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Mediation by elevated prolactin in the relationship between childhood trauma and first-episode drug-naïve schizophrenia

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Abstract

Background The elevated prolactin levels in first-episode drug-naïve (FEDN) schizophrenia patients may correlate with long-term stress caused by childhood trauma. This study aimed to assess the relationship between elevated prolactin levels and childhood trauma in FEDN schizophrenia patients, while also considering sex differences.

Methods Utilizing a cross-sectional design, the study involved 88 FEDN schizophrenia patients and 76 healthy controls (HCs). Evaluations encompassed measuring prolactin levels in peripheral blood and assessing mental health using the Positive and Negative Syndrome Scale (PANSS), the Childhood Trauma Questionnaire - Short Form (CTQ-SF), as well as evaluating resilience with the Connor-Davidson Resilience Scale (CD-RISC), perceived social support with the Perceived Social Support Scale (PSSS), and demographic characteristics to control for confounding factors. A mediation model was constructed using the RMediation package of the R software.

Methods The results suggested prolactin levels in FEDN schizophrenia patients were higher than in HCs(t=-9.938, $p=0.000$). Group classification (HCs vs. FEDN schizophrenia patients) (t = 9.291, $p=0.000$) and sex (t = 3.282, $p=0.001$) were influential factors for prolactin levels. Elevated prolactin(OR = 1.007, $p=0.000$), along with higher scores for childhood emotional(OR = 1.469, $p=0.006$)andsexual abuse(OR = 1.592, $p=0.018$) and lower social support(OR = 0.946, $p=0.026$), were associated with the onset of schizophrenia. Positive correlations were found between prolactin levels and childhood emotional ($r=0.268$, $p=0.002$) /sexual abuse($r=0.264$, $p=0.002$), with no sex differences. No significant relationship was observed between prolactin levels and PANSS scores. Mediation analysis revealed that childhood emotional abuse (95% CI: [0.059 ~ 0.293]) and sexual abuse (95% CI: [0.086 ~ 0.439]) had significant indirect effects on schizophrenia, mediated by elevated prolactin levels.

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Conclusion These findings suggest that childhood trauma may be associated with the onset of schizophrenia by influencing prolactin levels, highlighting the complex interplay between hormonal disruptions and early-life stress in the development of schizophrenia.

Keywords FEDN schizophrenia patients, Prolactin, Childhood trauma, Emotional abuse, Sexual abuse

Introduction

Schizophrenia is a common and severe mental disorder characterized by a range of positive symptoms, negative symptoms, and cognitive impairments. With a prevalence of nearly 1%, schizophrenia is one of the top 10 causes of disability worldwide [1]. The search for biological markers associated with the onset and clinical features of schizophrenia and other psychotic disorders has been a focus of substantial research for many decades. However, clinically translatable biomarkers in psychiatry remain elusive [2].

Prolactin is a polypeptide hormone primarily produced by the lactotrophs of the anterior pituitary gland [3]. It plays a key role in lactogenesis and also regulates a variety of physiological functions including immune response, reproductive behaviors, osmoregulation, and angiogenesis [4]. In addition, prolactin is involved in regulating nervous system-related processes, such as stress and trauma responses, energy balance, food intake, anxiety, neurogenesis, and pain [5]. Its secretion is controlled by dopamine from the tuberoinfundibular dopaminergic neurons and can be stimulated by factors such as estradiol, opioid peptides, oxytocin, thyrotropin-releasing hormone [6], psychosocial stress [7], and inflammation [8].

Elevated prolactin levels are commonly observed in patients with schizophrenia [9, 10]. While these increased levels are often linked to the use of antipsychotic medications that block dopamine receptors [11], recent findings suggest a more intricate relationship. Studies have shown elevated prolactin in antipsychotic-naive first-episode psychosis patients, indicating that hyperprolactinemia may also occur independently of medication [12–14]. Additionally, a meta-analysis confirmed higher prolactin levels in antipsychotic-naive patients with schizophrenia compared to healthy controls [15].Though it has been hypothesized that in antipsychotic-naive first-episode psychosis patients, hyperprolactinemia could be induced by stress [16],two studies failed to verify this hypothesis, as they found no correlation between perceived stress or life stressors and prolactin levels in first-episode psychosis patients [17, 18]. It may be because these studies only focused on acute and perceivable stress caused by recent life events but ignored the influence of early-life stress, and its ongoing potential to contribute to current stress levels. And the mechanism of action between long-term and recent stress is different [19]. This suggests that the study of stress and prolactin in schizophrenia patients should consider early-life stress, which would provide deeper insights into the role of prolactin in schizophrenia.

A multitude of studies have established childhood trauma as a significant early-life stressor [20, 21]. Childhood trauma encompasses a range of severe adverse experiences, including sexual, physical, and emotional abuse, and neglect [22]. Accumulating evidence suggests that exposure to such trauma during childhood may elevate the risk of schizophrenia [23–26]. One potential mechanism underlying this association could be the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis [27], which is recognized as the body's primary stress neuroendocrine system [28, 29]. Activation of the HPA axis contributes to dopamine sensitization in mesolimbic areas and increases stress-induced striatal dopamine release [30], while stress and dopamine are both the affective factors of prolactin. It is conceivable that the stress stemming from childhood trauma may modulate prolactin levels through the complex interplay between the HPA axis and dopaminergic signaling.

Given the associations between prolactin, childhood trauma, and schizophrenia, it is plausible to hypothesize that elevated prolactin levels in first-episode drug-naïve (FEDN) schizophrenia patients may stem from prolonged stress due to childhood trauma. This potential mechanism suggests there may be a pathway linking childhood trauma to schizophrenia via elevated prolactin levels, which remains unknown. Consequently, this study aims to verify this hypothesis. We will verify this hypothesis as follows: 1)compare prolactin levels between FEDN schizophrenia patients and healthy controls (HCs), and explore the relationship between prolactin levels and clinical symptoms in FEDN schizophrenia patients; 2)explore whether there is a correlation between prolactin levels and childhood trauma; 3)investigate whether changes in prolactin levels mediate the relationship between childhood trauma and schizophrenia; 4) Given that prolactin levels may differ between males and females [12, 31], we will also explore sex differences in our study.

Methods

Setting and recruitment

The inclusion criteria of FEDN schizophrenia patients were: an assessment based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR); age between 16 and 55; the course of the disease is more than one month but less than five years; no prior use of antipsychotic medication

or physical treatment; and provision of informed consent from both the patients and their family members.

The inclusion criteria of HCs were: interviewed by Structured Clinical Interview for DSM-5 Disorders (SCID-5); no personal or familial history of mental disorders; age between 16 and 55; and provision of informed consent to participate in the study.

Exclusion criteria for all participants were: poorly controlled thyroid disease, pituitary or ovarian alterations, significant central nervous system pathology, renal or liver insufficiency, and intellectual disabilities. For female participants, additional exclusions were applied for hormonal treatments, fertility treatments, menopause, pregnancy, or lactation.

This was a cross-sectional study conducted at the Department of Psychiatry, Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. Psychiatrists facilitated recruitment and verified drug-naivety through medical records. The study was approved by the Clinical Research Ethics Committee of the hospital.

Prolactin measurement

Blood tests were conducted on all participants to measure prolactin levels using a chemiluminescent microparticle immunoassay (CMIA) with reagents from Abbott Ireland Diagnostic Division. The assay sensitivity was 12.6 mIU/L. Prolactin levels were measured at 8 am after participants fasted overnight.

Instruments

Data on age, sex, body mass index (BMI), disease duration, educational level, smoking, and alcohol use were collected. Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) and early childhood trauma was evaluated using the Childhood Trauma Questionnaire - Short Form (CTQ-SF). Resilience and perceived social support were assessed with the Connor-Davidson Resilience Scale (CD-RISC) and the Perceived Social Support Scale (PSSS), respectively, to control for the impact of personal traits [32, 33] and social support on individuals who have experienced childhood trauma [34–36].

Statistical analysis

We utilized Statistical Product and Service Software Automatically (SPSSAU, Version 24.0) [37] for analyses, setting statistical significance at $p < 0.05$. The normality of numerical variables was assessed using the Kolmogorov-Smirnov test. Due to non-normal distribution, prolactin levels were log-transformed (base 10) for all analyses, except logistic regression, which does not require normalization. Demographic and clinical characteristics between HCs and FEDN schizophrenia patients were compared using two independent samples t-tests, Mann-Whitney U tests, and chi-squared tests. Linear regression was then employed to examine whether sex is an influential factor in prolactin levels, in which prolactin levels as independent variables, sex and group variables (HCs vs. FEDN schizophrenia patients) as dependent variables, age, BMI, alcohol use, and smoking as confounding variables. Subsequently, logistic regression was conducted to explore whether prolactin is an associated factor for schizophrenia, with group variables (HCs vs. FEDN schizophrenia patients) serving as the dependent variable, and prolactin and confounding factors as independent variables.

To explore the relationship between prolactin levels and clinical features of FEDN schizophrenia patients, partial correlation analyses were performed between prolactin levels and PANSS scale scores, separately for the total sample, male subgroup, and female subgroup, controlling for age, sex (for the total sample), and BMI. Based on the logistic regression results, partial correlation analyses were also conducted to examine the relationship between prolactin levels and childhood emotional abuse and sexual abuse, separately for the total sample, male subgroup, and female subgroup, controlling for age, sex (for the total sample), BMI, resilience, and social support. The results of partial correlation analyses were adjusted for multiple comparisons using the Bonferroni method.

Finally, the mediation analysis was conducted to assess the effect of childhood trauma(emotional abuse, sexual abuse) on the development of schizophrenia through prolactin, emotional abuse, and sexual abuse used as independent variables respectively, prolactin as the mediating variable, and grouped variable (HCs vs. FEDN schizophrenia patients) as the dependent variable; age, gender, BMI, resilience, and social support as control variables. Because the grouped variable(HCs vs. FEDN schizophrenia patients) is categorical, this analysis proceeded in three steps [38]: first, we used logistic regression to assess the direct effects of childhood trauma on schizophrenia; second, we applied linear regression to evaluate the effect of childhood trauma on prolactin levels; and third, we employed logistic regression to analyze the influence of childhood trauma on schizophrenia while considering prolactin levels (Supplementary material). The mediation analysis was run with the RMediation package of the R software [39], which is based on the distribution of the product, using the formula $Z_a{}^*Z_b$ (Z_a=a/SE (a), Z_b=b/SE (b)), to test the significance of the mediation effect [40], which asymmetric confidence intervals indicating significant mediation if excluding zero.

Results

Demographic and clinical characteristics

We included first-episode schizophrenia patients from October 2017 to June 2022. A total of 97 patients who had

never received antipsychotic treatment were selected. Additionally, 81 healthy controls were recruited. We excluded patients who lacked CTQ-SF scale data($n=6$), lacked PSSS scale data($n=2$), and 1 with a pituitary microadenoma, resulting in 88 patients included in the study. Among healthy controls, 3 lacked CTQ-SF scale data and 2 lacked basic information, leading to 76 healthy controls included in the study.

Significant differences in prolactin levels existed between FEDN schizophrenia patients and HCs, patients had higher prolactin levels than HCs(t=-9.938, $p=0.000$).There were also significant differences in age(U = 2363.000, $p=0.001$), and BMI(t = 3.200, $p=0.002$) between the two groups. Four dimensions of the CTQ-SF scale had significant differences between the two groups: emotional abuse(U = 1860.000, $p=0.000$), physical abuse(U = 2401.500, $p=0.001$),sexual abuse(U = 2276.500, $p=0.000$),physical neglect(t=-2.246, $p=0.026$). Differences in resilience(t = 2.534, $p=0.012$) and social support(t = 3.889, $p=0.000$) were also notable; no significant difference in sex, education, smoking, or alcohol use was observed between the two groups(Table 1).

Influential factors of prolactin levels

The results of linear regression(F = 20.304, $R^2=0.437$, $p=0.000$) indicated that the prolactin was affected by grouped variable(HCs vs. FEDN schizophrenia patients) (t = 9.291, $p=0.000$) and sex(males vs. females)(t = 3.282, $p=0.001$). The normalized coefficient for sex (males vs. females) was 0.215, indicating that prolactin levels in females are higher than in males, and that of grouped variable (HCs vs. FEDN schizophrenia patients) was $0.607>0$, also suggesting that the levels of prolactin in FEDN schizophrenia patients are higher than HCs (Table 2).

Associated factors of schizophrenia

Employing the logistic regression analysis to investigate associated factors of schizophrenia, the results indicated that prolactin (OR = 1.007, $p=0.000$), age(OR = 1.226, $p=0.000$), sex(OR = 0.262, $p=0.047$), emotional abuse(OR = 1.469, $p=0.006$), sexual abuse(OR = 1.592, $p=0.018$)and social support(OR = 0.946, $p=0.026$) were statistically significant(Table 3).

Table 1 Demographic and clinical characteristics

Variables	Healthy controls $N=76$	FEDN schizophrenia patients $N=88$	T / χ^2 / U	*p*-value
Age, Median (IQR)	20.063(3.4)	23.430(8.3)	2363.000[c]	0.001**
BMI, Mean ± SD	21.55 ± 2.94	20.20 ± 2.46	3.200[a]	0.002**
Sex, N, males (%)	47(61.8%)	52(59.1%)	0.129[b]	0.719
Disease duration (months), Median (IQR)	-	6(2,24)	-	-
Education, N (%):				
Middle school	11(14.47%)	18(20.45%)	1.271[b]	0.736
Senior high school/ technical secondary school	29(38.16%)	34(38.64%)		
Junior college/vocational school	17(22.37%)	16(18.18%)		
Undergraduate and above	19(25.00%)	20(22.73%)		
Smoking, yes (%)	6(7.9%)	9(10.2%)	0.267[b]	0.605
Alcohol use, yes (%)	0(0.0%)	4(4.5%)	5.067[b]	0.08
Prolactin, Mean ± SD	2.34 ± 0.26	2.83 ± 0.35	-9.938[a]	0.000**
PANSS scale:				
Total scores, Median (IQR)	-	74.5(21)	-	-
Positive symptom scores, Median (IQR)	-	19(7)	-	-
Negative symptoms scores, Mean ± SD	-	18.43(6.996)	-	-
General psychopathology scores, Median (IQR)	-	35(13)	-	-
CTQ-SF:				
Emotional Abuse, Median (IQR)	6.000(2.0)	9.000(5.0)	1860.000[c]	0.000**
Physical Abuse, Median (IQR)	5.000(1.0)	6.000(3.8)	2401.500[c]	0.001**
Sexual Abuse, Median (IQR)	5.000(0.0)	5.000(3.0)	2276.500[c]	0.000**
Emotional Neglect, Mean ± SD	13.34 ± 5.27	13.91 ± 4.73	-0.726[a]	0.469
Physical Neglect, Mean ± SD	9.47 ± 2.86	10.52 ± 3.08	-2.246[a]	0.026*
Resilience, Mean ± SD	64.92 ± 13.87	58.66 ± 17.75	2.534[a]	0.012*
Social support, Mean ± SD	61.91 ± 12.70	53.99 ± 13.26	3.889[a]	0.000**

Note: a: Two independent samples t-test; b: Chi-square test; c: Mann-Whitney U test; * $p<0.05$ ** $p<0.01$; FEDN: First-episode drug-naïve; IQR: Interquartile Range; SD: Standard Deviation; BMI: Body Mass Index; PANSS scale: Positive and Negative Syndrome Scale; CTQ-SF: the Childhood Trauma Questionnaire - Short Form

Table 2 Influential factors of prolactin levels

	Unnormalized coefficient		normalized coefficient	t	*p*-value	B 95% CI	
Variables	B	Std. Error				Upper limits	Lower limits
Age	0.001	0.004	0.008	0.119	0.905	-0.008	0.009
Sex(males vs.females)	0.173	0.053	0.215	3.282	0.001**	0.069	0.277
BMI	-0.002	0.009	-0.017	-0.259	0.796	-0.021	0.016
Alcohol use	-0.038	0.159	-0.015	-0.242	0.809	-0.352	0.275
Smoking	-0.074	0.091	-0.055	-0.818	0.414	-0.253	0.105
Group(HCs vs. FEDN schizophrenia patients)	0.478	0.051	0.607	9.291	0.000**	0.376	0.579
Normal	2.264	0.301	-	7.52	0.000**	1.669	2.858

Note: OR: Odds Ratio; BMI: Body Mass Index; $^{**}p < 0.01$. Std. Error: Standard Error; vs.:Versus

Table 3 Associated factors of schizophrenia

Variables	*p*-value	OR value	OR value 95% CI
Normal	0.261	0.016	0.000 ~ 21.258
Age	0.000**	1.226	1.100 ~ 1.366
Sex	0.047*	0.262	0.070 ~ 0.982
BMI	0.134	0.841	0.670 ~ 1.055
Prolactin	0.000**	1.007	1.005 ~ 1.010
CTQ-SF:			
Emotional Neglect	0.839	0.987	0.874 ~ 1.116
Physical Neglect	0.801	0.973	0.786 ~ 1.204
Emotional Abuse	0.006**	1.469	1.119 ~ 1.929
Physical Abuse	0.741	1.069	0.719 ~ 1.589
Sexual Abuse	0.018*	1.592	1.083 ~ 2.339
Resilience	0.670	0.992	0.958 ~ 1.028
Social Support	0.026*	0.946	0.901 ~ 0.993

Note: OR: Odds Ratio; BMI: Body Mass Index; CTQ-SF: Childhood Trauma Questionnaire - Short Form; $^{*}p < 0.05$, $^{**}p < 0.01$

The relationship between prolactin levels and clinical features of FEDN schizophrenia patients

After controlling for age, BMI, and sex, and applying the Bonferroni adjustment ($p = 0.05/10 = 0.005$), partial correlation analysis revealed no significant correlation between prolactin levels and PANSS scale scores in FEDN schizophrenia patients. Additionally, we conducted partial correlation analyses separately for male and female patients. Controlling of the same controls for age and BMI, and using the Bonferroni adjustment, we found no significant correlation between prolactin levels and PANSS scale scores in either male or female patients(Fig. 1).

The relationship between prolactin levels and childhood trauma

Partial correlation analyses, accounting for age, sex, BMI, resilience, and social support revealed significant positive correlations of prolactin with emotional abuse($r = 0.268$, $p = 0.002$) and sexual abuse($r = 0.264$, $p = 0.002$), after adjusting by Bonferroni($p = 0.05/15 \approx 0.003$) method. When analyzed only in males or females, the results suggested there was no significant correlation between prolactin and childhood trauma, suggesting that there was no sex difference in the association between childhood trauma and prolactin levels (Fig. 2).

The mediation analysis among childhood trauma, prolactin levels and schizophrenia

Because the relationship between childhood trauma and prolactin levels was independent of sex, sex differences were not analyzed separately in the mediation analysis. For the emotional abuse, the results showed the 95% confidence interval for the mediating effect of prolactin between emotional abuse and schizophrenia is [0.059 ~ 0.293], without the confidence interval including 0, indicating that the mediation effect of prolactin between emotional abuse and schizophrenia is significant. The results show the presence of partial mediation. For the sexual abuse, the results showed the 95% confidence interval for the mediating effect of prolactin between sexual abuse and schizophrenia is [0.086 ~ 0.439], also without the confidence interval including 0, indicating that the mediation effect of prolactin between sexual abuse and schizophrenia is significant. The results show the presence of partial mediation (Fig. 3).

Discussion

This study examined the link between prolactin levels, childhood trauma, and FEDN schizophrenia patients. We also explored the relationship between prolactin levels and clinical features in FEDN schizophrenia patients and thought of the difference in sex.

Differences in demographics, and clinical characteristics between FEDN schizophrenia patients and HCs

This study revealed higher baseline prolactin levels in FEDN schizophrenia patients compared to HCs, suggesting a disturbance in prolactin secretion independent of antipsychotic use. After controlling for other confounding factors, elevated prolactin was confirmed as an independent associated factor for schizophrenia which is consistent with other studies [12–14]. There are several hypotheses for elevated prolactin in FEDN schizophrenia

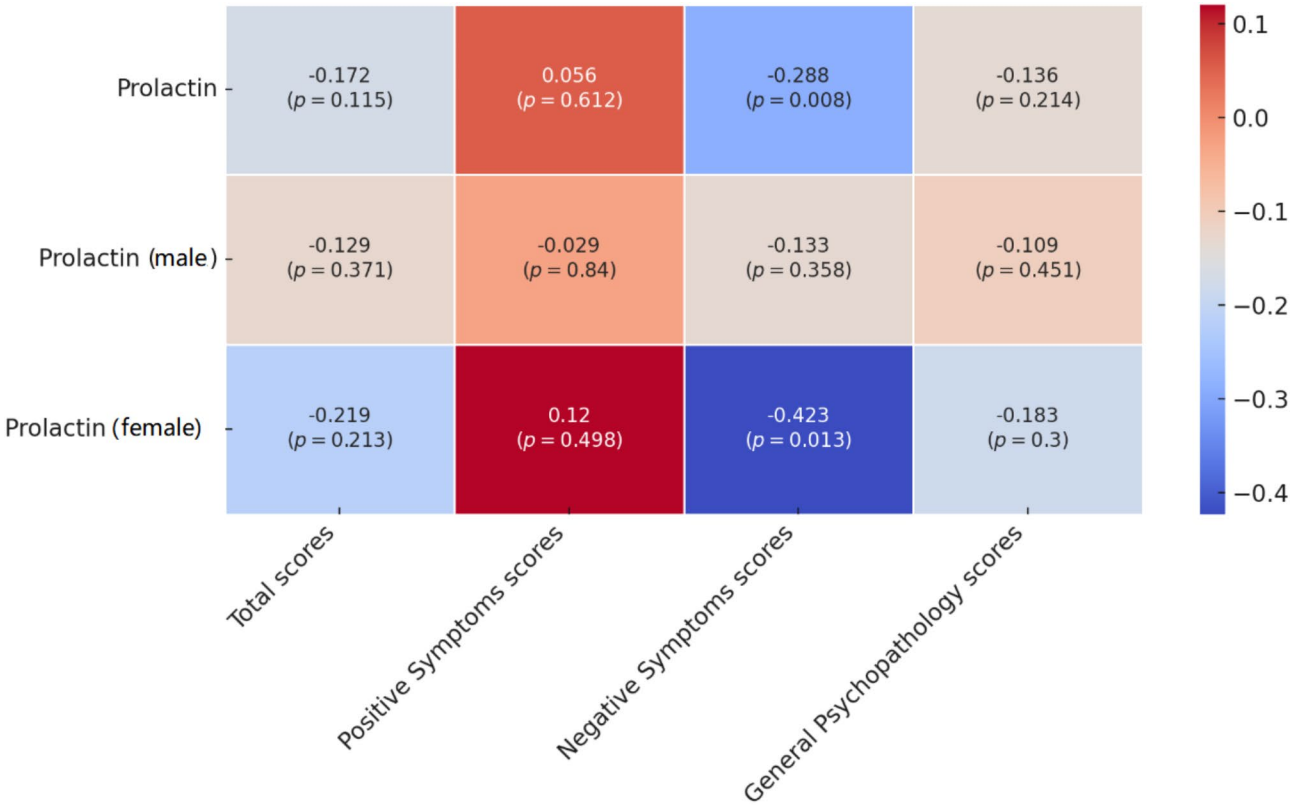

Fig. 1 The results of partial correlation analysis. After adjusting by Bonferroni($p = 0.05/10 = 0.005$), there was no significant correlation observed between prolactin and the PANSS scale scores in first episode drug-naïve (FEDN) schizophrenia patients($n = 88$), neither in male($n = 52$) or female patients($n = 36$)

patients: The synthesis and secretion of prolactin are mainly regulated by dopaminergic neurons in the anterior pituitary gland, which exerts an inhibitory effect on the release of prolactin [41]. The raised prolactin levels in psychosis may be stress-induced and the increase in dopamine found in striatal projections in psychotic states could be a regulatory mechanism to down-regulate increased prolactin levels [42]. Conversely, it could be that psychosis is correlated with reduced dopamine signaling within tuberoinfundibular pathways and this leads to raised prolactin levels. A further hypothesis would suggest the existence of a pre-existing genetic vulnerability, which predisposes, in situations of stress, both to an increase in prolactin and to the presentation of psychotic symptoms, through a dysregulation of dopaminergic pathways [43].

The results also showed that compared to HCs, FEDN schizophrenia patients had higher scores on several dimensions of the CTQ-SF [26, 44], yet received less social support [45, 46], which aligns with other research findings, suggesting that patients may have suffered more social adversity before the onset of the schizophrenia, which may become the risk factors to developing the schizophrenia.

Among the five dimensions of childhood trauma, only emotional and sexual abuse showed significant differences after adjusting for confounders. Research on the impacts of various trauma types on stress and schizophrenia yields inconsistent results [47]. This variability may stem from the complexity of differentiating the risks associated with diverse trauma types like sexual abuse, neglect, and bullying [48]. Often, children experience multiple traumas [49], which can be intertwined [50], further complicating the analysis.

The logistic regression analysis also revealed that age and sex were associated factors for schizophrenia, which may be related to the significant difference in age and sex between the two groups. After controlling for age and sex by logistic regression, it does not affect the interpretation of the results of other variables. A meta-analysis also found that increased prolactin levels often precede antipsychotic treatment and are not solely due to age or sex [43], suggesting the role of prolactin in schizophrenia may be independent of age and sex.

Sex differences in prolactin levels and their relationship to clinical features of FEDN schizophrenia patients

Prolactin levels in females are higher than in males, which is consistent with the findings of Lennartsson and

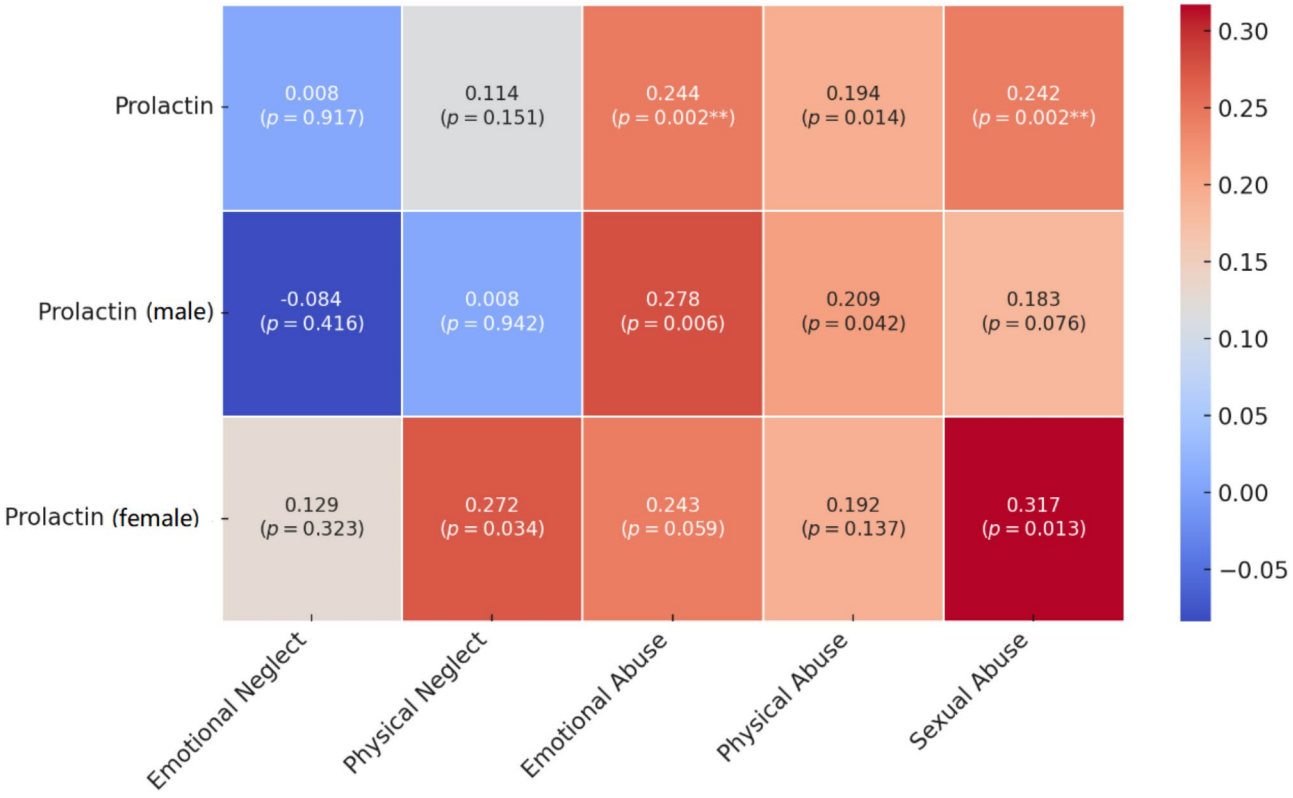

Fig. 2 The results of partial correlation analysis. After adjusting by Bonferroni($p = 0.05/15 \approx 0.003$),a significant positive correlation($r = 0.244$, $p = 0.002 < 0.003$) was observed between emotional abuse and prolactin($n = 164$); A significant positive correlation was observed between sexual abuse and prolactin ($r = 0.242$, $p = 0.002 < 0.003$). No significant correlation was observed only in either male($n = 99$) or female patients($n = 65$). $^{**}p < 0.003$

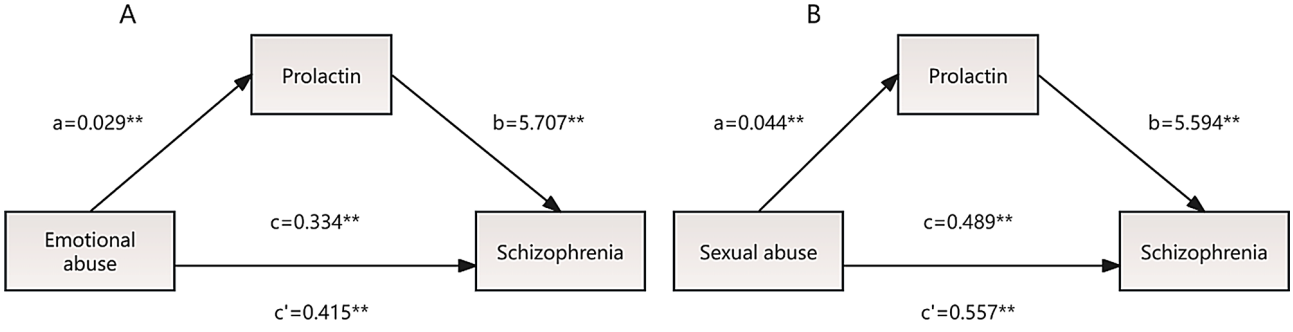

Fig. 3 The results of mediation analysis. **A**: Emotional abuse is associated with the onset of schizophrenia through the pathway of elevated prolactin. Total effect: c = 0.334**; mediation effect: a = 0.029**, SE(a) = 0.009; b = 5.707**, SE(b) = 0.877; Direct effect: c'=0.415**; The results show the presence of partial mediation. **B**: Sexual abuse is associated with the onset of schizophrenia through the pathway of elevated prolactin. Total effect: c = 0.489 **; mediation effect: a = 0.044**, SE(a) = 0.014; b = 5.594**, SE(b) = 0.877; Direct effect: c'=0.557**; The results show the presence of partial mediation. $^{**}p < 0.01$

Jonsdottir [7] as well as common understanding. No significant correlation between prolactin and the PANSS scale scores matter was observed in males or females. Similarly, our results aligned with those of Wasnik et al. [51], however, several other studies reported differing outcomes. Tharoor et al. found mildly elevated prolactin levels were correlated with higher total PANSS scale scores in women [52], while Delgado-Alvarado et al. found plasma prolactin levels showed a negative correlation with the SAPS(Scale for Assessment of Positive Symptoms) scores in antipsychotic naïve female patients with first-episode psychosis [12]. Additionally, Yuan et al. found serum prolactin levels in male patients were negatively associated with both negative symptoms and positive symptoms; In female patients, the serum prolactin levels were negatively associated only with negative symptoms [53]. Moreover, studies involving drug-treated schizophrenia patients have also produced inconsistent findings regarding the relationship between prolactin and PANSS scale scores [54–57]. The varying results suggest

that the relationship between prolactin levels and clinical features in schizophrenia patients remains unclear, indicating a need for larger sample studies or a meta-analysis to further explore this topic.

Emotional abuse and sexual abuse are associated with the onset of schizophrenia through the pathway of prolactin

The results indicated a positive association between prolactin levels and both childhood emotional and sexual abuse. However, when the analysis was conducted separately for male and female samples, no association emerged between prolactin levels and childhood trauma. This finding suggests that there are no sex differences in the relationship between prolactin and childhood trauma. However, there is no study have yet explored the relationship between prolactin and childhood trauma in FEDN schizophrenia patients. Given that prolactin is known to rise with stress, and is also a biomarker of chronic stress [58], childhood trauma can lead to long-term influence, and is associated with current stress [21], this may explain the association between increased prolactin and past trauma experiences.

This study suggested the hypothesis that childhood trauma may be correlated with developing schizophrenia through the pathway of prolactin. Consistent with broad research, childhood trauma is identified as a critical social factor that heightens the likelihood of schizophrenia onset [23–26]. There are several hypotheses about the mechanisms between childhood trauma and psychosis, such as psychoanalytic models and cognitive schemas, diathesis-stressor, social defeat, etc [59]. Our study confirms the diathesis-stressor model that people who suffer from childhood trauma experience long-term, chronic stress, during which the body may incur endocrine [60] like prolactin, neuroimmune [61], brain structure, and function changes [27], which ultimately raise the chance of developing schizophrenia.

Pariante CM et al. observed that the first-episode of a psychotic disorder was associated with a larger pituitary independently of the presence of antipsychotic treatment, and this could be due to activation of the HPA axis [62], which may suggest there was a potential correlation between stress and the lager pituitary volume. Prolactin, which is secreted by the anterior pituitary gland, may also be implicated in this relationship. Pariante CM et al. also found the increased pituitary volume induced by antipsychotics is linked to the stimulating effects of these drugs on lactotroph cells producing prolactin [63]. Thus, it is hypothesized that there may be a correlation between higher prolactin levels and larger pituitary volume in FEND schizophrenia patients. This hypothesis warrants further exploration in future studies to elucidate the underlying mechanisms and potential clinical implications.

Strengths and limitations

To the best of our knowledge, this is the first study to link childhood trauma to elevated prolactin levels in FEDN schizophrenia patients. We accounted for the effects of several known variables on prolactin levels, such as BMI [41], alcohol [64], and smoking [65].At the same time, we also considered the impact of resilience and social support on individuals who have experienced childhood trauma, which together helped effectively minimize the interference of confounding factors.

However, the study's cross-sectional nature limits causal interpretations, and using the retrospective CTQ-SF scale introduces potential bias. We didn't examine the effect of recent stress; future research should explore how long-term and recent stress interact to affect prolactin levels and the risk of schizophrenia onset. There is also a need to clarify whether abnormal concentrations of prolactin are specific markers of first-episode psychosis or are more generically linked to stress underlying severe mental disorders.

Conclusion

Prolactin levels are higher in FEDN schizophrenia patients than in HCs, and higher in females than in males. Elevated prolactin levels were found to be associated with childhood trauma, which may mediate the pathway linking childhood trauma to the onset of schizophrenia. These findings underscore the enduring impact of childhood trauma and suggest the potential diagnostic utility of monitoring prolactin levels in the early stages of schizophrenia. Furthermore, they emphasize the importance of offering timely support to individuals who have experienced childhood trauma.

Abbreviations

HPA Axis	Hypothalamic-Pituitary-Adrenal Axis
FEDN Schizophrenia Patients	First-Episode Drug-Naïve Schizophrenia Patients
HCs	Healthy Controls
CMIA	Chemiluminescent Microparticle Immunoassay
PANSS	Positive and Negative Syndrome Scale
CTQ-SF	Childhood Trauma Questionnaire - Short Form
CD-RISC	Connor-Davidson Resilience Scale
PSSS	Perceived Social Support Scale
SPSSAU	Statistical Product and Service Software Automatically
IQR	Interquartile Range
Std. Error	Standard Error
vs	Versus

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-06629-2 .

Supplementary Material 1

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Author contributions
QW and LL provided the evolution of overarching research goals, design of methodology, oversight and leadership responsibility for the research and acquisited of the financial support for the project leading to this publication. LL, XX, ZL, JD, JW, TL, MC, JM, YL, ZZ, QS, ST, ZD, SK and KZ were involved in the acquisition of the data, YP was involved in the analysis of the data and wrote the first draft of the paper. QW, JW, LL, YP and XZ were involved in the revision of the paper. All authors read and approved the final manuscript.

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Data availability
The dataset used and analyzed during the current study are available from the author upon reasonable request. Please contact panyq27@mail2.sysu.edu.cn or Weiql@mail.sysu.edu.cn to request access to the data.

Declarations

Ethics approval and consent to participate
This study had been approved by the Clinical Research Ethics Committee of Third Affiliated Hospital of Sun Yat-sen University and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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