychopathology, BDNF, and inflammatory cytokines, and suggested that we need to consider gender factors when exploring leptin in this patient population.

Acknowledgements
We sincerely thank all the study participants.

Author contributions
HL and LL: the study's design. LZ, PT, HF, MH, XY, WL: collection, analyses and interpretation of the data. LZ: drafting of the manuscript. HL and LL: revision of the manuscript. The final version of the publication was approved by all authors.

Funding
This study was supported by the National Key Clinical Specialty Project Foundation (CN).

Data availability
The data used for this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Medical Ethics Committee of Chaohu Hospital of Anhui Medical University (Approval NO. 201805-kyxm-03). All procedures were conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. In addition, all subjects and their legal guardians signed an informed consent form.

Consent for publication
Not applicable.

Competing interests
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.

Clinical trial number
Not applicable.

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Received: 10 February 2025 / Accepted: 13 May 2025
Published online: 22 May 2025

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