



## Metabolic syndrome and 10-year risk of cardiovascular events among schizophrenia inpatients treated with antipsychotics

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### Abstract

**Background:** The metabolic syndrome is highly prevalent among patients with schizophrenia. This study was conducted to determine the prevalence of metabolic syndrome and the risk of cardiovascular disease in the next 10 years among schizophrenic patients.

**Methods:** This cross sectional study was performed on 100 Iranian patients with schizophrenia in 2016. The prevalence of metabolic syndrome was determined by adult treatment panel III criteria, and 10-year cardiovascular risk was calculated by Framingham Risk Score. SPSS software was used to perform statistical analysis. Chi-square and Fisher's exact or extended Fisher's exact tests were used to compare dichotomous variables. Also, Mann-Whitney U test was applied to compare the quantitative variables. Significance level was considered to be less than or equal to 0.05.

**Results:** In this study, 83 participants (83%) were male and 17 (17%) were female. The prevalence of metabolic syndrome was 27% (21.7% in males and 52.9% in females,  $p=0.015$ ). Among all components of metabolic syndrome, low HDL-C in men and abdominal obesity in females were the most common disorders. Based on Framingham Risk Score, 76%, 16%, and 8% of patients had low, intermediate, and high level of risk, respectively. A significant difference was observed between the level of risk among participants with and without metabolic syndrome ( $p=0.042$ ).

**Conclusion:** In this study, patients with schizophrenia showed a high prevalence of metabolic syndrome, but most of them had low risk of developing cardiovascular disease. These results suggest regular screening and early interventions to modify the risk factors of metabolic syndrome.

**Keywords:** Antipsychotic, Cardiovascular disease, Metabolic syndrome, Schizophrenia

**Conflicts of Interest:** None declared

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### Introduction

Metabolic syndrome (MetS) is a multiplex disorder characterized by several risk factors (1). This disorder can

increase the risk of cardiovascular diseases (CVD) (1, 2). Thus, diagnosis of MetS seems to be a good idea for iden-

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#### ↑What is “already known” in this topic:

Metabolic syndrome (MetS) is a collection of metabolic disorders associated with increased risk of developing cardiovascular disease (CVD). Patients with schizophrenia, due to medications or unhealthy lifestyle, may be at greater risk of developing MetS. Furthermore, CVD risk in these patients may be higher than the general population.

#### →What this article adds:

Considering the lack of information about the prevalence of MetS and level of developing CVD risk in patients suffering from schizophrenia in Iran, the authors aimed to conduct this study. Also, here, it was found that the patients had a high prevalence of MetS, but most of them had a low risk of developing CVD.

tifying the high-risk individuals (3).

The mortality rate of patients with schizophrenia is 2 to 3 times higher than the general population (4, 5). Although suicide is an important cause of death among these patients, more cases of mortality are attributed to natural causes of death (5) and cardiovascular diseases are the number one cause (6).

Schizophrenic patients have a higher prevalence of MetS because of several factors such as physical inactivity, unhealthy diet, life stressors, and antipsychotic drugs (7). Many investigators have reported a high prevalence of conventional risk factors for CVD, especially MetS, in patients with schizophrenia (8-10). For example, Grover et al reported that the prevalence of metabolic syndrome among Indian patients was 40% (11). In Malaysia, Said et al found that the prevalence of MetS in patients with schizophrenia was 46.7% (10). Other researchers reported 38.1% prevalence among Egyptian patients (12), 51% among Australian patients (13), and 67.6% in British patients (14). In a study by Goff et al, 10-year risk of coronary heart disease (CHD) for male and female schizophrenic patients were significantly higher than the controls (9.4% vs 7.0% and 6.3% vs 4.2%, respectively) (15). In Cardiovascular Lipid and Metabolic Outcomes Research in Schizophrenia (CLAMORS study) by Bobes et al, the overall risk of CHD in 10 years was 6.8% in patients with schizophrenia. In addition, this risk was significantly greater in males than in females (8.3% vs 4.5%) (16).

In Iran, however, only several studies were conducted on the prevalence of MetS and risk of CVD in individuals with schizophrenia (17-20). Considering this lack of information, some comprehensive programs have been established for preventing CVD in these patients.

The present study aimed to determine the prevalence of MetS and to estimate the 10-year risk of CVD in patients with schizophrenia who had been treated with antipsychotic drugs in Yazd province, in the center of Iran.

## Methods

### Study design

In 2016, this cross sectional study was conducted on 100 schizophrenic patients who were selected using convenience sampling method. Accordingly, patients who had been admitted in the psychiatric hospital and were eligible were studied. The number of samples required for the study was calculated by considering 95% confidence level,  $p=0.28$  from similar studies, and  $d=0.09$  using the sample size formula for estimating the proportion. Single population proportion formula was then used to determine the sample size. This research was approved by the Ethics Committee of Yazd University of Medical Sciences. One of the participant's parents or next of kin was required to fill out the informed consent.

### Participants

Participants were recruited from the hospitalized patients whose diseases were diagnosed by a psychiatrist clinically according to the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). All patients were in the acute or chronic phase of the disease

and were under the antipsychotic treatment. Exclusion criteria included comorbidity of schizophrenia with other mental illnesses, mental retardation, addiction, familial hyperlipidemia disorder, pregnancy, epilepsy, history of antipsychotics treatment less than one year, and unwillingness to participate in the study.

### Demographic and clinical variables

Patient's age was calculated using the date of birth available from medical records. Other demographic information, including marital status and occupation, were asked from the patients' family members.

Smoking status (yes/no) was also determined by asking the nurse or the patient's family. Drugs used by patients, including antipsychotics, antihypertensive, hypoglycemic, and triglyceride lowering agents were checked using medical records.

Weight was also measured by a calibrated digital scale (Omron, Japan) with light clothes and without shoes (20). In addition, height was measured at standing position and without shoes by a tape fixed on the wall (13, 21). Waist circumference was measured by an inelastic tape at standing position while breathing normally at the point midway between the last rib and the top of the iliac crest (22). Furthermore, blood pressure (BP) was measured once using a mercury sphygmomanometer (ALPK2, Japan) in sitting position from the right arm.

All measurements were performed by one person and through the same measuring instruments.

In the next step, 5 milliliter blood specimen was drawn from each individual via venipuncture after 8-12 hours of fasting. Then, the blood samples were kept at room temperature for about 30 minutes. Next, clotted blood samples were centrifuged and the serum was separated. Finally, serum samples were analyzed by an auto analyzer (Alpha Classic, Iran), and Pars Azmoon kit was applied to measure the total cholesterol (TC) triglyceride (TG), high density lipoprotein cholesterol (HDL-C), and fasting blood sugar (FBS). All laboratory tests were performed in a single laboratory.

Moreover, body mass index (BMI) was calculated by the following formula:  $\text{weight (Kg)}/\text{height}^2 \text{ (m)}$ . According to the WHO recommendations for Asian populations, BMI of equal or more than  $30 \text{ kg/m}^2$  is considered as general obesity (23). Based on the American Diabetes Association (ADA) guidelines, diabetes was defined as FBS of 126 mg/dL and higher or consumption of hypoglycemic medications (24). According to the guidelines of National Heart Foundation of Australia, systolic blood pressure of 140 mmHg or above, and/or diastolic blood pressure of 90 mmHg or more, or consumption of antihypertensive drugs are considered as hypertension (25).

### Definition of the MetS

According to the third report of the National Cholesterol Education Program (also called ATP III), MetS is identified by the presence of 3 or more of the following components: waist circumference (WC) of more than 102 centimeter in males and more than 88 centimeter in females; HDL-C of less than 40 mg/dL in males and less than 50

mg/dL in females; TG equal to or higher than 150 mg/dL and/or treatment with triglyceride lowering medications; blood pressure (BP) equal to or higher than 130/85 mmHg and/or treatment with antihypertensive drugs; fasting glucose of 110 mg/dL or higher and/or treatment with glucose-lowering agents (26, 27).

### 10-year risk of cardiovascular events

To estimate the 10-year risk of CVD, Framingham Risk Score (FRS) was used. The FRS is a widely known algorithm for predicting the risk of fatal or nonfatal cardiovascular events, which can be used for identifying people who are at risk. The risk score is calculated separately for males and females using components of age, total cholesterol, smoking status, HDL level, systolic blood pressure, and antihypertensive drugs consumption. Individuals with risk of less than 10% are considered to be at low risk level, patients with risk of 10%-20% are considered to be at intermediate risk level, and patients who have risk of more than 20% are considered to be in the high risk group (28).

### Statistical analysis

The analysis was performed using SPSS software. Mean±standard deviation and frequency (percentage)

were applied for the quantitative and qualitative description of variables, respectively. Chi-square test was then applied to compare dichotomous variables. If frequencies were small in contingency tables, Fisher's exact test or extended Fisher's exact test were used. Mann-Whitney U test was also applied to compare the quantitative variables. In all the statistical tests, differences were considered significant if the p value was equal to or less than 0.05.

### Results

Participants included 83 male (83%) and 17 female (17%) patients with schizophrenia. The mean age of males was higher than that of females (44.41±13.72 vs 36.76±12.74, respectively). The difference in the mean of age between males and females was statistically significant (p=0.031).

The MetS was met in 27% (95%CI: 19-37) of patients. Almost half of the patients (51%) were active smokers (60.2% and 5.9% of males and females, respectively p<0.001). The prevalence of MetS in smokers and non-smokers was not significantly different (p=0.146) (Table 1).

The majority of participants were treated with combination of the first and second generation of antipsychotics.

Table 1. Demographic and clinical characteristics of Metabolic Syndrome versus none Metabolic Syndrome patients

Items	MetS (n=27)		Non-MetS (n=73)		All patients (n=100)		p
	n (%) or mean ±sd	95% CI	n (%) or mean ±sd	95% CI	n (%) or mean ±sd	95% CI	
Age	42.74±12.38	37.84-47.64	43.25±14.37	39.90-46.60	43.11±13.80	40.37-45.85	0.957 <sup>§</sup>
Gender							
Male	18 (66.7)	46-83	65 (89)	80-95	83 (83)	74-90	0.015*
Female	9 (33.3)	17-54	8 (11)	5-20	17 (17)	10-26	
Marital status							
Single	17 (63)	42-81	44 (60.3)	48-71	61 (61)	51-71	0.678 <sup>†</sup>
Married	7 (25.9)	11-46	24 (32.9)	22-45	31 (31)	22-41	
Divorced	3 (11.1)	2-29	5 (6.8)	2-15	8 (8)	4-15	
Job							
Employed	3 (11.1)	2-29	9 (12.3)	6-22	12 (12)	6-20	1.00*
Unemployed	24 (88.9)	71-98	64 (87.7)	78-94	88 (88)	80-94	
Smoking							
Yes	17 (63)	42-81	34 (46.6)	35-59	51 (51)	41-61	0.146 <sup>†</sup>
No	10 (37)	19-58	39 (53.4)	41-65	49 (49)	39-59	
Antipsychotic use							
FGA	5 (18.5)	6-38	14 (19.2)	11-30	19 (19)	12-28	0.732**
SGA	11 (40.7)	22-61	21 (28.8)	19-41	32 (32)	23-42	
FGA+SGA	10 (37)	19-58	33 (45.2)	34-57	43 (43)	33-53	
None	1 (3.7)	0.09-19	5 (6.8)	2-15	6 (6)	2-13	
Hypertension	19 (70.4)	50-86	22 (30.1)	20-42	41 (41)	31-51	<0.001 <sup>†</sup>
Diabetes mellitus	5 (18.5)	6-38	1 (1.4)	0.03-7	6 (6)	2-13	0.005*
General obesity	9 (33.3)	17-54	4 (5.5)	2-13	13 (13)	7-21	0.001**

CI: Confidence Interval. § Mann-Whitney U test, † Chi-square test, \*Fisher's exact test, \*\* Extended Fisher's exact test

Table 2. Prevalence of MetS (also, its components) and 10-Year Risk of CVD

Items	Male (n=83)		Female (n=17)		All patients (n=100)		p
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	
MetS	18 (21.7)	13-32	9 (52.9)	28-77	27 (27)	19-37	0.015*
Abdominal obesity	21 (25.3)	16-36	16 (94.1)	71-100	37 (37)	28-47	<0.001 <sup>†</sup>
High TG	25 (30.1)	21-41	8 (47.1)	23-72	33 (33)	24-43	0.176 <sup>†</sup>
Low HDL-C	48 (57.8)	46-68	14 (82.4)	57-96	62 (62)	52-72	0.058 <sup>†</sup>
High BP	12 (14.5)	8-24	1 (5.9)	0.1-29	13 (13)	7-21	0.459 <sup>†</sup>
High FBS	4 (4.8)	1-12	1 (5.9)	0.1-29	5 (5)	2-11	1.000 <sup>†</sup>
10-Year Risk of CVD							
Low Risk	60 (72.3)	61-82	16 (94.1)	71-100	76 (76)	66-84	
Intermediate Risk	15 (18.1)	10-28	1 (5.9)	0.1-29	16 (16)	9-25	0.195**
High Risk	8 (9.6)	4-18	0	0.1-29	8 (8)	4-15	

CI: Confidence Interval. † Chi-square test \*Fisher's exact test \*\*Extended Fisher's exact test

Among all the used antipsychotics, MetS group consumed the second-generation antipsychotics (SGA) more frequently, while non-MetS group had more frequent consumption of both the first-generation antipsychotics (FGA) and the SGA (Table 1).

Hypertension and diabetes were significantly more prevalent in MetS group than the non-MetS group ( $p < 0.001$  and  $p = 0.005$ , respectively) (Table 1).

Prevalence of MetS and 10-year risk of CVD are shown in Table 2. Among all components of MetS, low HDL-C in males and abdominal adiposity in females were the most common disorders (Table 2).

Most of the participants (76%, 95%CI: 66-84) were at low risk level for developing cardiovascular disease in the next 10 years. In addition, no significant difference was observed between the level of risk among males and females (Table 2). However, levels of risk among people with and without MetS were significantly different ( $p = 0.042$ ); the risk level probability of more than 10% (intermediate and high risk) in those with MetS was almost 2 times more than that of the non-MetS participants (Table 3).

Among all patients, 21.7% (95% CI: 13-32) of males and 5.9% (95% CI: 0.1-29) of females did not have any metabolic abnormality. The majority of males (28.9%) had 2 components of MetS criteria, whereas most of the female patients (35.3%) had 3 (Fig. 1). The mean number of MetS components was significantly higher in males ( $1.57 \pm 1.17$ ) than in females ( $2.53 \pm 1.23$ ) ( $p = 0.005$ ).

## Discussion

The results of this study demonstrated a high prevalence of MetS among patients suffering from schizophrenia. Gender was a factor associated with MetS, and MetS was significantly more prevalent in females than in male patients. Moreover, the calculated 10-year risk for CVD showed that most of the patients were at low risk category.

In this study, prevalence of MetS was 27%, whereas low HDL-C and abdominal obesity were the most prevalent components of MetS in male and female patients, respectively. In India, the prevalence of MetS among patients with schizophrenia was estimated as 29.3% by Das et al, and the reduced HDL-C was reported as the most common abnormality (29). Tseng et al reported that 41.4% of their sample, patients with schizophrenia or schizoaffective disorder, had MetS (30). Findings of the present study are consistent with the study of Das et al. This consistency in the results may be due to similar life styles of the studied populations and the type of antipsychotic agents in both studies.

The results of some studies indicated high prevalence of MetS among Iranian patients with schizophrenia (17-20). For example, this prevalence was reported as 30.4%, 28%, 27.4%, and 25.7% by Shakeri et al (20), Nayerifard et al (17), Rezaei et al (19), and Ghoreishi et al (18), respectively.

The results of this study are consistent with the Iranian studies mentioned above, which may be due to similarity in factors related to lifestyle, psychotropic medications, as well as racial and cultural similarities.

In this study, the prevalence of MetS in patients with schizophrenia was higher than that of the general population of Yazd (21.3%) reported by Rezaianzadeh et al (31). This discrepancy can be related to lack of antipsychotic consumption in the general population, level of physical activity, differences in eating habits, and smoking.

The reasons for the development of MetS in patients with schizophrenia are complex and may be related to genetic factors, side effects of antipsychotic drugs, and unhealthy lifestyle, including smoking, low physical activity, and unbalanced diet. Furthermore, these patients have less access to health care services (32).

In the present study, all patients were hospitalized and received antipsychotic treatment, so the high prevalence

Table 3. Prevalence of 10-Year Risk of CVD in Metabolic Syndrome versus none Metabolic Syndrome patients

Categories of Risk	MetS (n=27)		Non- MetS (n=73)		All patients (n=100)		p
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	
Low Risk	16 (59.3)	39-78	60 (82.2)	71-90	76 (76)	66-84	
Intermediate Risk	7 (25.9)	11-46	9 (12.3)	6-22	16 (16)	9-25	
High Risk	4 (14.8)	4-34	4 (5.5)	2-13	8 (8)	4-15	0.042*

CI: Confidence Interval. \*Extended Fisher's exact test

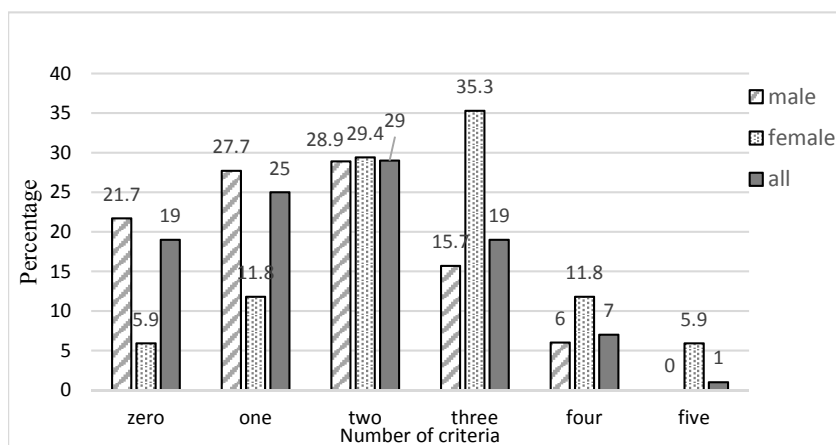


Fig. 1. The number of MetS criteria by gender



of MetS might have been related to the side effect of antipsychotic agents, physical inactivity, and unbalanced diet, such as low consumption of fruits and vegetables. Moreover, higher prevalence of MetS in female patients than males could be due to high rates of abdominal obesity, high TG level, and low HDL-C level.

No significant difference was found in taking antipsychotics among participants with or without MetS ( $p=0.732$ ). Tseng et al reported that among patients with schizophrenia or schizoaffective disorder who had MetS, 17.5%, 63.5%, and 19% were taking FGA, SGA, and combination of the first and the second generation antipsychotics, respectively. On the other hand, among patients without MetS, 19.7%, 61.2%, and 19.1% used FGA, SGA, and FGA+SGA, respectively (30). Also, Said et al showed that among patients with schizophrenia who had MetS, 21.4%, 50.8%, and 11.9% received FGA, SGA, and FGA+SGA, respectively (10). The role of antipsychotic agents in increasing the probability of developing metabolic syndrome has been shown in many studies (29, 33, 34). In fact, cardiometabolic risk factors are higher among treated schizophrenic patients than those who are drug free, especially SGAs are responsible for developing diabetes, weight gain, and dyslipidemia (35).

Patients with schizophrenia have elevated rates of smoking (5, 36). These people may consider smoking as a way of self-medication to alleviate negative psychotic symptoms (37, 38).

In this study, the prevalence of smoking was 51%, which was higher among patients with MetS than patients without MetS. High prevalence of smoking among these patients was demonstrated by many investigators. For instance, in CLAMORS study, 53.7% of patients were smokers (16). Said et al also found that prevalence of smoking among patients with schizophrenia was 28.1% and this prevalence was lower in people with MetS than in those who did not have MetS (10). Marthoenis et al stated that prevalence of smoking in patients with schizophrenia was 68.6% and MetS was not associated with smoking (39). In Iran, Ghoreishi et al reported that 50.5% of schizophrenic patients were smokers (18). Prevalence of smoking in this study was in line with the results of CLAMORS study and reports provided by Ghoreishi et al, but the results of the present study were not consistent with the findings of Said study in Malaysia.

With regards to the effect of smoking on raising the risk of MetS (40), the higher prevalence of smoking among participants with MetS, compared to individuals without MetS, is justifiable. The overall prevalence of smoking in our sample was very high which can be due to the following reasons: First, in this study, the frequency of male patients was almost 5 times higher than females and smoking was more common in males than in females. Second, socio-demographic and illness factors, such as age, employment status, level of education, and belief in the tranquility of cigarettes, were affective. Third, at the hospital where this study was conducted, the mental health staff did not encourage patients to stop smoking, as it was difficult for these patients to quit smoking or they had a high tendency to smoke cigarette.

The prevalence of hypertension was 41% in the present study, which was higher among MetS group than the non-MetS group. The results of a review by Hert et al revealed that the prevalence of hypertension among patients with schizophrenia varied from 19% to 58% (6). Ferreira et al indicated that 25% of patients with schizophrenia had hypertension (41), while Goff et al reported that 17% of schizophrenic patients were hypertensive (15). The prevalence of hypertension estimated in the present study was similar to the one reported in Hert's review; however, the frequency rate of this study was greater than the one reported by Ferreira et al or Goff et al. The differences between the findings of this study and others may be due to the genetic variations, differences in the life style, and antihypertensive drugs consumption as tranquilizer.

Hypertension in patients with schizophrenia may depend on genetic or environmental factors, such as weight gain, smoking, and sedentary lifestyle. Moreover, antipsychotic agents may lead to obesity that is closely related to the development of hypertension (42, 43). However, hypertension may be less frequent in patients with schizophrenia due to the blood pressure lowering effects of some antipsychotic agents (44).

In this study, it was observed that 6% of participants had diabetes and the prevalence of diabetes in patients with MetS was significantly higher than those without MetS. Goff et al reported that the prevalence of diabetes mellitus was 13% (15). Furthermore, Said et al stated that the prevalence of diabetes mellitus among patients with schizophrenia was 11.9% and it was significantly higher in patients with MetS than in those without MetS (10). The estimated prevalence of diabetes mellitus in this study was lower than the rate reported in similar studies, which may be related to different lifestyle factors that vary in different societies. Factors associated with the increased prevalence of diabetes among patients with schizophrenia include family history of diabetes, obesity, physical inactivity, and medication effects (4, 43).

In the present study, general obesity was detected in 13% of the patients. In CLAMORS study, prevalence of obesity was estimated as 30.8 % (16). In Washington, Bell et al stated that 42% percent of patients with schizophrenia were obese (45). Birkenaes et al also reported that prevalence of obesity among schizophrenic participants was 21.7% (46). In addition, Grover et al found that the prevalence of obesity among patients with MetS was significantly higher than those without MetS (11).

Prevalence of obesity in the present study was lower than that of similar studies, and the lower prevalence of obesity in the participants of this study, compared to similar studies, may be related to difference in lifestyle factors that vary in different societies.

Among the participants of the current study, 76%, 16%, and 8% had, respectively, low, intermediate, and high levels of risk according to Framingham score. Moreover, the frequency of males with intermediate and high-risk levels of CVD was greater than that of females in these levels. On the other hand, the prevalence of intermediate and high levels of CVD risk among individuals with MetS was significantly higher than those without MetS. Said et

al reported that 20.8% of patients with schizophrenia had a high/very high 10-year risk of CHD. In addition, the prevalence of high/very high level of risk was significantly higher among MetS group than non-MetS group (10). Tseng et al further stated that patients with MetS had a significantly higher risk of CVD than patients without MetS, according to FRS. Moreover, they reported that male patients had a significantly higher 10-year risk of CHD than females (30). The findings of this study are consistent with those of Said et al and Tseng et al, which may be due to the similar characteristics of the study populations (such as gender and age). In addition, people with MetS are at 3-fold increased risk of CVD; in fact, the components of MetS that assemble together, increase the risk of developing CVD and each component also increases this risk (47). Thus, in the present study, higher 10-year risk of CVD was expected in patients with MetS than in those without MetS. On the other hand, the higher level of risk among males than females may be due to the higher prevalence of smoking or higher mean of age in males.

This study had important clinical concepts. The patients suffering from schizophrenia had high prevalence of MetS and its components. In addition, the frequency of people at risk of developing CVD, especially among patients who had MetS, was remarkable. Patients with schizophrenia need to regularly check their physical health status, particularly for CVD risk factors. Specific measures are required to modify the risk factors of CVD, such as metabolic risk factors, smoking, lack of physical activity, and unhealthy diet. Furthermore, selecting appropriate antipsychotics and taking into account clinical conditions and side effects are of high importance.

This study had some limitations. First, because of its cross sectional nature, authors were not able to establish casual inferences. Second, due to lack of an appropriate sampling frame, random sampling was not possible and due to the low number of patients, a larger sample could not be gathered. Third, in the current study, outpatients were not included due to low severity of their disease, so the results may not be generalizable to this group. Fourth, it was not clear that whether consumption of antihypertensive drugs (such as Propranolol) by patients was for its sedation effects or for treating the hypertension, thus, the prevalence of hypertension might have been overestimated.

### Conclusion

This study demonstrated that patients with schizophrenia who consumed antipsychotics had an elevated prevalence of MetS. Also, it was found that most of participants were at low risk of developing CVD in the next 10 years, but this risk was high for patients with MetS. Considering the findings of this study as well as other recent reports, psychiatrists and health care staff should be informed about the potential metabolic side-effects of antipsychotics and unhealthy lifestyles among these patients. Furthermore, regular monitoring of metabolic risk factors is suggested. In addition, medical and behavioral interventions should be conducted for patients with MetS.

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### Conflict of Interests

The authors declare that they have no competing interests.

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