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REGULAR RESEARCH ARTICLE

Smoking Affects the Patterns of Metabolic Disorders and Metabolic Syndrome in Patients With First-Episode Drug-Naive Schizophrenia: A Large Sample Study Based on the Chinese Han Population

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Abstract

Objective: Although metabolic disorders and smoking are common in schizophrenia, few studies have investigated the effects of smoking on metabolic disorders or metabolic syndrome (MetS) in schizophrenia patients, especially in first-episode drug-naïve (FEDN) patients. We sought to investigate the differences in metabolic disorders and MetS between smoking and nonsmoking 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.

Results: FEDN schizophrenia patients had a higher smoking rate than controls (23.8% vs 14.0%, $P < .001$). After adjusting for confounding variables, the prevalence of MetS, overweight, hypertension, hypertriglyceridemia, elevated insulin, and insulin resistance in smoking patients was higher than those in nonsmoking patients, while overweight and hypertension were higher in the smoking controls than in nonsmoking controls (all $P < .05$). In smoking patients, triglyceridemia, high-density lipoprotein cholesterol, and fasting blood glucose were the main contributing components to MetS, while in nonsmoking patients, waist circumference, systolic blood pressure, triglyceridemia, high-density lipoprotein cholesterol, and fasting blood glucose were the main contributing components to MetS. In smoking patients, BMI and homeostatic model assessment for insulin resistance were associated factors of MetS (both $P < .05$). In nonsmoking patients, sex, BMI, insulin, and homeostatic model assessment for insulin resistance were associated factors of MetS (all $P < .05$).

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Significance Statement

It is well established that metabolic disorders and smoking are common in schizophrenia, but few studies have 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 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 nonsmoking patients with FEND schizophrenia.

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

Keywords: Metabolic disorders, metabolic syndrome, schizophrenia, smoking

Introduction

Schizophrenia is characterized by psychotic symptoms and cognitive deficts (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% shorter life expectancy than the general population (Mohamud et al., 2011). Many studies have shown that the leading cause of death in patients with schizophrenia is cardiovascular disease, which increases the risk of death by 3 times (Osby et al., 2000; Mohamud et al., 2011), while the main causes of cardiovascular disease are various metabolic disorders or metabolic syndrome (MetS) (Sullivan et al., 2009; Mitchell et al., 2013). MetS is characterized by central obesity, hypertension, and abnormal glucose 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 3 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; Šagud 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 Nybäck, 2005; Williams et al., 2005). In addition, patients with schizophrenia have great difficulties in quitting smoking in both the 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 nonsmoking 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 nonsmokers 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 nonsmoking patients with FEND schizophrenia in the following aspects: (1) the prevalence of metabolic disorders and MetS, (2) the main contributing components of MetS, and (3) the associated factors pattern of MetS. To our knowledge, this was the first study to investigate the differences in metabolic disorders and MetS between smoking and nonsmoking 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 Huilongguan Hospital. Informed consent was obtained from participants. A total 428 patients (206 males and 222 females) were recruited, and their inclusion criteria were: (1) 18 to 60 years old, (2) satisfied with the diagnostic criteria of schizophrenia according to the DSM-IV made by 2 independent psychiatrists using the Structure Clinical Interview for DSM-IV, (3) at first episode, (4) no previous treatment with psychotropic medicines, (5) the course of disease ≤5 years, and

Table 1. Demographic Characteristics and Metabolic Indexes in Patients and Controls

	Patients		Controls				
Demographic information	Smoker (n = 102)	Nonsmoker (n = 326)	Smoker (n = 61)	Nonsmoker (n = 374)	Diagnosis F (P)	Smoker F (P)	Diagnosis × smoker F (P)
Age (y)[a,c]	33.15 ± 11.36	32.61 ± 11.25	36.56 ± 11.97	32.85 ± 11.37	3.28 (.07)	4.35 (.04)	2.52 (.11)
Education (y)[a]	10.72 ± 3.38	11.29 ± 3.25	10.61 ± 3.70	11.74 ± 3.27	0.77 (.38)	4.86 (.03)	0.42 (.52)
Sex, male/female[a,b,c]	73/29	133/193	55/6	133/241			
Metabolic indexes							
BMI	24.27 ± 3.06	23.47 ± 2.65	23.99 ± 2.46	22.86 ± 2.08	5.56 (.02)	7.90 (.005)	0.08 (.78)
Waist circumference (cm)	83.59 ± 12.98	79.53 ± 11.89	79.37 ± 11.67	74.66 ± 11.54	25.90 (<.001)	0.22 (.64)	0.57 (.45)
Systolic BP (mmHg)	124.98 ± 13.20	117.99 ± 12.70	121.13 ± 12.08	112.90 ± 11.09	19.50 (<.001)	30.86 (<.001)	0.03 (.86)
Diastolic BP (mmHg)	80.96 ± 8.57	76.53 ± 8.66	77.44 ± 8.30	74.61 ± 6.82	16.93 (<.001)	16.75 (<.001)	2.13 (.15)
Total cholesterol (mmol/L)	4.38 ± 0.83	4.23 ± 1.02	4.33 ± 0.84	4.26 ± 0.92	0.01 (.93)	0.553 (0.46)	0.43 (.51)
Triglycerides (mmol/L)	1.78 ± 0.97	1.52 ± 0.92	1.35 ± 0.58	1.26 ± 0.45	29.62 (<.001)	3.96 (.047)	1.78 (.18)
HDLC (mmol/L)	1.28 ± 0.34	1.35 ± 0.39	1.47 ± 0.50	1.49 ± 0.32	27.84 (<.001)	0.09 (.77)	1.02 (.31)
LDLC (mmol/L)	2.68 ± 0.78	2.62 ± 0.82	2.67 ± 0.58	2.57 ± 0.74	0.17 (.68)	0.64 (.42)	0.01 (.94)
Fasting glucose (mmol/L)	5.26 ± 0.92	5.08 ± 0.83	4.94 ± 0.87	4.94 ± 0.69	10.96 (.001)	0.80 (.37)	1.97 (.16)
HbA1c (%)	5.68 ± 0.71	5.55 ± 0.66	5.25 ± 0.69	5.30 ± 0.50	41.50 (.01)	0.18 (.68)	3.01 (.08)
Insulin (μU/mL)	14.92 ± 7.76	12.68 ± 6.18	10.50 ± 4.51	9.75 ± 4.54	52.04 (<.001)	7.92 (.005)	2.13 (.15)
HOMA-IR	3.51 ± 1.97	2.89 ± 1.59	2.34 ± 1.23	2.14 ± 1.07	56.35 (<.001)	9.72 (.002)	2.73 (.10)

Abbreviations: 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.
[a]Indicates significant differences between smokers and nonsmokers.
[b]Indicates significant differences between smoking and nonsmoking patients.
[c]Indicates significant differences between smoking and nonsmoking controls.
[d]The P values for metabolic parameters were adjusted for age, sex, and education as covariate.
There were no significant diagnosis × smoker interactive effect on any metabolic indexes after Bonferroni correction.

Table 2. Clinical Characteristics of Smoking and Nonsmoking Patients With Schizophrenia

Variable	Smokers (n = 102)	Nonsmokers (n = 328)	F	P[a]
Age of onset (y)	31.86 ± 11.73	31.14 ± 11.69	0.69	.41
PANSS score				
Positive symptoms	27.46 ± 6.14	26. 96 ± 6.21	0.31	.58
Negative symptoms	32.17 ± 8.84	29.25 ± 9.03	6.18	.01
General psychopathology	62.01 ± 14.44	58.89 ± 14.90	2.32	.13
Total score	121.64 ± 24.03	115.10 ± 24.92	3.82	.05

Abbreviations: PANSS, Positive and Negative Syndrome Scale.
[a]The *P* values were adjusted for sex as covariates.

(6) 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 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 drug abuse/dependence were excluded. Pregnancy was identified by urine test. Alcohol or drug abuse/dependence was 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 Structure Clinical Interview for DSM-IV and PANSS. After training, the inter-rater correlation coefficients were >0.8.

Physical and Biochemical Measurements

The physical indicators such as blood pressure, weight, height, and waist circumference were determined by nurses. Biochemical indexes were detected in plasma samples collected after fasting overnight, including triglyceride, total cholesterol, 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 criteria (A. M. H. Lee et al., 2018), patients diagnosed with MetS should meet at least 3 of the following 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 ≥130 and/or diastolic BP ≥85 mm Hg or with drug treatment, (5) fasting blood glucose ≥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/m^2), 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 >24.9 μU/mL), and insulin resistance (HOMA-IR > 3) (Spence et al., 2019). In this study, only 8 of 428 patients (1.87%) were obese, and we merged overweight and obesity into 1 group.

Statistical Analysis

The normality of the variable distribution was determined using the Kolmogorov-Smirnov test. Chi-square test and ANOVA were performed for categorical variables and continuous variables, respectively. A 2-way ANCOVA (diagnosis × smoker) was conducted to explore the differences in metabolic indexes between smokers and nonsmokers, 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 nonsmokers 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 2-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 nonsmokers in patient and control groups, respectively. Finally, in patient group, to detect the contribution of metabolic components (5 components) to MetS, logistic regression was conducted in smoking and nonsmoking 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 nonsmoking patients respectively. The variables with $P < .1$ in univariate analysis were further included in logistic regression. Bonferroni corrections were conducted for multiple tests. All statistical analyses were calculated through SPSS version 23.0. The significant *P* value was set to <.05 (2-tailed test).

Results

Demography and Clinical Information of Participants

There were no differences in age, sex, and education levels between patients and controls (all $P > .05$). 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 ($\chi^2 = 13.55$, $P < .001$).

As shown in Table 1, smokers were older than nonsmokers (F = 4.35, $P = 0.04$), and smokers had fewer years of education than nonsmokers (F = 4.86, $P = 0.03$). Male participants smoke more commonly than female participants ($\chi^2 = 87.52$, $P < .001$). Further, men had a significant higher smoking rate than women in both the patients ($\chi^2 = 29.47$, $P < .001$) and the controls ($\chi^2 = 63.72$, $P < .001$). 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 Tables 1 and 2, there was difference in sex, but not in age, education, and age of onset between smoking and nonsmoking patients. Therefore, sex was controlled when comparing the differences in the prevalence of metabolic disorders and MetS between smoking and nonsmoking patients.

Physical and Biochemical Indexes in Patient and Control Groups

After controlling for age, sex, and education as covariates, 2-way ANCOVA showed that schizophrenia patients had higher waist circumference and levels of systolic BP, diastolic BP, triglycerides, fasting glucose, insulin, and HOMA-IR, but lower levels of HDLC (all $P_{Bonferroni} < .05$) compared with healthy controls (Table 1). There was no significant diagnosis × smoker interactive effect on any metabolic indexes after Bonferroni correction (all $P_{Bonferroni} > .05$).

Difference in Clinical Symptoms and the Prevalence of Each Metabolic Disorder Between Smoking and Nonsmoking Patients

As shown in Table 2, smoking patients experienced higher PANSS negative scores (F = 6.18, $P = .01$, $P_{Bonferroni} = .04$) than nonsmoking patients. There was no difference in other PANSS subscales or total score between smoking and nonsmoking patients.

Compared with nonsmoking patients, smoking patients had higher prevalence rates of overweight ($\chi^2 = 10.09$, $P = .001$), elevated systolic BP ($\chi^2 = 28.85$, $P < .0001$), elevated diastolic BP ($\chi^2 = 9.80$, $P = .002$), hypertriglyceridemia ($\chi^2 = 11.73$, $P = .001$), elevated insulin ($\chi^2 = 6.99$, $P = .008$), insulin resistance ($\chi^2 = 8.05$, $P = .005$), and MetS ($\chi^2 = 28.31$, $P < .001$). 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 nonsmoking patients ($P = .005$, $P < .001$, $P = .009$, $P = .001$, $P = .02$, $P = .01$, $P < .001$, respectively).

In health controls, only the prevalence rates of overweight, elevated systolic BP, and elevated diastolic BP were higher in smokers than those in nonsmokers ($P = .01$, $P < .001$, $P < .001$, respectively).

Difference in the Contributing Components to MetS Between Smoking and Nonsmoking Patients

As shown in Table 4, 2-way ANCOVA (smoker × MetS) showed that the interaction between smoker and MetS had no significant effect on any MetS components (all $P_{Bonferroni} > .05$). Further, we investigated the contribution of 5 metabolic components to MetS in smoking and nonsmoking patients respectively. There were different patterns of contributing components between smoking and nonsmoking patients. Logistic regression analysis showed that in smoking patients, triglyceridemia ($P = .001$, OR = 5.50, 95% CI: 2.02–15.01), HDLC ($P = .03$, OR = 0.04, 95% CI: 0.002–0.67), and fasting blood glucose ($P = .03$, OR = 3.14, 95% CI:

Table 3. Difference in the Prevalence of Metabolic Disorders and MetS Between Smoking and Nonsmoking Patients

Variable	Smoker (n = 102)	Nonsmoker (n = 326)	B	Wald $\chi 2$	P[a]	OR	95% CI
Overweight	39 (38.2%)	73 (22.4%)	0.71	7.90	.005	2.03	1.24–3.34
Elevated waist circumference	36 (35.3%)	85 (26.1%)	0.47	3.52	.06	1.61	0.98–2.64
Elevated systolic BP	46 (45.1%)	61 (18.7%)	1.22	22.96	<.001	3.38	2.05–5.56
Elevated diastolic BP	38 (37.3%)	71 (21.8%)	0.66	6.82	.009	1.94	1.18–3.20
Hypercholesterolemia	19 (18.6%)	52 (16.0%)	0.05	0.03	.86	1.05	0.58–1.92
Hypertriglyceridemia	47 (46.1%)	91 (27.9%)	0.79	10.50	.001	2.20	1.37–3.54
Hypo-HDLC	30 (29.4%)	101 (31.0%)	0.05	0.04	.83	1.06	0.64–1.75
Hyper-LDLC	28 (27.5%)	64 (19.6%)	-0.01	<0.001	.99	0.99	0.46–2.14
Elevated fasting glucose	24 (23.5%)	56 (17.2%)	0.46	2.53	.11	1.58	0.90–2.78
Elevated HbA1c	30 (29.4%)	79 (24.2%)	0.24	0.86	.35	1.28	0.76–2.13
Elevated insulin	16 (15.7%)	23 (7.1%)	0.89	5.97	.02	2.44	1.19–4.97
Insulin resistance	52 (51%)	115 (35.3%)	0.61	6.55	.01	1.84	1.15–2.93
MetS	38 (37.3%)	44 (13.5%)	1.46	27.34	<.001	4.31	2.49–7.44

Abbreviations: BP, Blood pressure; HDLC, High-density lipoprotein cholesterol; LDLC, Low-density lipoprotein cholesterol; HbA1c, Hemoglobin A1c; MetS, Metabolic syndrome.

[a]The P values were adjusted for sex as covariate.

1.15–8.52) were the main contributing components to MetS after adjusting for sex as a covariate. In nonsmoking patients, waist circumference ($P < .001$, OR = 1.08, 95% CI: 1.03–1.12), systolic BP ($P = .002$, 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 ($P < .001$, 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 Nonsmoking Patients

We further investigated whether there were different patterns of clinical correlates or metabolic parameters (except for the 5 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 $P < .05$). Then logistic regression analysis was 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 ($P = .001$ and $P = .005$, respectively).

In nonsmoking patients, BMI, HbA1c, insulin, and HOMA-IR were higher in MetS patients than those in non-MetS patients (all $P < .05$). Then logistic regression analysis was 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 ($P = .003$, $P < .001$, $P < .001$, and $P < .001$, respectively).

Discussion

The main results of this study were as follows: (1) FEDN patients with schizophrenia had a 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 nonsmoking patients; and (3) there were different patterns of the contributing components and related associated factors for MetS between smoking and nonsmoking patients.

Our study provided evidence that without the effects of antipsychotics, patients with first-episode schizophrenia had an increased smoking rate compared with controls. The reasons for the increased smoking rate in schizophrenia patients include biological and nonbiological 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, a previous study demonstrated that chronic schizophrenia patients who smoked had fewer symptoms than nonsmoking 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 nonsmoking patients.

This was the first study, to our knowledge, to demonstrate that smoking FEDN schizophrenia patients had a higher prevalence of MetS and metabolic disorders, including overweight, hypertension, hypertriglyceridemia, elevated insulin, and insulin resistance, than nonsmoking patients. Interestingly, in the healthy control group, only the prevalence of overweight and hypertension in the smoking controls were higher than those in nonsmoking 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 2 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-Müller 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 and 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). Many studies strongly support the hypothesis that the pro-inflammatory pathway is also involved in the pathophysiology of schizophrenia (Müller, 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). This evidence suggests that the immune inflammatory mechanism is involved in smoking, schizophrenia, and metabolic disorders/MetS 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 nonsmokers with schizophrenia (Bobes et al., 2010; Vancampfort et al., 2013). 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

Table 4. Demographic, Clinical, and Metabolic Parameters Between MetS and Non-MetS Patients

	Smoking patients		Non-smoking patients		Smoker	MetS	Smoker* MetS
Variable	MetS (n = 38)	Non- MetS (n = 64)	MetS (n = 44)	Non- MetS (n = 282)	F (P)	F (P)	F (P)
Age	33.00 ± 10.21	33.23 ± 12.07	31.71 ± 8.23	32.75 ± 11.65	0.36 (.55)	0.19 (.66)	0.08 (.77)
Education (y)	10.97 ± 3.95	10.56 ± 3.01	10.68 ± 3.65	11.38 ± 3.18	0.05 (.82)	0.13 (.72)	2.17 (.14)
Sex[a–d]	32/6	41/23	8/36	125/157			
Age of onset (y)	31.37 ± 10.51	32.15 ± 12.47	30.08 ± 8.66	31.30 ± 12.10	0.44 (.51)	0.42 (.52)	0.02 (.88)
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	23.49 ± 2.98	25.48 ± 3.45	23.16 ± 2.36	0.06 (.80)	43.01 (<.001)	0.66 (.42)
Total cholesterol (mmol/L)	4.56 ± 0.89	4.27 ± 0.77	4.38 ± 1.04	4.21 ± 1.01	0.50 (.48)	3.33 (.07)	0.10 (.76)
LDLC (mmol/L)[a]	2.94 ± 0.83	2.53 ± 0.71	2.75 ± 0.79	2.59 ± 0.82	0.16 (.69)	7.37 (.01)	1.23 (.27)
HbA1c (%)[a,b]	5.87 ± 0.81	5.57 ± 0.62	5.79 ± 0.85	5.51 ± 0.62	0.23 (.63)	10.90 (.001)	0.01 (.94)
Insulin (uU/mL)[b]	16.62 ± 7.77	13.92 ± 7.63	14.50 ± 6.22	12.40 ± 6.14	3.58 (.06)	7.94 .005)	0.07 (.79)
HOMA-IR[a,b]	4.22 ± 2.08	3.09 ± 1.79	3.92 ± 2.18	2.73 ± 1.41	2.16 (.14)	29.52 (<.001)	0.02 (.88)
MetS components							
Waist circumference (cm)[a,b]	89.93 ± 12.12	79.82 ± 12.05	89.53 ± 12.89	77.98 ± 10.96	3.55 (.06)	64.12 (< .001)	3.99 (.05)
Systolic BP (mmHg)[a,b]	132.58 ± 9.43	120.47 ± 13.09	129.27 ± 12.09	116.22 ± 11.88	1.76 (.19)	68.15 (<.001)	0.75 (.39)
Diastolic BP (mmHg)[a,b]	85.40 ± 7.82	78.33 ± 7.92	82.18 ± 8.49	75.64 ± 8.36	4.37 (.04)	40.32 (<.001)	0.002 (.97)
Triglycerides (mmol/L)[a,b]	2.38 ± 0.92	1.42 ± 0.81	2.27 ± 1.54	1.41 ± 0.72	0.05 (.82)	66.67 (<.001)	0.001 (.97)
HDLC (mmol/L)[a,b]	1.10 ± 0.26	1.40 ± 0.34	1.13 ± 0.25	1.38 ± 0.40	1.21 (.27)	35.68 (<.001)	0.09 (.77)
Fasting glucose (mmol/L)[a,b]	5.75 ± 1.18	4.97 ± 0.55	5.86 ± 1.25	4.96 ± 0.66	0.26 (.61)	66.79 (<.001)	0.39 (.53)

Abbreviations: BMI, body mass index; BP, blood pressure; HbA1c, hemoglobin A1c; HDLC, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; LDLC, low-density lipoprotein cholesterol; MetS, metabolic syndrome.

[a]Indicates significant differences between MetS and non-MetS in smoking patients.

[b]Indicates significant differences between MetS and non-MetS in nonsmoking patients.

[c]Indicates significant differences between smoking and nonsmoking in MetS patients.

[d]Indicates significant differences between smoking and nonsmoking in non-MetS patients.

[e]The *P* values for metabolic parameters were adjusted for sex as covariate.

Table 5. Risk Factors of MetS in Clinical Correlates and Other Metabolic Components Between Smoking and Nonsmoking Patients

Variable	B	Wald $\chi 2$	P	OR	95% CI
Smoking patients					
BMI	0.26	10.65	.001	1.30	1.11–1.53
HOMA-IR	0.34	7.87	.005	1.40	1.11–1.78
Non-smoking patients					
Sex	1.44	8.76	.003	4.20	1.62–10.85
BMI	0.37	21.15	<.001	1.45	1.24–1.70
Insulin	–0.41	14.77	<.001	0.67	0.54–0.82
HOMA-IR	1.73	20.10	<.001	5.65	2.65–12.05

Abbreviations: BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance; MetS, metabolic syndrome.

effect on metabolic disorders in schizophrenia patients than in the general population. In addition, we found that smoking and nonsmoking 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 nonsmoking patients were waist circumference, systolic BP, triglyceridemia, HDLC, and fasting blood glucose. Regarding the associated factors of MetS, there were different patterns between smoking and nonsmoking patients. BMI and HOMA-IR were associated factors for MetS in both smoking and nonsmoking patients, and sex and insulin were associated factors for MetS in nonsmoking patients. Our previous study also indicated sex difference in metabolic disorder patterns in schizophrenia patients (Zhou et al., 2020a). The underlying mechanisms of these different patterns between smoking and nonsmoking patients remain obscure and need further investigation. It is worth noting that previous meta-analysis showed that in the general population, heavy smokers had a stronger correlation with the risk of MetS 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 noted 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 needed to solve this problem. Secondly, some other factors should be considered in future research, including dietary style, lifestyle, and physical exercise. Lastly, the recruitment of FEDN patients is a strength because 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 such as 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 nonsmoking patients. There were different contributing components and associated factors of MetS between smoking and nonsmoking schizophrenia patients. Therefore, in clinical practice, attention should be paid to quitting smoking in schizophrenia patients, which is of great importance to avoid the occurrence of MetS and metabolic disorders.

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Author Contribution

Z.L., X.L., and X.Y.Z. designed the study. S.W., Y.G., and Y.C. collected literatures and cleaned data. Z.L. and X.W. conducted statistical analysis. Z.L. and F.W. 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 X.Y.Z. on reasonable request.

Statement of Interest

The authors declare no conflicts of interest.

References

Aguilar MC, Gurpegui M, Diaz FJ, de Leon J (2005) Nicotine dependence and symptoms in schizophrenia: naturalistic study of complex interactions. Br J Psychiatry 186:215–221.

An HM, Tan YL, Tan SP, Shi J, Wang ZR, Yang FD, Huang XF, Soars JC, Kosten TR, Zhang XY (2016) Smoking and serum lipid profiles in schizophrenia. Neurosci Bull 32:383–388.

Andreassen OA, Djurovic S, Thompson WK, Schork AJ, Kendler KS, O'Donovan MC, Rujescu D, Werge T, van de Bunt M, Morris AP, McCarthy MI, Roddey JC, McEvoy LK, Desikan RS, Dale AM; International Consortium for Blood Pressure GWAS; Diabetes Genetics Replication and Meta-analysis Consortium; Psychiatric Genomics Consortium Schizophrenia Working Group (2013) Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors. Am J Hum Genet 92:197–209.

Berlin I (2008) Smoking-induced metabolic disorders: a review. Diabetes Metab 34:307–314.

Bobes J, Arango C, Garcia-Garcia M, Rejas J (2010) Healthy lifestyle habits and 10-year cardiovascular risk in schizophrenia spectrum disorders: an analysis of the impact of smoking tobacco in the CLAMORS schizophrenia cohort. Schizophr Res 119:101–109.

Britvic D, Maric NP, Doknic M, Pekic S, Andric S, Jasovic-Gasic M, Popovic V (2013) Metabolic issues in psychotic disorders with the focus on first-episode patients: a review. Psychiatr Danub 25:410–415.

Cena H, Fonte ML, Turconi G (2011) Relationship between smoking and metabolic syndrome. Nutr Rev 69:745–753.

Cerimele JM, Katon WJ (2013) Associations between health risk behaviors and symptoms of schizophrenia and bipolar disorder: a systematic review. Gen Hosp Psychiatry 35:16–22.

Chambers RA, Krystal JH, Self DW (2001) A neurobiological basis for substance abuse comorbidity in schizophrenia. Biol Psychiatry 50:71–83.

Dalack GW, Healy DJ, Meador-Woodruff JH (1998) Nicotine dependence in schizophrenia: clinical phenomena and laboratory findings. Am J Psychiatry 155:1490–1501.

de Leon J, Diaz FJ (2005) A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr Res 76:135–157.

Deng T, Lyon CJ, Minze LJ, Lin J, Zou J, Liu JZ, Ren Y, Yin Z, Hamilton DJ, Reardon PR, Sherman V, Wang HY, Phillips KJ, Webb P, Wong ST, Wang RF, Hsueh WA (2013) Class II major histocompatibility complex plays an essential role in obesity-induced adipose inflammation. Cell Metab 17:411–422.

George TP, Ziedonis DM, Feingold A, Pepper WT, Satterburg CA, Winkel J, Rounsaville BJ, Kosten TR (2000) Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. Am J Psychiatry 157:1835–1842.

Hansen T, et al. (2011) At-risk variant in TCF7L2 for type II diabetes increases risk of schizophrenia. Biol Psychiatry 70:59–63.

Hosseinzadeh A, Thompson PR, Segal BH, Urban CF (2016) Nicotine induces neutrophil extracellular traps. J Leukoc Biol 100:1105–1112.

Kaur G, Bagam P, Pinkston R, Singh DP, Batra S (2018) Cigarette smoke-induced inflammation: NLRP10-mediated mechanisms. Toxicology 398-399:52–67.

Kendler KS, Neale MC, MacLean CJ, Heath AC, Eaves LJ, Kessler RC (1993) Smoking and major depression. A causal analysis. Arch Gen Psychiatry 50:36–43.

Lane JM, Liang J, Vlasac I, Anderson SG, Bechtold DA, Bowden J, Emsley R, Gill S, Little MA, Luik AI, Loudon A, Scheer FA, Purcell SM, Kyle SD, Lawlor DA, Zhu X, Redline S, Ray DW, Rutter MK, Saxena R (2017) Genome-wide association analyses of sleep disturbance traits identify new loci and highlight shared genetics with neuropsychiatric and metabolic traits. Nat Genet 49:274–281.

Lee AMH, Ng CG, Koh OH, Gill JS, Aziz SA (2018) Metabolic syndrome in first episode schizophrenia, based on the National Mental Health Registry of Schizophrenia (NMHR) in a General Hospital in Malaysia: a 10-year retrospective cohort study. Int J Environ Res Public Health 15:933.

Lee J, Nurjono M, Wong A, Salim A (2012) Prevalence of metabolic syndrome among patients with schizophrenia in Singapore. Ann Acad Med Singap 41:457–462.

Leonard S, Gault J, Hopkins J, Logel J, Vianzon R, Short M, Drebing C, Berger R, Venn D, Sirota P, Zerbe G, Olincy A, Ross RG, Adler LE, Freedman R (2002) Association of promoter variants in the alpha7 nicotinic acetylcholine receptor subunit gene with an inhibitory deficit found in schizophrenia. Arch Gen Psychiatry 59:1085–1096.

Li Z, Liu L, Lin W, Zhou Y, Zhang G, Du X, Li Y, Tang W, Zhang X (2020) NRG3 contributes to cognitive deficits in chronic patients with schizophrenia. Schizophr Res 215:134–139.

LLerena A, de la Rubia A, Peñas-Lledó EM, Diaz FJ, de Leon J (2003) Schizophrenia and tobacco smoking in a Spanish psychiatric hospital. Schizophr Res 60:313–317.

Lv Q, Hu Q, Zhang W, Huang X, Zhu M, Geng R, Cheng X, Bao C, Wang Y, Zhang C, He Y, Li Z, Yi Z (2020) Disturbance of oxidative stress parameters in treatment-resistant bipolar disorder and their association with electroconvulsive therapy response. Int J Neuropsychopharmacol 23:207–216.

Malan-Müller S, Kilian S, van den Heuvel LL, Bardien S, Asmal L, Warnich L, Emsley RA, Hemmings SM, Seedat S (2016) A systematic review of genetic variants associated with metabolic syndrome in patients with schizophrenia. Schizophr Res 170:1–17.

Manzella F, Maloney SE, Taylor GT (2015) Smoking in schizophrenic patients: a critique of the self-medication hypothesis. World J Psychiatry 5:35–46.

Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M (2013) Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders–a systematic review and meta-analysis. Schizophr Bull 39:306–318.

Mohamud WN, Ismail AA, Sharifuddin A, Ismail IS, Musa KI, Kadir KA, Kamaruddin NA, Yaacob NA, Mustafa N, Ali O, Harnida S, Bebakar WM (2011) Prevalence of metabolic syndrome and its risk factors in adult Malaysians: results of a nationwide survey. Diabetes Res Clin Pract 91:239–245.

Müller N (2018) Inflammation in schizophrenia: pathogenetic aspects and therapeutic considerations. Schizophr Bull 44:973–982.

Osby U, Correia N, Brandt L, Ekbom A, Sparén P (2000) Mortality and causes of death in schizophrenia in Stockholm County, Sweden. Schizophr Res 45:21–28.

Penninx BWJH, Lange SMM (2018) Metabolic syndrome in psychiatric patients: overview, mechanisms, and implications. Dialogues Clin Neurosci 20:63–73.

Postolache TT, Del Bosque-Plata L, Jabbour S, Vergare M, Wu R, Gragnoli C (2019) Co-shared genetics and possible risk gene pathway partially explain the comorbidity of schizophrenia, major depressive disorder, type 2 diabetes, and metabolic syndrome. Am J Med Genet B Neuropsychiatr Genet 180:186–203.

Reddy P, Lent-Schochet D, Ramakrishnan N, McLaughlin M, Jialal I (2019) Metabolic syndrome is an inflammatory disorder: a conspiracy between adipose tissue and phagocytes. Clin Chim Acta 496:35–44.

Sacco KA, Bannon KL, George TP (2004) Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders. J Psychopharmacol 18:457–474.

Šagud M, Vuksan-Ćusa B, Jakšić N, Mihaljević-Peleš A, Rojnić Kuzman M, Pivac N (2018) Smoking in schizophrenia: an updated review. Psychiatr Danub 30:216–223.

Slagter SN, van Vliet-Ostaptchouk JV, Vonk JM, Boezen HM, Dullaart RP, Kobold AC, Feskens EJ, van Beek AP, van der Klauw MM, Wolffenbuttel BH (2013) Associations between smoking, components of metabolic syndrome and lipoprotein particle size. BMC Med 11:195.

Spence JD, Viscoli CM, Inzucchi SE, Dearborn-Tomazos J, Ford GA, Gorman M, Furie KL, Lovejoy AM, Young LH, Kernan WN; IRIS Investigators (2019) Pioglitazone therapy in patients with stroke and prediabetes: a post hoc analysis of the IRIS randomized clinical trial. JAMA Neurol 76:526–535.

Strand JE, Nybäck H (2005) Tobacco use in schizophrenia: a study of cotinine concentrations in the saliva of patients and controls. Eur Psychiatry 20:50–54.

Stubbs B, Vancampfort D, De Hert M, Mitchell AJ (2015) The prevalence and predictors of type two diabetes mellitus in people with schizophrenia: a systematic review and comparative meta-analysis. Acta Psychiatr Scand 132:144–157.

Su Y, Yang L, Li Z, Wang W, Xing M, Fang Y, Cheng Y, Lin GN, Cui D (2021) The interaction of ASAH1 and NGF gene involving in neurotrophin signaling pathway contributes to schizophrenia susceptibility and psychopathology. Prog Neuropsychopharmacol Biol Psychiatry 104:110015.

Sullivan PF, et al. (2009) Genome-wide association for major depressive disorder: a possible role for the presynaptic protein piccolo. Mol Psychiatry 14:359–375.

Sun K, Liu J, Ning G (2012) Active smoking and risk of metabolic syndrome: a meta-analysis of prospective studies. Plos One 7:e47791.

Vancampfort D, Probst M, Scheewe T, De Herdt A, Sweers K, Knapen J, van Winkel R, De Hert M (2013) Relationships between physical fitness, physical activity, smoking and metabolic and mental health parameters in people with schizophrenia. Psychiatry Res 207:25–32.

Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, Rosenbaum S, Correll CU (2015) Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry 14:339–347.

Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J (2007) Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 298:2654–2664.

Williams JM, Ziedonis DM, Abanyie F, Steinberg ML, Foulds J, Benowitz NL (2005) Increased nicotine and cotinine levels in smokers with schizophrenia and schizoaffective disorder is not a metabolic effect. Schizophr Res 79:323–335.

Zhou Y, Song X, Guo Y, Lang X, Li Z, Zhang XY (2020a) Sex differences in metabolic disorder patterns of first-episode drug-naive patients with schizophrenia. Psychoneuroendocrinology 124:105061.

Zhou Y, Li Y, Meng Y, Wang J, Wu F, Ning Y, Li Y, Cassidy RM, Li Z, Zhang XY (2020b) Neuregulin 3 rs10748842 polymorphism contributes to the effect of body mass index on cognitive impairment in patients with schizophrenia. Transl Psychiatry 10:62.

Zhou Y, Ren W, Sun Q, Yu KM, Lang X, Li Z, Zhang XY (2021) The association of clinical correlates, metabolic parameters, and thyroid hormones with suicide attempts in first-episode and drug-naïve patients with major depressive disorder comorbid with anxiety: a large-scale cross-sectional study. Transl Psychiatry 11:97.

Zhu S, Zhao L, Fan Y, Lv Q, Wu K, Lang X, Li Z, Yi Z, Geng D (2020) Interaction between TNF-α and oxidative stress status in first-episode drug-naïve schizophrenia. Psychoneuroendocrinology 114:104595.