RESEARCH

Exploring the relationship between lipid metabolism and cognition in individuals living with stable-phase Schizophrenia: a small cross-sectional study using Olink proteomics analysis

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Abstract

Background Cognitive impairment is a core symptom of schizophrenia. Metabolic abnormalities impact cognition, and although the influence of blood lipids on cognition has been documented, it remains unclear. We conducted a small cross-sectional study to investigate the relationship between blood lipids and cognition in patients with stable-phase schizophrenia. Using Olink proteomics, we explored the potential mechanisms through which blood lipids might affect cognition from an inflammatory perspective.

Methods A total of 107 patients with stable-phase schizophrenia and cognitive impairment were strictly included. Comprehensive data collection included basic patient information, blood glucose, blood lipids, and body mass index. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) and the MATRICS Consensus Cognitive Battery (MCCB). After controlling for confounding factors, we identified differential metabolic indicators between patients with mild and severe cognitive impairment and conducted correlation and regression analyses. Furthermore, we matched two small sample groups of patients with lipid metabolism abnormalities and used Olink proteomics to analyze inflammation-related differential proteins, aiming to further explore the association between lipid metabolism abnormalities and cognition.

Results The proportion of patients with severe cognitive impairment (SCI) was 34.58%. Compared to patients with mild cognitive impairment (MCI), those with SCI performed worse in the Attention/Alertness (t = 2.668, $p = 0.009$) and Working Memory (t = 2.496, $p = 0.014$) cognitive dimensions. Blood lipid metabolism indicators were correlated with cognitive function, specifically showing that higher levels of TG ($r = -0.447$, $p < 0.001$), TC ($r = -0.307$, $p = 0.002$), and LDL-C ($r = -0.607$, $p < 0.001$) were associated with poorer overall cognitive function. Further regression analysis indicated that TG (OR = 5.578, $P = 0.003$) and LDL-C (OR = 5.425, $P = 0.001$) may be risk factors for exacerbating cognitive impairment in individuals with stable-phase schizophrenia. Proteomics analysis revealed that, compared to individuals with stable-phase schizophrenia and normal lipid metabolism, those with hyperlipidemia had elevated levels of 10 inflammatory proteins and decreased levels of 2 inflammatory proteins in plasma, with these changes correlating

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with cognitive function. The differential proteins were primarily involved in pathways such as cytokine-cytokine receptor interaction, chemokine signaling pathway, and IL-17 signaling pathway.

Conclusion Blood lipids are associated with cognitive function in individuals with stable-phase schizophrenia, with higher levels of TG, TC, and LDL-C correlating with poorer overall cognitive performance. TG and LDL-C may be risk factors for exacerbating cognitive impairment in these patients. From an inflammatory perspective, lipid metabolism abnormalities might influence cognition by activating or downregulating related proteins, or through pathways such as cytokine-cytokine receptor interaction, chemokine signaling pathway, and IL-17 signaling pathway.

Keywords Schizophrenia, Cognition, Blood lipids, Olink

Introduction

Schizophrenia is a prevalent clinical psychiatric disorder characterized by positive symptoms, negative symptoms, and cognitive impairments [1]. Among these, cognitive impairment is recognized as a core symptom that significantly affects the quality of life and prognosis for individuals living with schizophrenia. Nearly all individuals living with schizophrenia (approximately 98%) experience cognitive deficits [2]. Compared to healthy controls, people living with schizophrenia exhibit impairments across multiple cognitive domains, including memory [3], executive function [4], processing speed [5], verbal fluency [6], and social cognition [7]. These deficits vary in severity and may be influenced by factors such as age, substance use, untreated illness duration, symptom dimensions, treatment regimens, and childhood trauma [8]. In addition, metabolic abnormalities are also key factors affecting cognition, though conclusions in this area remain inconsistent. This topic has garnered increasing attention in recent years for further exploration.

Metabolic abnormalities are risk factors for cardiovascular and cerebrovascular diseases [9]. It is noteworthy that severe metabolic abnormalities can affect cognition [10], a phenomenon widely reported in non-psychiatric patients [11, 12]. The executive function of patients with hypertension, for example, tends to be poorer [13], and fluctuations in BMI can impact cognitive function [14]. Certainly, the close relationship between cognitive impairment and metabolic abnormalities should similarly apply to patients with schizophrenia. Existing research has shown that individuals living with schizophrenia who have metabolic abnormalities exhibit poorer cognitive function compared to those without such abnormalities [15]. This impairment specifically manifests in attention, memory, and reasoning tasks, and typically develops after the onset of the illness [16, 17]. Moreover, antipsychotic medications are the cornerstone of schizophrenia treatment. However, research indicates that approximately 50% of patients experience metabolic side effects after using antipsychotics, especially second-generation antipsychotics [18]. These side effects can include weight gain, dyslipidemia, insulin resistance, and elevated prolactin

levels [19]. This further increases the risk of metabolic syndrome in patients with schizophrenia. Certainly, we believe that besides focusing on the relationship between metabolic syndrome and cognition, the relationships between specific individual aspects such as lipid levels, body weight, and blood glucose with cognition require further exploration.

Given the potential influence of various confounding factors such as the illness course, recovery of general psychiatric symptoms, and the type and dosage of antipsychotic medications on cognition, current research on the relationship between metabolism and cognition predominantly focuses on individuals experiencing their first episode of schizophrenia [20]. It is well known that in the short term, metabolic abnormalities alone may not immediately translate into cognitive impairment [21]. However, as the condition stabilizes and the disease progresses, the cumulative effects of metabolic abnormalities, combined with the "catalytic" effect of schizophrenia itself, may make it easier to detect the relationship between metabolic abnormalities and cognition. Therefore, exploring the relationship between metabolic abnormalities and cognition during the stable phase and implementing comprehensive interventions targeting potential risk factors in a timely manner may bring significant benefits to patients on long-term stable antipsychotic medication.

Recent studies have gradually linked lipid dysregulation, inflammation, and cognition. C-reactive protein (CRP), a reliable biomarker of inflammatory status, has been shown to predict cognitive improvement when low CRP levels are combined with high levels of HDL-C [22]. Genetic variations associated with CRP and plasma lipids (including HDL, LDL-C, and TG) have also been linked to an increased risk of Alzheimer's disease [23]. Peripheral inflammation and chronic low-grade inflammation can affect the central nervous system [24], as increases in circulating pro-inflammatory factors and free fatty acids may alter the permeability of the blood–brain barrier, potentially leading to changes in hippocampal function [25]. Variations in inflammation levels may also impact cognitive

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function by influencing plasma phospholipids [26]. In studies related to psychiatric disorders, patients with bipolar disorder have higher levels of apolipoprotein B compared to those with unipolar depression, and this may represent a risk factor for cognitive impairment [27]. Elucidating the role of inflammation as a potential bridge could deepen our understanding of the pathophysiological mechanisms by which lipids impact cognition.

In recent years, high-throughput omics technologies have rapidly advanced, providing new perspectives for a deeper understanding of physiological and pathological mechanisms. Proteomics is a systems biology approach that serves as a "bridge," reflecting upstream DNA or RNA abnormalities and predicting changes in various downstream metabolites [28]. Blood plasma, characterized by its safety and easy accessibility, is a stable and ideal sample used in research for various diseases. Multiple quantifiable proteins in plasma can serve as biomarkers for the diagnosis and prediction of complex diseases, reflecting various biological processes such as signal transduction, immune inflammation, and transport [29]. This study utilizes Olink proteomics technology to analyze inflammation-related protein changes in the blood plasma of individuals clinically diagnosed with stable-phase schizophrenia. From an inflammatory perspective, it aims to preliminarily explore the potential association and molecular mechanisms between lipid metabolism abnormalities and cognitive impairment, providing a basis for further clinical and experimental research.

In this study, we conducted a small cross-sectional analysis of individuals previously diagnosed with stable-phase schizophrenia, aiming to comprehensively gather their basic information and metabolic markers. These included blood glucose, lipid profiles (TG, TC, LDL, HDL), body mass index (BMI), as well as cognitive-related scores segmented into various dimensions. Taking into account the influence of confounding factors and controlling for gender, age, and illness duration, we observed differential metabolic markers between the two patient groups. Furthermore, through regression analysis, we identified lipid metabolism abnormalities as risk factors for cognitive impairment. Following this, we strictly matched two small sample groups of patients with lipid metabolism abnormalities based on gender, age, illness duration, and educational level. We utilized Olink proteomics analysis to investigate differential inflammatory-related proteins, aiming to further explore the association between lipid metabolism abnormalities and cognition. In summary, our primary objective is to identify risk factors for cognitive impairment in individuals living with stable-phase schizophrenia under specific conditions and

to elucidate potential mechanisms linking lipid metabolism abnormalities with cognitive dysfunction.

Methods
Participants

The research subjects are patients from the closed management ward of the Mental Neurological Disease Hospital in Heilongjiang Province, China. They meet the diagnostic criteria for schizophrenia according to the International Classification of Diseases, 10th Revision (ICD-10). Diagnosis was confirmed upon admission by two experienced psychiatrists. Inclusion criteria: (1) Age between 25–65 years, Han Chinese ethnicity. (2) The patient's condition has been stable for at least 6 months, with the Positive and Negative Syndrome Scale (PANSS) of ≤ 60, and scores of ≤ 3 on the items delusions, conceptual disorganization, hallucinatory behavior, blunted affect, social withdrawal, lack of spontaneity, and mannerisms/posturing [30].(3) Stable dose of monotherapy with antipsychotic medication (olanzapine) for at least 6 months [31]. (4) Education level of ≥ 6 years. (5) Montreal Cognitive Assessment (MoCA) score less than 25 [32]. Exclusion criteria: (1) Hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) or current use of antihypertensive medications. (2) History of head injury resulting in neurological sequelae, epilepsy, or neurosurgical history. (3) Presence of schizoaffective disorder, depressive disorders, bipolar affective disorder, or organic mental disorders. (4) History of drug abuse or alcohol abuse. (5) The presence of malignant tumors, severe cardiovascular and cerebrovascular diseases, and serious physical illnesses resulting from liver or kidney failure. Additionally, all patients are managed uniformly with a low-salt, low-fat diet, tobacco restriction, and daily centralized exercise training.

This study adheres to the Helsinki Declaration and is conducted under the auspices of the Heilongjiang Academy of Chinese Medicine. It has received approval from the ethics committee. Following an explanation of the study's nature, all patients and their relatives have provided informed consent.

Measurements
Clinical assessments

Gender, age, years of education (year), and illness duration (year) are collected from patient medical records. Current height and weight are measured to calculate Body Mass Index (BMI) using the formula: BMI = weight (kg) / height squared (m^2). Psychopathology is assessed using the PANSS, which comprises 30 items including scales for positive symptoms (7 items), negative symptoms (7 items), and general psychopathology (16 items). The PANSS is well-established for evaluating recent-week

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psychiatric symptoms with good reliability and validity. It is administered by two experienced psychiatrists, with inter-rater reliability coefficients exceeding 0.8.

Blood samples

Patients are not permitted to engage in vigorous physical activity for 8 h prior to blood collection. The following morning, between 6:30 and 7:30, trained nurses centrally collect fasting blood samples from patients. Each patient is required to provide two tubes of blood. (1) For biochemical analysis: Whole blood is collected using vacuum clot activator tubes. After standing at room temperature, serum is obtained by centrifugation at 3000 rpm for 10 min. Metabolic parameters including fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels are measured using an automatic biochemical analyzer (TBA-2000FR Biochemical analyzer). FBG, TC, TG, LDL-C were elevated at 6.2 mmol/L, 5.2 mmol/L, 1.7 mmol/L, and 3.4 mmol/L, respectively, while HDL-C was low at 1.0 mmol/L. (2) For Olink analysis: Whole blood from patients is collected using standard venipuncture technique into tubes containing EDTA. Within 30 min, the tubes are centrifuged at 3000 rpm for 10 min at 4 °C to remove blood cells. Plasma is then transferred to clean aliquot tubes and stored at -80 °C until analysis. Subsequent inflammatory markers were measured using Olink proteomics technology. All assays were conducted according to the manufacturer's protocols, as detailed in the "Olink Analysis" section.

Cognitive

Cognitive assessment is conducted using the MoCA scale to swiftly screen patients' cognitive functions. This scale has a maximum score of 30 points, with higher scores indicating better cognitive function. It demonstrates high reliability and validity across diverse populations and has been widely used for cognitive screening in patients with schizophrenia. Research suggests that a score below 25 indicates mild cognitive impairment, while a score below 23 indicates severe impairment [33]. An additional point is added to the total score if the years of education are ≤ 12 years (In this study, participants with 6–12 years of education had 1 point added to their total MoCA score). Further cognitive function assessment is performed using the Chinese version of the MATRICS Consensus Cognitive Battery (MCCB) [34]. This battery is specifically developed for cognitive assessment in schizophrenia and primarily includes seven domains: processing speed, attention/ Alertness, working memory, verbal learning, visual learning, problem solving, and social cognition. Finally, demographic data (including age, sex, education level, city of upbringing, and current city of residence) were used to convert raw scores from each test into Chinese standardized T-scores for statistical analysis. The T-scores have a mean of 50 and a standard deviation of 10. For domains with more than one test (working memory and processing speed), the T-scores were summed and then re-standardized. After obtaining T-scores for seven domains, they were summed and then standardized to create an overall composite score. All data collection is completed within 7 days.

Olink analysis

According to the manufacturer's instructions, protein levels are measured using the Olink® Inflammation Panel (Olink Proteomics AB, Uppsala, Sweden). The selection of the 92 biomarkers in the inflammation panel is predetermined by Olink Proteomics and cannot be customized. The Proximity Extension Assay (PEA) technology used in the Olink protocol is well-described and allows for the simultaneous analysis of 92 analytes using only 1 μL of each sample [35]. In brief, paired antibody probes labeled with oligonucleotides bind to their target proteins. If the two probes are in close proximity, the oligonucleotides will hybridize in a paired manner. The addition of DNA polymerase leads to a proximity-dependent DNA polymerization event, producing unique PCR target sequences. Subsequently, the obtained DNA sequences are detected and quantified using a microfluidic real-time PCR instrument (Biomark HD, Fluidigm). Internal extension controls and plate-to-plate controls are then used for data quality control and normalization to adjust for intra-run and inter-run variations. The final detection readings are expressed as Normalized Protein eXpression (NPX) values, which are arbitrary units on a log2 scale where higher values correspond to higher protein expression levels. All assay validation data, including detection limits, intra-assay and inter-assay precision data, can be found on the manufacturer's website at www.olink.com.

Data analysis

We used SPSS 26.0 software to conduct statistical analysis of demographic characteristics, clinical features, and cognitive functions. Specifically, categorical variables such as gender were represented using frequencies and percentages, and chi-square tests were conducted. We assessed the normality of data distribution using the Shapiro–Wilk test. For normally distributed continuous variables, t-tests were used, and results were represented using mean (Mean) and standard deviation (SD). For non-normally distributed data, non-parametric tests were used, and results were presented using median M (P25, P75). After controlling for factors other than

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differential metabolic indicators, partial correlation analysis was used to preliminarily explore the relationship between differential metabolic indicators and cognition. Furthermore, backward logistic regression was used to iteratively remove the least contributory variables from all potential predictors affecting cognition, in order to identify the optimal subset of predictor variables. The conditional likelihood ratio test was employed to determine which variables to exclude. Ultimately, the most influential predictors for the dependent variable were retained, and the logistic regression results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). All statistical tests were two-tailed, with a significance level set at $P < 0.05$.

Results

Participant characteristics

In the final dataset, complete information was collected from 107 patients, including 53 males and 54 females, resulting in a nearly equal gender ratio of approximately 1:1. The patients had an average age of (46.28 ± 8.24) years. The duration of illness ranged from 5 to 26 years, with a median duration of 12 years. The average years of education were 8.11 [6.87, 9.52] years. The average PANSS total score was (46.63 ± 5.95). Among them, 37 patients (34.6%) with stable schizophrenia exhibited severe cognitive impairment. There were no significant differences in age, illness duration, years of education, or PANSS scores between these patients and those with mild cognitive impairment in schizophrenia (all $p > 0.05$). The BMI of patients ranged from 21 to 31.25 kg/m^2. The average BMI for the two groups was (24.87 ± 2.16) kg/m^2 and (25.18 ± 1.88) kg/m^2, both indicating overweight status. However, the difference was not statistically significant (t = -0.737, $p = 0.463$). Meanwhile, FBG and HDL-C did not show significant differences (t = -1.511, $p = 0.134$; Z = -1.838, $p = 0.066$). In contrast, the severe cognitive impairment

Table 1 Demographics, clinical characteristics, and cognitive function of patients with schizophrenia

	SZ (*n* = 107)	MCI (*n* = 70)	SCI (*n* = 37)	t/c2/Z[a]	P
Age (years)	46.28 ± 8.24	46.53 ± 8.57	45.81 ± 7.67	0.427	0.670
Males, n (%)	53 (49.5%)	31 (44.3%)	22 (59.5%)	2.229	0.135
Education(years)	8.11[6.87,9.52]	8.15[6.99,9.97]	7.90[6.55,9.26]	-0.865	0.387
DUI (years)	12[8, 17]	12[8.75,18]	10[7.50,15]	-1.809	0.070
MoCA	22[16, 24]	23[23, 24]	16[15, 17]	-8.632	<0.001[**]
PANSS					
Total	46.63 ± 5.95	47.24 ± 5.44	45.46 ± 6.74	1.483	0.141
Positive symptom	11[8, 13]	11.04 ± 3.29	10.78 ± 3.44	0.381	0.704
Negative symptom	13[10, 18]	14.39 ± 7.05	13.70 ± 4.45	0.612	0.542
General psychopathology	21.52 ± 7.48	22.5[18, 27]	20.97 ± 7.85	-0.988	0.323
BMI (kg/m2)	24.77[23.44,26.04]	24.87 ± 2.16	25.18 ± 1.88	-0.737	0.463
FBG (mmol/L)	5.02 ± 0.50	4.96 ± 0.52	5.12 ± 0.45	-1.511	0.134
TC (mmol/L)	4.42 ± 0.71	4.30 ± 0.70	4.66 ± 0.67	-2.604	0.011[*]
TG (mmol/L)	1.64[1.18,2.15]	1.42 ± 0.54	2.20[1.85,2.52]	-5.535	<0.001[**]
LDL-C (mmol/L)	2.54[2.20,3.41]	2.39[2.00,2.61]	3.64[2.68,4.00]	-6.400	<0.001[**]
HDL-C (mmol/L)	1.26[1.07,1.43]	1.29 ± 0.26	1.14[1.00,1.39]	-1.838	0.066
MCCB					
Total	33.09 ± 6.47	34.61 ± 6.20	30.21 ± 6.05	3.52	0.001[**]
Information processing speed	38.28 ± 6.79	38.60 ± 6.58	37[30.50,42]	-0.957	0.338
Attention/Alertness	37.75 ± 5.62	38.77 ± 5.11	35.81 ± 6.08	2.668	0.009[**]
working memory	38.48 ± 5.81	39.47 ± 5.09	36.59 ± 6.64	2.496	0.014[*]
verbal learning	34.79 ± 6.16	35.31 ± 6.32	33.81 ± 5.78	1.204	0.231
visual learning	39.15 ± 5.13	38.91 ± 5.07	39.59 ± 5.29	-0.65	0.517
problem solving	31.16 ± 6.27	31.64 ± 5.74	30.24 ± 7.24	1.094	0.276
social cognition	35.50 ± 4.94	35.36 ± 4.63	35.76 ± 5.55	-0.396	0.693

MCI mild cognitive impairment, *SCI* severe cognitive impairment, *DUI* duration of illness, *MoCA* Montreal Cognitive Assessment, *PANSS* Positive and Negative Syndrome Scale, *BMI* body mass index, *FBG* fasting blood glucose, *TG* triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *MCCB* MATRICS Consensus Cognitive Battery

[a] The statistical values represent comparisons between groups: MCI vs. SCI

*$p < 0.05$, **$p < 0.01$

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group exhibited significantly higher levels of TG, TC, and LDL-C compared to the mild cognitive impairment group (Z = -5.535, $p < 0.001$; t = -2.604, $p = 0.011$; Z = -6.400, $p < 0.001$) (Table 1).

Cognitive function

The MoCA scores of the 107 participants were 22 [16, 24], with a maximum of 24 and a minimum of 14. The MCCB scores were 33.09 ± 6.47, with a maximum of 48 and a minimum of 19. When categorized, the MCCB score ranges for the mild cognitive impairment and severe cognitive impairment groups were MCCB (21–48; 19–45), respectively. There were significant differences in MoCA and MCCB scores between the mild cognitive impairment group and the severe cognitive impairment group (Z = -8.632, $p < 0.001$; t = 3.52, $p = 0.001$). In terms of MCCB dimensions, compared to the mild cognitive impairment group, the severe cognitive impairment group performed worse in the Attention/Alertness and Working Memory dimensions, with statistically significant differences (t = 2.668, $p = 0.009$; t = 2.496, $p = 0.014$). However, no significant differences were observed between the two groups in other cognitive domains (all $p > 0.05$) (Table 1).

The correlation between blood lipids and cognition, and regression analysis

After controlling for factors other than the differential metabolic indicators, partial correlation analysis was conducted across the entire sample to examine the relationship between differential metabolic indicators (TG, TC, and LDL-C) and MoCA scores. The results showed that TC ($r = -0.307$, $p = 0.002$), TG ($r = -0.447$, $p < 0.001$), and LDL-C ($r = -0.607$, $p < 0.001$) were all negatively correlated with MoCA scores. In the regression model, variables such as age, sex, illness duration, BMI, years of education, and HDL-C were gradually excluded, leaving FBG, TC, TG, and LDL-C as the optimal predictors. Among these, only elevated TG (OR = 5.578, $P = 0.003$)

and LDL-C (OR = 5.425, $P = 0.001$) were associated with a decline in cognitive function, as shown in Table 2.

Oink proteomics

The above results suggest that TG and LDL-C may be risk factors for exacerbating cognitive impairment. To further explore the impact of blood lipids on cognition, we matched 20 cases of hyperlipidemia (defined according to Chinese lipid management guidelines as LDL-C $\geq$ 3.4 mmol/L and TG $\geq$ 1.7 mmol/L for a diagnosis of mixed hyperlipidemia) with 19 cases of individuals living with schizophrenia who had normal lipid metabolism, based on demographic characteristics. Using the Olink proteomics method, we screened for differential proteins and investigated their correlation with cognition, aiming to further explore the relationship between blood lipids and cognition at the molecular level. The hyperlipidemia group had significantly higher TG and LDL-C levels compared to the control group, with lower cognitive function scores. Other demographic and metabolic indicators were similar between the two groups, as shown in the Supplementary Material 1.

In the panel of 92 proteins related to inflammation, differential expression analysis revealed that 10 proteins were significantly higher in the SZHL (schizophrenia with hyperlipidemia) group, while 2 proteins were lower. MCP-3 has the largest logfold change in protein expression (logFC = 0.78, $p < 0.001$), followed closely by IFN-gamma (logFC = 1.64, $p = 0.001$), and nearly alongside is CD8A (logFC = 0.65, $p = 0.001$). Additionally, the following 7 proteins showed increased expression: IL10 (logFC = 0.58, $p = 0.003$), FGF-21 (logFC = 1.56, $p = 0.005$), CXCL11 (logFC = 0.65, $p = 0.008$), EN-RAGE (logFC = 0.97, $p = 0.022$), CCL3 (logFC = 0.42, $p = 0.023$), CXCL10 (logFC = 0.73, $p = 0.027$), and CXCL6 (logFC = 0.69, $p = 0.049$). In contrast, TWEAK (logFC = -0.27, $p = 0.032$) and FGF-5 (logFC = -0.18, $p = 0.025$) were lower compared to the control group. The differential protein data is presented in Table 3. The volcano plot depicting differential protein expression is shown in

Table 2 Regression analysis

	B	SE	Wald χ2	OR	95%CI	P
FBG	1.291	0.703	3.377	3.638	0.918–14.419	0.066
TC	0.827	0.509	2.640	2.286	0.843–6.195	0.104
TG	1.719	0.586	8.602	5.578	1.769–17.595	0.003[*]
LDL-C	1.691	0.490	11.890	5.425	2.075–14.183	0.001[*]

B Regression Coefficient, *SE* Standard Error, *OR* odds ratio, *CI* confidence interval

[*] $p < 0.01$

Table 3 Differential Protein Data

Assay	logFC	t	p
MCP-3	0.78	4.02	< 0.001[**]
IFN-gamma	1.64	3.60	0.001[**]
CD8A	0.65	3.58	0.001[**]
IL10	0.58	3.25	0.003[**]
FGF-21	1.56	3.02	0.005[**]
CXCL11	0.65	2.83	0.008[**]
EN-RAGE	0.97	2.41	0.022[*]
CCL3	0.42	2.38	0.023[*]
FGF-5	-0.18	-2.34	0.025[*]
CXCL10	0.73	2.33	0.027[*]
TWEAK	-0.27	-2.23	0.032[*]
CXCL6	0.69	2.03	0.049[*]

logFC Logfold change. Logfold changes and *p* values are calculated with limma package in R

[*] $p < 0.05$, [**] $p < 0.01$

Fig. 1, while the box plot is displayed in Fig. 2. Supplementary Material 2 provide detailed results for all samples. In addition, the correlation results between differential proteins and MoCA scores are presented in Table 4. Except for EN-RAGE and FGF-5, all other differential proteins show significant correlations with cognitive function (all $p < 0.05$). The GO Enrichment ScatterPlot is depicted in Fig. 3, and the KEGG Enrichment ScatterPlot is shown in Fig. 4.

Discussion

This study explored the relationship between lipid abnormalities and cognition in stable schizophrenia. The main findings indicate that individuals living with schizophrenia in a stable phase exhibit widespread cognitive impairments. Compared to patients with mild cognitive impairment, those with severe impairment perform worse in the cognitive dimensions of Attention/Alertness and working memory. Lipid metabolic indicators show correlations with cognitive function, with higher levels of TG, TC, and LDL-C correlating with poorer overall cognitive performance. Further regression analysis suggests that TG and LDL-C may be risk factors exacerbating cognitive impairment in individuals living with schizophrenia in a stable phase. Proteomics analysis reveals that, compared to individuals living with schizophrenia with normal lipid metabolism, those with hyperlipidemia exhibit elevated levels of 10 inflammatory proteins and decreased levels of 2, which correlate with cognitive function. The differential proteins are primarily involved in pathways such as Cytokine-cytokine receptor interaction, Chemokine signaling, and IL-17 signaling.

A twenty-year cohort study has indicated that midlife lipid levels correlate more strongly with cognition than those in later life. This suggests that lipid levels may have a direct impact on cognition that surpasses the cognitive decline associated with aging. Lipids may thus function as independent risk factors for cognitive decline. Moreover, elevated levels of TC, TG, and LDL-C are significantly
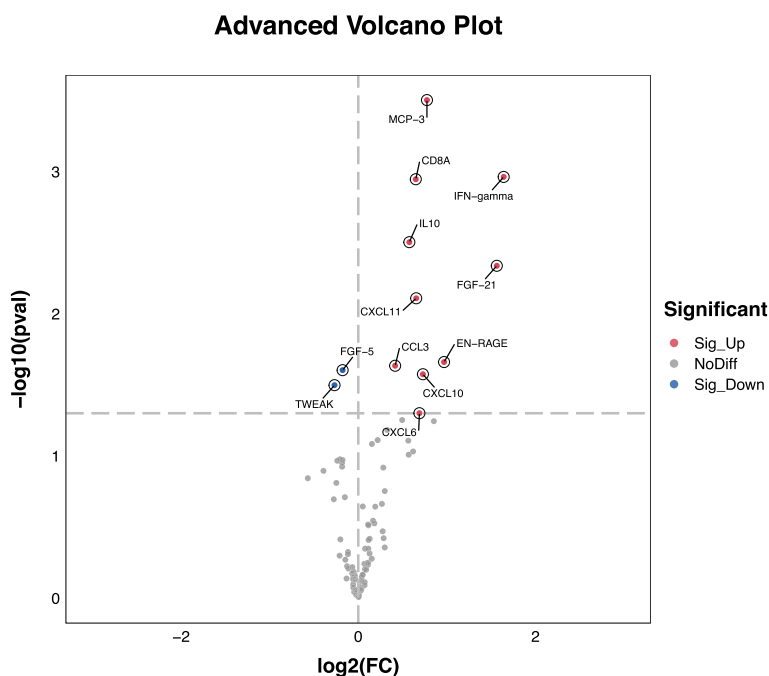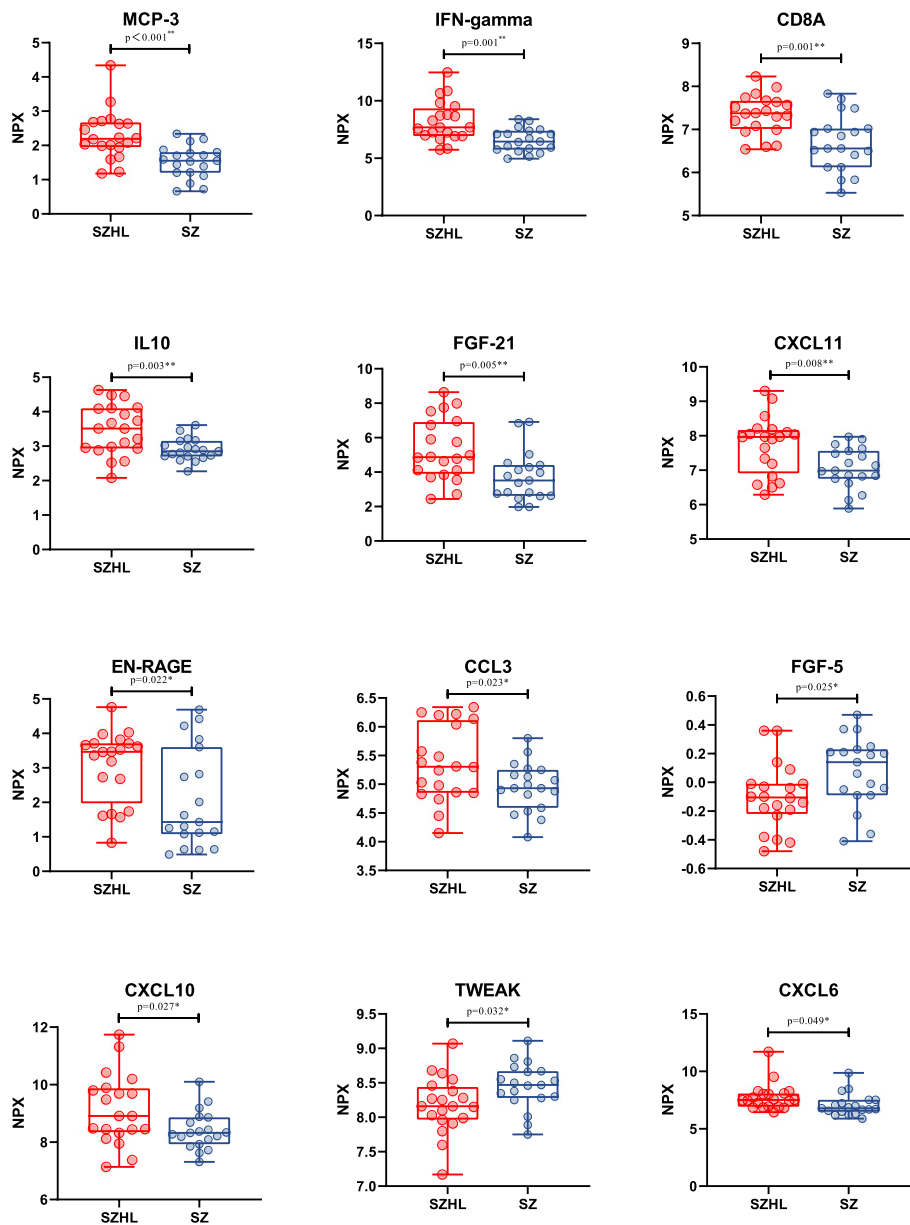

Fig. 1 Volcano plot

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Fig. 2 Box plot

NPX, Normalized Protein eXpression; SZHL, schizophrenia with hyperlipidemia; SZ, schizophrenia. *$p < 0.05$, **$p < 0.01$

Table 4 Differential Protein-MoCA Correlation

	MCP-3	IFN-gamma	CD8A	IL10	FGF-21	CXCL11	EN-RAGE	CCL3	FGF-5	CXCL10	TWEAK	CXCL6
r	-0.626	-0.705	-0.618	-0.531	-0.556	-0.626	-0.294	-0.475	0.22	-0.584	0.43	-0.388
P	< 0.001**	< 0.001**	< 0.001**	0.001**	< 0.001**	< 0.001**	0.069	0.002**	0.178	< 0.001**	0.006**	0.015*

r, correlation coefficient, assessed using the Spearman's rank correlation test

* $p < 0.05$, ** $p < 0.01$

associated with substantial declines in attention. Additionally, higher levels of total cholesterol and triglycerides are linked to significant declines in memory [36]. In our study, we similarly found significant differences in TG, TC, and LDL-C levels between two groups of patients with distinct cognitive functions. These differences in
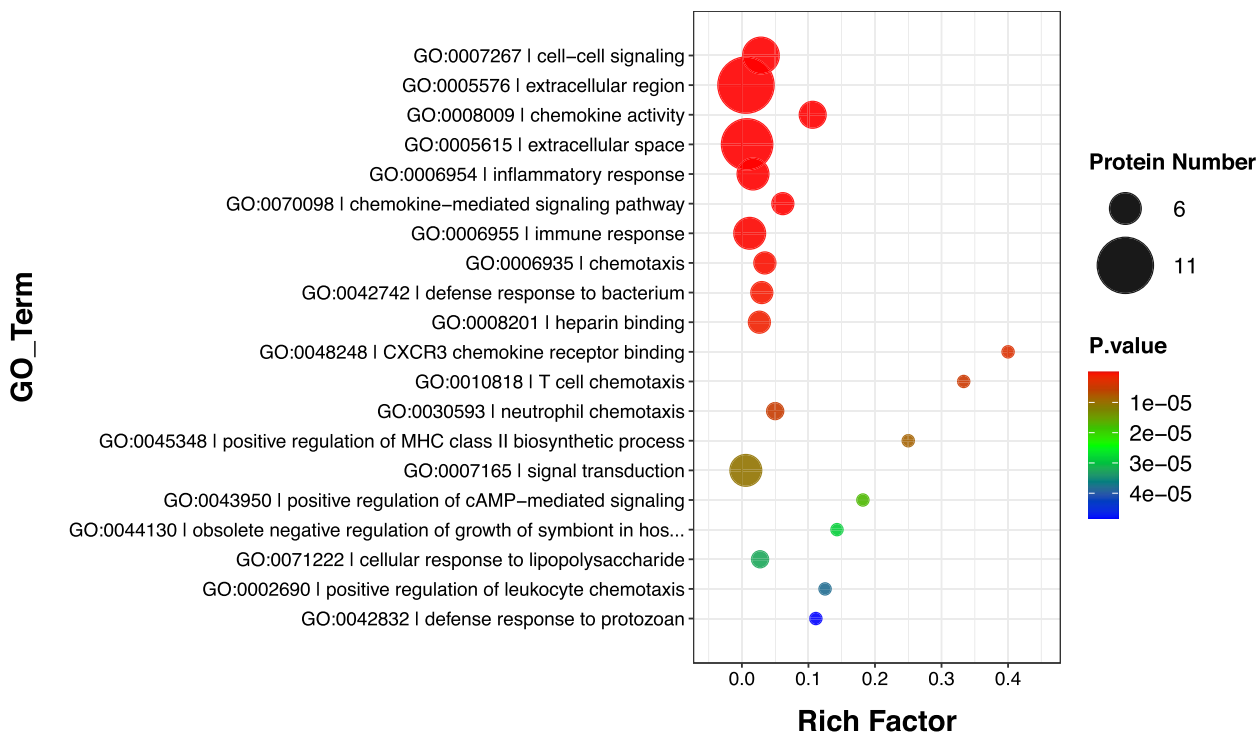
GO Enrichment ScatterPlot

Fig. 3 GO Enrichment ScatterPlot

cognitive function were primarily observed in memory and attention. Additionally, abnormalities in lipid levels, particularly elevated TG and LDL-C, may act as risk factors exacerbating cognitive impairment in individuals living with schizophrenia. In both groups in our study, we did not observe significant differences in HDL-C levels, which aligns with findings from similar research [37]. Interestingly, in elderly individuals aged 75 and older, HDL-C has been found to correlate with cognition [38]. This suggests that the protective role of HDL-C in brain function may be less apparent in middle-aged and older patients.

Lipids can directly affect neurodegeneration, and alterations in brain cholesterol homeostasis may be similar to the neuropathology observed in Alzheimer's disease. Specifically, elevated levels of LDL-C, TC, and TG may be closely associated with increased β-amyloid protein and hippocampal atrophy [39]. Lipid abnormalities can disrupt brain network integrity, exacerbate cognitive decline, and increase the risk of Alzheimer's disease [40]. However, conclusions from studies on the relationship between lipid levels and cognition have been inconsistent. For example, a study conducted in three cities found that hypertriglyceridemia and low LDL-C were associated with declines in MMSE scores [41]. Additionally, a

seven-year follow-up study found no correlation between lipid levels and cognition [42]. Possible explanations for these inconsistent results include selection bias due to differences in regions, ethnicities, and lifestyles, variations in the duration of follow-up periods [43], or a reverse causality between lipid levels and cognition [44, 45]. Additionally, a cross-sectional study in China reported that high TG levels may reduce the risk of cognitive impairment in urban men, while high LDL-C levels increase the risk in urban women. This suggests that there may also be gender and urban–rural differences in the relationship between lipid levels and cognition [46]. Although conclusions are inconsistent, the general trend acknowledges that high lipid levels can affect cognition. From a treatment perspective, lipid-lowering agents (LLAs) can slow cognitive decline in Alzheimer's disease and have neuroprotective effects, which may provide strong support for this association [47].

In a survey on the prevalence of dementia among individuals living with schizophrenia in the United States, it was found that 21% of the patients had severe cognitive impairment [48]. In a large cohort study involving 8,011,773 individuals, it was found that 27.9% of elderly people living with schizophrenia were diagnosed with dementia. In contrast, the dementia diagnosis rate was
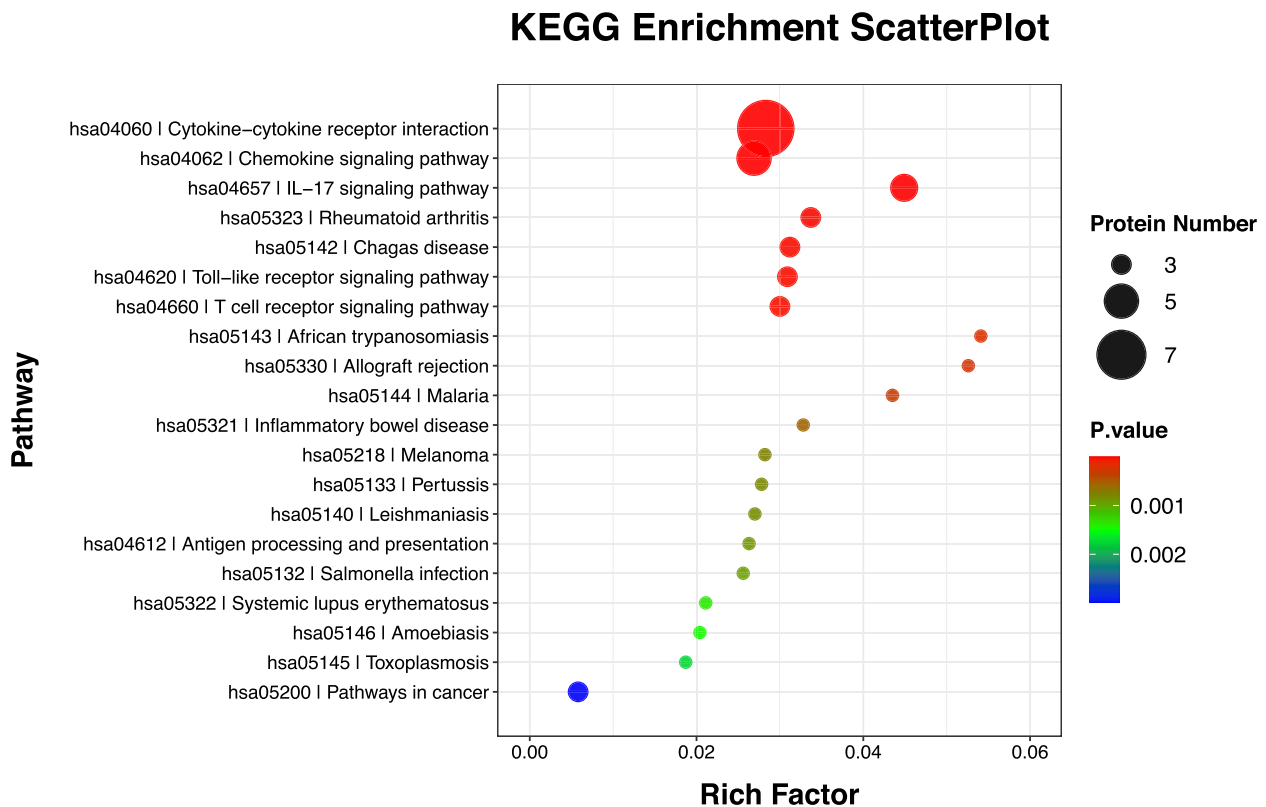
KEGG Enrichment ScatterPlot

Fig. 4 KEGG Enrichment ScatterPlot

only 1.3% among those without psychosis [49]. The high prevalence of dementia among people living with schizophrenia can be explained by a decline in cognitive reserve in this specific population, compounded by the cumulative effects of various metabolic risk factors. These factors may push them beyond clinical risk thresholds, thereby accelerating the progression of dementia [50]. In this study, the prevalence of severe cognitive impairment among people living with schizophrenia included was 34.58%, slightly higher than the aforementioned research. We speculate this might be due to the limitation of a smaller sample size. Furthermore, we did not track the baseline cognitive levels at the time of schizophrenia diagnosis. Additionally, the patients included in our study were all long-term hospitalized under closed management, leading to relatively limited lifestyles and recreational activities, potentially accelerating the progression of dementia.

Schizophrenia has often been referred to as a cognitive disorder, with patients frequently exhibiting multidimensional cognitive impairments compared to healthy controls [51]. In our preliminary findings, patients with severe cognitive impairment in the stable phase of schizophrenia showed poorer performance in working memory and attention/alertness, while no significant

differences were observed in other domains. Similar findings have been reported in a comparative study investigating schizophrenia with metabolic disturbances and metabolic syndrome, where patients with metabolic syndrome exhibited worse working memory performance, with minimal differences in other areas [52]. Additionally, a study on healthy individuals found that subtle changes in lipid profiles could lead to reduced hippocampal integrity, resulting in cognitive impairment [53]. These phenomena suggest that memory might be more sensitive to cognitive impairment induced by metabolic abnormalities, or that metabolic disturbances may specifically affect certain cognitive domains. However, the exact mechanisms remain to be confirmed. Working memory and attention are closely related to cognitive control, which functionally involves the frontal lobe [54]. Higher medial frontal gamma-aminobutyric acid (GABA) concentrations are associated with better working memory performance [55]. Current research indicates a close relationship between blood lipids and GABA [56, 57], suggesting that lipids may influence the function of specific brain regions by affecting related neurotransmitters.

Monocyte chemotactic protein (MCP)-3 is a chemokine involved in attracting monocytes and neutrophils. Elevated levels of MCP-3 can be observed in

patients with increased body fat [58]. CC chemokine receptor (CCR2) is the best-known receptor for MCP-3. MCP-3 stimulates CCR2 located on monocytes and macrophages, which is associated with the pathogenesis of atherosclerosis [59]. A decrease in MCP-3 levels may lead to a loss of its chemotactic effect on leukocytes, resulting in reduced recruitment of inflammatory cells. Conversely, an increase in MCP-3 levels may lead to increased inflammation [60]. Although direct clinical associations between MCP-3 and cognition have not been established, studies in rats with traumatic brain injury have shown that MCP-3 is upregulated within 24 h post-injury. Other inflammatory factors occur later and remain relatively stable, suggesting that MCP-3 may play a crucial role in rapid inflammatory responses and induction of long-term brain damage and neuronal dysfunction. This imbalance in excitatory and inhibitory neurons in the hippocampus could ultimately affect cognitive function [61]. In addition, early systemic lupus erythematosus often presents with neuropsychiatric symptoms. In mouse models, cognitive dysfunction has been observed alongside elevated plasma MCP-3 levels [62]. Therefore, based on this limited evidence, it can be inferred that the elevation of chemotactic factors may play a regulatory role in subtle changes in brain function.

It is generally believed that interferon-γ (IFN-γ) can promote inflammation in microglial cells. Recent studies have shown that IFN-γ plays a unique role in the activation of microglial cells, and its role in driving neuroinflammation in cognitive impairment is increasingly being recognized [63]. IFN-γ can exacerbate synaptic damage and even promote the release of nitric oxide, which is sufficient to impair synaptic signaling and cognitive function [64]. In mice, injections of IFN-γ inhibit the proliferation of neural stem cells and progenitor cells, and induce apoptosis of immature neurons, ultimately leading to impaired neurogenesis in the adult hippocampus [65]. In mice, IFN-γ has been shown to cross the blood–brain barrier intact and enter the central nervous system parenchyma via transport systems. This phenomenon is particularly pronounced when the blood–brain barrier is compromised under pathological conditions. IFN-γ can enter the central nervous system parenchyma extensively and uncontrollably during conditions such as bacterial and viral infections, Alzheimer's disease, and systemic inflammation [66]. Specifically, in cognitively impaired APP/PS1 mice, anti-IFN-γ antibody therapy has been shown to improve these cognitive-related neuroimmunological changes [67]. This suggests that increased levels of IFN-γ can contribute to cognitive impairment.

CD8 + T cells are a subset of T cells characterized by the surface expression of the CD8α and CD8β heterodimer. CD8 + T cells are the predominant T cell type in cognitive-related brain structures [68, 69]. The development of cognitive impairment is associated with the infiltration of CD8 + T cells into cognitive-related brain structures [70, 71]. In cognitively impaired elderly individuals, overexpression of the CD8β chain has been found [72]. CD8 + T cells may also contribute to neuronal damage and cognitive impairment through the release of IFN-γ [73]. In peripheral blood diagnosed with mild cognitive impairment, more CD8 + TEMRA cells producing IFN-γ were found [70]. These cytokines increase the permeability of the blood–brain barrier, promoting the migration of T cells into the central nervous system parenchyma, which may gradually catalyze cognitive impairment.

FGF-21 is an important member of the fibroblast growth factor family [74]. Recent studies indicate that increased levels of FGF-21 in non-elderly metabolic syndrome patients are associated with cognitive decline, suggesting that FGF-21 may serve as a risk factor for cognitive decline [75]. In our study, we observed similar findings where individuals living with schizophrenia and hyperlipidemia had higher levels of FGF-21, which were negatively correlated with cognitive function. However, contrasting findings suggest that FGF-21 may act as a neuroprotective factor with potential to alleviate neurodegenerative diseases. For instance, FGF-21 treatment has been shown to effectively increase synaptic plasticity in the hippocampus, reduce neuronal apoptosis, and improve cognitive impairment in insulin-resistant rats [76]. Intracerebroventricular injection of FGF-21 can reshape brain glucose and neurotransmitter metabolism, exerting neuroprotective effects against cognitive impairment [77]. Based on this, we should expect to find decreased levels of FGF-21 in the hyperlipidemia group rather than increased levels. One possible explanation is that elevated levels of FGF-21 may indicate more severe cognitive impairment under feedback regulation. Specific mechanisms require further research.

Similar to FGF-21, IL-10 is an anti-inflammatory cytokine. Most studies have found that an increase in IL-10 is often associated with better cognitive function [78, 79]. However, contrasting this, scientists have discovered unexpected negative effects of IL-10 on cognition and Aβ protein homeostasis in APP mouse models expressing IL-10 [80]. Coincidentally, in an aging study conducted in Berlin, higher levels of IL-10 were significantly associated with poorer executive function in elderly individuals [81]. In our study, we also found that higher levels of IL-10 may be associated with poorer cognition in individuals living with stable-phase schizophrenia. Future research may need to explore blocking IL-10 to further elucidate its effects on cognition in specific disease models.

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Chemokines and their receptors play roles in the central nervous system, being present on both glial cells and neurons, and participating in intercellular communication [82]. The important physiological and pathological roles of CXCL10 and CXCL11 in the central nervous system are gradually being elucidated [83]. For example, in dementia patients, CXCL10 levels are positively correlated with β-amyloid protein [84]. Cerebrospinal fluid concentrations of CXCL10 in subjects with mild cognitive impairment are significantly higher compared to controls [85]. In a comparative study between mild cognitive impairment and depression, levels of CXCL6 and CXCL11 are higher in mild cognitive impairment patients than in elderly depression patients [86]. Furthermore, CCL3 has been found to be highly expressed in adult Alzheimer's disease patients and elevated in epileptic mouse models [87, 88]. These findings strengthen the potential role of chemokines as mediators in communication with neurological disorders.

EN-RAGE is also commonly known as S100-A12. The S100 protein family has previously been shown to be associated with cognition [89]. In a large prospective cohort study using Olink inflammation proteomics, EN-RAGE was found to be associated with overall dementia and Alzheimer's disease incidence [90]. In this study, although EN-RAGE showed differential expression between groups, no statistical correlation with cognition was found. This could potentially be attributed to the influence of a small sample size, indicating the need for further research in future studies.

Among the downregulated proteins, TWEAK is notable. TWEAK is a TNF family ligand that exerts pleiotropic effects through its receptor Fn14, including stimulating the production of inflammatory cytokines and inducing neuronal death [91]. In a large cohort study on peripheral inflammation biomarkers and cognition, higher levels of TWEAK were found to be associated with better memory scores and lower risk of dementia [92]. This suggests a potentially protective role of TWEAK on cognition, which could potentially explain the findings in the user's study where TWEAK levels were lower in people living with schizophrenia with severe cognitive impairment compared to those with mild cognitive impairment. Meanwhile, another downregulated protein, FGF-5, has not yet been found to have a close association with cognition and requires further investigation.

The strength of this study lies in its first-time exploration of the relationship between cognition and lipid metabolism in patients with stable-phase schizophrenia. Using omics approaches, the study preliminarily detected plasma differential proteins in two small sample groups of patients with different lipid metabolism

levels and examined their associations with cognition. We included patients managed in a closed ward, who had similar dietary, exercise, and daily living habits, with strict restrictions on the use of tobacco and alcohol. The limitations of this study include the following aspects: (1) As a small cross-sectional study, it can partially reflect the associations between different variables, but it cannot establish causal relationships. Future research should involve long-term follow-up and longitudinal studies within the same individuals to further elucidate the complex relationship between lipid metabolism and cognition in people living with schizophrenia. (2) We used the MoCA to define different levels of cognitive impairment, with cutoffs based on currently limited research. Although MoCA is a reliable tool for detecting cognitive impairment, it is not specifically designed for schizophrenia populations and may not be fully sensitive to the specific cognitive deficits observed in schizophrenia. As a result, the generalizability of the current findings may be limited. Future studies should consider using specialized cognitive assessment tools designed for psychiatric disorders in larger-scale studies. (3) Due to time constraints, we only included patients with cognitive impairment and did not include non-cognitively impaired patients as controls. Future research should more comprehensively include patients with varying levels of cognitive function, as well as healthy individuals, in larger-scale cross-sectional comparisons to address the limitations of the current small sample size. (4) We only measured and compared routine blood lipid levels, including TG, TC, LDL-C, and HDL-C. Future studies should conduct more comprehensive examinations of other lipid metabolism indicators, including different lipoprotein levels, and perform detailed subgroup analyses to explore the associations between various types of lipid metabolism abnormalities and cognition. (5) Different types and combinations of antipsychotic medications can affect both metabolism and cognition. To control for confounding effects, we included only participants who were using a single antipsychotic drug, but did not take into account the specific types and combinations of antipsychotic medications used by the participants. In future research, we plan to include the type and combination of antipsychotic medications as variables for more in-depth analysis. (6) We did not systematically assess other potential clinical comorbidities beyond the exclusion criteria. Future research should include comprehensive evaluations of comorbidities to better understand their impact on the relationship between metabolic abnormalities and cognitive impairment in schizophrenia.

Conclusion

Lipid levels in patients with stable-phase schizophrenia are associated with cognitive function, specifically showing that higher levels of TG, TC, and LDL-C are linked to poorer overall cognitive function. TG and LDL-C may be risk factors for exacerbating cognitive impairment in these patients. From an inflammatory perspective, preliminary proteomics in a small sample suggest that lipid metabolism abnormalities may influence cognition through the activation or down-regulation of related proteins, potentially involving pathways such as cytokine-cytokine receptor interaction, chemokine signaling pathway, and IL-17 signaling pathway. Nonetheless, our study suggests that improving lipid management may benefit cognitive rehabilitation in people living with schizophrenia. The complex relationship between lipid levels and cognition, as well as the precise mechanisms involved, require further research to be confirmed.

Abbreviations

MCI	Mild cognitive impairment
SCI	Severe cognitive impairment
MoCA	Montreal Cognitive Assessment
PANSS	Positive and Negative Syndrome Scale
BMI	Body mass index
FBG	Fasting blood glucose
TG	Triglyceride
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
MCCB	MATRICS Consensus Cognitive Battery

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Clinical trial number

Not applicable.

Statement

This paper has not been previously published. The authors are responsible for all content in the article and have the authority to prepare the manuscript and decide to submit it for publication. All listed authors have agreed to submit the manuscript to the journal.

Authors' contributions

Y.Z. made the drafting. X.C. and Y.Z. designed the study. D.W. and X.C. conducted the investigation and collected the data. T.W., Y.X., H.L., and T.W. managed the data. Y.H., J.L., and J.L. reviewed and revised the draft. All authors approved the final submitted version.

Availability of data and materials

The key data is provided within the manuscript and supplementary information files. Detailed data supporting this study can be obtained by directly contacting the authors. However, the availability of this data is restricted as it was obtained and used under the permission of Heilongjiang Academy of Chinese Medicine and Heilongjiang Provincial Hospital of Neurology and Psychiatry, and thus is not publicly available. Access can be granted upon reasonable request and with the approval of Heilongjiang Academy of Chinese Medicine.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Heilongjiang Academy of Chinese Medicine (Approval Number: 2023–050-01). Informed consent was obtained from all participants and their families.

Competing interests

The authors declare no competing interests.

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