Metabolic syndrome following a first episode of psychosis: results of a 1-year longitudinal study conducted in metropolitan Lisbon, Portugal

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Abstract

Objective: We aimed to assess the prevalence and course of metabolic syndrome (MetS) and the associated metabolic parameters during the year following a first episode pf psychosis (FEP).
Methods: We performed a 1-year longitudinal observation of 60 patients who experienced FEP. MetS was defined using the modified definition of the National Cholesterol Education Program Adult Treatment Panel III. We assessed the metabolic parameters and socio-demographic and psychopathological data for the participants.
Results: The mean age of the participants was 27.1 years, and 33.3% of them were women. There was an increase in the prevalence of MetS from 6.7% to 11.7% during the year following the baseline assessment during the year following the baseline assessment ($p = 0.250$). There were also significant increases in the prevalences of abnormal triglyceride concentration, waist circumference, and high-density lipoprotein (HDL)-cholesterol concentration during this period. In addition, there was a considerable worsening of the metabolic profile of the participants. No baseline parameters were identified to be predictors of MetS over the 1-year follow-up period.
Conclusions: We can conclude that metabolic abnormalities are common in patients with FEP and that these rapidly worsen during the first year following the diagnosis of FEP. Studies on interventions are needed to reduce metabolic risk to cardiovascular diseases following the FEP.

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Introduction

According to the results of previous studies, the life expectancy of patients with psychotic diseases, and particularly schizophrenia, is 13 to 30 years shorter than that of the general population.[1,2] Moreover, the risk of mortality in patients with schizophrenia is two or even three times higher than in the general population.[3–5] The key factors that explain this difference are cardiovascular diseases and suicide.[6] During the last 25 years, the risk of suicide has increased 18-fold. However, the high incidences of morbidity and mortality in patients with schizophrenia are principally associated with the presence of coronary heart disease.[7,8] The mortality rate associated with coronary heart disease is significantly higher in patients with schizophrenia than in the general population.[8]

Metabolic syndrome (MetS) can be defined as a combination of risk factors for cardiovascular disease and is associated with higher risks of cardiovascular mortality and morbidity.[9,10] MetS is also associated with other diseases, such as benign prostatic hyperplasia and obstructive sleep apnea syndrome.[11–13] Therefore, clinicians should screen for and treat MetS as early as possible to minimize cardiovascular mortality. Furthermore, it is essential to ensure adequate and timely screening of patients with mental disorders; otherwise, opportunities to help can be lost. In addition, there are certain barriers to the monitoring of metabolic status in patients with psychosis.[14,15] In particular, this population faces numerous challenges in obtaining properly integrated healthcare services. Therefore, the metabolic screening of such patients requires urgent improvement, involving a reorganization of the service in its current form, better communication, incentives for improvements, better education and training, more robust accreditation, and government leadership initiatives. There is no unanimous opinion regarding whether patients with psychotic disorders are subject to higher risks of cardiovascular diseases because of antipsychotic treatment, poor lifestyle, or the presence of a psychotic disorder.[16]

The most studied factor associated with obesity in patients with psychosis is antipsychotic medication. Weight gain occurs in patients taking such medication, is most rapid in the early stage of treatment, and is accompanied by central obesity.[17] Antipsychotic treatment is associated with a greater appetite, an unhealthy diet, disordered eating behavior, and sedentary behavior with lower energy expenditure.[18–21] The exact mechanisms whereby antipsychotics induce weight gain are not completely understood. Antipsychotics with high affinity for 5-HT2C or muscarinic receptors are associated with the greatest risk of weight gain, but other serotonin, histamine, and dopamine receptors may also be involved.[22] In addition, the eating habits of patients experiencing psychosis are impaired because of impaired executive function, which limits the restraints to food consumption and facilitates disinhibition.[23] This is associated with insensitivity of reward systems, which changes the preferences of

patients toward less nutritious foods, containing high levels of sugar, salt, and fat, in patients with psychosis from the early stages of the disorder.[24]

Indications of predispositions toward both psychotic and metabolic disorders have been identified in the same individuals. In addition, the existence of several pathophysiological mechanisms that underpin metabolic disturbances are well recognized in patients with psychosis, including adipokine dysregulation, inflammation, smoking, poor lifestyle, and obesity.[25]

Obesity in patients with psychosis is present even before antipsychotic treatment is commenced. Candidate obesity gene variants have been shown to be present in patients who experience a first episode of psychosis (FEP).[26] Moreover, unhealthy dietary habits and low levels of physical activity contribute to the obesity and metabolic disturbances present in patients with psychosis.[21,27] Specifically, they consume diets that lack fruit and fiber and are rich in simple sugars. In addition, they undertake less physical activity, especially moderate and vigorous physical activity, and show more sedentary behavior, with more time spent lying down and sleeping each day.[20,28,29]

One of the most challenging areas of research with respect to FEP is immune dysfunction, which is largely associated with adipocyte dysfunction. Numerous proteins and cytokines that are secreted by adipose tissue have been shown to play physiological roles in the human body, including in inflammation, coagulation, vascular remodeling, regulation of blood pressure, lipid metabolism, glucose metabolism, energy balance, and appetite.[30,31] These include the adipokines interleukin (IL)-6, tumor necrosis factor (TNF)-α, insulin-like growth factor-1, leptin, resistin, nesfatin 1, apelin, visfatin, and C-reactive protein; and sex hormones.[32] Several previous studies have demonstrated that high circulating concentrations of these substances are present in patients with psychotic disorders, both during the early and later phases.[30,31,33] Several types of adipokine receptors have been identified in components of the central nervous system and have been demonstrated to affect brain function.[34] This provides an important link between obesity/MetS and psychotic disorders, namely greater monocyte/macrophage activation and inflammation.

There have been few substantial longitudinal studies of patients who experience FEP that have aimed to determine the prevalence of MetS and related factors, despite the numerous clinical implications. Moreover, the results of the studies that have been conducted to date have been contradictory. We wished to involve patients in their routine clinical care and to overcome the limitations of previously published studies of this relationship. First, most of the studies were cross-sectional; therefore, causal relationships could not be identified.[35–39] Second, the majority of the published studies only included patients with schizophrenia.[35–37,40–42] Considering the diagnostic instability associated with FEP and that the diagnosis is typically adjusted in a significant proportion of the patients, it is important to study patients with a broader spectrum of affective and non-affective psychoses, to ensure a more accurate evaluation of the prevalence of MetS in patients with FEP.[43] Third, the results of studies conducted previously cannot be relied on when making decisions in modern clinical practice, because procedures have changed. For example, in the majority of these studies, inpatients were recruited, whereas patients who did not require hospitalization and those with milder forms of the disease were excluded.

We aimed to perform a longitudinal study of patients with FEP in which we would measure the prevalence of MetS,

characterize its course, and assess metabolic parameters throughout the first year following the diagnosis of the disease. Furthermore, we aimed to identify baseline parameters that might represent predictors of changes in the metabolic profiles of patients with early-stage psychosis.

Material and methods

Participants

The setting of this prospective observational longitudinal study was a healthcare facility in two Portuguese hospitals with psychiatric departments. Two early-intervention teams were involved in the study: Centro Hospitalar Universitário Lisboa Norte in the Programa de Intervenção nas Fases Iniciais da Psicose (PROFIP) and Hospital Vila Franca de Xira in the first-episode psychosis program (PPEP). Centro Hospitalar Universitário Lisboa Norte, a tertiary care university hospital, has a catchment area that includes approximately 350,000 people. The PROFIP program has been described previously.[44] The secondary care general hospital Vila Franca de Xira Hospital, located in the northern metropolitan area of Lisbon, has a catchment area that includes approximately 245,000 people. Trained staff assessed all the patients that were consecutively diagnosed with FEP. The therapeutic program consisted of group and individual psychosocial treatments, low-dose atypical antipsychotic medication, and family interventions.

The baseline criteria for the inclusion of patients were as follows: 1) age 16 to 40 years; 2) first diagnosis of a psychotic disorder made according to DSM-IV (American Psychiatric Association, 1994); in particular, delusional disorder, schizophrenia, bipolar psychotic disorder, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, major depressive disorder with psychotic features, or cannabis-induced psychosis; and 3) place of residence within the catchment areas of the PROFIP and PPEP services. Patients who could not complete or understand the required assessments and those with organic psychosis were excluded. The participants were evaluated twice: at baseline, provided that the conditions were appropriate for the assessment and the FEP had been clinically stabilized, and 1 year later. Patients were eligible for inclusion in the study if they met the criteria during the period between January 2017 and April 2018.

The study was approved by the ethics committee of each hospital (Centro Hospitalar Universitário Lisboa Norte: January 2017; Hospital Vila Franca de Xira: June 2016) and complied with the principles of the Declaration of Helsinki. The participants also provided their written informed consent. We de-identified all of the data during the study to guarantee the anonymity of the participants. The reporting of the study conforms to the STROBE guidelines.[45]

Clinical measures

Clinical and sociodemographic information was collected at baseline using a questionnaire that was completed by the research staff. The required details were age, marital status, employment, education, details of previous hospitalizations, details of the use of cannabis and tobacco, and any family history of psychiatric disease. The waist circumference and blood pressure of the participants were measured twice: at baseline and 1 year later. Waist circumference was measured in the standing position at the end of normal expiration, midway between the superior border of the iliac crest and the inferior costal margin. Blood pressure was measured using an automatic sphygmomanometer in the supine position. The Global

Assessment of Functioning (GAF) and Positive and Negative Syndrome Scale (PANSS) were completed for each participant during both evaluations, and the patients also completed the Beck Depression Inventory (BDI) themselves.[46–48]

Metabolic assessments

We used the modified definition of MetS published by the National Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATP-III).[49,50] Participants were diagnosed with MetS if they met three or more of the following criteria: 1. Waist circumference >102 cm in men and >88 cm in women; 2. Serum triglyceride (TG) concentration >1.7 mmol/L or the use of an anti-hyperlipidemic drug; 3. High blood pressure (≥85 mmHg diastolic or ≥130 mmHg systolic) or the use of an antihypertensive drug; 4. Low high-density lipoprotein (HDL)-cholesterol concentration (<1.04 mmol/L for men and <1.3 mmol/L for women); and 5. High fasting serum glucose concentration (≥5.6 mmol/L) or a diagnosis of type 2 diabetes mellitus.

Overnight fasting was obligatory for the collection of blood samples. An assigned technician who was not involved in the clinical evaluation made the measurements of the laboratory parameters for each participant (total cholesterol, glucose, TG, low-density lipoprotein (LDL)-cholesterol, and HDL-cholesterol concentrations). The serum concentrations of TG, HDL-cholesterol, and total cholesterol were measured using enzymatic assays, and the Friedewald equation was used to calculate the LDL-cholesterol concentration.[51]

Statistical analysis

Continuous and categorical variables are presented as means with standard deviations and frequencies, respectively. Normality was evaluated using the Kolmogorov–Smirnov test. Comparisons of the baseline characteristics of the participants between the hospital teams were made using the Mann–Whitney U-test. The metabolic data at baseline and 1 year later were compared using the Wilcoxon matched pairs signed rank test. The prevalences of MetS and metabolic abnormalities were compared between the time points using McNemar's test. Stepwise multiple regression analysis was used to identify potential predictors of MetS after 1 year of follow-up (the dependent variable), using the psychopathology, metabolic parameters, and demographic characteristics at baseline as independent variables. Statistical significance was accepted when $p < 0.05$. Data were analyzed using SPSS version 24 (IBM Corp., Armonk, NY, USA).

Results

Participants

We studied 60 patients admitted to PROFIP (n = 33) or PPEP (n = 27). The mean age of the PPEP patients was higher (mean years 29.6 *vs.* 24.2; $p = 0.003$), but their educational level was lower (mean number of years of education 10.1 *vs.* 11.7; $p = 0.016$). However, the employment and sex distribution of the participants did not differ between the teams.

At baseline, 33.3% of the participants were women and the mean age of the entire group was 27.1 years. The majority of the participants (95%) were hospitalized at baseline. The mean duration of untreated psychosis (DUP) was approximately 313 days. Schizophrenia spectrum disorders was the most common diagnosis (50% of the participants). The clinical and demographic characteristics of the participants at baseline are presented in Table 1.

Table 1. Socio-demographic and clinical baseline parameters of the participants.

Parameter	Value in patients with first-episode psychosis, n = 60
Mean age (SD)	27.10 (7.93)
Sex, n (%)	
Women	20 (33.3%)
Men	40 (66.7%)
Duration of education, years, mean (SD)	11.28 (3.34)
Unemployment, n (%)	24 (40%)
Marital status, n (%)	
Living with partner/Married	6 (10%)
Single/Divorced	54 (90%)
Hospitalization at baseline, n (%)	
Yes	57 (95%)
No	3 (5%)
Tobacco user, n (%)	
Yes	34 (56.7%)
No	26 (43.3%)
Cannabis user, n (%)	
Yes	37 (61.7%)
No	23 (38.3%)
Family history of psychiatric disease, n (%)	43 (71.7%)
DUP, days, mean (SD)	312.87 (722.74)
Diagnosis, n (%)	
Schizophrenia spectrum	30 (50%)
Affective psychosis spectrum	16 (26.7%)
Other psychosis	14 (23.3%)
PANSS score, mean (SD)	
PANSS positive subscale	19.08 (7.32)
PANSS negative subscale	17.38 (7.11)
PANSS general subscale	36.22 (9.03)
GAF, mean (SD)	47.43 (17.27)
BDI, mean (SD)	13.55 (10.45)

SD, standard deviation; DUP, duration of untreated psychosis; PANSS, positive and negative syndrome scale; GAF, global assessment of functioning; BDI, Beck Depression Inventory.

"Schizophrenia spectrum disorders" included schizophrenia, schizophreniform disorder, delusional disorder, and schizoaffective disorder. "Affective psychosis" included bipolar disorder with psychotic symptoms and depressive disorders with psychotic symptoms. "Other psychosis" included acute and transient psychotic disorders, brief psychotic disorders, and psychosis not otherwise specified.

Metabolic profiles of the participants

Table 2 presents the laboratory measurements for the participants obtained at baseline and 1 year later. There was an apparent increase in the prevalence of metabolic syndrome, from 6.7% to 11.7%, between baseline and follow-up, but the difference was not statistically significant ($p = 0.250$). Of the entire cohort, 8.3% at baseline and 15% at follow-up had two criteria for MetS. At the follow-up examination, all of the metabolic parameters had deteriorated. There were significant increases in mean triglyceride concentration ($p = 0.042$) and mean waist circumference ($p < 0.001$), and a significant decrease in mean HDL-cholesterol ($p = 0.028$). There were also significant increases in the prevalences of abnormal triglyceride concentration ($p = 0.040$), waist circumference ($p = 0.039$), and HDL-cholesterol concentration ($p = 0.019$) between baseline and the 1-year follow-up examinations.

At both time points, the prevalence of MetS appeared to be lower in women, but there were no significant differences at baseline ($p = 0.291$, 0% women *vs.* 6.7% men) or follow-up ($p = 0.57$, 3.3% women *vs.* 8.3% men).

Predictors of MetS

We next attempted to identify baseline parameters that were predictors of MetS at follow-up. MetS served as the dependent variable, and age, duration of education, sex, marital status, diagnostic group, a family history of psychiatric diseases, the use of tobacco or cannabis, the BDI and GAF scores, PANSS subscale scores, DUP, and all the metabolic and anthropometric components of MetS at baseline were interrogated as potential predictors. All the parameters with $p < 0.15$ on univariate analysis were included in the multivariate analysis. These were DUP ($p = 0.119$), the duration of education ($p = 0.126$),

Table 2. Metabolic parameters at baseline and 12 months later.

Parameter	Baseline	12 months later	*p*-value
Waist circumference, cm, mean (SD)	83.58 (10.14)	102.50 (99.41)	<0.001*
Abnormal waist circumference (≥102 cm in men, ≥88 cm in women), n (%)	6 (10%)	13 (21.7%)	0.039*
Serum triglycerides, mmol/L, mean (SD)	0.886 (0.42)	1.095 (0.75)	0.042*
Abnormal triglyceride concentration (>1.7 mmol/L) or treatment, n (%)	4 (6.7%)	6 (10%)	0.040*
Serum HDL-cholesterol (mmol/L), mean (SD)	1.368 (0.34)	1.295 (0.31)	0.028*
Abnormally low HDL-cholesterol (<1.04 mmol/L in men, <1.3 mmol/L in women), n (%)	13 (21.7%)	15 (25%)	0.019*
Blood pressure (mmHg), mean (SD)			
Systolic	122.18 (13.50)	123.17 (13.01)	0.583
Diastolic	66.15 (10.16)	68.02 (9.80)	0.190
Abnormal blood pressure (≥130/85 mmHg) or treatment, n (%)	19 (31.7%)	21 (35.0%)	0.990
Fasting plasma glucose concentration (mmol/L), mean (SD)	4.963 (0.77)	5.014 (0.45)	0.338
Abnormal fasting blood glucose (≥5.6 mmol/L) or diabetes, n (%)	3 (5.0%)	8 (13.3%)	0.344
MetS, n (%)	4 (6.7%)	7 (11.7%)	0.250
Number of MetS criteria, n (%)			
0	29 (48.3%)	24 (40%)	
1	22 (36.6%)	20 (33.3%)	
2	5 (8.3%)	9 (15.0%)	
3	3 (5.0%)	5 (8.3%)	
4	1 (1.7%)	2 (3.3%)	
5	0 (0%)	0 (0%)	
TG/HDL ratio	1.48	1.94	

SD, standard deviation; HDL, high-density lipoprotein; MetS, metabolic syndrome; TG, triglyceride. *$p < 0.05$.
Comparisons of the prevalences of abnormal values of metabolic parameters and MetS were performed using McNemar's test, and comparisons of mean metabolic and anthropometric values were performed using the Wilcoxon matched-pairs signed rank test.

baseline waist circumference ($p = 0.006$), the baseline general subscale of PANSS ($p = 0.132$), baseline systolic blood pressure ($p = 0.055$), and baseline HDL-cholesterol concentration ($p = 0.017$). However, none of these was found to be significant on multivariate binary logistic regression, and therefore to be a predictor of MetS at 12-months of follow-up.

Psychopharmacological treatment

At both assessments, all of the participants were being treated with atypical antipsychotics, predominantly *via* the oral route (75% and 63.3% at baseline and follow-up, respectively). At both evaluations, the participants were being prescribed risperidone as the most atypical antipsychotic alone or in combination with other medicines, orally (45% and 26.7% at baseline and follow-up, respectively). The injectable antipsychotics used were long-acting aripiprazole and paliperidone, which were administered intramuscularly. Table 3 lists the prescribed psychopharmacological treatments at the two time points.

Table 3. Psychopharmacological drugs being used at baseline and 12 months later.

	Baseline	12 months later
Antipsychotic treatment, n (%)		
Atypical antipsychotic	60 (100%)	60 (100%)
Route of antipsychotic, n (%)		
Only oral	45 (75%)	38 (63.3%)
Only LA IM	1 (1.7%)	11 (18.3%)
Both	14 (23.3%)	11 (18.3%)
Type of atypical antipsychotic, n (%)		
Clozapine, oral	2 (3.3%)	5 (8.3%)
Olanzapine, oral	14 (23.3%)	11 (18.3%)
Quetiapine, oral	1 (1.6%)	9 (15.0%)
Risperidone, oral	27 (45.0%)	16 (26.7%)
Paliperidone, oral/IM	12 (20.0%)	18 (30%)
Aripiprazole, oral/IM	17 (28.3%)	15 (25.0%)
Amissulpride, oral	1 (1.7%)	1 (1.7%)
Chlorpromazine equivalents, mean (SD) dose, mg[52,53]	295.4 (220.6)	297.4 (236.0)
Other drugs, n (%)		
Anticholinergics	6 (10%)	17 (28.3%)
Antidepressants	12 (20%)	21 (35%)
Mood stabilizers	3 (5%)	4 (6.7%)
Benzodiazepines	3 (5%)	3 (5%)

LA: long-acting; IM: intramuscular; SD: standard deviation.

Discussion

The present study is the first to assess the prevalences of MetS and metabolic parameters in patients diagnosed with non-affective or affective FEP longitudinally in Portugal. The prevalence of MetS was found to be 6.7% at baseline and 11.7% 1 year later, with the prevalence having increased in almost three-fourths of the participants over this period. We have also identified a worsening of the HDL-cholesterol and triglyceride concentrations and the waist circumference of the participants over this period, and increases in the prevalences of abnormalities of these parameters. These findings emphasize that there is a high likelihood of developing cardiovascular risk factors during the early stages of psychosis and a rapid deterioration in the metabolic profile at the same time. Thus, we have provided additional evidence that patients with FEP are predisposed toward metabolic dysfunction in the relatively short term.

The present findings are consistent with the those of previous longitudinal studies.[36,54–57] A prevalence of MetS of 6.6% was reported by Bioque *et al.* in patients with FEP, according to the criteria of the International Diabetes Federation, with a prevalence of 14.6% 2 years later, corresponding to a 120% increase.[55] A prevalence of 2.3% was identified in a study of Brazilian patients with FEP at baseline, according to the NCEP criteria, and 6 months later it was 9.1%, representing an almost three-fold increase.[54] Thus, both previous studies and the present study have demonstrated worsening of the metabolic profiles of patients with FEP. We have shown an apparent 75% increase in the prevalence of MetS, and the majority of

previous studies have also demonstrated significant increases in the prevalence of MetS during the early stages of psychosis (6 months to 2 years). The incidence of MetS during the first year identified in the present study (5%) is similar to those identified previously over the same time period (from 3.95% to 5.5%).[58,59] However, none of these studies identified significant predictors of MetS at baseline or 1 year later, as in the present study.

There have been few studies of the prevalence of MetS in the general population in Portugal. The prevalence of MetS in the Valsim cross-sectional multi-center study of 18- to 29 year-old patients attending Portuguese primary care facilities was 6.2%.[60] This is a similar prevalence to that obtained for patients with FEP at baseline in the present study, but the prevalence in these patients 1 year later was almost twice as high. The prevalences identified in the PORMETS cross-sectional study of 4004 patients attending primary care facilities throughout Portugal[61] were 5% and 16% in 18- to 30-year-olds and 31- to 40-year-olds, respectively. Thus, the MetS prevalence identified in the present study is higher than that in the general population, but this difference only became evident after one year. The most common criterion for MetS in the PORMETS study was high blood pressure, whereas in the present study it was abnormal waist circumference. It should be noted that the PORMETS and Valsim studies were of primary care users, and therefore the level of prevalence of MetS would probably be lower in the real general population of Portugal. In addition, there were differences in the definitions of MetS that were used. MetS was defined using the ATP-III criteria in the Valsim study and using the HARM2009 criteria in the PORMETS study.[49,62] The MESYAS cross-sectional study of 7256 members of the working population of Spain defined MetS using the

modified ATP-III criteria,[49] and showed a 2.5% to 5% prevalence in 20- to 39-year-olds,[63] which was lower than in the present study, in which we used the same definition of MetS. However, the results of all the studies discussed imply that the prevalence of MetS is high 1 year following a diagnosis of FEP.

Some other previous cross-sectional studies have shown a high prevalence of MetS in patients with psychoses, such as schizophrenia. As expected, the prevalence of MetS in patients with chronic schizophrenia seems to be higher than that in patients with FEP. For example, Sahpolat et al. stated that the prevalence of MetS in Turkish patients with schizophrenia was 40%,[38] Grover et al. calculated the same prevalence in Indian patients with schizophrenia,[64] and other studies have calculated prevalences of 51% and 67.6% in Australian and British patients with schizophrenia, respectively.[65,66]

A number of factors that are associated with MetS, including body mass, lifestyle, obesity, adipokine dysregulation, and inflammation, have been shown to be associated with psychosis.[25]

Diet, smoking, and physical activity affect the prevalence of MetS in patients with psychosis.[67] The importance of these variables have not been thoroughly investigated, but patients with FEP have more unhealthy lifestyles than healthy individuals of similar ages. This is evident in terms of higher prevalences of cigarette smoking and alcohol abuse; poor dietary habits, with the consumption of large amounts of saturated fatty acids, carbohydrates, and salt; and small amounts of fruit and vegetables; and low levels of physical activity.[29,67,68] A recent study showed that the majority of patients with FEP have unhealthy dietary habits, as defined by a lack of consumption of a Mediterranean-style diet, and that this poor diet was associated with a low educational level.[67] However,

we did not evaluate or control for the diet or physical activity of the participants in the present study.

In our research, waist circumference was the parameter that most significantly changed during the 12-month follow-up period ($p < 0.001$). This is consistent with the important role of adipocytes in both psychotic disorders and MetS, and suggests that excess weight may have a deleterious effect on the immune system, manifesting in a pro-inflammatory effect on the central nervous system.[31,69,70] Previous studies have revealed an association of chronic inflammation and adipokines with psychosis and evidence of immune dysfunction.[71] These immunological changes include high concentrations of pro-inflammatory cytokines and chemokines in the circulation and cerebrospinal fluid, as well as changes in immune cell function in the central nervous system.[72,73] Adipose tissue directly or indirectly secretes pro-inflammatory cytokines and proteins (IL-6, TNF-α, insulin-like growth factor-1, leptin, resistin, apelin, visfatin, CCL22, and nesfatin-1),[30,31,33,74] and patients with schizophrenia also show activation of microglia, which contributes to the high serum concentrations of pro-inflammatory cytokines.[73,75] Some of these substances are present and/or have receptors in parts of the central nervous system, but their exact roles in the pathophysiology of psychosis are still being studied. It is interesting to note that recent studies revealed that baseline metabolic and inflammatory parameters may be diagnostic, associated with the severity of the symptoms, and/or be predictors of the treatment response in FEP.[76,77]

The previous studies also characterized the changes in the lipid profiles of patients following a diagnosis of FEP, which include a decrease in HDL-cholesterol concentration and an increase in triglyceride concentration, resulting in an increase in the triglyceride-to-HDL ratio. It is important to note that this ratio is an independent predictor of cardiovascular disease and mortality[77] and a marker of atherogenesis.[79,80] The TG/HDL ratios of the participants in the present study were high (baseline, 1.48; 1-year follow-up, 1.94), consistent with the presence of cardiovascular risk factors.

The male participants in the present study tended to have higher prevalences of MetS at baseline ($p = 0.291$, 0% women vs. 6.7% men) and follow-up ($p = 0.571$, 3.3% women vs. 8.3% men), consistent with the results of previous studies of patients with FEP.[81,82] However, the male participants in the present study had worse metabolic profiles in the early stages of psychosis than those in previous studies,[55,83] and these findings are consistent with those obtained in studies of the general population.[84]

The baseline evaluation was made soon after the diagnosis of FEP, during the first few days of treatment. Therefore, the medication is likely to have had a minor effect on the findings at baseline. However, the medication used may have affected the incidence of MetS during the follow-up period. Nevertheless, at both time points, medications with moderate or low metabolic impacts were used, and because few participants developed MetS during the study, no further analysis was performed regarding the antipsychotic medication.

Assessments of glucose homeostasis, and in particular oral glucose tolerance testing, were suggested to be an effective way of evaluating cardiovascular and metabolic risk in patients with FEP in the report by Garcia-Rizo et al.[36] The cross-sectional study reported therein aimed to calculate the prevalence of MetS in patients with FEP and controls. The glucose homeostasis of the 84 patients with FEP varied greatly. To some extent, the results we have obtained in the present study are not consistent with this, but we did not perform

homeostatic model assessment, oral glucose tolerance testing, or any other assessment of glucose homeostasis. However, we contend that the assessment of MetS is a useful means of judging the risk of cardiovascular disease in patients with FEP, and the measurement of parameters related to MetS is more feasible in clinical psychiatric research than other assessments of glucose homeostasis.

One limitation of the present study was the small sample size, which could have reduced the likelihood of identifying predictors of MetS and prevented an assessment of the effect of antipsychotic treatment. In addition, it would have been desirable to compare the prevalence of MetS in the psychiatric patients with that of a control group. However, we have compared our findings with those of a study of primary care data, in an attempt to overcome this limitation. Furthermore, we did not analyze the effects of each of the second-generation antipsychotics used by the participants on their metabolism. Finally, we did not account for potential confounding factors, such as physical activity and diet.

In conclusion, the present findings suggest that the prevalence of metabolic abnormalities in patients with FEP is high, and that these rapidly worsen during the early stages of the disorder. Further studies should be conducted to analyze the effects of specific interventions on these metabolic parameters and on the morbidity and mortality associated with cardiovascular disease in patients with FEP. In addition, the effects of each of the second-generation antipsychotics on the metabolism and inflammation of patients with FEP should be assessed.

Author contributions

RC, PL, CG, and MLF participated in the clinical work. RC and PL performed the literature review. CG and MLF supervised the project and contributed to the manuscript content and editing. All the authors contributed to the manuscript revision and read and approved the submitted version.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. Capasso RM, Lineberry TW, Bostwick JM, et al. Mortality in schizophrenia and schizoaffective disorder: An Olmsted County, Minnesota cohort: 1950–2005. *Schizophr Res* 2008; 98: 287–294.
2. Wahlbeck K, Westman J, Nordentoft M, et al. Outcomes of Nordic mental health systems: Life expectancy of patients with mental disorders. *Br J Psychiatry* 2011; 199: 453–458.
3. Brown S. Excess mortality of schizophrenia. A meta-analysis. *Br J Psychiatry* 1997; 171: 502–508.
4. Casadebaig F and Philippe A. [Mortality in schizophrenic patients. 3 years follow-up of a cohort]. *Encéphale* 1999; 25: 329–337.
5. Rössler W, Salize HJ, Van Os J, et al. Size of burden of schizophrenia and psychotic disorders. *Eur Neuropsychopharmacol* 2005; 15: 399–409.
6. Healy D, Le Noury J, Harris M, et al. Mortality in schizophrenia and related

psychoses: Data from two cohorts, 1875–1924 and 1994–2010. *BMJ (Open)* 2012; 2: e001810.

7. Brown S, Kim M, Mitchell C, et al. Twenty-five year mortality of a community cohort with schizophrenia. *Br J Psychiatry* 2010; 196: 116–121.

8. Hennekens CH, Hennekens AR, Hollar D, et al. Schizophrenia and increased risks of cardiovascular disease. *Am Heart J* 2005; 150: 1115–1121.

9. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001; 24: 683–689.

10. Mitchell AJ, Vancampfort D, De Herdt A, et al. Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. *Schizophr Bull* 2013; 39: 295–305.

11. Kim DH, Kim B, Han K, et al. The relationship between metabolic syndrome and obstructive sleep apnea syndrome: A nationwide population-based study. *Sci Rep* 2021; 11: 1–8751.

12. Almendros I, Basoglu ÖK, Conde SV, et al. Metabolic dysfunction in OSA: Is there something new under the sun? *J Sleep Res* 2022; 31: e13418.

13. Wu S, He H, Wang Y, et al. Association between benign prostate hyperplasia and metabolic syndrome in men under 60 years old: A meta-analysis. *J Int Med Res* 2019; 47: 5389–5399.

14. Haupt DW, Rosenblatt LC, Kim E, et al. Prevalence and predictors of lipid and glucose monitoring in commercially insured patients treated with second-generation antipsychotic agents. *Am J Psychiatry* 2009; 166: 345–353.

15. Lambert TJR and Newcomer JW. Are the cardiometabolic complications of schizophrenia still neglected? Barriers to care. *Med J Aust* 2009; 190: S39–S42.

16. Ryan MCM, Collins P, and Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. *Am J Psychiatry* 2003; 160: 284–289.

17. Zhang Q, Deng C, and Huang XF. The role of ghrelin signalling in second-generation antipsychotic-induced weight gain. *Psychoneuroendocrinology* 2013; 38: 2423–2438.

18. Fountaine RJ, Taylor AE, Mancuso JP, et al. Increased food intake and energy expenditure following administration of olanzapine to healthy men. *Obesity (Silver Spring)* 2010; 18: 1646–1651.

19. Kluge M, Schuld A, Himmerich H, et al. Clozapine and olanzapine are associated with food craving and binge eating: Results from a randomized double-blind study. *J Clin Psychopharmacol* 2007; 27: 662–666.

20. Stubbs B, Williams J, Gaughran F, et al. How sedentary are people with psychosis? A systematic review and meta-analysis. *Schizophr Res* 2016; 171: 103–109.

21. Dipasquale S, Pariante CM, Dazzan P, et al. The dietary pattern of patients with schizophrenia: A systematic review. *J Psychiatr Res* 2013; 47: 197–207.

22. Lett TAP, Wallace TJM, Chowdhury NI, et al. Pharmacogenetics of antipsychotic-induced weight gain: Review and clinical implications. *Mol Psychiatry* 2012; 17: 242–266.

23. Knolle-Veentjer S, Huth V, Ferstl R, et al. Delay of gratification and executive performance in individuals with schizophrenia: Putative role for eating behavior and body weight regulation. *J Psychiatr Res* 2008; 42: 98–105.

24. Minichino A, Ando A, Francesconi M, et al. Investigating the link between drug-naive first episode psychoses (FEPs), weight gain abnormalities and brain structural damages: Relevance and implications for therapy. *Prog Neuropsychopharmacol Biol Psychiatry* 2017; 77: 9–22.

25. Penninx BWJH, Lange SMM. Metabolic syndrome in psychiatry patients: overview, mechanisms, and implications. *Dialog Clin Neurosci* 2018; 20: 63–72.

26. Gassó P, Arnaiz JA, Mas S, et al. Association study of candidate genes with obesity and metabolic traits in antipsychotic-treated patients with first-episode psychosis over a 2-year period. *J Psychopharmacol* 2020; 34: 514–523.

27. Zurrón Madera P, Casaprima Suárez S, García Álvarez L, et al. Eating and nutritional habits in patients with schizophrenia. *Rev Psiquiatr Salud Ment* 2022; 15: 54–60.

28. Scheewe TW, Jörg F, Takken T, et al. Low physical activity and cardiorespiratory fitness in people with schizophrenia: A comparison with matched healthy controls and associations with mental and physical health. *Front Psychiatry* 2019; 10: 87.

29. Stubbs B, Firth J, Berry A, 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.

30. Sahpolat M, Ari M, and Kokacya MH. Plasma apelin, visfatin and resistin levels in patients with first episode psychosis and chronic schizophrenia. *Clin Psychopharmacol Neurosci* 2020; 18: 109–115.

31. Beumer W, Drexhage RC, De Wit H, et al. Increased level of serum cytokines, chemokines and adipokines in patients with schizophrenia is associated with disease and metabolic syndrome. *Psychoneuroendocrinology* 2012; 37: 1901–1911.

32. Ronti T, Lupattelli G, and Mannarino E. The endocrine function of adipose tissue: An update. *Clin Endocrinol (Oxf)* 2006; 64: 355–365.

33. Sahpolat M and Ari M. Plasma nesfatin 1 level in patients with first attack psychosis. *Bratisl Lek Listy* 2017; 118: 77–79.

34. Beumer W, Gibney SM, Drexhage RC, et al. The immune theory of psychiatric diseases: A key role for activated microglia and circulating monocytes. *J Leukoc Biol* 2012; 92: 959–975.

35. Chen S, Broqueres-You D, Yang G, et al. Male sex may be associated with higher metabolic risk in first-episode schizophrenia patients: A preliminary study. *Asian J Psychiatr* 2016; 21: 25–30.

36. Garcia-Rizo C, Fernandez-Egea E, Oliveira C, et al. Metabolic syndrome or glucose challenge in first episode of psychosis? *Eur Psychiatry* 2017; 41: 42–46.

37. Petrikis P, Tigas S, Tzallas AT, et al. Parameters of glucose and lipid metabolism at the fasted state in drug-naïve first-episode patients with psychosis: Evidence for insulin resistance. *Psychiatry Res* 2015; 229: 901–904.

38. Sahpolat M and Ari M. Higher prevalence of metabolic syndrome and related factors in patients with first-episode psychosis and schizophrenia: A cross-sectional study in Turkey. *Nord J Psychiatry* 2021; 75: 73–78.

39. Smith J, Griffiths LA, Band M, et al. Cardiometabolic risk in first episode psychosis patients. *Front Endocrinol (Lausanne)* 2020; 11: 564240.

40. Chen S, Broqueres-You D, Yang G, et al. Relationship between insulin resistance, dyslipidaemia and positive symptom in Chinese antipsychotic-naive first-episode patients with schizophrenia. *Psychiatry Res* 2013; 210: 825–829.

41. Zhai D, Cui T, Xu Y, et al. Cardiometabolic risk in first-episode schizophrenia (FES) patients with the earliest stages of both illness and antipsychotic treatment. *Schizophr Res* 2017; 179: 41–49.

42. Lee AMH, Ng CG, Koh OH, et al. Metabolic syndrome in first episode schizophrenia, based on the national mental health registry of schizophrenia (NMHR) in a general hospital in Malaysia: A 10-year retrospective cohort study. *Int J Environ Res Public Health* 2018; 15: 1–13.

43. McGorry PD. Early intervention in psychosis: Obvious, effective, overdue. *J Nerv Ment Dis* 2015; 203: 310–318.

44. Coentre R, Mendes T, Rebelo A, et al. PROFIP: A Portuguese early intervention programme for first-episode psychosis in Lisbon. *Early Interv Psychiatry* 2019; 13: 1525–1529.

45. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.

46. Kay SR, Fiszbein A, and Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; 13: 261–276.

47. Hall RCW. Global assessment of functioning. A modified scale. *Psychosomatics* 1995; 36: 267–275.

48. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry* 1961; 4: 561–571.

49. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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) final report. *Circulation* 2002; 106: 3143–3421.

50. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 2005; 112: 2735–2752.

51. Knopfholz J, Disserol CCD, Pierin AJ, et al. Validation of the Friedewald formula in patients with metabolic syndrome. *Cholesterol* 2014; 2014: 261878.

52. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry* 2003; 64: 663–667.

53. Taylor D, Paton C, and Kapur S. *The Maudsley prescribing guidelines in psychiatry*. 12th ed. Wiley-Blackwell, 2015.

54. Attux C, Quintana MI, and Chaves AC. Weight gain, dyslipidemia and altered parameters for metabolic syndrome on first episode psychotic patients after six-month follow-up. *Braz J Psychiatry* 2007; 29: 346–349.

55. Bioque M, García-Portilla MAP, García-Rizo C, et al. Evolution of metabolic risk factors over a two-year period in a cohort of first episodes of psychosis. *Schizophr Res* 2018; 193: 188–196.

56. Pérez-Iglesias R, Martínez-García O, Pardo-Garcia G, et al. Course of weight gain and metabolic abnormalities in first treated episode of psychosis: The first year is a critical period for development of cardiovascular risk factors. *Int J Neuropsychopharmacol* 2014; 17: 41–51.

57. Russell A, Ciufolini S, Gardner-Sood P, et al. Inflammation and metabolic changes in first episode psychosis: Preliminary results from a longitudinal study. *Brain Behav Immun* 2015; 49: 25–29.

58. Saloojee S, Burns JK, and Motala AA. Metabolic syndrome in antipsychotic naive African patients with severe mental illness in usual care. *Early Interv Psychiatry* 2018; 12: 1137–1143.

59. Srihari VH, Phutane VH, Ozkan B, et al. Cardiovascular mortality in schizophrenia: Defining a critical period for prevention. *Schizophr Res* 2013; 146: 64–68.

60. Fiuza M, Cortez-Dias N, Martins S, et al. Metabolic syndrome in Portugal: Prevalence and implications for cardiovascular risk–results from the VALSIM. *Rev Port Cardiol* 2008; 27: 1495–1529.

61. Raposo L, Severo M, Barros H, et al. The prevalence of the metabolic syndrome in Portugal: The PORMETS study. *BMC Public Health* 2017; 17: 555.

62. Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation task force on epidemiology and prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; 120: 1640–1645.

63. Alegría E, Cordero A, Laclaustra M, et al. [Prevalence of metabolic syndrome in the Spanish working population: MESYAS registry]. *Rev Esp Cardiol* 2005; 58: 797–806.

64. Grover S, Aggarwal M, Dutt A, et al. Prevalence of metabolic syndrome in patients with schizophrenia in India. *Psychiatry Res* 2012; 200: 1035–1037.

65. John AP, Koloth R, Dragovic M, et al. Prevalence of metabolic syndrome among Australians with severe mental illness. *Med J Aust* 2009; 190: 176–179.

66. Heald A, Pendlebury J, Anderson S, et al. Lifestyle factors and the metabolic syndrome in schizophrenia: A cross-sectional study. *Ann Gen Psychiatry* 2017; 16: 12.

67. Saugo E, Lasalvia A, Bonetto C, et al. Dietary habits and physical activity in first-episode psychosis patients treated in community services. Effect on early

anthropometric and cardio-metabolic alterations. *Schizophr Res* 2020; 216: 374–381.

68. Grossman M, Bowie CR, Lepage M, et al. Smoking status and its relationship to demographic and clinical characteristics in first episode psychosis. *J Psychiatr Res* 2017; 85: 83–90.

69. Bolu A, Aydın MS, Akgün A, et al. Serum levels of high sensitivity C-reactive protein in drug-naïve first-episode psychosis and acute exacerbation of schizophrenia. *Clin Psychopharmacol Neurosci* 2019; 17: 244–249.

70. Juncal-Ruiz M, Riesco-Dávila L, De la Foz VOG, et al. The effect of excess weight on circulating inflammatory cytokines in drug-naïve first-episode psychosis individuals. *J Neuroinflammation* 2018; 15: 63.

71. Strous RD and Shoenfeld Y. Schizophrenia, autoimmunity and immune system dysregulation: A comprehensive model updated and revisited. *J Autoimmun* 2006; 27: 71–80.

72. Frydecka D, Krzystek-Korpacka M, Lubeiro A, et al. Profiling inflammatory signatures of schizophrenia: A cross-sectional and meta-analysis study. *Brain Behav Immun* 2018; 71: 28–36.

73. Volk DW. Role of microglia disturbances and immune-related marker abnormalities in cortical circuitry dysfunction in schizophrenia. *Neurobiol Dis* 2017; 99: 58–65.

74. Laurikainen H, Vuorela A, Toivonen A, et al. Elevated serum chemokine CCL22 levels in first-episode psychosis: Associations with symptoms, peripheral immune state and in vivo brain glial cell function. *Transl Psychiatry* 2020; 10: 94.

75. Monji A, Kato TA, Mizoguchi Y, et al. Neuroinflammation in schizophrenia especially focused on the role of microglia. *Prog Neuropsychopharmacol Biol Psychiatry* 2013; 42: 115–121.

76. Nettis MA, Pergola G, Kolliakou A, et al. Metabolic-inflammatory status as predictor of clinical outcome at 1-year follow-up in patients with first episode psychosis. *Psychoneuroendocrinology* 2019; 99: 145–153.

77. Ramos Ferreira S, Moura D, Oliveira P, et al. Metabolic parameters as possible diagnostic predictors in first-episode psychosis: An exploratory retrospective cohort study. *Early Interv Psychiatry* 2021. DOI: 10.1111/EIP.13257.

78. Ösby U, Correia N, Brandt L, et al. Mortality and causes of death in schizophrenia in Stockholm County, Sweden. *Schizophr Res* 2000; 45: 21–28.

79. Dobiášová M and Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: Correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER(HDL)). *Clin Biochem* 2001; 34: 583–588.

80. Frohlich J and Dobiášová M. Fractional esterification rate of cholesterol and ratio of triglycerides to HDL-cholesterol are powerful predictors of positive findings on coronary angiography. *Clin Chem* 2003; 49: 1873–1880.

81. Cordes J, Bechdolf A, Engelke C, et al. Prevalence of metabolic syndrome in female and male patients at risk of psychosis. *Schizophr Res* 2017; 181: 38–42.

82. Mitchell AJ, Vancampfort D, Sweers K, et al. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders-a systematic review and meta-analysis. *Schizophr Bull* 2013; 39: 306–318.

83. Patel JK, Buckley PF, Woolson S, et al. Metabolic profiles of second-generation antipsychotics in early psychosis: Findings from the CAFE study. *Schizophr Res* 2009; 111: 9–16.

84. Tillin T, Forouhi N, Johnston DG, et al. Metabolic syndrome and coronary heart disease in South Asians, African-Caribbeans and white Europeans: A UK population-based cross-sectional study. *Diabetologia* 2005; 48: 649–656.