Comparison of the metabolic syndrome risk factors in antipsychotic naïve and chronic schizophrenia patients

Soleimani Robabeh, Shokrgozar Somayeh, Shekarriz-Fumani Masoomeh, Jalali Seyede Melikad

Abstract

Aim: This study aimed to compare the prevalence of MetS and cardiovascular risk factors in antipsychotic naïve schizophrenia (AN-SZ) and chronic schizophrenia (C-SZ) patients. Also, the effects of lifestyle, physical activity and clinical characteristics of these patients on metabolic syndrome were explored.

Method: In this cross-sectional study, 150 patients, 16-65 aged years were included. All subjects were recruited from the Psychiatric clinic of a tertiary hospital, Rasht, Iran. The severity of symptoms was assessed by the Positive and Negative Syndrome Scale. Physical activity and lifestyle were evaluated by the Baecke and Lifestyle questionnaires.

Results: Fifty AN-SZ patients and 100 C-SZ patients participated. The rate of abdominal obesity was 29.2% for females and 10.3% for males. The C-SZ patients had significantly fewer healthy habitual physical activity and lifestyle, compared with AN-SZ patients. The prevalence of MetS in the AN-SZ and C-SZ groups was 8% and 23%, respectively (odds ratio [OR] 3.13). Binary logistic regression revealed age and unhealthy lifestyle to be significant predictors of MetS (adjusted OR 1.09 and 0.65, respectively).

Discussion: We found with increasing each 10 years, the odds of MetS to increase 2.37 times. There was a significant negative association between a healthy lifestyle of SZ patients and MetS. For lifestyle habits, a decrease in the LSQ score by each one-point increases the odds of MetS by 45%.

Conclusions: We found a higher prevalence of obesity and MetS in C-SZ patients. The results of the present study showed a significant relationship between age, LSQ score and MetS development. Future studies are recommended to explore the importance of weight management and nutrition control for reducing the rate of MetS.

schizophrenia; antipsychotic agents; metabolic syndrome; obesity

INTRODUCTION

Cardiovascular morbidity is increasingly recognized as the leading cause of mortality and reduced life expectancy in patients with schizophrenia [1]. Patients with schizophrenia are at a greater risk of type 2 diabetes, with prevalence rates reaching more than twofold those of...
the general population [2]. In a meta-analysis, Mitchell et al. showed about 40% of these patients to have lipid profile alteration [3]. Accumulating evidence indicates that the risk of metabolic syndrome (MetS) is elevated in this group of patients [4]. The incidence of myocardial infarction and stroke in patients with metabolic syndrome (MetS) is three times that of normal populations. It has clearly been shown that the second-generation antipsychotic drugs such as clozapine and olanzapine were associated with impaired glucose metabolism, insulin resistance and the onset of type 2 diabetes [5]. Another risk factor for increased mortality in this group of patients is unhealthy lifestyle habits, such as poor dietary habits, sedentary behaviors, smoking [5, 6]. Indeed, studies are showing that metabolic syndrome and its components might be attributed to low levels of physical activity and high rates of cigarette smoking or alcohol abuse [7]. Also, a recent analysis revealed ten gene variants associated with both cardiovascular risk factors and schizophrenia susceptibility, mainly triglycerides and low – and high-density lipoproteins. Genetic dyslipidemia in schizophrenia is consistent with evidence for white matter abnormalities and myelin dysfunction and supports the neurodevelopmental hypothesis [8]. The interaction of these factors with genetic vulnerability and poor somatic care causes a negative effect on the life expectancy of patients with schizophrenia [9].

Mitchell et al. [10] were conducted a meta-analysis and found lower cardio-metabolic risk in early schizophrenia than in chronic schizophrenia (9.8% versus 35.3%). In another meta-analysis, these researchers pointed out that comparison of the prevalence of cardio-metabolic abnormalities between first-episode or drug-naïve patients and general population control data is impossible due to a very limited number of studies [11]. Metabolic dysregulations in multiple-episode schizophrenia patients are similar to those observed in patients with other mental disorders. However, little is known about metabolic abnormalities in antipsychotic naïve schizophrenia (AN-SZ) patients [6]. Although there are clear links between mental disorders and the incidence of metabolic diseases, only several papers existed about the effects of dietary habits on metabolic syndrome in patients with schizophrenia. Moreover, previous meta-analyses showed less physical activity, high levels of sedentary behavior and low cardiorespiratory fitness levels in patients with schizophrenia [12-14]. To date, it is not established whether, compared to AN-SZ patients, physical activity participation and weight management and nutrition are worse in chronic schizophrenia (C-SZ) patients.

AIM

The primary aims of this study were to determine the prevalence of metabolic syndrome and risk factors of CVD in the AN-SZ patients and C-SZ patients and to investigate predictors of MetS in our population.

METHODS

The study protocol was approved by the ethical committee of Guilan University of Medical Sciences (IR.GUMS.REC.1396.391), Rasht (Iran) and complied with the rules delineated in the Helsinki Declaration. All subjects were recruited from the Psychiatric clinic of the Shafa Hospital, Rasht, Iran from May 2017 to October 2018. Fifty AN-SZ patients were selected from the patients diagnosed with schizophrenia at the time of their first clinical contact for the psychiatric symptoms at the outpatient Psychiatric clinic of the Shafa Hospital. Similarly, 100 sex-matched C-SZ people were recruited. All subjects were outpatients between 16 and 65 years old. These patients met Diagnostic and Statistical Manual of Mental Disorder “Fifth Edition” (DSM-V) [15] criteria for schizophrenia. Patients were excluded if they had a comorbid substance use disorder (other than tobacco), evidence of type 2 diabetes mellitus before the diagnosis of schizophrenia, and currently pregnant or nursing. To be eligible, C-SZ patients were required to have been treated with a stable dose of antipsychotic or anticholinergic medication in the previous 6 months. In addition, subjects needed to demonstrate a minimum period of 4 weeks symptom stability, defined as no more than 20% change on consecutive ratings on the Positive and Negative Syndrome Scale (PANSS) [16].
Data collection

Written informed consent was obtained from each participant or his/her legal guardian. The severity of positive and negative symptoms was assessed by the PANSS. The original PANSS scale is composed of three subscales, including the positive, negative, and general psychopathology subscales [16]. In recent years, a factor analysis of PANSS showed two more factors: cognitive and depressive factor [17, 18]. The cognitive factor is composed of three PANSS items: “Conceptual disintegration” (P2), “Difficulty in abstract thinking” (N5), and “Poor attention” (G11), which is used to measure cognitive function. The depressive factor consists of three other PANSS items: “Anxiety” (G2), “Guilt feelings” (G3), and “Depression” (G6).

Cardiovascular risk factors

Blood samples were collected between 8 and 10 am. The specimens were drawn after overnight 12-hr fasting for the definition of plasma FBS, TG, HDL-C. FBS and TG were distinguished based on the Colorimetric-Enzymatic methods (glucose oxidase), and HDL-C was evaluated according to immunoinhibition methods, all of them by commercial kits (Pars Azmoon Inc., Tehran, Iran) using a BT3000 automatic analyzer. The National Cholesterol Education Program’s Adult Treatment Panel III (NCEP-ATP III) criteria were used to diagnose metabolic syndrome [19]. The metabolic syndrome is defined as the presence of three or more of the following risk factors: (i) waist circumference >102 cm in men or >88 cm in women; (ii) blood pressure (BP) ≥130/85 mmHg; (iii) fasting triglycerides (TG) level ≥150 mg/dL; (iv) fasting high-density lipoproteins (HDL) level <40 mg/dL (in men) or <50 mg/dL (in women); and (v) fasting blood sugar (FBS) level ≥110 mg/dL. The cutoff value of waist circumference proposed by ATP III for WC was a debate topic. The Iranian National Committee of Obesity (INCO) also proposed a revised ATP III criteria with a regional cutoff value of WC>95 cm for men and women [20]. In the current study, we followed this cutoff for patients.

BAECKE PHYSICAL ACTIVITY QUESTIONNAIRE (BPAQ)

The validated Persian version of BPAQ was used for this study to assess physical performance of participants in the previous 12 months. The questionnaire consists of 16 questions organized into three sections: physical activity at work; sport during leisure time; and physical activity during leisure excluding sport [21]. The sum of the three subscales (range 3 to 15) gives an indicator of habitual physical activity, with higher scores indicating being more physically active. The Baecke questionnaire has been used previously in patients with schizophrenia [22].

THE LIFE STYLE QUESTIONNAIRE (LSQ)

The LSQ was constructed by Lali et al [23] in Iran. It is a multidimensional instrument for assessing and measuring lifestyle. All items are responded on a 4-point Likert scale scoring in the range from 0 (never) to 3 (always). The higher score on each component represents the better lifestyle. In the current study, weight management and nutrition subscale (seven items) was used. The validity of this questionnaire was confirmed by factor analysis and its reliability using the internal reliability method. Cronbach’s Alpha of the questionnaire in various subscales was reported ranging from 0.79 to 0.89 [24].

Statistical analysis

Based on the study of Pallava et al. [25], assuming an alpha of 20% and a statistical power of 80%, and an allocation ratio of 2:1, we concluded a needed sample of 150 patients to compare the prevalence of metabolic syndrome in patients with antipsychotic naïve and chronic schizophrenia. The G*Power free software (version 3.1.9.2, University of Dusseldorf, Germany) was used for sample size calculation.

We presented frequencies for categorical variables, means and standard deviation for continuous variable. The AN-SZ and C-SZ groups were compared with student’s t-tests and the Chi-squared test for categorical variables. The scores of the weight management and nutrition subscale, as well as the BPAQ were examined among
patients with or without MetS. To identify risk factors associated with MetS in SZ patients, we employed univariate and multiple Firth-penalized logistic regressions. We included as predictors: age, sex, alcohol usage, smoking, duration of illness, PANSS, LSQ, BPAQ, antipsychotic treatment (with four levels: no drug, olanzapine, risperidone, other antipsychotic drugs) and antipsychotic dosage. We detected multicollinearity between two independent variables (age and duration of illness). Hence, we removed the duration of illness from the final model. The global fit of the random-effects logistic model to the data was analyzed using the Hosmer-Lemeshow test. Crude and adjusted odds ratios are reported with 95% confidence intervals (95% CI) and P-values. All data were analyzed using Stata 14.0. All statistical tests were two-sided and a P-value ≤0.05 was considered statistically significant.

RESULTS

Of the included patients, 50 were categorized as having AN-SZ and 100 as C-SZ. In both groups, 48% of participants were female. Participants of the two groups were matched on gender. Mean age of patients was 36.8±11.1 years. The AN-SZ patients, however, had a significantly less mean age than did C-SZ patients (P<0.001). Mean duration of illness in the two groups was 2.5 and 13.9 years, respectively. Among the C-SZ patients, 63% had at least one schizophrenia-related hospitalization annually. Fifty out of 150 patients (33.3%) were current smokers, 5 (3.3%) had given up smoking and 95 (63.3%) had never smoked. The rate of smoking in men was significantly more than in women (57.7% vs. 13.9%). The mean number of cigarettes smoked daily was 14.3±14.1. Of those who smoked cigarettes, 14 (25.5%) were heavy smokers (≥20/day). In total, 8 participants (4 men and 4 women) were drinkers. The rate of a moderate-heavy drinker in AN-SZ and C-SZ groups were 6% and 3%, respectively.

Table 1. Sociodemographic and clinical characteristics of the patients in the antipsychotic naïve schizophrenia and chronic schizophrenia groups

|                                | Antipsychotic naïve schizophrenia group | Chronic schizophrenia group | P-value* |
|--------------------------------|----------------------------------------|-----------------------------|----------|
| Age (years)                    | 29.5±7.9                               | 40.5±10.8                   | <0.001   |
| Education (%)                  |                                        |                             | 0.20     |
| ≤ High school grade            | 50                                     | 44                          |          |
| Some college                   | 50                                     | 53                          |          |
| ≥ College grade                | 0                                      | 3                           |          |
| Marital status (%)             |                                        |                             | 0.55     |
| Single                         | 64                                     | 58                          |          |
| Married                        | 28                                     | 28                          |          |
| Divorced/Separated             | 8                                      | 14                          |          |
| Occupational status (%)        |                                        |                             | 0.001    |
| Active                         | 36                                     | 17                          |          |
| Unemployed/jobless             | 64                                     | 83                          |          |
| Smoking (%)                    | 34                                     | 38                          | 0.72     |
| Alcohol (%)                    | 8                                      | 4                           | 0.44     |
| Alcohol dose*                  |                                        |                             | 0.33     |
| Light                          | 2                                      | 1                           |          |
| Moderate                       | 6                                      | 2                           |          |
| Heavy                          | 0                                      | 1                           |          |
| Substance abuse                | 10                                     | 17                          |          |
The analysis of the total score of the PANSS showed no significant difference in the two groups. However, the general psychopathology subscale of the PANSS was significantly higher in the AN-SZ group than in the C-SZ group. Patients in the C-SZ group had fewer healthy habitual physical activity and lifestyle, compared with subjects in the AN-SZ group.

Of the participants in the C-SZ group, 38% were prescribed olanzapine, 26% risperidone, and 16% fluphenazine. Of the participants in this group, 92% were treated with second-generation antipsychotics, 38% were treated with first-generation antipsychotics and 30% were treated with a combination of antipsychotics.

The C-SZ patients were showed more frequently obesity (BMI≥30 kg/m²) compared with those in the AN-SZ group (18% and 10%, respectively, p =0.003). In total, 29.2% of females and 10.3% of males had high waist circumference meeting the INCO criterion for abdominal obesity (p=0.003). Of the participants, 86% (129/150) had evidence of dyslipidemia, defined as the presence of at least one abnormal lipid parameter or treatment with lipid-lowering drugs. Twenty-eight of the 150 patients (18.7%) had FBS level ≥110 mg/dL. Hypertension was present in 11 subjects (7.3%).

Twenty-three percent of subjects in the C-SZ group and 8% of subjects in the AN-SZ group showed MetS (odds ratio (OR) 3.13, p =0.02) (Table 2).
Table 2. Percentage of metabolic syndrome and cardiovascular risk factors in the first-episode schizophrenia and chronic schizophrenia groups

| Risk factor                                      | Antipsychotic naïve schizophrenia group | Chronic schizophrenia group | P-value* |
|--------------------------------------------------|----------------------------------------|----------------------------|----------|
| Metabolic syndrome                               | 8                                      | 23                         | 0.02     |
| WC > 95 (INCO criterion)                         | 10                                     | 24                         | 0.04     |
| HT ≥ 130/85 mmHg                                 | 0                                      | 11                         | 0.02     |
| TG ≥ 150 mg/dL                                   | 20                                     | 32                         | 0.12     |
| HDL < 40 (♂) or < 50 (♀) mg/dL                  | 78                                     | 83                         | 0.61     |
| FBS ≥ 110 mg/dL                                  | 6                                      | 25                         | 0.01     |

† WC: Waist circumference; HT: hypertension; TG: triglyceride; HDL: High density lipoprotein cholesterol; FBS: Fasting blood sugar

* Chi squared test

According to NCEP-ATP III criteria for metabolic syndrome, MetS frequency in the C-SZ decreased to 22% (versus 8% in the AN-SZ group; OR 3.24, p =0.03). Only one patient with MetS (25.0%) had diabetes mellitus in the AN-SZ group. Whereas the rate of diabetes in C-SZ patients was 87.0% (Table 3).

Table 3. The frequency of one or more risk factor of metabolic syndrome in the antipsychotic naïve (AN-SZ) and chronic (C-SZ) schizophrenia groups

| Risk factor | AN-SZ group | C-SZ group |
|-------------|-------------|------------|
| 0           | 18          | 12         |
| 1           | 58          | 41         |
| 2           | 16          | 24         |
| 3           | 8           | 10         |
| 4           | 0           | 8          |
| 5           | 0           | 5          |

Amongst all SZ patients, the presence of the MetS was associated with higher age and lower habitual physical activity and worse lifestyle (Table 4).

Table 4. Comparison of clinical characteristics of schizophrenia patients with or without metabolic syndrome

| Metabolic syndrome | Yes (n=27) | No (n=123) | P-value* |
|--------------------|------------|------------|----------|
| Age (years)        | 45.9±10.9  | 34.8±10.2  | <0.001   |
| Age of onset (years) | 28.7±9.8  | 26.5±7.2  | 0.19     |
| PANSS † total       | 88.9±17.3  | 94.2±16.8  | 0.14     |
| Positive symptom    | 24.2±8.0   | 27.1±8.6   | 0.11     |
| Negative symptom    | 23.8±7.9   | 23.6±8.6   | 0.94     |
| General psychopathology | 40.9±10.3 | 43.4±12.2 | 0.32     |
| Cognitive factor    | 9.0±0.4    | 9.6±0.2    | 0.14     |
| Depressive factor   | 7.0±0.2    | 6.6±0.3    | 0.34     |
| Habitual physical activity | 5.6±1.2 | 6.1±1.2 | 0.04     |
| Weight management and nutrition | 3.7±2.0 | 7.7±3.4 | <0.001 |

† Positive and Negative Syndrome Scale

* Student’s t test
Firth-penalized logistic regression revealed a significant effect of age (Beta 0.08, p < 0.001, Figure 1). Older patients (≥50 years) with schizophrenia had more MetS than younger patients (<30 years). The frequency of MetS in these age groups was 44.0% and 5.3%, respectively. Our findings showed that there was a linear trend of increased MetS with increasing age of patients ($\chi^2_{\text{trend}}$ = 18.60, P < 0.001). As seen in Table 5, the results of logistic regression showed a significant association among a higher score of LSQ and MetS (adjusted OR 0.66, p < 0.001). The Hosmer–Lemeshow test showed that the model was a good fit (P = 0.798). The Nagelkerke Pseudo-$R^2$ was 0.448.

Table 5. The results of the logistic regression of the potential predictor variables and metabolic syndrome in schizophrenia patients.

| Predictor variables | Crude OR | 95% CI     | P-value | Adjusted OR | 95% CI     | P-value |
|---------------------|----------|------------|---------|-------------|------------|---------|
| Age                 | 1.09     | 1.04, 1.13 | <0.001  | 1.09        | 1.03, 1.15 | 0.001   |
| Gender              |          |            |         |             |            |         |
| Female              | ref      |            |         |             |            |         |
| Male                | 0.40     | 0.17, 0.95 | 0.04    | 0.38        | 0.12, 1.25 | 0.11    |
| Group               |          |            |         |             |            |         |
| Naïve               | Ref      | 1.07, 9.15 | 0.04    | 0.32        | 0.04, 3.02 | 0.33    |
| Chronic             | 3.13     |            |         |             |            |         |
| Alcohol             | 0.88     | 0.14, 5.34 | 0.89    | -           |            |         |
| Smoke               | 0.36     | 0.13, 0.97 | 0.04    | 0.79        | 0.21, 2.97 | 0.73    |
| Duration of illness | 1.01     | 1.00, 1.01 | <0.001  | -           |            |         |
Comparison of the metabolic syndrome risk factors in antipsychotic naïve and chronic schizophrenia

### DISCUSSION

In this study, 25% of C-SZ patients had FBS >110mg/dL, compared with 6% of AN-SZ patients. We found an insignificant difference in the prevalence of dyslipidemia between the two groups, likely due to a ceiling effect or using lipid-lowering drugs. There was a significant negative association between a healthy lifestyle of SZ patients and risk factors of CVD (such as hypertension, FBS, and TG). Our results showed that 82% of patients in the AN-SZ group and 88% of those in C-SZ had at least one MetS risk factor. Malik et al. (26) revealed that adjusted Hazard ratios CVD mortality were 1.73 for those with 1 to 2 MetS risk factors and 2.71 for those with metabolic syndrome, compared with those with no MetS risk factor. Moreover, those with MetS and even 1 to 2 MetS risk factors were at increased risk for overall mortality. The prevalence rate of MS in our study was determined to be 18.0 % according to NCEP-ATP III diagnostic criteria. The prevalence rate of MS in the AN-SZ and the C-SZ patients was determined to be 8.0% and 23.0 %, respectively. The rates found in our study are lower than the most previous studies (27-29). This condition may be due to young age of our participants and our diagnostic criteria of MetS.

To assess the concurrent effect of several other predictor factors (both continuous and categorical) on the MetS outcome, we conducted multivariable logistic regression. Some factors were significant predictors of MetS on univariate analysis. Univariable Firth-penalized logistic regression revealed that C-SZ patients had almost three times the odds for MetS (OR 3.13), as compared to the AN-SZ group. However, this did not reach statistical significance in multivariable analysis. In contrast, Vancompfort et al. [11] revealed that medicated C-SZ patients have a significantly increased risk for developing MetS compared with first-episode AN-SZ patients.

We found that the female gender had an association with MetS in SZ patients on univariable, but not multivariable analysis. In most of the studies [30], the prevalence rate of MetS did not differ according to gender.

The results of the present study showed a significant relationship between age, LSQ score and MetS development. A number of studies [3, 31] have demonstrated that age had a significant association with MetS and predictably our study found older patients had significantly more MetS compared with younger ones. This was statistically significant on both univariate and multivariate analysis in our study. An increase in age by each one year increases the odds of MetS by 9% (OR of 1.09). It is merit to note that this increase for continuous predictors is multiplicative. In our patients, with increasing each 10 years, the odds of MetS increases 2.37 (1.08 ^ 10) times. As seen in Table 5, as the value of age increases the odds of MetS being a one is increasing from 5.3% in age less than 30 years to 44.0% in age equal or more than 50 years. The present study revealed unhealthy lifestyle of our SZ patients.

---

| Daily antipsychotic dosage † | 1.00 | 1.00, 1.00 | 0.32 | - |
|-----------------------------|------|-----------|------|---|
| PANSS                       | 0.98 | 0.96, 1.01| 0.15 | - |
| LSQ                         | 0.63 | 0.52, 0.77| <0.001| 0.65 | 0.51, 0.83 | 0.001 |
| BPAQ                        | 0.66 | 0.45, 1.00| 0.05 | 1.12 | 0.64, 1.94 | 0.70 |

Antipsychotic

No drug | ref | 1.86, 18.67 | 0.003 | 2.67 | 0.36, 19.56 | 0.33 |
Olanzapine | 5.90 | 1.16, 15.40 | 0.03 | 1.06 | 0.11, 9.86 | 0.96 |
Risperidone | 4.23 | 1.40, 22.27 | 0.01 | 1.59 | 0.18, 13.79 | 0.67 |
Others | 5.58 | | | |

† mg chlorpromazine equivalent

OR: odds ratio; CI: confidence interval; PANSS: Positive And Negative Syndrome Scale; LSQ: Life Style Questionnaire; BPAQ: Baecke Physical Activity Questionnaire

Archives of Psychiatry and Psychotherapy, 2021; 3: 44–54
sode AN-SZ patients take less exercise and have a diet rich in saturated fats and poor in fibers, compared with controls. In the line of our finding, Malhotra et al. [33] revealed an association between MetS and lower scores on domains of health responsibility and nutrition habit domain in schizophrenia patients. Our findings serve as support for the importance of weight management and nutrition control in SZ patients. For lifestyle habits, a decrease in the LSQ score by each one-point increases the odds of MetS by 45% (OR of 0.65). However, this finding should be considered with caution due to some issues. For example, the LSQ may be prone to bias. Furthermore, the questionnaire was not previously validated in the target population. Therefore, the use of objective and validated self-report methods for measuring lifestyle may improve the current knowledge regarding the role of nutrition and weight management in schizophrenia. Several studies [34-36] have demonstrated the benefits of body-weight control, healthy diet in reducing the risk of diabetes mellitus.

Compared to naïve patients, we found that receiving olanzapine was associated with a significantly increased odds of MetS (OR 5.90). The Clinical Antipsychotic Trials of Intervention Effectiveness schizophrenia study [37] demonstrated that olanzapine was associated with increasing negative effects on weight, lipids, and glucose metabolism, compared with perphenazine, quetiapine, risperidone, and ziprasidone. In the present study, on multivariable analysis, the association between olanzapine and MetS was not found to be significant. Olanzapine usage accounted for only 24% of our patients and thus limited power secondary to low numbers may explain our contradictory findings.

We found no significant difference in MetS when looking at severity of schizophrenia (PANSS), and do not feel that PANSS (total or subscales scores) alone represents a prognostic factor to predict the outcome. The findings in the literature are somewhat conflicting. In a cross-sectional study by Wójciak et al. [38] a significant positive correlation was found between the intensity of negative symptoms in female patients and the concentration of high-density lipoprotein (HDL) cholesterol. Also, a trend for negative correlation with BMI was observed. In a logistic regression analysis, Wang et al. [39] found that schizophrenia patients with a metabolically abnormal obese phenotype had reduced negative symptoms (OR 1.29). Saatcioglu et al. [30] observed depressive and negative symptoms to be more widespread in patients with the diagnosis of MetS. In contrast, Lin et al. found that BMI at follow-up was related to positive symptoms, but not negative symptoms at baseline in AN-SZ patients. Although our finding did not confirm the role of severity of symptoms and MetS, it is worth to probe the association between different domains of symptoms and MetS in SZ patients.

In the present study, we found that the association between physical activity and MetS did not reach statistical significance on multivariate analysis. This finding is because of associations between physical activity and other predictors. Baecke physical activity questionnaire is a self-reported tool that is prone to both systematic and random errors. Future studies will likely clarify this issue further.

We wish to acknowledge some limitations in our study. First, we were not able to adjust the results for the type and duration of antipsychotic treatment. Second, we did not assess socioeconomic status which could contribute to the increased cardio-metabolic risk observed in SZ patients. Third, due to the cross-sectional design of the current study, it is necessary for our results to be validated. Finally, absence of control group for identification of the prevalence rate of MetS, physical activity and lifestyle habits is an important limitation of the study.

CONCLUSIONS

The current study demonstrated that the illness of schizophrenia was associated with various aspects of the MetS, which in turn may explain increased CVD mortality in these patients. Age significantly predicted metabolic syndrome in SZ patients. Our results underscore the association between lifestyle characteristics and MetS development within SZ patients. Thus, future studies are recommended to evaluate the impact of various interventions on the improvement of lifestyle habits in these patients, which may reduce obesity and metabolic abnormalities.
REFERENCES

1. Laursen TM, Nordentoft M, Mortensen PB. Excess early mortality in schizophrenia. Annu Rev Clin Psychol. 2014;10:425-448.

2. De Hert M, Correll CU, Bobes J, Celikovic-Bakmas M, Cohen D, Asai I, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World psychiatry. 2011;10(1):52-77.

3. Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders: a systematic review and meta-analysis. Schizophr Bull. 2013;39(2):306-318.

4. Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, Rosenbaum S, Correll CU. 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. 2015;14(3):339-347.

5. Henderson DC, Vincenzi B, Andrea N, Ulloa M, Copeland PM. Pathophysiological mechanisms of increased cardiometabolic risk in people with schizophrenia and other severe mental illnesses. Lancet Psychiatry. 2015;2(5):452-464.

6. Lis M, Stanczykiewicz B, Liškiewicz P, Misiaż B. Impaired hormonal regulation of appetite in schizophrenia: A narrative review dissecting intrinsic mechanisms and the effects of antipsychotics. Psichoneuroendocrinology. 2020;119:104744.

7. Carney R, Cotter J, Bradshaw T, Firth J, Yung AR. Cardiometabolic risk factors in young people at ultra-high risk for psychosis: A systematic review and meta-analysis. Schizophr Res. 2016;170(2-3):290-300.

8. Andreasen OA, Djurovic S, Thompson WK, Schork AJ, Kendler KS, O'Donovan MC, et al. Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors. Am J Hum Genet. 2013;92(2):197-209.

9. Penninx BWJH, Lange SMJ. Metabolic syndrome in psychiatric patients: overview, mechanisms, and implications. Dialogues Clin Neurosci. 2018;20(1):63-73.

10. Mitchell AJ, Vancampfort D, De Herdt A, Yu W, De Hert M. Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. Schizophrenia bulletin. 2013;39(2):295-305.

11. Vancampfort D, Wampers M, Mitchell AJ, Correll CU, De Herdt A, Probst M, et al. A meta-analysis of cardio-metabolic abnormalities in drug naïve, first-episode and multi-episode patients with schizophrenia versus general population controls. World Psychiatry. 2013;12(3):240-250.

12. Stubbs B, Firth J, Berry A, Schuch FB, Rosenbaum S, Gaughran F, et al. How much physical activity do people with schizophrenia engage in? A systematic review, comparative meta-analysis and meta-regression. Schizophr Res. (2016) 176:431–440.

13. Stubbs B, Williams JE, Gaughran F, Craig T. How sedentary are people with psychosis? A systematic review and meta-analysis. Schizophr Res. (2016) 171:103–109.

14. Vancampfort D, Rosenbaum S, Schuch F, Ward PB, Richards J, Mugisha J, et al. Cardiorespiratory fitness in severe mental illness: a systematic review and meta-analysis. Sports Med. (2017) 47:343–352.

15. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub. 2013.

16. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bull. 1987;13(2):261-276.

17. Rodriguez-Jimenez R, Bagney A, Mezquita L, Martinez-Gras I, Sanchez-Morla EM, Mesa N, et al. Cognition and the five-factor model of the positive and negative syndrome scale in schizophrenia. Schizophr Res. 2013;143(1):77-83.

18. Walliwork RS, Fortgang R, Hashimoto R, Weinberger DR, Dickinson D. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. Schizophr Res. 2012;137(1-3):246-250.

19. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-2497.

20. Azizi F, Hadaegh F, Khalili D, Esteghamati A, Hosseinpah F, Delavari A, et al. Appropriate definition of metabolic syndrome among Iranian adults: report of the Iranian National Committee of Obesity. Arch Iran Med. 2010;13(5):426-428.

21. Sadeghisani M, Dehghan Manshadi F, Azimi H, Montazeri A. Validity and Reliability of the Persian Version of Baecke Habitual Physical Activity Questionnaire in Healthy Subjects. Asian J Sports Med. 2016;7(3):e31778.

22. Vancampfort D, De Hert M, Sweers K, De Herdt A, Detraux J, Probst M. Diabetes, physical activity participation and exercise capacity in patients with schizophrenia. Psychiatry Clin Neurosci. 2013;67(6):451-456.

23. Lali M, Abedi A, Kajbaf MB. Construction and validation of the lifestyle questionnaire (LSQ). Psychological research. 2012;5(1):64-80.

24. Ahmadi AZ, Soltani M, Imani MM. A comparative study of the role of life style and identity style and belief system in donating blood in volunteers and non-volunteers in yazd. Scie J Iran Blood Tran Org. 2016; 13(2): 89-97.

25. Pallava A, Chadda RK, Sood M, Lakshmy R. Metabolic syndrome in schizophrenia: a comparative study of antipsychotic-free/naive and antipsychotic-treated patients from India. Nord J Psychiatry. 2012;66(3):215-221.
26. Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation. 2004;110(10):1245-1250.

27. McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr Res. 2005;80(1):19-32.

28. Heiskanen T, Niskanen L, Lyytikäinen R, Saarinen PI, Hintikka J. Metabolic syndrome in patients with schizophrenia. J Clin Psychiatry. 2003;64(5):575-579.

29. Cohn T, Prud'homme D, Streiner D, Kameh H, Remington G. Characterizing coronary heart disease risk in chronic schizophrenia: high prevalence of the metabolic syndrome. Can J Psychiatry. 2004;49(11):753-760.

30. Saatioglu O, Kalkan M, Fistikci N, Erek S, Kilic KC. Relationship Between Metabolic Syndrome and Clinical Features, and Its Personal-Social Performance in Patients with Schizophrenia. Psychiatr Q. 2016;87(2):265-280.

31. Abou Kassm S, Hoertel N, Naja W, McMahon K, Barrière S, Blumenstock Y, et al. Metabolic syndrome among older adults with schizophrenia spectrum disorder: Prevalence and associated factors in a multicenter study. Psychiatry research. 2019;275:238-246.

32. Spelman LM, Walsh PI, Sharifi N, Collins P, Thakore JH. Impaired glucose tolerance in first-episode drug-naive patients with schizophrenia. Diabet Med. 2007;24(5):481-485.

33. Malhotra N, Kulhara P, Chakrabarti S, Grover S. Lifestyle related factors & impact of metabolic syndrome on quality of life, level of functioning & self-esteem in patients with bipolar disorder & schizophrenia. Indian J Med Res. 2016;143(4):434-442.

34. Panagiotakos DB, Polychronopoulos E. The role of Mediterranean diet in the epidemiology of metabolic syndrome; converting epidemiology to clinical practice. Lipids Health Dis. 2005;12:4-7.

35. He FJ, Markandu ND, MacGregor GA. Modest salt reduction lowers blood pressure in isolated systolic hypertension and combined hypertension. Hypertension. 2005;46(1):66-70.

36. Arif AA, Rohrer JE. Patterns of alcohol drinking and its association with obesity: data from the Third National Health and Nutrition Examination Survey, 1988-1994. BMC Public Health. 2005;5:126.

37. Nasrallah HA. Metabolic findings from the CATIE trial and their relation to tolerability. CNS Spectr. 2006;11(S7):32-39.

38. Wójciak P, Domowicz K, Rybakowski JK. Metabolic indices in schizophrenia: Association of negative symptoms with higher HDL cholesterol in female patients. The World Journal of Biological Psychiatry. 2020;1-8.

39. Wang J, Zhang Y, Liu Z, Yang Y, Zhong Y, Ning X, et al. Schizophrenia patients with a metabolically abnormal obese phenotype have milder negative symptoms. BMC psychiatry. 2020;20(1):1-9.