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Síndrome metabólico en pacientes con primer episodio psicótico que nunca han tomado antipsicóticos

TESIS DOCTORAL

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Metabolic syndrome in antipsychotic naïve patients with first-episode psychosis

Memoria presentada para optar al título de doctor por la Universidad de Sevilla
presentada por:

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A mi mamá y a mi papá, de quienes estoy incondicionalmente orgullosa.

A mi querido esposo y a mi pequeño Federico por su compañía

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Abreviaturas

MetS: Síndrome metabólico

PEP: Primer episodio psicótico

IDF: International Diabetes Federation (IDF)

ATP-III: Adult Treatment Panel III

DSM: Manual diagnóstico y estadístico de los trastornos mentales

PAFIP: Programa de atención a las fases iniciales de la psicosis

PA: Perímetro abdominal

HDL: High Density Lipoprotein

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Abstract

Metabolic syndrome in antipsychotic naïve patients with first-episode psychosis

Background

The association between the psychotic disorders and metabolic syndrome (MetS) is widely knowledged and it has been mainly attributed to antipsychotics. 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; however most studies on naïve patients have focused on the search for specific metabolic alterations, without exploring the presence of all MetS components together.

Methods

In the first step of this doctoral thesis, a systematic review and meta-analysis that included studies in patients with first psychotic episode (FEP) without prior exposure to antipsychotic treatment "naïve" was carried out. In the second step, and once the limitations of the studies carried out on this topic were known, a cross-sectional study on the prevalence of metabolic syndrome in patients with naïve FEP and then a longitudinal study about its follow-up to 3 years were carried out. For this, the dataset of the PAFIP Program for Attention to the Initial Phases of Psychosis, which is a reference program for psychosis at national and international level, was used.

Results

In the meta-analysis it was found that the prevalence of metabolic syndrome in patients with FEP strictly naïve was 13.2%. (95% CI 8.7–19.0) (n = 1009, k = 13). In addition, it was observed that patients with FEP have twice the risk of developing metabolic syndrome than the general population regardless of the use of antipsychotics (OR 2.52, p

= 0.007). The main sources of heterogeneity were the disparity of criteria used to define metabolic syndrome and the ethnicity. Through the study of a representative sample of naïve patients it became evident that the prevalence of metabolic syndrome is similar to that of controls, however, it was confirmed that patients with FEP have more baseline metabolic alterations than healthy controls. After analyzing the baseline prevalence of metabolic syndrome in FEP, controls and follow-up at 3 years, it was found that the FEP group had a worse evolution compared to the control group, regardless of the use of antipsychotics.

Conclusions

Patients with FEP have a higher risk of metabolic syndrome and more metabolic disturbances than the general population. These alterations are not due exclusively to the use of antipsychotics. There are several causes that could justify the presence of these alterations in young patients, one of them is the hypothesis of schizophrenia as part of a systemic disease that originates in the early stages of development and that in addition to the brain, involves other organs. Social determinants of health and exposure to environmental factors at critical stages of neurodevelopment contribute to the increased risk of both psychotic disorder and metabolic syndrome. Women with first psychotic episode present some specific alterations more frequently than men prior to the use of antipsychotics. On the other hand, it is necessary to have cardiovascular risk measurement tools validated in young people with first psychotic episodes.

Resumen

Síndrome metabólico en pacientes con primer episodio psicótico que nunca han tomado antipsicóticos

Antecedentes

La relación entre esquizofrenia y síndrome metabólico (MetS) es ampliamente conocida y se ha atribuido principalmente a los antipsicóticos. En la última década se han publicado estudios en pacientes con trastorno psicótico que presentan alteraciones metabólicas a pesar de nunca haber tomado antipsicóticos, sin embargo, la mayoría se han centrado en la búsqueda de alteraciones metabólicas específicas sin explorar la presencia de todos los componentes de síndrome metabólico en conjunto.

Métodos

En una primera fase de esta tesis doctoral, se realizó una revisión sistemática y metaanálisis que incluyó estudios en pacientes con primer episodio psicótico (PEP) sin exposición previa al tratamiento antipsicótico "naïve". En una segunda fase y una vez conocidas las limitaciones de los estudios realizados sobre este tema, se hizo un estudio transversal y después longitudinal sobre la prevalencia de síndrome metabólico en pacientes con PEP naïve y su evolución a 3 años. Para ello se utilizó el dataset del Programa de Atención a las Fases Iniciales de la Psicosis PAFIP, que es programa de referencia de psicosis a nivel nacional e internacional.

Resultados

En el meta-análisis se encontró que la prevalencia de síndrome metabólico en pacientes con PEP estrictamente naïve fue 13.2%. (95% CI 8.7–19.0) (n = 1009, k = 13). Además, se observó que los pacientes con PEP tienen el doble de riesgo de presentar síndrome metabólico que la población general independientemente del uso de antipsicóticos (OR 2.52, p = 0.007). Las principales fuentes de heterogeneidad fueron la disparidad de criterios usados para definir síndrome metabólico y la etnicidad. A través del estudio en una muestra representativa de pacientes naïve se hizo evidente que la prevalencia de síndrome metabólico es similar a la de los controles, sin embargo, se confirmó que los pacientes con PEP tienen más alteraciones metabólicas basales que los controles sanos. Después de analizar la prevalencia basal de síndrome metabólico en PEP, controles y el seguimiento a los 3 años, se encontró que el grupo PEP tuvo una peor evolución en comparación con el grupo control, independientemente del uso de antipsicóticos.

Conclusiones

Los pacientes con trastorno psicótico tienen más riesgo de síndrome metabólico y más alteraciones metabólicas que la población general. Estas alteraciones no se deben exclusivamente al uso de antipsicóticos. Hay varias causas que podrían justificar la presencia de esas alteraciones en pacientes jóvenes, una de ellas es la hipótesis de la esquizofrenia como parte de una enfermedad sistémica que tiene origen en etapas tempranas del desarrollo y que además del cerebro, compromete otros órganos. Los determinantes sociales de la salud y la exposición a factores ambientales en etapas críticas del neurodesarrollo contribuyen al aumento de riesgo de presentar trastorno psicótico y síndrome metabólico. Las mujeres con primer episodio psicótico presentan algunas alteraciones específicas y diferentes a los hombres previamente al uso de antipsicóticos.

Por otra parte, es necesario tener herramientas de medida de riesgo cardiovascular validadas en población joven con primer episodio psicótico.

Introducción

Esquizofrenia y síndrome metabólico

El cerebro es un órgano complejo y aún desconocido, del que hoy se sabe, está genéticamente organizado y marcado por la exposición del ambiente externo e interno o "exposoma" que, en etapas críticas del desarrollo, sobre todo en fases muy tempranas, son determinantes de muchas alteraciones, entre ellas la esquizofrenia cuyo origen se enmarca en una alteración del desarrollo cerebral.

La esquizofrenia es un síndrome clínico caracterizado por síntomas psicóticos y deterioro psicosocial que conduce a importantes costes humanos y económicos. Su etiología, aún en estudio, combina factores genéticos que podrían estar modulados por factores ambientales (Penninx & Lange, 2018; Postolache et al., 2019; Wong et al., 1997). Tanto la esquizofrenia como las enfermedades cardiovasculares derivadas del síndrome metabólico están estrechamente relacionadas y ambas tienen un alto impacto en la mortalidad y discapacidad a nivel mundial.

Aunque el foco de la mayor parte de la investigación se ha puesto sobre los antipsicóticos como los principales responsables de la diabetes, sobrepeso y alteraciones lipídicas en pacientes con esquizofrenia, desde una perspectiva histórica (Kohen, 2004) a través de una revisión de estudios (Kooy, 1919; Lorenz, 1922; Raphael & Parsons, 1921), realizados en tiempos en que no se usaban los antipsicóticos y con las limitaciones metodológicas de la época, describe la relación de la diabetes mellitus con la esquizofrenia, se puede observar que en ese entonces, ya se relacionaba la esquizofrenia con las alteraciones en la glucemia y la predisposición a la diabetes. Así mismo, por 1939, cuando uno de los tratamientos usados para la esquizofrenia era la pirexia inducida por insulina, sin estar en la búsqueda de ello, ya se observaba que en algunos pacientes con

esquizofrenia y fenotipos específicos había resistencia insulínica. De manuscritos de la época, (Sánchez, 1939) se recogen afirmaciones que apuntaban a ello: “La pirexia la hemos observado en los límites extremos de la receptividad personal a la insulina es decir en pacientes demasiado sensibles a la insulina o en aquellos otros que resisten dosis inverosímiles” .

El aumento de la prevalencia de MetS en pacientes con esquizofrenia en comparación con la población general es ampliamente conocida (Kraemer et al., 2011), y se ha atribuido principalmente al uso de antipsicóticos atípicos (Newcomer et al., 2002; Vancampfort et al., 2015), así como a otros factores de riesgo que se acumulan a lo largo de vida como el sedentarismo, la mala alimentación, el consumo de tabaco y la falta de autocuidado debido a los propios síntomas negativos de la enfermedad (Bobes et al., 2007).

Según la literatura existente, la prevalencia del MetS en la población general oscila entre el 6% y el 45% (Moore et al., 2017), mientras que en pacientes con esquizofrenia que toman antipsicóticos oscila entre el 35,3% (Mitchell, Vancampfort, De Herdt, et al., 2013; Vancampfort et al., 2015) al 49 % (Kraemer et al., 2011).

Causas de mortalidad en esquizofrenia

La esperanza de vida de las personas con esquizofrenia es 20 años menor que en la población general, donde el 60% de las causas de muerte prematura están relacionadas con enfermedades cardiovasculares (Pillinger et al., 2019). Es decir, existe una tasa de mortalidad sumamente elevada, que es más del doble que en la población general (Walker et al., 2015). La mayor parte se deben a causas naturales, principalmente eventos cardiovasculares, por encima de causas psiquiátricas como el suicidio (Correll et al., 2017; Laursen, 2019; Moreno-Küstner et al., 2021). Este exceso de mortalidad se ha relacionado con los efectos adversos de la medicación, las altas tasas de comorbilidad

somática, las desigualdades en el acceso al tratamiento de enfermedades somáticas y el envejecimiento acelerado. En este sentido, la hiperlipidemia (61 %), el tabaquismo (55 %), la obesidad (41 %), la diabetes (19 %), la hipertensión (17 %) y las enfermedades respiratorias (Perez-Pinar et al., 2016; Suetani et al., 2021) son los factores de riesgo cardiovascular más prevalentes en pacientes con esquizofrenia.

Criterios diagnósticos de síndrome metabólico

Uno de los indicadores de riesgo cardiovascular más estudiado es el síndrome metabólico (MetS), que consiste en un grupo de parámetros que indican la probabilidad de desarrollar enfermedades cardíacas y diabetes (Eckel et al., 2005). Los criterios más utilizados para el diagnóstico de MetS son los de IDF (International Diabetes Federation, 2006) y los ATPIII (Adult Treatment Panel III, 2001), que difieren entre sí en el punto de corte de los parámetros que se consideran patológicos.

Tabla 1

Criterios de síndrome metabólico

ATP-IIIA	Diagnosis is made when three or more are present: • Waist circumference of more than 102 cm in men or more than 88 cm in women. • Waist circumference ≥94 cm for Mediterranean men or ≥80 cm for Mediterranean women • Fasting triglyceride level of 150 mg/dL or higher. • Blood pressure level of 130/85 mm Hg or higher. • Low HDL-C level (defined as < 1.04 mmol/L [40 mg/dL] in men or < 1.29 mmol/L [50 mg/dL] in women) • Fasting hyperglycemia (defined as glucose level ≥5.6 mmol/L [100 mg/dL]) or previous diagnosis of diabetes or IGT

IDF	• **Central obesity and any 2 out of these 4 other factors:** • Triglyceride level of 1.7 mmol/L (150 mg/dL) or higher. • Low HDL-C level (defined as < 1.04 mmol/L [40 mg/dL] in men or < 1.29 mmol/L [50 mg/dL] in women) • Blood pressure of 130/85 mm Hg or higher. • Fasting hyperglycemia (defined as glucose level ≥5.6 mmol/L [100 mg/dL]) or previous diagnosis of diabetes or IGT.
JIS-2009	• > 3 out of these parameters: • Fasting glucose>100mg/dL • Blood pressure level of 130/85 mm Hg or higher. • Fasting triglyceride level of 150 mg/dL or higher. • Low HDL-C level (defined as < 1.04 mmol/L [40 mg/dL] in men or < 1.29 mmol/L [50 mg/dL] in women)
WHO	• Insulin resistance is defined as type 2 diabetes mellitus (DM) or impaired fasting glucose (IFG) (> 100 mg/dl) or impaired glucose tolerance (IGT), plus two of the following: • Abdominal obesity (waist-to-hip ratio > 0.9 in men or > 0.85 in women, or body mass index (BMI) > 30 kg/m^2. • Triglycerides 150 mg/dl or greater, and/or high-density lipoprotein (HDL)-cholesterol < 40 mg/dl in men and < 50 mg/dl in women. • Blood pressure (BP) 140/90 mmHg or greater. • Microalbuminuria (urinary albumin secretion rate 20 µg/min or greater, or albumin-to-creatinine ratio 30 mg/g or greater).

Evidencia sobre alteraciones metabólicas en pacientes con esquizofrenia previas al uso de antipsicóticos

En la última década se han publicado estudios en pacientes con trastorno psicótico que presentan alteraciones metabólicas a pesar de nunca haber recibido tratamiento antipsicótico, específicamente alteraciones en la glucosa y en los lípidos (Kirkpatrick et

al., 2009, 2012; Pillinger, Beck, Gobjila, et al., 2017; Pillinger, Beck, Stubbs, et al., 2017). Teniendo en cuenta estos hallazgos, en diversas investigaciones (Chadda et al., 2013; Cordes et al., 2016; Ryan et al., 2004), se propone una hipótesis de vulnerabilidad para el desarrollo de trastornos metabólicos independiente del uso de antipsicóticos en pacientes con esquizofrenia. En esta línea, una meta-revisión sistemática reciente (Pillinger et al., 2019) encontró que además de alteraciones en el sistema nervioso central, también hay asociaciones significativas entre la esquizofrenia y alteraciones en otros sistemas como el endocrino, inmunológico y cardiometabólico. Todo esto, previo al inicio del tratamiento farmacológico.

La mayoría de los estudios hechos en pacientes nunca tratados con antipsicóticos se han centrado en la búsqueda de alteraciones metabólicas específicas: (peso, índice de masa corporal, perímetro abdominal (PA) o alteraciones de la glucosa y los lípidos), sin explorar la presencia de todos los componentes de MetS en conjunto. La evidencia de estos estudios indica mayores tasas de resistencia a la insulina, alteraciones de la glucosa basal (B. I. Perry et al., 2016a; Pillinger, Beck, Gobjila, et al., 2017) y dislipidemia (Misiak et al., 2017; B. I. Perry & Singh, 2018; Pillinger, Beck, Stubbs, et al., 2017; Pillinger et al., 2018) en pacientes sin tratamiento previo con un primer episodio psicótico (PEP). Además, los niveles alterados de otros factores bioquímicos no incluidos en la definición MetS como los niveles plasmáticos de cortisol (Misiak et al., 2017), ACTH, homocisteína (Ayesa-Arriola et al., 2012; Misiak et al., 2014; Shih et al., 2021; Zhang et al., 2021) proteína C reactiva (Fernandes et al., 2016; Steiner et al., 2019) y leptina (Misiak et al., 2019) se han encontrado también en esta población.

La esquizofrenia más allá del cerebro

Aunque tradicionalmente se ha considerado que la esquizofrenia es un trastorno mental que comprende un conjunto de síntomas positivos y negativos, cada vez existe

más evidencia de que además de las funciones cerebrales alteradas que causan los síntomas psicóticos, también hay funciones cerebrales asociadas a la presentación de otras manifestaciones clínicas más allá de las psiquiátricas. Dicho de otra forma y partiendo de la base ~~de~~ que la esquizofrenia es un trastorno del neurodesarrollo y según la hipótesis de la esquizofrenia como una enfermedad sistémica, esta se consideraría un trastorno en donde varias funciones cerebrales se ven afectadas y además hay síntomas psicóticos. Los síntomas psicóticos, serían entonces un hallazgo añadido a todas las manifestaciones del gran síndrome.

La evidencia empírica apoya el uso de los criterios diagnósticos del DSM IV - 5 y CIE - 10 para clasificar los trastornos psicóticos. Sin embargo, los criterios diagnósticos no son equivalentes al concepto que se tiene de una enfermedad. Es decir, la esquizofrenia, más que un trastorno exclusivamente de síntomas positivos y negativos podría considerarse una entidad clínica con características tanto psiquiátricas como no psiquiátricas, (Kirkpatrick et al., 2014). En esta línea, existen estudios que enmarcan los síntomas de la esquizofrenia dentro de una enfermedad sistémica y que podría presentar manifestaciones metabólicas tempranas como las que se exponen a lo largo esta tesis doctoral.

Existe amplia evidencia de la asociación entre esquizofrenia y otras entidades clínicas. Por ejemplo, en el (Brainstorm consortium (2018), que ha analizado datos de 1,190,000 de individuos, se encontró que hay heredabilidad compartida entre esquizofrenia y trastornos afectivos y esquizofrenia y trastorno obsesivo compulsivo o esquizofrenia y trastornos de ansiedad (Anttila et al., 2018). Así mismo, fenotípicamente es frecuente encontrar comorbilidades psiquiátricas con el diagnóstico de esquizofrenia (Swets et al., 2014).

Con respecto a las alteraciones no psiquiátricas, e independientemente de los efectos adversos metabólicos ampliamente conocidos tras el tratamiento con antipsicóticos atípicos (Kraemer et al., 2011; Mitchell, Vancampfort, Sweers, et al., 2013; Vancampfort et al., 2015) y no relacionados con los hábitos de vida como la dieta y la actividad física (Dixon et al., 2000; Kirkpatrick et al., 2012), se ha demostrado que la prevalencia de diabetes y resistencia a la insulina está aumentada en pacientes con esquizofrenia. Así mismo, la diabetes y la esquizofrenia comparten factores de riesgo comunes más allá del efecto de los fármacos, como por ejemplo complicaciones obstétricas, riesgo poligenético (Fernandez-Egea et al., 2008; Mukerjee et al., 1996; Wright et al., 1995) y factores prenatales y gestacionales (Ozanne & Hales, 2002). A la evidencia también se suma, el hallazgo de otras alteraciones metabólicas además de la glicemia, como son las alteraciones de lípidos y más recientemente alteraciones en la tasa de filtración glomerular (García-Rizo et al., 2022).

En esta línea, la publicación "El concepto de la esquizofrenia" (Kirkpatrick, 2009; Kirkpatrick et al., 2014), describe que la esquizofrenia podría no ser un trastorno que se limite al cerebro, sino más bien un síndrome que compromete varios sistemas del cuerpo humano. De hecho, la evidencia demuestra que, en muchos pacientes, hay fases de la enfermedad en donde los síntomas psicóticos no son la dimensión que tiene más impacto en el funcionamiento y que, por el contrario, el deterioro físico predomina más que el psiquiátrico. En consecuencia, el término neurodesarrollo, según esta hipótesis, debería ser reemplazado por el término trastorno del desarrollo, ya que no es solo el sistema nervioso el que se desarrolla con anormalidad.

Al respecto, Pillinger et al., (2019) en su publicación "Is psychosis a multisystem disorder?", propone dos posibles explicaciones, además del modelo de Kirkpatrik que como se ha descrito, pone al cerebro como un órgano más dentro de los otros que están

afectados a causa de un factor que desencadena alteraciones en sistemas diferentes al sistema nervioso. Los otros dos modelos expuestos, (Pillinger et al., 2019) serían en primer lugar un factor de riesgo como causante de alteraciones a nivel del sistema nervioso central y síntomas psicóticos y que, en consecuencia, puede desencadenar otra disfunción no relacionada con el sistema nervioso. El segundo modelo hace referencia a que un factor de riesgo o vulnerabilidad compartido desde la etapa prenatal, podría resultar en una alteración del neurodesarrollo que produce trastorno psicótico y además en alteraciones de otros sistemas.

Se habla de un trastorno multisistémico cuando hay condiciones en donde varios sistemas están alterados y uno de ellos, predomina sobre los demás (Ayme & Chute, 2010). En esta definición, cabría la esquizofrenia, ya que como se ha mencionado existe sólida evidencia de alteraciones de otros sistemas presentes en el momento del primer episodio psicótico.

Con fundamento en la evidencia presentada surge la pregunta de investigación que da sentido a esta tesis doctoral: ¿Cuál es la prevalencia de síndrome metabólico en pacientes con primer episodio psicótico que nunca en su vida han tomado antipsicóticos?

Justificación

A pesar de los avances en la comprensión de la asociación entre MetS y esquizofrenia, todavía no está claro cuál es la prevalencia del MetS en pacientes con PEP que nunca han tomado antipsicóticos.

Previamente se ha advertido de la importancia del estudio de los trastornos psicóticos más allá del sistema nervioso central y de la valoración del riesgo cardiovascular y la salud física en general de los pacientes con esquizofrenia debido a la alta mortalidad por causas no psiquiátricas. Con la elaboración de esta tesis se pretende añadir a la evidencia un estudio de esquizofrenia más allá de la psicopatología y de las voces, considerando otras funciones de la fisiología humana como el sistema metabólico, que muy frecuentemente se ve comprometido bien sea por causa o por efecto como se ha descrito anteriormente.

Tal y como se ha expuesto, hay una evidencia muy amplia sobre el efecto de algunos antipsicóticos atípicos en el desarrollo del MetS y también hay evidencia de alteraciones metabólicas aisladas en pacientes con primer episodio psicótico. Sin embargo, solo unas pocas investigaciones han explorado la presencia del MetS a través de un análisis de todos sus componentes en pacientes no tratados previamente con antipsicóticos. Por lo tanto, no está claro si independientemente del uso de antipsicóticos los pacientes con trastorno psicótico presentan más riesgo de tener MetS que la población general.

Hasta la fecha, solo se han realizado dos metaanálisis en pacientes “naïve” con PEP. (Vancampfort et al., 2013) publicó un metaanálisis sobre alteraciones metabólicas en pacientes con esquizofrenia tanto en fase temprana como en fase crónica de la enfermedad que no habían tomado antipsicóticos. Un segundo metanálisis (Mitchell,

Vancampfort, Sweers, et al., 2013) encontró que la prevalencia en pacientes con poco tiempo de exposición a los antipsicóticos fue del 9,8%. Estos dos trabajos reportan los datos más sólidos. Sin embargo, los mismos autores de ambos trabajos destacan varias limitaciones, como la dificultad de analizar de forma independiente a pacientes naïve con un primer episodio psicótico, ya que incluyeron estudios con primeros episodios expuestos a antipsicóticos durante un tiempo indeterminado. Además, el grupo de pacientes "no tratados" incluía pacientes en cualquier fase de la enfermedad, por lo que la prevalencia en este grupo puede confundirse por la presencia de otros factores de riesgo que se desarrollan a lo largo del tiempo, como la edad, el sedentarismo, el estilo de vida.

Teniendo en cuenta esas limitaciones y la necesidad de aclarar la prevalencia de MetS en pacientes con trastorno psicótico independientemente de los antipsicóticos, en una primera fase de esta tesis doctoral, se realizó un metaanálisis de estudios que incluyó los primeros episodios psicóticos con una exposición estrictamente de 0 días de tratamiento antipsicótico, en una población mayor de 18 años.

En una segunda fase de esta tesis y una vez hecho el metaanálisis, se encontró que la mayoría de los artículos que estudian la prevalencia de MetS tienen algunas limitaciones relevantes entre las que se destacan el pequeño tamaño de la muestra (Effat et al., 2012; Enez Darcin et al., 2015; Grover et al., 2015; Martín Otaño et al., 2013; Sahpolat & Ari, 2020), la falta de comparación con un grupo control (De Hert et al., 2008; Grover et al., 2015; Kraemer et al., 2011; Martín Otaño et al., 2013; Medved et al., 2009; Owiredu et al., 2012; Srivastava et al., 2018), la falta de un análisis de estratificación de género y el hecho de que los pacientes no eran estrictamente pacientes sin tratamiento previo con antipsicóticos, por ejemplo, pacientes que habían recibido tratamiento durante varias semanas se clasificaron como “naïve” (Chiliza et al., 2015; Correll et al., 2014; Fleischhacker et al., 2013; Pallava et al., 2012; Srihari et al., 2013a). Por este motivo y la

necesidad de seguir sumando evidencia para aclarar la relación entre MetS y primeros episodios psicóticos en pacientes que nunca han tomado antipsicóticos, se realizó un estudio transversal y después longitudinal sobre la prevalencia de MetS en pacientes con PEP naïve. Para ello se utilizó el dataset del Programa de Atención a las Fases Iniciales de la Psicosis PAFIP, que es programa de referencia de psicosis a nivel nacional e internacional.

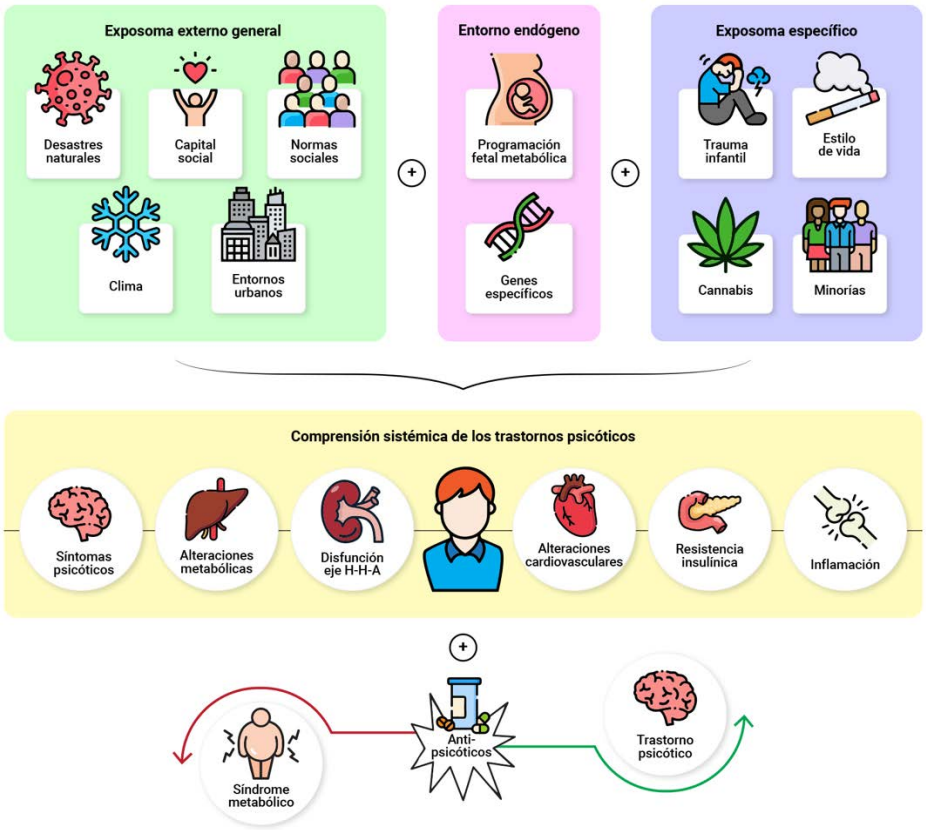

Figura. 1. Factores comunes entre síndrome metabólico y trastorno psicótico previos al inicio de los fármacos antipsicóticos. Estos factores podrían ser los causantes de las alteraciones metabólicas encontradas en pacientes en las fases iniciales de la psicosis, independientemente del tratamiento antipsicótico. Desde una comprensión sistémica de la enfermedad, los síntomas psicóticos, serían solo una manifestación del síndrome.

Objetivos e hipótesis

Objetivo general

Explorar la prevalencia de síndrome metabólico en pacientes con primer episodio psicótico que nunca en su vida han tomado antipsicóticos.

Objetivos específicos

- Establecer la prevalencia de síndrome metabólico en pacientes que nunca han tomado antipsicóticos, a través de una revisión sistemática de la literatura y un metaanálisis.
- Determinar la prevalencia de síndrome metabólico a través de un estudio transversal en una muestra representativa de pacientes con primer episodio psicótico que nunca han tomado antipsicóticos, teniendo en cuenta el análisis de factores sociodemográficos y los hábitos de riesgo como el consumo de sustancias.
- Explorar las alteraciones metabólicas basales que podrían predecir el desarrollo síndrome metabólico a los 3 años, incluyendo factores sociodemográficos y el fármaco antipsicótico elegido inicialmente para el tratamiento.

Hipótesis

Los pacientes con primer episodio psicótico tienen más alteraciones metabólicas que la población general y estas no se deben exclusivamente al uso de antipsicóticos

Métodos

Este estudio se realizó siguiendo rigurosamente la metodología PRISMA y MOOSE (Moher et al., 2009; Stroup et al., 2000) que incluye los siguientes pasos: estrategia de búsqueda en 4 bases de datos, selección de estudios tras selección de títulos y resúmenes, selección de estudios de acuerdo a los criterios de inclusión y exclusión tras lectura completa de los artículos, contacto con los autores de estudios potencialmente útiles pero que tenían los datos incompletos, extracción de los datos en formulario normalizado, evaluación mediante escala de calidad, pruebas de heterogeneidad, análisis de subgrupos y meta-regresiones. El registro se encuentra en PROSPERO (CRD42020180930).

Fase de revisión sistemática y metaanálisis

En base a la hipótesis descrita se planteó la pregunta PICOS (Patients, Intervention, Comparison, Outcome, Studies).

P: pacientes con primer episodio psciótico, seleccionados con criterios diagnósticos de acuerdo a DSM o CIE-10

I: con datos analíticos necesarios para determinar la presencia o ausencia de síndrome metabólico

C: que se comparen o no con controles

O: Síndrome metabólico de acuerdo a los criterios IDF o a los criterios ATP-3

S: Estudios transversales, estudios longitudinales que en su evaluación basal contemplaran medidas metabólicas en pacientes naïve.

Fase de estudio transversal y longitudinal

La segunda fase incluye en primer lugar un estudio transversal en una muestra representativa de 303 pacientes con PEP y 153 controles. En segundo lugar, un seguimiento longitudinal a los tres años de 244 pacientes con PEP y 166 controles.

Una vez hecho el metaanálisis, y teniendo en cuenta las limitaciones de los artículos incluidos en el mismo, se hizo un estudio transversal para calcular la prevalencia de síndrome metabólico en pacientes de la cohorte PAFIP con primer episodio psicótico que nunca habían estado expuestos a los antipsicóticos y compararlos con controles sanos.

Después se hizo un estudio longitudinal también con pacientes de la cohorte PAFIP, en donde se compararon las alteraciones metabólicas basales previas al uso de antipsicóticos con las alteraciones a los 3 años y se diseñó un modelo para predecir cuáles alteraciones basales tendrían más influencia en la aparición de MetS a los 3 años.

La muestra corresponde a pacientes con fases iniciales tomada de la cohorte PAFIP de Cantabria (Mayoral Van-Son et al., 2021; Pelayo-Teran et al., 2008), de cuyo dataset se estudiaron los datos de MetS en pacientes naïve y en donde se tuvieron en cuenta todas las limitaciones de los estudios previos sobre el tema que fueron incluidos en el meta-análisis, por ejemplo: la ausencia de controles, el análisis por sexo y el ajuste por otras variables de exposoma externo específico como el consumo de sustancias y factores sociodemográficos. Además, se hizo un análisis predictivo a 3 años.

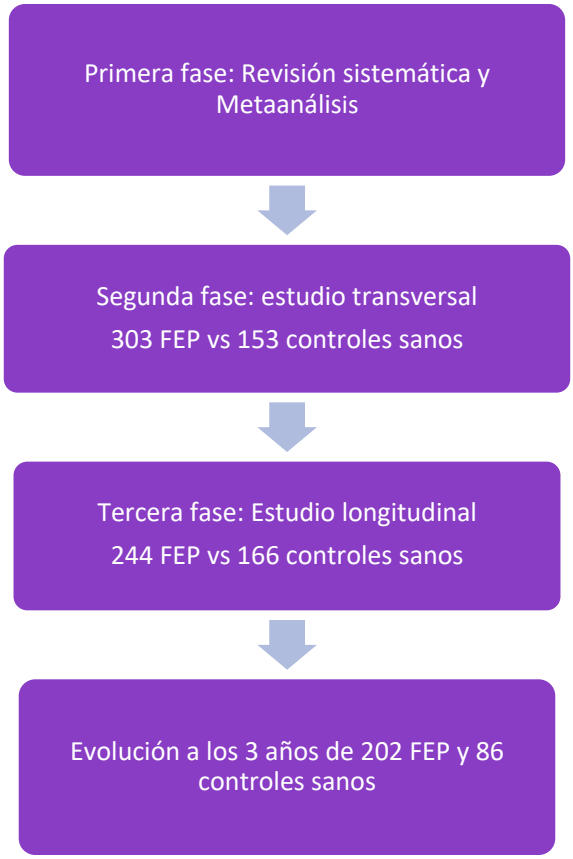

Figura 2. Fases metodológicas de la tesis doctoral

La metodología y resultados se explican detalladamente en los tres artículos publicados en revistas de alto impacto y el correspondiente material suplementario que se expone a continuación

Resultados

Metaanálisis (Garrido-Torres et al., 2021)

La prevalencia de MetS en pacientes con PEP estrictamente naïve es del 13.2%. (95% CI 8.7–19.0) (n = 1009, k = 13). Tras realizar los análisis de sensibilidad expuestos detalladamente en el artículo, no hubo cambios significativos en la prevalencia. Los pacientes con PEP naïve tienen el doble de riesgo de presentar MetS que los controles pareados por edad y sexo. (OR 2.52, p = 0.007). Al evaluar la prevalencia de MetS global, se encontró una alta heterogeniedad entre los estudios [I2 = 81.03%, Q = 63, df(12), p = 0.00]. En el análisis de subgrupos, se encontró que esta heterogeneidad fue aportada principalmente por los criterios usados para definir MetS [I2 = 83.0%, Q = 7.57, df(2), p = 0.023]. Además en la metaregresiones hechas, se encontró que otra de las fuentes de heterogeniedad fue la etnicidad. La disparidad de criterios para definir MetS aportó el 7% de heterogeniedad y la etnicidad aportó el 3%.

Estudio transversal (Garrido-Torres, Ruiz-Veguilla, Alameda, et al., 2022)

La prevalencia de MetS en los PEP fue similar a la de los controles (5.6 % vs 5.12 %; $x2 = 0.004$, p = 0.821). No habiendo diferencias significativas en ambos grupos. Los pacientes con PEP presentan mayor prevalencia de alteraciones metabólicas con respecto a los controles. (60.7 % vs 36.5 %; $x^2 = 24.16$, $p < 0.001$; OR = 2.686, CI 95 % 1.8–4.0)

Las mujeres con PEP son más propensas a presentar mayor prevalencia de PAalterado que los hombres con PEP. (hombres: n = 14, 8.6 % vs mujeres: n = 29, 20.7 %, x^2 9.09 p =0.003). Esta diferencia no se observó en el grupo control.

En el modelo de regresión logística, se encontró una asociación estadísticamente significativa entre HDL y PEP (OR:1.87, IC del 95%: 1.78 – 2. 96, p=0.007), que continuó siendo significativa tras el ajuste con sexo, nivel educativo, estado civil, bajo

nivel socioeconómico familiar, zona urbana, desempleo, estado actual de estudiante, consumo de cannabis, alcohol y cocaína (OR:2.228, IC del 95%: 1.12- 4.464, p=0.024). Así mismo, la asociación entre presión arterial alta y psicosis (OR:8.031, IC del 95%: 3.61 -17.85, p=0.001) también fue significativa (OR:7.564, IC del 95%: 6.16 – 23.14, p=0.001) tras el ajuste con dichos factores de confusión.

La asociación entre la PEP y la perímetro abdominal alterada (OR:2.418, IC del 95% 1.112 - 4.464, p = 0.026) se vio influenciada por el sexo femenino (OR: 1.553, IC del 95% 0.79 - 3.053, p = 0.043) y el estado actual de educación (estudiando actualmente o no) (OR: 1.44, IC del 95% 0.189 - 1.023 p = 0.048)

Se encontraron diferencias significativas en consumo de cannabis entre PEP y controles (n =120, 39.9 % vs n =42, 26.9 %, *x*2 7.523 p =0.00). 57% de PEP reportaron consumo de tabaco y mayor número de cigarrillos al día (PEP: mean/SD 17.34±9.71 vs HC: mean/SD 72±10.92 mm/ Hg, t-student 4.095, p < 0.001). Sin embargo, cuando exploramos el efecto del consumo de sustancias en los parámetros metabólicos, no encontramos asociaciones significativas.

Estudio longitudinal (Garrido-Torres, Ruiz-Veguilla, Olivé Mas, et al., 2022)

A los 3 años los pacientes con PEP tuvieron peor evolución que los controles. La prevalencia aumentó de 6.6% hasta el 18.3% ($p = 0.001$) en los PEP y de 5.4% a 8.1% ($p = 0.063$) en los controles

En el modelo multivariante se encontró que en el grupo de PEP, los valores basalmente alterados de HDL (OR = 0.9, $p = 0.008$), triglicéridos (OR = 1.1, $p = 0.043$) y perímetro abdominal (OR = 1.1, $p = 0.011$) se asocian al desarrollo de MetS a los 3 años independientemente del tipo de tratamiento antipsicótico, la edad o el sexo.

Artículos publicados

Metabolic syndrome in antipsychotic-naïve patients with first-episode psychosis: a systematic review and meta-analysis. Psychological Medicine. 2021, 51(14), 2307–2320. IF JCR 2021 10.592 (D1)

Psychological Medicine

cambridge.org/psm

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

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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

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 (⩾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].

https://doi.org/10.1017/S0033291721002853

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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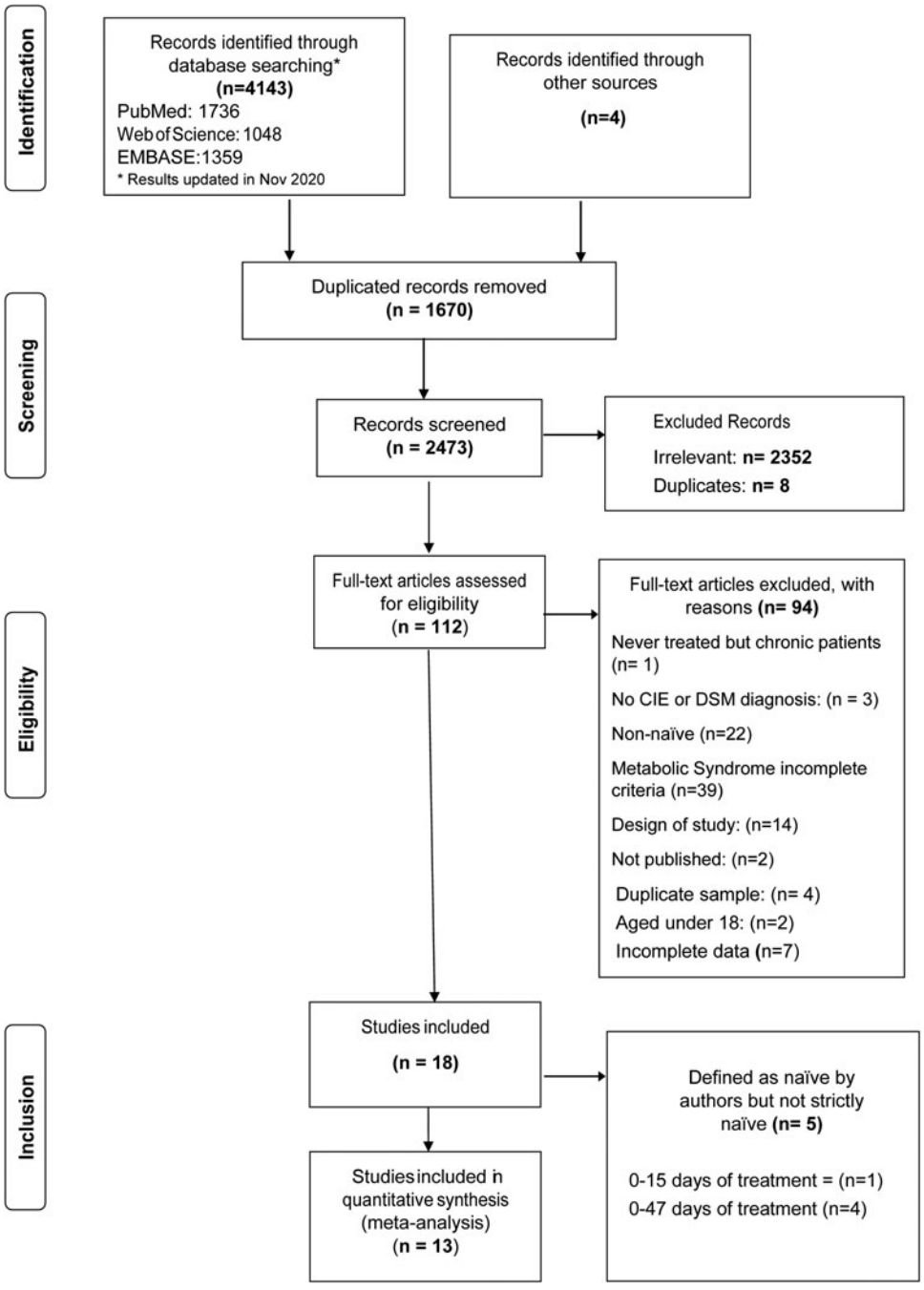

Fig. 1. PRISMA flow diagram.

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

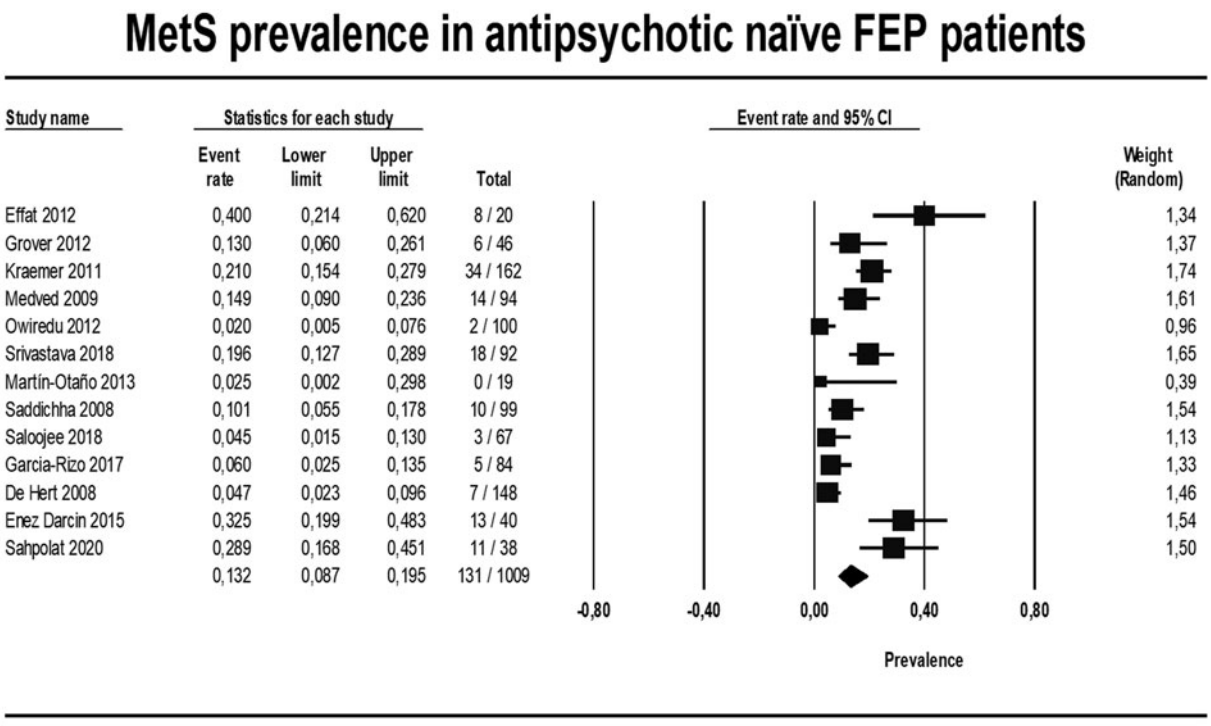

Fig. 2. Forest plot showing MetS prevalence in strictly naïve patients (0 days).

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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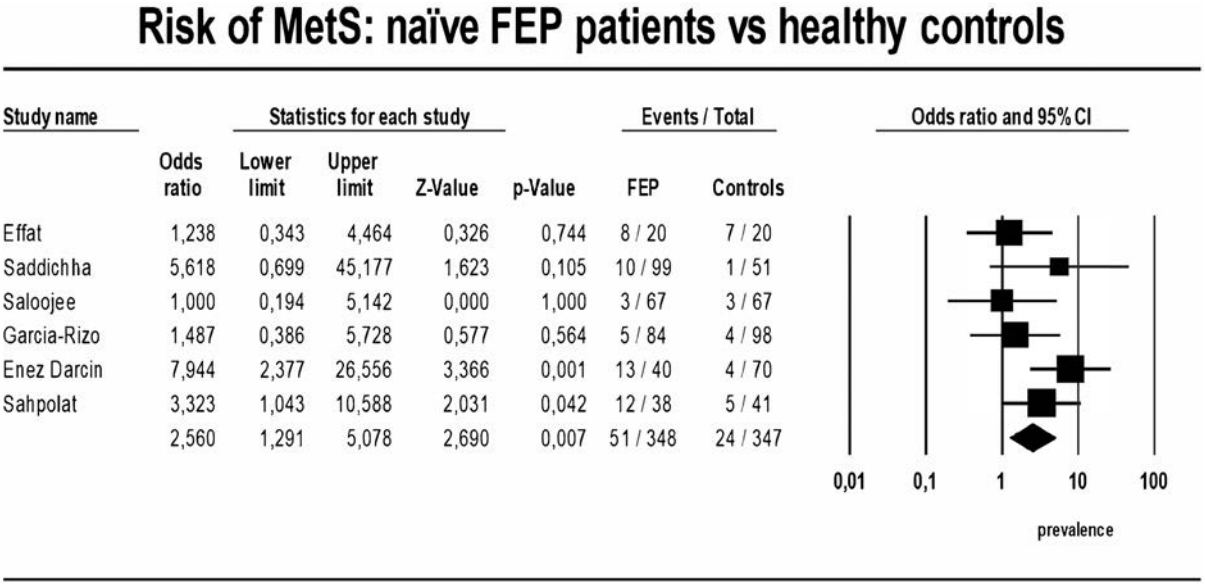

Fig. 3. Forest plot showing comparison between naïve (0 days) first-episode psychosis patients *v.* healthy controls.

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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References

Aas, M., Dieset, I., Hope, S., Hoseth, E., Mørch, R., Reponen, E., … Melle, I. (2017). Childhood maltreatment severity is associated with elevated C-reactive protein and body mass index in adults with schizophrenia and

bipolar diagnoses. *Brain, Behavior, and Immunity*, *65*, 342–349. doi: 10.1016/j.bbi.2017.06.005

Alameda, L., Levier, A., Gholam-Rezaee, M., Golay, P., Vandenberghe, F., Delacretaz, A., … Conus, P. (2020). Psychological trauma occurring during adolescence is associated with an increased risk of greater waist circumference in early psychosis patients treated with psychotropic medication. *PLoS ONE*, *15*(12), e0242569. doi: 10.1371/journal.pone.0242569

Alberti, K., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., … Smith, S. C. J. (2009). 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*, *120*(16), 1640–1645. doi: 10.1161/CIRCULATIONAHA.109.192644

Alberti, K., & Zimmet, P. Z. (1998). Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic Medicine : A Journal of the British Diabetic Association*, *15*(7), 539–553. doi: 10.1002/(SICI)1096-9136(199807)15:7 < 539::AID-DIA668>3.0.CO;2-S

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA, USA: American Psychiatric Publishing, Inc. 10.1176/appi.books.9780890425596.

Arai, H., Yamamoto, A., Matsuzawa, Y., Saito, Y., Yamada, N., Oikawa, S., … Kita, T. (2006). Prevalence of metabolic syndrome in the general Japanese population in 2000. *Journal of Atherosclerosis and Thrombosis*, *13*(4), 202–208. doi: 10.5551/jat.13.202

Barendregt, J. J., Doi, S. A., Lee, Y. Y., Norman, R. E., & Vos, T. (2013). Meta-analysis of prevalence. *Journal of Epidemiology and Community Health*, *67*(11), 974–978. doi: 10.1136/jech-2013-203104

Bobes, J., Arango, C., Aranda, P., Carmena, R., Garcia-Garcia, M., & Rejas, J. (2007). Cardiovascular and metabolic risk in outpatients with schizophrenia treated with antipsychotics: Results of the CLAMORS Study. *Schizophrenia Research*, *90*(1–3), 162–173. doi: 10.1016/j.schres.2006.09.025

Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. (2005). Comprehensive meta-analysis version 2.

Chadda, R. K., Ramshankar, P., Deb, K. S., & Sood, M. (2013). Metabolic syndrome in schizophrenia: Differences between antipsychotic-naïve and treated patients. *Journal of Pharmacology & Pharmacotherapeutics*, *4*, 176–183. doi: 10.4103/0976-500X.114596.

Chaturvedi, N. (2003). Ethnic differences in cardiovascular disease. *Heart (British Cardiac Society)*, *89*(6), 681–686. doi: 10.1136/heart.89.6.681

Chiliza, B., Asmal, L., Oosthuizen, P., van Niekerk, E., Erasmus, R., Kidd, M., … Emsley, R. (2015). Changes in body mass and metabolic profiles in patients with first-episode schizophrenia treated for 12 months with a first-generation antipsychotic. *European Psychiatry : The Journal of the Association of European Psychiatrists*, *30*(2), 277–283. cmedm. 10.1016/j.eurpsy.2014.11.013

Coleman, J. R. I., Krapohl, E., Eley, T. C., & Breen, G. (2018). Individual and shared effects of social environment and polygenic risk scores on adolescent body mass index. *Scientific Reports*, *8*(1), 6344. doi: 10.1038/s41598-018-24774-5

Cordes, J., Bechdolf, A., Engelke, C., Kahl, K. G., Balijepalli, C., Lösch, C., … Moebus, S. (2017). Prevalence of metabolic syndrome in female and male patients at risk of psychosis. *Schizophrenia Research*, *181*, 38–42. doi: 10.1016/j.schres.2016.09.012

Correll, C. U., Robinson, D. G., Schooler, N. R., Brunette, M. F., Mueser, K. T., Rosenheck, R. A., … Kane, J. M. (2014). Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: Baseline results from the RAISE-ETP study. *JAMA Psychiatry*, *71*(12), 1350–1363. doi: 10.1001/jamapsychiatry.2014.1314

Crespo-Facorro, B., Prieto, C., & Sainz, J. (2019a). Altered gene expression in antipsychotic-induced weight gain. *NPJ Schizophrenia*, *5*(1), 7. doi: 10.1038/s41537-019-0075-y

Davies, C., Segre, G., Estrade, A., Radua, J., De Micheli, A., Provenzani, U., … Fusar-Poli, P. (2020). Prenatal and perinatal risk and protective factors for psychosis: A systematic review and meta-analysis. *The Lancet. Psychiatry*, *7*(5), 399–410. doi: 10.1016/S2215-0366(20)30057-2

De Hert, M., Schreurs, V., Sweers, K., Van Eyck, D., Hanssens, L., Sinko, S., … van Winkel, R. (2008). Typical and atypical antipsychotics differentially affect long-term incidence rates of the metabolic syndrome in first-episode patients with schizophrenia: A retrospective chart review. *Schizophrenia Research*, *101*(1–3), 295–303. doi: 10.1016/j.schres.2008.01.028

De Lucia Rolfe, E., Ong, K. K., Sleigh, A., Dunger, D. B., & Norris, S. A. (2015). Abdominal fat depots associated with insulin resistance and metabolic syndrome risk factors in black African young adults. *BMC Public Health*, *15*, 1013. doi: 10.1186/s12889-015-2147-x

Eckel, R. H., Grundy, S. M., & Zimmet, P. Z. (2005). The metabolic syndrome. *Lancet (London, England)*, *365*(9468), 1415–1428. doi: 10.1016/S0140-6736(05)66378-7

Effat, S., Elsamei, A., Elghonemy, S., & Roushdy, T. (2012). Metabolic syndrome in a sample of drug-naive Egyptian patients with psychotic disorders. *Middle East Current Psychiatry*, *19*, 23–31. 10.1097/01.XME.0000407822.53401.30.

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal*, *315*(7109), 629–634. doi: 10.1136/bmj.315.7109.629

Enez Darcin, A., Yalcin Cavus, S., Dilbaz, N., Kaya, H., & Dogan, E. (2015). Metabolic syndrome in drug-naïve and drug-free patients with schizophrenia and in their siblings. *Schizophrenia Research*, *166*(1–3), 201–206. doi: 10.1016/j.schres.2015.05.004

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001). Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*, *285*(19), 2486–2497. doi: doi:10.1001/jama.285.19.2486

Fleischhacker, W. W., Siu, C. O., Bodén, R., Pappadopulos, E., Karayal, O. N., Kahn R. S., … EUFEST study group. (2013). Metabolic risk factors in first-episode schizophrenia: Baseline prevalence and course analysed from the European first-episode schizophrenia trial. *The International Journal of Neuropsychopharmacology*, *16*(5), 987–995. doi: 10.1017/S1461145712001241.

Ford, E. S., Giles, W. H., & Dietz, W. H. (2002). Prevalence of the metabolic syndrome among US adults: Findings from the third National Health and Nutrition Examination Survey. *JAMA*, *287*(3), 356–359. doi: 10.1001/jama.287.3.356

Garcia-Rizo, C., Fernandez-Egea, E., Oliveira, C., Meseguer, A., Cabrera, B., Mezquida, G., … Kirkpatrick, B. (2017). Metabolic syndrome or glucose challenge in first episode of psychosis? *European Psychiatry: The Journal of the Association of European Psychiatrists*, *41*, 42–46. doi: 10.1016/j.eurpsy.2016.10.001

Grover, S., Nebhinani, N., Chakrabarti, S., Parakh, P., & Ghormode, D. (2012). Metabolic syndrome in antipsychotic naïve patients diagnosed with schizophrenia. *Early Intervention in Psychiatry*, *6*(3), 326–331. cmedm. 10.1111/j.1751-7893.2011.00321.x

Grundy, S. M. (2006). Metabolic syndrome: Connecting and reconciling cardiovascular and diabetes worlds. *Journal of the American College of Cardiology*, *47*(6), 1093–1100. doi: 10.1016/j.jacc.2005.11.046

Hasnain, M. (2015). Genetic vulnerability in antipsychotic drug-induced diabetes. *The Lancet Psychiatry*, *2*(12), 1049–1051. doi: 10.1016/S2215-0366(15)00310-7

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *British Medical Journal*, *327*, 557–560. doi: 10.1136/bmj.327.7414.557

International Diabetes Federation (2006). The metabolic syndrome. The IDF Consensus Worldwide Definition of the Metabolic Syndrome.

Kirkpatrick, B., Garcia-Rizo, C., Fernandez-Egea, E., Miller, B., & Bernardo, M. (2011). Metabolic abnormalities in newly diagnosed, antipsychotic-naive patients with schizophrenia and related disorders. *Schizophrenia Bulletin*, *37*, 26.

Kirkpatrick, B., Miller, B., García-Rizo, C., & Fernandez-Egea, E. (2014). Schizophrenia: A systemic disorder. *Clinical Schizophrenia & Related Psychoses*, *8*(2), 73–79. doi: 10.3371/CSRP.KIMI.031513

Kraemer, S., Minarzyk, A., Forst, T., Kopf, D., & Hundemer, H.-P. (2011). Prevalence of metabolic syndrome in patients with schizophrenia, and

metabolic changes after 3 months of treatment with antipsychotics – results from a German observational study. *BMC Psychiatry*, *11*, 173. doi: 10.1186/1471-244X-11-173

Lasserre, A. M., Glaus, J., Vandeleur, C. L., Marques-Vidal, P., Vaucher, J., Bastardot, F., … Preisig, M. (2014). Depression with atypical features and increase in obesity, body mass index, waist circumference, and fat mass: A prospective, population-based study. *JAMA Psychiatry*, *71*(8), 880–888. doi: 10.1001/jamapsychiatry.2014.411

Lear, S. A., James, P. T., Ko, G. T., & Kumanyika, S. (2010). Appropriateness of waist circumference and waist-to-hip ratio cutoffs for different ethnic groups. *European Journal of Clinical Nutrition*, *64*(1), 42–61. doi: 10.1038/ejcn.2009.70

Martín Otaño, L., Barbadillo Izquierdo, L., Galdeano Mondragón, A., Alonso Pinedo, M., & Querejeta Ayerdi, I. (2013). After six months of antipsychotic treatment: Is the improvement in mental health at the expense of physical health? *Revista de Psiquiatria y Salud Mental*, *6*(1), 26–32. cmedm. 10.1016/j.rpsm.2012.04.001

McEvoy, J. P., Meyer, J. M., Goff, D. C., Nasrallah, H. A., Davis, S. M., Sullivan, L., … Lieberman, J. A. (2005). Prevalence of the metabolic syndrome in patients with schizophrenia: Baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophrenia Research*, *80*(1), 19–32. doi: 10.1016/j.schres.2005.07.014

Medved, V., Kuzman, M. R., Jovanovic, N., Grubisin, J., & Kuzman, T. (2009). Metabolic syndrome in female patients with schizophrenia treated with second generation antipsychotics: A 3-month follow-up. *Journal of Psychopharmacology*, *23*, (8), 915.

Mitchell, A. J., Vancampfort, D., De Herdt, A., Yu, W., & De Hert, M. (2013). Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. *Schizophrenia Bulletin*, *39*(2), 295–305. doi: 10.1093/schbul/sbs082

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(7), e1000097. doi: 10.1371/journal.pmed.1000097

Moola, S., Moon, Z., Tufanaru, C., Aromataris, E., Sears, K., Sfectcu, R., & Currie, M. (2020). Chapter 7: Systematic reviews of etiology and risk. In JBI. Manual for Evidence Synthesis. Available at https://synthesismanual.jbi.global.

Moore, J. X., Chaudhary, N., & Akinyemiju, T. (2017). Metabolic syndrome prevalence by race/ethnicity and sex in the United States, National Health and Nutrition Examination Survey, 1988–2012. *Preventing Chronic Disease*, *14*, E24. doi: 10.5888/pcd14.160287

Munn, Z., Moola, S., Lisy, K., Riitano, D., & Tufanaru, C. (2015). Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *International Journal of Evidence-Based Healthcare*, *13*(3), 147–153. doi: 10.1097/XEB.0000000000000054

Newcomer, J. W., Haupt, D. W., Fucetola, R., Melson, A. K., Schweiger, J. A., Cooper, B. P., & Selke, G. (2002). Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Archives of General Psychiatry*, *59*(4), 337–345. doi: 10.1001/archpsyc.59.4.337

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan – A web and mobile app for systematic reviews. *Systematic Reviews*, *5*(1), 210. doi: 10.1186/s13643-016-0384-4

Owiredu, W. K. B. A., Osei, O., Amidu, N., Appiah-Poku, J., & Osei, Y. (2012). Prevalence of metabolic syndrome among psychiatric patients in the Kumasi Metropolis, Ghana. *Journal of Medical and Biomedical Science*, *1*(2), 38.

Pallava, A., Chadda, R. K., Sood, M., & Lakshmy, R. (2012). Metabolic syndrome in schizophrenia: A comparative study of antipsychotic-free/naive and antipsychotic-treated patients from India. *Nordic Journal of Psychiatry*, *66*(3), 215.

Patel, J. K., Buckley, P. F., Woolson, S., Hamer, R. M., McEvoy, J. P., Perkins, D. O., & Lieberman, J. A. (2009). Metabolic profiles of second-generation antipsychotics in early psychosis: Findings from the CAFE study. *Schizophrenia Research*, *111*(1–3), 9–16. doi: 10.1016/j.schres.2009.03.025

Perry, B. I., Upthegrove, R., Crawford, O., Jang, S., Lau, E., McGill, I., … Khandaker, G. M. (2020). Cardiometabolic risk prediction algorithms for young people with psychosis: A systematic review and exploratory analysis. *Acta Psychiatrica Scandinavica*, *142*, 215–232. doi: 10.1111/acps.13212.

Pillinger, T., Beck, K., Gobjila, C., Donocik, J. G., Jauhar, S., & Howes, O. D. (2017). Impaired glucose homeostasis in first-episode schizophrenia: A systematic review and meta-analysis. *JAMA Psychiatry*, *74*(3), 261–269. doi: 10.1001/jamapsychiatry.2016.3803

Pillinger, T., Beck, K., Stubbs, B., & Howes, O. D. (2017). Cholesterol and triglyceride levels first-episode psychosis systematic review and meta analysis. *British Journal of Psychiatry*, *211*(6), 339.

Pillinger, T., D'Ambrosio, E., McCutcheon, R., & Howes, O. D. (2019). Is psychosis a multisystem disorder? A meta-review of central nervous system, immune, cardiometabolic, and endocrine alterations in first-episode psychosis and perspective on potential models. *Molecular Psychiatry*, *24*(6), 776–794. doi: 10.1038/s41380-018-0058-9

Pillinger, T., McCutcheon, R. A., Vano, L., Mizuno, Y., Arumuham, A., Hindley, G., … Howes, O. D. (2020). Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: A systematic review and network meta- analysis. *The Lancet Psychiatry*, *7*(1), 64–77. doi: 10.1016/S2215-0366(19)30416-X

Ryan, M. C. M., Sharifi, N., Condren, R., & Thakore, J. H. (2004). Evidence of basal pituitary-adrenal overactivity in first episode, drug naïve patients with schizophrenia. *Psychoneuroendocrinology*, *29*(8), 1065–1070. doi: 10.1016/j.psyneuen.2003.08.011

Saddicha, S., Ameen, S., & Akhtar, S. (2007). Metabolic syndrome in drug-naïve first-episode psychosis treated with atypical antipsychotics. *The Australian and New Zealand Journal of Psychiatry*, *41*(7), 629.

Sahpolat, M., & Ari, M. (2021). Higher prevalence of metabolic syndrome and related factors in patients with first-episode psychosis and schizophrenia: A cross-sectional study in Turkey. *Nordic Journal of Psychiatry*, *75*(1), 73–78. doi: 10.1080/08039488.2020.1815080.

Saloojee, S., Burns, J. K., & Motala, A. A. (2018). Metabolic syndrome in antipsychotic naive African patients with severe mental illness in usual care. *Early Intervention in Psychiatry*, *12*(6), 1137–1143. doi: 10.1111/eip.12428

Srihari, V. H., Phutane, V. H., Ozkan, B., Chwastiak, L., Ratliff, J. C., Woods, S. W., & Tek, C. (2013). Cardiovascular mortality in schizophrenia: Defining a critical period for prevention. *Schizophrenia Research*, *146*(1–3), 64–68. doi: 10.1016/j.schres.2013.01.014

Srivastava, S., Bhatia, M. S., & Sharma, A. (2018). Comparative study of quality of life and metabolic syndrome in schizophrenia patients who are receiving treatment versus antipsychotic naïve, first episode patients from a tertiary care hospital. *Asian Journal of Psychiatry*, *31*, 121–123. doi: 10.1016/j.ajp.2018.02.009

Stiles, E., Alcover, K. C., Stiles, B., Oluwoye, O., & McDonell, M. G. (2020). Cannabis use and metabolic syndrome among clients with first episode psychosis. *Early Intervention in Psychiatry*, *15*(4), 1051–1055. doi: 10.1111/eip.13030.

Stroup, D. F., Berlin, J. A., Morton, S. C., Olkin, I., Williamson, G. D., Rennie, D., … Thacker, S. B. (2000). Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*, *283*(15), 2008–2012. doi: 10.1001/jama.283.15.2008

Tek, C., Kucukgoncu, S., Guloksuz, S., Woods, S. W., Srihari, V. H., & Annamalai, A. (2016). Antipsychotic-induced weight gain in first-episode psychosis patients: A meta-analysis of differential effects of antipsychotic medications. *Early Intervention in Psychiatry*, *10*(3), 193–202. doi: 10.1111/eip.12251

Tomasik, J., Lago, S. G., Vazquez-Bourgon, J., Papiol, S., Suarez-Pinilla, P., Crespo-Facorro, B., … Bahn, S. (2019). Association of insulin resistance with schizophrenia polygenic risk score and response to antipsychotic treatment. *JAMA Psychiatry*, *76*, 864–867. doi: 10.1001/jamapsychiatry.2019.0304.

Vancampfort, D., Stubbs, B., Mitchell, A. J., De Hert, M., Wampers, M., Ward, P. B., … Correll, C. U. (2015). Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: A systematic review and

meta-analysis. *World Psychiatry : Official Journal of the World Psychiatric Association (WPA)*, *14*(3), 339–347. cmedm. doi:10.1002/wps.20252

Vancampfort, D., Vansteelandt, K., Correll, C. U., Mitchell, A. J., De Herdt, A., Sienaert, P., … De Hert, M. (2013). Metabolic syndrome and metabolic abnormalities in bipolar disorder: A meta-analysis of prevalence rates and moderators. *American Journal of Psychiatry*, *170*(3), 265–274.

Vazquez-Bourgon, J., Ortiz-Garcia de la Foz, V., Suarez-Pereira, I., Iruzubieta, P., Arias-Loste, M. T., Setien-Suero, E., … Crespo Facorro, B. (2019). Cannabis consumption and non-alcoholic fatty liver disease. A three years longitudinal study in first episode non-affective psychosis patients. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *95*, 109677. doi: 10.1016/j.pnpbp.2019.109677

Vazquez-Bourgon, J., Setien-Suero, E., Pilar-Cuellar, F., Romero-Jimenez, R., Ortiz-Garcia de la Foz, V., Castro, E., & Crespo-Facorro, B. (2019). Effect of cannabis on weight and metabolism in first-episode non-affective psychosis: Results from a three-year longitudinal study. *Journal of Psychopharmacology*, *33*(3), 284. doi: 10.1177/0269881118822173

Vidot, D. C., Prado, G., Hlaing, W. M., Florez, H. J., Arheart, K. L., & Messiah, S. E. (2016). Metabolic syndrome among marijuana users in the United States: An analysis of National Health and Nutrition Examination Survey Data. *The American Journal of Medicine*, *129*(2), 173–179. doi: 10.1016/j.amjmed.2015.10.019

Viechtbauer, W., & Cheung, M. W.-L. (2010). Outlier and influence diagnostics for meta-analysis. *Research Synthesis Methods*, *1*(2), 112–125. doi: 10.1002/jrsm.11

World Health Organization (1999). Definition, diagnosis and classification of diabetes mellitus and its complications: Report of a WHO Consultation. Part 1, Diagnosis and classification of diabetes mellitus. Geneva, World Health Organization.

Material suplementario

Supplemental

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

Authors: Garrido-Torres N., Rocha-Gonzalez I., Rodriguez-Gangoso A., Canal-Rivero M., Vilches A., Alameda L., Crespo-Facorro B., Ruiz-Veguilla M.

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Tables

Table S1. PRISMA statement and checklist

Section/topic	#	Checklist item	Page(s)
	TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
	ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
	INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
	METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4 & table S3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4 & table S3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures	7
Risk of bias across studies	15	Specify any assessment of risk of bias (i.e. Newcastle-Ottawa Scale (NOS), that may affect the cumulative evidence.	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
	RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1 and 2
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Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study a summary data for each intervention group.	Table 1
Synthesis of results	21	Present results of study analysed.	6
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	DISCUSSION		
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Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
	FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support; role of funders for the systematic review.	2

Table S2. Moose checklist

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	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 the later stages of disease; thus a meta-analysis examining MetS in this population is needed.
√	Hypothesis statement	Altered metabolic parameters in FEPs are not exclusively due to antipsychotic treatments.
√	Description of study outcomes	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 and WHO
√	Type of exposure or intervention used	
√	Type of study designs used	Cross sectional studies or baseline assessment of prospective and retrospective cohort studies
√	Study population	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
Reporting of search strategy should include		
√	Qualifications of searchers	The credentials of the investigators are indicated in the author list.

√	Search strategy, including time period included in the synthesis and keywords	The search strategy is included in table 3 of supplemental material
√	Databases and registries searched	We searched the website of Science Core Collection, Embase and Medline via Embase and PubMed platforms from inception until November 2020.
√	Use of hand searching	Included studies of relevant systematic reviews/ meta-analyses and the references from the included studies were manually screened and searched.
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the results section and PRISMA flowchart.
√	Method of addressing articles published in languages other than English	Only articles in the English language were selected.
√	Method of handling abstracts and unpublished studies	Only original individual studies that were fully accessible were included in our study.
√	Description of any contact with authors	Authors were contacted in the case of missing data or for further information, through email. If no response was given, there was one further attempt at contact.
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies are relevant to the population characteristics, study design and study outcomes.
√	Assessment of confounding	We did not investigate confounding factors
√	Assessment of study quality and stratification or regression on possible predictors of study results	We evaluated the quality of the included studies using the JBI tool
√	Assessment of heterogeneity	Heterogeneity was assessed with the I^2 index.
√	Description of statistical methods in sufficient detail to be replicated	A random-effects meta-analysis was used. Heterogeneity among study point estimates was assessed using Q statistics. The proportion of the total variability in the effect size estimates was evaluated with the I^2 index.
√	Provision of appropriate tables and graphics	Figures are included to reflect the literature search process and forest plots of the meta-analyses conducted. Tables are also provided to depict additional data of all analyses conducted and to present relevant key information
Reporting of results should include		
√	Table summarizing individual study estimates and overall estimate	We reported this in the results and supplementary section.
√	Table giving descriptive information for each study included	We have presented descriptive information for each study in the tables within the supplementary material.
√	Results of sensitivity testing	Subgroup analyses were conducted as specified in the manuscript.

√	Indication of statistical uncertainty of findings	We discuss in our limitations some potential bias that should be taken into account when interpreting our findings.
Reporting of discussion should include		
√	Quantitative assessment of bias	Our discussion discusses potential bias that have been taken into account
√	Justification for exclusion	We excluded studies based on the rationale of other meta-analysis and our own judgement and this is documented in the methods section, supported with tables in SM and discussed in the main manuscript.
√	Assessment of quality of included studies	
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	We have addressed this point in the discussion section.
√	Generalization of the conclusions	We have addressed this point in the discussion section.
√	Guidelines for future research	We have addressed this point in the discussion section.
√	Disclosure of funding source	We have addressed this point at the end of the discussion section

Table S3. Search Strategy

Pubmed Search Query

((("first-episode"[All Fields] AND ("psychotic disorders"[MeSH Terms] OR ("psychotic"[All Fields] AND "disorders"[All Fields]) OR "psychotic disorders"[All Fields] OR "psychosis"[All Fields])) OR ("first-episode"[All Fields] AND ("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "schizophrenias"[All Fields] OR "schizophrenia s"[All Fields])) OR "FEP"[All Fields] OR "FES"[All Fields] OR ("psychotic disorders"[MeSH Terms] OR ("psychotic"[All Fields] AND "disorders"[All Fields]) OR "psychotic disorders"[All Fields] OR "psychosis"[All Fields]) OR ("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "schizophrenias"[All Fields] OR "schizophrenia s"[All Fields])) AND ("antipsychotic-naive"[All Fields] OR "antipsychotic-free"[All Fields] OR "drug-naive"[All Fields] OR "drug-free"[All Fields] OR "neuroleptic-naive"[All Fields] OR "neuroleptic-free"[All Fields] OR "never-medicated"[All Fields] OR "untreated"[All Fields]) AND ("cholesterol"[MeSH Terms] OR "cholesterol"[All Fields] OR "cholesterol s"[All Fields] OR "cholesterole"[All Fields] OR "cholesterols"[All Fields] OR "HDL"[All Fields] OR ("oxidized low density lipoprotein"[Supplementary Concept] OR "oxidized low density lipoprotein"[All Fields] OR "ldl"[All Fields]) OR ("triglycerid"[All Fields] OR "triglycerides"[MeSH Terms] OR "triglycerides"[All Fields] OR "triglyceride"[All Fields] OR "triglycerids"[All Fields]) OR ("lipid s"[All Fields] OR "lipidate"[All Fields] OR "lipidated"[All Fields] OR "lipidates"[All Fields] OR "lipidation"[All Fields] OR "lipidations"[All Fields] OR "lipide"[All Fields] OR "lipides"[All Fields] OR "lipidic"[All Fields] OR "lipids"[MeSH Terms] OR "lipids"[All Fields] OR "lipid"[All Fields]) OR ("lipoprotein s"[All Fields] OR "lipoproteine"[All Fields] OR "lipoproteins"[MeSH Terms] OR "lipoproteins"[All Fields] OR "lipoprotein"[All Fields]) OR "MetS"[All Fields] OR ("metabolic"[All Fields] OR "metabolical"[All Fields] OR "metabolically"[All Fields] OR "metabolics"[All Fields] OR "metabolism"[MeSH Terms] OR "metabolism"[All Fields] OR "metabolisms"[All Fields] OR "metabolism"[MeSH Subheading] OR "metabolic networks and pathways"[MeSH Terms] OR ("metabolic"[All Fields] AND "networks"[All Fields] AND "pathways"[All Fields]) OR

"metabolic networks and pathways"[All Fields] OR "metabolities"[All Fields] OR "metabolization"[All Fields] OR "metabolize"[All Fields] OR "metabolized"[All Fields] OR "metabolizer"[All Fields] OR "metabolizers"[All Fields] OR "metabolizes"[All Fields] OR "metabolizing"[All Fields]) OR ("blood pressure"[MeSH Terms] OR ("blood"[All Fields] AND "pressure"[All Fields]) OR "blood pressure"[All Fields] OR "blood pressure determination"[MeSH Terms] OR ("blood"[All Fields] AND "pressure"[All Fields] AND "determination"[All Fields]) OR "blood pressure determination"[All Fields] OR ("blood"[All Fields] AND "pressure"[All Fields]) OR "blood pressure"[All Fields] OR "arterial pressure"[MeSH Terms] OR ("arterial"[All Fields] AND "pressure"[All Fields]) OR "arterial pressure"[All Fields] OR ("blood"[All Fields] AND "pressure"[All Fields])) OR (("metabolic"[All Fields] OR "metabolical"[All Fields] OR "metabolically"[All Fields] OR "metabolics"[All Fields] OR "metabolism"[MeSH Terms] OR "metabolism"[All Fields] OR "metabolisms"[All Fields] OR "metabolism"[MeSH Subheading] OR "metabolic networks and pathways"[MeSH Terms] OR ("metabolic"[All Fields] AND "networks"[All Fields] AND "pathways"[All Fields]) OR "metabolic networks and pathways"[All Fields] OR "metabolities"[All Fields] OR "metabolization"[All Fields] OR "metabolize"[All Fields] OR "metabolized"[All Fields] OR "metabolizer"[All Fields] OR "metabolizers"[All Fields] OR "metabolizes"[All Fields] OR "metabolizing"[All Fields]) AND ("dysregulate"[All Fields] OR "dysregulated"[All Fields] OR "dysregulates"[All Fields] OR "dysregulating"[All Fields] OR "dysregulation"[All Fields] OR "dysregulations"[All Fields])))

Translations
psychosis: "psychotic disorders"[MeSH Terms] OR ("psychotic"[All Fields] AND "disorders"[All Fields]) OR "psychotic disorders"[All Fields] OR "psychosis"[All Fields]
schizophrenia: "schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "schizophrenias"[All Fields] OR "schizophrenia's"[All Fields]
psychosis: "psychotic disorders"[MeSH Terms] OR ("psychotic"[All Fields] AND "disorders"[All Fields]) OR "psychotic disorders"[All Fields] OR "psychosis"[All Fields]
schizophrenia: "schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "schizophrenias"[All Fields] OR "schizophrenia's"[All Fields]
cholesterol: "cholesterol"[MeSH Terms] OR "cholesterol"[All Fields] OR "cholesterol's"[All Fields] OR "cholesterole"[All Fields] OR "cholesterols"[All Fields]
LDL: "oxidized low density lipoprotein"[Supplementary Concept] OR "oxidized low density lipoprotein"[All Fields] OR "ldl"[All Fields]
triglycerides: "triglycerid"[All Fields] OR "triglycerides"[MeSH Terms] OR "triglycerides"[All Fields] OR "triglyceride"[All Fields] OR "triglycerids"[All Fields]
lipids: "lipid's"[All Fields] OR "lipidate"[All Fields] OR "lipidated"[All Fields] OR "lipidates"[All Fields] OR "lipidation"[All Fields] OR "lipidations"[All Fields] OR "lipide"[All Fields] OR "lipides"[All Fields] OR "lipidic"[All Fields] OR "lipids"[MeSH Terms] OR "lipids"[All Fields] OR "lipid"[All Fields]
lipoproteins: "lipoprotein's"[All Fields] OR "lipoproteine"[All Fields] OR "lipoproteins"[MeSH Terms] OR "lipoproteins"[All Fields] OR "lipoprotein"[All Fields]
metabolic: "metabolic"[All Fields] OR "metabolical"[All Fields] OR "metabolically"[All Fields] OR "metabolics"[All Fields] OR "metabolism"[MeSH Terms] OR "metabolism"[All Fields] OR "metabolisms"[All Fields] OR "metabolism"[Subheading] OR "metabolic networks and pathways"[MeSH Terms] OR ("metabolic"[All Fields] AND "networks"[All Fields] AND "pathways"[All Fields]) OR "metabolic networks and pathways"[All Fields] OR "metabolities"[All Fields] OR "metabolization"[All Fields] OR "metabolize"[All Fields] OR "metabolized"[All Fields] OR "metabolizer"[All Fields] OR "metabolizers"[All Fields] OR "metabolizes"[All Fields] OR "metabolizing"[All Fields]
blood pressure: "blood pressure"[MeSH Terms] OR ("blood"[All Fields] AND "pressure"[All Fields]) OR "blood pressure"[All Fields] OR "blood pressure determination"[MeSH Terms] OR ("blood"[All Fields] AND "pressure"[All Fields] AND "determination"[All Fields]) OR "blood pressure determination"[All Fields] OR ("blood"[All Fields] AND "pressure"[All Fields]) OR "blood pressure"[All Fields] OR "arterial

pressure"[MeSH Terms] OR ("arterial"[All Fields] AND "pressure"[All Fields]) OR "arterial pressure"[All Fields] OR ("blood"[All Fields] AND "pressure"[All Fields])
metabolic: "metabolic"[All Fields] OR "metabolical"[All Fields] OR "metabolically"[All Fields] OR "metabolics"[All Fields] OR "metabolism"[MeSH Terms] OR "metabolism"[All Fields] OR "metabolisms"[All Fields] OR "metabolism"[Subheading] OR "metabolic networks and pathways"[MeSH Terms] OR ("metabolic"[All Fields] AND "networks"[All Fields] AND "pathways"[All Fields]) OR "metabolic networks and pathways"[All Fields] OR "metabolities"[All Fields] OR "metabolization"[All Fields] OR "metabolize"[All Fields] OR "metabolized"[All Fields] OR "metabolizer"[All Fields] OR "metabolizers"[All Fields] OR "metabolizes"[All Fields] OR "metabolizing"[All Fields]
dysregulation: "dysregulate"[All Fields] OR "dysregulated"[All Fields] OR "dysregulates"[All Fields] OR "dysregulating"[All Fields] OR "dysregulation"[All Fields] OR "dysregulations"[All Fields]

EMBASE Search Query

('first episode' AND ('psychosis'/exp OR 'psychosis' OR (('psychotic'/exp OR psychotic) AND ('disorders'/exp OR disorders)) OR 'psychotic disorders'/exp OR 'psychotic disorders' OR 'psychosis'/exp OR psychosis) OR ('first episode' AND ('schizophrenia'/exp OR 'schizophrenia' OR 'schizophrenia'/exp OR schizophrenia OR schizophrenias OR 'schizophrenia s')) OR fep OR fes OR (('psychotic'/exp OR psychotic) AND ('disorders'/exp OR disorders)) OR 'psychotic disorders'/exp OR 'psychotic disorders' OR 'psychosis'/exp OR psychosis OR 'schizophrenia'/exp OR schizophrenia OR schizophrenias OR 'schizophrenia s') AND ('antipsychotic naive' OR 'antipsychotic free' OR 'drug naive' OR 'drug free' OR 'neuroleptic naive' OR 'neuroleptic free' OR 'never medicated' OR untreated) AND ('cholesterol'/exp OR 'cholesterol' OR 'cholesterol'/exp OR cholesterol OR 'cholesterol s' OR cholesterole OR cholesterols OR 'hdl'/exp OR hdl OR 'oxidized low density lipoprotein[supplementary concept]' OR 'oxidized low density lipoprotein'/exp OR 'oxidized low density lipoprotein' OR 'ldl'/exp OR ldl OR triglycerid OR 'triacylglycerol'/exp OR 'triacylglycerol' OR 'triglycerides'/exp OR triglycerides OR 'triglyceride'/exp OR triglyceride OR triglycerids OR 'lipid s' OR lipidate OR lipidated OR lipidates OR 'lipidation'/exp OR lipidation OR lipidations OR lipide OR lipides OR lipidic OR 'lipid'/exp OR 'lipid' OR 'lipids'/exp OR lipids OR 'lipid'/exp OR lipid OR 'lipoprotein s' OR lipoproteine OR 'lipoproteins'/exp OR 'lipoproteins' OR 'lipoproteins'/exp OR lipoproteins OR 'lipoprotein'/exp OR lipoprotein OR mets OR metabolic OR metabolical OR metabolically OR metabolics OR 'metabolism'/exp OR 'metabolism' OR 'metabolism'/exp OR metabolism OR metabolisms OR (metabolic AND networks AND pathways) OR 'metabolic networks and pathways'/exp OR 'metabolic networks and pathways' OR metabolities OR 'metabolization'/exp OR metabolization OR metabolize OR metabolized OR metabolizer OR metabolizers OR metabolizes OR metabolizing OR (('blood'/exp OR blood) AND ('pressure'/exp OR pressure) AND determination) OR 'blood pressure determination'/exp OR 'blood pressure determination' OR 'blood pressure'/exp OR 'blood pressure' OR (arterial AND ('pressure'/exp OR pressure)) OR 'arterial pressure'/exp OR 'arterial pressure' OR (('blood'/exp OR blood) AND ('pressure'/exp OR pressure)) OR ((metabolic OR metabolical OR metabolically OR metabolics OR 'metabolism'/exp OR 'metabolism' OR 'metabolism'/exp OR metabolism OR metabolisms OR (metabolic AND networks AND pathways) OR 'metabolic networks and pathways'/exp OR 'metabolic networks and pathways' OR metabolities OR 'metabolization'/exp OR metabolization OR metabolize OR metabolized OR metabolizer OR metabolizers OR metabolizes OR metabolizing) AND (dysregulate OR dysregulated OR dysregulates OR dysregulating OR dysregulation OR dysregulations))) AND [embase]/lim

Web of Science Core Collection

Search in All Databases

TS=(first-episode psychosis or first-episode schizophrenia or FEP or FES or psychosis or schizophrenia) AND
#1 Results = 332828
TS=(antipsychotic-naïve or antipsychotic-free or drug-naïve or drug-free or neuroleptic-naïve or neuroleptic-free or never-medicated or untreated) AND
#2 Results = 307388
TS=(cholesterol or HDL or LDL or triglycerides or lipids or lipoproteins or metabolic syndrome or metabolic or blood pressure or metabolic dysregulation)
#3 Results = 5051070
#3 AND #2 AND #1
#4 Results = 1048

Table S4. Diagnostic manuals' codes associated with the relevant psychosis diagnoses included

Diagnosis	Code used within ICD-10	Code used within DSM-IV
Schizophrenia	F20	295.10/295.20/ 295.30/295.60/ 295.90
Brief psychotic disorder	F23	-
Schizophreniform disorder	F20.81	Schizophreniform disorder
Bipolar disorder with psychotic features	F31.2	296.04/296.44/ 296.54/296.64
Schizoaffective disorder	F25.0	295.70
Psychosis, not otherwise specified	F29	298.9

Table S5. Inclusion criteria for outcomes measures used to metabolic syndrome

The instruments below were chosen for being the most common instruments used to assess metabolic syndrome in general population and were chosen by authors after careful examination of relevant reviews in the field and based on their previous experience in clinical practise. If during the full text screening, a new instrument not included in the initially considered, it was discussed in a group meeting whether it should be included or not. Only

validated instruments were considered, which means that they went through a validation study process, where the usual parameters of quality were examined (inter-rater reliability, concurrent validity etc…)

ATP-IIIA	Diagnosis is made when three or more are present: • Waist circumference of more than 102 cm in men or more than 88 cm in women. • Fasting triglyceride level of 150 mg/dL or higher. • Blood pressure level of 130/85 mm Hg or higher. • Low HDL-C level (defined as < 1.04 mmol/L [40 mg/dL] in men or < 1.29 mmol/L [50 mg/dL] in women)
IDF	• **Central obesity and any 2 out of these 4 other factors:** • Triglyceride level of 1.7 mmol/L (150 mg/dL) or higher. • Low HDL-C level (defined as < 1.04 mmol/L [40 mg/dL] in men or < 1.29 mmol/L [50 mg/dL] in women) • Blood pressure of 130/85 mm Hg or higher. • Fasting hyperglycemia (defined as glucose level ≥5.6 mmol/L [100 mg/dL]) or previous diagnosis of diabetes or IGT.
JIS-2009	• > 3 out of these parameters: • Fasting glucose>100mg/dL • Blood pressure level of 130/85 mm Hg or higher. • Fasting triglyceride level of 150 mg/dL or higher. • Low HDL-C level (defined as < 1.04 mmol/L [40 mg/dL] in men or < 1.29 mmol/L [50 mg/dL] in women)
WHO	• Insulin resistance is defined as type 2 diabetes mellitus (DM) or impaired fasting glucose (IFG) (> 100 mg/dl) or impaired glucose tolerance (IGT), plus two of the following: • Abdominal obesity (waist-to-hip ratio > 0.9 in men or > 0.85 in women, or body mass index (BMI) > 30 kg/m^2. • Triglycerides 150 mg/dl or greater, and/or high-density lipoprotein (HDL)-cholesterol < 40 mg/dl in men and < 50 mg/dl in women. • Blood pressure (BP) 140/90 mmHg or greater. • Microalbuminuria (urinary albumin secretion rate 20 µg/min or greater, or albumin-to-creatinine ratio 30 mg/g or greater).

Table S6 All (18) full text selected studies, quality assessment and their respective reasoning for the exclusion of meta-analysis (K=18)

Autor	Year	Patients	Strictly Naïve (0 days)	MetS	Risk of bias	Reason of exclusion
Chilliza	2015	FEP	Yes	Yes	Low	Not strictly naive
Grover	2012	Schizophrenia	Yes	Yes	Low	Included
Kraemer	2011	FEP	Yes	Yes	Low	Included
Medved	2009	FEP	Yes	Yes	Low	Included
Owiredu	2012	Schizophrenia	Yes	Yes	Moderate	Included
Pallava	2012	FEP	No	Yes	Low	Not strictly naive
Srivastava	2018	FEP	Yes	Yes	Moderate	Included
Martin Otano	2013	FEP	Yes	Yes	Low	Included
Kraemer	2011	FEP	Yes	Yes	Low	Included
Saloojee	2018	FEP	Yes	Yes	Moderate	Included
Fleichhacker	2013	FEP	No	Yes	Low	Not strictly naive
De hert	2008	FEP	Yes	Yes	Low	Included
Enez Darcin	2015	FEP	Yes	Yes	Moderate	Included
Sahpolat	2020	FEP	Yes	Yes	Moderate	Included
Srihari	2013	FEP	No	Yes	Low	Not strictly naive
Garcia Rizo	2017	FEP	Yes	Yes	Low	Included
Correll	2014	FEP	No	Yes	Low	Not strictly naive
Effat	2012	FEP	Yes	Yes	Low	Included
Saddicha	2008	FEP	Yes	Yes	Low	Included

Table S7. Full text excluded articles and their respective reasoning for exclusion (K=94)

Author	Title	Reason of exclusion
Aguilar, Eva, Coronas, Ramon, Caixas, Assumpta	Metabolic syndrome in patients with schizophrenia and antipsychotic treatment	No naïve
Al-Amin, Md. Mamun, Uddin, Mir Muhammad Nasir, Reza, Hasan Mahmud	Effects of Antipsychotics on the Inflammatory Response System of Patients with Schizophrenia in Peripheral Blood Mononuclear Cell Cultures	No MetS
Alvarez-Jimenez, M, Conzalez-Blanch, C, Perez-Iglesias, R, Crespo-Facorro, B, Vazquez-Barquero, JL	Attenuation of antipsychotic-induced weight gain with early behavioural intervention in drug-naive first episode psychosis patients: a randomized controlled trial	Type of Study
Argo, Tami, Carnahan, Ryan, Barnett, Mitchell, Holman, Timothy L., Perry, Paul J.	Diabetes prevalence estimates in schizophrenia and risk factor assessment	No naïve
Arranz, B, Duenas, R, Ramirez, N, Fernandez, P, Sarro, S, San, L	Initial stages of insulin resistance in young antipsychotic-free and not in antipsychotic-naive schizophrenic patients	No MetS
Atbasoglu, E. Cem, Gumus-Akay, Guvem, Guloksuz, Sinan, Saka, Meram Can, Ucok, Alp, Alptekin, Koksal, Gullu, Sevim, van Os, Jim	Higher schizotypy predicts better metabolic profile in unaffected siblings of patients with schizophrenia	No naïve
Baeza, Immaculada, Castro-Fornieles, Josefina, Deulofeu, Ramon, de la Serna, Elena, Goti, Javier, Salvà, Joan, Bernardo, Miquel	Plasma homovanillic acid differences in clinical subgroups of first episode schizophrenic patients	No MetS
Baptista, Trino, Serrano, Ana, Uzcategui, Euderruh, ElFakih, Yamily, Rangel, Nairy, Carrizo, Edgardo, Fernandez, Virginia, Connell, Lisette, Araujo de Baptista, Enma, Quiroz, Segundo, Uzcategui, Marycelvia, Rondon, Juana, Matos, Yimber, Uzcategui, Lilia, Gomez, Roald, Valery, Lenin, Novoa-Montero, Dario	The metabolic syndrome and its constituting variables in atypical antipsychotic-treated subjects: Comparison with other drug treatments, drug-free psychiatric patients, first-degree relatives and the general population in Venezuela	No naïve
Barnett, A. H., Mackin, P., Chaudhury, I., Farooqi, A., Gadsby, R., Heald, A., Hill, J., Millar, H., Peveler, R., Rees, A., Singh, V., Taylor, D., Vora, J., Jones, P. B.	Minimising metabolic and cardiovascular risk in schizophrenia: diabetes, obesity and dyslipidaemia	No naïve
Bocchio-Chiavetto, Luisella, Zanardini, Roberta, Tosato, Sarah, Ventriglia, Mariacarla, Ferrari, Clarissa, Bonetto, Chiara, Lasalvia, Antonio, Giubilini, Franco, Fioritti, Angelo, Pileggi, Francesca, Pratelli, Michela, Pavanati, Michele, Favaro, Angela, De Girolamo, Giovanni, Frisoni, Giovanni Battista, Ruggeri, Mirella, Gennarelli, Massimo	Immune and metabolic alterations in first episode psychosis (FEP) patients	No MetS
Brunero, Scott, Lamont, Scott	Systematic screening for metabolic syndrome in consumers with severe mental illness	No MetS
Bushe, Chris	Glucose Abnormalities in Schizophrenia, Bipolar and Major Depressive Disorders	No naïve
Çakici, Nuray, Mill, Nina H van, Roza, Sabine J, Haan, Lieuwe De, Luik, Annemarie I, Beveren, Nico J van	T68. SUBCLINICAL PSYCHOTIC PHENOMENA ARE ASSOCIATED WITH MARKERS OF AN ALTERED METABOLISM IN A LARGE COMMUNITY SAMPLE.	No psychosis
Castillo Sanchez, Miguel, Fabregas Escurriola, Mireia, Berge Baquero, Daniel, Goday Arno, Albert, Valles Callol, Joan Antoni	Psychosis, cardiovascular risk and associated mortality: Are we on the right track?	No naïve

Castillo, Rolando I., Rojo, Leonel E., Henriquez-Henriquez, Marcela, Silva, Hernán, Maturana, Alejandro, Villar, María J., Fuentes, Manuel, Gaspar, Pablo A.	From Molecules to the Clinic: Linking Schizophrenia and Metabolic Syndrome through Sphingolipids Metabolism	Type of study
Chen, D. C., Du, X. D., Yin, G. Z., Yang, K. B., Nie, Y., Wang, N., Li, Y. L., Xiu, M. H., He, S. C., Yang, F. D., Cho, R. Y., Kosten, T. R., Soares, J. C., Zhao, J. P., Zhang, X. Y.	Impaired glucose tolerance in first-episode drug-naive patients with schizophrenia: relationships with clinical phenotypes and cognitive deficits	No MetS
Chen, Jinhong, Tan, Liwen, Long, Zhou, Wang, Lifeng, Hu, Li, Yang, Dong	Drug-naive patients with schizophrenia have metabolic disorders that are not associated with polymorphisms in the LEP (-2548G/A) and 5-HTR2C (-759C/T) genes	No MetS
Chen, Song, Broqueres-You, Dong, Yang, Guigang, Wang, Zhiren, Li, Yanli, Wang, Ning, Zhang, Xiangyang, Yang, Fude, Tan, Yunlong	Relationship between insulin resistance, dyslipidaemia and positive symptom in Chinese antipsychotic-naive first-episode patients with schizophrenia	No MetS
Chen, Song, Broqueres-You, Dong, Yang, Guigang, Wang, Zhiren, Li, Yanli, Yang, Fude, Tan, Yunlong	Male sex may be associated with higher metabolic risk in first-episode schizophrenia patients: A preliminary study	No MetS
Choong, Eva, Quteineh, Lina, Cardinaux, Jean-Rene, Gholam-Rezaee, Mehdi, Vandenberghe, Frederik, Dobrinas, Maria, Bondolfi, Guido, Etter, Manuela, Holzer, Laurent, Magistretti, Pierre, von Gunten, Armin, Preisig, Martin, Vollenweider, Peter, Beckmann, Jacques S., Pralong, Francois P., Waeber, Gerard, Kutalik, Zoltan, Conus, Philippe, Bochud, Murielle, Eap, Chin B.	Influence of CRTC1 Polymorphisms on Body Mass Index and Fat Mass in Psychiatric Patients and the General Adult Population	No naïve
Chouinard, Virginie-Anne, Henderson, David C., Dalla Man, Chiara, Valeri, Linda, Gray, Brianna E., Ryan, Kyle P., Cypess, Aaron M., Cobelli, Claudio, Cohen, Bruce M., Ongur, Dost	Impaired insulin signaling in unaffected siblings and patients with first-episode psychosis	No MetS
Citrome, L, Blonde, L, Damatarca, C	Metabolic issues in patients with severe mental illness	No naïve
Cohn, TA, Wolever, T, Bois, D, Zipursky, RB, Remington, G	First episode and neuroleptic free patients with schizophrenia have reduced insulin sensitivity: A minimal model analysis	No MetS
Cordes, J., Bechdolf, A., Moebus, S.	Prevalence of the metabolic syndrome in patients at risk of psychosis	No psychosis
Cordes, Joachim, Bechdolf, Andreas, Engelke, Christina, Kahl, Kai G., Balijepalli, Chakrapani, Lösch, Christian, Klosterkötter, Joachim, Wagner, Michael, Maier, Wolfgang, Heinz, Andreas, de Millas, Walter, Gaebel, Wolfgang, Winterer, Georg, Janssen, Birgit, Schmidt-Kraepelin, Christian, Schneider, Frank, Lambert, Martin, Juckel, Georg, Wobrock, Thomas, Riedel, Michael, Moebus, Susanne	Prevalence of metabolic syndrome in female and male patients at risk of psychosis	No psychosis
Curtis, Jackie, Henry, Catherine, Watkins, Andrew, Newall, Hannah, Samaras, Katherine, Ward, Philip B.	Metabolic abnormalities in an early psychosis service: a retrospective, naturalistic cross-sectional study	No Naïve
Darcin, Asli Enez, Cavus, Sercin Yalcin, Dilbaz, Nesrin, Kaya, Hasan, Dogan, Eylem	Metabolic syndrome in drug-naive and drug-free patients with schizophrenia and in their siblings	Type of Study
Dasgupta, Anindya, Singh, Om Prakash, Rout, Jayanta Kumar, Saha, Tanmay, Mandal, Sonai	Insulin resistance and metabolic profile in antipsychotic naive schizophrenia patients	No MetS
Duda-Sobczak, Anna, Wierusz-Wysocka, Bogna	Diabetes mellitus and psychiatric diseases	No naïve

Ebert, Tanya, Midbari, Yael, Shmilovitz, Ronen, Kosov, Ira, Kotler, Moshe, Weizman, Abraham, Ram, Anca	Metabolic effects of antipsychotics in prepubertal children: a retrospective chart review	No naïve
Emul, Murat, Kalelioglu, Tevfik	Etiology of cardiovascular disease in patients with schizophrenia: current perspectives	Type of study
Enger, Cheryl, Jones, Meghan E, Kryzhanovskaya, Ludmila, Doherty, Michael, McAfee, Andrew T	Risk of developing diabetes and dyslipidemia among adolescents with bipolar disorder or schizophrenia.	No naïve
Foley, Debra L., Mackinnon, Andrew, Watts, Gerald F., Shaw, Jonathan E., Magliano, Dianna J., Castle, David J., McGrath, John J., Waterreus, Anna, Morgan, Vera A., Galletly, Cherrie A.	Cardiometabolic Risk Indicators That Distinguish Adults with Psychosis from the General Population, by Age and Gender	No naïve
Fraguas, David, Merchán-Naranjo, Jessica, Laita, Paula, Parellada, Mara, Moreno, Dolores, Ruiz-Sancho, Ana, Cifuentes, Alicia, Giráldez, Marisa, Arango, Celso	Metabolic and hormonal side effects in children and adolescents treated with second-generation antipsychotics	No MetS
Ganesh, Suhas, Ashok, Abhishekh Hulegar, Kumar, Chennaveerachari Naveen, Thirthalli, Jagadish	Prevalence and determinants of metabolic syndrome in patients with schizophrenia: A systematic review and meta-analysis of Indian studies	Type of Study
Graham, Karen A., Cho, Hyunsoon, Brownley, Kimberly A., Harp, Joyce B.	Early treatment-related changes in diabetes and cardiovascular disease risk markers in first episode psychosis subjects	No naïve
Grimm, Oliver, Kaiser, Stefan, Plichta, Michael M., Tobler, Philippe N.	Altered reward anticipation: Potential explanation for weight gain in schizophrenia?	No naïve
Hepgul, N., Pariante, C. M., Dipasquale, S., DiForti, M., Taylor, H., Marques, T. R., Morgan, C., Dazzan, P., Murray, R. M., Mondelli, V.	Childhood maltreatment is associated with increased body mass index and increased C-reactive protein levels in first-episode psychosis patients	No MetS
Horsdal, Henriette Thisted, Benros, Michael Eriksen, Kohler-Forsberg, Ole, Krogh, Jesper, Gasse, Christiane	Metabolic profile at first-time schizophrenia diagnosis: a population-based cross-sectional study	No MetS
Khuhro, Quratulain, Channa, Naseem Aslam, Amur, Safdar Ali, Mugheri, Muhammad Haneef, Paras, Muzna, Soomro, Najaf Ali	Atypical Antipsychotics and Dyslipidemia- Experience at Psychiatry Hospital Hyderabad, Pakistan	No MetS
Kirkpatrick, Brian W., Garcia-Rizo, Clemente, Fernandez-Egea, E., Miller, Brian, Bernardo, M.	METABOLIC ABNORMALITIES IN NEWLY DIAGNOSED, ANTIPSYCHOTIC-NAIVE PATIENTS WITH SCHIZOPHRENIA AND RELATED DISORDERS	No MetS
Luckhoff, H. K., Kilian, S., Olivier, M. R., Phahladira, L., Scheffler, F., du Plessis, S., Chiliza, B., Asmal, L., Emsley, R.	Relationship between changes in metabolic syndrome constituent components over 12months of treatment and cognitive performance in first-episode schizophrenia	Type of Study
Maayan, Lawrence, Correll, Christoph U.	Weight gain and metabolic risks associated with antipsychotic medications in children and adolescents	No naïve
Malhotra, Nidhi, Grover, Sandeep, Chakrabarti, Subho, Kulhara, Parmanand	Metabolic syndrome in schizophrenia.	Type of Study
Misiak, Błażej, Stańczykiewicz, Bartłomiej, Łaczmański, Łukasz, Frydecka, Dorota	Lipid profile disturbances in antipsychotic-naive patients with first-episode non-affective psychosis: A systematic review and meta-analysis	No MetS
Mizrahi, Romina, Agid, Ofer, Borlido, Carol, Suridjan, Ivonne, Rusjan, Pablo, Houle, Sylvain, Remington, Gary, Wilson, Alan A., Kapur, Shitij	Effects of antipsychotics on D3 receptors: a clinical PET study in first episode antipsychotic naive patients with schizophrenia using [11C]-(+)-PHNO	No MetS
Mondelli, Valeria, Pariante, Carmine M.	Metabolic syndrome and obesity in psychosis: the possible mechanisms	Type of Study
Osby, Urban, Olsson, Eric, Edman, Gunnar, Hilding, Agneta, Eriksson, Sven V., Ostenson, Claes Goran	Psychotic disorder is an independent risk factor for increased fasting glucose and waist circumference	No naïve

Padmavati, Ramachandran, McCreadie, Robin G., Tirupati, Srinivasan	Low prevalence of obesity and metabolic syndrome in never-treated chronic schizophrenia	never teated but chronic patients. No FEP
Park, Jong Suk, Kim, Chan-Hyung, Ahn, Chul Woo, Kim, Kyung-Rae,	A determinant of insulin resistance in patients with schizophrenia	No MetS
Pascual-Marqui, R. D., Lehmann, D., Koenig, T., Kochi, K., Merlo, M. C., Hell, D., Koukkou, M.	Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia	No MetS
Perez-Iglesias, Rocio, Martinez-Garcia, Obdulia, Pardo-Garcia, Gema, Antonio Amado, Jose, Teresa Garcia-Unzueta, M., Tabares-Seisdedos, Rafael, Crespo-Facorro, Benedicto	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	Type of Study
Perez-Iglesias, Rocio, Mata, Ignacio, Pelayo-Teran, Jose M., Amado, Jose A., Garcia-Unzueta, Maria T., Berja, Ana, Martinez-Garcia, Obdulia, Vazquez-Barquero, Jose L., Crespo-Facorro, Benedicto	Glucose and lipid disturbances after 1 year of antipsychotic treatment in a drug-naive population	Type of Study
Petrikis, Petros, Tigas, Stelios, Tzallas, Alexandros T., Papadopoulos, Ioannis, Skapinakis, Petros, Mavreas, Venetsanos	Parameters of glucose and lipid metabolism at the fasted state in drug-naive first-episode patients with psychosis: Evidence for insulin resistance	No MetS
Pillinger, Toby, Beck, Katherine, Stubbs, Brendon, Howes, Oliver D.	Cholesterol and triiglyceride levels first-episode psychosis systematic review and meta analysis	No MetS
Pillinger, Toby, D'Ambrosio, Enrico, McCutcheon, Robert, Howes, Oliver D.	Is psychosis a multisystem disorder? A meta-review of central nervous system, immune, cardiometabolic, and endocrine alterations in first-episode psychosis and perspective on potential models	Type of Study
Pillinger, Toby, D'Ambrosio, Enrico, McCutcheon, Rob, Howes, Oliver	F18. IS SCHIZOPHRENIA A MULTI-SYSTEM DISORDER? CONSIDERING NEUROLOGICAL, IMMUNE, CARDIOMETABOLIC, AND ENDOCRINE ALTERATIONS IN FIRST EPISODE PSYCHOSIS	No naïve
Reddy, S., Goudie, C., Agius, M.	2755 – The metabolic syndrome in untreated schizophrenia patients: prevalence and suggested mechanisms.	No published. No response from authors
Russell, Alice, Ciufolini, Simone, Gardner-Sood, Poonam, Bonaccorso, Stefania, Gaughran, Fiona, Dazzan, Paola, Pariante, Carmine M., Mondelli, Valeria	Inflammation and metabolic changes in first episode psychosis: Preliminary results from a longitudinal study	No MetS
Santo, Paola, Lasalvia, Antonio	Risk factors associated with metabolic abnormalities in first-episode psychotic patients. A systematic review	Type of Study
Sengupta, Sarojini, Parrilla-Escobar, Maria A., Klink, Ruby, Fathalli, Ferid, Ng, Ying Kin, Stip, Emmanuel, Baptista, Trino, Malla, Ashok, Joober, Ridha	Are metabolic indices different between drug-naive first-episode psychosis patients and healthy controls?	No MetS
Sugawara, Norio, Yasui-Furukori, Norio, Sato, Yasushi, Umeda, Takashi, Kishida, Ikuko, Yamashita, Hakuei, Saito, Manabu, Furukori,	Prevalence of metabolic syndrome among patients with schizophrenia in Japan	No naïve

Hanako, Nakagami, Taku, Hatakeyama, Mitsunori, Nakaji, Shigeyuki, Kaneko, Sunao		
Sun, Langston, Getz, Mara, Daboul, Sulaima, Jay, Melanie, Sherman, Scott, Rogers, Erin, Aujero, Nicole, Rosedale, Mary, Goetz, Raymond R., Weissman, Judith, Malaspina, Dolores, Ahmad, Samoon	Independence of diabetes and obesity in adults with serious mental illness: Findings from a large urban public hospital	No MetS
Suriya Moorthi, M	A Comparative study Between First Generation and Second Generation Antipsychotics over the Development of Metabolic Syndrome in persons with First Episode Drug Naïve Schizophrenia.	Type of Study
Thakore, JH	Metabolic syndrome and schizophrenia	No naïve
Thakore, Jogin H.	Metabolic disturbance in first-episode schizophrenia	No naïve
Uzbekov, Marat G., Misionzhnik, Eduard, Gurovich, Isaak, Shmukler, Alexander, Moskvitina, Tatjana	Aspects of metabolic changes in first-episode drug-naive schizophrenic patients	No MetS
van Nimwegen, Lonneke J. M., Storosum, Jitschak G., Blumer, Regje M. E., Allick, Gideon, Venema, Henk W., de Haan, Lieuwe, Becker, Hiske, van Amelsvoort, Therese, Ackermans, Mariette T., Fliers, Eric, Serlie, Mireille J. M., Sauerwein, Hans P.	Hepatic insulin resistance in antipsychotic naive schizophrenic patients: stable isotope studies of glucose metabolism	No MetS
Vázquez Bourgon, J., Pérez-Iglesias, R., Ortiz-García de la Foz, V., Crespo-Facorro, B.	Long-term metabolic effect of second-generation antipsychotics in first episode of psychosis: Abstract of the 25th European Congress of Psychiatry	No MetS
Vázquez-Bourgon, Javier, Pérez-Iglesias, Rocío, Ortiz-García de la Foz, Víctor, Suárez Pinilla, Paula, Díaz Martínez, Álvaro, Crespo-Facorro, Benedicto	Long-term metabolic effects of aripiprazole, ziprasidone and quetiapine: a pragmatic clinical trial in drug-naïve patients with a first-episode of non-affective psychosis	No MetS
Vázquez-Bourgon, Javier, Sanchez Blanco, Lucía, Landera Rodriguez, Ruth, Setién Suero, Esther, Romero Jiménez, Rodrigo, Tordesillas-Gutiérrez, Diana, Ayesa Arriola, Rosa, Crespo-Facorro, Benedicto	F101. CANNABIS USE AND HEPATIC STEATOSIS IN PSYCHOSIS: RESULTS FROM A 3-YEAR LONGITUDINAL STUDY	No MetS
Vazquez-Bourgon, Javier, Setien-Suero, Esther, Pilar-Cuellar, Fuencisla, Romero-Jimenez, Rodrigo, Ortiz-Garcia de la Foz, Victor, Castro, Elena, Crespo-Facorro, Benedicto	Effect of cannabis on weight and metabolism in first-episode non-affective psychosis: Results from a three-year longitudinal study	No MetS
Verma, Swapna K., Subramaniam, Mythily, Liew, Alvin, Poon, Lye Yin	Metabolic Risk Factors in Drug-Naive Patients With First-Episode Psychosis	No MetS
Vinay, H.R., Sundar, G.S. Keerthi, Behere, Rishikesh V., Arasappa, Rashmi, Rao, Naren P., Venkatasubramanian, Ganesan, Sivakumar, P.T., Gangadhar, B.N.	Effect of risperidone on metabolic parameters in antipsychotic-naïve schizophrenia: A prospective one year follow-up study	Type of Study
Wood, Stephen J., Berger, Gregor E., Lambert, Martin, Conus, Phillipe, Velakoulis, Dennis, Stuart, Geoffrey W., Desmond, Patricia, McGorry, Patrick D., Pantelis, Christos	Prediction of functional outcome 18 months after a first psychotic episode: a proton magnetic resonance spectroscopy study	No MetS
Wu, Xiaoli, Huang, Zeping, Han, Hongying, Zhong, Zhiyong, Gan, Zhaoyu, Guo, Xiaofeng, Diao, Feici, Han, Zili, Zhao, Jingping	The comparison of glucose and lipid metabolism parameters in drug-naive, antipsychotic-treated, and antipsychotic discontinuation patients with schizophrenia	No MetS

Wu, Xiaoli, Huang, Zeping, Wu, Renrong, Zhong, Zhiyong, Wei, Qinling, Wang, Houliang, Diao, Feici, Wang, Jihui, Zheng, Liangrong, Zhao, Jingping, Zhang, Jinbei	The comparison of glycometabolism parameters and lipid profiles between drug-naive, first-episode schizophrenia patients and healthy controls	No MetS
Yezhe Lin, Yanmin Peng, Shen He, Jingjie Xu, Yuan Shi, Yousong Su, Cuizhen Zhu, Xinyi Zhang, Rubai Zhou, Donghong Cui	Serum IL-1ra, a novel biomarker predicting olanzapine-induced dyslipidemia and hyperleptinemia in Schizophrenia	No MetS
Zhai, Desheng, Cui, Taizhen, Xu, Yahui, Feng, Yihang, Wang, Xin, Yang, Yuxin, Li, Songji, Zhou, Dushuang, Dong, Gaopan, Zhao, Ying, Yang, Yunlei, Zhang, Ruiling	Cardiometabolic risk in first-episode schizophrenia (FES) patients with the earliest stages of both illness and antipsychotic treatment	No MetS
Zhai, Desheng, Lang, Yan, Feng, Yihang, Liu, Yijun, Dong, Gaopan, Wang, Xin, Cao, Ying, Cui, Taizhen, Ni, Chenyang, Ji, Yonggan, Zhang, Xiaodan, Zhao, Ying, Zhang, Ruiling	Early onset of cardiometabolic risk factor profiles in drug naive adolescents and young adults with first-episode schizophrenia	No MetS
Zhang, Yamin, Wang, Qiang, Reynolds, Gavin P, Yue, Weihua, Deng, Wei, Yan, Hao, Tan, Liwen, Wang, Chuanyue, Yang, Guigang, Lu, Tianlan, Wang, Lifang, Zhang, Fuquan, Yang, Jianli, Li, Keqing, Lv, Luxian, Tan, Qingrong, Li, Yinfei, Yu, Hua, Zhang, Hongyan, Ma, Xin, Yang, Fude, Li, Lingjiang, Chen, Qi, Wei, Wei, Zhao, Liansheng, Wang, Huiyao, Li, Xiaojing, Guo, Wanjun, Hu, Xun, Tian, Yang, Ren, Hongyan, Ma, Xiaohong, Coid, Jeremy, Zhang, Dai, Li, Tao	Metabolic Effects of 7 Antipsychotics on Patients With Schizophrenia: A Short-Term, Randomized, Open-Label, Multicenter, Pharmacologic Trial.	Type of Study
Sjo, C., Bilenberg, N.	Second-generation antipsychotics and the metabolic syndrome in drug-naive adolescents	Age < 18
Bashyal, Bishnu, Goswami, Hiranya Kumar	Metabolic Syndrome and their association with drug naive Schizophrenia and Mood Disorders-A comparative study	Incomplete data
Bioque, Miquel, Paz Garcia-Portilla, Ma, Garcia-Rizo, Clemente, Cabrera, Bibiana, Lobo, Antonio, Gonzalez-Pinto, Ana, Diaz-Caneja, Covadonga M., Corripio, Iluminada, Vieta, Eduard, Castro-Fornieles, Josefina, Bobes, Julio, Gutierrez-Fraile, Miguel, Rodriguez-Jimenez, Roberto, Mezquida, Gisela, Llerena, Adrian, Saiz-Ruiz, Jeronimo, Bernardo, Miguel	Evolution of metabolic risk factors over a two-year period in a cohort of first episodes of psychosis	Incomplete data of total naïve sample
Chadda, Rakesh K., Ramshankar, Prashanth, Deb, Koushik S., Sood, Mamta	Metabolic syndrome in schizophrenia: Differences between antipsychotic-naive and treated patients	Duplicate sample
Keinanen, Jaakko, Mantere, Outi, Kieseppa, Tuula, Mantyla, Teemu, Torniainen, Minna, Lindgren, Maija, Sundvall, Jouko, Suvisaari, Jaana	Early insulin resistance predicts weight gain and waist circumference increase in first-episode psychosis - A one year follow-up study	No MetS data

Pallava, Abhishek, Chadda, Rakesh K., Sood, Mamta, Lakshmy, R	Metabolic syndrome in schizophrenia: A comparative study of antipsychotic-free/naive and antipsychotic-treated patients from India	Not strictly naive
Nyboe, L., Vestergaard, C. H., Moeller, M. K., Lund, H., Videbech, P.	Metabolic syndrome and aerobic fitness in patients with first-episode schizophrenia, including a 1-year follow-up	Not naïve data
Sjo, Christina Power, Stenstrøm, Anne Dorte, Bojesen, Anders Bo, Frølich, Jacob Stampe, Bilenberg, Niels	Development of Metabolic Syndrome in Drug-Naive Adolescents After 12 Months of Second-Generation Antipsychotic Treatment	Age < 18
Smith, Jo, Griffiths, Lisa, Horne, Dominic	Prevalence of Cardiometabolic Risk Factors in First Episode Psychosis Patients	Not peer review published
Arango, Celso, Giraldez, Miriam, Merchan-Naranjo, Jessica, Baeza, Inmaculada, Castro-Fornieles, Josefina, Alda, Jose-Angel, Martinez-Cantarero, Carmen, Moreno, Carmen, de Andres, Pilar, Cuerda, Cristina, de la Serna, Elena, Correll, Christoph U., Fraguas, David, Parellada, Mara	Second-Generation Antipsychotic Use in Children and Adolescents: A Six-Month Prospective Cohort Study in Drug-Naive Patients	Age < 18
Anjum, Shazia, Bathla, Manish, Panchal, Saminder, Singh, Gurvinder Pal, Singh, Manpreet	Metabolic syndrome in drug naïve schizophrenic patients	MetS Prevalence is not reported
Grover, Sandeep, Nebhinani, Naresh, Padmavati, Ramachandran, Chadda, Rakesh K., Tirupati, Srinivasan, Pallava, Abhishek	Metabolic syndrome in antipsychotic naive patients with schizophrenia: pooled analysis of data from three Indian studies	Duplicate sample
Parrilla, M. A., Sengupta, S. M., Kin, N. M., Klink, R., Stip, E., Baptista, T., Malla, A., Joober, R.	Comparison of baseline metabolic variables between drug-naive first-episode psychosis patients and healthy controls	Duplicate sample

Table S8. Contact with authors

Autor	Year	Patients	Strictly Naïve (0 days)	MetS	Risk of bias	Reason of exclusion	Author contacted	Response
Bashyal	2015	FEP	Yes	Yes	Moderate	Incomplete data	Yes	yes
Bioque	2018	FEP	Yes	Yes	low	Incomplete data of total naïve sample	Yes	yes
Keinanen	2015	FEP	Yes	Yes	low	No MetS data	Yes	no
Nyboe	2015	FEP	Yes	Yes	Moderate	Not naïve data	Yes	no
Smith	2016	FEP	Yes	Yes	Moderate	Not peer review published	Yes	no
Anjum	2018	Schizophrenia	Yes	Yes	low	MetS Prevalence is not reported	Yes	no
Effat	2012	FEP	Yes	Yes	Low	Included	Yes	yes

Table S9. Operationalization of the diagnostic criteria for MetS

Criteria	Utilised by	Total number of studies
ATP-IIIA	De Hert 2008 Kraemer 2011 Otaño-Matín 2012 García-Rizo 2017	4
Both ATP-IIIA & IDF	Grover 2011 Enez Darzin 2015 Saddicha 2008 Sahpolat 2020 Owiredu 2012	5
IDF	Effat 2011 Medved 2009 Srivastava 2011	3
JIS-2009	Saloojee 2017	1
OMS	Owiredu 2012	1

Table S10. Sensitivity analyses and heterogeneity

Group SubGroup	No. of Studies	Sample size	Prevalence %	95% CI		Z score	P	Test of heterogeneity Q	df	I^2	P	Heterogeneity* between subgroups Q	df	P
MetS criteria														
ATP-IIIA	9	736	11.4	6.4	19.5	-14.31	<0.001	61.4	8	83.0	0.000	7.570	2	**0.023**
IDF	3	206	21.8	12.8	34.8	-7.73	<0.001	6.9	2	57.0	0.070			
Others	1	67	4.5	1.5	13.0	-5.18	<0.001	0.0	0	0.0	1.000			
Geographical location														
Europe	5	507	9.7	4.7	18.0	-5.65	<0.001	21.7	4	81.6	0.000	3.466	2	0.177
Asia	5	315	19.6	12.5	29.3	-5.21	<0.001	12.7	4	68.6	0.113			
Africa	3	187	8.3	1.0	44.0	-2.15	0.032	22.3	2	91.0	0.000			
Risk of bias														
Low	9	730	13.9	8.7	21.0	-6.798	<0.001	39.5	8	79.7	0.000	0.143	1	0.705
Moderate	4	279	11.0	8.5	32.0	-3.771	<0.001	31.1	5	83.9	0.000			

*Only ATP-IIIA and IDF included in the subgroup analysis

Table S11. Meta-regressions

Group	Q	df	p	R2
MetS criteria	3.60	2	0.165	0.07
Geographical location	2.66	2	0.648	0.00
Risk of bias	0.07	1	0.794	0.00
Ethnicity	17	3	0.000	0.50

Table S12. Grey Literature

Reports unrelated to MetS prevalence in FEP	118
Electronic resources	31
Magazines	30
Dissertations/Theses	14
Books	13
News	5
Conference proceedings	3
Electronic books	1
Videos	1
Opinion letter	1
Unpublished abstracts (Reddy et al., 2013)	2

Forest plots

We performed sensitivity analyses removing studies based on exposure to antipsychotics (0 days, 0 days & 0-14 days, and up to 47 days) and also one study removed analysis. Of particular note is that there is no significant difference in prevalence among the three groups. The prevalence of MetS in strictly naïve patients is 13.2% (Figure 2). The prevalence of MetS was 12.2% only with 0 days & 0-14 days of exposure, n=1085, k=14 (Figure S3) and 12.2% with up to 47 days of exposure, n=711, k=4 (Figure S4), while the overall prevalence of MetS patients reported as naïve in all the included studies was 12.3% (95% CI: 0.8-17) (n=1796, k=18).

Figure S1. Funnel plot

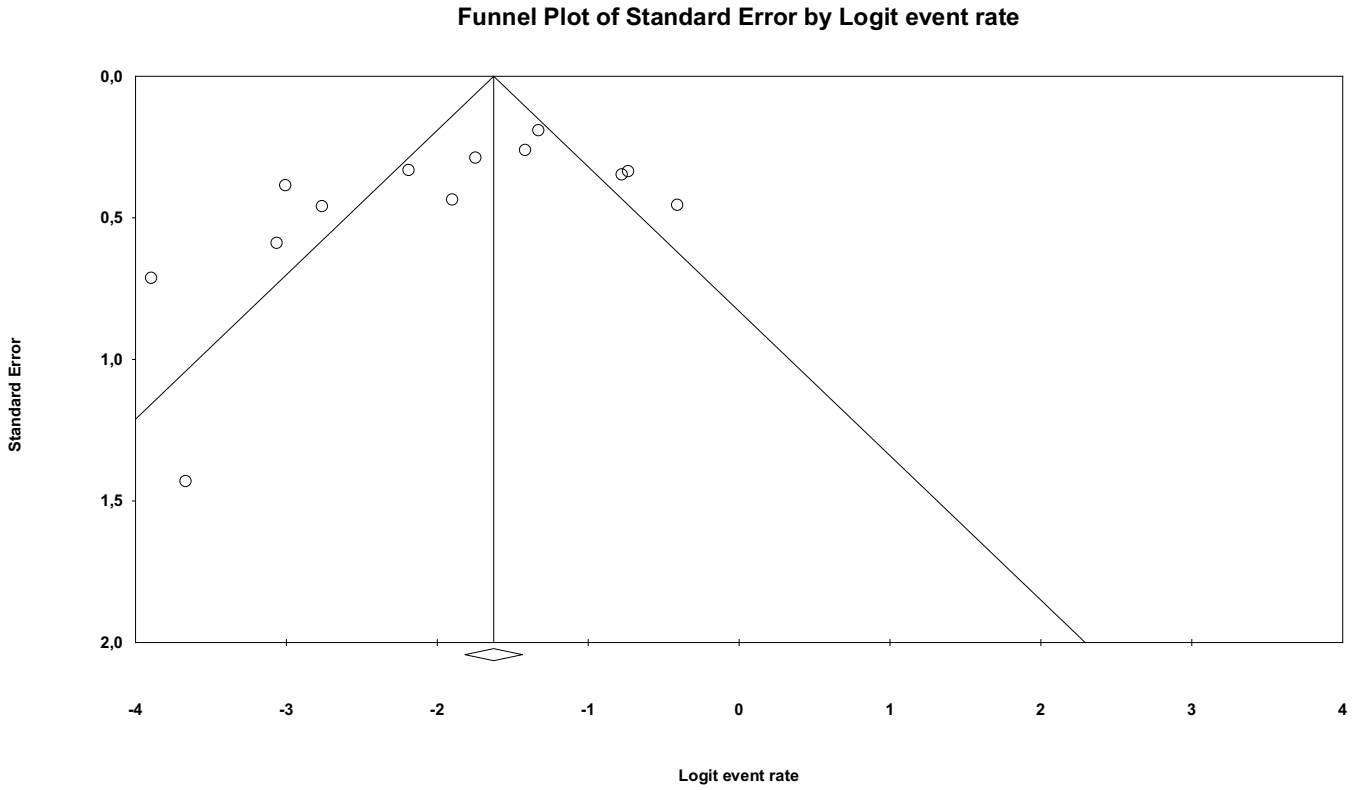

Figure S2. Forest plot showing one study removed analysis

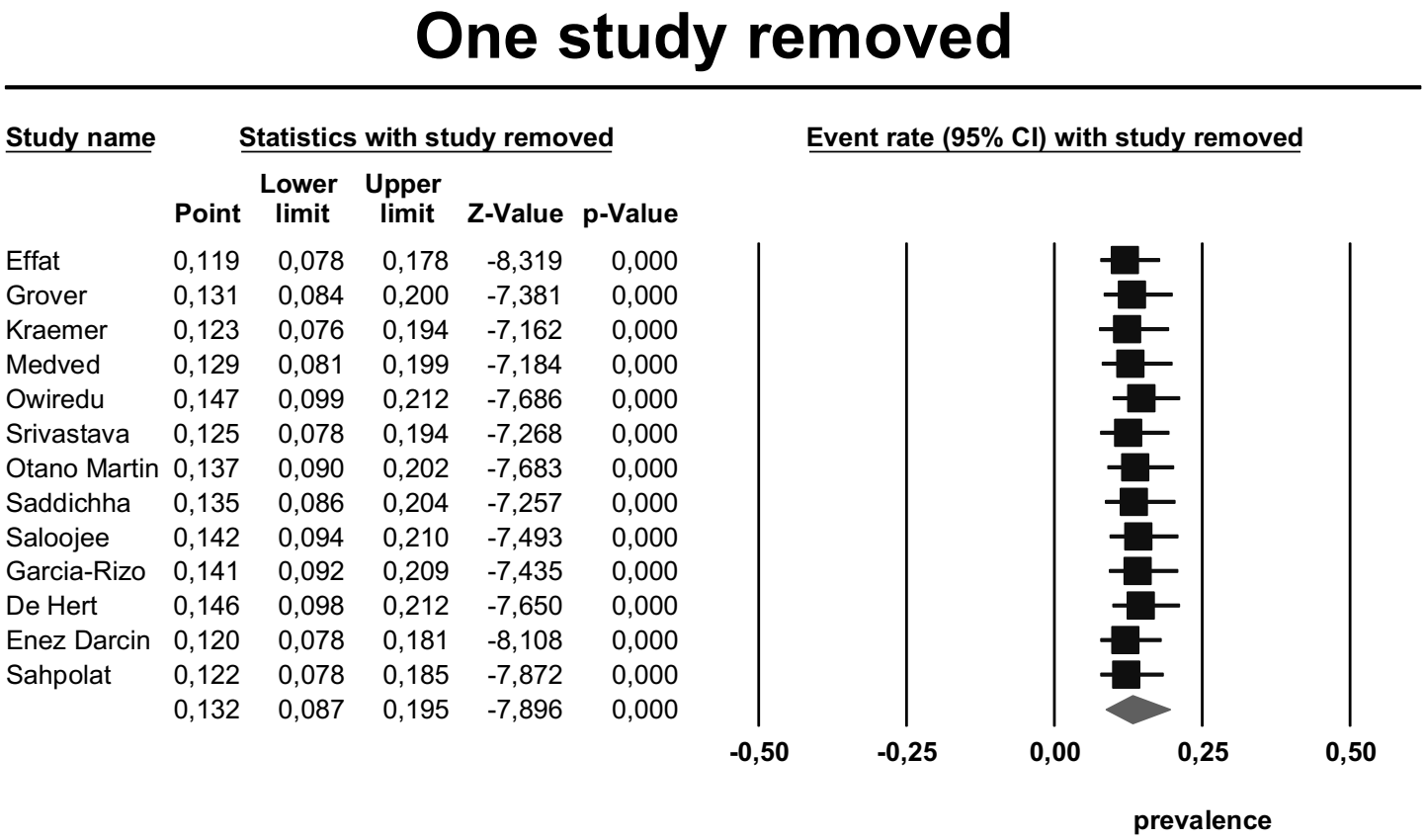

Figure S2. Forest plot showing one study removed analysis

Figure S3. Forest plot showing MetS prevalence in patients Strictly naïve (0 days) and minimally treated (0-14 days)

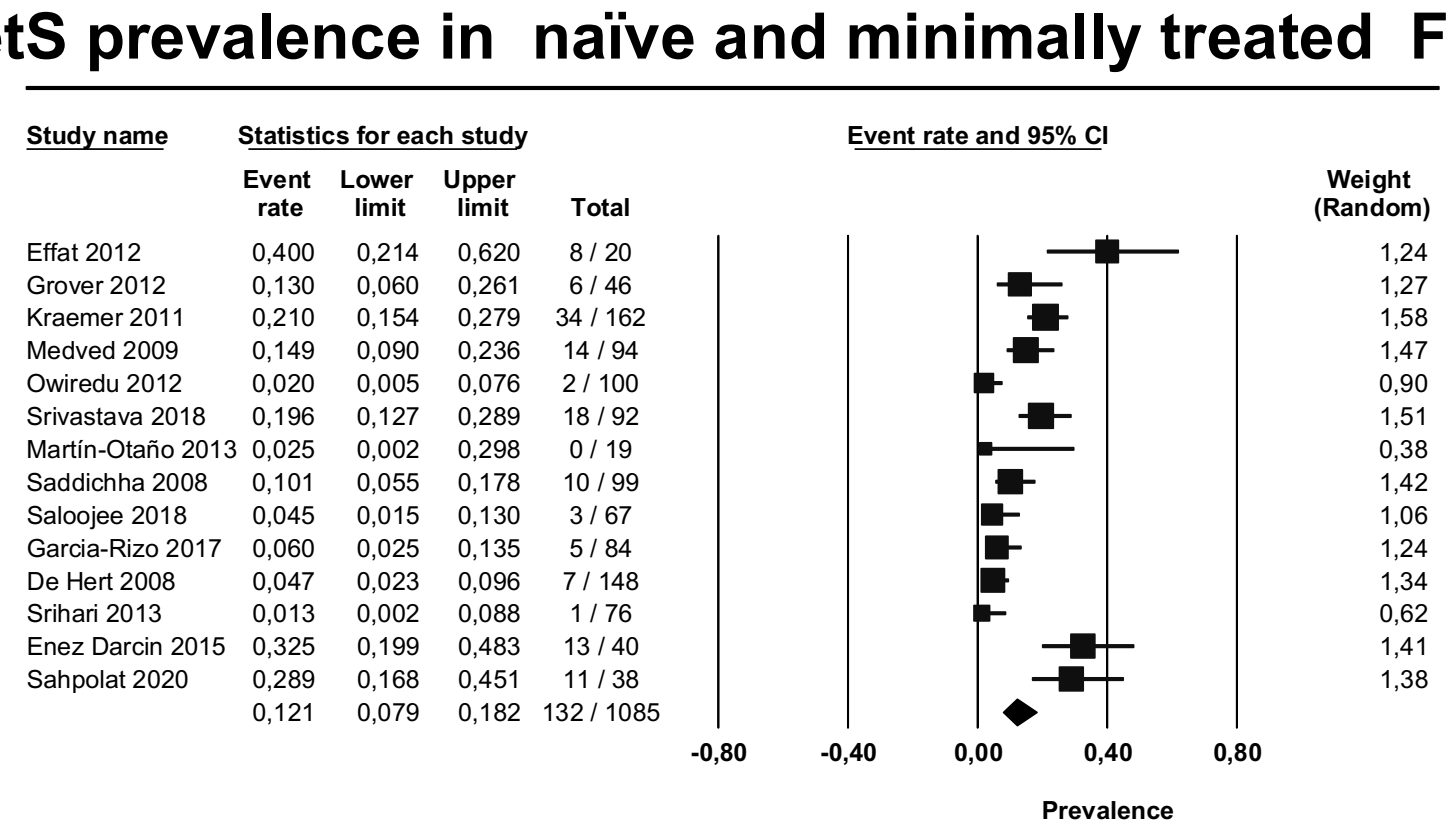

Figure S3. Forest plot showing MetS prevalence in strictly naïve patients (0 days) and minimally treated (0-15 days) patients

Figure S4. Forest plot showing MetS prevalence in patients treated up 47 days

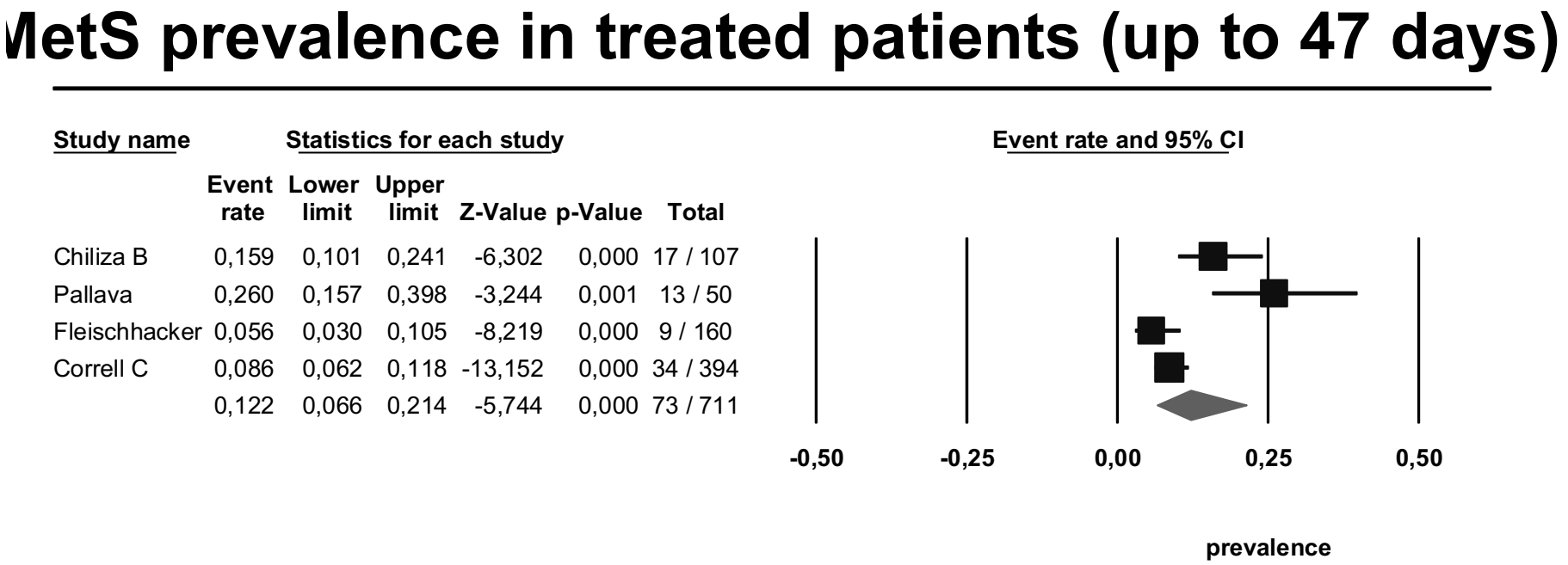

Figure S4. Forest plot showing MetS prevalence in treated patients (up to 47 days)

Figure S5. Forest plot showing MetS prevalence in patients minimally treated (0-14 days) and up to 47 days

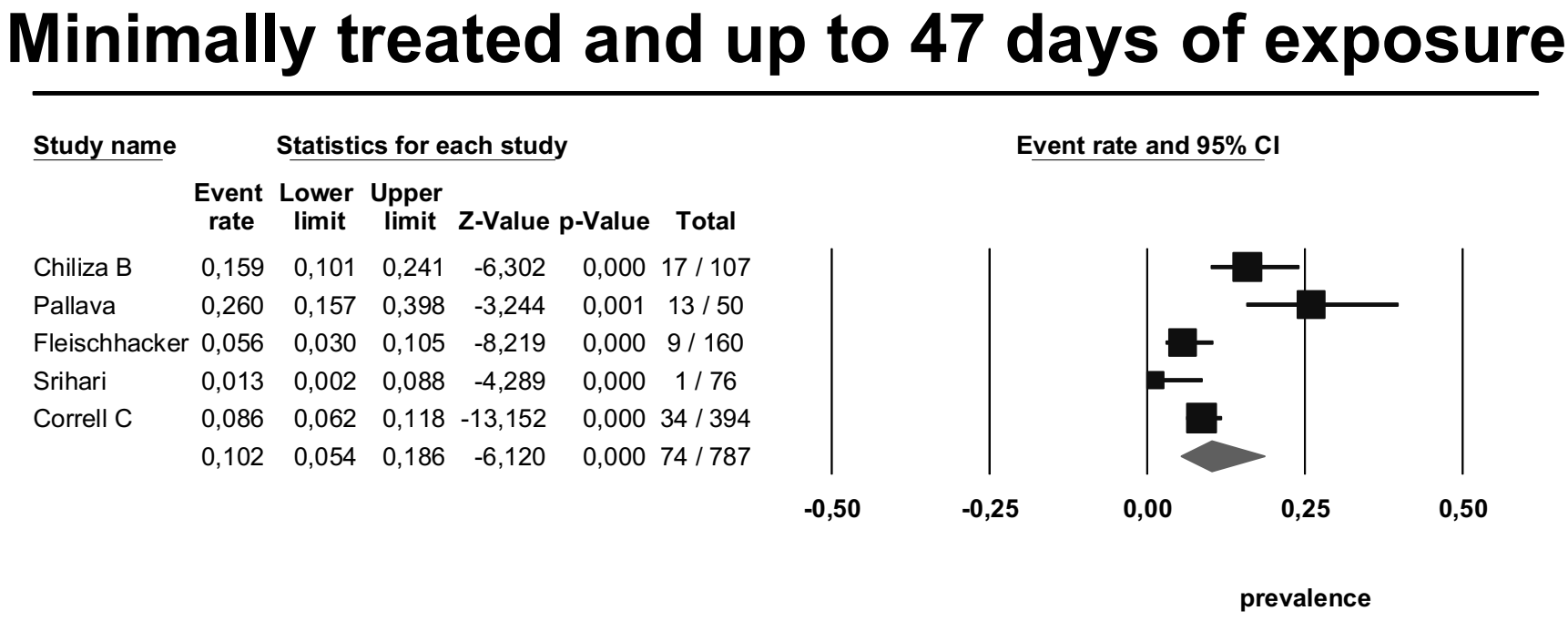

Figure S5. Forest plot showing MetS prevalence in minimally treated (0-14 days) patients and up to 47 days of exposu

Figure S6. Forest plot showing subgroups by geographical location

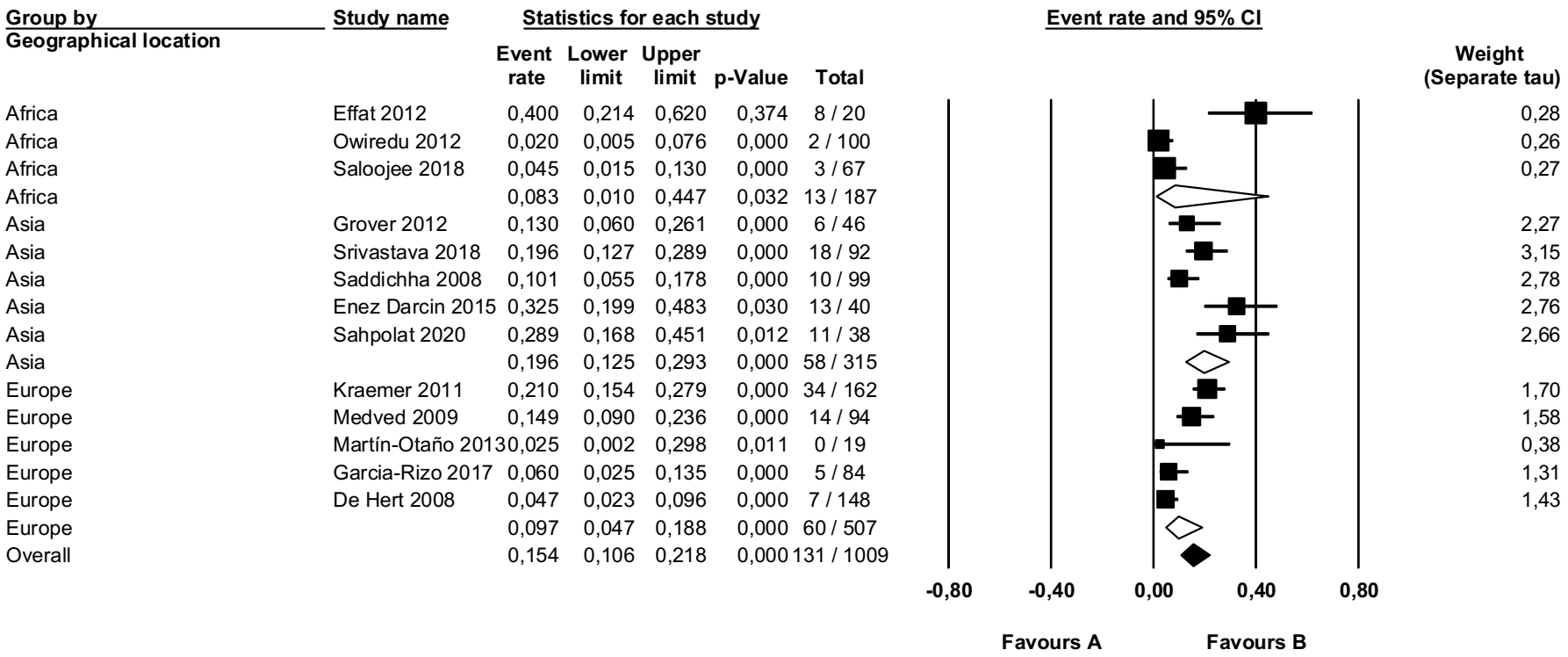

Figure S6. Forest plot showing subgroups by geographical location

Figure S7a. Sensitivity analysis by ethnicity removing afrodescendants

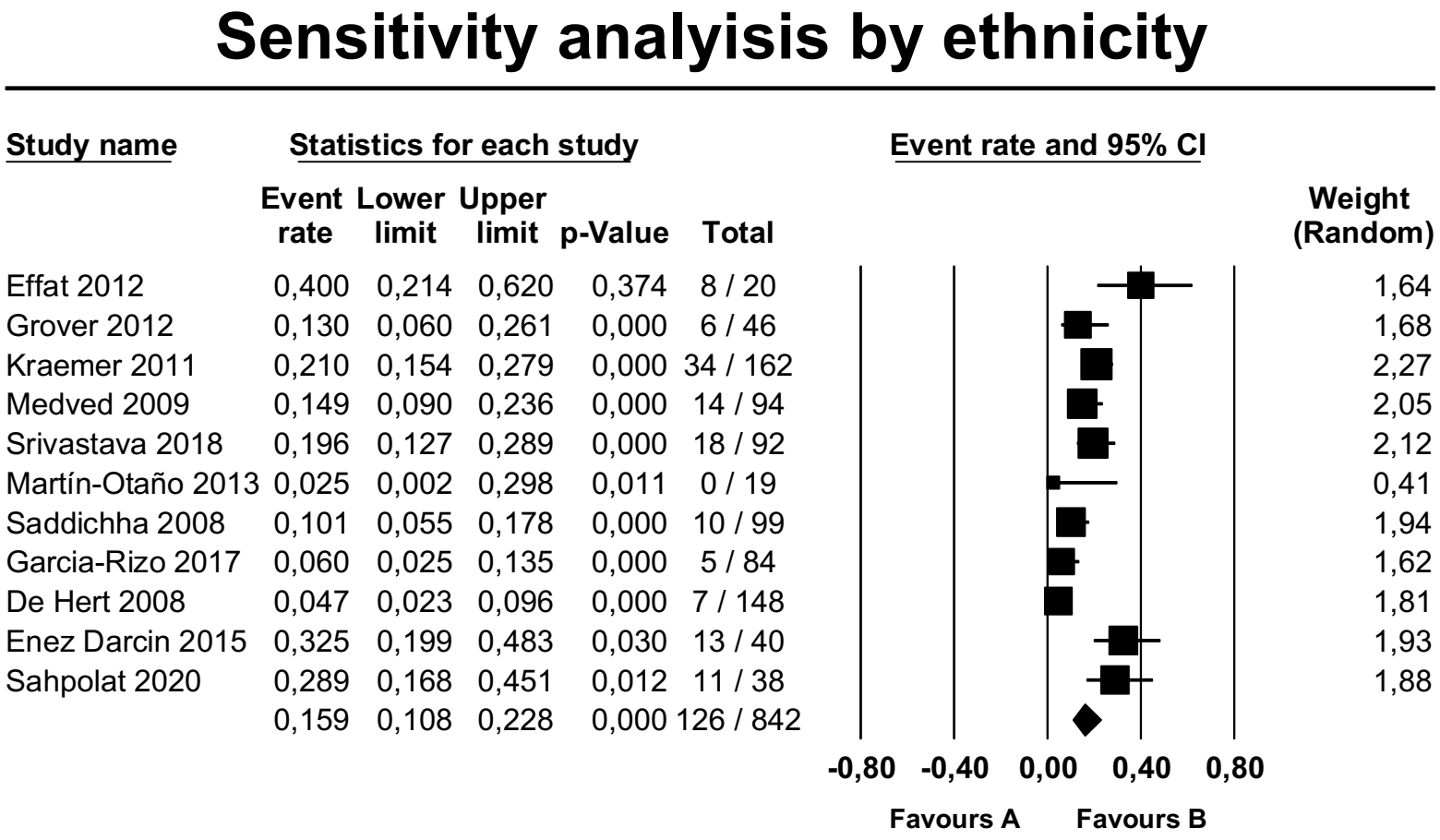

Figure S7a. Sensitivity analysis removing stidies with afro-descendants

Figure S7b. MetS prevalence in Afrodescendants

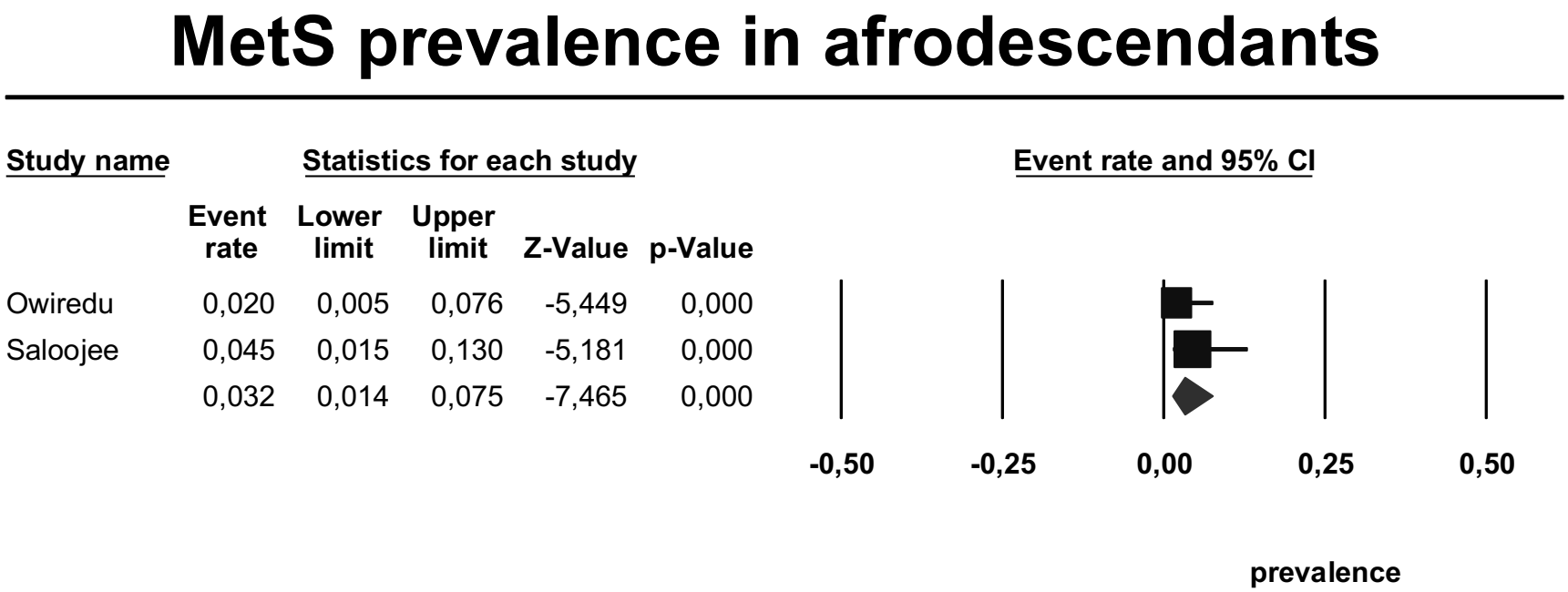

Figure S7b. MetS prevalence in studies conducted with afrodescendants naïve patients

Figure S7c. MetS prevalence in studies from India

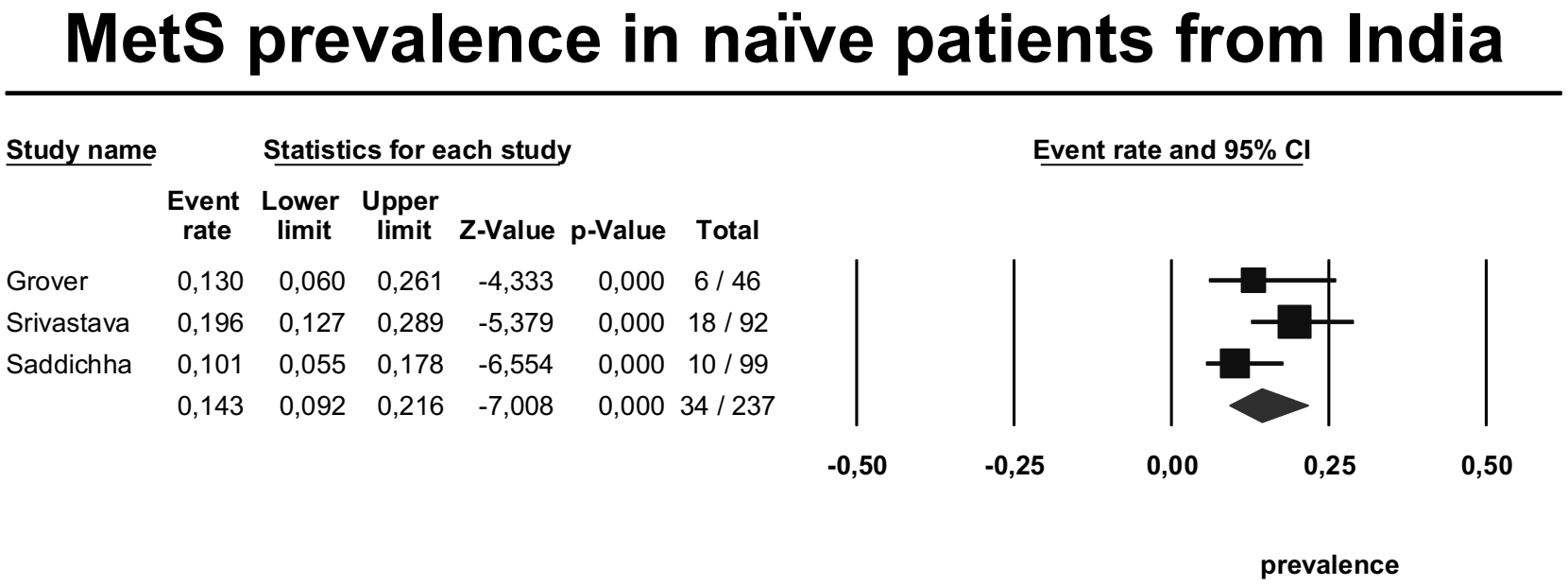

Figure S7c. MetS prevalence in studies from India

Figure S7d. MetS prevalence in Caucasian

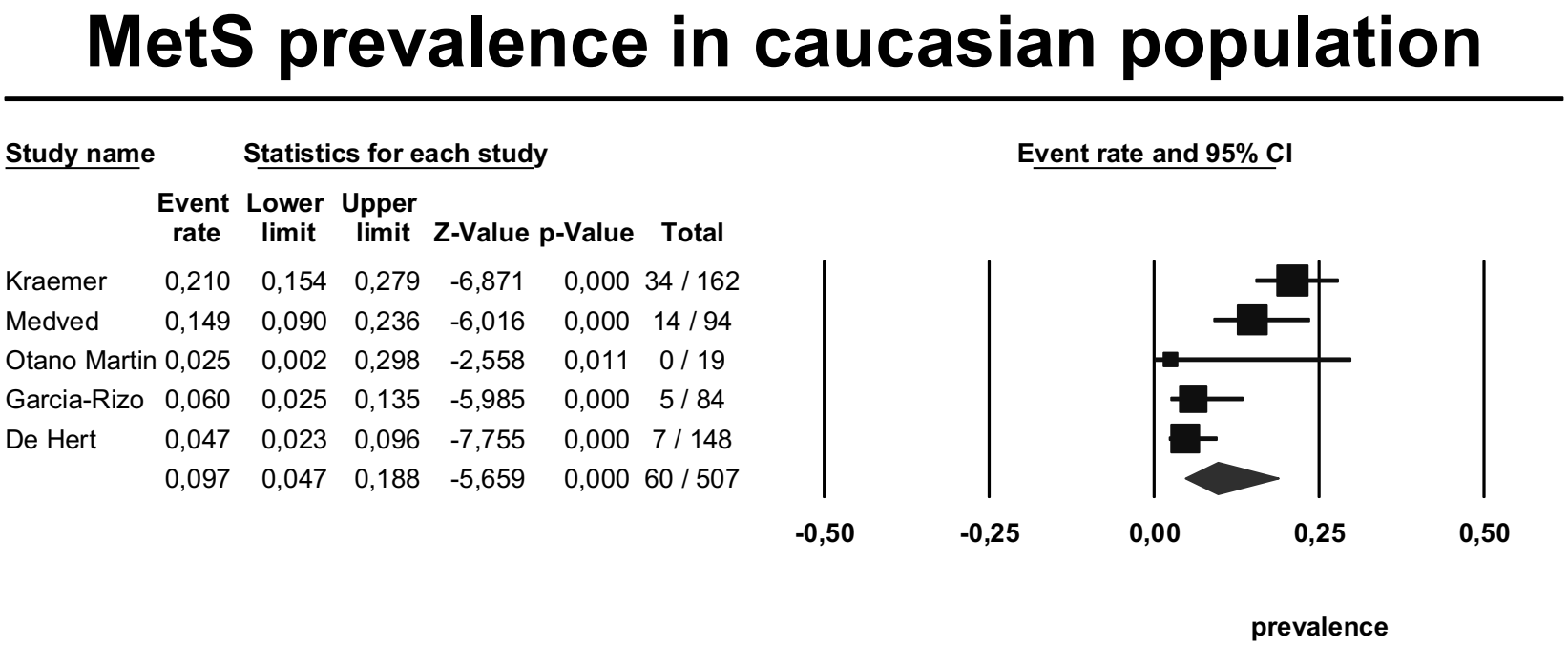

Figure S7d. MetS prevalence in naïve patients with psychosis: caucasian population

Figure S7e. MetS prevalence in Middle East

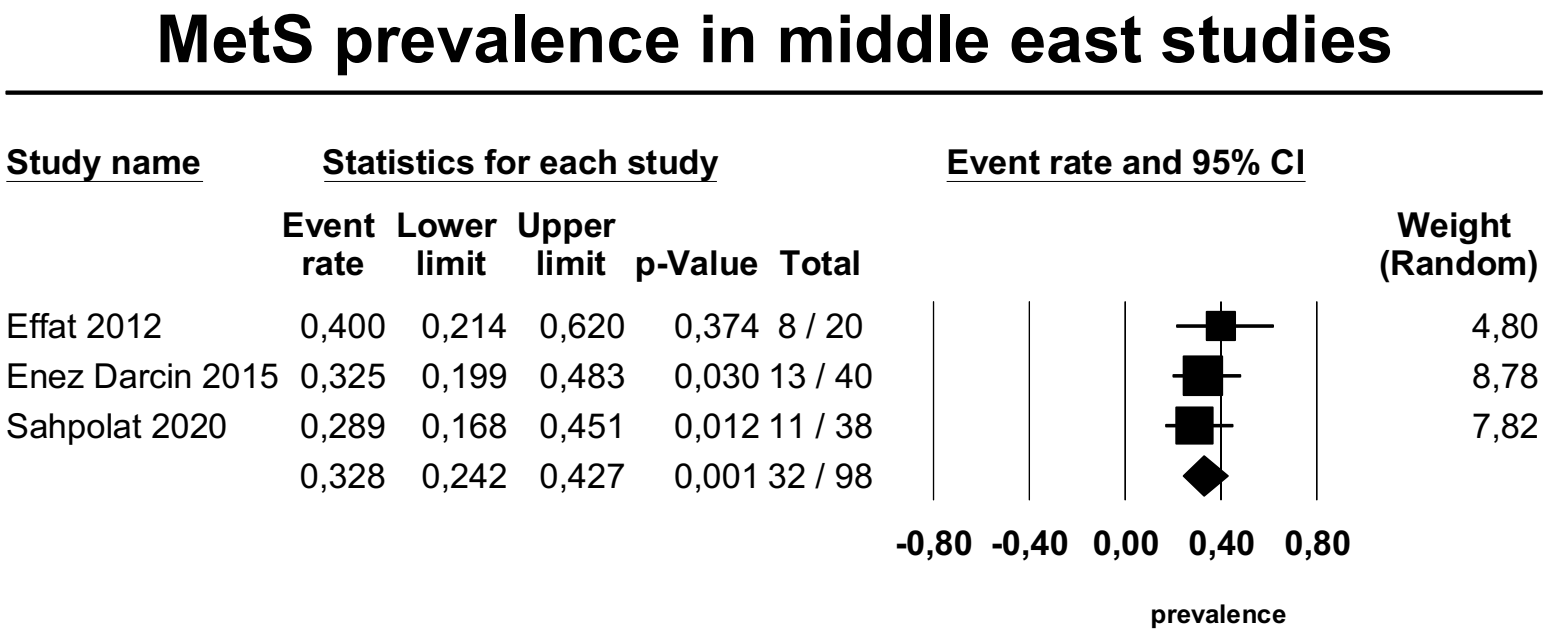

Figure S7e. MetS prevalence in naïve FEP patients from middle east

Figure S8. Forest plot showing subgroups by risk of bias

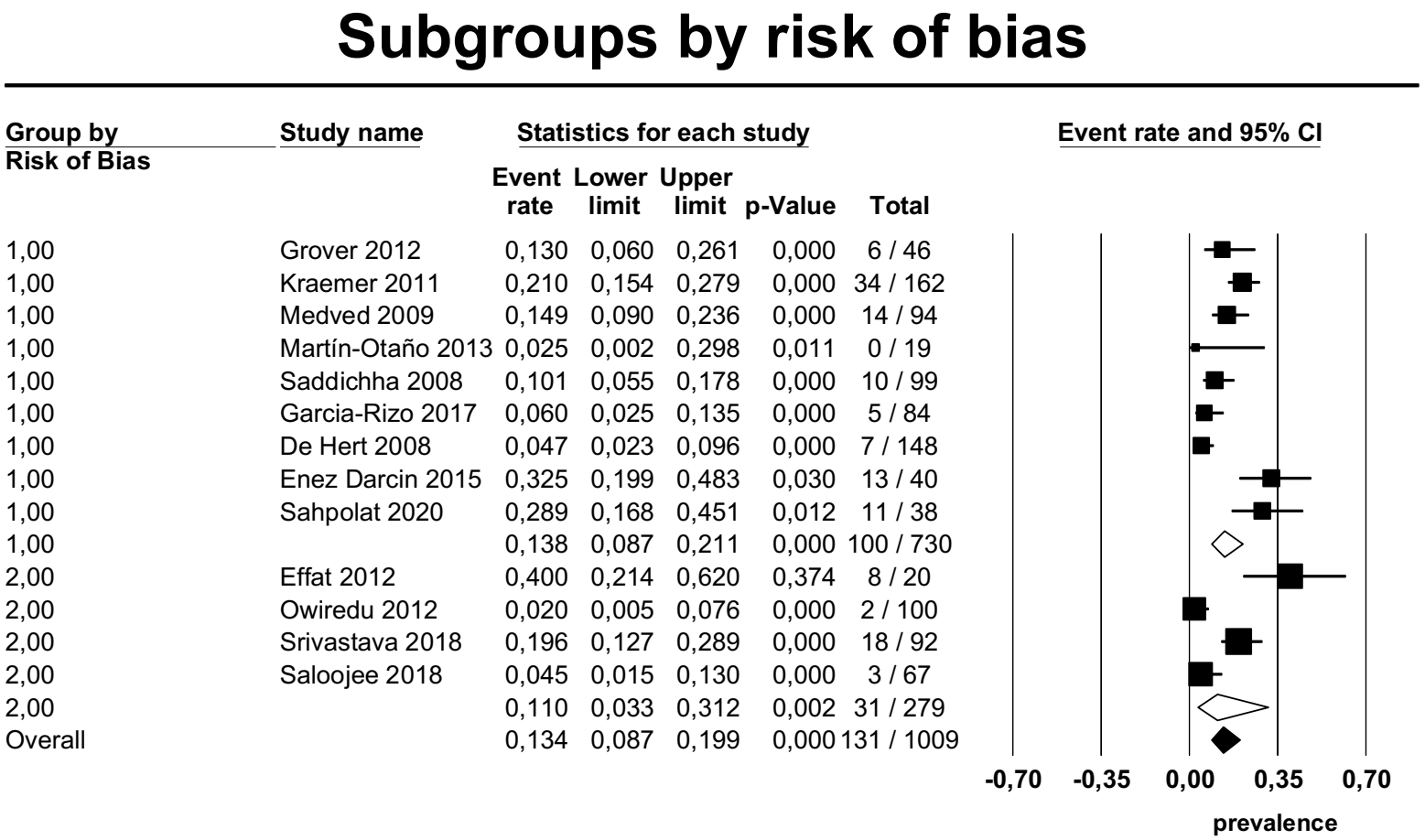

Figure S8. Forest plot showing subgroups by risk of bias

Figure S9. Subgroups analysis according to MetS criteria

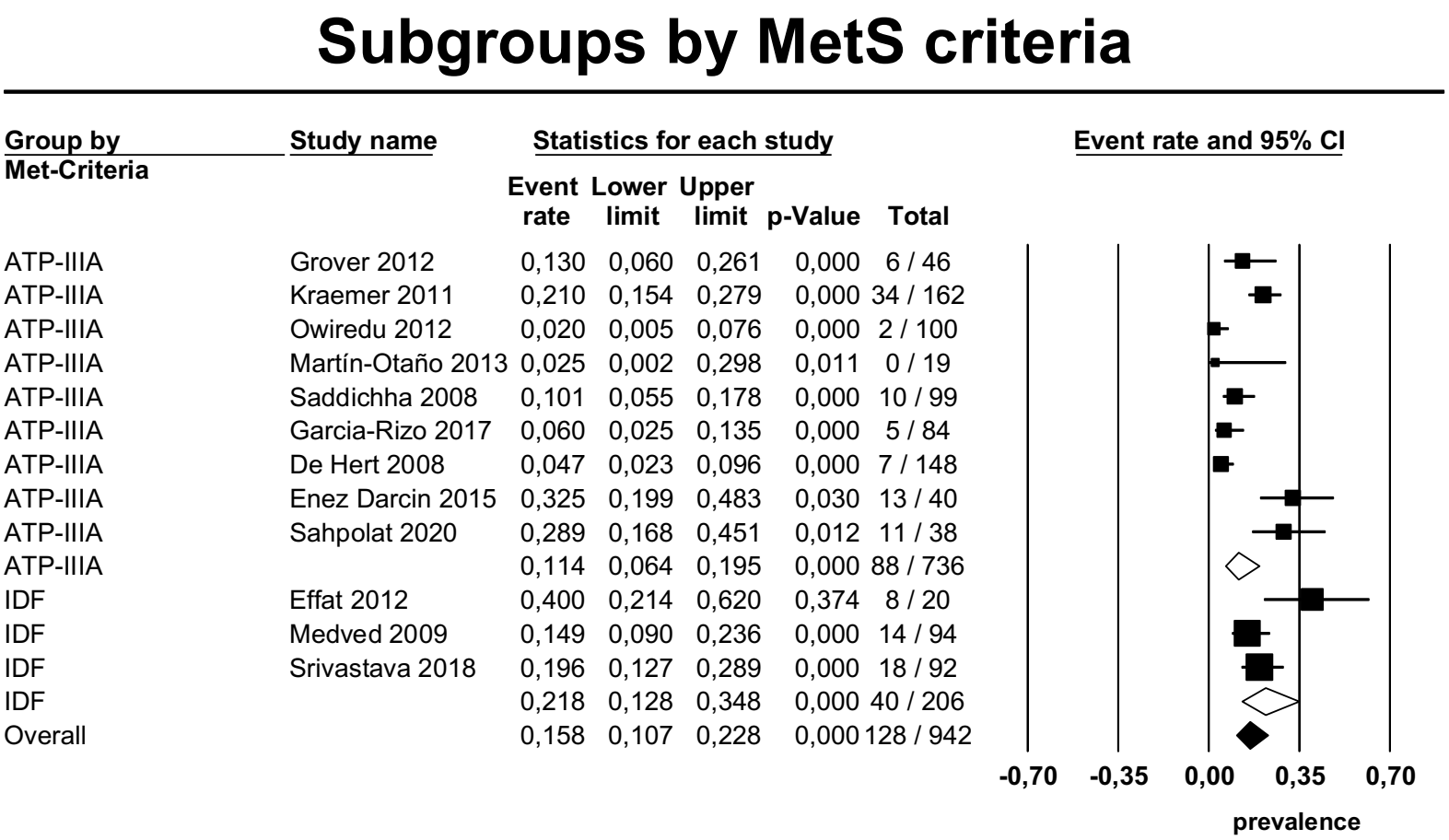

Figure S9. Subgroups analysis according to MetS criteria

Figure S10. Overall MetS prevalence in naïve (0 days) patients using IDF

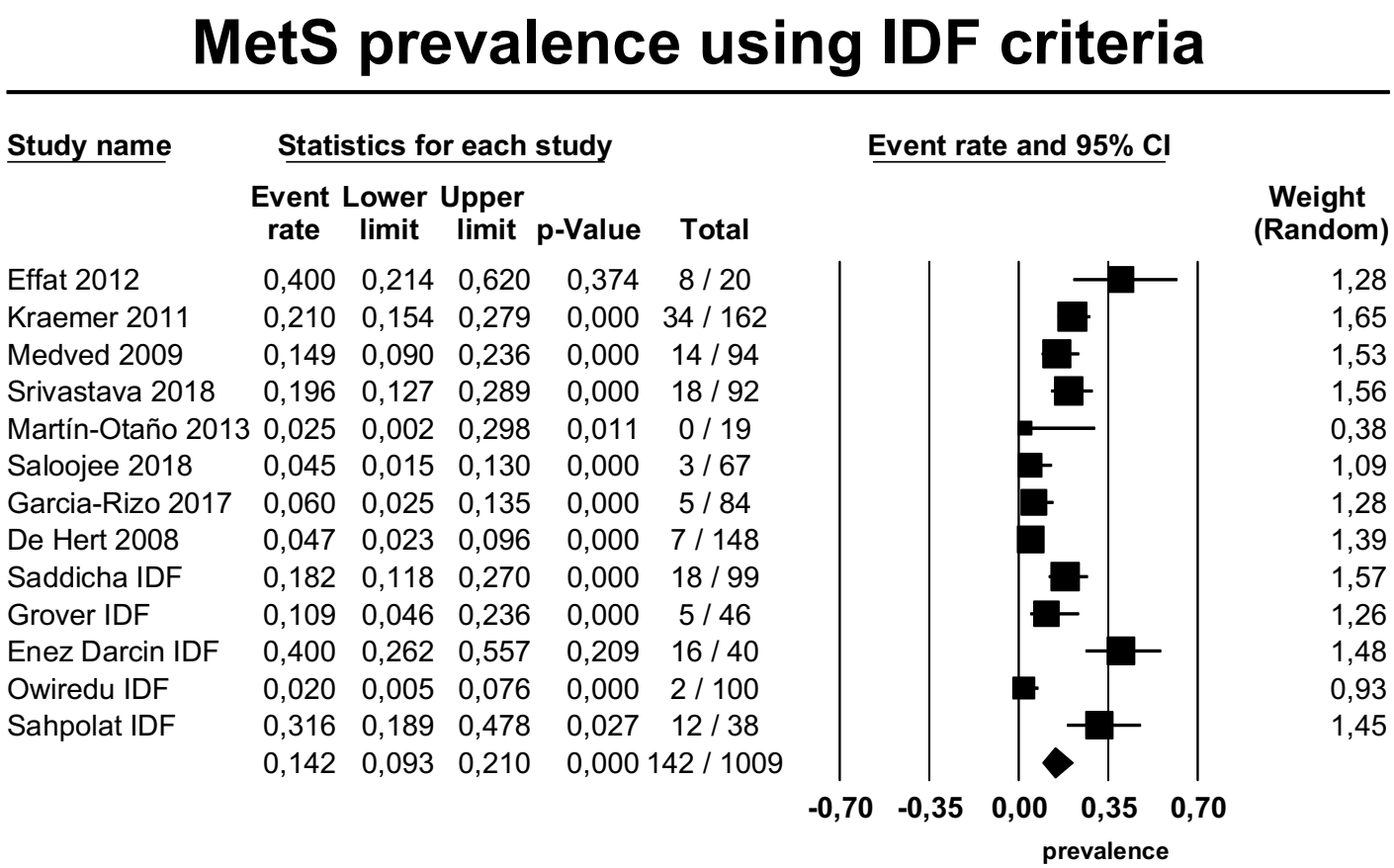

Figure S10. Overall MetS prevalence according to IDF criteria

Figure S11. Studies that reported both ATP-III and IDF criteria: Forest plot showing meta-analysis with ATP-III criteria

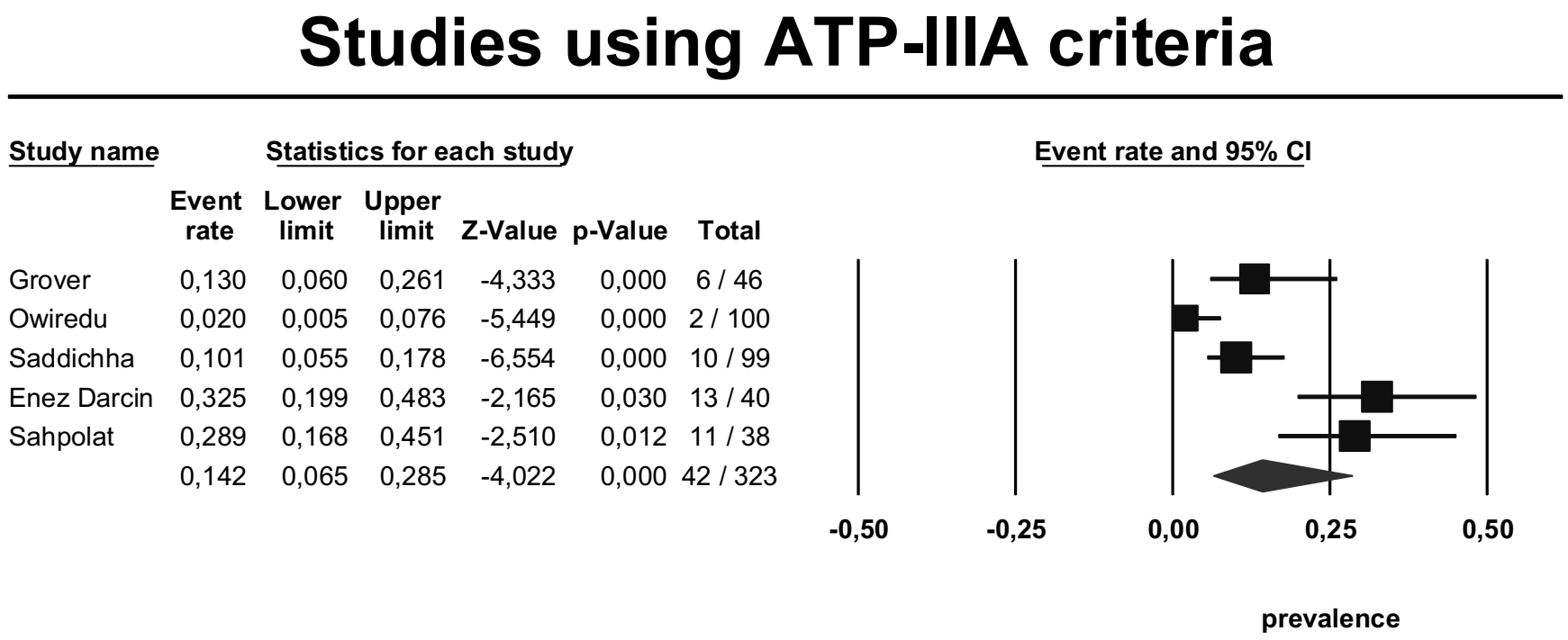

Figure S11. Studies thath reported both ATP-IIIA criteria and IDF criteria. Forest plot showing meta-analysis with ATP-IIIA cr

Figure S12. Studies that reported both ATP-III and IDF criteria: Forest plot showing meta-analysis with IDF criteria. (same studies than S11)

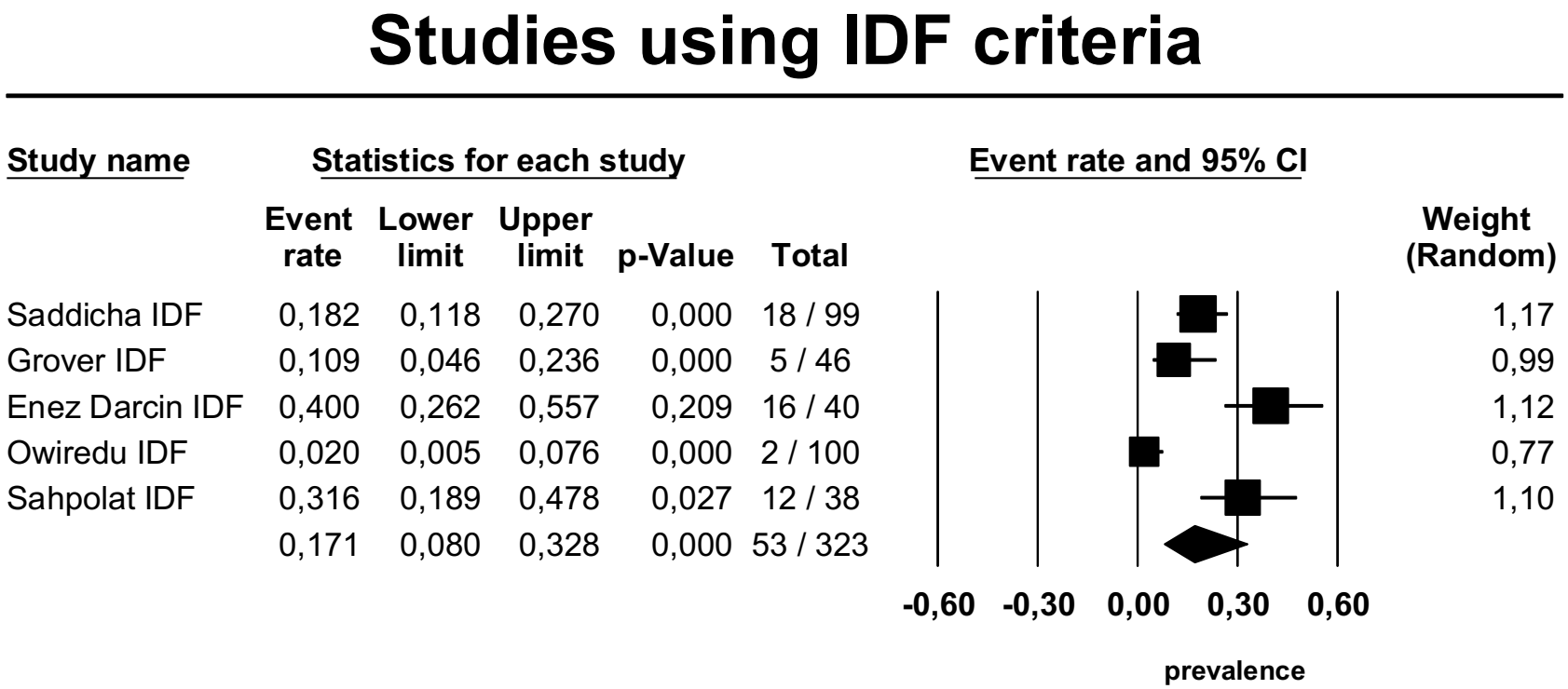

Figure S12. Studies that reported both ATP-IIIA and IDF criteria: forest plot showing MetS prevalence with IDF criteria

Figure S13. Forest plot showing studies that reported MetS prevalence in men

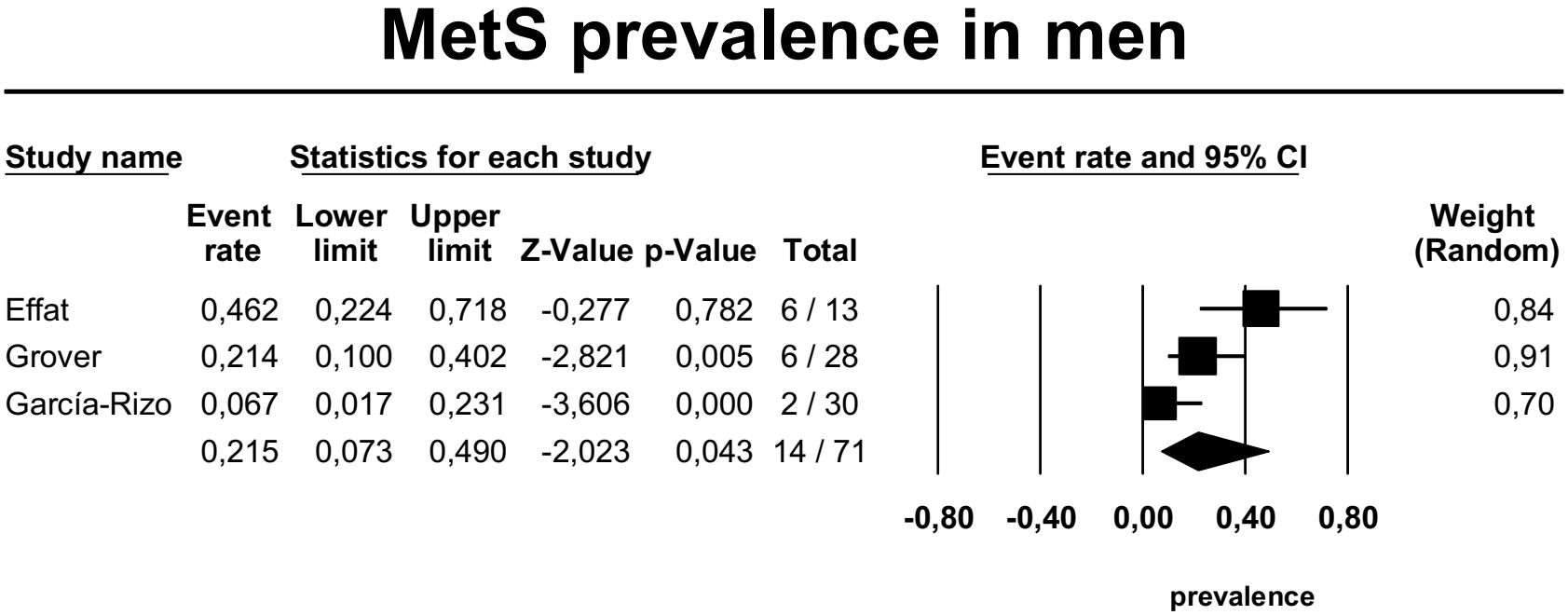

Figure S13. Forest plot showing studies that reported MetS prevalence in naïve men with FEP

Figure S14. Forest plot showing studies that reported MetS prevalence in women

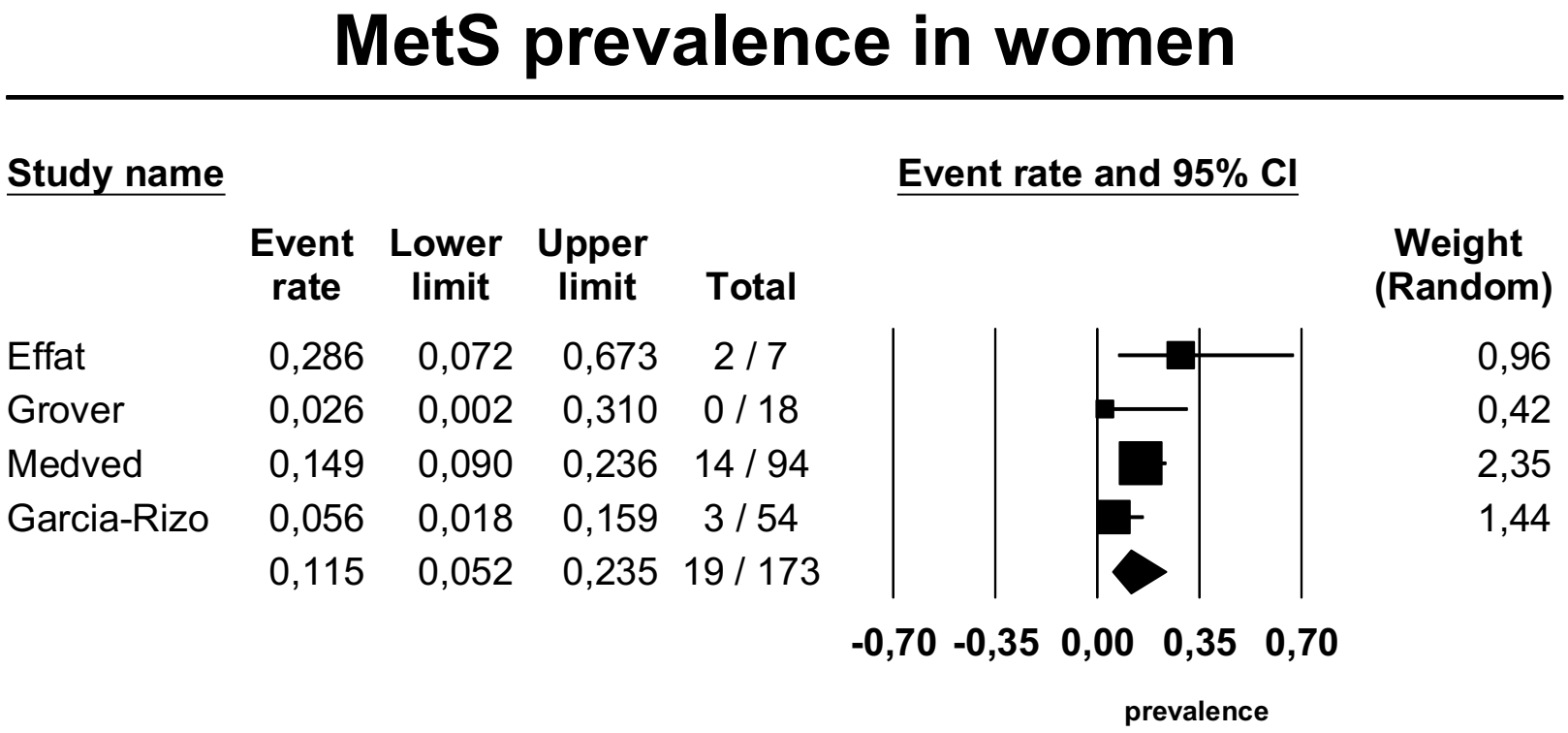

Figure S14. Forest plot showing studies that reported MetS prevalence in women with FEP

Quality Assessment procedures

Table S13. Quality Assessment Procedures

Author	Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Chiliza	2015	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Effat	2012	No	No	No	Yes	Yes	Yes	Yes	Yes	No	No
Grover	2011	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kraemer	2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Medved	2008	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Owiredu	2012	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pallava	2011	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Srivastava	2018	Yes	Yes	No	No	No	Yes	Yes	No	No	No
Otaño Martín	2012	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No
Saddichha	2008	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Saloojee	2017	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No
García-Rizo	2017	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fleischhacker	2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
De Hert	2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Srihari	2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Correll	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Enez Darcin	2015	Yes	Yes	No	Yes	Yes	No	No	Yes	No	No
Sahpolat	2020	Yes	Yes	No	Yes	Yes	No	No	Yes	No	No

The quality assessment was carried out by two independent reviewers (NGT and AR) using JBI appraisal for cohorts and also the version for prevalence studies. Those papers over which there was disagreement were discussed at a project group meeting.

JBI (cross sectional)

- Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and incidence data. Int J Evid Based Healthc. 2015;13(3):147–153.

JBI (cohorts)

- Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk . In: Aromataris E, Munn Z (Editors). JBI. Manual for Evidence Synthesis. JBI, 2020. Available from https://synthesismanual.jbi.global

Note: This scale has been adapted from the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data. The individual components listed below are summed to generate a total Methodological Quality score for each study. Total scores range from 0 to 10. For the total score grouping, studies were judged to be of low risk of bias (≥7 points), moderate risk of bias (4-6 points) and high risk of bias (<4 points).

1) **Was the sample representative of the target population?**
   a) Yes*
   b) No
   c) Unclear/no description
   d) Not applicable

2) **Were study participants recruited in an appropriate way?**
   a) Yes*
   b) No
   c) Unclear/no description
   d) Not applicable

3) **Was the sample size adequate?**
   a) Yes*
   b) No
   c) Unclear/no description
   d) Not applicable

4) **Were the study subjects and the setting described in detail?**
   a) Yes*
   b) No
   c) Unclear/no description
   d) Not applicable

5) **Was the data analysis conducted with sufficient coverage of the identified sample?**
   a) Yes*
   b) No
   c) Unclear/no description
   d) Not applicable

6) **Were the objective, standard criteria used for the measurement of the condition?**
   a) Yes*
   b) No
   c) Unclear/no description
   d) Not applicable

7) **Was the condition measured reliably?**
   a) Yes*
   b) No
   c) Unclear/no description
   d) Not applicable

8) **Was there an appropriate reporting of statistical analysis?**
   a) Yes*
   b) No
   c) Unclear/no description
   d) Not applicable

9) **Are all important confounding factors, subgroups, or potential differences identified and accounted for?**

a) Yes*
b) No

c) Unclear/no description

d) Not applicable

10) **Were subpopulations identified using objective criteria?**
a) Yes*
b) No

c) Unclear/no description

d) Not applicable

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. Schizophrenia research, 2022 *246*, 277–285 IF JCR 2022 4.662 (Q2)

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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.

References

Aas, M., Dieset, I., Hope, S., Hoseth, E., Mørch, R., Reponen, E., Steen, N.E., Laskemoen, J.F., Ueland, T., Aukrust, P., Agartz, I., Andreassen, O.A., Melle, I., 2017. Childhood maltreatment severity is associated with elevated C-reactive protein and body mass index in adults with schizophrenia and bipolar diagnoses. Brain Behav. Immun. 65, 342–349. https://doi.org/10.1016/j.bbi.2017.06.005.

Alameda, L., Levier, A., Gholam-Rezaee, M., Golay, P., Vandenberghe, F., Delacretaz, A., Baumann, P., Glatard, A., Dubath, C., Herane-Vives, A., Rodriguez, V., Solida, A., Do, K.Q., Eap, C.B., Conus, P., 2020. Psychological trauma occurring during adolescence is associated with an increased risk of greater waist circumference in early psychosis patients treated with psychotropic medication. PLoS One 15 (12), e0242569. https://doi.org/10.1371/journal.pone.0242569.

Alberti, K.G.M.M., Eckel, R.H., Grundy, S.M., Zimmet, P.Z., Cleeman, J.I., Donato, K.A., Fruchart, J.-C., James, W.P.T., Loria, C.M., Smith, S.C.J., 2009. 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 120 (16), 1640–1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644.

Allard-Ratick, M.P., Kindya, B.R., Khambhati, J., Engels, M.C., Sandesara, P.B., Rosenson, R.S., Sperling, L.S., 2021. HDL: fact, fiction, or function? HDL cholesterol and cardiovascular risk. Eur. J. Prev. Cardiol. 28 (2), 166–173. https://doi.org/10.1177/2047487319848214. Apr 10. Epub 2019 May 13. PMID: 33838035.

Ayesa-Arriola, R., Perez-Iglesias, R., Rodriguez-Sanchez, J.M., Mata, I., Gomez-Ruiz, E., Garcia-Unzueta, M., Martinez-Garcia, O., Tabares-Seisdedos, R., Vazquez-Barquero, J.L., Crespo-Facorro, B., 2012. Homocysteine and cognition in first-episode psychosis patients. Eur. Arch. Psychiatry Clin. Neurosci. 262 (7), 557–564. https://doi.org/10.1007/s00406-012-0302-2.

Bener, A., Al-Hamaq, A.O.A.A., Dafeeah, E.E., 2014. A two fold risk of metabolic syndrome in a sample of patients with schizophrenia: do consanguinity and family

history increase risk? Diabetes Metab. Syndr. 8 (1), 24–29. https://doi.org/10.1016/j.dsx.2013.10.003.
Canal-Rivero, M., Ruiz-Veguilla, M., Labad, J., Ayesa-Arriola, R., Vazquez-Bourgon, J., Mayoral-van Son, J., Setien-Suero, E., Ortiz-Garcia de la Foz, V., Crespo-Facorro, B., 2020. Predictors of weight acquisition induced by antipsychotic treatment and its relationship with age in a sample of first episode non-affective psychosis patients: a three-year follow-up study. Schizophr. Res. 222, 462–464. https://doi.org/10.1016/j.schres.2020.06.011.
Chiliza, B., Asmal, L., Oosthuizen, P., van Niekerk, E., Erasmus, R., Kidd, M., Malhotra, A., Emsley, R., 2015. Changes in body mass and metabolic profiles in patients with first-episode schizophrenia treated for 12 months with a first-generation antipsychotic. Eur. Psychiatry 30 (2), 277–283. https://doi.org/10.1016/j.eurpsy.2014.11.013 cmedm.
Cho, J.H., Rhee, E.J., Park, S.E., Kwon, H., Jung, J.H., Han, K.D., Park, Y.G., Park, H.S., Kim, Y.H., Yoo, S.J., Lee, W.Y., 2019. The risk of myocardial infarction and ischemic stroke according to waist circumference in 21,749,261 Korean adults: a nationwide population-based study. Diabetes Metab. J. 43 (2), 206–221. https://doi.org/10.4093/dmj.2018.0039.
Correll, C.U., Robinson, D.G., Schooler, N.R., Brunette, M.F., Mueser, K.T., Rosenheck, R. A., Marcy, P., Addington, J., Estroff, S.E., Robinson, J., Penn, D.L., Azrin, S., Goldstein, A., Severe, J., Heinssen, R., Kane, J.M., 2014. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. JAMA Psychiatry 71 (12), 1350–1363. https://doi.org/10.1001/jamapsychiatry.2014.1314.
Correll, C.U., Solmi, M., Veronese, N., Bortolato, B., Rosson, S., Santonastaso, P., Thapa-Chhetri, N., Fornaro, M., Gallicchio, D., Collantoni, E., Pigato, G., Favaro, A., Monaco, F., Kohler, C., Vancampfort, D., Ward, P.B., Gaughran, F., Carvalho, A.F., Stubbs, B., 2017. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry 16 (2), 163–180. https://doi.org/10.1002/wps.20420.
Coustals, N., Martelli, C., Brunet-Lecomte, M., Petillion, A., Romeo, B., Benyamina, A., 2020. Chronic smoking and cognition in patients with schizophrenia: a meta-analysis. Schizophr. Res. 222, 113–121. https://doi.org/10.1016/j.schres.2020.03.071.
De Hert, M., Schreurs, V., Sweers, K., Van Eyck, D., Hanssens, L., Sinko, S., Wampers, M., Scheen, A., Peuskens, J., van Winkel, R., 2008. Typical and atypical antipsychotics differentially affect long-term incidence rates of the metabolic syndrome in first-episode patients with schizophrenia: a retrospective chart review. Schizophr. Res. 101 (1–3), 295–303. https://doi.org/10.1016/j.schres.2008.01.028.
Dickerson, F., Origoni, A., Schroeder, J., Adamos, M., Katsafanas, E., Khushalani, S., Savage, C.L.G., Schweinfurth, L.A.B., Stallings, C., Sweeney, K., Yolken, R., 2018. Natural cause mortality in persons with serious mental illness. Acta Psychiatr. Scand. 137 (5), 371–379. https://doi.org/10.1111/acps.12880.
Eckel, R.H., Grundy, S.M., Zimmet, P.Z., 2005. The metabolic syndrome. Lancet (London, England) 365 (9468), 1415–1428. https://doi.org/10.1016/S0140-6736(05)66378-7.
Effat, S., et al., 2012. Metabolic syndrome in a sample of drug-naive egyptian patients with psychotic disorders. Int. J. Neuropsychopharmacol. 15, 48.
Enez Darcin, A., Yalcin Cavus, S., Dilbaz, N., Kaya, H., Dogan, E., 2015a. Metabolic syndrome in drug-naïve and drug-free patients with schizophrenia and in their siblings. Schizophr. Res. 166 (1–3), 201–206. https://doi.org/10.1016/j.schres.2015.05.004.
Enez Darcin, A., Yalcin Cavus, S., Dilbaz, N., Kaya, H., Dogan, E., 2015b. Metabolic syndrome in drug-naïve and drug-free patients with schizophrenia and in their siblings. Schizophr. Res. 166 (1–3), 201–206. https://doi.org/10.1016/j.schres.2015.05.004.
Fernandes, B.S., Steiner, J., Bernstein, H.-G., Dodd, S., Pasco, J.A., Dean, O.M., Nardin, P., Gonçalves, C.-A., Berk, M., 2016. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. Mol. Psychiatry 21 (4), 554–564. https://doi.org/10.1038/mp.2015.87.
Fernandez-Egea, E., Bernardo, M., Donner, T., Conget, I., Parellada, E., Justicia, A., Esmatjes, E., Garcia-Rizo, C., Kirkpatrick, B., 2009. Metabolic profile of antipsychotic-naive individuals with non-affective psychosis. Br. J. Psychiatry 194 (5), 434–438. https://doi.org/10.1192/bjp.bp.108.052605. May. PMID: 19407273; PMCID: PMC2703813.
First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. SCID-I/P, New York.
Fleischhacker, W.W., Siu, C.O., Bodén, R., Pappadopulos, E., Karayal, O.N., Kahn, R.S., EUFEST study group, 2013. Metabolic risk factors in first-episode schizophrenia: baseline prevalence and course analysed from the European First-Episode Schizophrenia Trial. Int. J. Neuropsychopharmacol. 16 (5), 987–995. https://doi.org/10.1017/S1461145712001241.
Garcia-Rizo, C., Fernandez-Egea, E., Oliveira, C., Meseguer, A., Cabrera, B., Mezquida, G., Kirkpatrick, B., 2017. Metabolic syndrome or glucose challenge in first episode of psychosis? Eur. Psychiatry 41 (1), 42–46. https://doi.org/10.1016/j.eurpsy.2016.10.001.
Garrido-Torres, N., Rocha-Gonzalez, I., Alameda, L., Rodriguez-Gangoso, A., Vilches, A., Canal-Rivero, M., Crespo-Facorro, B., Ruiz-Veguilla, M., 2021. Metabolic syndrome in antipsychotic-naive patients with first-episode psychosis: a systematic review and meta-analysis. Psychol. Med. 1–14 https://doi.org/10.1017/S0033291721002853.
Grover, S., Nebhinani, N., Chakrabarti, S., Parakh, P., Ghormode, D., 2012. Metabolic syndrome in antipsychotic naïve patients diagnosed with schizophrenia. Early Interv. Psychiatry 6 (3), 326–331. https://doi.org/10.1111/j.1751-7893.2011.00321.x cmedm.
Grundy, S.M., Cleeman, J.I., Daniels, S.R., Donato, K.A., Eckel, R.H., Franklin, B.A., Gordon, D.J., Krauss, R.M., Savage, P.J., Smith, S.C.J., Spertus, J.A., Costa, F., 2005. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation 112 (17), 2735–2752. https://doi.org/10.1161/CIRCULATIONAHA.105.169404.
Hagstrom, E., Roe, M.T., Hafley, G., Neely, M.L., Sidhu, M.S., Winters, K.J., Prabhakaran, D., White, H.D., Armstrong, P.W., Fox, K.A.A., Ohman, E.M., Boden, W.E., 2016. Association between very low levels of high-density lipoprotein cholesterol and long-term outcomes of patients with acute coronary syndrome treated without revascularization: insights from the TRILOGY ACS trial. Clin. Cardiol. 39 (6), 329–337. https://doi.org/10.1002/clc.22533.
Huang, P.L., 2009. A comprehensive definition for metabolic syndrome. Dis. Model. Mech. 2 (5–6), 231–237. https://doi.org/10.1242/dmm.001180.
Huang, M.-C., Lu, M.-L., Tsai, C.-J., Chen, P.-Y., Chiu, C.-C., Jian, D.-L., Lin, K.-M., Chen, C.-H., 2009. Prevalence of metabolic syndrome among patients with schizophrenia or schizoaffective disorder in Taiwan. Acta Psychiatr. Scand. 120 (4), 274–280. https://doi.org/10.1111/j.1600-0447.2009.01401.x.
Hukic, D.S., Ösby, U., Olsson, E., Hilding, A., Östenson, C.G., Gu, H.F., Ehrenborg, E., Edman, G., Schalling, M., Lavebratt, C., Frisén, L., 2017. Genetic variants of increased waist circumference in psychosis. Psychiatr. Genet. 27 (6), 210–218. https://doi.org/10.1097/YPG.0000000000000181. Dec. PMID: 28737528; PMCID: PMC5662154.
Jakobsen, A.S., Speyer, H., Norgaard, H.C.B., Karlsen, M., Hjorthoj, C., Krogh, J., Mors, O., Nordentoft, M., Toft, U., 2018. Dietary patterns and physical activity in people with schizophrenia and increased waist circumference. Schizophr. Res. 199, 109–115. https://doi.org/10.1016/j.schres.2018.03.016.
Jensen, K.G., Correll, C.U., Rudå, D., Klauber, D.G., Stentebjerg-Olesen, M., Fagerlund, B., Jepsen, J.R.M., Fink-Jensen, A., Pagsberg, A.K., 2017. Pretreatment cardiometabolic status in youth with early-onset psychosis: baseline results from the TEA trial. J. Clin. Psychiatry 78 (8), e1035–e1046. https://doi.org/10.4088/JCP.15m10479. Sep/Oct. PMID: 28102978.
Kahn, R., Buse, J., Ferrannini, E., Stern, M., 2005. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 28 (9), 2289–2304. https://doi.org/10.2337/diacare.28.9.2289.
Kirkpatrick, B., Miller, B., García-Rizo, C., Fernandez-Egea, E., 2014. Schizophrenia: a systemic disorder. Clin. Schizophr. Relat. Psychoses 8 (2), 73–79. https://doi.org/10.3371/CSRP.KIMI.031513.
Kraal, A.Z., Ward, K.M., Ellingrod, V.L., 2017. Sex differences in antipsychotic related metabolic functioning in schizophrenia spectrum disorders. Psychopharmacol. Bull. 47 (2), 8–21.
Kraemer, S., Minarzyk, A., Forst, T., Kopf, D., Hundemer, H.-P., 2011. Prevalence of metabolic syndrome in patients with schizophrenia, and metabolic changes after 3 months of treatment with antipsychotics—results from a german observational study. BMC Psychiatry 11, 173. https://doi.org/10.1186/1471-244X-11-173.
Lauritsen, J., Bruss, M., 2004. A Comprehensive Tool for Validated Entry and Documentation of Data. The EpiData Association.
Laursen, T.M., Munk-Olsen, T., Vestergaard, M., 2012. Life expectancy and cardiovascular mortality in persons with schizophrenia. Curr. Opin. Psychiatry 25 (2), 83–88. https://doi.org/10.1097/YCO.0b013e32835035ca.
Mackin, P., Waton, T., Watkinson, H.M., Gallagher, P., 2012. A four-year naturalistic prospective study of cardiometabolic disease in antipsychotic-treated patients. Eur. Psychiatry 27, 50–55.
Martín Otaño, L., Barbadillo Izquierdo, L., Galdeano Mondragón, A., Alonso Pinedo, M., Querejeta Ayerdi, I., 2013. After six months of anti-psychotic treatment: is the improvement in mental health at the expense of physical health? Revista de psiquiatria y salud mental 6 (1), 26–32. https://doi.org/10.1016/j.rpsm.2012.04.001 cmedm.
Marz, W., Kleber, M.E., Scharnagl, H., Speer, T., Zewinger, S., Ritsch, A., Parhofer, K.G., von Eckardstein, A., Landmesser, U., Laufs, U., 2017. HDL cholesterol: reappraisal of its clinical relevance. Clin. Res. Cardiol. 106 (9), 663–675. https://doi.org/10.1007/s00392-017-1106-1.
Medved, V., Kuzman, M.R., Jovanovic, N., Grubisin, J., Kuzman, T., 2009. Metabolic syndrome in female patients with schizophrenia treated with second generation antipsychotics: a 3-month follow-up. J. Psychopharmacol. 23 (8), 915.
Misiak, B., Frydecka, D., Slezak, R., Piotrowski, P., Kiejna, A., 2014. Elevated homocysteine level in first-episode schizophrenia patients—the relevance of family history of schizophrenia and lifetime diagnosis of cannabis abuse. Metab. Brain Dis. 29 (3), 661–670. https://doi.org/10.1007/s11011-014-9534-3.
Misiak, B., Stanczykiewicz, B., Laczmanski, L., Frydecka, D., 2017. Lipid profile disturbances in antipsychotic-naive patients with first-episode non-affective psychosis: a systematic review and meta-analysis. Schizophr. Res. 190, 18–27. https://doi.org/10.1016/j.schres.2017.03.031.
Misiak, B., Bartoli, F., Stramecki, F., Samochowiec, J., Lis, M., Kasznia, J., Jarosz, K., Stańczykiewicz, B., 2019. Appetite regulating hormones in first-episode psychosis: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 102, 362–370. https://doi.org/10.1016/j.neubiorev.2019.05.018.
Mitchell, A.J., Vancampfort, D., De Herdt, A., Yu, W., De Hert, M., 2013. 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. 39 (2), 295–305. https://doi.org/10.1093/schbul/sbs082.
Mitchell, A.J., Vancampfort, D., Sweers, K., van Winkel, R., Yu, W., De Hert, M., 2013. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders—a systematic review and meta-analysis. Schizophr. Bull. 39 (2), 306–318. https://doi.org/10.1093/schbul/sbr148. PubMed.

Moore, J.X., Chaudhary, N., Akinyemiju, T., 2017. Metabolic syndrome prevalence by Race/Ethnicity and sex in the United States, National Health and nutrition examination survey, 1988–2012. Prev. Chronic Dis. 14, E24. https://doi.org/10.5888/pcd14.160287.

Osborn, D.P.J., Hardoon, S., Omar, R.Z., Holt, R.I.G., King, M., Larsen, J., Marston, L., Morris, R.W., Nazareth, I., Walters, K., Petersen, I., 2015. Cardiovascular risk prediction models for people with severe mental illness: results from the prediction and management of cardiovascular risk in people with severe mental illnesses (PRIMROSE) research program. JAMA Psychiatry 72 (2), 143–151. https://doi.org/10.1001/jamapsychiatry.2014.2133.

Osby, U., Olsson, E., Edman, G., Hilding, A., Eriksson, S.V., Ostenson, C.G., 2014. Psychotic disorder is an independent risk factor for increased fasting glucose and waist circumference. Nordic J Psychiatry 68 (4), 251.

Owiredu, W.K.B.A., Osei, O., Amidu, N., Appiah-Poku, J., Osei, Y., 2012. Prevalence of metabolic syndrome among Psychiatric Patients in the Kumasi Metropolis, Ghana. En J. Med. Biomed. Sci. 1 (2), 38.

Pallava, A., Chadda, R.K., Sood, M., Lakshmy, R., 2012. Metabolic syndrome in schizophrenia: a comparative study of antipsychotic-free/naïve and antipsychotic-treated patients from India. Nordic J. Psychiatry 66 (3), 215–221. https://doi.org/10.3109/08039488.2011.621977.

Pelayo-Terán, J.M., Pérez-Iglesias, R., Ramírez-Bonilla, M., González-Blanch, C., Martínez-García, O., Pardo-García, G., Rodríguez-Sánchez, J.M., Roiz-Santiáñez, R., Tordesillas-Gutiérrez, D., Mata, I., Vázquez-Barquero, J.L., Crespo-Facorro, B., 2008. Epidemiological factors associated with treated incidence of first-episode non-affective psychosis in Cantabria: insights from the Clinical Programme on Early Phases of Psychosis. Early Interv. Psychiatry 2 (3), 178–187. https://doi.org/10.1111/j.1751-7893.2008.00074.x. Aug. PMID: 21352151.

Perez-Pinar, M., Mathur, R., Foguet, Q., Ayis, S., Robson, J., Ayerbe, L., 2016. Cardiovascular risk factors among patients with schizophrenia, bipolar, depressive, anxiety, and personality disorders. Eur. Psychiatry 35, 8–15. https://doi.org/10.1016/j.eurpsy.2016.02.004.

Perry, B.I., Singh, S.P., 2018. Letter to the editor: Lipid profile disturbances in antipsychotic-naive patients with first-episode non-affective psychosis. Schizophr. Res. 192, 461–462. https://doi.org/10.1016/j.schres.2017.03.046.

Perry, B.I., McIntosh, G., Weich, S., Singh, S., Rees, K., 2016. The association between first-episode psychosis and abnormal glycaemic control: systematic review and meta-analysis. Lancet Psychiatry 3 (11), 1049–1058. https://doi.org/10.1016/S2215-0366(16)30262-0.

Perry, B.I., Upthegrove, R., Crawford, O., Jang, S., Lau, E., McGill, I., Carver, E., Jones, P. B., Khandaker, G.M., 2020. Cardiometabolic risk prediction algorithms for young people with psychosis: a systematic review and exploratory analysis. Acta Psychiatr. Scand. 142 (3), 215–232. https://doi.org/10.1111/acps.13212.

Pillinger, T., Beck, K., Gobjila, C., Donocik, J.G., Jauhar, S., Howes, O.D., 2017. Impaired glucose homeostasis in first-episode schizophrenia: a systematic review and meta-analysis. JAMA Psychiatry 74 (3), 261–269. https://doi.org/10.1001/jamapsychiatry.2016.3803.

Pillinger, T., Beck, K., Stubbs, B., Howes, O.D., 2017. Cholesterol and triiglyceride levels first-episode psychosis systematic review and meta analysis. Br. J. Psychiatry 211 (6), 339.

Pillinger, T., Beck, K., Stubbs, B., Howes, O., 2018. S19. Evidence of the lipid paradox in psychosis: a META-analysis of cholesterol and triglyceride levels in FIRST episode psychosis. Schizophr. Bull. 44 https://doi.org/10.1093/schbul/sby018.806 edsair.

Pillinger, T., D'Ambrosio, E., McCutcheon, R., Howes, O.D., 2019. Is psychosis a multisystem disorder? A meta-review of central nervous system, immune, cardiometabolic, and endocrine alterations in first-episode psychosis and perspective on potential models. Mol. Psychiatry 24 (6), 776–794. https://doi.org/10.1038/s41380-018-0058-9.

Sahpolat, M., Ari, M., 2020. Higher prevalence of metabolic syndrome and related factors in patients with first-episode psychosis and schizophrenia: a cross-sectional study in Turkey. Nordic J. Psychiatry 1–6. https://doi.org/10.1080/08039488.2020.1815080.

Saito, I., Yamagishi, K., Kokubo, Y., Yatsuya, H., Iso, H., Sawada, N., Inoue, M., Tsugane, S., 2017. Association of high-density lipoprotein cholesterol concentration with different types of stroke and coronary heart disease: the Japan public health center-based prospective (JPHC) study. Atherosclerosis 265, 147–154. https://doi.org/10.1016/j.atherosclerosis.2017.08.032.

Schaffer, A., Verdoia, M., Barbieri, L., Aprami, T.M., Suryapranata, H., Marino, P., Luca, G.D., 2014. High-density lipoproteins and coronary artery disease: a single-center cohort study. Angiology 65 (8), 696–702. https://doi.org/10.1177/0003319713502253.

Shih, C.-C., Shih, Y.-L., Chen, J.-Y., 2021. The association between homocysteine levels and cardiovascular disease risk among middle-aged and elderly adults in Taiwan. BMC Cardiovasc. Disord. 21 (1), 191. https://doi.org/10.1186/s12872-021-02000-x.

Srihari, V.H., Phutane, V.H., Ozkan, B., Chwastiak, L., Ratliff, J.C., Woods, S.W., Tek, C., 2013. Cardiovascular mortality in schizophrenia: defining a critical period for prevention. Schizophr. Res. 146 (1–3), 64–68. https://doi.org/10.1016/j.schres.2013.01.014.

Srivastava, S., Bhatia, M.S., Sharma, A., 2018. Comparative study of quality of life and metabolic syndrome in schizophrenia patients who are receiving treatment versus antipsychotic naïve, first episode patients from a tertiary care hospital. Asian J. Psychiatr. 31, 121–123. https://doi.org/10.1016/j.ajp.2018.02.009.

Steiner, J., Frodl, T., Schiltz, K., Dobrowolny, H., Jacobs, R., Fernandes, B.S., Guest, P.C., Meyer-Lotz, G., Borucki, K., Bahn, S., Bogerts, B., Falkai, P., Bernstein, H.-G., 2020. Innate immune cells and C-reactive protein in acute first-episode psychosis and schizophrenia: relationship to psychopathology and treatment. Schizophr. Bull. 46 (2), 363–373. https://doi.org/10.1093/schbul/sbz068.

Stiles, E., Alcover, K.C., Stiles, B., Oluwoye, O., McDonell, M.G., 2020. Cannabis use and metabolic syndrome among clients with first episode psychosis. Early Interv. Psychiatry. https://doi.org/10.1111/eip.13030.

Suetani, S., Honarparvar, F., Siskind, D., Hindley, G., Veronese, N., Vancampfort, D., Allen, L., Solmi, M., Lally, J., Gaughran, F., Stubbs, B., Pillinger, T., 2021. Increased rates of respiratory disease in schizophrenia: a systematic review and meta-analysis including 619,214 individuals with schizophrenia and 52,159,551 controls. Schizophr. Res. 237, 131–140. https://doi.org/10.1016/j.schres.2021.08.022.

Sugawara, N., Yasui-Furukori, >N., Yamazaki, M., Shimoda, K., Mori, T., Sugai, T., Matsuda, H., Suzuki, Y., Ozeki, Y., Okamoto, K., Sagae, T., Someya, T., 2020. Predictive utility of body mass index for metabolic syndrome among patients with schizophrenia in Japan. Neuropsychiatr. Dis. Treat. 16, 2229–2236. https://doi.org/10.2147/NDT.S269619. Sep 30. PMID: 33061393; PMCID: PMC7533264.

Tian, Y., Wang, D., Wei, G., Wang, J., Zhou, H., Xu, H., Dai, Q., Xiu, M., Chen, D., Wang, L., Zhang, X.Y., 2021. Prevalence of obesity and clinical and metabolic correlates in first- episode schizophrenia relative to healthy controls. Psychopharmacology 238 (3), 745–753. https://doi.org/10.1007/s00213-020-05727-1.

Tirupati, S., Chua, L.-E., 2007. Obesity and metabolic syndrome in a psychiatric rehabilitation service. Aust. N. Z. J. Psychiatry 41 (7), 606–610 cmedm.

Vancampfort, D., Stubbs, B., Mitchell, A.J., De Hert, M., Wampers, M., Ward, P.B., Rosenbaum, S., Correll, C.U., 2015. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. World Psychiatry 14 (3), 339–347. https://doi.org/10.1002/wps.20252.

Vazquez Bourgon, J., Perez-Iglesias, R., Ortiz-Garcia de la Foz, V., Crespo-Facorro, B., 2017. Long-term metabolic effect of second-generation antipsychotics in first episode of psychosis. Eur. P 41 (S), S388. https://doi.org/10.1016/j.eurpsy.2017.02.431.

Vazquez-Bourgon, J., Perez-Iglesias, R., Ortiz-Garcia de la Foz, V., Suarez Pinilla, P., Diaz Martinez, A., Crespo-Facorro, B., 2018. Long-term metabolic effects of aripiprazole, ziprasidone and quetiapine: a pragmatic clinical trial in drug-naive patients with a first-episode of non-affective psychosis. Psychopharmacology 235 (1), 245–255. https://doi.org/10.1007/s00213-017-4763-x.

Vazquez-Bourgon, J., Ortiz-Garcia de la Foz, V., Suarez-Pereira, I., Iruzubieta, P., Arias-Loste, M.T., Setien-Suero, E., Ayesa-Arriola, R., Gomez-Revuelta, M., Crespo, J., Crespo Facorro, B., 2019. Data regarding the effect of cannabis consumption on liver function in the prospective PAFIP cohort of first episode psychosis. Data in Brief 27, 104415. https://doi.org/10.1016/j.dib.2019.104415.

Vazquez-Bourgon, J., Setien-Suero, E., Pilar-Cuellar, F., Romero-Jimenez, R., Ortiz-Garcia de la Foz, V., Castro, E., Crespo-Facorro, B., 2019. Effect of cannabis on weight and metabolism in first-episode non-affective psychosis: Results from a three-year longitudinal study. Int. J. Neuropsychopharmacol. 33 (3), 284.

Vazquez-Bourgon, J., Ibanez Alario, M., Mayoral-van Son, J., Gomez Revuelta, M., Ayesa Arriola, R., Juncal Ruiz, M., Ortiz-Garcia de la Foz, V., Crespo Facorro, B., 2020. A 3-year prospective study on the metabolic effect of aripiprazole, quetiapine and ziprasidone: a pragmaticclinical trial in first episode psychosis patients. Eur. Neuropsychopharmacol. https://doi.org/10.1016/j.euroneuro.2020.08.009.

Vázquez-Bourgon, J., Mayoral-van Son, J., Gómez-Revuelta, M., Juncal-Ruiz, M., Ortiz-García de la Foz, V., Tordesillas-Gutiérrez, D., Ayesa-Arriola, R., Bioque, M., Crespo-Facorro, B., 2021. Treatment discontinuation impact on long-term (10-year) weight gain and lipid metabolism in first-episode psychosis: results from the PAFIP-10 cohort. Int. J. Neuropsychopharmacol. 24 (1), 1–7. https://doi.org/10.1093/ijnp/pyaa066. Jan 20. PMID: 32840607; PMCID: PMC7816683.

Vidot, D.C., Prado, G., Hlaing, W.M., Florez, H.J., Arheart, K.L., Messiah, S.E., 2016. Metabolic syndrome among marijuana users in the United States: an analysis of National Health and nutrition examination survey data. Am. J. Med. 129 (2), 173–179. https://doi.org/10.1016/j.amjmed.2015.10.019.

Walker, E.R., McGee, R.E., Druss, B.G., 2015. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry 72 (4), 334–341. https://doi.org/10.1001/jamapsychiatry.2014.2502.

Wei, C.W., Chen, Y.Q., Ma, M., Xiu, M.H., Zhang, X.Y., 2020. Sex differences in the association of body mass index with symptoms and cognitive deficits in chinese patients with chronic schizophrenia. Transl. Psychiatry 10 (1), 18. https://doi.org/10.1038/s41398-020-0717-x.

Zakiev, E., Feng, M., Sukhorukov, V., Kontush, A., 2017. HDL-targeting therapeutics: past, present and future. Curr. Pharm. Des. 23 (8), 1207–1215. https://doi.org/10.2174/1381612822666161027153140.

Zhang, Q., He, H., Bai, X., Jiang, L., Chen, W., Zeng, X., Li, Y., Teixeira, A.L., Dai, J., 2021. Unveiling the metabolic profile of first-episode drug-naive schizophrenia patients: baseline characteristics of a longitudinal study among Han Chinese. Front. Psychiatry 12, 702720. https://doi.org/10.3389/fpsyt.2021.702720.

Material suplementario

Table S1. Health risk behaviors and MetS

	FEP n = 303				Controls n = 156			
		CI 95%				CI 95%		
	OR	Lower	Upper	p	OR	Lower	Upper	p
MetS								
Cannabis	0.81	0.29	2.26	0.691	2.89	0.69	12.1	0.131
Tabacco	1.07	0.39	2.90	0.882	0.97	0.23	4.03	0.971
Cocaine	1.46	0.40	5.34	0.565	4.12	0.74	23.0	0.082
Alcohol	0.47	0.16	1.39	0.164	0.18	0.02	1.56	0.084
Glycemia								
Cannabis	0.74	0.27	2.03	0.553	2.89	0.69	12.14	0.131
Tabacco	0.45	0.17	120	0.103	0.568	0.131	2.465	0.441
Cocaine	1.36	0.37	4.93	0.635	1.61	0.18	14.27	0.662
Alcohol	0.43	0.15	1.26	0.119	0.45	0.88	2.30	0.236
Triglycerides								
Cannabis	0.50	0.19	1.32	1.601	2.44	0.89	6.69	0.075
Tabacco	0.99	0.40	2.44	0.993	2.11	0.75	5.96	0.148
Cocaine	1	0.28	3.53	1.003	6.25	1.78	21.8	0.002
Alcohol	0.53	0.21	1.345	0.173	1.13	0.42	3.05	0.799
Blood pressure								
Cannabis	1.30	0.78	2.18	0.306	1.09	0.20	5.84	0.929
Tabacco	1.09	0.64	1.83	0.748	0.72	0.15	3.33	0.673
Cocaine	2.04	1.01	4.10	0.046	1.90	0.21	17.3	0.560
Alcohol	1.36	0.81	2.26	0.233	1.92	0.41	8.90	0.395
WC								
Cannabis	0.29	0.13	0.66	0.002	0.86	0.32	2.13	0.708
Tabacco	0.75	0.39	1.43	0.389	1.25	0.55	2.81	0.589
Cocaine	0.45	0.13	1.56	0.202	0.78	0.16	3.73	0.756
Alcohol	0.40	0.20	0.83	0.121	0.30	0.11	0.78	0.011
HDL								
Cannabis	1.22	0.745	2.00	0.428	2.39	1.04	5.48	0.035
Tabacco	1.90	1.131	3.20	0.015	1.45	0.65	3.21	0.356
Cocaine	1.26	0.62	2.51	0.521	2.81	0.85	9.29	0.079
Alcohol	0.97	0.59	1.59	0.911	1.19	0.54	2.63	0.659

MetS, metabolyc síndrome. WC, waist circunference. HDL, high density lipoprotein. The revised National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria require at least three of the following components: (1) (waist circumference ≥95
(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

Table S2. Metabolic alterations adjusted by social and health risk behaviors

	B	standard error	Wald	gl	Sig.	OR	95% C.I. para EXP(B)	
							Inferior	Superior
MetS								
FEP	0.716	0.64	1.251	1	0.263	2.046	0.584	7.174
Sex	-1.45	0.608	5.692	1	0.017	0.235	0.071	0.772
Currently student status	0.057	0.649	0.008	1	0.929	1.059	0.297	3.778
Education level	0.197	0.517	0.144	1	0.704	1.217	0.442	3.355
Low family socioeconomic status	-0.338	0.516	0.43	1	0.512	0.713	0.26	1.959
Urban zone	-0.809	0.596	1.842	1	0.175	0.445	0.138	1.433
Single	-0.627	0.545	1.323	1	0.25	0.534	0.184	1.555
Unemployed	-0.502	0.5	1.008	1	0.315	0.605	0.227	1.613
Cannabis	0.151	0.615	0.06	1	0.806	1.163	0.348	3.884
Cocaine	-1.105	0.709	2.428	1	0.119	0.331	0.082	1.33
Alcohol	1.354	0.596	5.157	1	0.023	3.873	1.204	12.462
Tobacco	-0.286	0.536	0.286	1	0.593	0.751	0.263	2.146
Hypertension								
FEP	3.385	0.772	19.197	1	<.001	28.746	6.342	130.29
Sex	-1.404	0.339	17.11	1	<.001	0.246	0.126	0.478
Currently student status	0.275	0.361	0.579	1	0.447	1.317	0.648	2.674
Education level	0.096	0.305	0.1	1	0.752	1.101	0.605	2.004
Low family socioeconomic status	0.106	0.299	0.126	1	0.723	1.112	0.619	1.996
Urban zone	-0.161	0.308	0.273	1	0.601	0.851	0.465	1.558
Single	-0.632	0.338	3.501	1	0.061	0.531	0.274	1.03
Unemployed	0.318	0.302	1.11	1	0.292	1.374	0.761	2.481
Cannabis	0.261	0.37	0.496	1	0.481	1.298	0.628	2.681
Cocaine	-0.502	0.446	1.268	1	0.26	0.605	0.252	1.451
Alcohol	0.162	0.321	0.254	1	0.615	1.175	0.627	2.204
Tobacco	-0.107	0.323	0.11	1	0.74	0.898	0.477	1.691
Abdominal								
FEP	-0.591	0.369	2.562	1	0.026	2.418	1.112	4.464
Sex	0.44	0.345	1.632	1	0.043	1.553	0.79	3.053
Currently student status	-0.822	0.431	3.634	1	0.048	1.44	0.189	1.023
Education level	-0.057	0.32	0.032	1	0.859	0.945	0.504	1.769
Low family socioeconomic status	0.515	0.318	2.614	1	0.106	1.673	0.897	3.124
Urban zone	-0.306	0.325	0.885	1	0.347	0.737	0.39	1.392
Single	-0.379	0.325	1.356	1	0.244	0.685	0.362	1.295
Unemployed	-0.043	0.312	0.019	1	0.891	0.958	0.52	1.765
Cannabis	0.747	0.436	2.935	1	0.087	2.11	0.898	4.958
Cocaine	-0.212	0.605	0.122	1	0.726	0.809	0.247	2.65
Alcohol	0.283	0.364	0.606	1	0.436	1.327	0.651	2.707
Tobacco	-0.193	0.319	0.366	1	0.545	0.824	0.441	1.542

Tryglicerides								
FEP	0.026	0.503	0.003	1	0.959	0.721	0.323	2.186
Sex	-1.424	0.531	7.203	1	0.007	0.241	0.085	0.681
Currently student status	-1.453	0.782	3.452	1	0.063	0.234	0.051	1.083
Education level	0.157	0.44	0.127	1	0.722	1.17	0.494	2.771
Low family socioeconomic status	0.664	0.465	2.038	1	0.153	1.942	0.781	4.834
Urban zone	-0.043	0.449	0.009	1	0.924	0.958	0.397	2.31
Single	-0.191	0.461	0.172	1	0.678	0.826	0.335	2.038
Unemployed	-0.364	0.422	0.744	1	0.388	0.695	0.304	1.589
Cannabis	0.499	0.528	0.894	1	0.344	1.648	0.585	4.637
Cocaine	-0.596	0.652	0.838	1	0.36	0.551	0.154	1.975
Alcohol	0.911	0.501	3.307	1	0.069	2.487	0.932	6.638
Tobacco	-0.324	0.454	0.511	1	0.475	0.723	0.297	1.759
Glycaemia								
FEP	0.883	0.728	1.469	1	0.349	1.970	0.476	8.149
Sex	0.027	0.55	0.002	1	0.96	1.028	0.35	3.018
Currently student status	0.061	0.65	0.009	1	0.925	1.063	0.298	3.797
Education level	0.329	0.526	0.391	1	0.532	1.39	0.495	3.898
Low family socioeconomic status	-0.072	0.5	0.021	1	0.885	0.93	0.349	2.478
Urban zone	0.279	0.503	0.307	1	0.579	1.322	0.493	3.542
Single	-0.595	0.534	1.239	1	0.266	0.552	0.194	1.572
Unemployed	-0.97	0.514	3.569	1	0.059	0.379	0.139	1.037
Cannabis	-0.679	0.664	1.045	1	0.307	0.507	0.138	1.865
Cocaine	-1.36	0.802	2.876	1	0.09	0.257	0.053	1.236
Alcohol	1.223	0.655	3.484	1	0.062	3.398	0.941	12.275
Tobacco	1.067	0.573	3.467	1	0.063	2.908	0.945	8.944
HDL								
FEP	0.937	0.382	6.023	1	0.014	2.553	1.208	5.398
Sex	0.171	0.294	0.34	1	0.56	1.187	0.667	2.111
Currently student status	0.072	0.336	0.046	1	0.83	1.075	0.556	2.076
Education level	-0.385	0.271	2.027	1	0.155	0.68	0.4	1.156
Low family socioeconomic status	-0.407	0.269	2.298	1	0.13	0.666	0.393	1.127
Urban zone	-0.507	0.286	3.136	1	0.077	0.602	0.343	1.056
Single	-0.383	0.292	1.728	1	0.189	0.682	0.385	1.207
Unemployed	-0.252	0.263	0.919	1	0.338	0.777	0.464	1.301
Cannabis	-0.218	0.329	0.437	1	0.509	0.804	0.422	1.534
Cocaine	0.033	0.413	0.006	1	0.937	1.033	0.46	2.321
Alcohol	0.249	0.297	0.705	1	0.401	1.283	0.717	2.294
Tobacco	-0.75	0.286	6.87	1	0.009	0.472	0.269	0.828

MetS, metabolyc síndrome. WC, waist circunference. HDL, high density lipoprotein. The revised National Cholesterol Education Program (NCEP) Adult Treatment Panel III.

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ORIGINAL ARTICLE

Metabolic syndrome and related factors in a large sample of antipsychotic naïve patients with first-episode psychosis: 3 years follow-up results from the PAFIP cohort

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KEYWORDS
Metabolic syndrome;
First episode psychosis;
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Abstract
Background: Latest studies in patients with first episode psychosis (FEP) have shown alterations in cardiovascular, immune and endocrinological systems. These findings could indicate a systemic onset alteration in the metabolic disease as opposed to justifying these findings exclusively by antipsychotics' side effects and long-term lifestyle consequences. In any case, this population is considered at higher risk for developing cardiometabolic disorders than their age-matched peers.
Methods: This is a prospective longitudinal study. Metabolic syndrome (MetS) prevalence between 244 subjects with FEP and 166 controls at 3 years was compared. Additionally, we explored whether baseline differences in any of the MetS components according to Adult Treatment Panel III definition and prescribed antipsychotic could help to predict the MetS development at 3 years.

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Results: Patients with FEP present a similar baseline prevalence of MetS (*6.6% vs 5.4%, p = 0.320*), according to ATP-III criteria. but with a higher prevalence of metabolic alterations than controls before the start of antipsychotic treatment. At 3-years follow-up the MetS prevalence had increased from 6.6% to 18.3% in the FEP group, while only from 5.4% to 8.1% in the control group. The multivariate model showed that, before antipsychotic exposure, a baseline altered waist circumference WC *(OR = 1.1, p = 0.011),* triglycerides *(OR = 1.1, p = 0.043)* and high-density lipoprotein HDL *(OR = 0.9, p = 0.008)* significantly predicted the presence of MetS at 3-years. We propose a predictive model of MetS at 3 years in 244 drug-naïve FEP patients.
Conclusion: We found that altered WC, HDL and triglycerides at baseline predicted the presence of full MetS after 3-years of initiating antipsychotic treatment. Our findings support the need for interventions to improve factors related to the physical health of FEP individuals.

PALABRAS CLAVE
Síndrome metabólico;
Primer episodio psicótico;
Nunca tratados con antipsicóticos

Síndrome metabólico en pacientes con primer episodio de psicosis que nunca han tomado tratamiento antipsicótico: seguimiento a 3 años de la cohorte PAFIP

Resumen
Antecedentes: Recientes estudios han demostrado que existe una relación entre alteraciones cardiovasculares, inmunes y endocrinas y pacientes que presentan un primer episodio psicótico (FEP). Estos hallazgos podrían sugerir que las alteraciones metabólicas que se observan en los pacientes con psicosis podrían ser parte de un componente sistémico y no deberse exclusivamente al uso de antipsicóticos o a las consecuencias del estilo de vida a largo plazo. En cualquier caso, se considera que las personas que presentan un FEP tienen mayor riesgo de desarrollar trastornos cardiometabólicos que los sujetos de su misma edad.
Métodos: Se trata de un estudio longitudinal prospectivo. Se comparó la prevalencia basal del síndrome metabólico (MetS) entre 244 sujetos con FEP y 166 controles y después a los 3 años. Además, se exploró si las diferencias iniciales en cualquiera de los componentes del MetS según la definición del Adult Treatment Panel III y el antipsicótico prescrito podrían ayudar a predecir el desarrollo del MetS a los 3 años.
Resultados: Los pacientes con FEP presentan una prevalencia basal similar de MetS *(6,6% vs. 5,4%, p = 0,320)*, según criterios ATP-III, pero una mayor prevalencia de alteraciones en los parámetros metabólicos individuales que los controles antes del inicio del tratamiento antipsicótico. A los 3 años de seguimiento, la prevalencia de MetS había aumentado del *6,6% al 18,3%* en el grupo FEP, mientras que solo del *5,4% al 8,1%* en el grupo de control. El modelo multivariante demostró que la circunferencia de la cintura WC *(OR = 1,1, p = 0,011)*, los triglicéridos *(OR = 1,1, p = 0,043)* y las lipoproteínas de alta densidad HDL *(OR = 0,9, p = 0,008)* alteradas previamente al uso de antipsicóticos predicen significativamente la presencia de MetS a los 3 años. Proponemos un modelo predictivo de MetS a los 3 años en 244 pacientes con FEP que nunca han tomado tratamiento antipsicótico.
Conclusión: Encontramos que WC, HDL y triglicéridos alterados al inicio del estudio predijeron la presencia de MetS después de 3 años de iniciar el tratamiento antipsicótico. Nuestros hallazgos respaldan la necesidad de intervenciones para mejorar los factores relacionados con la salud física de las personas con FEP.

Introduction

Metabolic syndrome (MetS) is a series of metabolic abnormalities that together are considered risk factors for developing diabetes and cardiovascular disease. 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 $\geq 30\,kg/m^2$).[1,2] On the other hand, schizophrenia is a clinical syndrome characterized by psychotic symptoms and psychosocial deterioration that leads to a debilitating illness, with significant human and economic costs. Its etiology, still under study, combines genetic factors modulated by unknown environmental factors.[3–5] Both schizophrenia and cardiovascular diseases derived from MetS have a high impact on mortality and disability worldwide.[6–8] In recent decades, a differential gap has become evident between the mortality of patients with

schizophrenia and the rest of the population, with a reduced life expectancy of up to 20 years in psychosis patients.[9–11] Around 60% of the causes of death in these patients are due to cardiovascular diseases, which are in great part explained by the higher risk of presenting MetS.[8]

Atypical antipsychotics can cause weight gain and considerable changes in the metabolism, which can increase the risk of type II diabetes and increase circulating cholesterol levels.[12–14] Weight gain, metabolic and liver adverse effects are highly frequent effect of atypical antipsychotics, and severity varies widely among individuals and treatments.[15] After the first year of treatment 30%[16] of patients suffering from a first episode of psychosis (FEP) experienced a weight gain higher than 20%. Thus, the first months of exposure to antipsychotic treatment is a critical period for development of obesity and metabolic abnormalities.[12,13,17] However, contrary to what was traditionally postulated, recent studies have shown that this cannot be attributed solely to antipsychotic treatment.[14,18,19] Latest studies in patients with FEP have shown alterations in cardiovascular, immune and endocrinological systems. These new findings could indicate a systemic onset alteration in the metabolic disease as opposed to justifying these findings exclusively by antipsychotics' side effects and long-term lifestyle consequences, as had traditionally been done.[20]

In any case, this population is considered at higher risk for developing cardiometabolic disorders than their age-matched peers.[18] However, although the high prevalence of MetS in these patients is widely known, the available risk-prediction algorithms, validated in the general population, could underestimate the risk in young people with psychosis. This fact seems to be mainly related to the role that age plays in these algorithms.[21] Cardiometabolic risk prediction algorithms are also common in clinical practice, including only three of them psychiatric predictors: QRISK3,[22] QDiabetes[23] and PRIMROSE.[24] Despite of this, they all appear to underestimate cardiovascular risk in young adults with or at risk of developing psychosis. Therefore, recent meta-analyses[21,25] state that, at this point it is not useful to use the pre-established diagnostic parameters in the general population for the diagnosis of MetS in patients with a FEP.

Our objectives will be to compare the MetS prevalence between FEP and controls at 3 years, and to explore whether baseline differences in any of the MetS components could help to predict the MetS development at 3 years.

Material and methods

Study design and setting

This is a prospective longitudinal study. Data were obtained from a longitudinal intervention program of FEP called PAFIP NCT02305823 (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 (Santander, Spain).[26,27] 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.

Participants

From February 2001 to October 2018, all referrals to PAFIP were screened for patients who met the following criteria: (1) 16–60 years old; (2) living in the catchment area; (3) experiencing their FEP; (4) no previous antipsychotic exposure; and (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; and (3) having a diagnosis of drug dependence. The diagnoses were confirmed using the Structured Clinical Interview for DSM-IV,[28] carried out by an experienced psychiatrist 6 months on from the baseline visit. Our operational definition of a FEP 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 a 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.

Anthropometric and metabolic syndrome assessment

Clinical measures of weight, height, waist circumference (WC) were registered. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also taken. Blood samples were drawn after 8 h fasting for glucose and lipid profile testing. In the current study, the Adult Treatment Panel III (ATPIII)[29] was used to define MetS. At baseline assessment, all individuals were drug-naïve and had not been exposed to antipsychotic treatment.

Laboratory analysis

All biochemical determinations were performed in our hospital. All measurements were obtained after an overnight fast. Fasting state, as well as treatment compliance, were reported by patients and their family members. Glucose, HDL cholesterol, and triglycerides were measured by automated methods on a TechniconDax (Technicon Instruments Corp, Tarrytown NY USA), using the reagents supplied by Boehringer-Mannheim (Mannheim, Germany). Low density lipoprotein (LDL) cholesterol was determined by the Friedewald et al. calculation[30]: LDL = total cholesterol − (HDL + [triglycerides/5]).

Statistics

Sample size

Sample size was calculated based on the reported data about MetS prevalence in patients with FEP 13.8% vs healthy controls 7%.[18] According to the parameter choices for a desired power of 0.90 and 95% confidence level we estimated that we would need 216 participants distributed over 108 cases

and 108 healthy controls. Sample size analysis was conducted using Epidata software.[31]

Data analysis

Data were analyzed using the Statistical Package for Social Sciences (IBM SPSS. Version 27.0. Armonk. NY: IBM Corp). For comparison between FEP and control groups of demographic characteristics, MetS and individual metabolic component, chi-square tests for categorical variables, *t*-student for independent samples or the Mann–Whitney test for continuous variables were used. A significance level of $p < 0.05$ (two-tailed) was applied. For the analysis of the baseline and follow up data at 3 years, *t*-student for paired samples or Wilcoxon test for quantitative measures and McNemar test for paired nominal data were used. Regression analyses using multivariate analysis controlling for age, sex, and type of antipsychotic drug (risperidone, ziprasidone, quetiapine vs. aripiprazole) were employed to examine the relationship between baseline metabolic values and MetS after 3 years. All metabolic alterations at 3 years (hyperglycemia, hypertriglyceridemia, altered WC, low HDL, high blood pressure) were investigated in separate models adjusted for sex, age and treatment.

For antipsychotic treatment comparison we followed an intention-to-treat approach and clustered the FEP patients into antipsychotic groups according to their prescribed antipsychotic at study entry: aripiprazole, risperidone, quetiapine and ziprasidone.

In the multivariate analysis we used an age younger than 30 years; women; and ziprasidone as reference population. The median age of the FEP group is 30 years. Relevant literature about MetS in general population[32] has reported that from 18 years to 70 years old, women have higher MetS prevalence than men. Although both aripiprazole and ziprasidone have been described as ''metabolically neutral'', recent head-to-head comparisons between antipsychotic groups have shown that ziprasidone presents even significantly smaller increments in weight and BMI than aripiprazole.[13,33]

Results

Demographic and treatment characteristics

The baseline sample consists of 244 cases of FEP and 166 controls; in FEP group the mean (SD) age was 32 years (10); median 30 years (23–39); 54% ($n = 117$) were men and 45.1% ($n = 96$) were women; and their ethnicity was mainly white (92%). The prescribed antipsychotics at study entry were aripiprazole ($n = 90$, 42.3%), risperidone ($n = 60$, 28.2%), ziprasidone ($n = 34$, 16.0%) and quetiapine ($n = 29$, 13.6%). In control group the mean (SD) age was 29.6 years (7.9); median 28.9 years (23–39); 62% ($n = 151$) were men and their ethnicity was largely white (99%).

Metabolic syndrome: baseline prevalence, 3 years follow-up and predictive analysis

Baseline MetS prevalence was similar between FEP and controls according to ATP-III and IDF criteria ATP-III (6.6% vs 5.4%, $p = 0.320$), IDF (5.3% vs 5.4), WHO (15.1% vs 8.8%) (Table S.1). However, the FEP group had a worse evolution compared to the control group; at 3 years the MetS prevalence had increased from 6.6% to 18.3% ($p = 0.001$) in the FEP group and from 5.4% to 8.1% ($p = 0.063$) in the control group (Tables 1 and 2). In the FEP group, the multivariate model, using the development of MetS at 3 years as a dependent variable and age, sex, prescribed antipsychotic at study entry and the numerical values of each of the individual components of MetS as covariates, showed that, before antipsychotic exposure, a baseline altered WC (OR = 1.1, $p = 0.011$), triglycerides (OR = 1.1, $p = 0.043$) and HDL (OR = 0.9, $p = 0.008$) significantly predicted the presence of MetS at 3-years. On the other hand, none of the 3 drugs included in the multivariate model (aripiprazole, risperidone, quetiapine) had a higher risk than the reference treatment (ziprasidone) of presenting MetS at 3 years. Age and sex were also not determining factors for developing MetS at 3 years (Table 3).

Comparison by specific metabolic components

Tables 1 and 2 provide data for mean values of WC, SBP, DBP, glucose, triglycerides and HDL, for both groups, at baseline and 3-years follow-up. We also observed differences between groups in the percentage of individuals in each group reaching some of the MetS criteria: low HDL (FEP 27% vs controls 17.5%, $p = 0.026$), high blood pressure (FEP 29.5% vs controls 4.8%, $p = 0.001$) and elevated WC (FEP 17.6% vs controls 29.5%, $p = 0.016$) (Table 1). Similarly, we observed, among the FEP group, a greater increment in the percentage of subjects reaching any of the individual MetS components.

Glucose

Individuals meeting the glucose criteria increased from 6.1% to 21.2% ($p = 0.001$) in the FEP group and from 4.8% to 8.1% ($p = 0.063$) in the control group (Table 2). In addition, the prevalence of hyperglycemia increased significantly more in the FEP group than in the control group at 3 years (FEP group 21.2% vs control group 8.1%, $p = 0.007$) (Table 1). Only in the FEP group did the mean value of glucose increase significantly at 3 years, from 86.36 mg/dL to 92.67 mg/dL ($p = 0.001$) (Table 2). The predictive model showed that being older than 30 years and having baseline glucose altered are factors for the development of hyperglycemia at 3 years (OR = 1.97, $p = 0.034$) (Table 3).

Lipids

The prevalence of altered HDL was higher among FEP patients than in controls at both time points (Table 2). Baseline HDL mean value was lower in the FEP group than in the control group (53.55 mg/dL vs 57.7 mg/dL, respectively; $p = 0.050$), and these differences remained at 3-years follow-up (51.71 mg/dL vs 58.30 mg/dL, respectively; $p < 0.001$). However, there were not significant differences in the average values of HDL within each group (Table 1). In the FEP group the predictive model showed that only having altered baseline HDL was risk factor for altered HDL at 3 years.

Table 1 Comparison of MetS prevalence and mean values of related components in FEP and control group.

	FEP patients *N* (%) *N* = 244	Control *N* (%) *N* = 166	Stats* *p*-Value
MetS prevalence**			
MetS baseline	16 (6.6)	9 (5.4)	0.324
Glucose ≥ 100 mg/dL	15 (6.1)	8 (4.8)	0.576
Blood pressure blood pressure ≥ 130/85 mmHg	72 (29.5)	7 (4.3)	<0.001
HDL ≤ 40 mg/dL in men and ≤50 mg/dL in women	66 (27)	29 (17.5)	0.026
Triglycerides ≥ 150 mg/dL	19 (7.8)	20 (12.1)	0.143
Waist circumference ≥ 102 cm in men and >88 cm in women	43 (17.6)	49 (29.5)	0.016
Body mass index over limits***	14 (5.7)	24 (14.4)	0.023
	N = 202	*N* = 86	Stats* *p*-Value
MetS 3 years	37 (18.3)	7 (8.1)	0.028
Glucose ≥ 100 mg/dL	43 (21.2)	7 (8.1)	0.007
Blood pressure blood pressure ≥ 130/85 mmHg	42 (20.7)	17 (20.5)	0.622
HDL ≤ 40 mg/dL in men and ≤ 50 mg/dL in women	51 (25.2)	10 (11.6)	0.006
Triglycerides ≥ 150 mg/dL	47 (23.2)	10 (11.6)	0.020
Waist circumference ≥ 102 cm in men and >88 cm in women	78 (38.6)	26 (30.6)	0.112
Body mass index over limits***	47 (23.2)	18 (19.8)	0.412

MetS components mean values	Mean (SD)	Mean (SD)	Stats* *p*-Value
Baseline			
Glucose (mg/dL)	86.36 (21.5)	84.49 (8.54)	0.205
Systolic blood pressure (mmHg)	119.08 (15.11)	106.14 (12.08)	0.001
Diastolic blood pressure (mmHg)	70.65 (11.61)	62.24 (8.77)	0.001
HDL (mg/dL)	53.55 (15.76)	57.71 (15.50)	0.050
Triglycerides (mg/dL)	85.27 (38.76)	86.6 (40.94)	0.141
Waist circumference (cm)	83.30 (12.16)	89.80 (13.51)	0.005
Body mass index (kg/m^2)	23.16 (4.26)	26.03(4.44)	0.001
3 years			
Glucose (mg/dL)	92.67 (16.65)	85.52 (15.11)	0.001
Systolic blood pressure (mmHg)	114.09 (14.94)	114.56 (13.66)	0.979
Diastolic blood pressure (mmHg)	70.67 (10.75)	70.42 (11.18)	0.851
HDL (mg/dL)	51.71 (13.93)	58.30 (15.18)	0.001
Triglycerides (mg/dL)	117.05 (72.96)	93.76 (56.73)	0.003
Waist circumference (cm)	90.67 (13.69)	88.56 (13.25)	0.227
Body mass index (kg/m^2)	26.60 (4.97)	26.27(4.51)	0.587

Abbreviations: FEP, First Episode Psychosis. SD, Standard deviation. HDL, High density lipoprotein.

* Statistics: chi squared and *t* student for independent samples or Mann–Whitney test were used. *p*-Value < 0.05 is significant.

** Mets prevalence and related components according to the Adult Treatment Panel III (ATP III): Glucose ≥ 100 mg/dL, blood pressure ≥ 130/85 mmHg, triglycerides ≥ 150 mg/dL, HDL ≤ 40 mg/dL in men and ≤50 mg/dL in women, waist circumference ≥ 102 cm in men and >88 cm in women.

*** Body mass index ≥ 30 kg/m^2.

With respect to triglycerides, the baseline prevalence of hypertriglyceridemia (≥150 mg/dL) was similar in both groups. However, at 3-years follow-up the prevalence was significantly greater in the FEP group than in the control group (23.3% vs 11.6%, respectively; $p = 0.020$). Triglycerides mean value significantly increased from 85.27 mg/dL to 117 mg/dL at 3 years in the FEP group ($p = 0.001$) while in the control group it remained similar (Table 2). In the FEP group the predictive model showed that being older than 30 years and having altered baseline tryglicerides were risks factor for the development of hypertriglyceridemia at 3 years (OR = 2.386, $p = 0.027$) (Table 3).

Blood pressure

The baseline prevalence of high blood pressure was significantly higher in the FEP group than in controls (29.5% vs 4.3%, $p < 0.001$). However, high blood pressure decreased significantly in FEP and increased significantly in control group, in consequence, we didn't find differences between FEP and controls at 3 years (Table 1). SBP mean value decreased significantly in the FEP group from 119 mmHg to 114 mmHg at 3 years ($p = 0.001$) and increased from 106.14 mmHg to 114.56 mmHg at 3 years in the control group ($p = 0.001$). DBP mean value increased significantly from 62.24 mmHg to 70.42 mmHg at 3 years in the control group

Table 2 Three years follow-up of MetS and related factors mean values and prevalence in FEP and controls.

	FEP				Controls			
	Baseline $N = 244$	3 years $N = 202$	Stats*	p	Baseline $N = 166$	3 years $N = 86$	Stats	p
MetS components mean values	Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)		
Waist circumference (cm)	83.30 (12.16)	90.67 (13.69)	−9.347	0.001	89.80 (13.51)	88.56 (13.25)	1.605	0.112
Body mass index (kg/m^2)	23.16 (4.26)	26.60 (4.97)	−15.358	0.001	26.03(4.44)	26.27(4.51)	−1.069	0.288
SBP (mm/Hg)	119.08 (15.11)	114.09 (14.94)	3.851	0.001	106.14 (12.08)	114.56 (13.66)	−5.563	0.001*
DBP (mm/Hg)	70.65 (11.61)	70.67 (10.75)	−0.021	0.983	62.24 (8.77)	70.42 (11.18)	−6.458	0.001*
Glucose (mg/dL)	86.36 (21.5)	92.67 (16.65)	−4.466	0.001	84.49 (8.54)	85.52 (15.11)	−0.79	0.432
Tryglicerides (mg/dL)	85.27 (38.76)	117.05 (72.96)	−7.287	0.001	86.6 (40.94)	93.76 (56.73)	−1.376	0.173
HDL (mg/dL)	53.55 (15.76)	51.71 (13.93)	1.839	0.067	57.71 (15.50)	58.30 (15.18)	0.17	0.865
MetS components prevalence	*N* (%)	*N* (%)	Mc Nemar	*p*	*N* (%)	*N* (%)	Mc Nemar	*p*
MetS**	16 (6.6)	37 (18.3)	Mc Nemar	<0.001	9 (5.4)	7 (8.1)	Mc Nemar	0.063
Glucose ≥ 100 mg/dL	15 (6.1)	43 (21.2)	Mc Nemar	0.001	8 (4.8)	7 (8.1)	Mc Nemar	0.063
Blood pressure ≥130/85 mmHg	72 (29.5)	42 (20.7)	Mc Nemar	0.011	7 (4.3)	17 (20.5)	Mc Nemar	0.001
HDL ≤40 mg/dL in men and ≤50 mg/dL in women	66 (27)	51 (25.2)	Mc Nemar	0.706	29 (17.5)	10 (11.6)	Mc Nemar	0.754
Triglycerides ≥150 mg/dL	19 (7.8)	47 (23.2)	Mc Nemar	<0.001	20 (12.1)	10 (11.6)	Mc Nemar	1.00
Waist circumference ≥102 cm in men and >88 cm in women	43 (17.6)	78 (38.6)	Mc Nemar	<0.001	49 (29.5)	26(30.6)	Mc Nemar	0.227
Body mass index > 30 kg/m^2**	14 (5.7)	47 (23.2)	Mc Nemar	0.001	24 (14.4)	45 (19.8)	Mc Nemar	0.225

Abbreviations: FEP, First Episode Psychosis. SD, Standard deviation. HDL, High density lipoprotein. SBP, Systolic blood pressure. DBP, Diastolic blood pressure.

* Statistics: *t* student for paired samples or wilcoxon test and McNemar test were used. *p*-Value < 0.05 is significant.

** Mets prevalence and related components according to the Adult Treatment Panel III (ATP III): Glucose ≥ 100 mg/dL, blood pressure ≥ 130/85 mmHg, triglycerides ≥ 150 mg/dL, HDL ≤ 40 mg/dL in men and ≤50 mg/dL in women, waist circumference ≥ 102 cm in men and >88 cm in women.

***Body mass index ≥ 30 kg/m^2.

($p = 0.001$) (Table 2). In FEP group, the predictive model showed that the development of high blood pressure at 3 years was influenced by risperidone treatment (with respect to ziprasidone) (Table 3).

Waist circumference

The baseline prevalence of altered WC was lower in the FEP group (19.1% vs 29.5%, $p = 0.016$), but we did not find differences in either group after 3 years (Table 1). WC mean value increased significantly from 83.30 cm to 90.67 cm at 3 years only in the FEP group (Table 2). In the FEP group, the predictive model showed that the baseline factors increasing the WC at 3 years were being male, having altered BMI and altered HDL (Table 3).

Body mass index

The baseline prevalence of obesity (BMI ≥ 30 kg/m^2) was lower in the FEP group (5.7% vs 11.8%, $p = 0.023$), but we did not find differences in either groups after 3 years. However, the prevalence increased significantly only in FEP group from 5.7% to 24.2% (Table 1). In the FEP group, the predictive model showed that the baseline factors increasing the risk of obesity (BMI ≥ 30 kg/m^2) at 3 years were being male, having altered baseline SBP, DBP, BMI and HDL (Table 3).

Discussion

After analyzing the baseline prevalence and clinical correlates of MetS in 244 FEP drug naïve patients and 166 controls and the follow up at 3 years, we found that the FEP group had a worse evolution compared to the control group: (i) the FEP group presented a clear greater increased in MetS prevalence at 3 years compared with controls. At 3-years follow-up the MetS prevalence had increased from 6.6% to 18.3% in the FEP group, while only from 5.4% to 8.1% in the control group; (ii) Altered baseline values of HDL or

Table 3 Summary of multiple binary logistic regression analysis.

	B	SD	Wald	df	Sig	OR	95% CI OR	
							Lower	Upper
Metabolic syndrome 3 years[**]								
Men	0.65	0.705	0.85	1	0.357	1.916	0.481	7.629
>30 years old (median)	−0.186	0.618	0.091	1	0.763	0.83	0.247	2.785
Aripiprazole (ref ziprasidone)	0.084	0.904	0.009	1	0.926	1.088	0.185	6.392
Risperidone (ref ziprasidone)	0.843	0.91	0.857	1	0.354	2.323	0.39	13.837
Quetiapine (ref ziprasidone)	0.219	1.034	0.045	1	0.833	1.244	0.164	9.446
Baseline SBP (mm/Hg)	0.032	0.03	1.133	1	0.287	1.032	0.974	1.095
Baseline DBP (mm/Hg)	−0.02	0.035	0.334	1	0.564	0.98	0.916	1.049
Baseline glucose (mg/dL)	0.022	0.028	0.618	1	0.432	1.022	0.968	1.08
Baseline Tryglicerides (mg/dL)	0.016	0.008	4.08	1	0.043[*]	1.016	1	1.031
Baseline HDL (mg/dL)	−0.082	0.031	7.07	1	0.008[*]	0.911	0.867	0.979
Baseline Waist circumference (cm)	0.065	0.025	6.474	1	0.011[*]	1.067	1.015	1.122
BMI (kg/m^2)[***]	0.238	0.127	3.545	1	0.060	1.269	0.99	1.627
Glucose 3 years								
Men	0.441	0.486	0.825	1	0.364	1.555	0.6	4.029
>30 years old (median)	0.679	0.457	2.204	1	0.034[*]	1.971	0.805	4.828
Aripiprazole (ref ziprasidone)	0.347	0.709	0.239	1	0.625	1.415	0.353	5.677
Risperidone (ref ziprasidone)	1.459	0.748	3.805	1	0.050	4.303	0.993	18.644
Quetiapine (ref ziprasidone)	0.539	0.831	0.42	1	0.517	1.714	0.336	8.746
Baseline SBP (mm/Hg)	−0.014	0.021	0.412	1	0.521	0.986	0.946	1.029
Baseline DBP (mm/Hg)	−0.022	0.029	0.6	1	0.439	0.978	0.924	1.035
Baseline glucose (mg/dL)	0.075	0.023	10.559	1	0.001[*]	1.078	1.03	1.128
Baseline Tryglicerides (mg/dL)	0.007	0.006	1.67	1	0.196	1.007	0.996	1.019
Baseline HDL (mg/dL)	−0.029	0.016	3.196	1	0.074	0.971	0.941	1.003
Baseline Waist circumference (cm)	0.047	0.028	2.719	1	0.099	1.048	0.991	1.108
BMI (kg/m^2)[***]	−0.09	0.084	1.17	1	0.279	0.914	0.776	1.076
Tryglicerides 3 years								
Men	0.683	0.398	2.947	1	0.086	1.981	0.908	4.322
>30 years old (median)	0.87	0.392	4.911	1	0.027[*]	2.386	1.106	5.149
Aripiprazole (ref ziprasidone)	−0.049	0.566	0.008	1	0.931	0.952	0.314	2.885
Risperidone (ref ziprasidone)	−0.388	0.612	0.402	1	0.526	0.678	0.204	2.252
Quetiapine (ref ziprasidone)	0.226	0.664	0.116	1	0.734	1.253	0.341	4.604
Baseline SBP (mm/Hg)	−0.013	0.022	0.34	1	0.560	0.987	0.945	1.031
Baseline DBP (mm/Hg)	−0.007	0.029	0.058	1	0.810	0.993	0.938	1.051
Baseline glucose (mg/dL)	0.009	0.014	0.485	1	0.486	1.01	0.983	1.037
Baseline Tryglicerides (mg/dL)	0.02	0.006	11.472	1	0.001[*]	1.021	1.009	1.033
Baseline HDL (mg/dL)	−0.025	0.019	1.826	1	0.177	0.975	0.94	1.011
Baseline Waist circumference (cm)	0.012	0.03	0.151	1	0.697	1.012	0.954	1.073
BMI (kg/m^2)[***]	0.075	0.072	1.065	1	0.302	1.078	0.935	1.242
Waist circumference								
Men	0.272	0.526	0.268	1	0.604	1.313	0.469	3.679
>30 years old (median)	−0.542	0.499	1.181	1	0.277	0.582	0.219	1.545
Aripiprazole (ref ziprasidone)	1.009	0.714	1.997	1	0.158	2.742	0.677	11.111
Risperidone (ref ziprasidone)	1.251	0.79	2.509	1	0.113	3.492	0.743	16.41
Quetiapine (ref ziprasidone)	−0.84	0.897	0.877	1	0.349	0.432	0.075	2.504
Baseline SBP (mm/Hg)	−0.048	0.024	4.078	1	0.053	0.953	0.909	0.999
Baseline DBP (mm/Hg)	0.053	0.031	2.956	1	0.086	1.055	0.993	1.121
Baseline glucose (mg/dL)	0.011	0.011	0.995	1	0.319	1.011	0.99	1.032
Baseline Tryglicerides (mg/dL)	0.004	0.007	0.449	1	0.503	1.004	0.992	1.018
Baseline HDL (mg/dL)	−0.044	0.018	6.15	1	0.013[*]	0.957	0.925	0.991
Baseline Waist circumference (cm)	−0.006	0.032	0.04	1	0.842	0.994	0.934	1.057
BMI (kg/m^2)[***]	0.591	0.124	22.715	1	0.001[*]	1.806	1.416	2.303

Table 3 (*Continued*)

	B	SD	Wald	df	Sig	OR	95% CI OR	
							Lower	Upper
High blood pressure 3 years								
Men	0.519	0.412	1.586	1	0.208	1.68	0.749	3.767
>30 years old (median)	0.128	0.412	0.097	1	0.756	1.137	0.507	2.548
Aripiprazole (ref ziprasidone)	−0.649	0.692	0.879	1	0.348	0.522	0.135	2.029
Risperidone (ref ziprasidone)	0.928	0.431	4.642	1	0.031*	2.53	1.087	5.884
Quetiapine (ref ziprasidone)	−1.983	9.176	0.244	1	0.998	1.78	1.089	6.987
Baseline SBP (mm/Hg)	0.043	0.023	3.501	1	0.061	1.044	0.998	1.093
Baseline DBP (mm/Hg)	0.014	0.03	0.235	1	0.628	1.014	0.957	1.075
Baseline glucose (mg/dL)	0.002	0.01	0.028	1	0.867	1.002	0.982	1.022
Baseline Tryglicerides (mg/dL)	0.005	0.006	0.575	1	0.448	1.005	0.993	1.016
Baseline HDL (mg/dL)	−0.006	0.015	0.166	1	0.684	0.994	0.966	1.023
Baseline Waist circumference (cm)	0.052	0.027	3.632	1	0.057	1.053	0.999	1.111
BMI (kg/m^2)***	−0.015	0.069	0.045	1	0.833	0.986	0.861	1.128
HDL 3 years								
Men	−1.887	0.587	4.323	1	0.054	0.152	0.048	0.479
>30 years old (median)	−0.819	0.499	2.69	1	0.101	0.441	0.166	1.173
Aripiprazole (ref ziprasidone)	−0.633	0.634	0.995	1	0.318	0.531	0.153	1.841
Risperidone (ref ziprasidone)	−0.29	0.672	0.186	1	0.667	0.749	0.200	2.796
Quetiapine (ref ziprasidone)	−2.066	0.924	4.993	1	0.052	0.127	0.021	0.776
Baseline SBP (mm/Hg)	−0.013	0.023	0.332	1	0.564	0.987	0.943	1.032
Baseline DBP (mm/Hg)	0.039	0.033	1.405	1	0.236	1.039	0.975	1.108
Baseline glucose (mg/dL)	0.019	0.012	2.564	1	0.109	1.02	0.996	1.044
Baseline Tryglicerides (mg/dL)	−0.001	0.006	0.027	1	0.87	0.999	0.987	1.011
Baseline HDL (mg/dL)	−0.159	0.031	26.164	1	0.001*	0.853	0.803	0.907
Baseline Waist circumference (cm)	−0.018	0.031	0.344	1	0.558	0.982	0.925	1.043
BMI (kg/m^2)***	0.068	0.079	0.748	1	0.387	1.071	0.917	1.25
BMI 3 years								
Men	0.168	0.527	3.560	1	0.038*	1.183	0.421	3.322
>30 years old (median)	−0.311	0.492	0.4	1	0.527	0.732	0.279	1.922
Aripiprazole (ref ziprasidone)	1.207	0.713	2.867	1	0.090	3.342	0.827	13.507
Risperidone (ref ziprasidone)	1.338	0.788	2.884	1	0.089	3.811	0.814	17.851
Quetiapine (ref ziprasidone)	−0.518	0.88	0.347	1	0.556	0.596	0.106	3.341
Baseline SBP (mm/Hg)	−0.059	0.024	5.815	1	0.016*	0.943	0.899	0.989
Baseline DBP (mm/Hg)	0.062	0.032	3.81	1	0.048*	1.063	1	1.131
Baseline glucose (mg/dL)	0.013	0.011	1.408	1	0.235	1.013	0.992	1.034
Baseline Tryglicerides (mg/dL)	0.001	0.007	0.01	1	0.919	1.001	0.988	1.014
Baseline HDL (mg/dL)	−0.047	0.018	7.235	1	0.007*	0.954	0.922	0.987
Baseline Waist circumference (cm)	−0.015	0.033	0.203	1	0.652	0.985	0.924	1.05
BMI (kg/m^2)***	0.64	0.127	25.192	1	0.001*	1.896	1.477	2.433

Abbreviations: CI, confidence interval. OR, odds ratio. SE, standard error. DF, degree freedom. Ref, reference.

* *p*-Value < 0.05 is significant.

** Mets prevalence and related components according to the Adult Treatment Panel III (ATP III): Glucose ≥ 100 mg/dL, blood pressure ≥ 130/85 mmHg, triglycerides ≥ 150 mg/dL, HDL ≤ 40 mg/dL in men and ≤50 mg/dL in women, waist circumference ≥ 102 cm in men and >88 cm in women.

*** Body mass index ≥ 30 kg/m^2.

triglycerides levels or WC were associated to presenting MetS 3 years later regardless of age, sex and type of antipsychotic treatment.

These results are of clinical relevancy, given the fact that the available cardiometabolic algorithms are of little use in FEP population due to several reasons: firstly, this is a population that tends to seek less medical attention, so there is a risk of underdiagnoses bias. On the other hand, certain alterations require a time course to develop the disease, although it is known that despite not reaching diagnostic threshold values, they can be associated with higher mortality and morbidity outcomes in the long term. Therefore, there would be a gap in early intervention for cardiovascular risk prediction in these patients that seems to be inherent to the disease. Subsequently, it is urgent to focus research on the main modifiable risk factors that contribute to these mortality figures. A more systemic understanding of schizophrenia could modify both the clinical evaluation and

the treatment offered to these patients in order to prevent and modify not only the neuropsychiatric symptoms but also the set of symptoms that contribute to reducing their life expectancy.

In a more detailed examination, our study showed differences between groups in the individual components of MetS. Thus, among the MetS individual components prevalence, low HDL, hypertriglyceridemia and hyperglycemia were more frequently altered in FEP group than in control group at 3-years follow-up, and this worsening was predicted by different variables: (i) Age was associated to presenting hypertriglyceridemia and hyperglycemia 3 years later. (ii) Prevalence and mean value of HDL was worse in the FEP group compared to control group, not only at baseline assessment but also at 3 years, but this alteration was not influenced by age, sex or treatment. Despite the young age of our sample, the prevalence of MetS increases significantly more in the FEP patients than in the control group. However, as in the general population,[32] age over 30 years is a risk factor for hyperglycemia and hypertriglyceridemia.

The association of the use of antipsychotic drugs and MetS is widely known.[15] Although antipsychotic medications typically alleviate positive symptoms and delay relapse, metabolic side-effects are particularly common in patients treated with second-generation antipsychotics, especially clozapine and olanzapine.[33] In this regard we may assume that the differences between FEP patients and controls in MetS prevalence at 3 years follow-up may be explained in part by the antipsychotic treatment exposure. Moreover, we found that the detection of increased blood pressure at three years is influenced by antipsychotic use. Despite of this we found no significant differences between antipsychotic drugs in the risk of developing MetS at 3 years follow-up. Clinical trials testing the effectiveness of atypical antipsychotics in drug-naïve young individuals, embodying a superlative model for the investigation of new molecular mechanisms underlying type 2 diabetes, hypertriglyceridemia, and other metabolic disturbances, are required to advance in the knowledge of glucometabolic disturbances beyond psychosis population.

With respect to MetS criteria, Garrido-Torres et al. (2021)[18] performed individual meta-analyses in studies where both IDF and ATP-IIIA criteria were used to diagnose MetS. They found that MetS prevalence in the same population is higher when diagnosed according to IDF than ATP-IIIA. In the current paper, we found similar results when we used ATP-IIIA criteria and IDF criteria but a higher Baseline MetS prevalence in both FEP and controls using WHO criteria. The pre-established diagnostic parameters in the general population for the diagnosis of MetS could be not useful in patients with a FEP.[21,25]

There is evidence supporting that the metabolic disturbances in psychosis may begin early, even prior to the antipsychotic exposure. Our results are somehow contrary to this previous evidence since we observed no significant differences between FEP patients and controls in baseline MetS prevalence. On the other hand we did find differences when comparing the individual components of MetS between groups. This is important since some if these individuals components at baseline may be a risk factors for developing MetS in the long-term; thus, our study showed that those FEP patients presenting altered HDL, tryglicerides and WC at baseline, where at greater risk of developing MetS at 3 years follow-up.

These results are in line with previous evidence. Among the MetS components a low HDL cholesterol level and a large WC are accepted as the most strongly correlated with the syndrome.[34,35] Measurements of the WC and HDL cholesterol level are recommended for the diagnosis and follow-up of MetS in patients with schizophrenia.[34,36] Our results show that from the beginning and up to 3 years, the prevalence and the mean value of HDL is worse in the FEP group than in controls. However, our attention is drawn to the fact that at the intragroup level, there are no changes from the beginning to 3 years, nor influence of sex, age or drug treatment, as there are in the rest of the components. This can be explained by the relationship between the pro-inflammatory state, schizophrenia and MetS.[37,38] With regard to dyslipemia, reduced HDL levels are correlated to a high inflammatory set point of monocytes and macrophages.[39,40] Likewise, an anti-inflammatory effect has been observed in some antipsychotics. In humans, the immunomodulatory effect of risperidone and aripiprazole has been demonstrated.[41] Along these lines, it has been described that the metabolic alterations observed in patients with schizophrenia could be the manifestation of a systemic inflammatory state that may or may not ''trigger'' in a vulnerable group of patients.[42] At a molecular level, other factors are probably contributing to the weight gain and related metabolic alterations observed in psychosis. Crespo-Facorro et al. (2019)[43] reported five obesity-related genes (*GPER*, *LTF*, *MMP8*, *OLR1*, and *OLFM4*) and four diabetes-related genes (*ALPL*, *LTF*, *MMP8*, and *OLR1*) to be differentially expressed in patients who received atypical antipsychotic treatment. These results suggest that altered gene expression caused by atypical antipsychotics may contribute to obesity and MetS in these patients.

On the other hand, epigenetic inheritance and prenatal development have recently received considerable attention within the research community as two factors to consider in the etiopathogenesis of obesity in the general population[44] and in individuals with mental disorders.[45] In this sense, a relationship between obesity, childhood maltreatment, and elevated inflammatory markers in adults with schizophrenia has been demonstrated.[46] Therefore, the relationship between early life stress, fetal metabolic programming and schizophrenia[47] through epigenetic markers has been established. Consequently, stressful psychosocial experiences in utero and/or during childhood can be interpreted as potentially modifiable risk factors.

Some limitations in this study should be noted. First, unfortunately, it is uncertain whether the patients have fully complied with antipsychotic treatment throughout the 3-years study period. Second, for antipsychotic comparisons we have followed and intention-to treat approach and clustered the FEP patients according to their prescribed antipsychotic at baseline, without considering that patients may have been changed to another antipsychotic during the study period since we could not perform per-protocol analysis. The type of antipsychotic included were at different risk for developing cardiovascular events, for instance risperidone is different from aripiprazole[48]; and third, we could not include into the analyses other variables known to affect weight change and MetS, such as diet and exercise. On the

other hand, the study counts with relevant strengths. For instance, our study is a representative sample of naïve FEP patients and controls with 3-year follow-up of metabolic syndrome and related components.

In conclusion, patients with FEP present a similar prevalence of MetS, but with a higher prevalence of metabolic alterations than controls before the start of antipsychotic treatment. However, at 3 years, the prevalence of MetS is higher in FEP than in controls.

Finally, in this work, we propose a predictive model of MetS at 3 years in 244 drug-naïve patients with FEP, in which altered WC, HDL and triglycerides at baseline predicted the presence of full MetS after 3-years of initiating antipsychotic treatment. Our findings support the need for interventions to improve factors related to the physical health of FEP individuals.

Authors' contributions

NG-T managed the literature searches, undertook the statistical analyses and wrote the first draft of the manuscript. BC-F designed the study, wrote the protocol, obtained the financial support and evaluated the patients. JV-B contributed to the interpretation of the data, contributed to the first draft of the manuscript and revised the manuscript critically. MR-V, JOM, ARG, MC-R, MG-R, MJ-R and RA-A revised the manuscript critically. All authors have revised and approved the final manuscript.

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Conflicts of interest

NG-T, MR-V, JOM, ARG, MC-R, MG-R, MJ-R and RA-A report no conflicts of interest. BC-F has received unrestricted research funding from Instituto de Salud Carlos III, MINECO, Gobierno de Cantabria, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), from the 7th European Union Framework Program and Lundbeck. He has also received honoraria for his participation as a consultant and/or as a speaker at educational events from Janssen Johnson & Johnson, Lundbeck, and Otsuka Pharmaceuticals. JV-B has received unrestricted research funding from Instituto de Investigación Marqués de Valdecilla (IDIVAL). He has also received honoraria for his participation as a consultant and/or as a speaker at educational events from Janssen-Cilag and Lundbeck.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rpsm.2022.05.003.

References

1. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet (Lond, Engl). 2005;365:1415–28, http://dx.doi.org/10.1016/S0140-6736(05)66378-7.
2. Huang PL. A comprehensive definition for metabolic syndrome. Dis Mod Mech. 2009;2:231–7, http://dx.doi.org/10.1242/dmm.001180.
3. Penninx BWJH, Lange SMM. Metabolic syndrome in psychiatric patients: overview, mechanisms, and implications. Dial Clin Neurosci. 2018;20:63–73, http://dx.doi.org/10.31887/DCNS.2018.20.1/bpenninx.
4. Postolache TT, Del Bosque-Plata L, Jabbour S, Vergare M, Wu R, Gragnoli C. Co-shared genetics and possible risk gene pathway partially explain the comorbidity of schizophrenia, major depressive disorder, type 2 diabetes, and metabolic syndrome. Am J Med Genet B Neuropsychiatr Genet. 2019;180:186–203, http://dx.doi.org/10.1002/ajmg.b.32712.
5. Wong DF, Pearlson GD, Tune LE, Young LT, Meltzer CC, Dannals RF, et al. Quantification of neuroreceptors in the living human brain: IV. Effect of aging and elevations of D2-like receptors in schizophrenia and bipolar illness. J Cereb Blood Flow Metab. 1997;17:331–42, http://dx.doi.org/10.1097/00004647-199703000-00010.
6. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, et al. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. Schizophr Bull. 2018;44:1195–203, http://dx.doi.org/10.1093/schbul/sby058.
7. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet (Lond, Engl). 2017;390:1151–210, http://dx.doi.org/10.1016/S0140-6736(17)32152-9.
8. Laursen TM. Causes of premature mortality in schizophrenia: a review of literature published in 2018. Curr Opin Psychiatry. 2019;32:388–93, http://dx.doi.org/10.1097/YCO.0000000000000530.
9. Adorjan K, Falkai P. Premature mortality, causes of death, and mental disorders. Lancet (Lond, Engl). 2019;394:1784–6, http://dx.doi.org/10.1016/S0140-6736(19)32521-8.
10. Laursen TM, Nordentoft M, Mortensen PB. Excess early mortality in schizophrenia. Ann Rev Clin Psychol. 2014;10:425–48, http://dx.doi.org/10.1146/annurev-clinpsy-032813-153657.
11. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gener Psychiatry. 2007;64:1123–31, http://dx.doi.org/10.1001/archpsyc.64.10.1123.
12. Vazquez-Bourgon J, Perez-Iglesias R, Ortiz-Garcia de la Foz V, Suarez Pinilla P, Diaz Martinez A, Crespo-Facorro B. Long-term metabolic effects of aripiprazole, ziprasidone and quetiapine: a pragmatic clinical trial

in drug-naive patients with a first-episode of non-affective psychosis. Psychopharmacology. 2018;235:245–55, http://dx.doi.org/10.1007/s00213-017-4763-x.

13. Vazquez-Bourgon J, Ibanez Alario M, Mayoral-van Son J, Gomez Revuelta M, Ayesa Arriola R, Juncal Ruiz M, et al. A 3-year prospective study on the metabolic effect of aripiprazole, quetiapine and ziprasidone: a pragmatic clinical trial in first episode psychosis patients. Eur Neuropsychopharmacol. 2020, http://dx.doi.org/10.1016/j.euroneuro.2020.08.009.
14. Vazquez-Bourgon J, Mayoral-van Son J, Gomez-Revuelta M, Juncal-Ruiz M, Ortiz-Garcia de la Foz V, Tordesillas-Gutierrez D, et al. Treatment discontinuation impact on long-term (10-years) weight gain and lipid metabolism in first-episode psychosis: results from the PAFIP-10 cohort. Int J Neuropsychopharmacol. 2020, http://dx.doi.org/10.1093/ijnp/pyaa066.
15. Rognoni C, Bertolani A, Jommi C. Second-generation antipsychotic drugs for patients with schizophrenia: systematic literature review and meta-analysis of metabolic and cardiovascular side effects. Clin Drug Invest. 2021;41:303–19, http://dx.doi.org/10.1007/s40261-021-01000-1.
16. Perez-Iglesias R, Mata I, Pelayo-Teran JM, Amado JA, Garcia-Unzueta MT, Berja A, et al. Glucose and lipid disturbances after 1 year of antipsychotic treatment in a drug-naive population. Schizophr Res. 2009;107:115–21, http://dx.doi.org/10.1016/j.schres.2008.09.028.
17. Perez-Iglesias R, Martinez-Garcia O, Pardo-Garcia G, Amado JA, Garcia-Unzueta MT, Tabares-Seisdedos R, 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, http://dx.doi.org/10.1017/S1461145713001053.
18. Garrido-Torres N, Rocha-Gonzalez I, Alameda L, Rodriguez-Gangoso A, Vilches A, Canal-Rivero M, et al. Metabolic syndrome in antipsychotic-naive patients with first-episode psychosis: a systematic review and meta-analysis. Psychol Med. 2021:1–14, http://dx.doi.org/10.1017/S0033291721002853.
19. Lang X, Liu Q, Fang H, Zhou Y, Forster MT, Li Z, et al. The prevalence and clinical correlates of metabolic syndrome and cardiometabolic alterations in 430 drug-naive patients in their first episode of schizophrenia. Psychopharmacology. 2021;238:3643–52, http://dx.doi.org/10.1007/s00213-021-05983-9.
20. Pillinger T, D'Ambrosio E, McCutcheon R, Howes OD. Is psychosis a multisystem disorder? A meta-review of central nervous system, immune, cardiometabolic, and endocrine alterations in first-episode psychosis and perspective on potential models. Mol Psychiatry. 2019;24:776–94, http://dx.doi.org/10.1038/s41380-018-0058-9.
21. Perry BI, Upthegrove R, Crawford O, Jang S, Lau E, McGill I, et al. Cardiometabolic risk prediction algorithms for young people with psychosis: a systematic review and exploratory analysis. Acta Psychiatr Scand. 2020;142:215–32, http://dx.doi.org/10.1111/acps.13212.
22. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ (Clin Res Ed.). 2017;357:j2099, http://dx.doi.org/10.1136/bmj.j2099.
23. Hippisley-Cox J, Coupland C. Development and validation of QDiabetes-2018 risk prediction algorithm to estimate future risk of type 2 diabetes: cohort study. BMJ (Clin Res Ed.). 2017;359:j5019, http://dx.doi.org/10.1136/bmj.j5019.
24. Osborn DPJ, Hardoon S, Omar RZ, Holt RIG, King M, Larsen J, et al. Cardiovascular risk prediction models for people with severe mental illness: results from the prediction and management of cardiovascular risk in people with severe mental illnesses (PRIMROSE) research program. JAMA Psychiatry. 2015;72:143–51, http://dx.doi.org/10.1001/jamapsychiatry.2014.2133.
25. Perry BI, Osimo EF, Upthegrove R, Mallikarjun PK, Yorke J, Stochl J, et al. Development and external validation of the Psychosis Metabolic Risk Calculator (PsyMetRiC): a cardiometabolic risk prediction algorithm for young people with psychosis. Lancet Psychiatry. 2021;8:589–98, http://dx.doi.org/10.1016/S2215-0366(21)00114-0.
26. Pelayo-Teran JM, Perez-Iglesias R, Ramirez-Bonilla M, Gonzalez-Blanch C, Martinez-Garcia O, Pardo-Garcia G, et al. Epidemiological factors associated with treated incidence of first-episode non-affective psychosis in Cantabria: insights from the Clinical Programme on Early Phases of Psychosis. Early Interv Psychiatry. 2008;2:178–87, http://dx.doi.org/10.1111/j.1751-7893.2008.00074.x.
27. Son J, Gomez-Revuelta M, Ayesa-Arriola M, Vazquez-Bourgon R, Foz J, de la VO-G, et al. Comparison of aripiprazole and risperidone effectiveness in first episode non-affective psychosis: rationale and design of a prospective, randomized, 3-phase, investigator-initiated study (PAFIP-3). Revista de Psiquiatria y Salud Mental. 2021;14:157–63, http://dx.doi.org/10.1016/j.rpsmen.2021.08.002.
28. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition (SCID-I/P). New York: Biometrics Research, New York State Psychiatric Institute; 2002.
29. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285:2486–97, http://dx.doi.org/10.1001/jama.285.19.2486.
30. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499–502.
31. Lauritsen J, Bruss M. A comprehensive tool for validated entry and documentation of data. The EpiData Association; 2004.
32. Moore JX, Chaudhary N, Akinyemiju T. Metabolic syndrome prevalence by race/ethnicity and sex in the United States. National Health and Nutrition Examination Survey, 1988–2012. Prevent Chronic Dis. 2017;14:E24, http://dx.doi.org/10.5888/pcd14.160287.
33. Pillinger T, McCutcheon RA, Vano L, Mizuno Y, Arumuham A, Hindley G, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry. 2020;7:64–77, http://dx.doi.org/10.1016/S2215-0366(19)30416-X.
34. Kato MM, Currier MB, Villaverde O, Gonzalez-Blanco M. The relation between body fat distribution and cardiovascular risk factors in patients with schizophrenia: a cross-sectional pilot study. Primary Care Compan J Clin Psychiatry. 2005;7:115–8, http://dx.doi.org/10.4088/pcc.v07n0307, quiz 119–20.
35. Valsamakis G, Chetty R, Anwar A, Banerjee AK, Barnett A, Kumar S. Association of simple anthropometric measures of obesity with visceral fat and the metabolic syndrome in male Caucasian and Indo-Asian subjects. Diab Med. 2004;21:1339–45, http://dx.doi.org/10.1111/j.1464-5491.2004.01361.x.
36. Henderson DC. Managing weight gain and metabolic issues in patients treated with atypical antipsychotics. J Clin Psychiatry. 2008;69:e04, http://dx.doi.org/10.4088/jcp.0208e04.
37. Beumer W, Drexhage RC, De Wit H, Versnel MA, Drexhage HA, Cohen D. Increased level of serum cytokines, chemokines and adipokines in patients with schizophrenia is associated with disease and metabolic syndrome. Psychoneuroendocrinology. 2012;37:1901–11, http://dx.doi.org/10.1016/j.psyneuen.2012.04.001.

38. Shafer-Eggleton J, Adams-Huet B, Jialal I. Chemerin ratios to HDL-cholesterol and adiponectin as biomarkers of metabolic syndrome. Endocr Res. 2020;45:241–5, http://dx.doi.org/10.1080/07435800.2020.1811724.
39. Li Y, Chen D, Sun L, Chen Z, Quan W. Monocyte/high-density lipoprotein ratio predicts the prognosis of large artery atherosclerosis ischemic stroke. Front Neurol. 2021;12:769217, http://dx.doi.org/10.3389/fneur.2021.769217.
40. Sarov-Blat L, Kiss RS, Haidar B, Kavaslar N, Jaye M, Bertiaux M, et al. Predominance of a proinflammatory phenotype in monocyte-derived macrophages from subjects with low plasma HDL-cholesterol. Arterioscler Thromb Vasc Biol. 2007;27:1115–22, http://dx.doi.org/10.1161/ATVBAHA.106.138990.
41. Juncal-Ruiz M, Riesco-Davila L, Ortiz-Garcia de la Foz V, Martinez-Garcia O, Ramirez-Bonilla M, Ocejo-Vinals JG, et al. Comparison of the anti-inflammatory effect of aripiprazole and risperidone in 75 drug-naive first episode psychosis individuals: a 3 months randomized study. Schizophr Res. 2018;202:226–33, http://dx.doi.org/10.1016/j.schres.2018.06.039.
42. Crespo-Facorro B, Ruiz-Veguilla M, Vazquez-Bourgon J, Sanchez-Hidalgo AC, Garrido-Torres N, Cisneros JM, et al. Aripiprazole as a candidate treatment of COVID-19 identified through genomic analysis. Front Pharmacol. 2021;12:646701, http://dx.doi.org/10.3389/fphar.2021.646701.
43. Crespo-Facorro B, Prieto C, Sainz J. Altered gene expression in antipsychotic-induced weight gain. NPJ Schizophr. 2019;5:7, http://dx.doi.org/10.1038/s41537-019-0075-y.
44. Danese A, Tan M. Childhood maltreatment and obesity: systematic review and meta-analysis. Mol Psychiatry. 2014;19:544–54, http://dx.doi.org/10.1038/mp.2013.54.
45. Alameda L, Trotta G, Quigley H, Rodriguez V, Gadelrab R, Dwir D, et al. Can epigenetics shine a light on the biological pathways underlying major mental disorders? Psychol Med. 2022:1–21, http://dx.doi.org/10.1017/S0033291721005559.
46. Aas M, Dieset I, Hope S, Hoseth E, Mørch R, Reponen E, et al. Childhood maltreatment severity is associated with elevated C-reactive protein and body mass index in adults with schizophrenia and bipolar diagnoses. Brain Behav Immunity. 2017;65:342–9, http://dx.doi.org/10.1016/j.bbi.2017.06.005.
47. Garcia-Rizo C, Bitanihirwe BKY. Implications of early life stress on fetal metabolic programming of schizophrenia: a focus on epiphenomena underlying morbidity and early mortality. Prog Neuro-Psychopharmacol Biol Psychiatry. 2020;101:109910, http://dx.doi.org/10.1016/j.pnpbp.2020.109910.
48. Cooper SJ, Reynolds GP, Barnes T, England E, Haddad PM, Heald A, et al. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. J Psychopharmacol (Oxf, Engl). 2016;30:717–48, http://dx.doi.org/10.1177/0269881116645254.

Material suplementario

Table S.1 Comparison of MetS prevalence using ATP-III, IDF and WHO criteria

	Baseline		3 years	
	FEP	Controls	FEP	Controls
IDF				
N	244	166	192	86
MetS prevalence n (%)	12 (4.9)	9 (5.4)	15 (7.8)	7 (8.1)
ATP-III				
N	244	166	202	86
MetS prevalence n (%)	16 (6.6)	9 (5.4)	37 (18.3)	7 (8.1)
WHO				
N	244	204	202	86
MetS prevalence n (%)	37 (15.1)	18 (10.8)	36 (17.8)	12 (14)

Abbreviations: FEP, First Episode Psychosis. ATP-III, Adult Treatment Panel III criteria: Glucose ≥ 100mg/dL, blood pressure ≥130/85 mmHg, triglycerides ≥150mg/dL, HDL ≤40mg/dL in men and ≤ 50mg/dL in women, waist circumference ≥102cm in men and >88cm in women. IDF, International Diabetes Federation criteria: altered waist circumference with two of the following: Glucose ≥ 100mg/dL, blood pressure ≥130/85 mmHg, triglycerides ≥150mg/dL, HDL ≤40mg/dL in men and ≤ 50mg/dL in women. WHO, World Health Organization criteria: Glucose ≥ 126 mg/dL, blood pressure ≥140/90 mmHg and two of the following: triglycerides ≥150mg/dL, HDL ≤35mg/dL in men and ≤ 39mg/dL in women, Body mass index (BMI) of more than 30 $kg/m^{2.}$

Discusión

Después de analizar la prevalencia basal de MetS en PEP, en los controles y el seguimiento a los 3 años, se encontró que en general los pacientes con PEP tienen una peor evolución en comparación con el grupo de controles. i) En el metaanálisis (Garrido-Torres et al., 2021) se observó que los pacientes con PEP tienen el doble de riesgo de presentar MetS que la población general independientemente del uso de antipsicóticos. ii) A través del estudio trasnversal en una muestra representativa de pacientes naïve (Garrido-Torres, Ruiz-Veguilla, Alameda, et al., 2022) se hizo evidente que la prevalencia de MetS es similar a la de los controles, sin embargo, se confirmó que los pacientes con PEP tienen más alteraciones metabólicas basales que los controles sanos. iii) La prevalencia y el valor medio del HDL alterada fueron peores en el grupo de PEP en comparación con el grupo control, no sólo en la evaluación basal sino también a los 3 años, pero esta alteración no se vio influenciada por la edad, el sexo, tratamiento, nivel educativo, estado civil, nivel socioeconómico familiar, entorno urbano, situación de desempleo, situación educativo o consumo de sustancias. iv); En el seguimiento a los 3 años, (Garrido-Torres, Ruiz-Veguilla, Olivé Mas, et al., 2022) se encontró que la prevalencia de MetS aumentó más en los PEP que en los controles y que los triglicéridos, el HDL y la perímetro abdominal alterados basalmente se asocian al riesgo de tener síndrome metabólico a los 3 años.

En un análisis más detallado, el estudio mostró diferencias entre los grupos en los componentes individuales de MetS. Así, el HDL, los triglicéridos y la glicemia se alteraron con mayor frecuencia en el grupo PEP que en el grupo control a los 3 años de seguimiento, y este empeoramiento se predijo por diferentes variables, en primer lugar, la edad se asoció a la presentación de hipertrigliceridemia e hiperglucemia 3 años después

y, en segundo lugar, el sexo y el nivel educativo aumentaron el riesgo de tener perímetro abdominal aumentada solamente en las mujeres con PEP.

Los pacientes con PEP tienen el doble de riesgo de presentar alteraciones metabólicas que la población general

Los pacientes con PEP, tienen el doble de riesgo de MetS que la población general, aunque no hayan tomado antipsicóticos. Es decir, los antipsicóticos no son la única causa del MetS. Existen otros factores que pueden explicar esas alteraciones que ya están presentes al inicio de la enfermedad.

El metaanálisis presentado en esta tesis doctoral (Garrido-Torres et al., 2021), es el primer metanálisis que incluye estudios con pacientes que nunca en su vida han estado expuestos a tratamiento antipsicótico. Los resultados son consistentes con otros metanálisis publicados, que incluyeron tanto pacientes con primer episodio psicótico expuestos a varias semanas de medicación como pacientes nunca tratados con antipsicóticos en etapas crónicas, encontrando una prevalencia de 9.8% (Mitchell, Vancampfort, De Herdt, et al., 2013). En contraste con esta investigación, fueron analizados específicamente los pacientes con un primer episodio psicótico sin exposición a antipsicóticos.

La prevalencia de MetS encontrada en los estudios transversal (Garrido-Torres, Ruiz-Veguilla, Alameda, et al., 2022) y longitudinal (Garrido-Torres, Ruiz-Veguilla, Olivé Mas, et al., 2022), en esta investigación, van en la línea de los realizados en poblaciones caucásicas en los cuales la prevalencia de MetS es más baja (Garcia-Rizo & Bitanihirwe, 2020; Martín Otaño et al., 2013b), en comparación con los estudios hechos en poblaciones no caucásicas (Effat et al., 2012; Sahpolat & Ari, 2020; Srihari et al., 2013). Sin embargo, a diferencia de los estudios encontrados en la revisión sistemática y

que no pudieron ser incluidos en el metaanálisis, el estudio transversal, aquí realizado, está hecho en pacientes que pueden considerarse verdaderamente naïve, ya que se aceptó como máximo dos días de tratamiento antipsicótico que incluye comparación con controles y análisis por sexo.

A pesar de la edad media joven de la muestra, la prevalencia de MetS aumentó significativamente más en los pacientes con PEP que en el grupo control. Sin embargo, al igual que en la población general (Moore et al., 2017), la edad de más de 30 años es un factor de riesgo para la hiperglucemia y la hipertrigliceridemia.

Es de notar, que aunque los antipsicóticos son indiscutiblemente eficaces en la mejoría de los síntomas psicóticos, la funcionalidad, la prevención de recaídas y la calidad de vida de las personas con esquizofrenia, los efectos secundarios metabólicos son comunes en pacientes tratados con antipsicóticos de segunda generación, particularmente clozapina y olanzapina (Pillinger et al., 2020). En este sentido, es de suponer que las diferencias entre los pacientes con PEP y los controles en la prevalencia de MetS a los 3 años de seguimiento pueden explicarse en parte por la exposición al tratamiento antipsicótico.

Además, se encontró que la detección de un aumento de la presión arterial a los tres años, está influenciada por el uso de antipsicóticos. A pesar de esto, no se encontraron diferencias significativas entre los tipos de fármacos analizados y el riesgo de desarrollar MetS a los 3 años de seguimiento, lo cual era de esperar, ya que recientemente se ha encontrado que el aripiprazol y la riesperidona, que fueron los fármacos analizados en el estudio longitudinal (Garrido-Torres, Ruiz-Veguilla, Olivé Mas, et al., 2022) tienen efectos metabólicos similares a largo plazo (Vázquez-Bourgon et al., 2022)

La esquizofrenia como parte de una enfermedad multisistémica

Una comprensión más sistémica de la esquizofrenia podría explicar el mayor riesgo metabólico en PEP independientemente del uso de antipsicóticos y podría modificar tanto la evaluación clínica como el tratamiento ofrecido a estos pacientes para prevenir y modificar no solo los síntomas neuropsiquiátricos, sino también el conjunto de síntomas que contribuyen a reducir su esperanza de vida.

La hipótesis de la esquizofrenia como una enfermedad sistémica ha sido propuesta por diferentes investigadores (Kirkpatrick et al., 2014; Mitchell & Dinan, 2010; Pillinger et al., 2019). Si se entiende la esquizofrenia como un conjunto de síntomas que va más allá de los síntomas psicóticos, se puede deducir que la exploración clínica exclusiva de síntomas psicóticos y del funcionamiento social es una exploración aún incompleta y que para que fuese realmente integral debería tener una evaluación física que incluyese otros sistemas. Así mismo, el tratamiento tanto farmacológico, como psicoterapéutico, como de rehabilitación social, no es un tratamiento completo necesariamente, si se aborda hacia los síntomas psicóticos exclusivamente. Es decir, la esquizofrenia podría considerarse una entidad clínica con manifestaciones psiquiátricas y manifestaciones no psiquiátricas y para que realmente el tratamiento sea beneficioso habría que enfocarse en todas sus dimensiones y sistemas, ya que como se ha expuesto, las muertes prematuras, se deben principalmente a causas no psiquiátricas.

En este contexto, recientes evidencias sugieren una vulnerabilidad genética que predispone específicamente a un subgrupo de individuos a presentar alteraciones metabólicas que se desencadenan por el uso de antipsicóticos (Crespo-Facorro et al., 2019). Además, el riesgo poligénico de esquizofrenia se asocia significativamente con la resistencia a la insulina en pacientes con esquizofrenia que no han recibido antipsicóticos (Tomasik et al., 2019), independientemente de factores demográficos, de

estilo de vida y clínicos seleccionados. Este resultado sugiere que la resistencia a la insulina es un sello distintivo de la esquizofrenia en lugar de un efecto secundario de los síntomas emergentes y apoya la hipótesis de que múltiples genes de susceptibilidad podrían ejercer efectos pleiotrópicos que ocurren simultáneamente entre las 2 condiciones. Adicionalmente, hay una asociación entre la resistencia a la insulina con la respuesta al tratamiento antipsicótico. Por lo tanto, los pacientes con esquizofrenia que presentan resistencia a la insulina podrían constituir un subgrupo de pacientes distinto y requerir un tratamiento personalizado adaptado a este endofenotipo.

Por otro lado, en una revisión reciente de modelos animales de esquizofrenia (Sanchez-Hidalgo et al., 2022) se ha encontrado relación entre la alteración reelina, que es una proteína asociadas con el neurodesarrollo y la esquizofrenia y dietas altas en grasa y calorías que inducen a la obesidad (Roberts et al., 2019), lo cual es otra evidencia de la interacción ambiental y genética en el desarrollo tanto de la esquizofrenia como de las alteraciones metabólicas.

Programación fetal metabólica

La programación fetal metabólica se refiere al de modificaciones epigenéticas que sufre el feto en respuesta a los estímulos recibidos de la madre para a asegurar su supervivencia. Se trata de un modelo que explicaría parcialmente la elevada frecuencia de alteraciones metabólicas en los pacientes con trastornos mentales y su reducida esperanza de vida. El peso al nacer es un marcador indirecto del ambiente intrauterino (Barker, 1990) y se ha demostrado que se asocia con parámetros metabólicos en la edad adulta, como la diabetes mellitus, obesidad abdominal e incremento de peso asociado al uso de antipsicóticos (García-Rizo et al., 2020; Garcia-Rizo & Bitanihirwe, 2020).

Además, varios estudios de cohortes han demostrado que la enfermedad cardiometabólica (Lawlor et al., 2006) y los trastorno psicóticos comparten factores

perinatales comunes, incluidos el bajo peso al nacer (Sørensen et al., 2016) y el parto prematuro (Morrison et al., 2016; Nosarti et al., 2012). Las deficiencias nutricionales en el útero pueden provocar cambios en el desarrollo neurológico que aumenten la vulnerabilidad a los trastornos psicóticos (Brown & Susser, 2008). Igualmente, estudios con roedores, han demostrado que el estrés prenatal aumenta el riesgo de diabetes y produce alteraciones de conducta homólogas a las de la esquizofrenia, en la descendencia (Koenig et al., 2002).

Exposoma específico: consumo de sustancias, estrés prenatal, trauma infantil

Además de los antipsicóticos, la dieta y el sedentarismo, la tendencia a la obesidad en un grupo de pacientes con esquizofrenia, puede estar influenciada por factores genéticos (Hasnain, 2015) y por el impacto de la adversidad social y el trauma en la infancia (Aas et al., 2017; Alameda et al., 2020). Se sabe que el trauma en la infancia se asocia a un peor funcionamiento social en las personas con trastorno psicótico (Christy et al., 2022). En este sentido, un aspecto a considerar en futuras investigaciones podría ser la posible vía que vincula el estrés psicosocial con los resultados relacionados con la obesidad en personas con trastorno psicótico, explorando el papel de la inflamación, las hormonas del estrés y los fundamentos genéticos y epigenéticos (Coleman et al., 2018).

Por otro lado, el tabaquismo es un factor de riesgo modificable, que se asocia con la mortalidad en personas con esquizofrenia (Dickerson et al., 2018). La alta prevalencia del consumo de tabaco y de cannabis en las personas con esquizofrenia es ampliamente conocida (Coustals et al., 2020). En la muestra del presente estudio, el 56% de los pacientes con PEP eran fumadores al inicio del estudio, siendo el consumo de tabaco mayor que en los controles. Sin embargo, el tabaco no está incluido en todos los algoritmos de riesgo metabólico como se discute más adelante en la sección de otros

predictores de riesgo cardiovascular. Así mismo, el consumo de cannabis se ha asociado con bajas probabilidades de MetS tanto en la población general (Vidot et al., 2016) y pacientes con PEP (Stiles et al., 2020), baja probabilidad de sobrepeso (Vazquez-Bourgon, Setien-Suero, et al., 2019) y baja probabilidad de hígado graso no alcohólico (Vazquez-Bourgon, Ortiz-Garcia de la Foz, et al., 2019a, 2019b) en pacientes con PEP a largo plazo.

Es necesario el estudio adicional del papel del cannabis en la modulación del MetS. El meta-análisis realizado (Garrido-Torres et al., 2021) solamente un estudio (Saloojee et al., 2018b) informó el consumo de cannabis. En el estudio transversal (Garrido-Torres, Ruiz-Veguilla, Alameda, et al., 2022) no fue observada influencia de cannabis en el desarrollo de MetS.

Exposoma general: capital social, entorno ambiental, normas culturales, etnicidad.

Varias investigaciones han abordado la influencia de los determinantes sociales en el MetS y los primeros episodios psicóticos, sin embargo se ha encontrado que independientemente de los hábitos de vida y de los antipsicóticos, existe asociación entre la resistencia a la insulina y PEP (Dixon et al., 2000; Kirkpatrick et al., 2012; Tomasik et al., 2019).

Una de las fortalezas de los artículos incluidos en esta tesis doctoral es que además de tener una muestra representativa, también se exploraron variables sociodemográficas. Se encontró que los pacientes con PEP son más frecuentemente solteros, viven solos y presentan un nivel socioeconómico más bajo que los controles. Estos factores son estresores adicionales, que pueden generar riesgo de comportamientos, como el consumo de tabaco y dietas poco saludables. Sin embargo, fue observado que la asociación entre HDL alterado y trastorno psicótico se mantiene independientemente de la influencia de estos factores confusores (sexo, nivel educativo, soltero, bajo nivel socioeconómico

familiar, zona urbana, desempleado, actualmente estudiante estado, consumo de cannabis, alcohol y cocaína). Así mismo, la asociación entre presión arterial alta y trastorno psicótico también sigue siendo significativa independientemente de estos. En el análisis exploratorio se encontró además que el nivel educativo y el sexo femenino aumentan el riesgo de tener mayor perímetro abdominal en personas con PEP.

El capital social hace referencia a aquellos aspectos potencialmente positivos de la vida social y se construye a través de redes, normas y confianza compartidas. La investigación sobre este constructo, su complejidad y el impacto en la salud general ha sido ampliamente estudiada, no habiendo un único consenso para su medición. Se acepta, que el capital social está compuesto básicamente por factores subjetivos que actúan para mantener unidas las redes y medidos por indicadores como la confianza, por ejemplo, el apoyo social y la satisfacción del vecindario y por factores que incluyen el apego a organizaciones como grupos religiosos, políticos, educativos y medido por la asistencia, la fuerza del compromiso y la inclusión en la sociedad. En este contexto, se sabe que la desventaja social y la barrera idiomática son factores de riesgo que influyen en el mayor riesgo de trastorno psicótico (Garrido-Torres, Alameda, Cristobal, et al., 2022) y también de MetS entre los grupos minoritarios, por lo tanto es necesario comprender mejor el impacto de tales fenómenos, así como explorar los factores que modulan esas asociaciones.

En el meta-análisis (Garrido-Torres et al., 2021), se identificó que una de las principales fuentes de heterogeneidad es el origen étnico, lo cual coincide con la mayoría de los estudios previos donde se han descrito diferencias étnicas en la prevalencia de MetS en pacientes con PEP (McEvoy et al., 2005; Tek et al., 2016). Teniendo en cuenta las diferencias en la contextura de la población asiática , más delgada con respecto a la occidental, no se puede medir el perímetro abdominal con los mismos criterios de MetS

(Lear et al., 2010). Además las poblaciones asiáticas tienen una menor prevalencia de obesidad (32,3% asiáticos frente a 38,6% occidentales) (Arai et al., 2006), colesterol HDL más bajo (8,2% frente a 37,1%) y triglicéridos más altos (23,0% frente a 30,0%). La prevalencia de MetS en la población general también podría ser menor que la de la población occidental. Cuatro de los estudios incluidos en la revisión sistemática (Chiliza et al., 2015; Correll et al., 2010; Owiredu et al., 2012; Saloojee et al., 2018a) mencionaron las diferencias étnicas como un posible elemento de confusión a la hora de determinar los resultados, y en dos de ellas (Chiliza et al., 2015; Saloojee et al., 2018a), se sugiere que esta es la principal fuente de variabilidad en la prevalencia de MetS en pacientes con PEP. La baja prevalencia de MetS en pacientes naïve podría explicarse porque se incluye una alta proporción de pacientes afrodescendientes (97%) y una alta prevalencia de consumo de cannabis (49,3%), ambos factores que pueden modificar el riesgo de presentar MetS . En la misma línea, se ha descrito (Patel et al., 2009) que para algunos grupos étnicos la prevalencia de MetS a las 52 semanas de tratamiento es casi el doble que la de los afrodescendientes. Por el contrario, varios estudios epidemiológicos han reportado que los afrodescendientes tienen un mayor riesgo de trastornos metabólicos como resistencia a la insulina y presión arterial alta (Chaturvedi, 2003). La explicación de esta contradicción podría ser la subestimación del riesgo de MetS en afrodescendientes jóvenes con PEP cuando se usan los criterios IDF y ATP-IIIA, ya que estos fueron creados inicialmente para poblaciones caucásicas y hay factores no debidamente tomados en cuenta, como la distribución de la grasa corporal y el riesgo de resistencia a la insulina (De Lucia Rolfe et al., 2015). Por lo tanto, partiendo de la base de ATP-IIIA y de IDF, varias sociedades científicas en países asiáticos y latinoamericanos han adaptado sus propios criterios de MetS.

En esta línea, se sabe que las poblaciones afrodescendientes tienen más riesgo de trastorno psicótico y a su vez de MetS. (Garrido-Torres, Alameda, Cristobal, et al., 2022; Garrido-Torres, Suarez-Suarez, Rocha-Gonzalez, et al., 2022; Garrido-Torres, Westmoreland, Piedra Cristóbal, et al., 2022). La literatura previa también ha informado sobre la asociación entre las alteraciones metabólicas, específicamente los lípidos, la presión arterial, la glucemia y la perímetro abdominal, dentro de algunos grupos étnicos y las formas en que la condición de minoría étnica se ha asociado con un peor perfil glucémico (Veru-Lesmes et al., 2018). Se ha demostrado que hay algunos grupos étnicos que, aun teniendo un perfil de HDL más benigno, presentan un riesgo cardiovascular elevado (Bravo & Velarde, 2015; Glueck et al., 1984). Hay factores sociales y ambientales como la pobreza, el estilo de vida y el capital social que podrían explicar por qué los grupos minoritarios migrantes tienen peores resultados metabólicos.

Por otro lado, existe una demanda por parte de la propia comunidad científica de realizar estudios de trastorno psicótico de una manera más inclusiva que permita explorar cómo las variaciones en los factores socioambientales en diferentes contextos sociales y geográficos podrían contribuir a diferentes factores de vulnerabilidad para los psicosis (Burkhard et al., 2021; Mote & Fulford, 2021). También es importante tener en cuenta que los criterios utilizados para el MetS pueden no ser adecuados para todos los grupos étnicos.

Dos de los estudios incluidos en el metanálisis, (Owiredu et al., 2012; Saloojee et al., 2018a) fueron los únicos realizados sobre la etnia afrodescendiente y la prevalencia global de MetS aumentó cuando estos fueron eliminados en los análisis de sensibilidad. En el meta-análisis (Garrido-Torres et al., 2021) se halló una prevalencia elevada de MetS en individuos con PEP que no habían recibido antipsicóticos y sugiere que el riesgo

cardiovascular en estos pacientes podría estar subestimado, especialmente en aquellos de origen no caucásico.

El papel del género

Otra de las fortalezas del estudio transversal, además de la muestra representativa y la nula exposición a antipsicóticos, es la estratificación por género en todos los análisis. Al respecto, se encontró que las mujeres con PEP son más propensas a presentar mayor perímetro abdominal que los hombres con PEP. Esta diferencia no se observó en el grupo control. Los resultados son congruentes con estudios previos que han demostrado que el trastorno psicótico per se aumenta el riesgo de perímetro abdominal elevado (Osby et al., 2014) y que las mujeres, presentan alteraciones metabólicas, independientemente del tratamiento antipsicótico (Zhang et al., 2021). Además, se han identificado variantes genéticas en pacientes con trastorno psicótico con perímetro abdominal elevado. (Hukic et al., 2017).

De la misma forma, las mujeres con esquizofrenia crónica, presentan una mayor prevalencia de MetS que los hombres (Bener et al., 2014; Huang, 2009; Kraal et al., 2017; Wei et al., 2020). Se sabe que el perímetro abdominal tiene una relación lineal significativa con el riesgo de infarto de miocardio y la enfermedad cerebrovascular (Cho et al., 2019) y que es mejor predictor de estos eventos que el índice de masa corporal. Las investigaciones futuras deben tener en cuenta si este hallazgo se acentúa con la introducción de algún antipsicótico concreto, y así llevar a cabo medidas de prevención específicas para las mujeres.

Otros predictores de riesgo cardiovascular en PEP

Los resultados expuestos a lo largo de los tres artículos son muy relevantes clínicamente, y se puede concluir que los algoritmos cardiometabólicos disponibles actualmente son de poca utilidad en la población de personas jóvenes con PEP debido a

varias razones: en primer lugar, se trata de una población que tiende a buscar menos atención médica, por lo que existe un riesgo de sesgo de infradiagnóstico. Por otro lado, ciertas alteraciones metabólicas requieren un curso de tiempo para llegar a desarrollar la enfermedad, aunque se sabe que, a pesar de no alcanzar valores de umbral diagnóstico, pueden asociarse con mayores resultados de morbilidad y morbilidad a largo plazo. Por lo tanto, aunque los algoritmos actuales son útiles en la población general, no detectan a tiempo las alteraciones metabólicas que predicen el riesgo cardiovascular y que tal y como se ha descrito a lo largo de toda la tesis doctoral son inherentes a la esquizofrenia y aparecen de forma muy temprana.

El MetS es un predictor de riesgo cardiovascular, sin embargo, a los 5 -10 años, el riesgo se calcula mejor con escalas clásicas (Framingham o SCORE), que incluyen edad, sexo, colesterol total, LDL y consumo de tabaco (Grundy, 2006). En este estudio se encontró que la prevalencia del consumo de tabaco es alta entre los pacientes con PEP; teniendo en cuenta que un gran porcentaje de los pacientes con esquizofrenia son fumadores, sería útil incluir la influencia del tabaco en los futuros predictores de riesgo cardiovascular diseñados específicamente para personas jóvenes con PEP.

Existen otros predictores de riesgo cardiovascular como el FRAMINGHAM, que predice el riesgo de enfermedad cardiovascular coronaria y que es el más utilizado en Estados Unidos, y la escala SCORE que predice la mortalidad cardiovascular en la población europea. Ambos instrumentos se realizan en base a la población general y tienen poca aplicabilidad en pacientes con trastorno psicótico ya que la prevalencia de enfermedades psiquiátricas no se especifica en la muestra que sirvió para su elaboración. La principal limitación de estas escalas de riesgo cardiovascular es que están diseñadas para pacientes mayores de 45 años, cuando la edad media de inicio de los trastornos psicóticos es mucho menor. Si se hubiese utilizado el Framinghan o el SCORE para medir

el riesgo utilizando la edad media de los estudios incluidos en esta tesis doctoral (edad media 32 años), el riesgo cardiovascular estaría subestimado. También hay que resaltar que estos instrumentos fueron desarrollados hace más de 2 décadas, es decir, antes de que se diera la voz de alarma sobre el déficit en la atención a la salud física de la población con esquizofrenia.

Entre los algoritmos existentes para predecir el riesgo cardiovascular en la esquizofrenia se encuentra PRIMROSE, que, aunque está validado en enfermedades mentales, está pensado para pacientes crónicos con esquizofrenia (Osborn et al., 2015) y no es útil en jóvenes con fases iniciales de psicosis (B. I. Perry et al., 2021). Así mismo, el metaanálisis que se incluye como compendio en esta tesis doctoral (Garrido-Torres et al., 2021) identificó la etnicidad como la principal fuente de heterogeneidad, lo que sugiere que la etnicidad debería considerarse en los algoritmos de predicción.

La alteración de parámetros metabólicos individuales como las alteraciones glucémicas o lipídicas, está ampliamente descrita en la literatura existente. En dos metanálisis recientes (B. I. Perry et al., 2016b; Pillinger, Beck, Gobjila, et al., 2017) encontraron una mayor resistencia a la insulina en la PEP sin fármacos en comparación con los controles. Por esta razón, se ha propuesto el uso de otros marcadores como la resistencia a la insulina como predictor de riesgo cardiovascular (Garcia-Rizo et al., 2017). La mayoría de los estudios analizados en el metaanálisis muestran que, de los componentes individuales, la perímetro abdominal y el HDL son los parámetros que más se relacionan con la prevalencia de MetS. Hasta la fecha, se han desarrollado varios algoritmos de predicción del riesgo cardiovascular, pero solo tres están validados en pacientes psiquiátricos (QRISK3, QDiabetes y PRIMROSE) sin embargo, solamente han sido validados con muestras de adultos mayores (B. I. Perry et al., 2020).

Aunque en el presente estudio transversal (Garrido-Torres et al., 2022), la prevalencia de MetS fue similar tanto en los PEP como en los controles sanos, surge la pregunta: ¿realmente el constructo de síndrome metabólico es un predictor adecuado en pacientes con PEP?, en los cuales ya está demostrado que existen alteraciones metabólicas basales previas al uso de antipsicóticos.

Limitaciones

Las principales limitaciones de este trabajo deben ser expuestas. Con respecto al metaanálisis, en primer lugar, se hizo todo lo posible para tener en cuenta la heterogeneidad potencial resultante de los diferentes criterios de MetS (realizar análisis de sensibilidad según los estudios que utilizaron IDF o ATP-IIIA y realizar metanálisis separados con estudios que informaron la prevalencia con ATPIII-A y con IDF), no fue posible tener en cuenta las variaciones en todos los criterios (p.ej. JIS-2009 y los criterios de la OMS). En segundo lugar, no fue posible excluir a los pacientes/controles a los que se les prescribieron otros psicofármacos que se sabe que afectan la función metabólica. Tampoco fue posible tener en cuenta el nivel de síntomas depresivos o de depresión comórbida en nuestras metarregresiones, un factor conocido por estar asociado con los resultados relacionados con la obesidad (Lasserre et al., 2014), por lo que no se puede excluir que la depresión influya en nuestras estimaciones de prevalencia. Ahora bien, no fue posible recopilar información sobre traumas previos y estrés prenatal ambos factores relacionados con el sobrepeso en personas con trastorno psicótico. En tercer lugar, se sabe que las personas con trastornos psicóticos tienen menos probabilidades de presentarse a los servicios de salud física en comparación con la población general. Como tal, existe el riesgo de subnotificación y, por lo tanto, de subestimar la prevalencia de MetS en esta cohorte.

Perspectivas de investigaciones futuras

La investigación futura debería centrarse en los predictores del riesgo cardiovascular, incluidos los factores moleculares y ambientales comunes, en tanto que los hallazgos de esta investigación, respaldan que los parámetros metabólicos alterados en los PEP no se deben exclusivamente a los tratamientos antipsicóticos.

Recientemente, en el Reino Unido se desarrolló y validó externamente la Calculadora de riesgo metabólico de trastorno psicótico (PsyMetRiC), la cual ha demostrado predecir hasta seis años de riesgo de MetS a partir de datos clínicos recopilados de forma rutinaria. El modelo completo incluye: edad, sexo, origen étnico, índice de masa corporal, tabaquismo, prescripción de medicamentos antipsicóticos metabólicamente activos, lipoproteínas de alta densidad y triglicéridos. (B. I. Perry et al., 2021). Esta calculadora fue validada en dos muestras europeas independientes: PsyMetab de Lausana, Suiza y la cohorte PAFIP de España. En el futuro, PsyMetRiC podría ayudar a identificar pacientes jóvenes con trastorno psicótico que presenten mayor riesgo cardiometabólico, de esta forma las intervenciones podrían dirigirse de manera efectiva para reducir la morbilidad y la mortalidad a largo plazo (B. Perry et al., 2022)

A pesar de que la relación entre MetS y PEP está clara, aún no se sabe si el MetS es específico de esquizofrenia o si también se observa en trastorno psicótico breve, trastorno bipolar o trastorno límite personalidad. Para resolver esta cuestión habría que diseñar estudios con muestras grandes. Así mismo, sería importante determinar si las alteraciones metabólicas están presentes en todos los trastornos psicóticos o si corresponden a un marcador de gravedad.

Es pertinente considerar que los ensayos clínicos que evalúen la efectividad de los antipsicóticos atípicos en pacientes jóvenes con PEP, requieren modelos que puedan estudiar los factores comunes endógenos que subyacen entre MetS y PEP.

También es importante caracterizar otros moderadores potenciales de los conocidos efectos secundarios de los antipsicóticos, incluidos los factores estresantes ambientales y el trauma infantil (ya que son moderadores de huellas epigenéticas (Tomassi & Tosato, 2017), el desempleo (Pandit et al., 2019), el consumo de tabaco, alcohol y cannabis (Scheffler et al., 2018) la etnicidad (Veru-Lesmes et al., 2018) la psicopatología (ya que los síntomas negativos podrían estar asociados con peores resultados metabólicos (Strassnig et al., 2007), los hábitos dietéticos y el ejercicio que contribuyen a las anomalías metabólicas y los pacientes en etapas tempranas de la enfermedad psicótica muestran malos hábitos de vida (Manzanares et al., 2014).

Además, las investigaciones futuras deben encaminarse a tener en cuenta la perspectiva de género y esclarecer si la mayor prevalencia de alteraciones metabólicas previas al uso de antipsicóticos en mujeres con PEP (aun cuando el PEP es un trastorno más frecuente en hombres) es un marcador de gravedad o si este hallazgo se acentúa con la introducción de algún antipsicótico concreto, y así llevar a cabo medidas de prevención específicas para las mujeres y recomendaciones en cuanto a la elección del tratamiento.

Conclusiones

- Los pacientes con primer episodio psicótico tienen más riesgo de síndrome metabólico y más alteraciones metabólicas que la población general.
- Estas alteraciones no se deben exclusivamente al uso de antipsicóticos.
- Hay varias causas que podrían justificar la presencia de esas alteraciones metabólicas previas al inicio de antipsicóticos en pacientes jóvenes. Una de ellas es la hipótesis de la esquizofrenia como parte de una enfermedad multisistémica con origen en etapas muy tempranas del desarrollo y que además del cerebro, compromete otros órganos.
- Es necesario tener herramientas de medida de riesgo cardiovascular de acuerdo a población joven con primer episodio psicótico
- Aunque los trastornos psicóticos, son más prevalentes en hombres, las mujeres con primer episodio psicótico presentan algunas alteraciones metabólicas específicas con más frecuencia que los hombres previos al uso de antipsicóticos.
- Las particularidades de la étnia y del género con respecto al riesgo de alteraciones metabólicas, deberían tenerse en cuenta en futuras investigaciones de cara a las recomendaciones terapéuticas y elección de antipsicóticos.

Conclusions

- Patients with FEP have a higher risk of metabolic syndrome and more metabolic disturbances than the general population.
- These alterations are not due exclusively to the use of antipsychotics.
- There are several causes that could justify the presence of these alterations in young patients, one of them is the hypothesis of schizophrenia as part of a systemic disease that originates in the early stages of development and that in addition to the brain, involves other organs.
- It is necessary to have cardiovascular risk measurement tools validated in young people with first psychotic episodes.
- Women with first psychotic episode present some specific alterations more frequently than men prior to the use of antipsychotics.
- Taking into account the particularities of ethnicity and gender in relation to the risk of developing metabolic syndrome in future research would assist in offering specific therapeutic recommendations to both populations.

Estancia internacional

Factores prenatales que influyen en las alteraciones metabólicas y en los trastornos del neurodesarrollo.

La herencia epigenética y el desarrollo prenatal han recibido recientemente una atención considerable dentro de la comunidad investigadora como dos factores a considerar en la etiopatogenia de la obesidad en la población general (Danese & Tan, 2014) y en individuos con trastornos mentales (Alameda et al., 2022). En este sentido, se ha demostrado una relación entre obesidad, maltrato infantil y marcadores inflamatorios elevados en adultos con esquizofrenia (Aas et al., 2017). Por lo tanto, se ha establecido la relación entre el estrés de la vida temprana, la programación metabólica fetal y la esquizofrenia (Garcia-Rizo & Bitanihirwe, 2020) a través de marcadores epigenéticos. En consecuencia, se ha demostrado que las experiencias psicosociales estresantes intrauterinas y/o durante la infancia dejan huellas epigenéticas y pueden interpretarse como factores de riesgo potencialmente modificables

En este contexto, cada vez hay más evidencia de los perjuicios que la actual pandemia SARS-COV-2 ha traído para la salud mental de las madres y de sus descendientes. Estudios epidemiológicos, realizados en otros periodos pandémicos, apoyan la idea de que la activación del sistema inmunitario durante el embarazo tiene importantes consecuencias para el neurodesarrollo fetal y parece estar estrechamente relacionada con los posteriores trastornos del desarrollo como la esquizofrenia y el autismo (Menninger, 1994; Torrey et al., 2012); existe una asociación epidemiológica entre la exposición a la infección por gripe (H1N1) durante el embarazo y un mayor riesgo de desarrollar trastornos neuropsiquiátricos, lo que sugiere que la activación del sistema

inmunitario materno y una respuesta inflamatoria en el feto pueden ser el origen de un desarrollo cerebral anormal (Khambadkone et al., 2020). No solo las pandemias de agentes infecciosos se han relacionado con un impacto intrauterino del sistema nervioso central, también otros desastres naturales (como terremotos, inundaciones), se han asociado a un impacto negativo en la salud mental de las madres, así como del neurodesarrollo del RN (Harville et al., 2010), siendo determinante el grado de nivel de exposición a la catástrofe. Para profundizar en el impacto del estrés emocional y la infección prenatal en el neurodesarrollo y en las alteraciones metabólicas, actualmente se están llevando a cabo varios estudios en cohortes de mujeres embarazadas durante la pandemia y sus futuros hijos. Entre ellos, está el proyecto MOM-COPE liderado por el profesor Livio Provenzi (Provenzi et al., 2020) y el proyecto *Signature* liderado por Nathalia Garrido Torres y el grupo de Psiquiatría traslacional. (Garrido-Torres, 2022).

Una de las críticas y aportes más frecuentemente hecha por los revisores en dos de los tres artículos que forman parte de este compendio , fue la consideración de factores prenatales y epigenéticos como causa de alteraciones metabólicas y del neurodesarrollo en pacientes, en el contexto de una comprensión sistémica de la esquizofrenia. Estos aspectos se han discutido tanto en los artículos publicados como en el apartado de programación fetal metabólica.

Por este motivo, durante tres meses de mi etapa predoctoral, tuve la oportunidad de realizar una estancia internacional, bajo la supervisión del profesor Livio Provenzi en el Developmental Psychology Lab de la Universidad de Pavía y el Pediatric Neuroscience Center del Neurological Institute Foundation Casimiro Mondino. El profesor Provenzi centra sus investigaciones en las huellas epigenéticas resultantes del estrés prenatal

durante la actual pandemia (Grumi et al., 2021; Provenzi et al., 2020, 2021, 2022). Estos meses, he podido analizar conjuntamente datos de la cohorte *signature* y de la cohorte MOM-COPE sobre el impacto del estrés prenatal en las alteraciones metabólicas y en el neurodesarrollo y redactar un manuscrito que se encuentra en revisión: **"The impact of SARS-COV-2 infection on offspring birth weight: new evidence data from signature cohort. Under review"**. Además he tenido la oportunidad de discutir con el Profesor Provenzi y con su equipo los resultados de estas tesis doctoral y los relacionados con los proyectos de estrés prenatal durante el embarazo para así ampliar la discusión de esta memoria y futuras investigaciones. Esta estancia me permitirá aspirar al título de doctor internacional.

Referencias

Aas, M., Dieset, I., Hope, S., Hoseth, E., Mørch, R., Reponen, E., Steen, N. E., Laskemoen, J. F., Ueland, T., Aukrust, P., Agartz, I., Andreassen, O. A., & Melle, I. (2017). Childhood maltreatment severity is associated with elevated C-reactive protein and body mass index in adults with schizophrenia and bipolar diagnoses. *Brain, Behavior, and Immunity*, *65*, 342–349. https://doi.org/10.1016/j.bbi.2017.06.005

Alameda, L., Levier, A., Gholam-Rezaee, M., Golay, P., Vandenberghe, F., Delacretaz, A., Baumann, P., Glatard, A., Dubath, C., Herane-Vives, A., Rodriguez, V., Solida, A., Do, K. Q., Eap, C. B., & Conus, P. (2020). Psychological trauma occurring during adolescence is associated with an increased risk of greater waist circumference in Early Psychosis patients treated with psychotropic medication. *PloS One*, *15*(12), e0242569. https://doi.org/10.1371/journal.pone.0242569

Alameda, L., Trotta, G., Quigley, H., Rodriguez, V., Gadelrab, R., Dwir, D., Dempster, E., Wong, C. C. Y., & Forti, M. D. (2022). Can epigenetics shine a light on the biological pathways underlying major mental disorders? *Psychological Medicine*, 1–21. https://doi.org/10.1017/S0033291721005559

Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Walters, R. K., Bras, J., Duncan, L., Escott-Price, V., Falcone, G. J., Gormley, P., Malik, R., Patsopoulos, N. A., Ripke, S., Wei, Z., Yu, D., Lee, P. H., Turley, P., Grenier-Boley, B., Chouraki, V., Kamatani, Y., … Murray, R. (2018). Analysis of shared heritability in common disorders of the brain. *Science (New York, N.Y.)*, *360*(6395). https://doi.org/10.1126/science.aap8757

Arai, H., Yamamoto, A., Matsuzawa, Y., Saito, Y., Yamada, N., Oikawa, S., Mabuchi, H., Teramoto, T., Sasaki, J., Nakaya, N., Itakura, H., Ishikawa, Y., Ouchi, Y., Horibe, H., Shirahashi, N., & Kita, T. (2006). Prevalence of metabolic syndrome in the general Japanese population in 2000. *Journal of Atherosclerosis and Thrombosis*, *13*(4), 202–208. https://doi.org/10.5551/jat.13.202

Ayesa-Arriola, R., Perez-Iglesias, R., Rodriguez-Sanchez, J. M., Mata, I., Gomez-Ruiz, E., Garcia-Unzueta, M., Martinez-Garcia, O., Tabares-Seisdedos, R., Vazquez-Barquero, J. L., & Crespo-Facorro, B. (2012). Homocysteine and cognition in first-episode psychosis patients. *European Archives of Psychiatry and Clinical Neuroscience*, *262*(7), 557–564. https://doi.org/10.1007/s00406-012-0302-2

Ayme, C., & Chute, J. (2010). Discusion paper: Multisystem disorders. *ICD Revision*. http://bit.ly/2nnilKW.

Barker, D. J. (1990). The fetal and infant origins of adult disease. *BMJ (Clinical Research Ed.)*, *301*(6761), 1111. https://doi.org/10.1136/bmj.301.6761.1111

Bener, A., Al-Hamaq, A. O. A. A., & Dafeeah, E. E. (2014). A two fold risk of metabolic syndrome in a sample of patients with schizophrenia: Do consanguinity and family history increase risk? *Diabetes & Metabolic Syndrome*, *8*(1), 24–29. https://doi.org/10.1016/j.dsx.2013.10.003

Bobes, J., Arango, C., Aranda, P., Carmena, R., Garcia-Garcia, M., & Rejas, J. (2007). Cardiovascular and metabolic risk in outpatients with schizophrenia treated with antipsychotics: Results of the CLAMORS Study. *Schizophrenia Research*, *90*(1–3), 162–173. https://doi.org/10.1016/j.schres.2006.09.025

Bravo, K., & Velarde, G. P. (2015). Ethnicity and coronary artery disease: The role of high-density lipoprotein—A change in paradigm. *Expert Review of*

Cardiovascular Therapy, *13*(8), 923–931. https://doi.org/10.1586/14779072.2015.1065178

Brown, A. S., & Susser, E. S. (2008). Prenatal nutritional deficiency and risk of adult schizophrenia. *Schizophrenia Bulletin*, *34*(6), 1054–1063. https://doi.org/10.1093/schbul/sbn096

Burkhard, C., Cicek, S., Barzilay, R., Radhakrishnan, R., & Guloksuz, S. (2021). Need for Ethnic and Population Diversity in Psychosis Research. *Schizophrenia Bulletin*, *47*(4), 889–895. https://doi.org/10.1093/schbul/sbab048

Chadda, R. K., Ramshankar, P., Deb, K. S., & Sood, M. (2013). Metabolic syndrome in schizophrenia: Differences between antipsychotic-naïve and treated patients. *Journal of Pharmacology & Pharmacotherapeutics*, *4*. edsair. https://doi.org/10.4103/0976-500X.114596

Chaturvedi, N. (2003). Ethnic differences in cardiovascular disease. *Heart (British Cardiac Society)*, *89*(6), 681–686. PubMed. https://doi.org/10.1136/heart.89.6.681

Chiliza, B., Asmal, L., Oosthuizen, P., van Niekerk, E., Erasmus, R., Kidd, M., Malhotra, A., & Emsley, R. (2015). Changes in body mass and metabolic profiles in patients with first-episode schizophrenia treated for 12 months with a first-generation antipsychotic. *European Psychiatry : The Journal of the Association of European Psychiatrists*, *30*(2), 277–283. cmedm. https://doi.org/10.1016/j.eurpsy.2014.11.013

Cho, J. H., Rhee, E. J., Park, S. E., Kwon, H., Jung, J. H., Han, K. D., Park, Y. G., Park, H. S., Kim, Y. H., Yoo, S. J., & Lee, W. Y. (2019). The Risk of Myocardial Infarction and Ischemic Stroke According to Waist Circumference in 21,749,261

Korean Adults: A Nationwide Population-Based Study. *Diabetes & Metabolism Journal*, *43*(2), 206–221. https://doi.org/10.4093/dmj.2018.0039

Christy, A., Cavero, D., & Navajeeva,S., murray-oshea, R., Rodriguez, V., Aas, M., Wrobel, A., Zafra, B., Moudiab, S., Sideli, L., **Garrido-Torres, N**, Salazar de Pablo, G, Alameda, L (2022). Association between childhood adversity and functional outcomes in people with psychosis: A meta-analysis. *Schizophrenia Bulletin*. https://doi.org/Accepted

Coleman, J. R. I., Krapohl, E., Eley, T. C., & Breen, G. (2018). Individual and shared effects of social environment and polygenic risk scores on adolescent body mass index. *Scientific Reports*, *8*(1), 6344. https://doi.org/10.1038/s41598-018-24774-5

Cordes, J., Bechdolf, A., & Moebus, S. (2016). Prevalence of the metabolic syndrome in patients at risk of psychosis. *European Psychiatry*, *33*(Supplement), S92–S92. edselp.http://www.bvsspa.es/papi/ezproxy.php?url=http://search.ebscohost.com/login.aspx?direct=true&db=edselp&AN=S0924933816000626&lang=es&site=eds-live&scope=site

Correll, C. U., Druss, B. G., Lombardo, I., O'Gorman, C., Harnett, J. P., Sanders, K. N., Alvir, J. M., & Cuffel, B. J. (2010). Findings of a U.S. national cardiometabolic screening program among 10,084 psychiatric outpatients. *Psychiatric Services (Washington, D.C.)*, *61*(9), 892–898. cmedm. https://doi.org/10.1176/ps.2010.61.9.892

Correll, C. U., Robinson, D. G., Schooler, N. R., Brunette, M. F., Mueser, K. T., Rosenheck, R. A., Marcy, P., Addington, J., Estroff, S. E., Robinson, J., Penn, D. L., Azrin, S., Goldstein, A., Severe, J., Heinssen, R., & Kane, J. M. (2014).

Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: Baseline results from the RAISE-ETP study. *JAMA Psychiatry*, *71*(12), 1350–1363. https://doi.org/10.1001/jamapsychiatry.2014.1314

Correll, C. U., Solmi, M., Veronese, N., Bortolato, B., Rosson, S., Santonastaso, P., Thapa-Chhetri, N., Fornaro, M., Gallicchio, D., Collantoni, E., Pigato, G., Favaro, A., Monaco, F., Kohler, C., Vancampfort, D., Ward, P. B., Gaughran, F., Carvalho, A. F., & Stubbs, B. (2017). Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: A large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry : Official Journal of the World Psychiatric Association (WPA)*, *16*(2), 163–180. https://doi.org/10.1002/wps.20420

Coustals, N., Martelli, C., Brunet-Lecomte, M., Petillion, A., Romeo, B., & Benyamina, A. (2020). Chronic smoking and cognition in patients with schizophrenia: A meta-analysis. *Schizophrenia Research*, *222*, 113–121. https://doi.org/10.1016/j.schres.2020.03.071

Crespo-Facorro, B., Prieto, C., & Sainz, J. (2019). Altered gene expression in antipsychotic-induced weight gain. *NPJ Schizophrenia*, *5*(1), 7. https://doi.org/10.1038/s41537-019-0075-y

Danese, A., & Tan, M. (2014). Childhood maltreatment and obesity: Systematic review and meta-analysis. *Molecular Psychiatry*, *19*(5), 544–554. https://doi.org/10.1038/mp.2013.54

De Hert, M., Schreurs, V., Sweers, K., Van Eyck, D., Hanssens, L., Sinko, S., Wampers, M., Scheen, A., Peuskens, J., & van Winkel, R. (2008). Typical and atypical antipsychotics differentially affect long-term incidence rates of the metabolic syndrome in first-episode patients with schizophrenia: A retrospective chart

review. *Schizophrenia Research*, *101*(1–3), 295–303. https://doi.org/10.1016/j.schres.2008.01.028

De Lucia Rolfe, E., Ong, K. K., Sleigh, A., Dunger, D. B., & Norris, S. A. (2015). Abdominal fat depots associated with insulin resistance and metabolic syndrome risk factors in black African young adults. *BMC Public Health*, *15*, 1013. https://doi.org/10.1186/s12889-015-2147-x

Dickerson, F., Origoni, A., Schroeder, J., Adamos, M., Katsafanas, E., Khushalani, S., Savage, C. L. G., Schweinfurth, L. A. B., Stallings, C., Sweeney, K., & Yolken, R. (2018). Natural cause mortality in persons with serious mental illness. *Acta Psychiatrica Scandinavica*, *137*(5), 371–379. https://doi.org/10.1111/acps.12880

Dixon, L., Weiden, P., Delahanty, J., Goldberg, R., Postrado, L., Lucksted, A., & Lehman, A. (2000). Prevalence and correlates of diabetes in national schizophrenia samples. *Schizophrenia Bulletin*, *26*(4), 903–912. https://doi.org/10.1093/oxfordjournals.schbul.a033504

Eckel, R. H., Grundy, S. M., & Zimmet, P. Z. (2005). The metabolic syndrome. *Lancet (London, England)*, *365*(9468), 1415–1428. https://doi.org/10.1016/S0140-6736(05)66378-7

Effat et al., S. (2012). Metabolic syndrome in a sample of drug-naive egyptian patients with psychotic disorders. In *INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY* (Vol. 15, p. 48).

Enez Darcin, A., Yalcin Cavus, S., Dilbaz, N., Kaya, H., & Dogan, E. (2015). Metabolic syndrome in drug-naïve and drug-free patients with schizophrenia and in their siblings. *Schizophrenia Research*, *166*(1–3), 201–206. https://doi.org/10.1016/j.schres.2015.05.004

Fernandes, B. S., Steiner, J., Bernstein, H.-G., Dodd, S., Pasco, J. A., Dean, O. M., Nardin, P., Gonçalves, C.-A., & Berk, M. (2016). C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: Meta-analysis and implications. *Molecular Psychiatry*, *21*(4), 554–564. https://doi.org/10.1038/mp.2015.87

Fernandez-Egea, E., Bernardo, M., Parellada, E., Justicia, A., Garcia-Rizo, C., Esmatjes, E., Conget, I., & Kirkpatrick, B. (2008). Glucose abnormalities in the siblings of people with schizophrenia. *Schizophrenia Research*, *103*(1–3), 110–113. edselp. http://www.bvsspa.es/papi/ezproxy.php?url=http://search.ebscohost.com/login.aspx?direct=true&db=edselp&AN=S0920996408002004&lang=es&site=eds-live&scope=site

Fleischhacker, W. W., Siu, C. O., Bodén, R., Pappadopulos, E., Karayal, O. N., Kahn, R. S., & EUFEST study group. (2013). Metabolic risk factors in first-episode schizophrenia: Baseline prevalence and course analysed from the European First-Episode Schizophrenia Trial. *The International Journal of Neuropsychopharmacology*, *16*(5), 987–995. https://doi.org/10.1017/S1461145712001241

García-Rizo, C., Bioque, M., Mezquida, G., Amoretti, S., Cuesta, M. J., Díaz-Caneja, C. M., Mas, S., Lobo, A., González-Pinto, A., Fraguas, D., Corripio, I., Vieta, E., Baeza, I., Bergé, D., Fernandez-Egea, E., Garriga, M., & Bernardo, M. (2020). Birth weight and antipsychotic induced weight gain: A prenatal programming approach in the PEPs study. *Schizophrenia Research*, *218*, 292–294. https://doi.org/10.1016/j.schres.2019.12.030

Garcia-Rizo, C., & Bitanihirwe, B. K. Y. (2020). Implications of early life stress on fetal metabolic programming of schizophrenia: A focus on epiphenomena underlying

morbidity and early mortality. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *101*, 109910. https://doi.org/10.1016/j.pnpbp.2020.109910

Garcia-Rizo, C., Fernandez-Egea, E., Oliveira, C., Meseguer, A., Cabrera, B., Mezquida, G., Bioque, M., Penades, R., Parellada, E., Bernardo, M., & Kirkpatrick, B. (2017). Metabolic syndrome or glucose challenge in first episode of psychosis? *European Psychiatry: The Journal of the Association of European Psychiatrists*, *41*, 42–46. https://doi.org/10.1016/j.eurpsy.2016.10.001

García-Rizo, C., Ortiz García de la Foz, V., Mayoral-van Son, J., Gómez-Revuelta, M., Juncal Ruiz, M., **Garrido-Torres**, N., Crespo-Facorro, B., & Vázquez-Bourgon, J. (2022). Reduced glomerular filter rate in antipsychotic-naïve patients with first-episode psychosis. *Schizophrenia Research*, *246*, 202–204. https://doi.org/10.1016/j.schres.2022.06.016

Garrido-Torres, N. (2022). Examining the immune signatures of SARS-CoV-2 infection in pregnancy and the impact on neurodevelopment: Protocol of the SIGNATURE longitudinal study. *Frontiers in Pediatrics*. https://doi.org/ Under review

Garrido-Torres, N., Alameda, L., Cristobal, J. P., Padilla, M. V., Robles, C. S., Canal-Rivero, M., Crespo-Facorro, B., & Ruiz-Veguilla, M. (2022). Examining the relationship between psychosis and immigration in Spain: The effect of cannabis use and language barrier in a large psychosis sample. *Journal of Psychiatric Research*, *145*, 361–365. https://doi.org/10.1016/j.jpsychires.2021.11.005

Garrido-Torres, N., Rocha-Gonzalez, I., Alameda, L., Rodriguez-Gangoso, A., Vilches, A., Canal-Rivero, M., Crespo-Facorro, B., & Ruiz-Veguilla, M. (2021). Metabolic syndrome in antipsychotic-naive patients with first-episode psychosis:

A systematic review and meta-analysis. *Psychological Medicine*, *51*(14), 2307–2320. https://doi.org/10.1017/S0033291721002853

Garrido-Torres, N., Ruiz-Veguilla, M., Alameda, L., Canal-Rivero, M., Ruiz, M. J., Gómez-Revuelta, M., Ayesa-Arriola, R., Rubio-García, A., Crespo-Facorro, B., & Vázquez-Bourgon, J. (2022). 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. *Schizophrenia Research*, *246*, 277–285. https://doi.org/10.1016/j.schres.2022.07.007

Garrido-Torres, N., Ruiz-Veguilla, M., Olivé Mas, J., Rodríguez Gangoso, A., Canal-Rivero, M., Juncal-Ruiz, M., Gómez-Revuelta, M., Ayesa-Arriola, R., Crespo-Facorro, B., & Vázquez-Bourgon, J. (2022). Metabolic syndrome and related factors in a large sample of antipsychotic naïve patients with first-episode psychosis: 3 years follow-up results from the PAFIP cohort. *Revista de Psiquiatría y Salud Mental*. https://doi.org/10.1016/j.rpsm.2022.05.003

Garrido-Torres, N., Suarez-Suarez, M. L., Rocha-Gonzalez, I., Alameda, L., Giner, L., Canal-Rivero, M., Crespo-Facorro, B., & Ruiz-Veguilla, M. (2022). Higher rates of first episode psychosis in immigrants admitted in inpatient unit at southwest Spain. *Psychiatry Research*, *308*, 114352. https://doi.org/10.1016/j.psychres.2021.114352

Garrido-Torres, N., Westmoreland, S., Piedra Cristóbal, J., Canal-Rivero, M., Crespo-Facorro, B., & Ruiz-Veguilla, M. (2022). The role of migrant status on metabolic alterations at the onset of psychosis. *Social Psychiatry and Psychiatric Epidemiology*. https://doi.org/Enviado

Glueck, C. J., Gartside, P., Laskarzewski, P. M., Khoury, P., & Tyroler, H. A. (1984). High-density lipoprotein cholesterol in blacks and whites: Potential ramifications

for coronary heart disease. *American Heart Journal*, *108*(3 Pt 2), 815–826. https://doi.org/10.1016/0002-8703(84)90677-x

Grover, S., Nebhinani, N., Padmavati, R., Chadda, R. K., Tirupati, S., & Pallava, A. (2015). Metabolic syndrome in antipsychotic naïve patients with schizophrenia: Pooled analysis of data from three Indian studies. *Early Intervention in Psychiatry*, *9*(5), 357–362. https://doi.org/10.1111/eip.12117

Grumi, S., Provenzi, L., Accorsi, P., Biasucci, G., Cavallini, A., Decembrino, L., Falcone, R., Fazzi, E. M., Gardella, B., Giacchero, R., Guerini, P., Grossi, E., Magnani, M. L., Mariani, E. M., Nacinovich, R., Pantaleo, D., Pisoni, C., Prefumo, F., Sabatini, C., … Borgatti, R. (2021). Depression and Anxiety in Mothers Who Were Pregnant During the COVID-19 Outbreak in Northern Italy: The Role of Pandemic-Related Emotional Stress and Perceived Social Support. *Frontiers in Psychiatry*, *12*, 716488. https://doi.org/10.3389/fpsyt.2021.716488

Grundy, S. M. (2006). Metabolic syndrome: Connecting and reconciling cardiovascular and diabetes worlds. *Journal of the American College of Cardiology*, *47*(6), 1093–1100. https://doi.org/10.1016/j.jacc.2005.11.046

Harville, E., Xiong, X., & Buekens, P. (2010). Disasters and perinatal health:a systematic review. *Obstetrical & Gynecological Survey*, *65*(11), 713–728. https://doi.org/10.1097/OGX.0b013e31820eddbe

Hasnain, M. (2015). Genetic vulnerability in antipsychotic drug-induced diabetes. *The Lancet. Psychiatry*, *2*(12), 1049–1051. https://doi.org/10.1016/S2215-0366(15)00310-7

Huang, P. L. (2009). A comprehensive definition for metabolic syndrome. *Disease Models & Mechanisms*, *2*(5–6), 231–237. https://doi.org/10.1242/dmm.001180

Hukic, D. S., Ösby, U., Olsson, E., Hilding, A., Östenson, C.-G., Gu, H. F., Ehrenborg, E., Edman, G., Schalling, M., Lavebratt, C., & Frisén, L. (2017). Genetic variants of increased waist circumference in psychosis. *Psychiatric Genetics*, *27*(6), 210–218. https://doi.org/10.1097/YPG.0000000000000181

Khambadkone, S. G., Cordner, Z. A., & Tamashiro, K. L. K. (2020). Maternal stressors and the developmental origins of neuropsychiatric risk. *Frontiers in Neuroendocrinology*, *57*, 100834. https://doi.org/10.1016/j.yfrne.2020.100834

Kirkpatrick, B. (2009). El concepto de esquizofrenia. *Revista de Psiquiatría y Salud Mental - Journal of Psychiatry and Mental Health*, *2*(3), 105–107. https://doi.org/10.1016/S1888-9891(09)72400-0

Kirkpatrick, B., Fernandez-Egea, E., Garcia-Rizo, C., & Bernardo, M. (2009). Differences in glucose tolerance between deficit and nondeficit schizophrenia. *Schizophrenia Research*, *107*(2–3), 122–127. https://doi.org/10.1016/j.schres.2008.09.023

Kirkpatrick, B., Miller, B., García-Rizo, C., & Fernandez-Egea, E. (2014). Schizophrenia: A systemic disorder. *Clinical Schizophrenia & Related Psychoses*, *8*(2), 73–79. https://doi.org/10.3371/CSRP.KIMI.031513

Kirkpatrick, B., Miller, B. J., Garcia-Rizo, C., Fernandez-Egea, E., & Bernardo, M. (2012). Is abnormal glucose tolerance in antipsychotic-naive patients with nonaffective psychosis confounded by poor health habits? *Schizophrenia Bulletin*, *38*(2), 280–284. https://doi.org/10.1093/schbul/sbq058

Koenig, J. I., Kirkpatrick, B., & Lee, P. (2002). Glucocorticoid hormones and early brain development in schizophrenia. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *27*(2), 309–318. https://doi.org/10.1016/S0893-133X(01)00396-7

Kohen, D. (2004). Diabetes mellitus and schizophrenia: Historical perspective. *The British Journal of Psychiatry. Supplement*, *47*, S64-66. https://doi.org/10.1192/bjp.184.47.s64

KOOY, F. H. (1919). HYPERGLYÆMIA IN MENTAL DISORDERS. *Brain*, *42*(3), 214–290. https://doi.org/10.1093/brain/42.3.214

Kraal, A. Z., Ward, K. M., & Ellingrod, V. L. (2017). Sex Differences in Antipsychotic Related Metabolic Functioning in Schizophrenia Spectrum Disorders. *Psychopharmacology Bulletin*, *47*(2), 8–21.

Kraemer, S., Minarzyk, A., Forst, T., Kopf, D., & Hundemer, H.-P. (2011). Prevalence of metabolic syndrome in patients with schizophrenia, and metabolic changes after 3 months of treatment with antipsychotics—Results from a German observational study. *BMC Psychiatry*, *11*, 173. https://doi.org/10.1186/1471-244X-11-173

Lasserre, A. M., Glaus, J., Vandeleur, C. L., Marques-Vidal, P., Vaucher, J., Bastardot, F., Waeber, G., Vollenweider, P., & Preisig, M. (2014). Depression with atypical features and increase in obesity, body mass index, waist circumference, and fat mass: A prospective, population-based study. *JAMA Psychiatry*, *71*(8), 880–888. https://doi.org/10.1001/jamapsychiatry.2014.411

Laursen, T. M. (2019). Causes of premature mortality in schizophrenia: A review of literature published in 2018. *Current Opinion in Psychiatry*, *32*(5), 388–393. https://doi.org/10.1097/YCO.0000000000000530

Lawlor, D. A., Davey Smith, G., Clark, H., & Leon, D. A. (2006). The associations of birthweight, gestational age and childhood BMI with type 2 diabetes: Findings from the Aberdeen Children of the 1950s cohort. *Diabetologia*, *49*(11), 2614–2617. https://doi.org/10.1007/s00125-006-0408-z

Lear, S. A., James, P. T., Ko, G. T., & Kumanyika, S. (2010). Appropriateness of waist circumference and waist-to-hip ratio cutoffs for different ethnic groups. *European Journal of Clinical Nutrition*, *64*(1), 42–61. https://doi.org/10.1038/ejcn.2009.70

LORENZ, W. F. (1922). SUGAR TOLERANCE IN DEMENTIA PRAECOX AND OTHER MENTAL DISORDERS. *Archives of Neurology & Psychiatry*, *8*(2), 184–196. https://doi.org/10.1001/archneurpsyc.1922.02190140075007

Manzanares, N., Monseny, R., Ortega, L., Montalvo, I., Franch, J., Gutierrez-Zotes, A., Reynolds, R. M., Walker, B. R., Vilella, E., & Labad, J. (2014). Unhealthy lifestyle in early psychoses: The role of life stress and the hypothalamic-pituitary-adrenal axis. *Psychoneuroendocrinology*, *39*, 1–10. https://doi.org/10.1016/j.psyneuen.2013.09.023

Martín Otaño, L., Barbadillo Izquierdo, L., Galdeano Mondragón, A., Alonso Pinedo, M., & Querejeta Ayerdi, I. (2013b). After six months of anti-psychotic treatment: Is the improvement in mental health at the expense of physical health? *Revista de Psiquiatria y Salud Mental*, *6*(1), 26–32. cmedm. https://doi.org/10.1016/j.rpsm.2012.04.001

Mayoral Van-Son, J., Gómez-Revuelta, M., Ayesa-Arriola, R., Vázquez-Bourgón, J., Foz, V. O.-G. de la, Ruiz-Veguilla, M., **Garrido-Torres**, N., Tordesillas-Gutiérrez, D., Setién-Suero, E., & Crespo-Facorro, B. (2021). Comparison of aripiprazole and risperidone effectiveness in first episode non-affective psychosis: Rationale and design of a prospective, randomized, 3-phase, investigator-initiated study (PAFIP-3). *Revista de Psiquiatría y Salud Mental*. https://doi.org/10.1016/j.rpsm.2021.01.004

McEvoy, J. P., Meyer, J. M., Goff, D. C., Nasrallah, H. A., Davis, S. M., Sullivan, L., Meltzer, H. Y., Hsiao, J., Scott Stroup, T., & Lieberman, J. A. (2005). Prevalence

of the metabolic syndrome in patients with schizophrenia: Baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophrenia Research*, *80*(1), 19–32. https://doi.org/10.1016/j.schres.2005.07.014

Medved, V., Kuzman, M. R., Jovanovic, N., Grubisin, J., & Kuzman, T. (2009). Metabolic syndrome in female patients with schizophrenia treated with second generation antipsychotics: A 3-month follow-up. In *JOURNAL OF PSYCHOPHARMACOLOGY* (Vol. 23, Issue 8, p. 915).

Menninger, K. A. (1994). Influenza and schizophrenia. An analysis of post-influenzal 'dementia precox,' as of 1918, and five years later further studies of the psychiatric aspects of influenza. 1926. *The American Journal of Psychiatry*, *151*(6 Suppl), 182–187. https://doi.org/10.1176/ajp.151.6.182

Misiak, B., Bartoli, F., Stramecki, F., Samochowiec, J., Lis, M., Kasznia, J., Jarosz, K., & Stanczykiewicz, B. (2019). Appetite regulating hormones in first-episode psychosis: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, *102*, 362–370. https://doi.org/10.1016/j.neubiorev.2019.05.018

Misiak, B., Frydecka, D., Slezak, R., Piotrowski, P., & Kiejna, A. (2014). Elevated homocysteine level in first-episode schizophrenia patients—The relevance of family history of schizophrenia and lifetime diagnosis of cannabis abuse. *Metabolic Brain Disease*, *29*(3), 661–670. https://doi.org/10.1007/s11011-014-9534-3

Misiak, B., Stanczykiewicz, B., Laczmanski, L., & Frydecka, D. (2017). Lipid profile disturbances in antipsychotic-naive patients with first-episode non-affective

psychosis: A systematic review and meta-analysis. *SCHIZOPHRENIA RESEARCH*, *190*, 18–27. https://doi.org/10.1016/j.schres.2017.03.031

Mitchell, A. J., & Dinan, T. G. (2010). Schizophrenia: A multisystem disease? *Journal of Psychopharmacology (Oxford, England)*, *24*(4 Suppl), 5–7. https://doi.org/10.1177/1359786810382059

Mitchell, A. J., Vancampfort, D., De Herdt, A., Yu, W., & De Hert, M. (2013). Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. *Schizophrenia Bulletin*, *39*(2), 295–305. cmedm. https://doi.org/10.1093/schbul/sbs082

Mitchell, A. J., Vancampfort, D., Sweers, K., van Winkel, R., Yu, W., & De Hert, M. (2013). Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders—A systematic review and meta-analysis. *Schizophrenia Bulletin*, *39*(2), 306–318. PubMed. https://doi.org/10.1093/schbul/sbr148

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Moore, J. X., Chaudhary, N., & Akinyemiju, T. (2017). Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988-2012. *Preventing Chronic Disease*, *14*, E24. https://doi.org/10.5888/pcd14.160287

Moreno-Küstner, B., Guzman-Parra, J., Pardo, Y., Sanchidrián, Y., Díaz-Ruiz, S., & Mayoral-Cleries, F. (2021). Excess mortality in patients with schizophrenia

spectrum disorders in Malaga (Spain): A cohort study. *Epidemiology and Psychiatric Sciences*, *30*, e11. https://doi.org/10.1017/S2045796020001146

Morrison, K. M., Ramsingh, L., Gunn, E., Streiner, D., Van Lieshout, R., Boyle, M., Gerstein, H., Schmidt, L., & Saigal, S. (2016). Cardiometabolic Health in Adults Born Premature With Extremely Low Birth Weight. *Pediatrics*, *138*(4), e20160515. https://doi.org/10.1542/peds.2016-0515

Mote, J., & Fulford, D. (2021). Now Is the Time to Support Black Individuals in the US Living With Serious Mental Illness-A Call to Action. *JAMA Psychiatry*, *78*(2), 129–130. https://doi.org/10.1001/jamapsychiatry.2020.2656

Mukerjee, S., Mahadik, S. P., Scheffer, R., Correnti, E. E., & Kelkar, H. (1996). Impaired antioxidant defense at the onset of psychosis. *Schizophrenia Research*, *19*(1), 19–26. https://doi.org/10.1016/0920-9964(95)00048-8

Newcomer, J. W., Haupt, D. W., Fucetola, R., Melson, A. K., Schweiger, J. A., Cooper, B. P., & Selke, G. (2002). Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Archives of General Psychiatry*, *59*(4), 337–345. https://doi.org/10.1001/archpsyc.59.4.337

Nosarti, C., Reichenberg, A., Murray, R. M., Cnattingius, S., Lambe, M. P., Yin, L., MacCabe, J., Rifkin, L., & Hultman, C. M. (2012). Preterm birth and psychiatric disorders in young adult life. *Archives of General Psychiatry*, *69*(6), E1-8. https://doi.org/10.1001/archgenpsychiatry.2011.1374

Osborn, D. P. J., Hardoon, S., Omar, R. Z., Holt, R. I. G., King, M., Larsen, J., Marston, L., Morris, R. W., Nazareth, I., Walters, K., & Petersen, I. (2015). Cardiovascular risk prediction models for people with severe mental illness: Results from the prediction and management of cardiovascular risk in people with severe mental

illnesses (PRIMROSE) research program. *JAMA Psychiatry*, *72*(2), 143–151. https://doi.org/10.1001/jamapsychiatry.2014.2133

Osby, U., Olsson, E., Edman, G., Hilding, A., Eriksson, S. V., & Ostenson, C. G. (2014). Psychotic disorder is an independent risk factor for increased fasting glucose and waist circumference. In *NORDIC JOURNAL OF PSYCHIATRY* (Vol. 68, Issue 4, p. 251).

Owiredu, W. K. B. A., Osei, O., Amidu, N., Appiah-Poku, J., & Osei, Y. (2012). Prevalence of metabolic syndrome among Psychiatric Patients in the Kumasi Metropolis, Ghana. In *JOURNAL OF MEDICAL AND BIOMEDICAL SCIENCE* (Vol. 1, Issue 2, p. 38).

Ozanne, S. E., & Hales, C. N. (2002). Early programming of glucose-insulin metabolism. *Trends in Endocrinology and Metabolism: TEM*, *13*(9), 368–373. https://doi.org/10.1016/s1043-2760(02)00666-5

Pallava, A., Chadda, R. K., Sood, M., & Lakshmy, R. (2012). Metabolic syndrome in schizophrenia: A comparative study of antipsychotic-free/naïve and antipsychotic-treated patients from India. *Nordic Journal of Psychiatry*, *66*(3), 215–221. https://doi.org/10.3109/08039488.2011.621977

Pandit, R., Cianci, D., Ter Hark, S. E., Winter-van Rossum, I., Ebdrup, B. H., Broberg, B. V., Garcia-Portilla, M. P., Bobes, J., Vinkers, C. H., Kahn, R. S., Guloksuz, S., Huitema, A. D. R., & Luykx, J. J. (2019). Phenotypic factors associated with amisulpride-induced weight gain in first-episode psychosis patients (from the OPTiMiSE cohort). *Acta Psychiatrica Scandinavica*, *140*(3), 283–290. https://doi.org/10.1111/acps.13074

Patel, J. K., Buckley, P. F., Woolson, S., Hamer, R. M., McEvoy, J. P., Perkins, D. O., & Lieberman, J. A. (2009). Metabolic profiles of second-generation antipsychotics

in early psychosis: Findings from the CAFE study. *Schizophrenia Research*, *111*(1–3), 9–16. https://doi.org/10.1016/j.schres.2009.03.025

Pelayo-Teran, J. M., Perez-Iglesias, R., Ramirez-Bonilla, M., Gonzalez-Blanch, C., Martinez-Garcia, O., Pardo-Garcia, G., Rodriguez-Sanchez, J. M., Roiz-Santianez, R., Tordesillas-Gutierrez, D., Mata, I., Vazquez-Barquero, J. L., & Crespo-Facorro, B. (2008). Epidemiological factors associated with treated incidence of first- episode non-affective psychosis in Cantabria: Insights from the Clinical Programme on Early Phases of Psychosis. *Early Intervention in Psychiatry*, *2*(3), 178–187. https://doi.org/10.1111/j.1751-7893.2008.00074.x

Penninx, B. W. J. H., & Lange, S. M. M. (2018). Metabolic syndrome in psychiatric patients: Overview, mechanisms, and implications. *Dialogues in Clinical Neuroscience*, *20*(1), 63–73. https://doi.org/10.31887/DCNS.2018.20.1/bpenninx

Perez-Pinar, M., Mathur, R., Foguet, Q., Ayis, S., Robson, J., & Ayerbe, L. (2016). Cardiovascular risk factors among patients with schizophrenia, bipolar, depressive, anxiety, and personality disorders. *European Psychiatry : The Journal of the Association of European Psychiatrists*, *35*, 8–15. https://doi.org/10.1016/j.eurpsy.2016.02.004

Perry, B. I., McIntosh, G., Weich, S., Singh, S., & Rees, K. (2016a). The association between first-episode psychosis and abnormal glycaemic control: Systematic review and meta-analysis. *The Lancet. Psychiatry*, *3*(11), 1049–1058. https://doi.org/10.1016/S2215-0366(16)30262-0

Perry, B. I., Osimo, E. F., Upthegrove, R., Mallikarjun, P. K., Yorke, J., Stochl, J., Perez, J., Zammit, S., Howes, O., Jones, P. B., & Khandaker, G. M. (2021). Development and external validation of the Psychosis Metabolic Risk Calculator (PsyMetRiC): A cardiometabolic risk prediction algorithm for young people with psychosis. *The*

Lancet. Psychiatry, *8*(7), 589–598. https://doi.org/10.1016/S2215-0366(21)00114-0

Perry, B. I., & Singh, S. P. (2018). Letter to the Editor: Lipid profile disturbances in antipsychotic-naive patients with first-episode non-affective psychosis. *Schizophrenia Research*, *192*, 461–462. https://doi.org/10.1016/j.schres.2017.03.046

Perry, B. I., Upthegrove, R., Crawford, O., Jang, S., Lau, E., McGill, I., Carver, E., Jones, P. B., & Khandaker, G. M. (2020). Cardiometabolic risk prediction algorithms for young people with psychosis: A systematic review and exploratory analysis. *Acta Psychiatrica Scandinavica*, *142*(3), 215–232. https://doi.org/10.1111/acps.13212

Perry, B., Vandenberghe, F., **Garrido-Torres**, N., Osimo, E., Piras, M., Vázquez-Bourgon, J., Upthegrove, R., Grosu, C., Ortiz-García de la Foz, V., Jones, P., & Crespo-Facorro, B. (2022). Testing International Transportability of The Psychosis Metabolic Risk Calculator (PsyMetRiC) for Young People with Psychosis: External Validation and Site-Specific Recalibration in Two Independent European Samples. *The Lancet Regional Health. Europe*. https://doi.org/Accepted

Pillinger, T., Beck, K., Gobjila, C., Donocik, J. G., Jauhar, S., & Howes, O. D. (2017). Impaired Glucose Homeostasis in First-Episode Schizophrenia: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, *74*(3), 261–269. https://doi.org/10.1001/jamapsychiatry.2016.3803

Pillinger, T., Beck, K., Stubbs, B., & Howes, O. (2018). S19. EVIDENCE OF THE LIPID PARADOX IN PSYCHOSIS: A META-ANALYSIS OF CHOLESTEROL AND TRIGLYCERIDE LEVELS IN FIRST EPISODE PSYCHOSIS. *Schizophrenia Bulletin*, *44*. edsair. https://doi.org/10.1093/schbul/sby018.806

Pillinger, T., Beck, K., Stubbs, B., & Howes, O. D. (2017). Cholesterol and triiglyceride levels first-episode psychosis systematic review and meta analysis. In *BRITISH JOURNAL OF PSYCHIATRY* (Vol. 211, Issue 6, p. 339).

Pillinger, T., D'Ambrosio, E., McCutcheon, R., & Howes, O. D. (2019). Is psychosis a multisystem disorder? A meta-review of central nervous system, immune, cardiometabolic, and endocrine alterations in first-episode psychosis and perspective on potential models. *MOLECULAR PSYCHIATRY*, *24*(6), 776–794. https://doi.org/10.1038/s41380-018-0058-9

Pillinger, T., McCutcheon, R. A., Vano, L., Mizuno, Y., Arumuham, A., Hindley, G., Beck, K., Natesan, S., Efthimiou, O., Cipriani, A., & Howes, O. D. (2020). Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: A systematic review and network meta- analysis. *The Lancet. Psychiatry*, *7*(1), 64–77. https://doi.org/10.1016/S2215-0366(19)30416-X

Postolache, T. T., Del Bosque-Plata, L., Jabbour, S., Vergare, M., Wu, R., & Gragnoli, C. (2019). Co-shared genetics and possible risk gene pathway partially explain the comorbidity of schizophrenia, major depressive disorder, type 2 diabetes, and metabolic syndrome. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics : The Official Publication of the International Society of Psychiatric Genetics*, *180*(3), 186–203. https://doi.org/10.1002/ajmg.b.32712

Provenzi, L., Grumi, S., Giorda, R., Biasucci, G., Bonini, R., Cavallini, A., Decembrino, L., Drera, B., Falcone, R., Fazzi, E., Gardella, B., Giacchero, R., Nacinovich, R., Pisoni, C., Prefumo, F., Scelsa, B., Spartà, M. V., Veggiotti, P., Orcesi, S., & Borgatti, R. (2020). Measuring the Outcomes of Maternal COVID-19-related Prenatal Exposure (MOM-COPE): Study protocol for a multicentric longitudinal

project. *BMJ Open*, *10*(12), e044585. https://doi.org/10.1136/bmjopen-2020-044585

Provenzi, L., Mambretti, F., Villa, M., Grumi, S., Citterio, A., Bertazzoli, E., Biasucci, G., Decembrino, L., Falcone, R., Gardella, B., Longo, M. R., Nacinovich, R., Pisoni, C., Prefumo, F., Orcesi, S., Scelsa, B., Giorda, R., & Borgatti, R. (2021). Hidden pandemic: COVID-19-related stress, SLC6A4 methylation, and infants' temperament at 3 months. *Scientific Reports*, *11*(1), 15658. https://doi.org/10.1038/s41598-021-95053-z

Provenzi, L., Villa, M., Mambretti, F., Citterio, A., Grumi, S., Bertazzoli, E., Biasucci, G., Decembrino, L., Gardella, B., Giacchero, R., Magnani, M. L., Nacinovich, R., Pisoni, C., Prefumo, F., Orcesi, S., Scelsa, B., Giorda, R., & Borgatti, R. (2022). Is Brain-Derived Neurotropic Factor Methylation Involved in the Association Between Prenatal Stress and Maternal Postnatal Anxiety During the COVID-19 Pandemic? *Frontiers in Psychiatry*, *13*, 950455. https://doi.org/10.3389/fpsyt.2022.950455

Raphael, t., & Parsons, j. p. (1921). Blood sugar studies in dementia praecox and manic-depressive insanity. *Archives of Neurology & Psychiatry*, *5*(6), 687–709. https://doi.org/10.1001/archneurpsyc.1921.02180300052005

Roberts, B. L., Bennett, B. J., Bennett, C. M., Carroll, J. M., Dalbøge, L. S., Hall, C., Hassouneh, W., Heppner, K. M., Kirigiti, M. A., Lindsley, S. R., Tennant, K. G., True, C. A., Whittle, A., Wolf, A. C., Roberts, C. T., Tang-Christensen, M., Sleeman, M. W., Cowley, M. A., Grove, K. L., & Kievit, P. (2019). Reelin is modulated by diet-induced obesity and has direct actions on arcuate proopiomelanocortin neurons. *Mol Metab*, *26*, 18–29. PubMed. https://doi.org/10.1016/j.molmet.2019.06.001

Ryan, M. C. M., Flanagan, S., Kinsella, U., Keeling, F., & Thakore, J. H. (2004). The effects of atypical antipsychotics on visceral fat distribution in first episode, drug-naive patients with schizophrenia. *Life Sciences*, *74*(16), 1999–2008. https://doi.org/10.1016/j.lfs.2003.08.044

Sahpolat, M., & Ari, M. (2020a). Higher prevalence of metabolic syndrome and related factors in patients with first-episode psychosis and schizophrenia: A cross-sectional study in Turkey. *Nordic Journal of Psychiatry*, 1–6. https://doi.org/10.1080/08039488.2020.1815080

Saloojee, S., Burns, J. K., & Motala, A. A. (2018a). Metabolic syndrome in antipsychotic naive African patients with severe mental illness in usual care. *Early Intervention in Psychiatry*, *12*(6), 1137–1143. https://doi.org/10.1111/eip.12428

Sánchez, L. J. (1939). *La pirexia insulínica*.

Sanchez-Hidalgo, A. C., Martin-Cuevas, C., Crespo-Facorro, B., & **Garrido-Torres**, N. (2022). Reelin Alterations, Behavioral Phenotypes, and Brain Anomalies in Schizophrenia: A Systematic Review of Insights From Rodent Models. *Frontiers in Neuroanatomy*, *16*, 844737. https://doi.org/10.3389/fnana.2022.844737

Scheffler, F., Kilian, S., Chiliza, B., Asmal, L., Phahladira, L., du Plessis, S., Kidd, M., Murray, R. M., Di Forti, M., Seedat, S., & Emsley, R. (2018). Effects of cannabis use on body mass, fasting glucose and lipids during the first 12months of treatment in schizophrenia spectrum disorders. *Schizophrenia Research*, *199*, 90–95. https://doi.org/10.1016/j.schres.2018.02.050

Shih, C.-C., Shih, Y.-L., & Chen, J.-Y. (2021). The association between homocysteine levels and cardiovascular disease risk among middle-aged and elderly adults in Taiwan. *BMC Cardiovascular Disorders*, *21*(1), 191. https://doi.org/10.1186/s12872-021-02000-x

Sørensen, H. J., Gamborg, M., Sørensen, T. I. A., Baker, J. L., & Mortensen, E. L. (2016). Childhood body mass index and risk of schizophrenia in relation to childhood age, sex and age of first contact with schizophrenia. *European Psychiatry : The Journal of the Association of European Psychiatrists*, *34*, 64–69. https://doi.org/10.1016/j.eurpsy.2016.01.2425

Srihari, V. H., Phutane, V. H., Ozkan, B., Chwastiak, L., Ratliff, J. C., Woods, S. W., & Tek, C. (2013a). Cardiovascular mortality in schizophrenia: Defining a critical period for prevention. *Schizophrenia Research*, *146*(1–3), 64–68. https://doi.org/10.1016/j.schres.2013.01.014

Srivastava, S., Bhatia, M. S., & Sharma, A. (2018). Comparative study of quality of life and metabolic syndrome in schizophrenia patients who are receiving treatment versus antipsychotic naïve, first episode patients from a tertiary care hospital. *Asian Journal of Psychiatry*, *31*, 121–123. https://doi.org/10.1016/j.ajp.2018.02.009

Steiner, J., Fernandes, B. S., Guest, P. C., Dobrowolny, H., Meyer-Lotz, G., Westphal, S., Borucki, K., Schiltz, K., Sarnyai, Z., & Bernstein, H.-G. (2019). Glucose homeostasis in major depression and schizophrenia: A comparison among drug-naïve first-episode patients. *European Archives of Psychiatry and Clinical Neuroscience*, *269*(4), 373–377. https://doi.org/10.1007/s00406-018-0865-7

Stiles, E., Alcover, K. C., Stiles, B., Oluwoye, O., & McDonell, M. G. (2020). Cannabis use and metabolic syndrome among clients with first episode psychosis. *Early Intervention in Psychiatry*. https://doi.org/10.1111/eip.13030

Strassnig, M., Miewald, J., Keshavan, M., & Ganguli, R. (2007). Weight gain in newly diagnosed first-episode psychosis patients and healthy comparisons: One-year

analysis. *Schizophrenia Research*, *93*(1–3), 90–98. https://doi.org/10.1016/j.schres.2007.02.024

Stroup, D. F., Berlin, J. A., Morton, S. C., Olkin, I., Williamson, G. D., Rennie, D., Moher, D., Becker, B. J., Sipe, T. A., & Thacker, S. B. (2000). Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*, *283*(15), 2008–2012. https://doi.org/10.1001/jama.283.15.2008

Suetani, S., Honarparvar, F., Siskind, D., Hindley, G., Veronese, N., Vancampfort, D., Allen, L., Solmi, M., Lally, J., Gaughran, F., Stubbs, B., & Pillinger, T. (2021). Increased rates of respiratory disease in schizophrenia: A systematic review and meta-analysis including 619,214 individuals with schizophrenia and 52,159,551 controls. *Schizophrenia Research*, *237*, 131–140. https://doi.org/10.1016/j.schres.2021.08.022

Swets, M., Dekker, J., van Emmerik-van Oortmerssen, K., Smid, G. E., Smit, F., de Haan, L., & Schoevers, R. A. (2014). The obsessive compulsive spectrum in schizophrenia, a meta-analysis and meta-regression exploring prevalence rates. *Schizophrenia Research*, *152*(2–3), 458–468. https://doi.org/10.1016/j.schres.2013.10.033

Tek, C., Kucukgoncu, S., Guloksuz, S., Woods, S. W., Srihari, V. H., & Annamalai, A. (2016). Antipsychotic-induced weight gain in first-episode psychosis patients: A meta-analysis of differential effects of antipsychotic medications. *Early Intervention in Psychiatry*, *10*(3), 193–202. https://doi.org/10.1111/eip.12251

Tomasik, J., Lago, S. G., Vazquez-Bourgon, J., Papiol, S., Suarez-Pinilla, P., Crespo-Facorro, B., & Bahn, S. (2019). Association of Insulin Resistance With

Schizophrenia Polygenic Risk Score and Response to Antipsychotic Treatment. *JAMA Psychiatry*. https://doi.org/10.1001/jamapsychiatry.2019.0304

Tomassi, S., & Tosato, S. (2017). Epigenetics and gene expression profile in first-episode psychosis: The role of childhood trauma. *Neuroscience and Biobehavioral Reviews*, *83*, 226–237. https://doi.org/10.1016/j.neubiorev.2017.10.018

Torrey, E. F., Bartko, J. J., & Yolken, R. H. (2012). Toxoplasma gondii and other risk factors for schizophrenia: An update. *Schizophrenia Bulletin*, *38*(3), 642–647. https://doi.org/10.1093/schbul/sbs043

Vancampfort, D., Stubbs, B., Mitchell, A. J., De Hert, M., Wampers, M., Ward, P. B., Rosenbaum, S., & Correll, C. U. (2015). Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: A systematic review and meta-analysis. *World Psychiatry : Official Journal of the World Psychiatric Association (WPA)*, *14*(3), 339–347. https://doi.org/10.1002/wps.20252

Vancampfort, D., Vansteelandt, K., Correll, C. U., Mitchell, A. J., De Herdt, A., Sienaert, P., Probst, M., & De Hert, M. (2013). Metabolic Syndrome and Metabolic Abnormalities in Bipolar Disorder: A Meta-Analysis of Prevalence Rates and Moderators. *American Journal of Psychiatry*, *170*(3), 265–274. asx. http://www.bvsspa.es/papi/ezproxy.php?url=http://search.ebscohost.com/login.aspx?direct=true&db=asx&AN=85840197&lang=es&site=eds-live&scope=site

Vázquez-Bourgon, J., Ortiz-García de la Foz, V., Gómez-Revuelta, M., Mayoral-van Son, J., Juncal-Ruiz, M., **Garrido-Torres**, N., & Crespo-Facorro, B. (2022). Aripiprazole and risperidone present comparable long-term metabolic profile; data from a pragmatic randomized controlled trial in drug-naïve first episode

psychosis. *The International Journal of Neuropsychopharmacology*, pyac033. https://doi.org/10.1093/ijnp/pyac033

Vazquez-Bourgon, J., Ortiz-Garcia de la Foz, V., Suarez-Pereira, I., Iruzubieta, P., Arias-Loste, M. T., Setien-Suero, E., Ayesa-Arriola, R., Gomez-Revuelta, M., Crespo, J., & Crespo Facorro, B. (2019a). Data regarding the effect of cannabis consumption on liver function in the prospective PAFIP cohort of first episode psychosis. *Data in Brief*, *27*, 104415. https://doi.org/10.1016/j.dib.2019.104415

Vazquez-Bourgon, J., Ortiz-Garcia de la Foz, V., Suarez-Pereira, I., Iruzubieta, P., Arias-Loste, M. T., Setien-Suero, E., Ayesa-Arriola, R., Gomez-Revuelta, M., Crespo, J., & Crespo Facorro, B. (2019b). Cannabis consumption and non-alcoholic fatty liver disease. A three years longitudinal study in first episode non-affective psychosis patients. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *95*, 109677. https://doi.org/10.1016/j.pnpbp.2019.109677

Vazquez-Bourgon, J., Setien-Suero, E., Pilar-Cuellar, F., Romero-Jimenez, R., Ortiz-Garcia de la Foz, V., Castro, E., & Crespo-Facorro, B. (2019). Effect of cannabis on weight and metabolism in first-episode non-affective psychosis: Results from a three-year longitudinal study. In *Journal of Psychopharmacology* (Vol. 33, Issue 3, p. 284).

Veru-Lesmes, F., Rho, A., King, S., Joober, R., Pruessner, M., Malla, A., & Iyer, S. N. (2018). Social Determinants of Health and Preclinical Glycemic Control in Newly Diagnosed First-Episode Psychosis Patients. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie*, *63*(8), 547–556. https://doi.org/10.1177/0706743718762097

Vidot, D. C., Prado, G., Hlaing, W. M., Florez, H. J., Arheart, K. L., & Messiah, S. E. (2016). Metabolic Syndrome Among Marijuana Users in the United States: An

Analysis of National Health and Nutrition Examination Survey Data. *The American Journal of Medicine*, *129*(2), 173–179. https://doi.org/10.1016/j.amjmed.2015.10.019

Walker, E. R., McGee, R. E., & Druss, B. G. (2015). Mortality in mental disorders and global disease burden implications: A systematic review and meta-analysis. *JAMA Psychiatry*, *72*(4), 334–341. https://doi.org/10.1001/jamapsychiatry.2014.2502

Wei, C. W., Chen, Y. Q., Ma, M., Xiu, M. H., & Zhang, X. Y. (2020). Sex differences in the association of body mass index with symptoms and cognitive deficits in Chinese patients with chronic schizophrenia. *Translational Psychiatry*, *10*(1), 18. https://doi.org/10.1038/s41398-020-0717-x

Wong, D. F., Pearlson, G. D., Tune, L. E., Young, L. T., Meltzer, C. C., Dannals, R. F., Ravert, H. T., Reith, J., Kuhar, M. J., & Gjedde, A. (1997). Quantification of neuroreceptors in the living human brain: IV. Effect of aging and elevations of D2-like receptors in schizophrenia and bipolar illness. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *17*(3), 331–342. https://doi.org/10.1097/00004647-199703000-00010

Wright, P., Takei, N., Rifkin, L., & Murray, R. M. (1995). Maternal influenza, obstetric complications, and schizophrenia. *The American Journal of Psychiatry*, *152*(12), 1714–1720. https://doi.org/10.1176/ajp.152.12.1714

Zhang, Q., He, H., Bai, X., Jiang, L., Chen, W., Zeng, X., Li, Y., Teixeira, A. L., & Dai, J. (2021). Unveiling the Metabolic Profile of First-Episode Drug-Naive Schizophrenia Patients: Baseline Characteristics of a Longitudinal Study Among Han Chinese. *Frontiers in Psychiatry*, *12*, 702720. https://doi.org/10.3389/fpsyt.2021.702720