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Metabolic syndrome in antipsychotic-naïve patients with first-episode psychosis: a systematic review and meta-analysis

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Review Article

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Abstract

Background. It is unclear what the prevalence of metabolic syndrome (MetS) in drug-naïve first-episode of psychosis (FEP) is, as previous meta-analyses were conducted in minimally exposed or drug-naïve FEP patients with psychotic disorder at any stage of the disease; thus, a meta-analysis examining MetS in naïve FEP compared with the general population is needed.

Methods. Studies on individuals with FEP defined as drug-naïve (0 days exposure to antipsychotics) were included to conduct a systematic review. A meta-analysis of proportions for the prevalence of MetS in antipsychotic-naïve patients was performed. Prevalence estimates and 95% CI were calculated using a random-effect model. Subgroup analyses and meta-regressions to identify sources and the amount of heterogeneity were also conducted.

Results. The search yielded 4143 articles. After the removal of duplicates, 2473 abstracts and titles were screened. At the full-text stage, 112 were screened, 18 articles were included in a systematic review and 13 articles in the main statistical analysis. The prevalence of MetS in naïve (0 days) FEP is 13.2% (95% CI 8.7–19.0). Ethnicity accounted for 3% of the heterogeneity between studies, and diagnostic criteria used for MetS accounted for 7%. When compared with controls matched by sex and age, the odds ratio is 2.52 (95% CI 1.29–5.07; $p = 0.007$).

Conclusions. Our findings of increased rates of MetS in naïve FEP patients suggest that we are underestimating cardiovascular risk in this population, especially in those of non-Caucasian origin. Our findings support that altered metabolic parameters in FEPs are not exclusively due to antipsychotic treatments.

Introduction

The life expectancy of people with schizophrenia is around 20 years shorter than that of the general population, and 60% of the causes of premature death of people with schizophrenia are related to cardiovascular diseases (Pillinger, D'Ambrosio, McCutcheon, & Howes, 2019). One of the most studied cardiovascular risk indicators is metabolic syndrome (MetS), which consists of a group of parameters that indicate the risk of developing cardiovascular disease and diabetes (Eckel, Grundy, & Zimmet, 2005). The criteria most used for the diagnosis of MetS are those of IDF (International Diabetes Federation, 2006) and ATPIII (Adult Treatment Panel III, 2001). These differ from each other in the cut-off point of the parameters that are considered pathological.

The increased prevalence of MetS in patients with schizophrenia compared to the general population is widely recognised (Kraemer, Minarzyk, Forst, Kopf, & Hundemer, 2011), and has been mainly attributed to the use of atypical antipsychotics (Newcomer et al., 2002; Vancampfort et al., 2015), as well as other risk factors that accumulate during the disease period, such as sedentary lifestyles, poor nutrition, tobacco consumption and the lack of self-care due to the negative symptoms of the disease themselves (Bobes et al., 2007). In the last decade, studies have been published with patients who had not received pharmacological treatment and who show that the metabolic alterations could not be exclusively due to antipsychotics (Kirkpatrick, Garcia-Rizo, Fernandez-Egea, Miller, & Bernardo, 2011; Pillinger et al., 2017; Pillinger, Beck, Stubbs, & Howes, 2017). Taking into account these findings, various pieces of research (Chadda, Ramshankar, Deb, & Sood, 2013; Cordes et al., 2017; Ryan, Sharifi, Condren, & Thakore, 2004) propose a vulnerability hypothesis for the development of

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metabolic disorders that is independent of the use of antipsychotics in patients with schizophrenia. Along these lines, a recent systematic meta-review (Pillinger et al., 2019) found, in addition to alterations in the central nervous system, significant associations between schizophrenia and alterations in other systems such as the endocrine, immune and cardio-metabolic systems. Likewise, there are studies that frame the symptoms of schizophrenia within a systemic disease that also has basal metabolic manifestations (Kirkpatrick, Miller, García-Rizo, & Fernandez-Egea, 2014).

Despite these advances in the understanding of the deleterious effects of MetS and its possible causes, it is still not clear what the prevalence of MetS in drug-naïve individuals with psychotic disorder is. This is an important limitation as most of the risk factors associated to MetS may play a role and tend to accumulate during the first years of disease (such as tobacco, sedentarism or the use of medication). This may be reflected by the important variation of MetS in patients under medication, ranging from 35.3% (Mitchell, Vancampfort, De Herdt, Yu, & De Hert, 2013; Vancampfort et al., 2015) to 49% (Kraemer et al., 2011). To date, only two meta-analyses in drug-naïve patients with psychotic disorders have been conducted: Vancampfort et al. (2013) conducted research on cardio-metabolic abnormalities in drug-naïve, first-episode and multi-episode patients with schizophrenia. One of their findings was that there was no significant difference between untreated (10%) and first-episode (15.9%) patients. A second meta-analysis (Mitchell et al., 2013) showed the prevalence in untreated patients was 9.8%. These two works report the most solid data; however, the authors of both papers highlight several limitations, such as the difficulty in independently analysing naïve patients with a first psychotic episode, since they included studies with first episodes exposed to antipsychotics for an indeterminate time. In addition, the 'untreated' patient group included patients in any phase of the disease, thus the prevalence in this group may be confounded by the presence of other risk factors that develop during the disease.

Taking into account those limitations and the need to clarify the prevalence of MetS in drug-naïve patients with psychosis, we conducted a meta-analysis of studies that strictly included first psychotic episodes with 0-day exposure to antipsychotic treatment, including a population aged above 18. This will lead to a clearer understanding of the prevalence of MetS in this population, allowing a better detection of such syndrome, and helping the development of specific interventions.

Methods

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000). It also followed a protocol registered in PROSPERO (CRD42020180930).

Search strategy

We searched the Web of Science Core Collection, Embase and Medline via Embase and PubMed platforms from inception until November 2020. Our queries combined natural and controlled terms related to: (first-episode psychosis or first-episode schizophrenia or FEP or FES or psychosis or schizophrenia) AND (antipsychotic-naïve or antipsychotic-free or drug-naïve or drug-free or neuroleptic-naïve or neuroleptic-free or never-medicated or untreated) AND (cholesterol or high-density lipoprotein (HDL) or low-density lipoprotein (LDL) or triglycerides or lipids or lipoproteins or MetS or metabolic or blood pressure or metabolic dysregulation) (online Supplementary Table S3). We manually screened all the references from the previous reviews in the field and extracted relevant articles from the citations of the included manuscripts. Articles identified were screened as abstracts, and after the exclusion of those which did not meet our inclusion criteria, the full texts of the remaining articles were assessed for eligibility. Then, final decisions were made regarding their inclusion in the review. We completed our search by manually reviewing the references of the included articles and extracting additional titles. Authors were contacted for missing data and to clarify overlaps. We also searched grey literature, and conducted a cross-reference search of relevant included studies and previous reviews. More details are provided in online Supplementary Tables S6 and S12.

Study selection

Two independent co-authors (NGT and ARG) screened titles and abstracts to identify studies that met the inclusion criteria outlined above using Rayyan (Ouzzani, Hammady, Fedorowicz, & Elmagarmid, 2016) software. The same two co-authors then considered eligible full texts among these articles and the final list of included articles was reached through consensus. The κ index was 0.931. Discrepancies over the eligibility of studies were resolved through discussion with additional co-authors (MRV and BCF).

Eligibility

Inclusion criteria: (i) studies on FEP patients; (ii) studies in which psychosis diagnosis was determined according to either DSM-IV, DSM IV-TR17, DSM-5 (American Psychiatric Association, 2013) or International Classification of Diseases, Ninth or Ten Revision (ICD-9 or ICD-10); (iii) studies on individuals with FEP defined by the study authors as either drug-naïve (0 days) or minimal exposure regardless of the duration to antipsychotics will be considered for systematic review and studies on individuals with FEP and drug-naïve (0-day exposure to antipsychotic treatment) will be included in prevalence meta-analysis; (iv) cross-sectional studies or baseline assessment of prospective and retrospective cohort studies; (v) studies in which MetS diagnosis was confirmed or rejected based on current endocrinal criteria; i.e. it was defined according to any of these four sets of criteria: ATPIII-A, IDF, JIS 2009 (Alberti et al., 2009), World Health Organization (Alberti & Zimmet, 1998); and (vi) subjects aged above 18.

Exclusion criteria: (i) studies on chronic patients ($\geqslant$5 years after the FEP), despite being naïve; (ii) studies on animals or *in vitro*; (iii) studies not designed to calculate prevalence: quasi-experimental studies as they are unsuitable for measuring prevalence, case and control studies as they are unsuitable for measuring prevalence, randomised clinical trials as they are not designed to calculate prevalence because their inclusion/exclusion criteria are often restrictive, and subjects are not representative of the general population (Munn, Moola, Lisy, Riitano, & Tufanaru, 2015); (iv) studies presenting data on MetS that did not fully meet any of the above four sets of criteria; and (v) subjects aged above 65 [if a small proportion (<5% of the sample is aged >65), the studies could be considered].

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Data extraction

DistillerSR (Evidence Partners, Canada) was used for data extraction, full text and quality assessment. Variables on data collection forms included age, sex, country, ethnic origin, diagnosis, study design, MetS criteria and samples. Data were collected independently by two co-authors (NGT and IRG). Two other independent co-authors (MRV and BCF) were available for mediation when inconsistencies arose.

Quality assessment

The Joanna Briggs Institute (Munn et al., 2015) for observational studies was used. This scale assesses observational studies and data needed to obtain prevalence. Total scores range from 0 to 10. For the total score grouping, risk of bias in studies was judged as low (⩾7 points), moderate (4–6 points) and high (<4 points). We used two versions, one for cross-sectional (Munn et al., 2015) and another for cohort (Moola et al., 2020) studies (online Supplementary Table S13).

Statistical analysis

We performed a meta-analysis of proportions for the prevalence of MetS in antipsychotic-naïve patients. Prevalence estimates and 95% CI were calculated using a random-effect model due to heterogeneity between the populations and characteristics of the included studies (Barendregt, Doi, Lee, Norman, & Vos, 2013). When prevalence estimates tend towards 0% or 100%, it overestimates the weight of individual studies in the meta-analysis (Barendregt et al., 2013). We generated Forest plots for the prevalence estimates and their 95% CI of the individual studies and pooled estimates. Forest plots were examined visually looking for potential outliers. We assessed heterogeneity between studies using the I^2 statistic, with an I^2 >50% indicating substantial heterogeneity according to others (Davies et al., 2020; Higgins, Thompson, Deeks, & Altman, 2003). We assessed the publication bias graphically using a funnel plot and the Egger's test (Egger, Smith, Schneider, & Minder, 1997). We explored sources of heterogeneity presence of potential outliers that could explain the heterogeneity [e.g. one individual study going in a different direction to all the others according to others (Davies et al., 2020; Higgins et al., 2003)] and with sensitivity, subgroup analyses and meta-regressions. For sensitivity analyses, we excluded studies with sample sizes smaller than 50 participants, and studies with either moderate or high risk of bias. We also conducted subanalyses in those studies that despite defining their studies as drug-naïve, included FEP participants with minimal exposure. We also performed an analysis of influence and outliers according to the methods proposed by Viechtbauer and Cheung (2010), and separate meta-analyses according to ATP-IIIA criteria and IDF. Lastly, we compared the results with a sex and age-matched control group. All analyses were performed using Comprehensive Meta-Analyses software (Borenstein, Hedges, Higgins, & Rothstein, 2005).

Results

Search results

The search yielded 4143 articles. After the removal of duplicates, 2473 abstracts and titles were screened. At the full-text stage, 112 were screened, 18 articles were included in a systematic review, 13 (De Hert et al., 2008; Effat et al., 2012; Enez Darcin, Yalcin Cavus, Dilbaz, Kaya, & Dogan, 2015; Garcia-Rizo et al., 2017; Grover, Nebhinani, Chakrabarti, Parakh, & Ghormode, 2012; Kraemer et al., 2011; Martín Otaño, Barbadillo Izquierdo, Galdeano Mondragón, Alonso Pinedo, & Querejeta Ayerdi, 2013; Medved, Kuzman, Jovanovic, Grubisin, & Kuzman, 2009; Owiredu, Osei, Amidu, Appiah-Poku, & Osei, 2012; Saddicha, Ameen, & Akhtar, 2007; Sahpolat & Ari, 2021; Saloojee, Burns, & Motala, 2018; Srivastava, Bhatia, & Sharma, 2018) articles were included in the main statistical analyses (prevalence of MetS in drug naïve, 0 days of antipsychotic medication) (Fig. 1) and an additional five studies that included up to 47 days were considered for the supplementary sensitivity analysis (see below).

Study and participant characteristics

We found 18 studies that reported patients with FEP and a drug-naïve condition. As expected, the definition of naïve was not defined exactly the same way in all the studies ranging between 0 and 47 days. The length of antipsychotic exposure was reported as 0 days in the majority of studies (Tables 1 and 2) ($k = 13$, $n = 1009$), up to 14 days in one study ($k = 1$, $n = 76$) (Srihari et al., 2013), and up to 47 days in four studies ($k = 4$, $n = 711$) (Chiliza et al., 2015; Correll et al., 2014; Fleischhacker et al., 2013; Pallava, Chadda, Sood, & Lakshmy, 2012) (Tables 3 and 4). For the sake of accuracy, to calculate the prevalence in our meta-analysis, only the 13 studies with strictly naïve patients (0-day exposure) were included, but we decided to keep the five studies that included medication use up to 47 days in order to provide a comparison in sensitivity analysis.

Across these 13 included studies, 1009 individuals with FEP and strictly naïve (0-day exposure) were included. Additionally, one study ($n = 76$) with minimally treated subjects (0–14 days) and four studies ($n = 711$) with subjects treated up to 47 days are available as post-hoc analyses in online Supplementary Figs. S2–S5. The age of participants ranged from 22 to 43 years and the percentage of female participants was 47.15% ($n = 471$). In most studies, diagnosis was confirmed after the FEP, schizophrenia being the most frequent (Table 1). All studies used validated criteria for the diagnosis of the MetS: ATP-IIIA ($N = 9$), IDF ($N = 3$), JIS ($N = 1$), both ATP-IIIA and IDF ($N = 5$). In the studies reporting data with ATP III and IDF, the former was chosen to calculate the overall prevalence. More details are provided in online Supplementary Table S8. Participants' ethnic origins were: Caucasian ($N = 5$), Indian ($N = 3$), Middle East ($N = 3$), Afro-descendants ($N = 2$) (online Supplementary Figs. S7a–e). Geographical location was Europe ($N = 5$), Africa ($N = 3$), Asia ($N = 5$) (Tables 1 and 2).

Pooled MetS prevalence

The total cases of MetS were 131 out of 1009 FEP subjects. The prevalence of MetS in strictly naïve patients with FEP is 13.2% (95% CI 8.7–19.0) ($n = 1009$, $k = 13$) (Fig. 2). Some studies did not fall within the pooled prevalence estimate (Effat et al., 2012; Enez Darcin et al., 2015; Owiredu et al., 2012). Three studies reported a high prevalence of 40% (Effat et al., 2012), 32% (Enez Darcin et al., 2015) and 31.5% (Sahpolat & Ari, 2021). The study visually furthest from the pooled prevalence estimate ($k = 1$, $n = 20$) (Effat et al., 2012) considered 'naïve' as either never treated (0-day exposure) or drug-free for at least 6 months before the commencement of the study (Table 1). The graphical funnel plot and Eggers test (Fig. S1 online supplemental) showed there is no evidence of publication bias, so no trim and fill adjustment was

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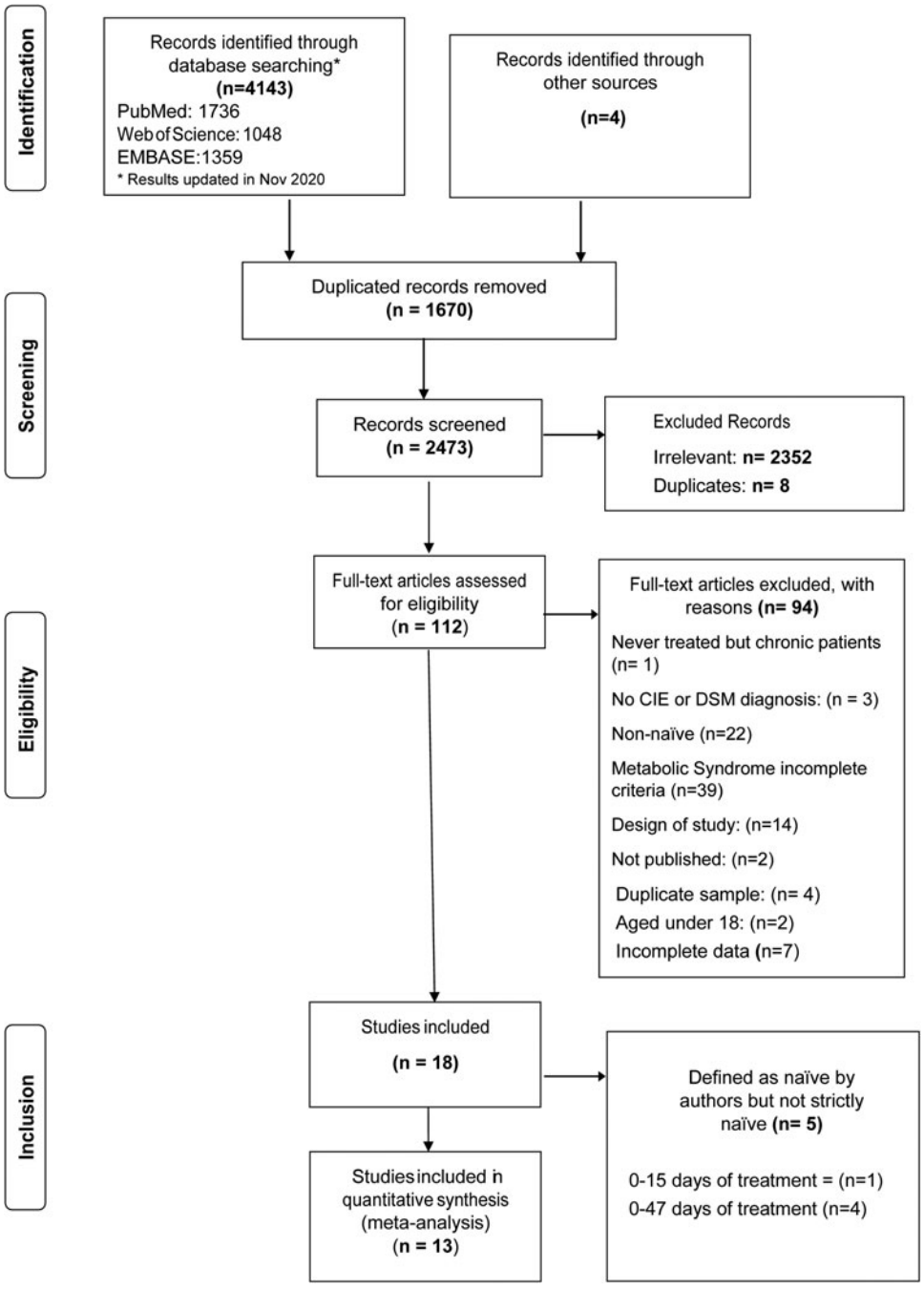

Fig. 1. PRISMA flow diagram.

needed ($p = 0.4507$). Only four studies reported the prevalence of MetS among women (Effat et al., 2012; Garcia-Rizo et al., 2017; Grover et al., 2012; Medved et al., 2009). The total cases of MetS among women were 19 out of 173. Overall prevalence estimate was 9.6% (95% CI 3–14; I^2 57.02%, $p = 0.06$). The total cases of MetS among men were 14 out of 165. Overall prevalence estimate in men was 12.5% (95% CI 3–39).

Sensitivity and subgroup analyses

Ethnicity and geographical location

The subgroup analysis of the 13 papers based on geographical location showed that the prevalence of MetS in studies performed in Europe was 9.7% (95% CI 5–18), in Africa 8.3% (95% CI 10–44) and in Asia 20% (95% CI 12–30). Studies in Asia showed the highest prevalence. We found that studies in Africa have the highest variability between their prevalence. Only two studies were performed in the Afro-descendant population, from Ghana and South Africa (Owiredu et al., 2012; Saloojee et al., 2018). We conducted sensitivity analysis removing those studies and we found changes in the overall prevalence from 13.2% to 16%. Separate meta-analysis based on subjects' ethnic origin showed that the prevalence of MetS in studies with Caucasian patients was 9.7% (95% CI 4.7–18), Afro-descendants 3.2% (95% CI 1.4–7.5). We pooled studies conducted in the Middle East and in India and found a MetS prevalence of 32.8% (95%

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Table 1. Characteristics of the studies included in the meta-analysis

Author	Design	Diagnosis	Exposure to antipsychotics (max. no of days)	Age mean (s.d.)	Women (*n*)	FEP naïve (*n*)	Controls MetS/*n* (prevalence %)	Findings
Effat	Cross-sectional	ICD-10: F20, F23, F31.2, F33.3	0	32.45 (14.7)	7	20	7/20 (35%)	Patients with severe mental illness are more likely to develop MetS even before the administration of neuroleptic medication. In this study, impaired Oral Glucose Tolerance Test (considered a gold standard for testing the risk of diabetes according to WHO, 1999), increased waist circumference and obesity (BMI430 kg/m2) showed significant correlations in the development of MetS among the groups studied.
Grover	Cross-sectional	ICD-10: F20	0	31 (12.2)	18	46		Findings of the present study suggest that although only few antipsychotic-naïve patients diagnosed with schizophrenia have metabolic syndrome, a significantly large proportion of patients have altered metabolic parameters.
Kraemer	Baseline assessment of longitudinal cohorts	ICD-10: F20	0	43 (14.0)	93	162		Unmedicated cohort had a significantly lower prevalence of MetS compared to any other previous antipsychotic treatment cohort.
Medved	Baseline assessment of longitudinal cohorts	DSM-IV: 295.10/ 295.20/295.30/ 295.60/295.90, 295.70, 297.1	0	31 (7.8)	94	94		Metabolic disturbances seemed to be prevalent in unmedicated schizophrenic patients, approximately 15% fulfilled criteria for full metabolic syndrome. It is striking that about one-third of unmedicated patients have low HDL and high triglycerides.
Owiredu	Cross-sectional	ICD-10: F23	0	26.2 (1.0)	58	100		The prevalence was significantly higher among psychiatric patients on treatment as compared to treatment-naïve group using NCEP ATP III (21.0% *v.* 2.0%; $p < 0.0001$) and IDF (29.0% *v.* 2.0%; $p < 0.0001$) criteria but not WHO (13.0% *v.* 14.0%; $p = 0.8372$). These overall prevalence rates were higher compared to the general Ghanaian population prevalence rates of 3.9%, 2.2% and 7.8% determined with the NCEP ATP III, WHO and IDF criteria respectively.
Srivastava	Cross-sectional	ICD-10: F20	0	–		92		Metabolic syndrome (MeS) was observed in 29.35% chronic patients, 19.56% antipsychotic-naïve first-episode schizophrenia.
Otaño-Martín	Baseline assessment of longitudinal cohorts	ICD-10: F20, F23, F20.81, F25	0	30.74 (9.3)	10	19		No metabolic syndrome was observed in antipsychotic naïve individuals.

(*Continued*)

Table 1. (*Continued.*)

Author	Design	Diagnosis	Exposure to antipsychotics (max. no of days)	Age mean (s.d.)	Women (*n*)	FEP naïve (*n*)	Controls MetS/*n* (prevalence %)	Findings
Saddichha	Baseline assessment of longitudinal cohorts	DSM-IV: 295.10/ 295.20/295.30/ 295.60/295.90	0	26.06 (5.5)	47	99	1/51 (1.96%)	Data confirmed the high prevalence of MetS for an Indian population of patients.
Saloojee	Baseline assessment of longitudinal cohorts	DSM-IV: 295.10/ 295.20/295.30/ 295.60/295.90, 295.70	0	22.8 (3.7)	19	67	3/67 (4.50%)	Authors state that a possible explanation for their finding of a low prevalence of MetS in antipsychotic-naïve individuals with SMI includes a high proportion of black African participants (97%) and an increased prevalence of cannabis abuse (49.3%).
García-Rizo	Baseline assessment of longitudinal cohorts	DSM-IV: 295.10/ 295.20/295.30/ 295.60/295.90	0	28.8 (8.3)	54	84	4/98 (4.00%)	MetS might not be an efficient risk factor for evaluating the cardiovascular risk in naïve patients. Authors propose the use of HOMA-IR, a method used to quantify insulin resistance.
De Hert	Baseline assessment of longitudinal cohorts	DSM-IV: 298.9	0	22.3 (3.2)	42	148		There was no significant difference in rates of MetS at the first episode between patients admitted to hospital today and patients admitted 15–20 years ago in the sample under study, although there were significant differences in rates on individual MetS criteria. This suggests that possible population lifestyle changes do not play an important role before treatment is started.
Enez Darcin	Cross-sectional	DSM-IV: 295.10/ 295.20/295.30/ 295.60/295.90	0	31.8 (10.3)	11	42	4/70 (5.71%)	The rates of the diagnoses of metabolic syndrome and metabolic disturbances were significantly higher in the patients with schizophrenia than in the controls, and the former group consisted of drug-naive and drug-free patients. This result highlights that there may be some factors other than antipsychotic drugs that could be responsible for the high risk and high prevalence of metabolic syndrome in individuals with schizophrenia.
Sahpolat	Cross-sectional	DSM-IV: 295.10/ 295.20/295.30/ 295.60/295.90	0	29.0 (9.6)	18	38	5/41 (12.19%)	The study reports that the mean FBG level was significantly higher in the FEPP (99.7 ± 18.6). The METSAR study demonstrated that the mean blood level of the HDL in Turkish adults was 49 mg/dl. Accordingly, the study found that the mean HDL level was significantly lower in the FEPP (40.9 ± 10.6 mg/dl).

Table 2. MetS prevalence of studies included in the meta-analysis

Author	Year	Country	FEP naïve (*n*)	MetS prevalence (95% CI)	Diagnostic criteria	Risk of bias
De Hert	2008	Belgium	148	5% (2–9)	ATP III-A	Low
Medved	2008	Croatia	94	15% (9–23)	IDF	Low
Saddichha	2008	India	99	10% (4.2–16) & 18.2 (10–25)	ATP III-A & IDF	Low
Grover	2011	India	46	13% (3–22) & 10.86% (0.2–20)	ATP III-A & IDF	Low
Kraemer	2011	Germany	162	21% (15–28)	ATP III-A	Low
Effat	2012	Egypt	20	40% (22–61)	IDF	Moderate
Otaño	2012	Spain	19	0% (0–17)	ATP III-A	Low
Owiredu	2012	Ghana	100	2% (0.7–4.7) & 2% (0.7–4.7) & 14% (7–20)	ATP III-A & IDF & OMS	Moderate
García-Rizo	2017	Spain	84	6% (3–13)	ATP III-A	Low
Saloojee	2017	South Africa	67	4% (2–12)	JIS-2009	Moderate
Srivastava	2018	India	92	20% (13–29)	IDF	Moderate
Enez Darcin	2015	Turkey	42	32% (18–47) & 39% (25–55)	ATP III & IDF	Moderate
Sahpolat	2020	Turkey	38	28.9% (16–45) & 31.5% (16.9–46.4)	ATP III-A & IDF	Moderate

CI 24–42) and of 14.3% (95% CI 9.2–21), respectively (online Supplementary Figs. S7a–e).

Antipsychotic exposure and diagnostic MetS criteria

Although our meta-analysis includes drug-naïve (0-day exposure) patients only, we additionally performed post hoc sensitivity analyses through one-study-removed analysis on five studies without a strictly naïve definition, one that included minimal exposure (0–14 days) and four that included up to 47-day exposure (Figs. S2–S4 online supplementary material). The use of the 0–14 range is based on the recent evidence about the time considered as minimal exposure (Pillinger, Beck, Gobjila, et al., 2017; Pillinger, Beck, Stubbs, et al., 2017) and the observed large changes in metabolic parameters in a median time of 6 weeks with some antipsychotics (Pillinger et al., 2020).

Our post hoc analysis shows no significant changes in prevalence after removing studies. The prevalence of MetS was 12.2% (studies with 0 and 0–14 days of exposure, $n = 1085$, $k = 14$) and 12.2% (47 days of exposure, $n = 711$, $k = 4$), while the prevalence of MetS patients reported as naïve in the eighteen studies was 12.3% (95% CI 0.8–17.0) ($n = 1796$, $k = 18$). All in all, these sensitivity analyses show that the prevalence in strictly naïve (0 days of exposure) is 13.2% (95% CI 8.7–19.0) (online Supplementary Figs. S2–S4). From the excluded studies observed in Table 4, the minimal exposure study (Srihari et al., 2013) has the lowest prevalence of MetS. More details are provided in Fig. 2 and in online Supplementary Figs. S2–S4.

Sensitivity analyses based on diagnostic MetS criteria were also conducted in 13 studies. Although it seems all of them yield different prevalence estimates, there are no statistically significant differences between them. However, it is worth flagging that MetS prevalence is higher when diagnosed according to IDF *v.* ATP-IIIA criteria (online Supplementary Figs. S9–S11). We found that although the prevalence is more than double the prevalence with IDF, the confidence intervals of the prevalence in both subgroups ATP III 10% (95% CI 6–15) and IDF 21.8% (95% CI 12–34) match the confidence intervals of the global prevalence estimator 12.9% (95% CI 8–18). This result can be clearly observed by visual inspection of the forest plot figure (online Supplementary Figs. S9–S11). Additionally, in the four studies where both IDF and ATP-IIIA criteria were used to diagnose MetS, we performed individual meta-analyses for IDF and for ATP-IIIA showing that MetS prevalence in the same population is higher when diagnosed according to IDF than ATP-IIIA (online Supplementary Figs. S9–S11).

Other sensitivity and subgroup analysis

Sensitivity analyses based on sample size and one-study-removed analysis were also conducted (online Supplementary Fig. S2). One study (Effat et al., 2012) may be an outlier based on visual inspection. However, when excluding it from the analysis, the overall prevalence estimate just changed from 13.2% (95% CI 8.7–19.5) to 12% (95% CI 8–18). This change is not statistically significant. The influence analysis of Effat's study is visually striking, but not significant because it has a low weight ($w = 1.34\%$).

Heterogeneity, quality assessment and meta-regressions

Heterogeneity was high for the primary analysis evaluating the pooled prevalence of MetS [$I^2 = 81.03\%$, $Q = 63$, df(12), $p = 0.00$]. Also heterogeneity between subgroups was observed in the stratified analysis by criteria used for MetS [$I^2 = 83.0\%$, $Q = 7.57$, df(2), $p = 0.023$]. We conducted meta-regressions using as covariates diagnostic criteria used for MetS, risk of bias, geographical location, ethnic origin of participants and patient settings. Geographical location is not a source of heterogeneity (R^2 0.00). Ethnicity accounted for 3% of the heterogeneity between studies, and diagnostic criteria used for MetS accounted for 7%. An additional meta-regression was performed using the MetS parameters of each study. The individual parameters for diagnosing MetS do not represent a source of heterogeneity for the prevalence estimates. The means of systolic blood pressure, diastolic blood pressure, serum glucose, HDL cholesterol and triglycerides are not significantly related to the estimated prevalence of MetS. The quality check agreement between the two raters was 81.8%. The risk of bias was graded as low (⩾7 points) for nine studies (De Hert et al., 2008; Enez Darcin et al., 2015;

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Table 3. Antipsychotic exposure and findings in not strictly naïve FEP

Author	Design	Diagnosis	Exposure to APs (max. no of days)	Age (mean)	Women (*n*)	FEP naïve (*n*)	Controls MetS/ *n* (prevalence %)	Findings
Srihari	Baseline assessment of longitudinal cohorts	DSM-IV: 295.10/ 295.20/295.30/ 295.60/295.90	14	22.4 (4.8)	8	76	2/156 (1.28%)	No elevations in the prevalence of metabolic syndrome (1.31% *v.* 1.28%) or 10-year risk of developing coronary heart disease (0.70% *v.* 0.74%) at treatment entry compared to healthy controls were detected. Both groups were well within the 'low risk' (below 10%) category.
Pallava	Cross-sectional	ICD10: F20, F22	42	28.10 (7.2)	28	50		Prevalence of 26% in the drug-free/naïve group and 50% in those on antipsychotic treatment appear higher.
Correll	Cross-sectional	DSM-IV: 295.10/ 295.20/295.30/ 295.60/295.90, 295.70 ICD-10: F23, F20.81	47	23.6 (5.0)	106	394		Early in psychotic illness and after a mean of only 6.7 weeks of antipsychotic exposure, lipid abnormalities and insulin resistance markers were elevated and significantly related to lifetime and individual antipsychotic exposure.
Fleischhacker ´	Baseline assessment of longitudinal cohorts	DSM-IV: 295.10/ 295.20/295.30/ 295.60/295.90, 295.70	42	25.4 (5.4)	59	160		Baseline MetS prevalence in patients was comparable to that reported in the general population, despite serious underlying individual risk factors existed. Findings showed that 58% had at least one pre-existing MetS risk factor. The MetS rate observed in the first-episode patients in EUFEST appears to be no higher than that in a general population of similar age.
Chiliza	Baseline assessment of longitudinal cohorts	DSM-IV: 295.10/ 295.20/295.30/ 295.60/295.90, 295.70	28	24 (6.5)	30	107		The baseline MetS rate of 16% in the sample is considerably higher than that reported in other studies. Authors acknowledged that this may reflect the particular risk of MetS even in young individuals in emerging economies globally. Cohort comprised largely individuals of mixed ethnicity in the greater Cape Town area – a community where the prevalence of MetS and diabetes has hugely increased in recent years and is predicted to reach epidemic proportions.

Table 4. Prevalence of metabolic syndrome in not strictly naïve patients with FEP

Author	Year	Country	FEP naïve (*n*)	MetS prevalence (95% CI)	Diagnostic criteria	Risk of bias
Pallava	2011	India	50	26% (16,40)	IDF	Low
Fleischhacker	2012	Sweden	160	6% (3,10)	ATP III-A	Low
Chiliza	2015	South Africa	107	16% (10,24)	ATP III-A	Low
Srihari	2013	USA	76	1.3% (0,3.9)	ATP III-A	Low
Correll C	2014	USA	394	8% (5.9, 11)	ATP III	Low

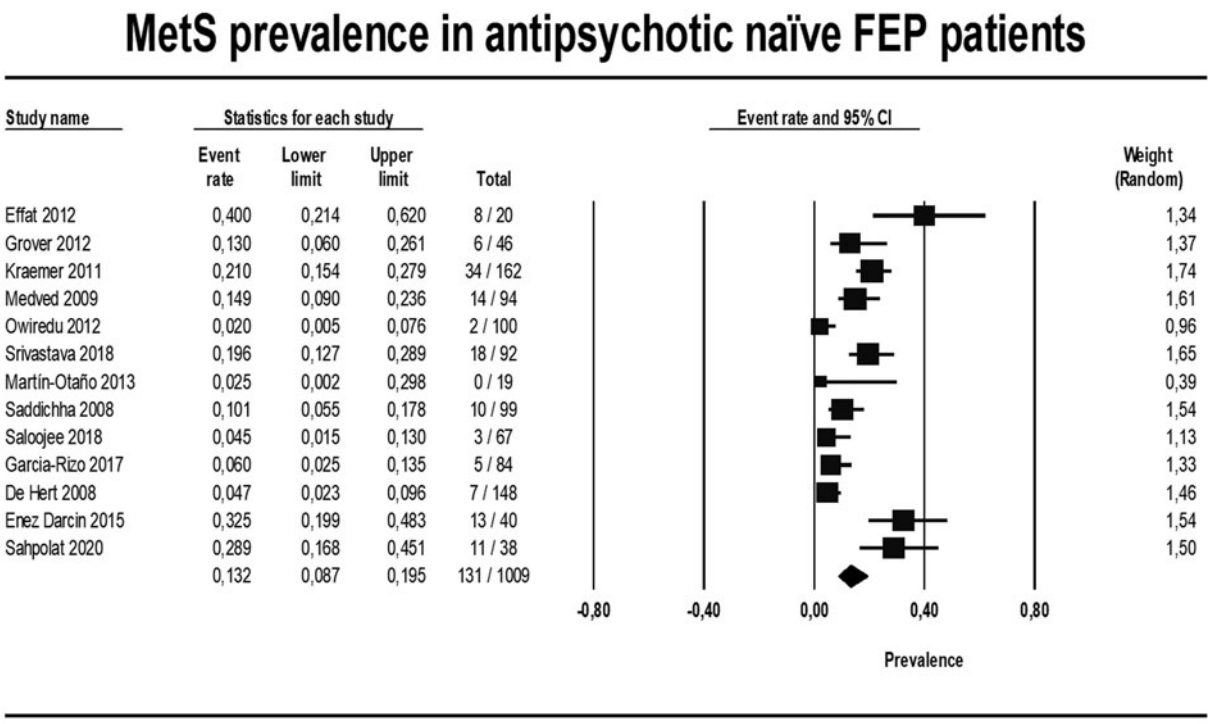

Fig. 2. Forest plot showing MetS prevalence in strictly naïve patients (0 days).

Garcia-Rizo et al., 2017; Grover et al., 2012; Kraemer et al., 2011; Martín Otaño et al., 2013; Medved et al., 2009; Saddicha et al., 2007; Sahpolat & Ari, 2021) and graded as medium (4–6 points) for four studies (Effat et al., 2012; Owiredu et al., 2012; Saloojee et al., 2018; Srivastava et al., 2018). Studies with a medium risk of bias ($k = 4$) reported a lower prevalence of 11% (95% CI 3.0–31.0) than studies with low risk of bias, which reported a prevalence of 13.9% (95% CI 8.0–21.0) but the difference between them is not statistically significant. Study quality scores of the 18 full-text selected studies may be found in online Supplementary Tables S6, S13 and Fig. S9.

Waist circumference

As for central obesity, nine of 13 studies reported data on waist circumference (De Hert et al., 2008; Effat et al., 2012; Enez Darcin et al., 2015; Kraemer et al., 2011; Medved et al., 2009; Owiredu et al., 2012; Saddicha et al., 2007; Saloojee et al., 2018). Patients in studies that reported a waist circumference larger than 90 cm had higher MetS prevalence than those with smaller than 90 cm (21% *v.* 7%; $p < 0.001$).

Control comparison

Of the 13 studies included, only six had control groups (348 cases and 347 controls) being all of them matched by sex and age (Effat et al., 2012; Enez Darcin et al., 2015; Garcia-Rizo et al., 2017; Saddicha et al., 2007; Sahpolat & Ari, 2021; Saloojee et al., 2018). In this context, three of them used ATP-III criteria, two used IDF criteria and one used JIS-2009 criteria. Following the analysis of these studies, we found that the odds of having MetS in naïve FEP individuals was double than in controls (OR 2.52, $p = 0.007$) (Fig. 3). Of note is that we used studies with naïve (0 days of exposure) patients to control comparison.

Discussion

This is the first meta-analysis of studies that strictly included patients with FEP with 0-day exposure to antipsychotic treatment. The prevalence of MetS in strictly naive patients with FEP is 13.2%. Our results are consistent with the most solid published meta-analysis on MetS in early stages of psychosis, including

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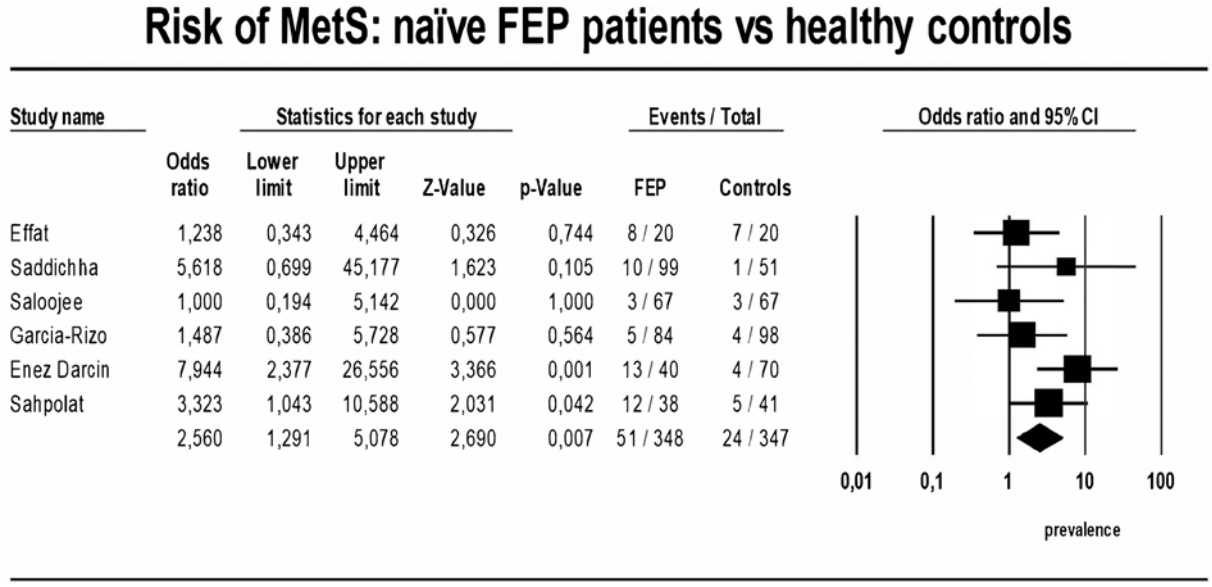

Fig. 3. Forest plot showing comparison between naïve (0 days) first-episode psychosis patients *v.* healthy controls.

patients under medication and untreated patients at any stage of the disease, where a prevalence of 9.8% was found (Mitchell et al., 2013). In contrast to this research, we specifically analysed patients with a first psychotic episode with no exposure to antipsychotics.

Naïve patients have double the amount of risk of MetS than general population

Our meta-analysis reports a higher risk of MetS in naïve patients with FEP compared to age-matched and sex-matched controls. We used studies with naïve patients (0 days of exposure) to control comparison, being all of them sex- and age-matched. The similar rates of MetS found in our study and in a previous meta-analysis (Vancampfort et al., 2013) conducted in chronic populations (OR = 2.52 against OR = 2.35) is an intriguing finding that requires further exploration. It could also mean that antipsychotic use is not the only factor that can explain MetS; and that other factors, for which we have not accounted in this work, and that can account for it are already present early in the disease. In addition to antipsychotics, diet and a sedentary lifestyle, the tendency towards obesity in a group of patients with schizophrenia may also be influenced by genetic factors (Hasnain, 2015) and by the impact of social adversity (Aas et al., 2017; Alameda et al., 2020). In this regard, one aspect to consider in future research could be the possible pathway linking social stress with obesity-related outcomes in people with psychosis, exploring the role of inflammation, stress hormones and the genetic and epigenetic underpinnings (Coleman, Krapohl, Eley, & Breen, 2018). Furthermore, current research suggests genetic vulnerability that specifically predisposes a subgroup of individuals to present metabolic alterations that are triggered by the use of antipsychotics (Crespo-Facorro, Prieto, & Sainz, 2019; Tomasik et al., 2019).

Two studies included in our systematic review but not included in our OR calculation (Correll et al., 2014; Fleischhacker et al., 2013) did not use age- and sex-matched controls, but compared their MetS prevalence results in naïve patients with the general population based on findings from the Third National Health and Nutrition Examination Survey USA (Ford, Giles, & Dietz, 2002). The EUFEST study (Fleischhacker et al., 2013) found a 5.6% prevalence of MetS in naïve patients, which is similar to the 6% MetS prevalence reported for men and women in the USA aged 20–29 years old in an analysis of 8814 adults aged >20 years from the NHANES-III (1988–1994) survey (Ford et al., 2002). However, the MetS rate observed in the FEP patients in EUFEST (Fleischhacker et al., 2013) appears to be no higher than that of a general population of similar age. In the RAISE-ETP study (Correll et al., 2014), a slightly higher prevalence of MetS was found in naïve patients compared to the general population (Ford et al., 2002) of the same age (8.6% *v.* 6.0%).

A recent study (Moore, Chaudhary, & Akinyemiju, 2017) reported that rates of MetS in the general US population (all ethnicities combined, 1988–2012) in the age range of 18–29 was approximately 10%, increasing to approximately 20% in the 30–49 age bracket. No studies included in our meta-analysis used the recent published data (Moore et al., 2017) as control groups. One study (Grover et al., 2012) found that the prevalence of MetS in naïve patients was lower than that of the general population (13% *v.* 39.5%). However, the population used as a control consisted mainly of women, with sedentary habits and with first-degree relatives who had a history of diabetes: all of these are cardiovascular risk factors. Therefore, the higher prevalence of MetS in naïve psychotics could be due to the fact that the latter were younger. For this reason, the Grover study was not used for the OR calculation.

Current criteria for MetS may not characterise risk in non-Caucasian populations

In our results, we identify that ethnic origin is a source of heterogeneity, which coincides with the majority of previous studies where ethnic differences have been described in the prevalence of MetS in patients with FEP (McEvoy et al., 2005; Tek et al., 2016). In this context, the slight complexion of the Asian population discourages the use of the same circumference criteria as for

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the population of European descent (Lear, James, Ko, & Kumanyika, 2010). Asian populations have a lower prevalence of obesity (32.3% Asians *v.* 38.6% Westerners) (Arai et al., 2006), lower HDL cholesterol (8.2% *v.* 37.1%), higher triglyceride (23.0% *v.* 30.0%) and abnormal glucose levels (11.3% *v.* 12.6%) compared to Western populations (Ford et al., 2002). The prevalence of MetS in the general population might also be lower than that of the Western population.

In four of the included studies, the systematic review (Chiliza et al., 2015; Correll et al., 2014; Owiredu et al., 2012; Saloojee et al., 2018) mentioned ethnic differences as a possible element of confusion when determining results, and in two of them (Chiliza et al., 2015; Saloojee et al., 2018), it is suggested that this is the main source of variability in the prevalence of MetS in patients with FEP. Additionally, the low prevalence of MetS in naïve patients could be explained because they include a high proportion of Afro-descendant patients (97%) and a high prevalence of cannabis use (49.3%), both of which are factors that can modify the risk of MetS. In the same line, it has been described (Patel et al., 2009) how for other ethnic groups the prevalence of MetS at 52 weeks of treatment is almost double that of Afro-descendants. On the contrary, several epidemiological studies reported that Afro-descendants have a higher risk of metabolic disorders such as insulin resistance and high blood pressure (Chaturvedi, 2003). The explanation for this contradiction could be the underestimation of the risk of MetS in Afro-descendants within the current definitions of MetS according to the IDF and ATP-IIIA criteria, since these were initially created for Caucasian populations and there are factors not duly taken into account, such as body fat distribution and risk of insulin resistance (De Lucia Rolfe, Ong, Sleigh, Dunger, & Norris, 2015). Hence, based on ATP-IIIA and IDF, various scientific societies in Asian and Latin American countries have adapted their own MetS criteria.

Other potential predictors of cardiovascular risks in FEP

MetS is a predictor of cardiovascular risk. Within 5–10 years, risk is best calculated with classic scales (Framingham or SCORE), which include age, gender, total cholesterol, LDL and tobacco use (Grundy, 2006). Our study found that the prevalence of tobacco use was 40%. Bearing in mind that a large percentage of patients with schizophrenia are smokers, it would be useful to include the influence of tobacco on future predictors of cardiovascular risk.

The alteration of individual metabolic parameters in naive FEP, such as glycaemic or lipid alterations, is widely described in the existing literature. In a recent meta-analysis, Pillinger et al. (2020) found increased insulin resistance in drug-naïve FEP compared with controls. For this reason, the use of other markers like insulin resistance as predictors of cardiovascular risk has been proposed (Garcia-Rizo et al., 2017). Several cardiovascular risk prediction algorithms have been developed, but only three are validated on psychiatric patients (QRISK3, QDiabetes and PRIMROSE) and these are validated with samples from only elderlies (Perry et al., 2020). Most of the analysed studies show that among the individual parameters, waist circumference relates the most to changes in MetS prevalence, finding MetS prevalence higher in those with the highest abdominal perimeter. Additionally, we found that the prevalence of altered waist circumference is 14% in naïve patients with FEP.

Limitations of the current work itself should be noted: heterogeneity across studies which may be due to disparity in MetS criteria. Although we tried our best to account for potential heterogeneity resulting from the different MetS criteria (conducting sensitivity analysis according to studies that used IDF or ATP-IIIA and conducting separated meta-analysis with studies that reported prevalence with ATPIII-A and with IDF) we were still unable to account for variations in all criteria (e.g. JIS-2009 and WHO criteria). We were not able to exclude patients/controls that were prescribed other psychiatric/physical health medications other than antipsychotics known to impact metabolic function and we could not account for the level of depressive symptom or comorbid depression in our meta-regressions, a factor known for being associated with obesity-related outcomes (Lasserre et al., 2014), thus we cannot exclude that depression is influencing our prevalence estimates. It is also known that people with psychotic disorders are less likely to present to physical health services compared with the general population. As such, there is a risk of under-reporting and thus under-estimating the prevalence of MetS in this cohort.

In terms of limitations related to the included studies in meta-analysis, two studies (Owiredu et al., 2012; Saloojee et al., 2018) were the only ones conducted on Afro-descendant ethnicity and the overall prevalence increased when those were removed in sensitivity analyses. However, one of them (Saloojee et al., 2018) was the only study that reported cannabis consumption, which has been associated with low odds of MetS in both general population (Vidot et al., 2016) and patients with FEP (Stiles, Alcover, Stiles, Oluwoye, & McDonell, 2020), low odds of overweightness (Vazquez-Bourgon et al., 2019) and low odds of non-alcoholic fatty liver (Vazquez-Bourgon et al., 2019) in patients with FEP. We were not able to see the influence of cannabis on prevalence accurately. Unfortunately, we do not have enough data to accurately see the influence of age on prevalence as most studies reported the mean and not age range, and the few reported age ranges are not mutually excluding. Besides, the control group studies remain relatively low.

To conclude, our findings of increased rates of MetS in patients with antipsychotic-naïve FEP suggest that we are underestimating cardiovascular risk in this cohort, especially in those of non-Caucasian origin. The role of cannabis in the modulation of MetS requires additional research. Early predictors of cardiovascular risk for schizophrenia should be determined considering different patient phenotypes according to precision medicine. Future research should focus on the predictors of cardiovascular risk including common molecular and environmental factors, as our findings support that altered metabolic parameters in FEPs are not exclusively due to antipsychotic treatments.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721002853.

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