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Metabolic profiling identifies TC and LDL as potential serum biomarkers for depressive symptoms in schizophrenia

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ABSTRACT

This study aimed to explore the relationship between serum levels of cardiometabolic biomarkers and depressive symptoms in schizophrenia patients treated with atypical antipsychotics. A total of 210 patients with schizophrenia and 70 healthy controls were recruited in our present study. All patients were rated on the 17-item Hamilton Depression Rating Scale (HAMD-17) to measure depressive symptoms and the Positive and Negative Syndrome Scale (PANSS) for psychopathology. Serum cardiometabolic biomarkers (HDL, LDL, TC, TG, GLU) in all participants were measured. Our results showed that schizophrenia patients had higher levels of serum GLU, TG, TC, LDL and BMI, but lower levels of HDL than controls (all $P < 0.05$). Compared to patients without depressive symptoms, those with depressive symptoms showed higher PANSS total, general psychopathology, positive and negative symptom scores (all $p < 0.05$), as well as higher serum levels of LDL ($p < 0.001$) and TC ($p = 0.011$). In addition, our correlation analysis showed that serum LDL ($P < 0.001$) and TC ($P = 0.045$) levels were positively associated with HAMD total scores in schizophrenia patients after age, sex and education levels were controlled. Our results suggest the appearance of depression in schizophrenia patients may be associated with high levels of metabolic parameters, especially TC and LDL.

1. Introduction

Schizophrenia is a severe and chronic psychiatric disorder that affects around 0.75% of the Chinese population (Huang et al., 2019). Antipsychotic drugs have been considered as the primary treatment which mainly includes typical and atypical antipsychotics. Atypical antipsychotics have been more frequently prescribed for schizophrenia patients currently due to their better therapeutic effects and fewer adverse events compared to typical antipsychotics (Zhang et al., 2017). However, atypical antipsychotics may have an even greater potential for inducing metabolic disturbances, including weight gain, obesity, diabetes, dyslipidemia, and the metabolic syndrome (MetS), which has become of considerable concern due to the high risk for adverse cardiovascular events (Penninx and Lange, 2018; Xu et al., 2018). Early evidence indicates patients would have a rapid weight increase in the initial period after starting antipsychotics (Dayabandara et al., 2017), and developed lipid and glucose abnormalities as soon as 2–3 months after treatment initiation (Pramyothin and Khaodhiar, 2010). In addition, these patients continue to gain weight over time (Dayabandara et al., 2017; Rummel-Kluge et al., 2010). Epidemiological studies have shown that cardiovascular disease and suicide are the main contributing factors to the increased mortality and shorter lifespan of patients with schizophrenia (Fang et al., 2018; Piotrowski et al., 2017). Thus, adverse metabolic side effects induced by atypical antipsychotics and suicide risk in schizophrenia patients are urgent clinical problems.

It has been well-established that depression is the most dangerous factor for suicide (Babu et al., 2008; Liu et al., 2017). Such symptoms are commonly seen in all stages of schizophrenia and increased further over time while underdiagnosed (Gozdzik-Zelazny et al., 2011). It has been reported that the prevalence rates of depression in schizophrenia range from 30% to 70% (Peitl et al., 2017). The depressive symptoms in schizophrenia patients are often associated with overall poorer functional outcomes, lower quality of life, greater risk of relapse and hospitalization (Tandon et al., 2009). Despite substantial information concerning the demographic and clinical risk factors for suicide and depression in patients with schizophrenia are well explored (Chang et al., 2015; Fang et al., 2018), the etiology and pathophysiology of depression in schizophrenia patients are not completely elucidated.

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Nutrition and physical activity seem to play important roles in depression, which might be mediated by glucose and lipid pathways. Accumulating evidences showing that physical training could alleviate depressive symptoms and even decrease the risk of future depression through influencing lipid levels (Harvey et al., 2018), and intake of omega-3 polyunsaturated fatty acid is also believed to exert a positive effect on lipid metabolism (Grosso et al., 2016). A recent study indicated that patients with a major depressive episode show increased levels of LDL cholesterol, and the severity of depressive symptoms correlates positively with LDL cholesterol levels (Wagner et al., 2019a). In addition, adjuvant atorvastatin (Haghighi et al., 2014) or low-dose omega-3 fatty acids (Tajalizadekhoob et al., 2011) could significantly improve depressive symptoms in patients with major depressive disorder (MDD). Taken together, glucose and lipid related pathways may play a critical role for the development of depressive symptoms, and the increased depressive symptoms in schizophrenia patients over the disease course may be related to the metabolic adverse effects of atypical antipsychotics. Unfortunately, no study to date has been conducted to explore this relationship in schizophrenia patients.

In the present study, we aimed to investigate possible differences between schizophrenia patients with and without significant depression based on cardiometabolic biomarkers (HDL, LDL, TC, TG, GLU), and further to closely examined whether altered levels of cardiometabolic biomarkers are associated with the severity of depressive symptoms in schizophrenia patients treated with atypical antipsychotic drugs. We hypothesized that altered glucose and lipid levels may be of value in reflecting the severity of depressive symptoms in schizophrenia patients.

2. Methods

2.1. Subjects

The patients were recruited between 10/2017 and 12/2018 from inpatients of the Shanghai Mental Health Center. Patients who fulfilled the following inclusion criteria were invited to participate in the study: (1) diagnosis of schizophrenia according to DSM- IV or ICD-10. All patients with a chart diagnosis of DSM- IV or ICD-10 schizophrenia were interviewed by at least two trained research psychiatrists to confirm the clinical diagnosis; (2) age between 18 and 50 years; (3) the patients were receiving atypical antipsychotic drugs only, with no typical antipsychotics, antidepressant or mood stabilizer was used within 1 month prior to study entry. Patients were excluded if they: (1) had head trauma with residual effects, neurological disorders; (2) pregnant or breastfeeding; (3) had comorbid substance abuse or dependence; (4) the patients received no drug(s), including statins or antidiabetic medication, with well-known effects on the study parameters. We also recruited 70 healthy individuals as controls. The healthy controls who had no history of any Axis I disorder, no first-degree relative with any Axis I disorder, and no lifetime substance abuse/dependence disorder were recruited from the community. All subjects were screened by a specialized psychiatrist using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition.

This study was performed in strict accordance with the Declaration of Helsinki and other relevant national and international regulations. The study protocol was approved by the Institutional Review Boards of the Shanghai Mental Health Center. Written consent to participate in the study was obtained from each participant prior to the performance of any procedures related to this study.

2.2. Clinical evaluation

The positive and negative syndrome scale (PANSS) was used to measure the severity of the psychotic symptoms exhibited by schizophrenia patients. Also, the depressive symptoms in schizophrenia patients were evaluated with the Hamilton Depression Rating Scale (HAMD). The total score is based on the first 17 items. Eight items are scored on a 5-point scale, ranging from 0 (not present) to 4 (severe). Nine items are scored from 0 (none) to 2 (symptom-specific severity descriptor). Patients were classified into two groups using HAMD rating cut-offs: ≤ 7 = not depressed (NDP) and ≥ 8 = depressed (DP) (Dai et al., 2018; Park et al., 2017).

All evaluations were conducted by experienced psychiatrists who were well trained for this project, and repeated assessments revealed that a correlation coefficient more than 0.8 was maintained.

2.3. Sample collection and measurement of cardiometabolic biomarkers

Following an overnight fast, blood samples from the patients and healthy controls were drawn in ice-cooled ethylenediaminetetraacetic acid tubes between 6:00 and 9:00 a.m. Serum was separated by centrifugation at 5 °C and stored at − 20 °C. Serum fasting glucose (GLU), triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL) and high density lipoprotein (HDL) levels were measured using an automatic Biochemical Analyzer (HITACHI 7170A, Hitachi, Ltd., Tokyo, Japan) (Zhang et al., 2017, 2014).

2.4. Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 23.0 was used for data analysis. Descriptive statistics were tabulated for the schizophrenia patients and healthy controls. Statistical significances were set at $P < 0.05$ and were examined using the Student's *t*-test or one-way ANOVA for continuous variables and chi-squared test for categorical variables between groups. And the analysis of covariance (ANCOVA) was performed to control for the effects of confounding variables. Pearson correlation coefficients were calculated to examine the relationships between depressive symptoms and other parameters in schizophrenia patients. In addition, partial correlation analysis was further used to control for the potential confounders. Continuous data were presented as mean ± SD and categorical data as number with factor/number without factor. The G*Power 3.1.9.2 program (https://www.softpedia.com/get/Science-CAD/ G-Power.shtml) was used to run a power calculation and determine the effect size.

3. Results

A total of 210 schizophrenia patients and 70 healthy controls were included in the final analysis. The demographic characteristics and serum cardiometabolic biomarkers for patients and control groups are summarized in Table 1. The patients and control groups were matched by age, sex and education levels (all $P > 0.05$). Our results demonstrated that serum GLU ($t = 4.077$, $P < 0.001$), TG ($t = 6.802$, $P < 0.001$), TC ($t = 11.313$, $P < 0.001$), LDL ($t = 2.517$, $P = 0.012$) levels and body mass index (BMI, $t = 11.722$, $P < 0.001$) were significant higher in patient group compared to controls, However, schizophrenia patients had a significant lower serum HDL levels ($t = 2.738$, $P = 0.007$) than controls. The statistical power of our study to detect

Table 1
Comparison between schizophrenia patients and healthy controls.

	Patients ($N = 210$)	Controls ($N = 70$)	t/X^2	P
Age (year)	35.95 ± 9.42	37.19 ± 6.37	1.232	0.219
Sex (male/female)	102/108	34/36	0.000	1.000
Education (year)	12.50 ± 3.04	12.54 ± 2.81	0.115	0.908
BMI (kg/m^2)	23.98 ± 3.80	20.59 ± 1.01	11.722	< 0.001
GLU (mmol/l)	5.42 ± 2.52	4.66 ± 0.55	4.077	< 0.001
HDL (mmol/l)	1.17 ± 0.31	1.25 ± 0.17	2.738	0.007
LDL (mmol/l)	2.65 ± 1.04	2.44 ± 0.39	2.517	0.012
TC (mmol/l)	4.66 ± 1.04	3.50 ± 0.61	11.313	< 0.001
TG (mmol/l)	1.53 ± 1.04	0.99 ± 0.27	6.802	< 0.001

Table 2
Differences between DP and NDP groups.

	DP groups (N = 113)	NDP groups (n = 97)	t/X^2	P
Age (year)	36.23 ± 9.55	35.63 ± 9.30	0.460	0.646
Sex (male/female)	58/55	44/53	0.744	0.388
Education (year)	12.06 ± 2.80	13.00 ± 3.25	2.222	0.027
Age of onset (year)	23.32 ± 6.58	24.18 ± 6.61	0.948	0.344
Course of disease (month)	157.83 ± 102.31	130.51 ± 87.32	2.088	0.038
Family history (yes/no)	87/26	67/30	1.674	0.196
BMI (kg/m^2)	24.08 ± 3.84	23.86 ± 3.77	0.423	0.673
PANSS	66.35 ± 10.93	53.53 ± 10.98	8.461	< 0.001
Positive symptom	14.04 ± 4.47	12.05 ± 4.52	3.191	0.002
Negative symptom	18.92 ± 5.93	14.27 ± 5.31	5.945	<0.001
General psychopathology	33.20 ± 5.82	27.29 ± 5.38	7.603	<0.001
GLU (mmol/l)	5.60 ± 3.12	5.21 ± 1.54	1.137	0.257
HDL (mmol/l)	1.14 ± 0.28	1.20 ± 0.34	1.414	0.159
LDL (mmol/l)	3.05 ± 0.96	2.19 ± 0.93	6.638	<0.001
TC (mmol/l)	4.83 ± 1.20	4.47 ± 0.78	2.556	0.011
TG (mmol/l)	1.64 ± 1.17	1.40 ± 0.85	1.655	0.099

the difference of GLU, HDL, LDL, TC, TG levels between patients and healthy controls was 78.55%, 46.16%, 30.82%, 100.00%, 96.63% respectively.

In the patients' group, 113 (53.8%) of 210 patients met the criteria for comorbid depressive symptoms and 97 (46.2%) did not. As presented in Table 2, there were no significant differences in terms of age, sex, education levels, BMI, age of onset and family history (All $P > 0.05$) between DP and NDP groups. There was also no significant difference in drug use between patients' groups ($X^2 = 7.070$, $P = 0.529$) (See in table S1). The PANSS total scores, negative symptom subscores, general psychopathology subscores (All $P < 0.001$) and positive symptom subscores ($P = 0.002$) were all significantly higher in DP groups than NDP groups. Our results showed that DP patients had a longer total disease course compared to NDP patients ($t = 2.088$, $P = 0.038$). In addition, serum levels of LDL ($t = 6.638$, $p < 0.001$) and TC ($t = 2.556$, $p = 0.011$) were higher in DP groups than NDP groups, Those differences remained significant after adjusting for the characteristics including age, sex and education levels (LDL: $F = 44.583$, $p < 0.001$; TC: $F = 6.210$, $p = 0.013$) (See in Fig. 1). Since two participants with extremely high LDL levels in DP groups, one participant with extremely high TC levels in DP and NDP groups, we considered those as potential outliers. We then removed those outliers and conducted sensitivity analysis, our results still showed that DP groups had higher serum LDL ($F = 41.123$, $p < 0.001$) and TC ($F = 6.612$, $p = 0.011$) levels compared to NDP groups after age, sex and education levels were controlled.

Our correlation analysis showed significant correlations between HAMD total score and the following parameters, the PANSS total score ($r = 0.642$, df = 210, $p < 0.001$), PANSS general psychopathology ($r = 0.609$, df = 210, $p < 0.001$), PANSS positive symptom ($r = 0.336$, df = 210, $p < 0.001$), PANSS negative symptom ($r = 0.432$, df = 210, $p < 0.001$), serum LDL ($r = 0.307$, df = 210, $p < 0.001$)and TC levels ($r = 0.151$, df = 210, $p = 0.028$) (Table 3). In addition, there was also a trend in a significant correlation between HAMD total score and total disease course ($r = 0.134$, $P = 0.052$). To further determine the relationship between metabolic parameters and depressive symptoms was independent with age, sex and education levels, partial correlation analysis was performed, and our results showed serum LDL ($r = 0.297$, $P < 0.001$) and TC ($r = 0.139$, $P = 0.045$) levels was positively correlated with HAMD total score (See in Fig. 2). After we excluded the potential outliers, those positive correlation still remained (LDL: $r = 0.298$, $P < 0.001$; TC: $r = 0.142$, $P = 0.042$).

Table 3
Correlations between demographic, clinical variables, glycolipid parameters and HAMD total scores in schizophrenia patients.

Variable	HAMD total scores r	P
Age	0.087	0.211
BMI	−0.009	0.901
Education	−0.087	0.211
Age of onset	−0.033	0.633
Course of disease	0.134	0.052
PANSS	0.642	<0.001
Positive symptoms	0.336	<0.001
Negative symptoms	0.432	<0.001
General psychopathology	0.609	<0.001
GLU	0.118	0.088
HDL	−0.054	0.435
LDL	0.307	<0.001
TC	0.151	0.028
TG	0.040	0.567

4. Discussion

In the present study, we found that 53.8% schizophrenia patients treated with atypical antipsychotics exhibited clinically significant depressive symptoms. In line with our presents study, previous studies used HAMD, MADRS both showed a similar prevalence of depressive

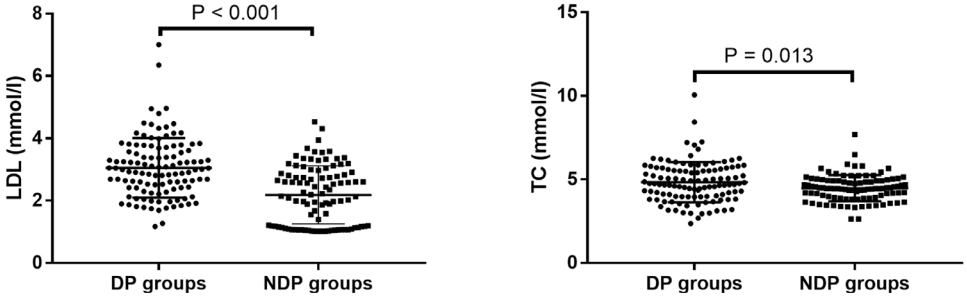

Fig. 1. Serum levels of LDL and TC in DP and NDP groups.
P value was calculated by adjusting for the characteristics including age, sex and education levels.
Each bar represents the mean level of LDL or TC. Error bars represent the standard deviation (SD).
Abbreviations: LDL, low density lipoprotein; TC, total cholesterol; DP, depressed patients; NDP, non-depressed patients.

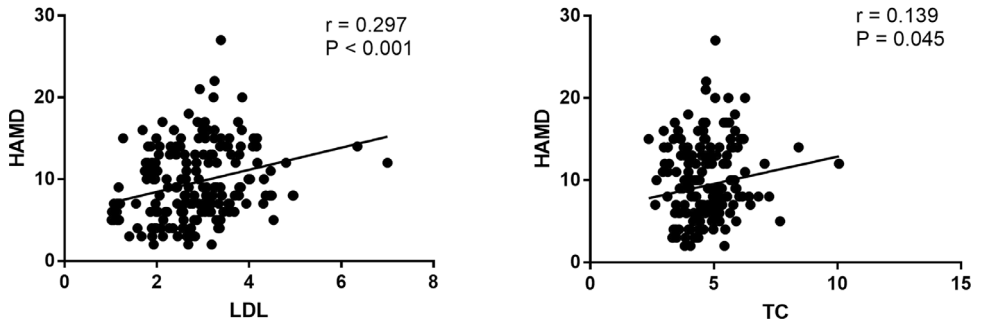

Fig. 2. Correlation between serum levels of LDL or TC and HAMD total scores in schizophrenia patients. .
Abbreviations: LDL, low density lipoprotein; TC, total cholesterol; HAMD, the Hamilton Depression Rating Scale.

symptoms in chronic schizophrenia patients (54.6%, 54.1 %, respectively) (Dai et al., 2018; Hou et al., 2016), but higher than the rate reported in first-episode schizophrenia patients evaluated by HAMD and Calgary Depression Rating Scale (CDSS) (Riedel et al., 2012; Chang et al., 2015; Herniman et al., 2017). Interestingly, existing literature reported different incidence rates in drug-treated schizophrenia, with some higher than ours (Peitl et al., 2016) and others slightly lower than the present study (Fang et al., 2019). These results suggest that the rate of depressive symptoms occurred in schizophrenia patients may be varied with the course of the disease and influenced by assessment tools. Early evidence also demonstrated that the rate of comorbid depression in schizophrenia increased further over time (Gozdzik-Zelazny et al., 2011). Interestingly, our results showed a longer total disease course in DP patients compared to NDP groups. There was also a robust trend toward significance in correlation between total disease course and the severity of depressive symptoms in schizophrenia patients. Add the fact that the appearance of depressive symptoms in schizophrenia lead to poor outcomes (Abramowitz et al., 2014; Chiappelli et al., 2014; Hou et al., 2016), the depressive symptoms in patients with schizophrenia should be paid enough attention to by clinicians. Thus, the DSM-5 includes depression as a dimension of psychosis, inviting a re-examination of its role in schizophrenia (Chang et al., 2015). However, most of these patients were not identified and treated with antidepressants in clinical practice (Becker et al., 1985; Rajkumar, 2015). What's more, the underlying mechanisms for the appearance of depressive symptoms in schizophrenia are still unclear.

Our results showed that patients treated with atypical antipsychotics had higher levels of glucose and lipid related parameters compared to controls. According to the data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), the prevalence of metabolic syndrome (MetS) in schizophrenia is 40.9% (Zhang et al., 2017), and most observations suggest higher prevalence of MetS with the atypical antipsychotics (Hirsch et al., 2017; Newcomer, 2004; Sapra et al., 2018). Our previous research also confirmed a high incidence of MetS in schizophrenia patients treated with olanzapine and clozapine (44% and 43.2%, respectively) (Zhang et al., 2017, 2014). MetS is described as clusters of obesity-related risk factors for chronic metabolic and cardiovascular diseases including abdominal obesity, hypertension, hyperglycaemia, insulin resistance, increased triglycerides and decreased high-density lipoprotein cholesterol based on based on the National Cholesterol Education Program—Adult Treatment Panel III (NCEP-ATP III) criteria (Lone et al., 2017). These metabolic adverse effects are often associated with non-compliance and medical problems, and further increase the risk of relapse (Godin et al., 2018).

To the best of our knowledge, this is the first study to examine the relationship between depressive symptoms and metabolic parameters in Chinese schizophrenia patients. The results of our study showed that DP patients had significantly higher levels of LDL and TC compared to NDP patients, and there was a positive correlation between depressive symptoms and serum LDL or TC levels in schizophrenia patients even after adjusting for the characteristics including age, sex and education levels. Substantial evidence supports the association between metabolic abnormalities and depressive symptoms in patients with major depressive disorder. For example, Wagner et al. revealed that higher HAMD scores were positively correlated with serum TC, TG and LDL levels in patients with a current major depressive episode (Wagner et al., 2019b). In addition, evidence indicated that adjuvant atorvastatin improved blood lipid levels and reduced depressive symptoms in major depressive patients (Haghighi et al., 2014). Furthermore, animal experiment found that cerebral lipid metabolism is involved in depression-like behavior in mouse (Gulbins et al., 2013). However, very few studies to date have examined the relationship between depressive symptoms and glucose and lipid metabolism in schizophrenia. To our knowledge, Suttajit and Pilakanta conducted the first study and confirmed the association between depressive symptoms and metabolic syndrome in Thailand schizophrenia patients (Suttajit and Pilakanta, 2013). Suicide as an important symptom item of depression, the early study also found higher lipid profile, especially serum TC and LDL levels were significantly associated with suicidal ideation in first-episode schizophrenia females (Misiak et al., 2015). Taken together, MetS caused by atypical antipsychotics may be associated with the increased depressive symptoms over the course of schizophrenia patients.

As we know, other variables like diet, smoking, exercise levels, sleep may have some effects on metabolic parameters and depressive symptoms to some extent. It should be noted that all schizophrenia patients in our present study were hospitalized. They have the same diet structure, the regular schedule of activities, went to bed and woke up at the same time each day and have banded from smoking (Shanghai has banned smoking in all public places since March 2017), So there were no significant differences in current diet, smoking, exercise levels, sleep time between schizophrenia patients. However, we do not know what happened for those before they were recruited. Since those factors are very difficult to measure accurately and to be controlled, further study can only minimize the impact of these factors when exploring the relationship between cardiometabolic parameters and depressive symptoms.

The underlying mechanisms for the relationship between increased serum levels of cardiometabolic parameters and depressive symptoms in schizophrenia could be described as follows. First, ample evidence indicated that the activation of the immune inflammatory system is involved in the pathogenesis of depression (Mao et al., 2018; Ren et al., 2017). Interestingly, our previous work showed that patients with both schizophrenia and MetS present an increased expression and production of inflammatory factors (Zhang et al., 2017), and we also found that omega-3 fatty acids have beneficial effects on lipid metabolism that parallel decreased inflammation levels in those patients (Xu et al., 2018). Thus, the activated inflammatory state links cardiometabolism to depressive symptoms in schizophrenia treated with atypical antipsychotics. Second, the aberrant of HPA axis and its related cortisol has been reported in schizophrenia patient (Aas et al., 2019). As we know,

the over-stimulation of the HPA axis has also been reported in relation to both depression (Keller et al., 2017) and metabolic syndrome (Diz-Chaves et al., 2016).

In our present study, we also found that depressive symptoms were significantly associated with other symptom dimensions, particularly negative and general psychopathology symptoms, which were more severe in DP patients than NDP patients. Previous studies have explored the relationship between depression and negative symptoms in patients with schizophrenia, and most of these studies have shown that depressive symptoms are positively correlated with negative symptoms (Dai et al., 2018; Majadas et al., 2012). The presence of depressive symptoms in patients with schizophrenia has been related with overall worse outcomes (Narvaez et al., 2008). The reasonable explanation of those associations is that the schizophrenia patients with depressive symptoms have more severe psychotic symptoms.

Several limitations should be considered in interpreting our results. First, the cross-sectional design of the study precludes any conclusions about the directionality of the association between depressive symptoms and serum levels of cardiometabolic biomarkers in schizophrenia. Thus, the present result has to be confirmed with longitudinal studies. Second, although all patients included in the present study were treated with atypical antipsychotics, we did not collect detailed information about medication use and unable to stratify samples by different atypical antipsychotic drugs due to drug type many. Third, only four metabolic parameters were measured in our present study, and there were other related metabolic biomarkers may influence the occurrence of depressive symptoms. Thus, more related lipid types should be measured and correct for multiple testing. Finally, since our small sample size especially for controls, the statistical power of our study to detect the difference of some metabolic parameters between patients and healthy controls was insufficient. Hence, a longitudinal study with larger samples and controlled confounding factors such as antipsychotics type is required to evaluate causal relations between more metabolic parameters and depressive symptoms in schizophrenia.

In summary, our results indicate the prevalence of clinically significant depressive symptoms of 53.8% in Chinese schizophrenia patients treated with atypical antipsychotics. Schizophrenia patients also had higher serum levels of cardiometabolic biomarkers compared to controls. Moreover, patients with depressive symptoms had significantly higher serum LDL and TC levels than patients without depressive symptoms, and depressive symptoms were positively correlated with serum LDL and TC levels in schizophrenia patients. In addition, our results showed that patients with depressive symptoms also had severe psychological symptoms evaluated by PANSS. Taken together, the appearance of depressive symptoms in schizophrenia is accompanied by more severe psychological symptoms and my caused by severe adverse metabolic side effects. Therefore, understanding and resolving the metabolic side effects would be helpful to alleviate the depressive symptoms in schizophrenia patients and to improve its prognosis.

Declaration of Competing Interest

The authors have no conflicts to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112522.

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