Metabolic Syndrome and Illness Severity Predict Relapse at 1-Year Follow-Up in Schizophrenia: The FACE-SZ Cohort

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ABSTRACT

Objective: Predicting relapse is a major challenge in schizophrenia from a clinical and medico-economic point of view. During recent decades, major psychiatric disorders have been found to be extensively associated with metabolic disorders, even before the illness onset, with a prevalence estimated to be 35% in this population. However, no study to date has, to our knowledge, explored the potential impact of metabolic syndrome (MetS) on relapse.

Methods: From 2010 to 2016, 185 patients (mean age = 32 years) with a *DSM-IV-TR* diagnosis of schizophrenia were included in the FondaMental Academic Centers of Expertise for Schizophrenia (FACE-SZ) cohort and followed up for 1 year. Multivariable logistic regression was performed to estimate the adjusted odds ratio for relapse.

Results: Thirty-seven percent of stabilized outpatients with schizophrenia (mean illness duration = 11 years) experienced a relapse at least once during the 1 year of follow-up. MetS strongly predicted relapse at 1 year, independently of illness severity, insight into illness, and treatment characteristics (including medication compliance). Patients with MetS at baseline had a 3 times higher risk (95% CI, 1.1–8.4) of experiencing a new episode of psychosis during the 12 months of follow-up.

Conclusions: Further studies should determine if reducing or preventing MetS could help to protect subjects with schizophrenia from relapse.

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Schizophrenia is a chronic, disabling mental illness with a progressive course and multiple relapses. The relapse rate within the first year after onset has been estimated to be approximately 35%, and the lifetime risk of relapse up to 80%.[1] Frequent relapses are associated with severe psychopathology and a worsening response to treatment and clinical prognosis along with impaired cognitive and daily functioning, which not only seriously affect quality of life but also place a heavy burden on families and society.[2]

Numerous studies have investigated risk factors for relapse in individuals with schizophrenia.[1,3,4] A recent review summarized the following risk factors: being male, younger age at onset, low premorbid level of functioning, duration of untreated psychosis, substance abuse, poor adherence to treatment, and poor insight into illness.[1,3–5] The use of second-generation antipsychotics, in particular clozapine or olanzapine, has been associated with lower relapse rates and inclusion in psychotherapy programs.[1] However, these studies mostly focused on early schizophrenia, and some authors[1,4,6] have suggested that risk factors for relapse may differ between the first and subsequent relapses. Major psychiatric disorders have long been known to be associated with metabolic disorders, even before the onset of illness,[7,8] and half of the loci (rs2535629 [chromosome 3] and rs11191454 [chromosome 10]) associated with schizophrenia are associated with extra-brain functions.[9] Each component of metabolic syndrome (MetS; defined by a collection of clinical and biological abnormalities resulting in a predisposition

Clinical Points

- Some authors have suggested that risk factors for relapse in schizophrenia could be different between the first and subsequent relapses. Although cardiovascular diseases are the primary cause of mortality in individuals with schizophrenia and bipolar disorder, no study has yet explored the potential impact of metabolic syndrome on relapse.
- Management of metabolic syndrome and cardiovascular risk factors in patients with schizophrenia could reduce not only the associated morbidity and mortality but also the relapses that are frequent in this chronically ill population.

to diabetes, cardiovascular disease, and stroke) has been associated with brain disturbances. Type 2 diabetes has been associated with degenerative brain illnesses[10,11] and hypercholesterolemia with increased oxidative stress at the blood-brain barrier.[12] Hypertension has been found to predict cognitive deficit in schizophrenia[13] and to have a higher impact on the brains of individuals with schizophrenia than on those of healthy controls. Metabolic disturbances may play a role in the onset, maintenance, and prognosis of psychiatric illnesses. Indeed, Pillinger et al[14] found that glucose dysregulation is present in first-episode psychosis, and a meta-analysis[15] showed that C-reactive protein (CRP) levels are increased in patients with schizophrenia; however, it is still unclear if increased CRP levels are causally related to schizophrenia.[16,17] Fagiolini et al[18] showed that the number of patients experiencing a depressive recurrence was significantly higher in the obese than in the non-obese group in a study of 175 patients with bipolar I disorder. Although cardiovascular diseases are the primary cause of mortality in individuals with schizophrenia,[19,20] no study has yet explored the potential impact of MetS on relapse.

Aims of the Study

The objective of our study was to determine risk factors, including MetS, for relapse after 1 year in a national French cohort of stabilized community-dwelling schizophrenia subjects. Our hypotheses were that relapse at 1 year would be associated with being male, younger age at onset, low premorbid level of functioning, the time interval between onset of positive psychotic symptoms and first appropriate treatment, substance abuse, poor adherence to treatment, poor insight into illness, and MetS.

METHOD

Design

The study sample was drawn from patients who were evaluated in hospitals belonging to a network of French Schizophrenia Expert Centers. The FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) cohort is based on a French national network of 10 Schizophrenia Expert Centers (Bordeaux, Clermont-Ferrand, Colombes, Créteil, Grenoble, Lyon, Marseille, Montpellier, Strasbourg, and Versailles) set up by a French scientific cooperation foundation (FondaMental Foundation; www.fondation-fondamental.org) created by the French Ministry of Research to build a platform that links systematic clinical assessment to research.[21]

All clinically stable outpatients (defined by no hospitalizations or changes in treatment during the 4 weeks before evaluation) aged 16 years and older with a *DSM-IV-TR*[22] diagnosis of schizophrenia or schizoaffective disorder were included in this study, which was conducted from 2010 to 2016. As this sample aimed to be representative of a stabilized community-dwelling national sample of outpatients with schizophrenia, unremitted patients with moderate to severe symptoms were also included in the Schizophrenia Expert Centers network. Diagnosis was confirmed by 2 trained psychiatrists of the Schizophrenia Expert Centers network. All patients were referred by their general practitioner or psychiatrist, who subsequently received a detailed evaluation report with suggestions for personalized interventions.[21] Patients were evaluated with a thorough, standardized assessment and were followed up every year for 3 years. The present study is a first-step study. Further analyses will be carried out when enough subjects will be seen at 2 and 3 years.

Ethical Approval

The study was carried out in accordance with ethical principles for medical research involving humans (World Medical Association, Declaration of Helsinki). The assessment protocol was approved by the relevant ethical review board (CPP-Ile de France IX, January 18, 2010). All data were collected anonymously. A non-opposition form was signed by all participants, as this study included data coming from regular care assessments.

Assessment

Clinical and sociodemographic measures. All patients were interviewed by members of the specialized multidisciplinary team of the Expert Center. They were interviewed by a trained psychiatrist who used the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Patient Edition (SCID-I/P),[23] to confirm the diagnosis. Information concerning patients' education, the onset and course of the illness, and patients' family history, somatic diseases, and comorbidities were also recorded. Schizophrenic symptomatology was assessed using the Positive and Negative Syndrome Scale (PANSS).[24] We also used 5-factor models for the PANSS items to evaluate specific domains of symptomatology. Five-factor models for interpreting the PANSS are thought to be more representative of the syndromes of schizophrenia than the original 3 subscales (ie, positive, negative, and psychopathology), especially in a chronic course. These 5 factors remain consistent whether patients are on or off medication and are consistently identified across subgroups of patients to include negative, positive, disorganized/autistic preoccupation, excited/activation (hostility/

aggression), and dysphoric mood/emotional distress (depression).[25] Current depressive symptoms were evaluated using the Calgary Depression Scale for Schizophrenia,[26] and manic symptoms were assessed using the Young Mania Rating Scale.[27] Ongoing psychotropic treatment, current cannabis and alcohol consumption, and tobacco smoking were also recorded. Insight was evaluated using the self-report Birchwood Insight Scale,[28] which has 8 items with 3 Likert-scale response levels; higher scores indicate better insight. Treatment adherence behavior was recorded using the Brief Adherence Rating Scale.[29]

Biological measurements. Routine blood samples were used to measure levels of triglycerides and glucose (requiring a 10-hour fast), as well as low-density lipoprotein, high-density lipoprotein (HDL) cholesterol, total cholesterol, and CRP. Sitting blood pressure (BP) and waist circumference were also measured. Two BP measurements were made 30 seconds apart, following 5 minutes of relaxed sitting. A third BP measurement was made only when the first 2 BP readings differed by more than 10 mm Hg, with the mean of the 2 closest readings used in the analysis. Waist circumference was measured midway between the lowest rib and the iliac crest while participants stood. This was performed with a tape measure equipped with a spring-loaded mechanism to standardize tape tension during measurement. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters.

Definition of MetS. MetS was defined according to the criteria of the International Diabetes Federation,[30] which requires that 3 or more of the following 5 criteria be met: high waist circumference (> 94 cm for men and > 80 cm for women), hypertriglyceridemia (≥ 1.7 mmol/L or on lipid-lowering medication), low HDL cholesterol level (< 1.03 mmol/L in men and < 1.29 mmol/L in women), high blood pressure (≥ 130/85 mm Hg or on antihypertensive medication), and high fasting glucose concentration (≥ 5.6 mmol/L or on glucose-lowering medication).

Definition of relapse. Psychotic relapse was defined in all expert centers by at least 1 acute self-reported psychotic episode during at least 1 week in the last 12 months. Psychotic relapse was defined independently of hospitalization because not all psychotic episodes require hospitalization and because hospitalization may be due to suicide attempt, mood episode, anxiety or difficulties in maintaining autonomy, or disturbances in relationships with the relatives.

Statistical Analysis

Sociodemographics, clinical data, and treatments are presented as the mean (SD) for continuous variables and frequency distribution for categorical variables. Univariable associations between demographic and clinical characteristics associated with relapse during follow-up were determined using the χ^2 test for categorical variables.

Continuous variables were analyzed with the Student *t* test for normally distributed data and the Mann-Whitney test in case of non-normal distributions. The decision to treat continuous variables as a continuous or categorical variable was based on the lowest value of the Akaike information criterion for the corresponding univariable logistic regression model. A multivariable logistic regression was performed to estimate the adjusted odds ratio and its corresponding 95% confidence interval (CI) for an association between each factor and the risk of relapse during follow-up. Variables with *P* values < .15 in univariable analysis were included in the multivariable logistic regression model. Sex and age were also included because of their sociodemographic interest. We used multiple imputations to address missing data. We created 5 datasets in which missing data were imputed from each patient's other covariables at baseline (PROC MI procedure of SAS software with the fully conditional specification method). In these imputations, missing values were randomly sampled from their predicted distributions. Analyses were run on each of the 5 datasets, and the results were combined per Rubin's rules. Analyses were conducted using SAS (release 9.3; SAS Statistical Institute, Cary, North Carolina). All statistical tests were 2-tailed, with the α level set at .05.

RESULTS

Between November 2013 and December 2015, 185 individuals with schizophrenia were followed for 1 year and data on relapse and MetS were obtained. The mean (SD) age was 32.4 (9.7) years, and 145 (78.4%) of the subjects were male. The mean (SD) duration of illness was 10.6 (9.7) years, and the mean (SD) total PANSS score was 70.5 (16.7). Of the 185 patients, 68 (36.8%) experienced a relapse at least once during the 1 year of follow-up. Among our sample, 29% (n = 54) had only 1 lifetime psychotic episode, and the relapse rate in this subgroup was 42% within the first year.

The differences in predictive variables (ie, demographic, clinical, and treatment variables) between individuals who relapsed and those who did not during the 1 year of follow-up are presented in Table 1. Individuals who relapsed during follow-up were more likely to have higher total, positive, and depressive scores on the PANSS at baseline. They also had more severe depressive symptoms and poorer adherence to medication. Concerning comorbidities, patients with relapse during follow-up were more likely to have MetS at baseline. The study of each of the components of MetS separately showed that hypertriglyceridemia and high fasting glucose seemed to be factors that drive the results, even though the associations were not significant. We found no association of relapse with the use of second-generation antipsychotics, olanzapine/clozapine treatment, antipsychotic polytherapy, or antidepressant and anxiolytic medication.

Multivariable analysis showed that baseline MetS and a higher level of disease severity increased the risk of relapse during the 1-year follow-up. After taking into account all potential confounders (age, sex, duration of illness, PANSS score, depressive symptoms, current anxiety disorders, adherence to medication, and use of second-generation antipsychotics), individuals with MetS had a 3-fold higher

Table 1. Factors Associated With Relapse in a Cohort of 185 Patients With Schizophrenia Followed Up After 1 Year[a]

Variable	All (N = 185)	Relapse During Follow-Up		P^b	Univariable Analysis	Multivariable Analysis
		No (n = 117)	Yes (n = 68)		OR (95% CI)	OR (95% CI)
Demographic Characteristics						
Sex						
Male	145 (78.4)	92 (63.5)	53 (36.6)	.91	1.0 (0.5–2.0)	0.8 (0.3–2.2)
Female	40 (21.6)	25 (62.5)	15 (37.5)		1 (reference)	1
Age, mean (SD), y	32.4 (9.7)	32.5 (8.8)	32.2 (11.1)	.86	0.9 (0.7–1.3)	1.0 (0.6–1.6)
Education level, mean (SD), y	12.3 (2.9)	12.6 (2.8)	11.8 (3.1)	.08	0.9 (0.8–1.0)	1.0 (0.8–1.1)
Living alone						
No	17 (12.4)	10 (8.7)	7 (10.9)	.62	1 (reference)	
Yes	162 (87.6)	105 (91.3)	57 (89.1)		0.8 (0.3–2.1)	
Disease Characteristics						
Age at schizophrenia onset, mean (SD), y	21.8 (6.3)	22.0 (6.4)	21.4 (6.3)	.58	1.0 (0.9–1.0)	
Duration of illness ≤ 5 y	58 (32.0)	32 (28.1)	26 (38.8)	.14	1.6 (0.8–3.1)	2.1 (0.8–5.9)
Duration of untreated psychosis, mean (SD), y	1.6 (3.2)	2.1 (4.4)	1.2 (2.2)	.16	0.9 (0.8–1.0)	
PANSS score, mean (SD)[c]						
Total	70.5 (16.6)	67.6 (16.5)	75.6 (15.7)	.001	**1.0 (1.0–1.1)**	**1.0 (1.0–1.1)**
Positive factor	8.8 (3.7)	8.1 (3.5)	9.9 (3.7)	.002	**1.1 (1.0–1.2)**	
Negative factor	17.8 (6.2)	17.5 (6.5)	18.5 (5.7)	.29	1.0 (0.97–1.08)	
Cognitive factor	8.5 (3.1)	8.3 (3.0)	8.9 (3.3)	.22	1.1 (0.9–1.2)	
Excitement factor	5.5 (2.2)	5.3 (2.4)	5.7 (2.0)	.33	1.1 (0.9–1.2)	
Depressive factor	7.2 (3.1)	6.7 (2.8)	7.9 (3.4)	.02	**1.1 (1.0–1.2)**	
Depressive symptoms (CDSS score), mean (SD)	3.8 (4.2)	3.1 (3.7)	5.1 (4.8)	.002	**1.1 (1.04–1.2)**	1.1 (0.9–1.2)
Manic symptoms (YMRS score), mean (SD)	2.0 (3.2)	1.8 (3.3)	2.3 (3.2)	.36	1.0 (0.9–1.1)	
Insight into illness (Birchwood Insight Scale score), mean (SD)	7.7 (2.0)	7.8 (1.9)	7.6 (2.2)	.70	0.9 (0.8–1.1)	
Comorbidities						
Current daily tobacco smoking	103 (58.5)	63 (57.3)	40 (60.6)	.66	1.1 (0.6–2.1)	
Current alcohol use disorder	12 (6.5)	8 (6.8)	4 (5.9)	1.0	0.8 (0.2–2.9)	
Current cannabis use disorder	20 (10.8)	12 (10.3)	8 (11.8)	.75	1.2 (0.5–3.0)	
Current anxiety disorders	57 (31.7)	31 (27.0)	26 (4.0)	.07	1.8 (0.9–3.4)	1.4 (0.6–3.3)
Metabolic syndrome	32 (20.1)	13 (13.5)	19 (30.2)	.01	**2.7 (1.2–6.1)**	**3.0 (1.1–8.4)**
Components of Metabolic Syndrome						
High blood pressure	41 (25.6)	22 (22.0)	19 (31.7)	.18	1.6 (0.8–3.4)	
High fasting glucose	22 (15.1)	10 (11.1)	12 (21.4)	.09	2.2 (0.9–5.5)	
Hypertriglyceridemia	37 (23.6)	18 (18.8)	19 (31.1)	.07	2.0 (0.9–4.1)	
High waist circumference	80 (53.7)	45 (48.9)	35 (61.4)	.16	1.7 (0.8–3.3)	
Low HDL cholesterol	55 (35.7)	31 (33.3)	24 (39.3)	.45	1.3 (0.7–2.5)	
Treatments at Baseline						
Adherence to medication (BARS score), mean (SD)	89.9 (21.3)	92.2 (18.8)	85.9 (24.7)	.02	0.98 (0.97–1.0)	1.0 (0.9–1.0)
Second-generation antipsychotic	146 (87.5)	97 (90.6)	49 (81.7)	.09	0.5 (0.2–1.2)	1.6 (0.4–6.5)
Olanzapine/clozapine	56 (33.7)	36 (34.0)	20 (33.3)	.93	1.0 (0.5–1.9)	
Antipsychotic polytherapy	54 (32.5)	35 (33.0)	19 (31.7)	.86	0.9 (0.5–1.8)	
Antidepressant	51 (30.5)	30 (28.0)	21 (35.0)	.35	1.4 (0.7–2.7)	
Anxiolytics	40 (23.9)	25 (23.4)	15 (25.0)	.81	1.1 (0.5–2.3)	
Lithium	4 (2.4)	2 (1.9)	2 (3.4)	.62	1.8 (0.3–13.3)	
Valproate	20 (12.0)	10 (9.4)	10 (16.7)	.17	1.9 (0.7–5.0)	

[a]Values shown as n (%) unless otherwise noted. The total n values used in calculating percentages sometimes vary due to missing data for some patients. Boldface indicates statistical significance in the univariable or multivariable analysis.
[b]Chi-square test for categorical variables and Student *t* test or Mann-Whitney test for continuous variables.
[c]The Wallwork 5-factor model was used to analyze PANSS subscores.
Abbreviations: BARS = Brief Adherence Rating Scale, CDSS = Calgary Depression Scale for Schizophrenia, HDL = high-density lipoprotein, PANSS = Positive and Negative Syndrome Scale, YMRS = Young Mania Rating Scale.

risk of experiencing a relapse during follow-up (OR = 3.0; 95% CI, 1.1–8.4).

DISCUSSION

Thirty-seven percent of individuals with schizophrenia experienced a relapse at least once during the 1 year of follow-up. MetS and severity of the illness were associated with a higher risk of relapse independently of potential confounders, including nonadherence to medication and a lower level of insight. Patients with MetS at baseline had a 3-fold higher risk of experiencing a new psychotic episode during the 1-year follow-up. There was no association of relapse with the use of second-generation antipsychotics, olanzapine/clozapine treatment, antipsychotic polytherapy, or antidepressant and anxiolytic medication.

These results are roughly comparable to those of previous studies. Most of the studies concerning relapse in schizophrenia have focused on adherence to medication. In the present study, multivariable analysis showed that adherence to medication was not associated with relapse at 1 year. This is consistent with previous findings[4] suggesting that adherence to medication is associated with the first relapse, but not subsequent relapses. With a mean duration

of illness of 11 years, most of the participants in the present study had already experienced relapse in the past. Male sex, a lower level of insight, and shorter duration of illness have been previously identified as risk factors for relapse in early schizophrenia (for review, see Porcelli et al[1]), which was not the case in the present study. These discrepancies may also be explained by the study design. Most of the previous studies included only first episodes or used data from randomized controlled trials, known to exclude severely ill or suicidal patients. In contrast, the present study was based on community-dwelling "real world" schizophrenia subjects with a mean (SD) illness duration of 10.6 (9.7) years. Twenty-nine percent of our patients had only 1 lifetime episode. We were thus able to evaluate the relapse rate in this subgroup and observed a relapse rate of 42% within the first year, which is slightly higher than those of other studies[31] reporting a relapse rate between 30% and 40% within the first year after the onset of schizophrenia. This discrepancy may also be explained by the use of different criteria in the literature to define relapse as well as the duration of follow-up, the diagnosis, and the characteristics of the setting.[32,33]

The relapse rate might have been expected to be lower in chronic schizophrenia patients due to better insight concerning the illness, decreased cannabis consumption, and a better adherence profile. On the contrary, the present study suggests that relapses remain highly prevalent throughout the illness and that MetS may be involved in this phenomenon, independently of illness severity.

The major finding of the present study is that MetS appears to be associated with relapse during 1 year in chronic schizophrenia patients. Many studies have evaluated risk factors for relpase in individuals with schizophrenia. Only 1 study has evaluated the evolution of metabolic risk factors on the course of the disease in a cohort of first episode psychosis: Bioque et al[34] showed that patients with cardiometabolic profiles have a progressive worsening in the major part of the analyzed variables during the follow-up period. However, our study is the first to assess the impact of MetS on the risk of relapse in individuals with chronic schizophrenia. Indirect clues have been previously found in populations with bipolar disorders and other chronic psychiatric illnesses that share common features with schizophrenia. Beyond the known biological underpinnings of the association between metabolic disturbances and brain dysfunction, MetS has been shown to be associated with clinical risk factors for relapse, including impaired general physical and psychological well-being, functioning, and quality of life.[35–38] In addition, the physical complications of MetS may compromise adherence to medication, leading to the cessation of treatment and relapse. In multivariable analysis, we found no association between MetS and adherence in the present study. However, adherence was evaluated only at baseline and at the end-point, which limits our study.

The rate of MetS was lower in the FACE-SZ cohort than in other European countries,[39] consistent with the results of the FACE-BD (FondaMental Academic Centers of Expertise for Bipolar Disorders) cohort in French bipolar disorder patients.[40] This difference may be due to a lower baseline risk in France arising from differences in several factors, including lifestyle, diet, tobacco use, medication regimens and/or access to care, or environmental and genetic risk factors. The difference in prevalence may also reflect differences in methods or sample characteristics, place of recruitment, or sample size. Of note, the prevalence of MetS in the present study (20%) is twice that of the general French population, despite the lower mean age in the present sample of 31 years versus 40 years in the general French population.[41]

The severity of the illness, measured by the PANSS, was associated with a greater risk of subsequent relapse in chronic patients in the present study, which is consistent with previous findings.[32,42–44] These results confirm that residual symptomatology and incomplete response to medication are highly predictive of relapse within the next 12 months, which was suggested by previous studies.[32]

Antipsychotic polytherapy was not associated with a higher relapse rate at 1 year, contrary to the results of a cohort of 185 schizophrenia patients followed for 2 years.[45] Clozapine and olanzapine have been associated with lower relapse rates in several studies,[1] but they have also been associated with a higher risk of MetS onset than other antipsychotics.[46] Here, we found no association between clozapine/olanzapine prescription at baseline and relapse at 1 year. This apparent discrepancy is due to the association of olanzapine and clozapine with increased MetS risk in interventional studies, ie, after first treatment onset. In the present sample, most of the subjects have been administered several other antipsychotics before inclusion, as the mean illness duration was 11 years. Due to the risk of memory bias and the difficulties for statistical analyses, previous treatments have not been reported, which is a limitation of the present work. Future studies should explore lifetime exposure to each antipsychotic to determine the role of antipsychotics in MetS onset and later relapse risk.

Together, the present results suggest that the association between MetS at baseline and relapse at 1-year follow-up is not related to medication. Further longitudinal studies are warranted to determine whether some antipsychotics are associated with higher or lower relapse rates at 1 year.

Our study has some additional limitations. First, certain potential predictors, such as the evaluation of maintenance therapy, total amount of antipsychotic medication, and psychotherapeutic approaches, were not included and may explain the association between MetS and relapse. Second, we lacked precise information concerning the date when patients experienced a relapse, not allowing us to perform survival analysis. Psychotic relapse was defined by the presence of an acute episode lasting more than 7 days in the 12 months between the first and the second evaluation. Relatives and treating psychiatrists were interviewed to limit the memory bias. However, no PANSS scale scores were reported at the time of the psychotic relapse.

Strengths of the study include the use of homogenous and exhaustive standardized diagnostic protocols across

the centers and the longitudinal design and inclusion of many potential confounding factors in the multivariable analysis (sociodemographic variables, mood and anxiety symptomatology, duration of the illness, adherence to treatment, and antipsychotic medication). Moreover, this is the first study to evaluate the potential impact of MetS on the relapse rate in a well-characterized cohort of schizophrenic patients.

Combined with previous results, the present study suggests that risk factors for relapse may vary throughout the evolution of schizophrenia. Most previous studies focused on early relapses and their association with poor adherence, poor insight into the illness, male sex, and cannabis consumption. Our study suggests that these risk factors disappear in a stabilized community-dwelling population with schizophrenia with mean illness duration of 11 years. Only the severity of the illness and MetS were found to predict relapse at the 1-year follow-up. Further studies are needed to determine whether targeting residual symptoms and MetS are effective strategies to prevent relapse in this chronically ill population. Despite almost 3 decades of studies on MetS in schizophrenia subjects, the rate of subjects with current MetS remains high, as demonstrated in the present study. To date, the recommendations to manage MetS were based only on the increased cardiovascular mortality in schizophrenia subjects in national databases. A recent study[47] has shown that antipsychotic-induced weight gain was not associated with decreased adherence to treatment in schizophrenia subjects. These results were confirmed in the present study, given that the association between MetS and relapse was found independently of treatment observance. Despite recent international guidelines for interventions to manage weight gain, monitoring of relevant physical health risk factors is frequently inadequate.[48] The present results suggest for the first time that managing metabolic syndrome is important not only for physical health but also for the illness course prognosis.

CONCLUSION

Beyond physical health outcomes, the present study suggests for the first time that treating metabolic syndrome may be crucial to prevent psychotic relapse in stabilized schizophrenia outpatients. However, effective interventions to reduce MetS in schizophrenia remain few in number with limited effectiveness. The present study suggests that differentiating physical and mental health is not effective for the prognosis of schizophrenia and that coordinated multidisciplinary care may be eagerly needed to improve the course of this illness. The benefit-risk ratio of each antipsychotic should also include these data in regard to potential metabolic side effects.

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