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Prevalence of metabolic syndrome and related factors in a large sample of antipsychotic naïve patients with first-episode psychosis: Baseline results from the PAFIP cohort

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ABSTRACT

Background: Few investigations have been carried out on metabolic syndrome in antipsychotic- naïve patients with schizophrenia.
Methods: Our primary objective was to compare the prevalence of Metabolic Syndrome (MetS), as defined by the National Cholesterol Education Program, Adult Treatment Panel III in 2001 (NCEP-ATP III), between a Spanish cohort of 303 drug-naïve patients with a first episode of psychosis (FEP) without any previous cardiovascular condition, and 153 healthy individuals.
Results: Participants included 303 patients with FEP (M:F 53:46) and 153 control subjects (M:F 56:43). The mean and standard deviation ages were 31(9.38) and 29 (7.57) years in the study and control groups respectively ($F = 4.09$; $p = 0.93$). We found that the prevalence of MetS in drug-naïve patients with FEP (5.6 %) was similar to the prevalence of MetS in age-sex matched controls (5.12 %). However, 60.7 % of patients with FEP met at least one of the five MetS components, while among the control subjects only 36.5 % met at least one component. Additionally, we found that other factors not included among the operational definition of MetS, but still important in cardiovascular risk, were also altered.
Conclusion: FEP patients have a greater risk of presenting at least one altered MetS component than healthy controls which could indicate the need of development of screening methods detecting cardiovascular risk. Likewise, gender differences in metabolic components such as waist circumference, which is a predictor of cardiovascular events have been found. Similarly, research should focus on metabolic risk predictors that include not only MetS, but also specific parameters for the early psychosis population.

Abbreviations: MetS, metabolic syndrome; BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; WC, waist circumference; PAFIP, (Programa de Atención a las Fases Iniciales de Psicosis) Intervention Program of First episode psychosis.

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1. Introduction

People with schizophrenia have an elevated mortality rate, which is more than twice as high than that of the general population (Walker et al., 2015). Natural causes of death, mainly cardiovascular events, account for most of the premature mortality in patients with schizophrenia (Correll et al., 2017; Laursen et al., 2012). This excess mortality has been related to adverse effects of medication, high rates of somatic comorbidity, inequalities in access to somatic disease treatment and accelerated ageing. In this sense, hyperlipidaemia (61 %), smoking (55 %), obesity (41 %), diabetes (19 %) hypertension (17 %) (Perez-Pinar et al., 2016) and respiratory disease (Suetani et al., 2021) are the most prevalent cardiovascular risk factors in patients with schizophrenia.

Several of these conditions are interrelated, frequently co-occur and share underlying mechanisms, increasing the risk of developing cardiovascular disease and diabetes, so they have been grouped forming the metabolic syndrome (MetS). Diagnostic criteria include high triglyceride values, low high-density lipoprotein (HDL) cholesterol, high blood pressure, high blood glucose levels and abdominal obesity (either increased abdominal circumference or BMI $\geq$ 30 kg/m^2) (Eckel et al., 2005; Huang, 2009; Kahn et al., 2005). According to the existing literature, the prevalence of MetS in the general population ranges from 6 % to 45 % (Moore et al., 2017), while in patients with schizophrenia taking antipsychotics it ranges from 35.3 % (Mitchell et al., 2013a; Vancampfort et al., 2015) to 49 % (Kraemer et al., 2011). Antipsychotic exposure is probably the main risk factor for weight gain and related metabolic alterations in psychosis (Canal-Rivero et al., 2020; Correll et al., 2014; Vazquez Bourgon et al., 2017; Vazquez-Bourgon et al., 2018, 2020); in this sense treatment discontinuation was associated with partial reversal of weight gain and better metabolic progression (Mackin et al., 2012; Vazquez-Bourgon, Mayoral van-son, et al., 2021). Despite this, previous studies (Fernandez-Egea et al., 2009; Garcia-Rizo et al., 2017; Jensen et al., 2017; Perry et al., 2016) have proposed that antipsychotic naïve patients with psychosis already show metabolic disturbances at onset.

Most studies on naïve patients have focused on the search for specific metabolic alterations (weight, BMI, or glucose and lipid alterations), without exploring the presence of all MetS components together. The evidence from these studies indicates greater rates in drug naïve patients with a first episode of psychosis (FEP), of insulin resistance, alterations of basal glucose (Perry et al., 2016; Pillinger et al., 2017a; Pillinger et al., 2017b) and dyslipidaemia (Misiak et al., 2017; Perry and Singh, 2018; Pillinger et al., 2018). In addition, the altered levels of other biochemical factors not included in the MetS definition such as plasma levels of cortisol (Misiak et al., 2017), ACTH, homocysteine (Ayesa-Arriola et al., 2012; Misiak et al., 2014; Shih et al., 2021; Zhang et al., 2021), C-reactive protein (Fernandes et al., 2016; Steiner et al., 2020), and leptine (Misiak et al., 2019) have been found in drug naïve patients with psychosis.

However, only a few investigations have explored the presence of MetS through the analysis of all of its components in antipsychotic-naïve patients with psychosis. Moreover, these studies had some relevant limitations among which stand out the small sample sizes (Effat et al., 2012; Enez Darcin et al., 2015b; Grover et al., 2012; Martín Otaño et al., 2013; Sahpolat and Ari, 2020), the lack of a comparison with a control group (De Hert et al., 2008; Grover et al., 2012; Kraemer et al., 2011; Martín Otaño et al., 2013; Medved et al., 2009; Owiredu et al., 2012; Srivastava et al., 2018), the lack of gender stratification analysis and the fact that patients were not strictly antipsychotic-naïve patients, for example they had a few weeks of medication and were categorised as drug naïve (Chiliza et al., 2015; Correll et al., 2014; Fleischhacker et al., 2013; Pallava et al., 2012; Srihari et al., 2013). Based on most of these studies, there was found (Mitchell et al., 2013b) to be a MetS prevalence of 10 % in naïve patients with psychosis and a recent meta-analysis (Garrido-Torres et al., 2021) reported increased rates of MetS in drug-naïve patients with psychosis compared with age and sex-matched controls, especially in those of non-Caucasian origin.

The aim of this study was to explore whether people with a FEP presented a greater rate of MetS at inclusion, before the exposure to antipsychotic medication (truly naïve: 0 days of antipsychotic medication), than those from a non-psychosis control group. We present baseline results of MetS prevalence and related metabolic parameters in a representative sample of antipsychotic FEP naïve patients.

2. Material and methods

2.1. Study setting

Data were obtained from a longitudinal intervention program of FEP called PAFIP (Programa de Atención a las Fases Iniciales de Psicosis) conducted at the outpatient clinic and the inpatient unit of the University Hospital Marqués de Valdecilla, Spain (Pelayo-Terán et al., 2008). Conforming to international standards for research ethics, this program was approved by the local institutional review board (the Clinical Research Ethics Committee of Cantabria). Patients meeting inclusion criteria and their families provided written informed consent prior to their inclusion in the program.

2.2. Participants

From February 2001 to October 2018, all referrals to PAFIP were screened for patients who met the following criteria: (1) 15–60 years old; (2) living in the catchment area; (3) experiencing their first episode of psychosis; (4) no previous antipsychotic exposure (5) DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, psychotic disorder not otherwise specified, or schizoaffective disorder. Patients were excluded for any of the following reasons: (1) meeting DSM-IV criteria for intellectual disability, (2) having a history of neurological disease or head injury. The diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (First et al., 2002), carried out by an experienced psychiatrist 6 months on from the baseline visit. Our operational definition of a "first episode of psychosis" included individuals suffering from their first episode of nonaffective psychosis (meeting the inclusion criteria defined above) regardless of the duration of untreated psychosis. A group of subjects, without psychiatric illness, was recruited as control group between April 2010 and January 2012. Their assessment included sociodemographic questionnaires, anthropometric measures and blood extraction for laboratory testing. Control subjects were matched for age and gender with study subjects. All subjects provided written informed consent prior to their inclusion in the study, which was approved by the local ethics committee (the Clinical Research Ethics Committee of Cantabria).

2.3. Study design and metabolic assessment

Our primary research objective was to compare the prevalence of MetS, defined by the revised National Cholesterol Education Program, Adult Treatment Panel III in 2005 (NCEP-ATP III) as a composite measure that indicates the risk of developing cardiovascular disease and diabetes, between a Spanish cohort of drug-naïve patients at their inclusion due to their first psychosis episode and a group of healthy individuals. The revised National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria (Alberti et al., 2009; Grundy et al., 2005) require at least three of the following components: (1) abdominal obesity (waist circumference $\geq$94 cm for Mediterranean men or $\geq$80 cm for Mediterranean women), (2) triglycerides $\geq$150 mg/dL, (3) HDL cholesterol $\leq$40 mg/dL for men or 50 mg/dL for women, (4) systolic/diastolic blood pressure $\geq$130/85 mmHg or receiving drug treatment, and (5) fasting plasma glucose $\geq$100 mg/dL. Blood samples were drawn after 8 h fasting for glucose and lipid profile testing. In the current study, the revised Adult Treatment Panel III (ATPIII) was used to define MetS. We also examine the individual components within the Mets such as: High-density lipoprotein (HDL), glycaemia, high blood

pressure (HBP), triglycerides and waist circumference (WC). Relevant metabolic parameters not included in the MetS composite measure, such as Total cholesterol, Low-density lipoprotein LDL, Homeostasis Model Assesment HOMA, Homocysteine, C-reactive protein (CRP), Vit B12, insulin, leptine and anthropometric measurements such as body mass index (BMI) were also examined.

Health risk behaviors and demographic information were collected at the study inception from patients, relatives and medical records. Specifically, we considered: age, sex, ethnicity, years of education, family history of psychosis, socioeconomic status, living area, living status, relationship status and employment status. Other factors not included in the operational definition of MetS were also explored, such as alcohol, cannabis, tobacco, LSD and amphetamine use, which were self-reported as 'present/absent'. Additionally, tobacco and cannabis consumption were reported as number of cigarettes per day.

2.4. Statistics

2.4.1. Sample size

Sample size was calculated based on the reported data about MetS prevalence in patients with FEP 13.8 % vs healthy controls 7 % (Garrido-Torres et al., 2021). According to the parameter choices, for a desired power of 0.80 and 90 % confidence level, we estimated that we would need 456 participants distributed in 303 cases and 153 healthy controls. Sample size analysis was conducted using Epidata software (Lauritsen and Bruss, 2004).

2.4.2. Data analysis

We conducted a cross-sectional analysis of baseline clinical assessment data. Frequency analyses were conducted to determine demographic variables, and the prevalence of cardiometabolic and health risk factors. The prevalence was calculated by dividing the total number of events (MetS) by the total sample size and multiplying the result by 100. The prevalence of MetS was calculated overall and by gender. For estimates of prevalence, subjects with missing information on MetS criteria were assumed not to have met that criterion. Data were analysed using means SD for continuous data and frequency tables for categorical data. Significant associations in contingency tables (cross tabulations) were assessed using the standard χ^2 test. If an expected cell count in the cross tabulation was <5, then the Fishers exact test was used. For continuous variables (weight, BMI, waist, systolic blood pressure, diastolic blood pressure, glycemia, triglycerides, HDL, LDL, total cholesterol, HOMA, homocysteine, CRP, vitamin B12, insulin, leptin): the presence of non-normal distribution was explored. When non-normal distribution was observed, a non-parametric test (Mann-Whitney *U* test) was conducted, whereas a parametric test (independent sample *t*-test) was used when distribution was normal. *t*-Tests were also performed on categorical data to determine sex differences across outcome measures. A two tailed t-test was used to compare differences in continuous variables, and a p-value < 0.05 was considered to be statistically significant.

In order to explore the influence of other variables and confirm that the association between metabolic alterations and FEP remained after adjustment, we used a multivariate logistic regression where the outcome was MetS, the exposure was FEP and the confounders were sex, education level, single, low family socioeconomic status, urban zone, unemployed, currently student status. Additionally we performed separated logistic regressions for every MetS component (waist circumference, systolic blood pressure, diastolic blood pressure, glycemia, triglycerides, HDL). Analysis was conducted using Statistical Package for Social Sciences (IBM SPSS, Version 28.0, Armonk, NY: IBM Corp).

3. Results

3.1. Sample characteristics

Participants included 303 patients with FEP (M:F 53:46) and 153 control subjects (M:F 56:43). The mean ages were 31 and 29 years in the study and control groups respectively ($F = 4.09$; $p = 0.93$), and 87 % were of white Caucasian ethnicity. There were significant differences in the demographic characteristics between the FEP group and the control one: FEP patients were more frequently unemployed (42.3 % vs 23.3 % $x^2 = 15.33$, $p = 0.001$) and were more frequently single (62.8 % vs 44.2 %, x^2 24.59 $p = 0.001$) than healthy controls. No differences in socioeconomic family status between FEP patients and controls were found (54.7 % vs 63.5 %, $x^2 = 3.14$, $p = 0.076$) (Table 1).

3.2. MetS prevalence in FEP patients and controls

The prevalence of MetS defined as a composite category including HDL, HBP, WC, triglycerides and glycaemia in naïve patients with FEP was similar to that in age-sex matched controls (5.6 % vs 5.12 %; $x^2 = 0.004$, $p = 0.821$) (Table 2). Despite this, we observed significant differences between groups in the frequency of participants meeting some of the 5 MetS individual components. In the FEP group there were significantly more individuals with high blood pressure (HBP) (27.4 % vs 4.5 %; $x^2 = 34.2$, $p < 0.001$), low HDL (31.7 % vs 19.9 %; $x^2 = 7.17$, $p = 0.007$) and high LDL (46.4 % vs 36.5 % $x^2 = 4.046$, $p = 0.044$). Interestingly, we also observed differences between FEP group and control group in the number of altered MetS components for those participants without MetS. Thus, FEP patients had a greater risk of meeting at least one of the MetS components (60.7 % vs 36.5 %; $x^2 =$

Table 1
Sociodemographic characteristics.

	FEP		Controls		Statistical	p
	303		156			
	n	%	n	%		
Age						
Mean	31.20		29.63		24.09	0.93
SD	9.38		7.57			
Sex						
Men	163	53.8	97	56.6	2.94	0.086
Women	140	46.2	59	43.4		
Ethnicity						
Caucasian	274	90.4	151	98.7	10.957	0.001
Non- caucasian	29	9.6	2	1.3		
Arabic	2	0.7	0	0		
Subsaharian	8	2.6	0	0		
Asian	1	0.3	0	0		
Hispanic	18	5.9	2	1.3		
Socioeconomic						
Urban	214	70.9	63	69.2	0.089	0.765
Single	204	62.8	69	44.2	24.59	<0.001
Unemployed	126	42.3	37	23.7	15.33	<0.001
Low family socioeconomic status	163	54.7	94	63.5	3.14	0.076
DSM-IV diagnosis						
Schizophrenia	151	49.8				
Brief psychotic disorder	40	13.2				
Unspecified psychotic disorder	30	9.9				
Schizophreniform disorder	78	25.7				
Schizoaffective disorder	3	1.0				
Delusional disorder	1	0.33				
In-patient	196	64.6				
out-patient	107	35.3				
Education level						
Low	143	47.5	52	33.1	6.43	0.013
Others	160	52.7	101	64.3		
Currently studying	67	22.1	29	18	3.36	0.67

FEP, First episode psychosis; Statistically significant differences: $p < 0.05$.

Table 2
Prevalence of metabolic syndrome and related factors.

	FEP n = 303	HC n = 156	Test value	p
Metabolic syndrome n (%)	17 (5.6)	8 (5.12)	0.04[a]	0.821
Glycaemia	18 (5.6)	8 (5.1)	0.12[a]	0.450
Triglycerides	23 (7.6)	18 (11.1)	1.97[a]	0.160
HDL	96 (31.7)	31 (19.9)	7.17[a]	0.007
Blood pressure	83 (27.4)	7 (4.5)	34.27[a]	0.001
Waist	43 (14.2)	29 (18.6)	1.24[a]	0.220
LDL	140 (46.4)	57 (36.5)	4.04[a]	0.044
Women				
Metabolic syndrome n (%)	5 (3.6)	1 (1.7)	0.002[a]	0.480
Glycaemia	10 (7.1)	1 (1.7)	0.065[b]	0.111
Triglycerides	7 (5)	1 (1.7)	0.054[b]	0.440
HDL	46 (32.9)	11 (18.6)	4.102[a]	0.043
Blood pressure	23 (16.4)	1 (1.7)	8.49[a]	0.004
Waist	29 (20.7)	12 (20.3)	0.004[a]	0.952
LDL	57 (40.7)	20 (33.9)	0.813[a]	0.367
Men				
Metabolic syndrome n (%)				
Glycaemia	8 (4.9)	7 (7.2)	0.596[a]	0.440
Triglycerides	16 (9.8)	17(17.5)	3.262[a]	0.071
HDL	50 (30.7)	20 (20.6)	3.126[a]	0.077
Blood pressure	60 (36.8)	6 (6.2)	30.11[a]	0.001
Waist	14 (8.6)	17 (17.5)	4.625[a]	0.032
LDL	83 (51.2)	37 (38.1)	4.181[a]	0.041
	12 (7.4)	1 (7.2)	0.002[a]	0.965
Heath risk behaviors				
All				
Cocaine	39 (13)	13 (8.3)	2.247[a]	0.134
Alcohol	136 (45.6)	65 (41.7)	0.654[a]	0.419
Cannabis	120 (39.9)	42 (26.9)	7.523[a]	0.006
Tobacco	167 (57.2)	79 (50.6)	1.762[a]	0.184
LSD	10 (3.4)	4 (2.6)	0.275[a]	0.600
Amphetamines	15 (5.1)	8 (5.1)	0.001[a]	0.971
Body mass index				
All				
Underweight	29 (9.8)	3 (1.9)	9.448[a]	0.002
Normal weight	195 (65.9)	78 (50.6)	9.845[a]	0.002
Overweight	58(19.6)	54 (35.1)	12.96[a]	<0.001
Obese	14(4.7)	19 (12.9)	8.628[a]	0.003
Men				
Underweight	11 (6.9)	0	6.896[a]	0.009
Normal weight	101 (63.1)	42 (43.8)	9.135[a]	0.003
Overweight	38 (23.8)	37 (38.5)	6.338[a]	0.012
Obese	10 (6.3)	17 (17.7)	8.350[a]	0.004
Women				
Underweight	18 (13.2)	3 (5.2)	2.738[a]	0.098
Normal weight	94 (69.1)	36 (27.7)	0.914[a]	0.339
Overweight	20 (14.7)	17 (29.3)	5.691[a]	0.018
Obese	4 (2.9)	2 (83.4)	0.035[a]	0.852

FEP: First episode psychosis; HC: Healthy controls. The revised National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria require at least three of the following components: (1) abdominal obesity (waist circumference ≥94 cm for Mediterranean men or ≥80 cm for Mediterranean women), (2) triglycerides ≥150 mg/dL, (3) HDL cholesterol ≤40 mg/dL for men or 50 mg/dL for women, (4) systolic/diastolic blood pressure ≥130/85 mmHg or receiving drug treatment, and (5) fasting plasma glucose ≥100 mg/dL.

[a] Chi-square test.

[b] Fisher's exat test Statistically significant differences: $p < 0.05$.

24.16, $p < 0.001$; OR = 2.686, CI 95 % 1.8–4.0) (Table 3).

These differences in the individual MetS components between groups were similar to the results observed when comparing the mean values of blood pressure, but contradictory when comparing the mean values of the rest of MetS components, relevant metabolic parameters and anthropometric measurements (Table 4). For instance, FEP patients presented significantly higher systolic blood pressure (FEP: mean/SD 118±15.4 vs HC: mean/SD 107±12 mm/Hg, t-student 2.51, $p < 0.001$), and higher diastolic blood pressure (FEP: mean/SD 70.45 +/− 11.36 vs HC:63.29 +/− 8.84 mm/Hg, t-student 4.94, $p < 0.001$). Additionally, we observed lower weight and BMI (64.7 vs 74.4 kgs, $p < 0.001$; and 22.7 vs 25.3 kg/m^2, $p < 0.001$, respectively), and lower mean levels of cholesterol and LDL (175.3 vs 186.9 mg/dL, $p < 0.001$; and 105.1 vs 112.5 mg/dL, $p = 0.012$) than healthy controls. In the logistic regression model, the association between altered HDL and psychosis (OR:1.87, 95 % CI 1.78–2.96, $p = 0.007$) remains statistically significant after adjustment by possible confounders (OR:2.228, 95 % CI 1.12–4.464, $p = 0.024$) (sex, education level, single, low family socioeconomic status, urban zone, unemployed, currently student status, cannabis, alcohol and cocaine consumption). Similarly the association between high blood pressure and psychosis (OR:8.031, 95 % CI 3.61–17.85, $p = 0.001$) also remains significant after adjustment (OR:7.564, 95 % CI 6.16–23.14, $p = 0.001$) (Table 5). Moreover, in this exploratory analysis we found that the association between FEP and altered waist circumference is influenced by female sex and education level (Supplementary material).

3.3. Gender differences in the study group

Men from both groups (FEP and control) presented larger WC than women in each group (FEP: mean/SD 85.67+/− 11.5 vs 79.27 ±1.14, t-student 0.31, $p = 0.001$; and HC: mean/SD 90.74 +/− 12.02 vs 80.28 ±11.03, t-student 0.78, $p < 0.001$) (Table 6a). However, when we explored gender differences in WC according to MetS criteria, we observed in that the FEP group women met more the WC criteria than men (n = 14, 8.6 % vs n = 29, 20.7 %, x^2 9.09 $p = 0.003$) (Table 6b) Additionally, men in the FEP and control groups presented higher blood pressure measurements than women (Table 6a), however men with FEP (n = 60, 36.8 % vs n = 23, 16.4 %, x^2 15.73 $p \leq 0.001$) presented higher blood pressure more frequently than women with FEP. No other gender differences were observed (Table 6b).

3.4. Health risk behaviors

We found significant differences in cannabis consumption between FEP and controls (n = 120, 39.9 % vs n = 42, 26.9 %, x^2 7.523 $p = 0.00$) (Table 2) 57 % of FEP reported tobacco consumption, and we found that FEP patients smoked a greater number of cigarettes per day than the controls (FEP: mean/SD 17.34±9.71 vs HC: mean/SD 72±10.92 mm/Hg, t-student 4.095, $p < 0.001$). However, when we explored the effect of drug consumption (cannabis, alcohol and tobacco) on altered metabolic parameters we did not find any difference between FEP and healthy controls (Supplementary material).

4. Discussion

This study analyzes MetS prevalence in a large and representative sample of antipsychotic-naïve patients with FEP and age-sex matched controls. We found that the prevalence of MetS in antipsychotic-naïve patients with FEP (5.6 %) was similar to the prevalence of MetS in controls (5.12 %). However, it is striking that 60.3 % of patients with FEP met at least one of the five MetS criteria vs 36.5 % of controls. Additionally, and coinciding with previous studies (Misiak et al., 2014) we found that other factors not included in the operational definition of MetS, but still important in cardiovascular risk, were also more frequently present in FEP, such as tobacco smoking or high homocysteine levels. Thus, patients with FEP presented more frequently altered values of HDL, homocysteine and high blood pressure (HBP), the latter being more pronounced in men with FEP. All of these are cardiovascular risk markers.

With respect to gender differences in the risk of presenting MetS components, we found that women with FEP are more prone to present greater WC than men with FEP. This gender difference was not observed in the control group. Our results are congruent with previous studies that have demonstrated that psychotic disorder per se increases the risk for elevated waist circumference (Osby et al., 2014),for example genetic variants of increased waist circumference in psychosis have been identified (Hukic et al., 2017) and that first episode schizophrenia patients, especially women, present subclinical metabolic abnormalities, independent of antipsychotic treatment (Zhang et al., 2021). Likewise, in

Table 3
Number of altered metabolic syndrome components.

	FEP		HC		Test value	p	OR	CI 95 %	
	n = 303	%	n = 156	%					
At least one altered MetS component	184	60.7	57	36.5	24.160[a]	0.001*	2.686	1.802	4.003
Only one altered component	127	41.9	33	21.2	19.540[a]	0.001*	2.690	1.720	4.205
Only two altered components	40	13.2	16	10.3	0.834[a]	0.361	1.331	0.720	2.461
3 altered components	12	4.0	4	2.6	0.597[a]	0.440	1.567	0.497	4.941
4 altered components	5	1.7	4	2.6	0.447[a]	0.504	0.638	0.169	2.409

FEP: First episode psychosis; HC: Healthy controls: CI Confidence interval; OR odd ratio. 3 and 4 altered components means Metabolic Syndrome. The revised National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria require at least three of the following components: (1) abdominal obesity (waist circumference ≥94 cm for Mediterranean men or ≥80 cm for Mediterranean women), (2) triglycerides ≥150 mg/dL, (3) HDL cholesterol ≤40 mg/dL for men or 50 mg/dL for women, (4) systolic/diastolic blood pressure ≥130/85 mmHg or receiving drug treatment, and (5) fasting plasma glucose ≥100 mg/dL.

[a] Chi-square test. FEP patients have greater risk of presenting at least one of the MetS component.

* Statistically significant differences: $p < 0.05$.

Table 4
Individual metabolic parameters.

	FEP		HC		F	Sig
	Mean	SD	Mean	SD		
Weight (kg)	64.67	13.72	74.44	16.12	3.165[a]	<0.001
Waist (cm)	82.51	11.46	86.79	12.68	2.152[a]	<0.001
Systolic blood pressure (mm/hg)	118.68	15.40	107.72	12.12	2.511[a]	<0.001
Diastolic blood pressure (mm/hg)	70.45	11.36	63.39	8.84	4.944[a]	<0.001
Glycemia (mg/dL)	85.26	18.09	84.55	10.98	0.537[a]	0.655
Triglycerides (mg/dL)	84.69	47.76	93.04	51.57	2.359[a]	0.085
HDL (mg/dL)	53.02	15.10	55.78	15.54	0.133[a]	0.064
LDL (mg/dL)	105.11	30.493	112.54	28.94	0.029[a]	0.012
Cholesterol (mg/dL)	175.27	38.220	186.92	32.204	0.602[a]	<0.001
BMI	22.67	3.76	25.29	4.16	2.077[a]	<0.001
HOMA	2.18	0.81	2.06	0.69	1.184[a]	0.786
Homocysteine (umol/L)	13.73	6.70	11.15	3.00	18.706[a]	<0.001
PCR	0.26	0.37	0.393	0.33	0.240[a]	0.06
Vit B12 pmol/L	431.93	187.64	418.79	158.64	3.345[a]	0.458
Insulin U/mL	8.90	7.86	9.30	5.35	1.763[a]	0.581
Leptin ng/mL	9.09	11.55	9.76	8.70	1.517[a]	0.504

FEP: First episode psychosis; HC Healthy controls; SD standar deviation. The revised National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria require at least three of the following components: (1) abdominal obesity (waist circumference ≥94 cm for Mediterranean men or ≥80 cm for Mediterranean women), (2) triglycerides ≥150 mg/dL, (3) HDL cholesterol ≤40 mg/dL for men or 50 mg/dL for women, (4) systolic/diastolic blood pressure ≥130/85 mmHg or receiving drug treatment, and (5) fasting plasma glucose ≥100 mg/dL. Statistically significant differences: $p < 0.05$.

[a] t-Student test.

chronic schizophrenia patients, some reports demonstrate than the female gender is significantly associated with a higher prevalence of metabolic syndrome (Bener et al., 2014; Huang et al., 2009; Kraal et al., 2017; Wei et al., 2020). It has been reported (Cho et al., 2019) that WC had a significant linear relationship with the risk of myocardial infarction and ischemic stroke and predicted cardiovascular events better than BMI. Future research should take into account whether this finding is accentuated with the introduction of some antipsychotic treatment, and thus carry out specific prevention measures for women.

In this line, BMI has been proposed as being potentially useful in the prediction of MetS in various populations with or without schizophrenia (Tirupati and Chua, 2007; Sugawara et al., 2020) and BMI has been positively associated with positive symptom severity in drug naïve patients with psychosis (Tian et al., 2021). However, other studies such CHANGE trial (Jakobsen et al., 2018) found that the average energy intake of obese people with schizophrenia was not higher than that of the general population. This suggests that the overweightness in schizophrenia results from physical inactivity and the metabolic adverse effects of antipsychotics. Similarly, we found that overweightness and obesity are less frequent in FEP than in controls, prior to antipsychotic exposure, but when stratified analyses per sex were performed we found that an elevated abdominal circumference is more frequent in women with FEP. Many factors may lead to these contradictory results, such as different mediating factors between schizophrenia and metabolic alterations. For example, recent studies (Alameda et al., 2020) have found that severe stress during adolescence could contribute to increased waist circumference in patients with psychosis.

The high prevalence of cardiovascular disease in patients with schizophrenia contrasts with the low prevalence of MetS in patients who are in the initial stages of the disease. This can be explained either because the subsequent use of antipsychotics is what worsens the prevalence of cardiovascular disease, or because MetS may be a marker that underestimates such risk. Although MetS is a predictor of cardiovascular risk, it is a construct that was designed to predict cardiovascular risk in the general population, without considering the characteristics of the population with psychosis such as the usual young age or the high prevalence of smoking, sedentary lifestyles, poor self-care and barriers to consulting primary care. The individual alteration of metabolic parameters such as HDL, HBP and homocysteine in naive FEP patients has been widely documented (Enez Darcin et al., 2015a). HDL has been shown to be an independent cardiovascular risk marker for coronary heart disease (Hagstrom et al., 2016; Schaffer et al., 2014; Zakiev et al., 2017; Allard-Ratick et al., 2021) Several studies have shown that HDL levels are inversely associated with the risk of cardiovascular events (Saito et al., 2017). Saito et al. (2017) reported that HDL levels are inversely associated with the risk of ischemic stroke. In contrast to LDL cholesterol, HDL correlates with cardiovascular risk only in healthy individuals without a history of cardiovascular disease (Marz et al., 2017).

In the general population, low HDL should prompt examination of

Table 5
Metabolic alterations and psychosis adjusted by social and health risk behaviors.

	n	%	Crude OR			p-Value	Adjusted OR[a]			p-Value
				95 % CI				95 % CI		
			OR	Lower	Upper		OR	Lower	Upper	
MetS										
Controls	8	5.6	1				1			
FEP	17	5.1	1.1	0.464	2.608	0.829	2.046	0.584	7.174	0.263
HDL										
Controls	31	19.9	1				1			
FEP	96	31.7	1.87	1.178	2.967	0.007	2.553	1.208	5.398	0.014
Glycaemia										
Controls	8	5.1	1				1			
FEP	18	5.9	1.168	0.496	2.751	0.721	1.970	0.476	8.149	0.349
WC										
Controls	29	18.6	1				1			
FEP	43	14.2	0.724	0.432	1.214	0.220	2.418	1.112	4.464	0.026
Hypertension										
Controls	7	4.5	1				1			
FEP	83	27.4	8.031	3.612	17.853	0.001	28.746	6.342	130.290	<0.001
Tryglicerides										
Controls	18	11.5	1				1			
FEP	23	7.6	0.63	0.329	1.206	0.160	0.721	0.323	2.186	0.959

The revised National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria require at least three of the following components: (1) abdominal obesity (waist circumference ≥94 cm for Mediterranean men or ≥80 cm for Mediterranean women), (2) triglycerides ≥150 mg/dL, (3) HDL cholesterol ≤40 mg/dL for men or 50 mg/dL for women, (4) systolic/diastolic blood pressure ≥130/85 mmHg or receiving drug treatment, and (5) fasting plasma glucose ≥100 mg/dL.

[a] Adjusted by sex, currently student status, education level, low family socioeconomic status, urban zone, single, unemployed, cannabis, cocaine, alcohol and tabaco consumption. WC, waist circumference.

additional metabolic and inflammatory pathologies. Low HDL occurs much more frequently in patients with MetS or diabetes mellitus and are also associated with systemic inflammation, e.g. with cigarette smoking, chronic inflammatory diseases or chronic kidney disease. In this line, recent studies suggest that schizophrenia is not only a brain disease, but also a disorder with impairments throughout the body (Kirkpatrick et al., 2014) and which involves multiple systems from illness onset, such as the immune, cardiometabolic, and hypothalamic-pituitary adrenal systems (Pillinger et al., 2019). In our study, we found a higher prevalence of altered HDL and HBP in naïve FEP patients compared to healthy controls, and a higher prevalence of HBP in men than in women among the psychosis group. With regard to LDL, in contrast with a recent meta-analysis, (Pillinger et al., 2017b), we found a lower prevalence of altered LDL in FEP than in controls.

While the prevalence of MetS was similar in all samples, we wonder if MetS is actually an adequate predictor of early cardiovascular risk in patients with psychosis, in whom it is already demonstrated that there are baseline metabolic alterations prior to the use of antipsychotics. There are other cardiovascular risk predictors such as the Framingham score that predicts the risk of coronary cardiovascular disease in the United States, and the SCORE that predicts mortality from cardiovascular coronary cerebrovascular cause in the European population. These scales are made based on the general population and have little applicability in patients with psychosis because the prevalence of psychosis or other psychiatric diseases is not specified in the sample that served for their preparation. They were also published about 2 decades ago, that is, before the alarm was raised about the deficit in care for the physical health of the population with schizophrenia.

The main limitation of these cardiovascular risk scales is that they are designed for patients over 45 years of age, when the mean age of onset of psychosis is much lower. If we used the Framinghan or the SCORE to measure risk using our sample (mean age 32 years), the cardiovascular risk would be underestimated. Among the existing algorithms to predict cardiovascular risk in schizophrenia is PRIMROSE, which, although it is validated in mental illness, was intended for chronic patients with schizophrenia (Osborn et al., 2015) and is not useful in young people with early stages of psychosis (Perry et al., 2020). Likewise, a recent meta-analysis (Garrido-Torres et al., 2021) of the MetS prevalence in naïve patients with psychosis found higher MetS prevalence in FEP than controls and identified ethnicity as the main source of heterogeneity, suggesting that ethnicity should be considered in the prediction algorithms.

Smoking is a modifiable risk factor, which is associated with mortality in people with schizophrenia (Dickerson et al., 2018). The high prevalence of tobacco consumption among people with schizophrenia and the association between smoking and cognitive impairment is also well known (Coustals et al., 2020). In our sample, 56 % of patients with FEP were smokers at study intake, the tobacco use being higher than among controls. However, tobacco is not included among the MetS criteria. Likewise, cannabis consumption has been associated to low odds of MetS in both the general population (Vidot et al., 2016) and patients with FEP (Stiles et al., 2020), low odds of overweightness (Vazquez-Bourgon et al., 2019b) and low odds of non-alcoholic fatty liver (Vazquez-Bourgon et al., 2019a) in patients with FEP at long-term. However, when we explored the association between cannabis use and MetS at baseline we did not find an effect of cannabis on MetS prevalence.

Our study counts on several strengths like the non-antipsychotic exposure and large sample size, the control group comparison, and the gender analysis. Additionally, we explored social variables and found that naïve FEP patients are more frequently single, unemployed, living alone and with lower socioeconomic status than controls. These factors can form into additional everyday stresses for individuals, leading to risk behaviors, such as tobacco use and unhealthy diets. This study highlights that there may be some factors, other than antipsychotic drugs, that could be related to the risk for MetS in patients with schizophrenia. Some limitations should be noted; in the first place, we were not able to collect information about previous depression and trauma, both factors related to overweightness in those with early psychosis (Aas et al., 2017; Alameda et al., 2020). Likewise, prenatal development and fetal metabolic programming have recently received considerable attention as a factor to consider in the etiopathogenesis of obesity in the general population and in individuals with psychosis but unfortunately we do not have this information. Secondly, cross-sectional data cannot be used to infer causality because temporality is not known. Thirdly, we decided to exclude individuals with prior cardiovascular conditions as an

Table 6a
Gender differences in anthropometric and metabolic measurements.

	Men		Women		t-Statistic	p
	Mean	SD	Mean	SD		
FEP						
Glycaemia mg/dL	86.18	22.76	84.18	10.24	0.24	0.310
Tryglicerides mg/dL	91.37	55.85	76.91	34.765	8.19	0.004*
HDL mg/dL	48.36	11.82	58.45	16.66	10.37	0.001*
Systolic blood pressure mm/hg	121.55	14.21	115.08	16.26	0.11	0.001*
Diastolic blood pressure mm/hg	71.86	11.49	68.41	10.74	0.36	0.001*
Waist circumference cm	85.67	11.15	79.27	1.14	0.31	0.001*
Body mass index	233.72	375.12	22.21	422.41	0.072	0.080
LDL md/dL	103.96	32.16	106.44	28.49	0.94	0.333
HC						
Glycaemia mg/dL	87.01	8.84	80.51	12.88	0.57	0.448
Tryglicerides mg/dL	102.9	57.92	76.85	33.55	7.29	0.008
HDL mg/dL	50.64	12.45	64.22	16.49	6.49	0.012*
Systolic blood pressure mm/hg	112.66	10.45	99.59	10.18	0.93	0.001*
Diastolic Blood pressure mm/hg	65.88	9.04	65.88	9.04	11.91	0.001*
Waist circumference cm	90.74	12.02	80.28	11.03	0.78	0.001*
Body mass index	26.17	4.07	23.83	3.91	0.17	0.001*
LDL mg/dL	112.18	31.21	113.15	24.99	2.31	0.130

FEP: First episode psychosis, HC: Healthy Controls. Statistically significant differences: $p < 0.05$. The revised National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria require at least three of the following components: (1) abdominal obesity (waist circumference ≥94 cm for Mediterranean men or ≥80 cm for Mediterranean women), (2) triglycerides ≥150 mg/dL, (3) HDL cholesterol ≤40 mg/dL for men or 50 mg/dL for women, (4) systolic/diastolic blood pressure ≥130/85 mmHg or receiving drug treatment, and (5) fasting plasma glucose ≥100 mg/dL.
* Statistically significant differences: $p < 0.05$.

analytic sample criterion and we recognize that this may has biased the sample against identifying drug-naïve FEP individuals with pre-psychosis cardiovascular events and risk factors. And lastly, we recruited and evaluated FEP patients and healthy controls with different time ranges (2001–2018 vs. 2010–2012).

In summary, MetS could underestimate cardiovascular risk in young FEP patients. FEP patients have a greater risk of presenting at least one altered MetS component than healthy controls that could indicate the need for development of screening methods detecting cardiovascular risk. Likewise, gender differences in metabolic components such as WC, which is by itself a predictor of cardiovascular events, have been found associated and therefore require special attention. Keeping in mind that HDL is also an independent cardiovascular risk marker for coronary heart disease and can be increased through lifestyle changes, early intervention in psychosis should include preventive measures such nutrition and physical activity advice and tobacco intervention. Similarly, research should focus on metabolic risk predictors that include not only MetS, but also specific parameters for the early psychosis population.

Table 6b
Gender differences in prevalence of MetS components and related factors.

	Men		Women		x^2	p
	n = 163	%	n = 140	%		
FEP						
Glycaemia	8	4.9	10	7.1	0.673	0.412
Tryglicerides	16	9.8	7	5.0	2.490	0.115
HDL	50	30.7	46	32.9	0.166	0.684
Blood pressure	60	36.8	23	16.4	15.730	0.001*
WC	14	8.6	29	20.7	9.090	0.003*
Overweight	38	23.8	20	14.7	3.817	0.050
LDL	83	51.2	57	40.7	3.342	0.068
Cocaine	31	19.4	8	5.8	12.165	0.001*
Tobacco	98	63.3	69	50	5.520	0.019*
Cannabis	93	57.2	27	19.3	46.240	0.001*
HC						
Glycaemia	7	7.2	1	1.7	2.290	0.129
Tryglicerides	17	17.5	1	1.7	9.000	0.003*
HDL	20	29.6	11	18.6	0.090	0.764
Blood pressure	6	6.2	1	1.7	1.726	0.189
WC	17	17.5	12	20.3	0.192	0.661
Overweight	37	38.5	17	29.3	1.352	0.245
LDL	37	38.1	20	33.9	0.285	0.593
Cocaine	13	13.4	0	0	8.626	0.003*
Tobacco	46	47.4	33	55.9	1.063	0.303
Cannabis	35	36.1	7	11.9	10.936	0.001*

FEP: First episode psychosis; HC: Healthy controls; HDL high-density lipoprotein; LDL Low-density lipoprotein; WC Waist Circumference. If cell count in the cross tabulation was <5, the Fishers exact test was used. The revised National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria require at least three of the following components: (1) abdominal obesity (waist circumference ≥94 cm for Mediterranean men or ≥80 cm for Mediterranean women), (2) triglycerides ≥150 mg/dL, (3) HDL cholesterol ≤40 mg/dL for men or 50 mg/dL for women, (4) systolic/diastolic blood pressure ≥130/85 mmHg or receiving drug treatment, and (5) fasting plasma glucose ≥100 mg/dL.
* Statistically significant differences: $p<0.05$

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.07.007.

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