Smoking affects the patterns of metabolic disorders and metabolic syndrome in patients with first-
episode drug-naive schizophrenia - a large sample study based on Chinese Han population

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Abstract

Objective

Although metabolic disorders and smoking are common in schizophrenia, few studies investigated the effects of smoking on metabolic disorders or metabolic syndrome (MetS) in schizophrenia patients, especially in first-episode drug-naïve (FEDN) patients. To investigate the differences in metabolic disorders and MetS between smoking and non-smoking FEDN schizophrenia patients.

Methods

A total of 428 FEDN schizophrenia patients and 435 controls were recruited. Blood pressure, waist circumference, body mass index (BMI), lipid profiles and glucose metabolism were measured. The psychopathology was evaluated by Positive and Negative Syndrome Scale (PANSS).

Results

FEDN schizophrenia patients had higher smoking rate than controls (23.8% vs. 14.0%, p<0.001). After adjusting for confounding variables, the prevalence of MetS, overweight, hypertension, hypertriglyceridemia, elevated insulin and insulin resistance in smoking patients were higher than those in non-smoking patients, while overweight and hypertension in the smoking controls were higher than those in non-smoking controls (all p<0.05). In smoking patients, triglyceridemia, HDLC and fasting blood glucose were the main contributing components to MetS, while in non-smoking patients, waist circumference, systolic BP, triglyceridemia, HDLC and fasting blood glucose were the main contributing components to MetS. In smoking patients, BMI and HOMA-IR were associated factors of MetS (both p<0.05). In non-smoking patients, sex, BMI, insulin and HOMA-IR were associated factors of MetS (all p<0.05).

Conclusions

Our study indicates that smoking schizophrenia patients have a higher prevalence of MetS and metabolic disorders than non-smoking patients. Moreover, smoking and non-smoking patients have different contributing components and associated factors for MetS.

Keywords: Schizophrenia; metabolic disorders; metabolic syndrome; smoking.
**Significance Statement**

It is well established that metabolic disorders and smoking are common in schizophrenia, but few studies investigated the effects of smoking on metabolic disorders or metabolic syndrome (MetS) in schizophrenia patients, especially in first-episode drug-naïve (FEDN) patients. To our best knowledge, this is the first large-sample multiple-center study to compare the differences in the prevalence, clinical correlates and associated factors of metabolic disorders and MetS between smoking and non-smoking patients with FEND schizophrenia.
Introduction

Schizophrenia is characterized with psychotic symptoms and cognitive deficits (Li et al., 2020; Zhu et al., 2020; Su et al., 2021). It has been reported that schizophrenia patients have a higher mortality rate and a 20% reduction in life expectancy than the general population (Mohamud et al., 2011). A great number of studies have shown that the leading cause of death in patients with schizophrenia is cardiovascular disease (CVD), which increases the risk of death by 3 times (Osby et al., 2000; Mohamud et al., 2011), while the main causes of CVD are various metabolic disorders or metabolic syndrome (MetS) (Sullivan et al., 2009; Mitchell et al., 2013). MetS is characterized by central obesity, hypertension, abnormal glucose metabolism and lipid metabolism. There is already evidence that schizophrenia patients have 2-3 times higher incidence of MetS than the general population, and about 30% of patients suffer from MetS (Sullivan et al., 2009; Stubbs et al., 2015; Vancampfort et al., 2015). Although the mechanism of the increased incidence of metabolic disorders or MetS in patients with schizophrenia is still unclear, it has been reported that schizophrenia itself (Britvic et al., 2013), common genetic pathway risk (Hansen et al., 2011; Deng et al., 2013; Lane et al., 2017; Zhou et al., 2020b), antipsychotics, reduced physical activity, unhealthy diet habits, and even smoking may lead to metabolic disorders and MetS in patients with schizophrenia (Bobes et al., 2010; Mitchell et al., 2013; Vancampfort et al., 2015). According to reports, smoking is associated with a variety of metabolic disorders in the general population, including obesity, abdominal dyslipidemia, abnormal lipoprotein metabolism, type 2 diabetes mellitus and MetS (Berlin, 2008; Slagter et al., 2013). It is well established that individuals with schizophrenia smoke almost three times as much as the general population, and previous studies have indicated that the smoking rate is as high as 50%-90% (Williams et al., 2005; Sagud et al., 2018). Furthermore, severe mental illnesses are closely associated with smoking, and the link between smoking and schizophrenia may be stronger than other severe mental illnesses, such as mood disorders (LLerena et al., 2003; de Leon and Diaz, 2005). Previous evidence also suggests that smokers with schizophrenia have a higher proportion of heavy smokers and absorb more nicotine
from each cigarette than smokers without schizophrenia (Strand and Nyback, 2005; Williams et al., 2005). In addition, patients with schizophrenia have great difficulties in quitting smoking in both short term and long term (George et al., 2000). The above evidence indicates that there is a close potential link between schizophrenia and smoking, although the mechanism is still unclear.

With regard to the high smoking rate in schizophrenia patients and the close relationship between smoking and metabolic disorders, previous evidence indicates that smoking patients have a 2.63 times higher risk of the 10-year cardiovascular events than non-smoking patients. Cessation of smoking can benefit schizophrenia patients and reduce the risk of 10-year cardiovascular events by nearly 90% (Bobes et al., 2010). The study by Lee et al., reported that MetS incidence in smokers with schizophrenia was 2.46 times greater than that in non-smokers with schizophrenia (J. Lee et al., 2012). However, the study did not take into account the use of antipsychotic drugs in the included patients, and data on the effects of smoking on metabolic disorders or MetS in schizophrenia patients are limited, especially first-episode drug-naive (FEDN) patients. It is worth noting that disease onset, disease duration and atypical antipsychotics increase the incidence of metabolic disorders and MetS (Mitchell et al., 2013). Therefore, FEDN patients provide us with the possibility of minimizing confounding factors and investigating the effects of smoking on metabolic disorders or MetS in schizophrenia.

Therefore, the present study aimed to investigate whether there were differences between smoking and non-smoking patients with FEND schizophrenia in the following aspects: (1) the prevalence of metabolic disorders and MetS; (2) the main contributing components of MetS, (3) the associated factors pattern of MetS. To our best of knowledge, this was first to investigate the differences in metabolic disorders and MetS between smoking and non-smoking patients with FEDN schizophrenia.
Participants and Methods

Participants and clinical interview

This study was reviewed and approved by the Institutional Review Boards of the First Hospital of Shanxi Medical University and Beijing Hui-long-guan Hospital. Informed consents were obtained from participants. A total of 428 patients (206 males and 222 females) were recruited, and their inclusion criteria were: (1) 18 to 60 years old, Chinese Han population; (2) satisfied with the diagnostic criteria of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), made by two independent psychiatrists using the Structure Clinical Interview for DSM-IV (SCID); (3) at first episode (4) no previous treatment with psychotropic medicines; (4) the course of disease ≤5 years; (5) Chinese Han population. Patients with any other major Axis I disorder were excluded. A total of 435 healthy controls (188 males and 247 females) were recruited. They had no any major Axis I disorder diagnosis or family history of mental disorders. All participants who were pregnant or had organic brain diseases, other severe physical diseases or alcohol or drugs abuse/dependence were excluded. Pregnancy was identified by urine test. Alcohol or drugs abuse/dependence were identified by self-reported alcohol or drug use and medical records (Lv et al., 2020; Zhou et al., 2021).

Clinical symptom measurements

Clinical psychopathology was evaluated by using the Positive and Negative Syndrome Scale (PANSS). All psychiatrists involved in this study were trained in the use of SCID and PANSS. After training, the inter-rater correlation coefficients were greater than 0.8.

Physical and biochemical measurements

The physical indicators such as blood pressure, weight, height and waist circumference were detected by nurses. Biochemical indexes were detected in plasma samples collected after fasting overnight, including triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol.
(LDLC), high density lipoprotein cholesterol (HDLC), blood glucose, glycosylated hemoglobin (HbA1c), insulin and insulin resistance which was identified by the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR).

Identification of metabolic disorders and MetS

According to the specific ethnic adjustment (waist circumference) for the National Cholesterol Education Program-Third Adult Treatment Panel (NCEP ATP III-A) criteria (A. M. H. Lee et al., 2018), patients diagnosed with MetS should meet at least the following three aspects: (1) elevated waist circumference (Chinese male ≥90 cm, female ≥80 cm); (2) hypertriglyceridemia ≥150 mg/dL (1.7 mmol/L); (3) hypo-HDLC, male <40 mg/dL (1.03 mmol/L) and female <50 mg/dL (1.29 mmol/L) or with drug treatment; (4) systolic blood pressure (SBP) ≥130 and/or diastolic BP (DBP) ≥85 mm Hg or with drug treatment; (5) fasting blood glucose (FBG) ≥100 mg/dL (5.6 mmol/L), or previously diagnosed as type 2 diabetes.

Other metabolic disorders were determined as follows: overweight (body mass index, BMI ≥25kg/m²), hypercholesterolemia (total cholesterol > 200 mg/dL or 5.18mmol/L), hyper-LDLC (LDLC > 120 mg/dL or 3.12 mmol/L), elevated HbA1c (HbA1c >5.9%), elevated fasting insulin (insulin >24.9uU/mL) and insulin resistance (HOMA-IR>3) (Spence et al., 2019). In this study, only 8 out of 428 patients (1.87%) were obese, and we merged overweight and obesity into one group.

Statistical analysis

The normality of the variable distribution was determined using Kolmogorov-Smirnov test. Chi-square test and analysis of variance (ANOVA) was performed for categorical variables and continuous variables, respectively. A two-way ANCOVA (diagnosis × smoker) was conducted to explore the differences in metabolic indexes between smokers and non-smokers, taking each metabolic index as dependent variable, and diagnosis and smoker as fixed factors, while adjusting
for confounding factors. The main effects of diagnosis, smoker, and the diagnosis × smoker interaction in each model were examined. Then ANCOVA was conducted to compare the differences in metabolic indexes between smokers and non-smokers in patient and control groups, separately. To investigate the difference in the prevalence of each metabolic abnormality between patients and controls, logistic regression was used to adjust for covariates.

A two-way ANCOVA (smoker × MetS) was also conducted to explore the differences in clinical correlates and metabolic indexes between smokers with and without MetS. The main effects of diagnosis, smoker, and the diagnosis × smoker interaction in each model were detected. Then ANCOVA was conducted to compare the differences in metabolic indexes between smokers and non-smokers in patient and control groups, respectively. Finally, in patient group, to detect the contribution of metabolic components (five components) to MetS, logistic regression was conducted in smoking and non-smoking patients respectively. Logistic regression was also applied to examine whether clinical variables and other metabolic indexes were associated with the occurrence of MetS in smoking and non-smoking patients respectively. The variables with a p value less than 0.1 in univariate analysis were further included in logistic regression. Bonferroni corrections were conducted for multiple tests. All statistical analyses were calculated through SPSS 23.0 version. The significant p value was set to less than 0.05 (two-tailed test).

Results

Demography and clinical information of participants

There were no differences in age, sex and education levels between the patients and the controls (all p>0.05). A total of 102 (23.8%) of the 428 schizophrenia patients were smokers, while 61 (14.0%) of the 435 controls were smokers. The smoking rate of schizophrenia patients was higher than that of controls ($\chi^2=13.55$, p<0.001).
As shown in Table 1, smokers were older than non-smokers (F=4.35, p=0.04), and smokers had fewer years of education than non-smokers (F=4.86, p=0.03). Male participants smoke more commonly than female participants ($\chi^2=87.52$, p< 0.001). Further, men had a significant higher smoking rate than women in both the patients ($\chi^2=29.47$, p< 0.001) and the controls ($\chi^2=63.72$, p< 0.001). Therefore, age, sex and education were controlled as covariates in the following 2×2 ANOVA analyses (diagnosis × smoker) that compared metabolic indexes.

As shown in Table 1 and Table 2, there was a difference in sex, but not in age, education and age of onset between smoking and non-smoking patients. Therefore, sex was controlled when comparing the differences in the prevalence of metabolic disorders and MetS between smoking and non-smoking patients.

**Physical and biochemical indexes in patient and control groups**

After controlling age, sex and education as covariates, two-way ANCOVA showed that schizophrenia patients had higher levels of waist circumference, systolic BP, diastolic BP, triglycerides, fasting glucose, insulin, and HOMA-IR, but lower levels of HDLC (all $p_{\text{Bonferroni}}<$0.05) compared with healthy controls (Table 1). There were no significant diagnosis* smoker interactive effect on any metabolic indexes after Bonferroni correction (all $p_{\text{Bonferroni}}>$0.05).

**Difference in clinical symptoms and the prevalence of each metabolic disorder between smoking and non-smoking patients**

As shown in table 2, smoking patients experienced higher PANSS negative score (F=6.18, p=0.01, $p_{\text{Bonferroni}}=0.04$) than non-smoking patients. There was no difference in other PANSS subscales or total score between smoking and non-smoking patients.

Compared with non-smoking patients, smoking patients had higher prevalence rates of overweight ($\chi^2=10.09$, p= 0.001), elevated systolic BP ($\chi^2=28.85$, p< 0.0001), elevated diastolic BP ($\chi^2=9.80$, p= 0.002), hypertriglyceridemia ($\chi^2=11.73$, p= 0.001), elevated insulin ($\chi^2=6.99$, p= 0.008),
insulin resistance (χ²=8.05, p = 0.005) and MetS (χ²=28.31, p < 0.001). As male patients had a higher smoking rate than female patients, therefore, as shown in Table 3, after adjusting for sex, the prevalence rates of overweight, elevated systolic BP, elevated diastolic BP, hypertriglyceridemia, elevated insulin, insulin resistance and MetS were higher in smoking patients than those in non-smoking patients (p= 0.005, p<0.001, p=0.009, p=0.001, p=0.02, p=0.01, p<0.001, respectively).

In health controls, only the prevalence rates of overweight, elevated systolic BP and elevated diastolic BP were higher in smokers than those in non-smokers (p= 0.01, p<0.001, p<0.001, respectively).

**Difference in the contributing components to MetS between smoking and non-smoking patients**

As shown in Table 4, two-way ANCOVA (Smoker*MetS) showed that the interaction between smoker and MetS had no significant effect on any MetS components (all p_Bonferroni>0.05). Further, we investigated the contribution of five metabolic components to MetS in smoking and non-smoking patients respectively. There were different patterns of contributing components between smoking and non-smoking patients. Logistic regression analysis showed that in smoking patients, triglyceridemia (p=0.001, OR=5.50, 95%CI: 2.02-15.01), HDLC (p=0.03, OR=0.04, 95%CI: 0.002-0.67) and fasting blood glucose (p=0.03, OR=3.14, 95%CI: 1.15-8.52) were the main contributing components to MetS, after adjusting for sex as a covariate. In non-smoking patients, waist circumference (p<0.001, OR=1.08, 95%CI: 1.03-1.12), systolic BP (p=0.002, OR=1.10, 95%CI: 1.04-1.18), triglyceridemia (p=0.001, OR=2.55, 95%CI: 1.48-4.40), HDLC (p=0.002, OR=0.08, 95%CI: 0.02-0.40) and fasting blood glucose (p<0.001, OR=3.89, 95%CI: 2.17-6.97) were the main contributing components to MetS, after adjusting for sex as a covariate.
Difference in associated factors of MetS between smoking and non-smoking patients

We further investigated whether there were different patterns of clinical correlates or metabolic parameters (except for the five components of MetS) related to the occurrence of MetS. As shown in Table 4, ANCOVA showed that in smoking patients, BMI, LDL, HbA1c and HOMA-IR were higher in MetS patients than those in non-MetS patients (all p<0.05). Then logistic regression analysis were conducted including these metabolic indexes and sex as independent variables. As shown in Table 5, BMI and HOMA-IR were associated with the occurrence of MetS in smoking patients (p=0.001 and p=0.005, respectively).

In non-smoking patients, BMI, HbA1c, insulin and HOMA-IR were higher in MetS patients than those in non-MetS patients (all p<0.05). Then logistic regression analysis were conducted including these metabolic indexes and sex as independent variables. As shown in Table 5, sex, BMI, insulin and HOMA-IR were correlated with the occurrence of MetS in smoking patients (p=0.003, p<0.001, p<0.001 and p<0.001, respectively).

Discussion

The main results of this study were as follows: (1) FEDN patients with schizophrenia had higher smoking rate than healthy controls; (2) the prevalence rates of MetS, overweight, hypertension, hypertriglyceridemia, elevated insulin and insulin resistance in smoking schizophrenia patients were significantly higher than those in non-smoking patients; (3) there were different patterns of the contributing components and related associated factors for MetS between smoking and non-smoking patients.

Our study provided evidence that without the effects of antipsychotics, patients with first-episode schizophrenia had increased smoking rate compare with controls. The reasons for the increased smoking rate in schizophrenia patients include biological and non-biological factors (Dalack et al., 1998; An et al., 2016). First, there is accumulating evidence that genetic factors affect
the susceptibility to both smoking and schizophrenia, and they may share the same genetic pathways (Kendler et al., 1993; Leonard et al., 2002). Second, neurobiological mechanisms affect the vulnerability of smoking and schizophrenia. Previous preclinical and clinical evidence indicates that the nicotinergic system in the central nervous system plays a critical role in the regulation of other neurotransmitter systems, while the central nicotine system in patients with schizophrenia has a primary defect, resulting in abnormal sensory gating (Dalack et al., 1998; Leonard et al., 2002). Third, some reports have shown that smoking in patients with schizophrenia may be an attempt to improve drug side effects and self-relieve symptoms, especially negative symptoms and cognitive impairment (Dalack et al., 1998; Chambers et al., 2001; Sacco et al., 2004). However, some contradictory results indicate that smoking is linked with symptoms of schizophrenia patients (Aguilar et al., 2005; Cerimele and Katon, 2013), and nicotine can increase the number of nicotine receptors in the brain and enhance the activity of dopamine neurons, which is related to the positive symptom of schizophrenia (Manzella et al., 2015; An et al., 2016). The most likely cause of inconsistent results may be that the enrolled patients were at different stages of the disease or received different drug treatments. For example, previous study demonstrated that chronic schizophrenia patients who smoked had fewer symptoms than non-smoking chronic patients, and these patients received stable doses of antipsychotics for at least 12 months (An et al., 2016). In our current study, we found that smoking FEDN patients displayed more severe negative symptoms than non-smoking patients.

This was the first study to demonstrate that smoking FEDN schizophrenia patients had a higher prevalence of MetS and metabolic disorders, including overweight, hypertension, hypertriglyceridermia, elevated insulin and insulin resistance than non-smoking patients. Interestingly, in the healthy control group, only the prevalence of overweight and hypertension in the smoking controls were higher than those in non-smoking controls. These findings indicate that the metabolic disorders of smokers in schizophrenia patients are more serious and prominent than those in healthy controls. The possible reasons can be explained in two aspects. On the one hand,
the effects of schizophrenia itself and smoking on metabolic disorders may overlap. On the other hand, smoking may have different effects on schizophrenia and healthy people. The detailed possible reasons are as follows: first, there is increasing evidence that schizophrenia itself, without the effects of antipsychotics, may cause metabolic disorders and MetS (Penninx and Lange, 2018). Previous genome-wide association studies have reported that schizophrenia may share genetic variants or pathways with metabolic disorders, MetS traits or MetS, such as obesity, dyslipidemia, waist circumference, and blood pressure (Andreassen et al., 2013; Malan-Muller et al., 2016; Lane et al., 2017; Postolache et al., 2019). Meanwhile, nicotine can also increase the development of metabolic disorders and MetS. The effects of smoking on blood pressure, lipid and glucose metabolism may be partly attributed to stimulation of the sympathetic nervous system and increased levels of circulating insulin antagonistic hormones, including catecholamines, cortisol and growth hormone, which cause more severe hypertension, hypertriglyceridemia, insulin resistance and hyperinsulinemia (Willi et al., 2007; Cena et al., 2011; Sun et al., 2012). Second, it is well established that smoking can promote pro-inflammatory activities and induce pro-inflammatory states (Hosseinzadeh et al., 2016; Kaur et al., 2018). A large number of studies strongly support the hypothesis that the pro-inflammatory pathway is also involved in the pathophysiology of schizophrenia (Muller, 2018; Zhu et al., 2020). Meanwhile, it is generally believed that the inflammatory pathway plays a critical role in the pathogenesis of metabolic disorders and MetS (Reddy et al., 2019). These evidences suggest that the immune inflammatory mechanism is involved in smoking, schizophrenia and metabolic disorders/metabolic syndrome at the same time, which provides a possible clue that the immune inflammation mechanism may mediate the role of smoking in metabolic disorders in patients with schizophrenia. Third, one of the reasons why smoking causes more metabolic disorders in schizophrenia patients than in the general population may also be related to behavioral factors, such as poor lifestyle. For example, previous studies have reported that smokers are less likely to exercise regularly or control daily intake of salt, saturated fat, and high-calorie diets than non-smokers with schizophrenia (Bobes et al., 2010; Vancampfort et al.,
Fourth, previous evidence has shown that compared with smokers without schizophrenia, smokers with schizophrenia have increased levels of nicotine intake from cigarettes (15), which suggests that smoking has a greater effect on metabolic disorders in schizophrenia patients than in the general population. In addition, we found that smoking and non-smoking patients have different contributing components to MetS, and different risk patterns of MetS. The main contributing components of MetS in smoking patients were triglyceridemia, HDLC and fasting blood glucose, while the main contributing components of MetS in non-smoking patients were waist circumference, systolic BP, triglyceridemia, HDLC and fasting blood glucose. With regard to the associated factors of MetS, there were different patterns between smoking and non-smoking patients. BMI and HOMA-IR were associated factors for MetS in both smoking and non-smoking patients, and sex and insulin were associated factors for MetS in non-smoking patients. Our previous study also indicated sex difference in metabolic disorder patterns in schizophrenia patients (Zhou et al., 2020a). Up till now, the underlying mechanisms of these different patterns between smoking and non-smoking patients still remain obscure and need further investigation. It is worth to note that previous meta-analysis showed that in the general population, heavy smokers had a stronger correlation with the risk of metabolic syndrome than light smokers (Sun et al., 2012). In our current cross-sectional study, we did not find differences in smoking years or daily smoking between MetS and non-MetS patients. However, further prospective cohort studies should investigate the relationship between total smoking and MetS in schizophrenia patients.

Several limitations should be concerned in this study. First of all, as mentioned above, this was a cross-sectional study, which could not examine the causal relationship, so further prospective studies are need to solve this problem. Secondly, some other factors should be considered in future research, including dietary style, lifestyle and physical exercise. Last but not least, the recruitment of first-episode and drug-naive patients is a strength that the effects of antipsychotics and disease episodes can be eliminated, but the results might not be generalized to other patients with different
ethnic and clinical backgrounds like chronic patients receiving antipsychotics. Further studies should be conducted to validate our results in other patients with different ethnic and clinical backgrounds.

In summary, our results show a higher prevalence of MetS and metabolic disorders in smoking FEDN patients with schizophrenia compared with non-smoking patients. There were different contributing components and associated factors of MetS between smoking and non-smoking schizophrenia patients. Therefore, in clinical practice, attention should be paid to quitting smoking in schizophrenia patients, which is of great significance to avoid the occurrence of metabolic syndrome and metabolic disorders.
Conflicts of interest

The authors declare no conflicts of interest.

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Author Contribution

ZL, XL, and XYZ. designed the study. SW, YG and YC collected literatures and cleaned data. ZL and XW did statistical analysis. ZL and FW wrote the manuscript. X.Y.Z. reviewed and revised the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author XYZ upon reasonable request.
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Table 1. Demographic characteristics and metabolic indexes in patients and controls

| Demographic information | Patients                  | Controls                  | Diagnosis F (p) | Smoker F (p) | Diagnosis* Smoker F (p) |
|-------------------------|---------------------------|---------------------------|-----------------|-------------|------------------------|
| Age (years) \(^{a, c}\) | 33.15±11.36               | 32.61±11.25               | 36.56±11.97     | 32.85±11.37 | 3.28 (0.07)            |
| Education (years) \(^a\) | 10.72±3.38                | 11.29±3.25                | 10.61±3.70      | 11.74±3.27  | 0.77 (0.38)            |
| Sex, male/female \(^{a, b, c}\) | 73/29                     | 133/193                   | 55/6            | 133/241     |                        |
| Metabolic indexes       |                           |                           |                 |             |                        |
| BMI                     | 24.27±3.06                | 23.99±2.46                | 22.86±2.08      | 23.47±2.65  | 5.56 (0.02)            |
| Measure                      | Group 1        | Group 2        | Group 3        | p-value 1  | p-value 2  | p-value 3  |
|-----------------------------|----------------|----------------|----------------|------------|------------|------------|
| Waist circumference (cm)    | 83.59±12.98    | 79.53±11.89    | 74.66±11.54    | 25.90      | 0.22 (0.64)| 0.57 (0.45)|
| Systolic BP (mmHg)          | 124.98±13.20   | 117.99±12.70   | 112.90±11.09   | <0.001     | <0.001     | <0.001     |
| Diastolic BP (mmHg)         | 80.96±8.57     | 76.53±8.66     | 74.61±6.82     | <0.001     | <0.001     | <0.001     |
| Total cholesterol (mmol/L)  | 4.38±0.83      | 4.23±1.02      | 4.26±0.92      | 0.01 (0.93)| 0.553 (0.46)| 0.43 (0.51)|
| Triglycerides (mmol/L)      | 1.78±0.97      | 1.52±0.92      | 1.26±0.45      | <0.001     | 0.047 (0.46)| 1.78 (0.18)|
| HDLC (mmol/L)               | 1.28±0.34      | 1.35±0.39      | 1.47±0.50      | <0.001     | 0.09 (0.77)| 1.02 (0.31)|
| LDLC (mmol/L)               | 2.68±0.78      | 2.62±0.82      | 2.67±0.58      | 0.17 (0.68)| 0.64 (0.42)| 0.01 (0.94)|
| Fasting glucose (mmol/L)    | 5.08±0.83      | 4.94±0.87      | 4.94±0.69      | 10.96      | 0.80 (0.37)| 1.97 (0.16)|
| HbA1c (%)                   | 5.68±0.71      | 5.55±0.66      | 5.25±0.69      | 41.50 (0.01)| 0.18 (0.68)| 3.01 (0.08)|
| Insulin (uU/mL)             | 14.92±7.76     | 12.68±6.18     | 10.50±4.51     | <0.001     | (0.005)    |            |
| HOMA-IR                     | 3.51±1.97      | 2.89±1.59      | 2.34±1.23      | 2.14±1.07  | 56.35      | 9.72       | 2.73 (0.10)|
\( (<0.001) \quad (0.002) \)

\( ^a \) Indicates significant differences between smokers and non-smokers.

\( ^b \) Indicates significant differences between smoking and non-smoking patients.

\( ^c \) Indicates significant differences between smoking and non-smoking controls.

\( ^d \) The p values for metabolic parameters were adjusted for age, sex and education as covariate.

BP: Blood pressure; HDL-C: High-density lipoprotein (HDL) cholesterol; LDL-C: Low-density lipoprotein (HDL) cholesterol; HbA1c: Hemoglobin A1c; HOMA-IR: Homeostatic model assessment for insulin resistance;

There were no significant diagnosis* smoker interactive effect on any metabolic indexes after Bonferroni correction.
Table 2. Clinical characteristics of smoking and non-smoking patients with schizophrenia.

| Variable                      | Smokers (N=102) | Non-smokers (N=328) | F     | p*   |
|-------------------------------|-----------------|---------------------|-------|------|
| Age of onset (years)          | 31.86±11.73     | 31.14±11.69         | 0.69  | 0.41 |
| PANSS score                   |                 |                     |       |      |
| Positive symptoms             | 27.46±6.14      | 26.96±6.21          | 0.31  | 0.58 |
| Negative symptoms             | 32.17±8.84      | 29.25±9.03          | 6.18  | 0.01 |
| General psychopathology       | 62.01±14.44     | 58.89±14.90         | 2.32  | 0.13 |
| Total score                   | 121.64±24.03    | 115.10±24.92        | 3.82  | 0.05 |

*a* The p values were adjusted for sex as covariates.
Table 3. Difference in the prevalence of metabolic disorders and MetS between smoking and non-smoking patients

| Variable                     | Smoker (N=102) | Non-smoker (N=326) | B  | Wald χ2 | p  | OR   | 95%CI   |
|------------------------------|----------------|--------------------|----|---------|----|------|---------|
| Overweight                   | 39 (38.2%)     | 73 (22.4%)         | 0.71 | 7.90   | 0.005 | 2.03 | 1.24-3.34 |
| Elevated waist circumference | 36 (35.3%)     | 85 (26.1%)         | 0.47 | 3.52   | 0.06  | 1.61 | 0.98-2.64 |
| Elevated systolic BP         | 46 (45.1%)     | 61 (18.7%)         | 1.22 | 22.96  | <0.001 | 3.38 | 2.05-5.56 |
| Elevated diastolic BP        | 38 (37.3%)     | 71 (21.8%)         | 0.66 | 6.82   | 0.009 | 1.94 | 1.18-3.20 |
| Hypercholesterolemia         | 19 (18.6%)     | 52 (16.0%)         | 0.05 | 0.03   | 0.86  | 1.05 | 0.58-1.92 |
| Hypertriglyceridemia         | 47 (46.1%)     | 91 (27.9%)         | 0.79 | 10.50  | 0.001 | 2.20 | 1.37-3.54 |
| Hypo-HDLC                    | 30 (29.4%)     | 101 (31.0%)        | 0.05 | 0.04   | 0.83  | 1.06 | 0.64-1.75 |
| Hyper-LDLC                   | 28 (27.5%)     | 64 (19.6%)         | -0.01 | <0.001 | 0.99  | 0.99 | 0.46-2.14 |
| Elevated fasting glucose     | 24 (23.5%)     | 56 (17.2%)         | 0.46 | 2.53   | 0.11  | 1.58 | 0.90-2.78 |
| Elevated HbA1c               | 30 (29.4%)     | 79 (24.2%)         | 0.24 | 0.86   | 0.35  | 1.28 | 0.76-2.13 |
| Elevated insulin             | 16 (15.7%)     | 23 (7.1%)          | 0.89 | 5.97   | 0.02  | 2.44 | 1.19-4.97 |
|                |      |            |     |     |     |     |
|----------------|------|------------|-----|-----|-----|-----|
| Insulin resistance | 52 (51%) | 115 (35.3%) | 0.61 | 6.55 | 0.01 | 1.84 | 1.15-2.93 |
| MetS            | 38 (37.3%) | 44 (13.5%) | 1.46 | 27.34 | <0.001 | 4.31 | 2.49-7.44 |

* The p values were adjusted for sex as covariate.
Table 4. Demographic, clinical and metabolic parameters between Mets and Non-Mets patients

| Variable                        | Smoking patients       | Non-smoking patients | Smoker MetS | MetS | Smoker* MetS |
|---------------------------------|------------------------|----------------------|-------------|------|-------------|
|                                 | MetS (N=38)            | Non- MetS (N=64)     | (N=282)     |      |             |
| Age                             | 33.00±10.21            | 33.23±12.07          | 31.71±8.23  | 32.75±11.65 | 0.36 (0.55) |
| Education (Years)               | 10.97±3.95             | 10.56±3.01           | 10.68±3.65  | 11.38±3.18 | 0.05 (0.82) |
| Sex a,b,c,d                     | 32/6                   | 41/23                | 8/36        | 125/157 |             |
| Age of onset (Years)            | 31.37±10.51            | 32.15±12.47          | 31.08±8.66  | 31.30±12.10 | 0.44 (0.51) |
| Smoking years                   | 5.20±4.61              | 5.09±5.36            | -           | -     |             |
| Cigarettes per day              | 8.47±6.10              | 9.70±7.06            | -           | -     |             |
| Metabolic indexes               |                        |                      | Smoker e    | MetS e | Smoker* MetS e |
| BMI a,b                         | 25.59±2.76             | 25.48±3.45           | 23.49±2.98  | 23.16±2.36 | 0.06 (0.80) |
| Total cholesterol (mmol/L)      | 4.27±0.77              | 4.38±1.04            | 4.21±1.01   | 4.21±1.01 | 0.50 (0.48) |

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|                          | Mean ± Standard Deviation | p Value | Significance Level |
|--------------------------|---------------------------|---------|--------------------|
| **LDLC (mmol/L)**        |                           |         |                    |
| a                        | 2.94 ± 0.83               |         |                    |
| b                        | 2.53 ± 0.71               |         |                    |
|                          | 2.75 ± 0.79               |         |                    |
|                          | 2.59 ± 0.82               |         |                    |
|                          | 0.16 (0.69)               |         |                    |
|                          | 7.37 (0.01)               |         |                    |
|                          | 1.23 (0.27)               |         |                    |
| **HbA1c (%)**            |                           |         |                    |
| a,b                      | 5.87 ± 0.81               |         |                    |
|                          | 5.57 ± 0.62               |         |                    |
|                          | 5.79 ± 0.85               |         |                    |
|                          | 5.51 ± 0.62               |         |                    |
|                          | 0.23 (0.63)               |         |                    |
|                          | 10.90 (0.001)             |         |                    |
|                          | 0.01 (0.94)               |         |                    |
| **Insulin (uU/mL)**      |                           |         |                    |
| b                        | 16.62 ± 7.77              |         |                    |
|                          | 13.92 ± 7.63              |         |                    |
|                          | 14.50 ± 6.22              |         |                    |
|                          | 12.40 ± 6.14              |         |                    |
|                          | 3.58 (0.06)               |         |                    |
|                          | 7.94 (0.005)              |         |                    |
|                          | 0.07 (0.79)               |         |                    |
| **HOMA-IR**              |                           |         |                    |
| a,b                      | 4.22 ± 2.08               |         |                    |
|                          | 3.09 ± 1.79               |         |                    |
|                          | 3.92 ± 2.18               |         |                    |
|                          | 2.73 ± 1.41               |         |                    |
|                          | 2.16 (0.14)               |         |                    |
|                          | 29.52 (0.88)              |         |                    |
|                          | (<0.001)                  |         |                    |
| **MetS components**      |                           |         |                    |
| **Waist circumference (cm)** | 79.82 ± 12.05           |         |                    |
| a,b                      | 89.53 ± 12.89             |         |                    |
|                          | 77.98 ± 10.96             |         |                    |
|                          | 3.55 (0.06)               |         |                    |
|                          | 64.12 (0.05)              |         |                    |
|                          | 3.99 (0.05)               |         |                    |
|                          | (<0.001)                  |         |                    |
| **Systolic BP (mmHg)**   |                           |         |                    |
| a,b                      | 132.58 ± 9.43             |         |                    |
|                          | 120.47 ± 13.09            |         |                    |
|                          | 129.27 ± 12.09            |         |                    |
|                          | 116.22 ± 11.88            |         |                    |
|                          | 1.76 (0.19)               |         |                    |
|                          | 68.15 (0.39)              |         |                    |
|                          | 0.75 (0.97)               |         |                    |
|                          | (<0.001)                  |         |                    |
| **Diastolic BP (mmHg)**  |                           |         |                    |
| a,b                      | 85.40 ± 7.82              |         |                    |
|                          | 78.33 ± 7.92              |         |                    |
|                          | 82.18 ± 8.49              |         |                    |
|                          | 75.64 ± 8.36              |         |                    |
|                          | 4.37 (0.04)               |         |                    |
|                          | 40.32 (0.97)              |         |                    |
|                          | 0.002 (0.97)              |         |                    |
|                          | (<0.001)                  |         |                    |
| **Triglycerides (mmol/L)** | 2.38 ± 0.92               |         |                    |
| a,b                      | 1.42 ± 0.81               |         |                    |
|                          | 2.27 ± 1.54               |         |                    |
|                          | 1.41 ± 0.72               |         |                    |
|                          | 0.05 (0.82)               |         |                    |
|                          | 66.67 (0.97)              |         |                    |
|                          | 0.001 (0.97)              |         |                    |
|                          | (<0.001)                  |         |                    |
| **HDLC (mmol/L)**        |                           |         |                    |
| a,b                      | 1.10 ± 0.26               |         |                    |
|                          | 1.40 ± 0.34               |         |                    |
|                          | 1.13 ± 0.25               |         |                    |
|                          | 1.38 ± 0.40               |         |                    |
|                          | 1.21 (0.27)               |         |                    |
|                          | 35.68 (0.77)              |         |                    |
|                          | 0.09 (0.77)               |         |                    |
|                          | (<0.001)                  |         |                    |
| **Fasting glucose**      |                           |         |                    |
|                          | 5.75 ± 1.18               |         |                    |
|                          | 4.97 ± 0.55               |         |                    |
|                          | 5.86 ± 1.25               |         |                    |
|                          | 4.96 ± 0.66               |         |                    |
|                          | 0.26 (0.61)               |         |                    |
|                          | 66.79 (0.53)              |         |                    |
|                          | 0.39 (0.53)               |         |                    |
(mmol/L)\textsuperscript{a,b} (<0.001)

\textsuperscript{a} Indicates significant differences between MetS and non-MetS in smoking patients.

\textsuperscript{b} Indicates significant differences between MetS and non-MetS in non-smoking patients.

\textsuperscript{c} Indicates significant differences between smoking and non-smoking in MetS patients.

\textsuperscript{d} Indicates significant differences between smoking and non-smoking in non-MetS patients.

\textsuperscript{e} The \( p \) values for metabolic parameters were adjusted for sex as covariate.

BMI: Body mass index; LDLC: Low-density lipoprotein cholesterol; HbA1c: Hemoglobin A1c; HOMA-IR: Homeostatic model assessment for insulin resistance; BP: Blood pressure; HDLC: High-density lipoprotein cholesterol.
Table 5. Risk factors of MetS in clinical correlates and other metabolic components between smoking and non-smoking patients

| Variable      | B    | Wald χ² | p      | OR   | 95%CI   |
|---------------|------|---------|--------|------|--------|
| **Smoking patients** |      |         |        |      |        |
| BMI           | 0.26 | 10.65   | 0.001  | 1.30 | 1.11-1.53 |
| HOMA-IR       | 0.34 | 7.87    | 0.005  | 1.40 | 1.11-1.78 |
| **Non-smoking patients** |      |         |        |      |        |
| Sex           | 1.44 | 8.76    | 0.003  | 4.20 | 1.62-10.85 |
| BMI           | 0.37 | 21.15   | <0.001 | 1.45 | 1.24-1.70 |
| Insulin       | -0.41| 14.77   | <0.001 | 0.67 | 0.54-0.82 |
| HOMA-IR       | 1.73 | 20.10   | <0.001 | 5.65 | 2.65-12.05 |

BMI: Body mass index; HOMA-IR: Homeostatic model assessment for insulin resistance.