Current Neuropharmacology, 2022, *20,* 1969-1977

RESEARCH ARTICLE

Differing Prevalence and Correlates of Metabolic Syndromes Between Chlorpromazine and Clozapine: A 10-year Retrospective Study of a Male Chinese Cohort

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ARTICLE HISTORY

Received: September 01, 2021
Revised: January 06, 2022
Accepted: February 28, 2022

DOI:
10.2174/1570159X20666220302153123

Abstract: ***Background*:** Antipsychotics are known to be associated with metabolic syndromes (MetS). Chlorpromazine (CPZ) and Clozapine (CLZ) are currently the most commonly used antipsychotics in low-income districts of China. However, potential differences in the long-term effects of CPZ and CLZ on MetS in schizophrenia inpatients are not well understood. Here, we aimed to identify any MetS profile differences between long-term schizophrenia patients who were prescribed either CPZ or CLZ at a primary psychiatric hospital.

***Methods*:** We recruited a total of 204 male schizophrenia patients who received either CPZ or CLZ. We measured their weight, height, body mass index (BMI), waist circumference (WC), diastolic blood pressure (DBP), and systolic blood pressure (SBP), as well as their biochemical indicators, including fasting blood glucose (FBS), triglycerides (TG), cholesterol (TC), high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c).

***Results*:** The MetS prevalence in the CPZ and CLZ groups was 31% and 37.5%, respectively. The CLZ group had significantly higher DBP levels and a higher incidence of dyslipidemia (HDL-c) but lower HDL-c and TC levels than the CPZ group. We also determined that smoking history, BMI, and duration of hospitalisation were risk factors for the development of MetS. Moreover, we found that CPZ and CLZ were correlated with the same risk for developing MetS and that BMI was a vital risk factor of MetS for both the CPZ and CLZ groups.

***Conclusion*:** Long-term CPZ and CLZ prescriptions were associated with similar profiles for developing MetS of schizophrenia patients.

Keywords: Schizophrenia, metabolic syndrome, antipsychotics, dyslipidemia, diabetes, retrospective cohort study.

1. INTRODUCTION

Schizophrenia patients experience a two- to three-fold higher mortality rate than the general population, and have their life expectancies reduced by an average of 10-25 years [1, 2]. Cardiovascular diseases (CVDs) are the primary cause of premature death in schizophrenia patients [3]. Previous studies have shown that metabolic abnormalities or metabolic syndromes (MetS) are the main contributors to CVD development in schizophrenia patients [4]. MetS can induce many CVD consequences, including disordered hemodynamics, microvascular dysfunction, abnormal myocardial metabolism, atherosclerosis, calcification, infarction, and heart failure [4]. Additionally, MetS is a significant risk factor for patients with diabetes and CVD and is a predictive factor for CVD in schizophrenia patients [5]. MetS conditions include abdominal obesity, hypertension, hyperglycemia, and dyslipidemia. Although the causes behind the increased rates of MetS and metabolic abnormalities in patients with schizophrenia are still unclear, several studies suggest that visceral adiposity [6, 7], insulin resistance, ge-

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1875-6190/22 $65.00+.00

netic predispositions [8-11], immune abnormalities [12], lifestyle habits [13], smoking [14] and antipsychotic agents [15] may play important roles.

Antipsychotics have been associated with increased risks for weight gain, type 2 diabetes (or impaired glucose tolerance), and dyslipidemia [16, 17]. Reported MetS prevalence varies between different studies—ranging from 10.1% to 69.3% in patients with schizophrenia [18, 19]. These inconsistencies might be due to differences in observation period disease stages or in antipsychotic treatments [20, 21]. For example, a 20-year longitudinal study reported that first-episode schizophrenia patients had a MetS prevalence of 8.3%, but the MetS rate increased to 58.3% after 20 years of CLZ use [18]. Lee *et al.* showed that the MetS prevalence was 18.8% for patients treated with quetiapine, 22.0% for patients treated with aripiprazole, 33.3% for patients treated with amisulpride and paliperidone, 34% for patients treated with olanzapine, 35% for patients treated with risperidone, 39.4% for patients treated with haloperidol, and 44.7% for patients treated with CLZ [22]. Said *et al.* reported that MetS prevalence was 33.3% for patients treated with CPZ, 18.5% for patients treated with sulpiride, 18.5% for patients treated with perphenazine, 11.2% for patients treated with haloperidol, and 7.4% for patients treated with trifluoperazine [23].

CPZ (the first effective typical antipsychotic agent) and CLZ (the gold standard atypical antipsychotic agent) are the most commonly prescribed antipsychotics in low-income districts of China. In the early stages of CLZ therapy, patients with schizophrenia have significantly higher risks of obesity and weight gain [24]. Likewise, patients show weight increases after three months of CPZ use [25]. However, any potential differences in the long-term (*e.g.*, longer than 10 years) effects of these two antipsychotic agents on MetS conditions in schizophrenia inpatients have not been extensively studied.

Thus, this retrospective cohort study included schizophrenia patients hospitalised for more than ten years and had been treated with CLZ or CPZ monotherapy. We aimed to investigate whether there were differences in the prevalence, or associated correlations of MetS between these two groups during these long hospitalisation courses.

2. MATERIALS AND METHODS

2.1. Subjects

Our protocol was approved by the Shanghai First Minzheng Mental Health Center (study number: YJZXLL 2015031). All patients involved in this study were recruited from the hospital between July 2015 and July 2016. All patients and/or their guardians provided informed consent.

The inclusion criteria were: 1) patients who met the diagnosis for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-4); 2) patients who were continuously hospitalised for more than 10 years; 3) patients who received monotherapy treatment with either CPZ or CLZ. The exclusion criteria were: 1) patients with MetS or any abnormal MetS indicators when hospitalised; 2) patients whose antipsychotic agent treatment regimens had been altered for more than one month.

We calculated sample sizes using PASS15.0 software, and the power calculation method was set as a normal approximation. The power and α were set to 0.9 and 0.05, respectively. We assumed that the CLZ and CPZ groups were the same sizes. With regard to the effect size, we hypothesised the MetS incidence within the CPZ group would be 0.1, and the MetS incidence within the CLZ group would be 0.3, and set the input type as proportions. The minimum sample size was calculated to be 82. We recruited 104 CLZ patients, and 100 CPZ patients (all male schizophrenia inpatients at the First Minzheng Mental Health Center), reaching the minimum numbers needed for statistical efficacy.

2.2. Data Collection Procedure

The socio-demographic and clinical information, including duration of illness, duration of hospitalisation, smoking, psychiatric agents, physical disease medications, and daily drug dosages, were collected from structured interviews and medical records.

Moreover, weight, height, WC, and resting blood pressure [including DBP and SBP] were measured. WC was defined as the narrowest area above the anterior superior iliac spine of the waist. The resting blood pressure was recorded as an average of two measurements—in both resting and sitting positions. Body mass index (BMI) was calculated according to the following formula: BMI = weight/(height^2). Other biochemical indicators, including fasting blood glucose (FBS), TG, TC, HDL-c, and LDL-c, were collected from venous blood following 8 hours of fasting. All researchers involved in these procedures were trained in structured clinical information collection.

2.3. Definition of MetS

We defined MetS following the standards of the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) [26]. MetS was diagnosed when patients met at least three of the five following criteria: 1) WC>=90cm, which is a modified standard for Asian men [27, 11]. 2) TG level >=150mg/dL; 3) HDL-c level <=40mg/dL; 4) SBP >=130mmHg and/or DBP >=85mmHg; 5) FBS levels >=100mg/dL.

2.4. Statistical Analyses

IBM SPSS (version 22.0) was used for statistical analyses. Kolmogorov-Smirnov tests were used to examine the normality of data distributions. Continuous variables were analysed using variance (ANOVA) or Mann-Whitney U tests. Categorical variables were analysed using Chi-square tests or Fisher's exact tests. A general linear model (GLM) was performed to compare metabolic parameters between the CPZ and CLZ groups. Univariate and multivariate logistic regression was applied to determine the odds ratio (OR) and 95% confidence intervals (95% CI) between sociodemographic variables, clinical variables, and MetS status. Statistical significance was set as $p< 0.05$ (with a two-sided test).

3. RESULTS

3.1. Differences in Sociodemographic Factors between the CPZ and CLZ Groups

Sociodemographic characteristics of participants are shown in Table **1**. The CPZ group had a significantly higher

Table 1. Sociodemographic characteristics of CPZ *vs*. CLZ groups.

-	CPZ	CLZ	F/x^2	*P*-Value
Age (years)	60.2±8.5	59.4±8.7	0.417	0.519
Smoking history	-	-	-	-
Yes	64	50	5.243	0.022*
No	36	54		
Education (years)	8.4±2.1	8.6±2.1	0.436	0.51
Age of onset (Years)	24.1±8.5	22.5±5.9	2.493	0.116
Duration of hospitalisation (months)	280.8±116.7	291.9±106.4	0.502	0.479
BMI	23.4±3.8	24.0±3.7	2.533	0.113

Table 2. Metabolic parameters of CPZ *vs*. CLZ groups.

-	CPZ	CLZ	F	*P*-Value	FDR Correction [Δ]
WC (cm)	86.18±10.74	85.97±12.07	0.154	0.695	No
Systolic BP (mmHg)	125.14±8.53	126.61±8.32	2.176	0.142	No
Diastolic BP (mmHg)	78.05±6.75	80.28±5.23	6.587	0.011	Yes
HDL-c (mg/dl)	1.10±0.35	0.95±0.25	15.421	<0.001	Yes
TG (mg/dl)	1.33±0.97	1.43±0.78	0.776	0.379	No
FBS (mg/dL)	5.15±1.15	5.09±0.88	0.088	0.767	No
LDL-c (mg/dl)	2.58±0.70	2.40±0.64	4.286	0.04	No
TC (mg/dl)	4.59±0.90	4.26±0.81	9.898	0.002	Yes

Δ: FDR multiple correct p value; Yes: the difference was significant; No: the difference was not significant.

rate of smoking history than the CLZ group (p=0.022). There were no significant differences in age, education, age of onset, or duration of hospitalisation between the CPZ and CLZ groups (all p's >0.05).

3.2. Metabolic Parameters of the CPZ Group *vs*. the CLZ group

Table **2** shows the metabolic parameters of patients in the CPZ and CLZ groups. ANOVA analyses revealed that HDL-c, DBP, and TC levels were significantly different between the two different groups after adjusting for smoking history. The CLZ group had significantly higher DBP than the CPZ group (p=0.011), while the CLZ group showed lower HDL-c and TC levels than the CPZ group. (p<0.001, p=0.002, respectively).

3.3. Differences in MetS Prevalence and Associated Components between the CPZ and CLZ Groups

According to NCEP ATP III criteria, MetS prevalence was 31% (n = 31) in the CPZ group and 37.5% (n = 39) in the CLZ group. However, there was no statistically significant difference in MetS prevalence between patients who had been taking CPZ and patients who had been taking CLZ (p = 0.219), even after adjusting for smoking history in the logistic regression model (Table **3**).

We also performed logistic regression models to calculate MetS prevalence after adjusting for smoking history. We found that the CPZ group had a decreased prevalence of low HDL-c levels than the CLZ group. However, there was no significant difference in the prevalence of WC, hyperglycemia, hypertension (both SBP and DP), or hyperlipemia (TG) between the two groups (all p's >0.05); (Table **3**).

3.4. Factors Associated with MetS

We used univariate analyses and multivariate logistic regression analyses to investigate factors associated with MetS in our patients. As shown in Table **4**, the univariate logistic analysis revealed that smoking history, BMI, and duration of hospitalisation were significant risk factors for MetS. The previous two factors were associated with an increased risk of MetS (OR=1.929, 95%CI: 1.061-3.507, p=0.031, OR=1.376, 95% CI: 1.234-1.534, p<0.001), while duration of hospitalisation was actually associated with a decreased risk of MetS (OR=0.996, 95% CI: 0.993-0.999, p=0.004). Current age, antipsychotics, TC, LDL-c, and age of onset were not associated with MetS risk. Furthermore, the multivariate logistic analysis showed BMI remained a risk factor for MetS. However, the multivariate logistic model eliminated the effects of smoking and length of hospitalisation.

Table 3 Comparison of MetS prevalence and associated components CPZ *vs*. CLZ groups.

-	CPZ % (n)	CLZ % (n)	Exp(B)	*P*-value	95%CI
WC (>=90cm)	40%(40)	32.7%(34)	0.855	0.607	0.471-1.554
Hyperglycemia	36%(36)	28.8%(30)	0.727	0.294	0.4-1.319
Hypertension (SBP)	37%(37)	46.2%(48)	1.528	0.145	0.864-2.7
Hypertension (DBP)	10%(10)	15.4%(16)	1.459	0.388	0.619-3.441
Hyperlipaemia (HDL-c)	47%(47)	70.2%(73)	2.937	<0.001*	1.621-5.324
Hyperlipaemia (TG)	25%(25)	25%(26)	1.009	0.979	0.531-1.917
MetS	31%(31)	37.5%(39)	1.451	0.219	0.801-2.628

Table 4. Logistic regression analyses the associated factors of MetS.

-	Univariate Logistic			Multivariate Logistic		
-	Exp（B）	95% CI	*P-value*	Exp（B）	95% CI	*P-value*
Age	0.969	0.936-1.003	0.07	0.955	0.838-1.089	0.495
Smoking history	-					
No	Reference Group					
Yes	1.929	1.061-3.507	0.031*	1.567	0.769-3.194	0.216
Antipsychotics						
CPZ	Reference Group					
CLZ	0.827	0.465-1.472	0.519	0.718	0.353-1.461	0.361
BMI	1.376	1.234-1.534	<0.001*	1.345	1.201-1.507	<0.001*
TC	1.163	0.834-1.622	0.374	0.844	0.335-2.126	0.719
LDL-c	1.42	0.92-2.192	0.113	1.293	0.398-4.202	0.669
Age of onset	1.037	0.997-1.079	0.073	1.05	0.92-1.198	0.472
Duration of hospitalisation	0.996	0.993-0.999	0.004*	0.998	0.993-1.002	0.273

3.5. Difference in Factors Associated with MetS between the CPZ and CLZ Groups

We performed multivariate logistic regression analysis to compare potential differences in the factors associated with MetS between the CPZ and CLZ groups. As shown in Table **5**, there were similar factors associated with MetS in both the CPZ and CLZ groups. BMI was associated with MetS in the CPZ and CLZ groups, while age, smoking history, TC, LDL-c, age of onset, and hospitalisation were not associated with MetS in either group.

4. DISCUSSION

This study investigated the prevalence of factors associated with MetS in individuals with schizophrenia who had received long-term antipsychotic treatment. We found several interesting results, including that the prevalence of MetS was 31.0% in the CPZ group and 37.5% in the CLZ group, rates that were much higher than those seen in the general population [28, 29]. We also found that the CLZ group had significantly higher DBP levels and higher incidences of dyslipidemia (HDL-c) but lower HDL-c and TC levels than the CPZ group. Additionally, long-term CPZ and CLZ treatment had no differential effects on the rate of MetS development. Finally, there was a set of factors contributing to the development of MetS in both groups. For example, BMI was associated with MetS in both the CPZ and CLZ groups.

The prevalence of MetS in mainland China was approximately equal to the rate found in a study in Taiwan (where the total prevalence of MetS was 34.9%, and the male prevalence was 31.5% among 650 patients with schizophrenia or schizoaffective disorder) [30]. However, our rate was higher than that found in other studies in Asia. For example, the prevalence is only 15.8% in Japan [31] and 26.9% in Singapore [32]. Our results also showed higher prevalence rates compared with most European studies. These inconsistencies are likely due to several factors. Varying MetS diagnostic criteria were used in the different studies, including ATP III, IDF, JASSO, and other standards of diagnosis. In addition, the participants in our study had been hospitalised for at least

Table 5. Multivariate logistic analyses the associated factors of MetS CPZ vs. CLZ groups.

-	CPZ			CLZ		
-	**Exp (B)**	**95% CI**	***P-value***	**Exp（B）**	**95% CI**	***P-value***
Age	1.035	0.962-1.114	0.356	1.037	0.967-1.112	0.313
Smoking history	-			-		
No	Reference Group			Reference Group		
Yes	1.239	0.416-3.688	0.701	1.232	0.456-3.327	0.68
BMI	1.372	1.164-1.617	<0.001*	1.566	1.266-1.937	<0.001*
TC	0.967	0.228-4.107	0.963	0.664	0.183-2.409	0.533
LDL-c	1.109	0.172-7.142	0.913	1.698	0.319-9.039	0.535
Age of onset	0.994	0.928-1.064	0.86	0.936	0.85-1.031	0.179
Duration of hospitalisation	0.997	0.99-1.064	0.269	0.996	0.99-1.002	0.188

10 years, while the individuals in most of the other studies had typically been hospitalised for less than 2 years. Moreover, diet, habitation, lifestyle, healthcare conditions, and clinical management could also have influenced factors in the different studies.

Antipsychotic agents play a crucial role in the metabolic status of patients with schizophrenia. Over the past two decades, studies on the relationship between second-generation antipsychotics (SGAs) and the development of metabolic disorders have become increasingly common. There is a general perception that most atypical antipsychotics are correlated with higher MetS incidences than typical antipsychotics [33]. Our results showed significant between-group differences in HDL-c and TC levels between the CLZ and CPZ groups. We also illustrated that both CLZ and CPZ significantly impacted BMI, supporting the notion that CLZ contributes to weight gain and/or obesity. Previous evidence has shown that unlike TC, CLZ significantly impacted TG [19], findings that were inconsistent with ours. CLZ was the first atypical antipsychotic and was the first-line treatment for drug-resistant schizophrenia [34]. CLZ was also the medication most associated with type 2 diabetes, hypertension, and dyslipidemia. Potential central mechanisms of CLZ-induced metabolic abnormalities include that CLZ is a potent agonist of the serotonergic and histaminergic systems and has thus been associated with increased food intake and weight gain [35]. Recent studies have shown several underlying periphery mechanisms associated with CLZ-induced metabolic disorders. Desmethylclozapine, one of the metabolites of CLZ, had a greater 5-HT2C antagonistic effect than CLZ. It also activates M1 receptors, 5-HT1A receptors, and certain D2 receptors [36, 37]. Reynolds *et al.* showed that adverse outcomes such as weight gain, hyperglycemia, and hyperlipidemia result from the more potent 5-HT2C antagonist induced by norclozapine [38]. Some studies have also indicated that plasma norclozapine levels were associated with changes in body weight, serum glucose and lipids levels [39, 40]. In addition, many studies suggest that chronic inflammation also plays an important role in MetS pathogenesis, as pro-inflammatory cytokines and complement C3 have been reported to be related to CLZ-induced metabolic disorders [41, 42]. Other evidence suggests the potential mechanisms of genes and antioxidant enzymes, involved in weight gain [43]. More than 200 genes or markers are associated with CLZ-induced obesity [44]. CPZ is a prototypical antipsychotic with a high affinity for 5-HT2A receptors [45]. This affinity may be one of the major reasons for significant weight and blood glycemia increases. In addition, CPZ can inhibit 5-HT2C receptors in the hypothalamus, increasing food consumption [46, 47]. Other clinical research has shown that CPZ is associated with hypercholesterolemia but not with TG [48]. Furthermore, CPZ reportedly increases visceral fat weight and plasma insulin levels but decreases plasma adiponectin and leptin levels [49]. Amamoto *et al.* also found that abnormally elevated serum TNF-α levels were significantly associated with CPZ-induced MetS. Thus, abnormal inflammation is also one of the peripheral mechanisms involved in CPZ-induced metabolic abnormalities [49]. There are similarities and differences in the mechanisms underlying the metabolic disorders caused by CLZ and CPZ. In this study, MetS incidence was similar between the CLZ and CPZ groups. Thus, there may be other confounding factors related to MetS incidence in the context of these drugs that need further exploration.

Although the effects of different antipsychotic drugs on MetS are inconsistent [50], it is well-established that SGAs affected MetS to a greater degree than first-generation antipsychotics (FGAs). However, our results showed no significant differences between CLZ and CPZ treatment on the prevalence of MetS, consistent with a large clinical trial in Taiwan [30]. A recent clinical study also supported our results which revealed that the patients prescribed with monopharmaceutical or polypharmaceutical, typical or atypical antipsychotics had identical MetS prevalence [32]. In this study, we investigated the characteristics of MetS among schizophrenia patients who had been hospitalised for more than 10 years. This research design maximises control over multiple external factors that could influence the development of MetS. Our results showed that the risk of MetS was similar between patients treated with CLZ and CPZ.

Potential explanations for these findings include that the length of hospital stay itself was the determining factor or that inpatients and outpatients had differing MetS prevalences. A Japanese clinical study showed that length of stay contributed to differences in MetS rates between outpatients and inpatients (48.1% *versus* 15.8%) [31]. A more recent study showed that longer hospital stays decreased the likelihood of developing MetS, and decreased the overall prevalence of MetS [51]. That could be because patients with longer hospital stays benefit from better care, ample psychoeducation, and/or health warnings about MetS. In addition, Shi *et al.* [52] found that patients who stayed in the hospital longer were more often prescribed higher doses of medicines such as hypoglycemic agents and antihypertensive and anti-lipid drugs. Furthermore, hospital-based care lends itself well to the efficient treatment of abnormal metabolic status. All inpatients receive healthy diets, regular lifestyle interventions, appropriate opportunities for exercise, and monitoring for physical disease [53, 54]. Additionally, long-term hospitalisation also means social isolation and monotonous activities, which may affect the metabolic status of inpatients with schizophrenia. Our results challenge the accepted view that SGAs are associated with higher metabolic risks than FGAs. But this conclusion could also be related to our specific population-- schizophrenic inpatients hospitalised for more than 10 years.

It is well known that food intake and exercise status affect the incidence of MetS. All of our participants were long-term inpatients fed almost the same daily diet and had their exercise habits guided by specific staff members. Thus, we did not include food preference or exercise status in our logistic regression analyses. Gender differences are also important influencing factors in clinical research [55, 56]. In examining gender differences in the occurrence of MetS with clozapine, Zhang *et al.* have found that MetS prevalence in schizophrenic patients treated with CLZ differed significantly as a function of gender [*i.e.*, there was a higher incidence of MetS in women than in men (p=0.02)] [42]. Other studies also support the conclusions that women have higher MetS rates than men [57, 58]. However, it is unclear whether there is a sex difference in MetS occurrences in patients using CPZ. There was no relevant literature to answer this question, which we speculated may be because (1) there were few articles on CPZ-induced MetS (likely because metabolic disorders did not attract attention when antipsychotics were first developed), or (2) in the limited number of articles that reported FGAs and MetS, the CPZ sample sizes were very small.

Our study had several unique features. We observed the metabolic status of schizophrenia patients who had been hospitalised for long periods of time and had received fundamental living and healthcare interventions. Thus, our conclusions may partly apply to lower-income populations. The fact that the patients had been hospitalised for at least 10 years was one of the most important features of the current study. Such an extended horizon meant that we could fully observe the natural process of MetS under controlled conditions. To the best of our knowledge, this was the first study to report on the metabolic status of schizophrenia patients who had been hospitalised for at least ten years. Although CLZ had been previously and consistently identified as the medication most strongly correlated with the development of metabolic abnormalities [59], we observed a different outcome-- namely that there was no difference between CLZ and CPZ treatment on long-term metabolic status outcomes.

There were several limitations inherent to our study. First, our subjects were of Chinese Han descent, so they may not be generalisable to other ethnic groups. Further studies on different ethnic groups should be conducted. Second, because we examined only 204 male patients, our results did not analyse the effects of gender differences. The results should be confirmed in future studies involving female subjects and larger sample sizes. Finally, some patients could have been on other medications for other conditions, which may have affected their metabolic changes.

CONCLUSION

In summary, long-term CPZ and CLZ treatment did not lead to differing MetS and prevalence, or differing effects on MetS development. Similar patterns contributed to the development of MetS for the CPZ and CLZ groups. BMI was associated with MetS in both groups. Although different antipsychotics did not correlate with differences in MetS rates, antipsychotic medication prescriptions should still be carefully monitored. It is also necessary to monitor other physiological parameters, particularly BMI.

LIST OF ABBREVIATIONS

MetS	=	Metabolic Syndrome
CPZ	=	Chlorpromazine
CLZ	=	Clozapine
BMI	=	Body Mass Index
WC	=	Waist Circumference
DBP	=	Diastolic Blood Pressure
SBP	=	Systolic Blood Pressure
FBS	=	Fasting Blood Glucose
TG	=	Triglycerides
TC	=	Cholesterol
HDL-c	=	High-density Lipoprotein Cholesterol
LDL-c	=	Low-density Lipoprotein Cholesterol

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Shanghai First Minzheng Mental Health Center, China (study number: YJZXLL 2015031).

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. All human procedures followed were in accordance with the Helsinki Declaration of 1975.

CONSENT FOR PUBLICATION

All patients and their guardians provided informed consent.

STANDARDS OF REPORTING

STROBE guidelines has been followed.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

This study was funded by the National Natural Science Foundation of China, 81671336; the National Key Research and Development Program, 2017YFC0909200; the Shanghai Science and Technology Innovation Action Plan Medical Innovation Research Special Project, 21Y11921200.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

We are particularly grateful to Dr. Meiti Wang, Dr. Yezhe Lin, Dr. Ying Chen, and Dr. Kai Shi for collecting samples. We also extend our gratitude to the Shanghai First Minzheng Mental Health Center doctors for their coordination and help.

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