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Association between fasting blood glucose and psychotic symptoms in Chinese patients with first-episode drug-naïve major depressive disorder

Xingzhi Xia[1,2†], Hanxu Deng[1,2†], Wei Ren[2,3], Lin Yang[2,3], Yingzhao Zhu[2,3], Yaozhi Liu[2,4], Junjun Liu[5], Xueli Zhao[2], Fengnan Jia[2], Xiangdong Du[1,2*] and Xiangyang Zhang[6*]

Abstract

Introduction Psychotic depression (PD) is a highly debilitating disorder characterized by hallucinations and/or delusions accompanied by depression. A variety of neurotransmitters, hormones and corresponding receptors in the endocrine system are involved in the onset and progression of depression, and fasting blood glucose (FBG) can be an important indicator for monitoring the stability of the endocrine system. The aim of this study was to investigate the relationship between FBG and PD in a Chinese population with first-episode drug-naïve (FEDN) major depressive disorder (MDD).

Methods In this study, 1718 outpatient individuals diagnosed with first-episode drug-naïve major depressive disorder (FEDN MDD) were included. The association between PD and FBG levels was identified through multivariable binary logistic regression analysis. To investigate potential non-linear relationships, a two-piecewise linear regression model was utilized. Additionally, interaction and stratified analyses were performed based on gender, educational background, marital status, presence of comorbid anxiety, and history of suicide attempt.

Results Multivariate logistic regression analysis showed that FBG was positively associated with the risk of PD in FEDN MDD patients (OR = 1.68, 95% CI: 1.31 to 2.13; $P < 0.05$). Smoothed plots showed a non-linear relationship between FBG and PD, while the inflection point of FBG was calculated using a two-segmented logistic regression model to be 6.23 mmol/L. On the right side of the inflection point, the probability of PD increased substantially by 278% (OR = 3.78, 95% CI: 1.75 to 8.18, $p < 0.001$), while no significant association was observed on the left side of the inflection point (OR = 1.06, 95% CI: 0.73 to 1.52, $p = 0.772$).

†Xingzhi Xia and Hanxu Deng contributed equally to this work and share first authorship.

*Correspondence:
Xiangdong Du
xiangdong-du@163.com
Xiangyang Zhang
zhangxy@psych.ac.cn

Full list of author information is available at the end of the article

Conclusions Our investigation revealed a nonlinear relationship between FBG and PD in patients with FEDN MDD, thereby informing more effective intervention strategies for managing psychotic symptoms in individuals with depression.

Keywords Major depressive disorder, Fasting blood glucose (FBG), Psychotic symptom, First episode, Drug naïve

Introduction

Major depressive disorder (MDD) is one of the most common mental disorders in modern society, which not only seriously jeopardizes people's quality of life, but also puts a huge burden on families and society due to its high suicide and disability rates [1, 2]. However, the treatment effectiveness and compliance for MDD are limited [3]. The characteristics of MDD are symptoms of depression lasting for more than 2 weeks, leading to emotional distress, functional impairment, health problems, and suicide [4]. Psychotic depression (PD) is a highly debilitating disease characterized by hallucinations and/or delusions accompanying depression [5, 6]. Recent epidemiological studies indicate that the prevalence of PD among MDD patients can range from 10–10.92% [7, 8], while the lifetime prevalence of PD is reported to be between 0.35% and 1% [9]. Meanwhile, patients with MDD comorbid with PD have a higher risk of suicide and mortality rates [10–12] and are more difficult to treat than patients with non-psychotic depression (NPD) [13, 14]. Due to the complexities of diagnosing and treating PD, early identification of patients is essential. This facilitates timely interventions, improving psychiatric symptom management and reducing healthcare risks. Studies have shown a significantly higher prevalence of abnormal blood glucose levels in patients presenting with psychotic symptoms compared to the general population [15, 16]. This underscores the potential of fasting blood glucose (FBG) as a pivotal biomarker, offering valuable insights into the pathophysiology of MDD with PD and informing the development of tailored therapeutic strategies.

The etiology of MDD is complex and multifactorial, encompassing a diverse array of biological, psychological, and social risk factors. Genetic predisposition, particularly a family history of psychiatric disorders or bipolar disorder, substantially elevates the risk of MDD development [17, 18]. Psychological factors, including chronic stress exposure, antecedent trauma, and maladaptive coping strategies, play pivotal roles in precipitating MDD onset [19]. Additionally, social determinants, such as inadequate social support networks and socioeconomic deprivation, have been consistently implicated as significant risk factors for MDD [20]. In recent years, an increasing number of studies have begun to focus on the role of metabolic factors in depression, particularly changes in blood glucose levels [21–23]. Elevated blood sugar levels not only affect physical health, but may also exacerbate depressive symptoms [24], such as the appearance of psychiatric symptoms, by affecting neurotransmitter metabolism and brain function. Research indicates that abnormalities in fasting blood glucose (FBG) levels may be associated with the severity of depressive symptoms, suggesting a potential role in PD [21, 22]. Previous studies have shown that MDD patients with elevated FBG are 2.33 times more likely to experience psychiatric symptoms than patients without elevated FBG [21].

Although there have been studies exploring the relationship between FBG and depression, there is still a lack of systematic research on the specific association between FBG and PD. Therefore, this study aims to explore the relationship between FBG and PD, especially in MDD patients who have had their first episode and have not taken medication, in order to reduce the impact of drug intervention. We will use targeted statistical analysis methods to deeply analyze the nonlinear relationship between FBG levels and PD, providing a new perspective for understanding the biological mechanisms of depression. Through this study, we hope to reveal the role of FBG in the development of PD, providing new ideas for clinical intervention and scientific basis for improving the prognosis of patients with depression.

Methods

Subjects

This cross-sectional study was conducted at the First Hospital of Shanxi Medical University, a general hospital in Taiyuan, Shanxi Province, China. A total of 1,718 FEDN MDD patients (588 males and 1,130 females) who met the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV-TR criteria were enrolled in the study during 2016–2018.

The criteria for participant inclusion encompassed: (1) individuals of Han Chinese descent; (2) aged between eighteen and sixty years; (3) documented diagnosis of major depressive disorder as per DSM-IV criteria, confirmed by two proficient clinical psychiatrists; (4) manifestation of initial depressive symptoms without prior exposure to antidepressant or antipsychotic medications; (5) duration of illness not exceeding 24 months; (6) attainment of a minimum Hamilton Depression Scale (HAMD-17) score of 24; and (7) absence of previous medication for glycemic control. Exclusion criteria entailed: (1) presence of significant physical illness such as organic brain disease or severe infections; (2) diagnosis of any additional DSM-IV Axis I disorder primarily

assessed through SCID examination; (3) current pregnancy or lactation; and (4) dependence or abuse of alcohol or substances, with the exception of tobacco use [25]. Before enrollment, all participants provided informed consent, following which they completed a questionnaire.

Sociodemographic characteristics and clinical assessment

First of all, Socio-demographic characteristics and general information including age, gender, marital status, education, age of onset and duration of illness were collected from all patients by trained researchers using a structured self-designed questionnaire. Weight, height, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were additionally measured according to standard methods and calibrated equipment, while body mass index (BMI) was calculated.

This investigation employed the 17-item Hamilton Depression Scale (HAMD) [26] for the evaluation of depression severity and the 14-item Hamilton Anxiety Rating Scale (HAMA) for the assessment of anxiety severity [27]. To uphold the integrity of data collection, two expert psychiatrists obtained the aforementioned data utilizing the Structured Clinical Interview for DSM Disorders (SCID) without access to the clinical background of the participants. The inter-scale reliabilities pertaining to the aggregate scores derived from the HAMD, HAMA, and PANSS-P [28] were evaluated through multiple assessments, yielding observer correlation coefficients surpassing 0.8. These findings align with and support prior research endeavors [29, 30], the cut-off point 15 of the PANSS-P was used to identify PD in patients with FEDN MDD. Suicide attempts were operationally defined as self-injurious actions intended to terminate life, yet not resulting in fatality. This determination was made through a direct inquiry conducted via a personal interview with the individual or a relevant family member, posing the question, "Have you (or the patient) endeavored to engage in suicidal behavior during your (or their) lifetime?" Those respondents indicating an affirmative response were categorized as having made a suicide attempt.

Blood samples

Blood samples in the form of serum and plasma were procured from the participants between the hours of 7 am and 9 am, subsequently partitioned into aliquots, and preserved at a temperature sufficiently below −70 degrees Celsius. Prior to the blood extraction, the patients were mandated to observe an overnight fasting period. The assessment of fasting blood glucose levels was conducted by research assistants who were kept unaware of the predefined experimental hypothesis. To simplify subsequent data analyses, the individuals were stratified into three equitably sized categories according to their serum fasting blood glucose (FBG) concentrations, delineated as low, moderate, and high groups.

Statistical analysis

Continuous variables were reported in accordance with their respective distributions. For non-normally distributed data, the median and interquartile range (IQR) were presented, while normally distributed variables were expressed as the mean with standard deviation (SD). Categorical variables were delineated as frequencies and percentages. To evaluate disparities among the tertile groups based on serum fasting blood glucose (FBG) levels, either a one-way ANOVA test, Kruskal-Wallis H test, or $\chi 2$ test was utilized. The linear association between serum FBG levels and psychotic symptoms was estimated using logistic regression models, with serum FBG level examined both as a continuous and categorical variable based on tertiles. Unadjusted and adjusted odds ratios (ORs) were presented with 95% confidence intervals (CIs). Sensitivity analyses were conducted to ensure the robustness of the data analysis. Additionally, to determine a *p*-value for trend, serum FBG level was transformed into a categorical variable. We categorized the patients into three tertiles based on FBG levels: low (T1: 3.7-5.0 mmol/L), moderate (T2: 5.1–5.5 mmol/L), and high (T3: 5.6–8.2 mmol/L). The variance inflation factor (VIF) was employed to assess multicollinearity among independent variables, with covariates possessing VIF values exceeding 5.0 being excluded from the final model. Potential confounders were selected based on their impact on serum FBG level and psychotic disorder (PD), with variables having a greater than 10% change in estimates or a *p*-value of less than 0.10 in univariable analysis being considered. Three models were constructed to ascertain the stability of the results: an unadjusted model, Model I adjusted for sex and age, and Model II adjusted for age, gender, education, HAMA, HAMD, TGAb, TPOAb, TC, TG, FBG, HDL-c, LDL-c, SBP, and DBP. The potential non-linear relationship between serum FBG levels and PD was evaluated using smoothing plots, and the threshold impact designated by the smoothing plot was investigated using a two-piecewise linear regression model based on the generalized estimating equation (GEE), with the inflection point calculated using a recursive algorithm. Stratified analyses were conducted based on sex, education, marital status, comorbid anxiety, and suicide attempt. Interaction effects within various subgroup variables were assessed using the log-likelihood ratio test. All statistical analyses were performed using the R software packages (http://www.r-project.org, The R Foundation) and Empower Stats (http://www.empowerstats.com, X&Y Solution, Inc., Boston, Massachusetts, United States), with GraphPad Prism 8.0 utilized for generating

visualizations. Statistical significance was defined as a two-tailed p-value of less than 0.05.

Results

Baseline characteristics

The study enrolled a total of 1718 patients with first episode drug-naive (FEDN) major depressive disorder (MDD), comprising 588 men and 1130 women. Participant characteristics were categorized based on tertiles of serum fasting blood glucose (FBG) levels, as outlined in Table 1. Significant correlations were observed between serum FBG level tertiles and various variables, including duration of illness, age at onset, Hamilton Depression Rating Scale (HAMD) score, Hamilton Anxiety Rating Scale (HAMA) score, Thyroid-Stimulating Hormone (TSH), Thyroglobulin Antibodies (TGAb), Thyroid Peroxidase Antibodies (TPOAb), Total Cholesterol (TC), Triglycerides (TG), High-Density Lipoprotein cholesterol (HDL-c), Low-Density Lipoprotein cholesterol (LDL-c), Body Mass Index (BMI), Systolic Blood Pressure

Table 1 Baseline characteristics of participants

Variables	FBG tertile (mmol/l)			*P*-value
	T1 (3.7-5.0)	T2(5.1–5.5)	T3(5.6–8.2)	
N	571	572	575	
Age (years)	34.0 ± 12.2	34.9 ± 12.4	35.7 ± 12.7	0.077
Duration of illness (months)	4.0 (3.0–7.0)	6.0 (3.0–8.0)	6.0 (3.0–9.0)	< 0.001
Age at onset (years)	33.9 ± 12.1	34.7 ± 12.2	35.5 ± 12.5	0.090
HAMD	29.5 ± 2.9	30.2 ± 2.9	31.2 ± 2.8	< 0.001
HAMA	20.4 ± 3.2	20.5 ± 3.4	21.4 ± 3.7	< 0.001
TSH (uIU/ml)	3.8 ± 2.4	5.0 ± 2.0	6.4 ± 2.6	< 0.001
TGAb (IU/l)	20.4 (14.3–30.1)	21.6 (13.9–37.0)	22.4 (15.4–89.8)	< 0.001
TPOAb (IU/l)	16.7 (12.2–28.9)	16.6 (12.2–33.3)	19.5 (12.7–49.0)	< 0.001
FT3 (pmol/l)	4.9 ± 0.7	4.9 ± 0.7	4.9 ± 0.7	0.866
FT4 (pmol/l)	16.7 ± 3.2	16.6 ± 3.0	16.7 ± 3.1	0.850
TC (mmol/l)	4.9 ± 1.0	5.3 ± 1.0	5.6 ± 1.1	< 0.001
HDL-c (mmol/l)	1.3 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	< 0.001
TG (mmol/l)	2.1 ± 1.0	2.1 ± 0.9	2.3 ± 1.0	< 0.001
LDL-c (mmol/l)	2.7 ± 0.8	3.0 ± 0.8	3.2 ± 0.9	< 0.001
BMI (kg/m^2)	24.1 ± 1.9	24.5 ± 1.9	24.5 ± 2.0	< 0.001
Systolic pressure (mmHg)	116.1 ± 11.0	119.6 ± 10.5	122.7 ± 10.2	< 0.001
Diastolic pressure (mmHg)	74.8 ± 6.7	75.6 ± 6.4	77.4 ± 6.8	< 0.001
Gender (n,%)				0.332
Male	209 (36.6%)	187 (32.7%)	192 (33.4%)	
Female	362 (63.4%)	385 (67.3%)	383 (66.6%)	
Education (n,%)				0.840
Junior high school	127 (22.2%)	138 (24.1%)	148 (25.7%)	
Senior high school	260 (45.5%)	247 (43.2%)	253 (44.0%)	
College	153 (26.8%)	155 (27.1%)	141 (24.5%)	
Postgraduate	31 (5.4%)	32 (5.6%)	33 (5.7%)	
Marital status (n,%)				0.457
Single	177 (31.0%)	166 (29.0%)	159 (27.7%)	
Marriage	394 (69.0%)	406 (71.0%)	416 (72.3%)	
Suicide attempt (n,%)				< 0.001
No	477 (83.5%)	484 (84.6%)	411 (71.5%)	
Yes	94 (16.5%)	88 (15.4%)	164 (28.5%)	
Comorbid anxiety (n,%)				< 0.001
No	131 (22.9%)	125 (21.9%)	82 (14.3%)	
Yes	440 (77.1%)	447 (78.1%)	493 (85.7%)	
Psychotic symptoms (n,%)				< 0.001
No	532 (93.2%)	524 (91.6%)	491 (85.4%)	
Yes	39 (6.8%)	48 (8.4%)	84 (14.6%)	

Note: The variables are presented as n (%) or the mean ± SD or median (quartile 1-quartile 3), FBG: fasting blood glucose; HAMD: 17-item Hamilton Rating Scale for Depression; HAMA: 14-item Hamilton Anxiety Rating Scale; TSH: thyroid-stimulating hormone; TGAb: thyroglobulin antibody; TPOAb: thyroid peroxidase antibody; FT3: free triiodothyronine; FT4: free thyroxine; TC: total cholesterol; HDL-c, high-density lipoprotein cholesterol; TG: triglyceride; LDL-c: low-density lipoprotein cholesterol; BMI: body mass index

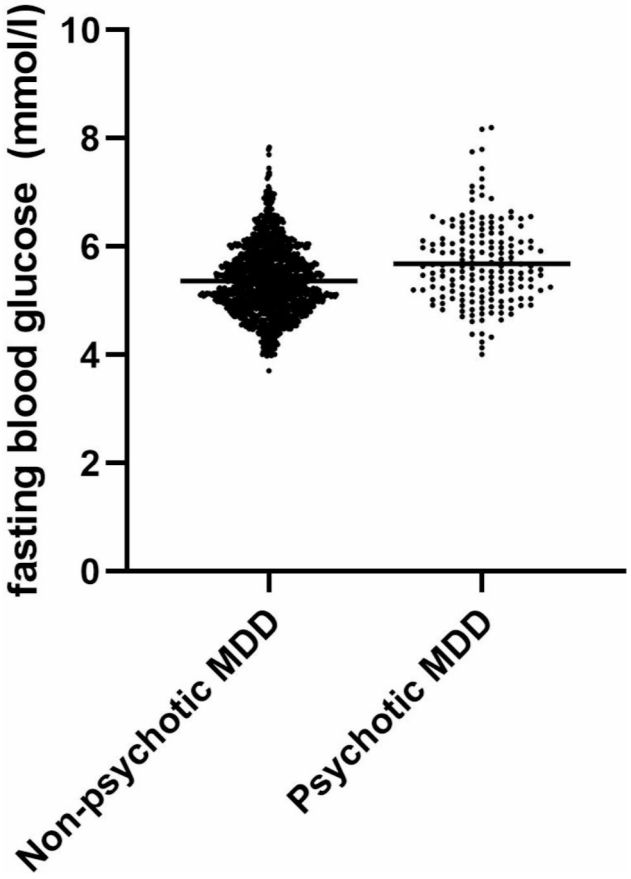

Fig. 1 Distribution of fasting blood glucose (FBG) levels in MDD patients with and without psychotic symptoms

(SBP), Diastolic Blood Pressure (DBP), history of suicide attempt, comorbid anxiety, and psychotic symptoms (all $p < 0.05$). Figure 1 illustrates the distribution of FBG levels in FEDN MDD patients with and without psychotic symptoms.

Relationship between FBG and psychotic symptoms

The fully adjusted analysis in Table 2 revealed a significant association between higher serum fasting blood glucose (FBG) levels and an increased risk of psychotic disorder (PD) (OR = 1.68, 95% CI: 1.31 to 2.13; $p < 0.05$). To further investigate the relationship between serum FBG levels and PD, generalized additive models were utilized and presented in Fig. 2. The analysis indicated a non-linear correlation between serum FBG levels and PD, with a significant *p*-value for non-linearity (< 0.05). Subsequently, a two-segment logistic regression model identified an inflection point at a serum FBG level of 6.23 mmol/L. The results from the generalized additive models illustrated a non-linear pattern between serum FBG levels and PD, showing a significant *p*-value for non-linearity (< 0.05). The two-segment logistic regression model revealed that for each unit increase in serum FBG level on the right side of the inflection point, the likelihood of PD substantially increased by 278% (OR = 3.78, 95% CI: 1.75 to 8.18, $p < 0.001$). However, on the left side of the inflection point, there was no significant evidence of a relationship between serum FBG levels and PD (OR = 1.06, 95% CI: 0.73 to 1.52, $p = 0.772$), as detailed in Table 3. Among the study participants, 180 individuals had a serum FBG level equal to or greater than 6.23 mmol/L, while 1538 individuals had a serum FBG level less than 6.23 mmol/L.

Subgroup analyses

Figure 3 illustrates the findings of the subgroup analysis, showing consistent patterns across different subgroups, such as sex (male, female), marital status (single, married), education level (junior high school, senior high school, college, postgraduate), and comorbid anxiety status (no, yes). There were no significant interaction effects observed in any of these subgroups, with all *p*-values for interaction being greater than 0.05.

Discussion

In this population-based cross-sectional study, the association between serum FBG level and PD was examined after adjusting for covariables. The findings revealed a special association, indicating that higher serum FBG levels were linked to PD. This finding is consistent with the results of previous research [21]. Furthermore, a non-linear correlation was observed, with an inflection point identified at 6.23 mmol/L. Below this threshold, there

Table 2 Relationship between fasting blood glucose and psychotic symptoms in different models

Variable	Crude Model		Model I		Model II	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
FBG	2.05 (1.63, 2.58)	<0.001	2.02 (1.60, 2.55)	<0.001	1.68 (1.31, 2.13)	<0.001
FBG (tertile)						
T1	0.80 (0.52, 1.24)	0.320	0.82 (0.53, 1.27)	0.365	0.95 (0.61, 1.49)	0.827
T2	Refrence		Refrence		Refrence	
T3	1.87 (1.63, 2.72)	0.001	1.86 (1.28, 2.71)	0.001	1.61 (1.10, 2.13)	<0.001
P for trend	< 0.001		< 0.001		0.007	

Abbreviations: CI, confidence interval; Crude Model adjusted for none; Model Iadjusted for age, sex; Model IIadjusted for age, sex, education, HAMD, HAMA, TSH, A-TG, A-TPO, TC, HDL-c, TG, LDL-c, BMI, SBP, DBP

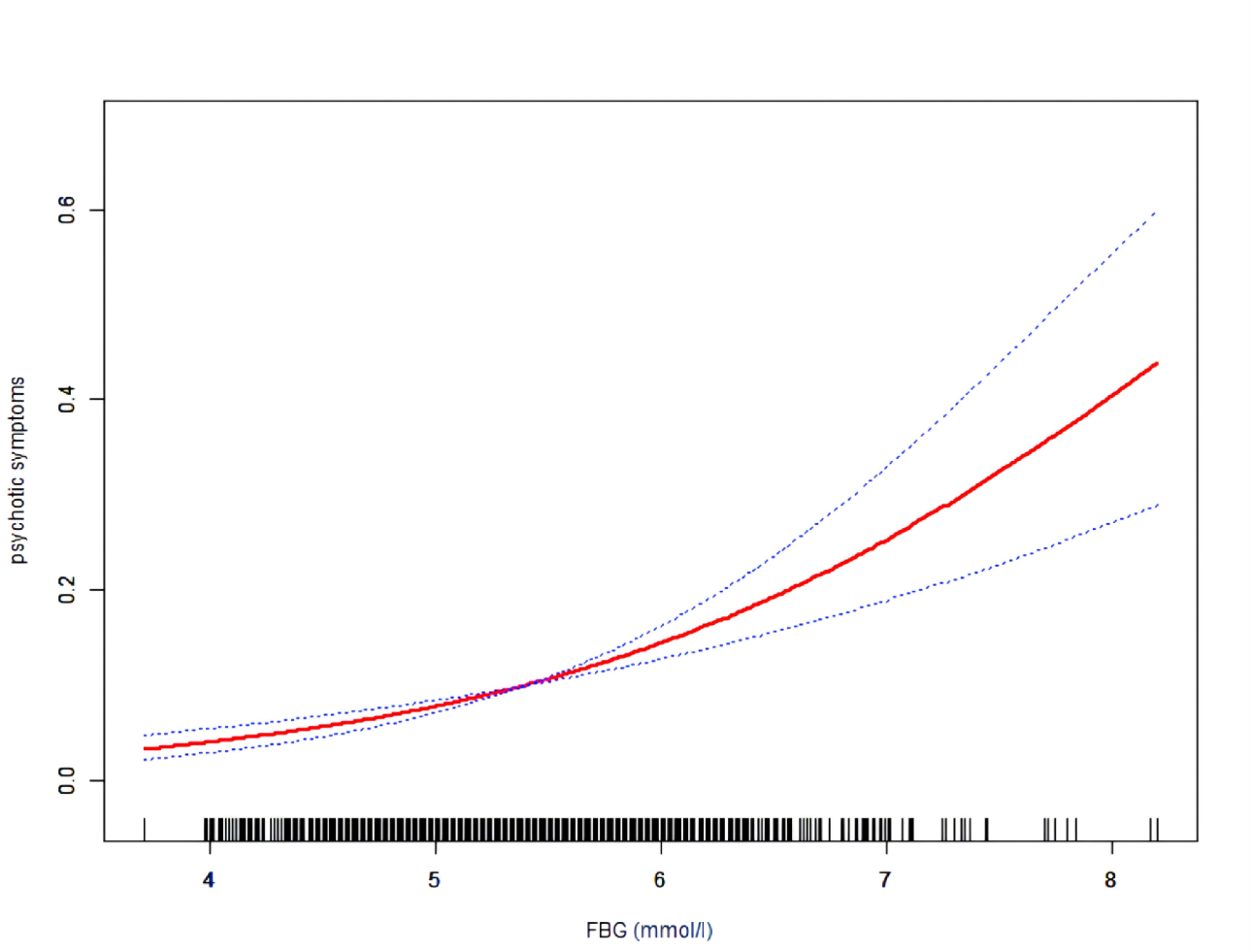

Fig. 2 The relationship between fasting blood glucose and the probability of psychotic symptoms. A nonlinear relationship between fasting blood glucose and the probability of psychotic symptoms was observed after adjusting for age, sex, education, HAMD, HAMA, TSH, A-TG, A-TPO, TC, HDL-c, TG, LDL-c, BMI, SBP, DBP

Table 3 The results of two-piecewise logistic regression model

Inflection point of FBG	Effect size (OR)	95%CI	*P*
Inflection point	6.23		
<6.23 (mmol/l)	1.06	0.73 to 1.52	0.772
≥ 6.23 (mmol/l)	3.78	1.75 to 8.18	<0.001
Log likehood ratio test			0.011

Effect: psychotic symptoms; Cause: FBG (mmol/l); adjusted for age, sex, education, HAMD, HAMA, TSH, A-TG, A-TPO, TC, HDL-c, TG, LDL-c, BMI, SBP, DBP

was no significant evidence of a relationship between serum FBG levels and PD. However, when FBG levels exceeded 6.23 mmol/L, the probability of PD substantially increased by 278% for each unit increase in serum FBG level. The consistency of the results across different subgroups, including gender, education, marital status, and comorbid anxiety, suggests that the relationship between serum fasting blood glucose levels and psychotic symptoms was robust and not influenced by these demographic or clinical factors. This finding enhances the reliability and generalizability of the study findings [31], indicating that the association between serum FBG levels and psychotic disorder is stable across diverse subgroups within the study population. However, given that these subgroup analyses are secondary endpoints with reduced statistical power, the findings should be interpreted cautiously. Although no significant interaction effects were observed, further research is needed to clarify the relationship between serum FBG levels and psychotic disorders in major depressive disorder. These findings provide novel insights into the complex relationship between FBG levels and PD in patients with MDD.

Firstly, the increase in FBG levels may reflect insulin resistance or glucose metabolism disorders [32], which have been shown to be closely related to the occurrence and development of depression [33]. The following mechanisms may explain how elevated FBG levels lead to the development and exacerbation of PD. First, elevated

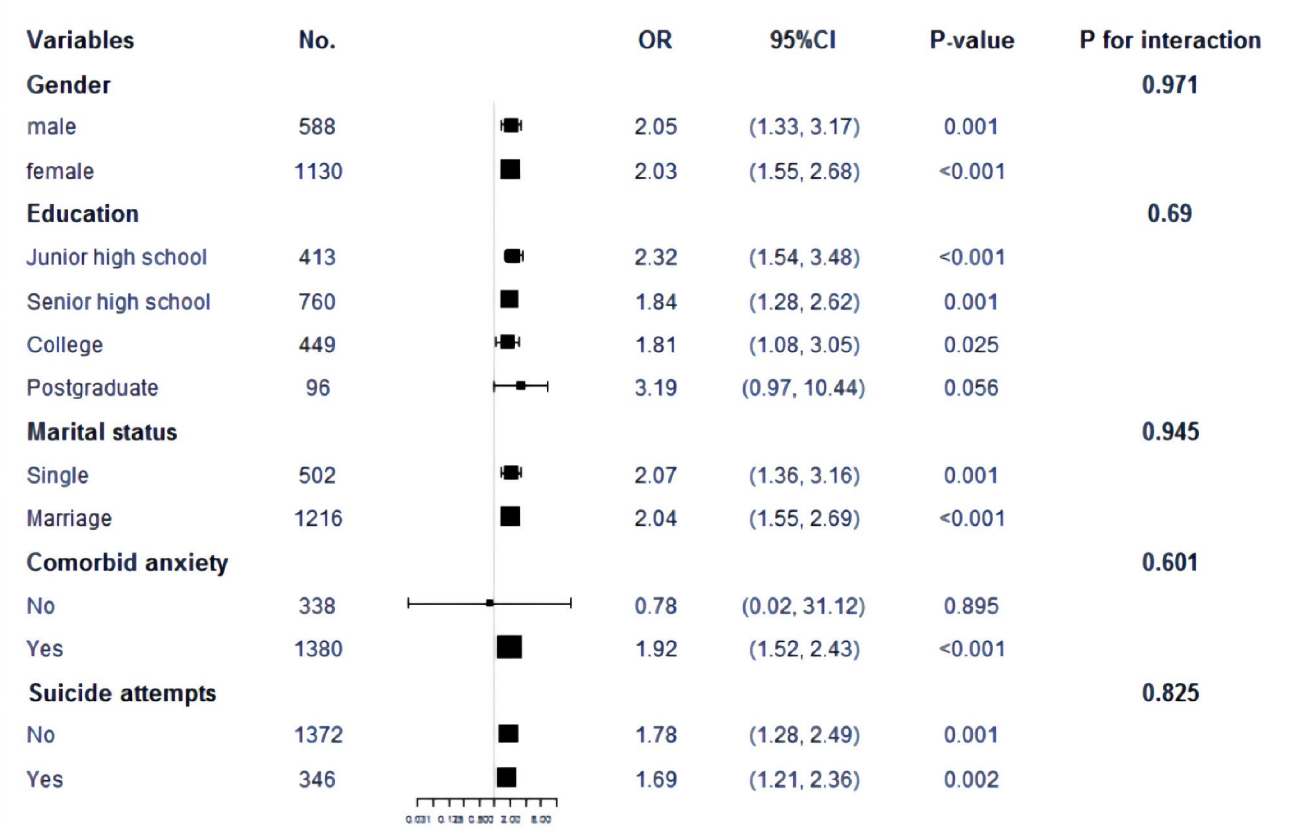

Fig. 3 Subgroup analysis of the association between fasting blood glucose and comorbid anxiety. The OR (95% CI) was derived from the Logistic regression model. (Age, sex, education, HAMD, HAMA, TSH, A-TG, A-TPO, TC, HDL-c, TG, LDL-c, BMI, SBP and DBP were adjusted)

FBG levels often indicate insulin resistance, which can induce systemic inflammation. Chronic inflammation can penetrate the central nervous system, leading to neuroinflammation [34]. Neuroinflammation has been associated with various psychiatric disorders, including psychotic depression [35]. The elevated levels of pro-inflammatory cytokines can disrupt the brain's normal functioning [36], particularly in areas that regulate mood and perception, potentially leading to psychotic symptoms. Second, proper glucose metabolism is essential for the synthesis and functioning of neurotransmitters such as serotonin, dopamine, and glutamate, which play critical roles in mood regulation and cognitive function [37]. Elevated FBG levels can impede glucose metabolism, leading to neurotransmitter imbalances [38]. These imbalances could contribute to both depressive and psychotic symptoms, as neurotransmitter dysregulation has been implicated in the pathophysiology of psychotic depression [39]. Third, chronic hyperglycemia can cause oxidative stress, which leads to the production of reactive oxygen species (ROS). These ROS can damage neuronal cells, affect synaptic plasticity, and impair brain function [40–42]. Neuronal damage can result in cognitive deficits and mood dysregulation, thus contributing to the symptoms of psychotic depression [43]. Next, elevated blood glucose levels are associated with dysregulation of the HPA axis [44], which governs the body's response to stress [45]. Dysregulation of the HPA axis can result in abnormal cortisol levels, which have been linked to depressive and psychotic symptoms [46]. The overactivity of the HPA axis is associated with the severity of depression [47–51], which may also lead to the occurrence of psychotic symptoms. Lastly, high fasting blood glucose levels can lead to structural abnormalities in the brain, such as reduced volume of white and gray matter [52, 53], especially in the hippocampus region [41]. The hippocampus is crucial for emotion regulation and cognition [54, 55]. There is a close relationship between the decrease in volume of white matter and gray matter and the occurrence of psychotic symptoms [56, 57].

Secondly, the non-linear relationship at the FBG level suggests the existence of a threshold effect, where below a specific level, the relationship between FBG and PD is not significant, but once it exceeds this threshold, the risk significantly increases. This phenomenon may be related to the body's ability to regulate blood sugar levels [58]. When FBG levels are within the normal range, the body can maintain metabolic balance through various

mechanisms. However, when blood sugar levels continue to rise, it may lead to hormonal imbalances and trigger symptoms of mental illness. The threshold effect described suggests critical points for early intervention. Monitoring FBG levels in patients could help identify those at increased risk of developing psychiatric conditions. This proactive approach could lead to timely and targeted interventions, such as lifestyle modifications, dietary adjustments, or pharmacological treatments, to prevent the onset or exacerbation of mental health issues. And future research should explore whether interventions targeting blood glucose regulation can concurrently reduce the risk or severity of psychiatric disorders. Longitudinal studies and randomized controlled trials could provide more robust evidence on the potential benefits of such interventions.

In addition, subgroup analysis results showed that factors such as gender, marital status, education level, and comorbid anxiety status did not have a significant interactive effect on the relationship between FBG and PD. This indicates that the impact of FBG levels on PD risk is consistent across different populations, suggesting that the association is broadly applicable and may not be influenced by specific demographic characteristics. Such consistency enhances the reliability of the study findings, suggesting that FBG levels could be an important risk indicator across diverse populations. The confirmed relationship between FBG and PD across subgroups underscores the importance of considering FBG levels in assessing first-episode drug-naïve major depressive disorder. Clinicians should focus on metabolic health to better identify high-risk patients. Understanding FBG and PD can help in developing tailored intervention strategies, especially for monitoring and managing blood glucose. These personalized treatments may enhance overall outcomes and improve symptoms. Although no significant interaction effects were found in the subgroup analysis, future research could explore other influencing factors like lifestyle and social support, opening new research avenues.

It is essential to acknowledge several limitations of the study. Firstly, the cross-sectional design restricts the establishment of causal relationships between serum fasting blood glucose (FBG) levels and psychotic disorder (PD). Secondly, the variability in FBG testing methods across different hospitals may lead to differences in reference standards, necessitating caution when interpreting the inflection point at 6.23 mmol/L. Thirdly, the reliance on patient and family interviews for medication history collection introduces the potential for recall bias, potentially impacting data accuracy. Fourthly, the recruitment of all major depressive disorder (MDD) patients from the outpatient department of a general hospital in Shanxi Province, China, may limit the generalizability of the findings to inpatients, community patients, or outpatients from different regions or racial groups. Therefore, future research should consider adopting longitudinal design and controlling for more potential confounding factors to further validate the relationship between FBG and PD.

In summary, this study revealed a non-linear relationship between FBG levels and PD, emphasizing the importance of metabolic abnormalities in patients with depression. This discovery provides new ideas for clinical intervention, suggesting that paying attention to the metabolic status of patients with depression may help improve the management of psychiatric symptoms. Future research should further explore the impact of changes in FBG levels on depression and related psychiatric symptoms, in order to provide more effective intervention strategies for clinical practice.

Conclusions

In conclusion, the study observed a nonlinear association between serum fasting blood glucose (FBG) levels and psychotic disorder (PD) in Chinese patients with first episode drug-naive (FEDN) major depressive disorder (MDD). An inflection point was identified around 6.23, indicating a potential threshold effect. On the right side of the inflection point, a positive correlation between FBG levels and PD was noted, suggesting that higher FBG levels beyond this point may be associated with an increased risk of PD. However, no such correlation was evident on the left side of the inflection point. These findings highlight the complexity of the relationship between FBG levels and PD, emphasizing the need for further research to elucidate the underlying mechanisms and clinical implications of this association.

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Author contributions

X X and H D wrote the main manuscript text. W R, L Y and Y Z prepared Tables 1, 2 and 3. Y L, X Z and F J prepared Figs. 1, 2 and 3. J L made the statistical analysis. X D and X Z revised the manuscript. All authors reviewed the manuscript.

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Data availability

The data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board (IRB) of Shanxi Medical University (No. 2016-Y27) and performed in accordance with the

Declaration of Helsinki. All subjects in this study signed a written informed consent form to participate in this study.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Xuzhou Medical University, Xuzhou, China
[2]Suzhou Guangji Hospital, The Affiliated Guangji Hospital of Soochow University, Suzhou, China
[3]Medical College of Soochow University, Suzhou, China
[4]School of Psychiatry, North Sichuan Medical College, Nanchong, Sichuan, China
[5]Nanjing Meishan Hospital, Nanjing, China
[6]CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China

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