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Alterations in body mass index and waist-to-hip ratio in never and minimally treated patients with psychosis: A systematic review and meta-analysis

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ABSTRACT

Background: Obesity is up to 4 times higher in patients with schizophrenia than in the general population. However, the link between obesity and schizophrenia in the absence of antipsychotic use is unclear. Therefore, we aimed to examine differences in obesity measures (body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR)) in antipsychotic-naive and minimally treated (up to 2 weeks of lifetime antipsychotic exposure) patients with psychosis compared to healthy controls (HCs).

Methods: A systematic search was conducted using Ovid Medline®, PsycINFO, and Embase. Standardized mean differences (SMDs) in obesity measures between groups were calculated. Separate sensitivity analyses were performed to examine the effects of age, sex, and ethnicity; antipsychotic exposure; and schizophrenia-related psychosis on SMDs.

Results: A total of 23 studies were included in the meta-analysis (BMI = 23, WC = 9, WHR = 5). BMI was lower (SMD = −0.19, 95% CI = −0.34 to −0.05, $P = 0.009$) and WHR was elevated (SMD = 0.34, 95% CI = 0.14 to 0.55, $P = 0.001$) in patients. These differences remained after analyses were restricted to patients matched with HCs for age, sex, and ethnicity; to antipsychotic-naive patients; and to patients with schizophrenia-related diagnoses.

Conclusions: Differences in BMI and WHR were observed in never and minimally treated patients with psychosis compared to HCs. Future research is warranted to understand these alterations in the context of body fat biomarkers and neuropathology of psychiatric disorders, independent of the effects of antipsychotics.

1. Introduction

Obesity is up to 4 times higher in patients with schizophrenia than in the general population (Koffarnus et al., 2016; Silverstone et al., 1988), with a prevalence of approximately 50% (Vancampfort et al., 2015). It is a leading cause of cardiovascular disease, which is the largest contributor to increased mortality, shortening life expectancy by 15 to 20 years in patients with schizophrenia (Brown, 1997; Hennekens et al., 2005; Ringen et al., 2014). While weight gain from antipsychotics such as olanzapine and clozapine is common (Newcomer, 2005), it is presently unclear whether obesity is also linked to schizophrenia and other psychotic disorders, independent of antipsychotic effects.

Multiple meta-analyses have shown an elevated obesity risk in patients with severe mental illnesses, including schizophrenia compared to healthy controls (HCs) (Mitchell et al., 2013b; Vancampfort et al., 2015; Vancampfort et al., 2013). However, these studies included patients with a long-term history of antipsychotic use, and therefore do not provide evidence for whether obesity risk is elevated in the absence of antipsychotic medication.

Many factors other than antipsychotics may be involved in increasing obesity risk in patients with schizophrenia. Personal factors such as physical inactivity, unhealthy diet, substance abuse, and poor education are associated with obesity (Carney et al., 2016; Koola et al., 2012; Vancampfort et al., 2010). Furthermore, lifestyle factors, such as diet and level of physical activity, may differ among patients with schizophrenia

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spectrum disorders and non-schizophrenia-related affective psychosis (Bly et al., 2014). Environmental factors such as poor socioeconomic status and lack of integration between mental and physical health services may also contribute to obesity (McGrath et al., 2008; Vancampfort et al., 2013). Ethnic and sex differences in obesity have also been observed (Lear et al., 2007; Minichino et al., 2017; Piers et al., 2003; Shimokata et al., 1989). Of note, recent evidence points to common pathophysiological processes underlying obesity and schizophrenia (Lou et al., 2014; Minichino et al., 2017; Mueller et al., 2012; Xu et al., 2013).

The available literature suggests that clinically established cases of obesity and obesity-related metabolic conditions are not more common in antipsychotic-naive (i.e. no lifetime exposure to antipsychotics) or first-episode patients with psychosis in comparison to HCs. A meta-analysis found no difference in the prevalence of type 2 diabetes, an obesity-related complication, between antipsychotic-naive patients with psychosis and HCs (Mitchell et al., 2013a). Similarly, case-control studies have generally found that antipsychotic-naive or first-episode patients with psychosis are of normal body weight (Enez Darcin et al., 2015; Padmavati et al., 2010; Weiser et al., 2004; Wyatt et al., 2003). However, metabolic abnormalities at a subclinical level may be present in the patient population, as demonstrated by recent meta-analyses that found lower cholesterol levels (Misiak et al., 2017; Pillinger et al., 2017b), and elevated triglycerides (Misiak et al., 2017; Pillinger et al., 2017b), plasma glucose, and insulin resistance (Perry et al., 2016; Pillinger et al., 2017a) in antipsychotic-naive patients with psychosis compared to HCs. These meta-analyses included studies that matched antipsychotic-naive patients and HCs based on body mass index (BMI) to minimize its influence on study results.

In the present paper, we aimed to comprehensively evaluate differences in obesity measures (i.e. BMI (measures overall obesity); waist circumference (WC, measures abdominal obesity); and waist-to-hip ratio (WHR, measures abdominal obesity)) in antipsychotic-naive and minimally treated (up to 2 weeks of lifetime antipsychotic exposure) patients with psychosis compared to HCs by conducting a systematic review and meta-analysis. Based on previous reports (Misiak et al., 2017; Pillinger et al., 2017b), we expected to see differences in obesity measures between the two groups.

2. Methods and materials

2.1. Literature search

This systematic review and meta-analysis were conducted according to guidelines established by the Preferred Reporting Items for Systematic reviews and Meta-Analysis group (Moher et al., 2009). A systematic search of Ovid databases (Medline®, PsycINFO, and Embase) for English language publications from 1860 to May 2018 was performed (last search on May 15, 2018) to identify all studies, including cross-sectional and longitudinal studies, reviews, or case reports examining obesity measures in patients with psychosis. The search was conducted using the following terms: ("schizophrenia" or "schizoaffective" or "psychosis" or "first episode" or "FEP" or "early psychosis") and ("antipsychotic-naive" or "antipsychotic-free" or "neuroleptic-naive" or "neuroleptic-free" or "drug-naive" or "drug-free" or "unmedicated" or "untreated") and ("obesity" or "obese" or "overweight" or "metabolic" or "weight" or "body mass index" or "BMI" or "waist circumference" or "waist to hip ratio"). Two authors independently performed the search and assessed for eligibility (P.S. and E.P.), and two authors independently extracted the data (P.S. and J.K.).

2.1.1. Eligibility

Full-length articles were included if: (a) they included both HCs and patients with schizophrenia, schizophrenia-related disorders (i.e. non-affective psychosis), or other psychotic disorders, including affective psychosis; (b) the patient sample was antipsychotic-naive, defined as no lifetime exposure to antipsychotics, or patients with minimal antipsychotic treatment, defined as up to 2 weeks of lifetime exposure to antipsychotics (determined based on previous studies (Pillinger et al., 2017b; Sarpal et al., 2015; Szeszko et al., 2014)); (c) BMI, WC, and/or WHR measures were assessed in both patient and HC groups; and (d) sufficient data were provided to calculate standardized mean differences (SMDs) of obesity measures between patient and control groups. Full-length articles were excluded if: (a) they lacked HCs; (b) patient and HCs groups were matched for BMI, WC, and/or WHR; (c) patients had >2 weeks of lifetime exposure to antipsychotics; (d) obesity measures for both patient and HCs groups were not reported, and (e) obese and overweight participants were excluded. For studies with completely overlapping samples, only the study with the largest sample size was included. For studies with partially overlapping samples, both were included in the main analyses.

2.2. Recorded variables

The following variables were recorded from each included study: BMI, WC, and/or WHR; variables that were matched between patients and HCs; antipsychotic exposure status; psychiatric diagnoses; age; sex (%male); and illness severity (e.g. Positive and Negative Syndrome Scale, PANSS (Kay et al., 1987); and/or Brief Psychiatric Rating Scale, BPRS (Overall and Gorham, 1962)).

The main outcomes considered were BMI, WC, and WHR in antipsychotic-naive or minimally treated patients with psychosis and HCs.

2.3. Data analysis

2.3.1. Group differences between patients and healthy controls

Independent *t*-tests were conducted to test for differences in continuous demographic variables between patients and HCs. Chi-squared tests were used for categorical variables.

2.3.2. Meta-analysis

The meta-analysis, including sensitivity analyses, were conducted using Review Manager Version 5.2 (http://tech.cochrane.org/revman). The meta-regression analyses and publication bias evaluation were performed using Comprehensive Meta-Analysis software (www.meta-analysis.com). Differences in obesity measures between patients with psychosis and HCs were determined by calculating SMDs, using mean and standard deviation (SD) values. When medians and interquartile ranges (IQR) were reported for data with a skewed distribution, study authors were contacted for mean and SD values. Effect sizes were interpreted as small (SMD = 0.2), medium (SMD = 0.5) or large (SMD = 0.8) (Iwata et al., 2015). Random effects model was employed to adjust for heterogeneity among studies (DerSimonian and Laird, 1986). The significance of pooled SMD was assessed at $P \leq 0.05$, using 2-sided 95% confidence intervals (CIs). Positive SMDs represented elevated obesity measures in the patient group and negative values reflected lower measures in the patient group.

The I^2 statistic was used to assess study heterogeneity in the main analyses (Higgins and Thompson, 2002; Higgins et al., 2003). When significant heterogeneity was found ($I^2 \geq 50\%$), one-leave-out sensitivity analyses were performed to examine the influences of each study on the overall effect sizes and statistical significance.

Funnel plots and Egger's regression tests (Egger et al., 1997) were used to assess the risk of publication bias in the main analyses. The risk of bias in all studies was evaluated using the Risk of Bias Assessment Tool for Nonrandomized Studies (Kim et al., 2013), which used the following criteria: participant selection, confounding variables, measurement of exposure, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting.

2.3.3. Sensitivity analyses and meta-regression

Three separate sensitivity analyses were performed to examine the effects of: (a) age, sex, and ethnicity; (b) antipsychotic exposure; and (c) non-schizophrenia-related affective psychosis (e.g. bipolar disorder). Furthermore, sensitivity analyses restricted to studies with a low risk of bias were conducted. Finally, for studies with partially overlapping samples, sensitivity analyses excluding overlapping samples were also conducted by only including the study with the largest sample size.

Meta-regression analyses were conducted to determine the impact of patients' age, sex (%male), and illness severity on SMDs in obesity measures.

The statistical significance of all analyses was established at $P \leq 0.05$.

3. Results

3.1. Included studies

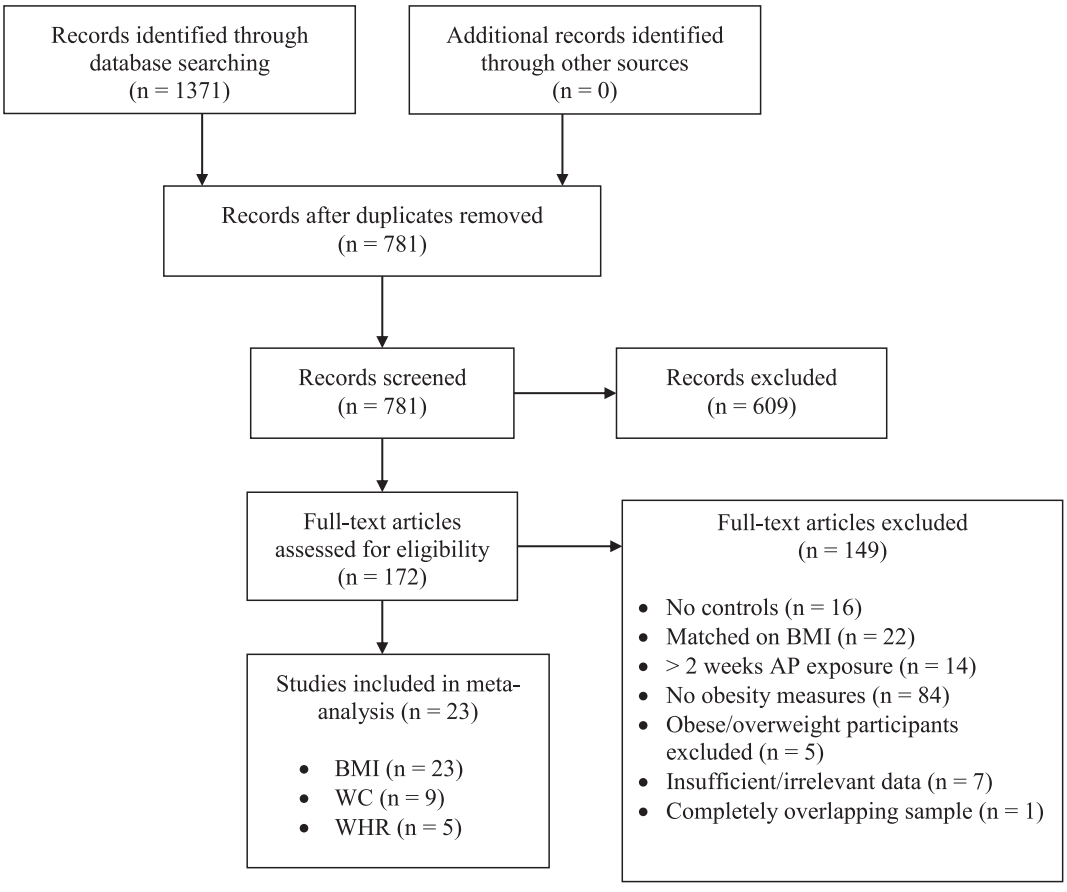
A total of 23 studies were found eligible for the meta-analysis (Fig. 1 and Table 1) (Arranz et al., 2004; Balotsev et al., 2017; Cai et al., 2012; Chen et al., 2013, 2016; Dasgupta et al., 2010; Emsley et al., 2015; Fawzi and Fawzi, 2012; Fawzi et al., 2011; Jensen et al., 2017; Jindal et al., 2010; Masopust et al., 2015; McEvoy et al., 2013; Padmavati et al., 2010; Reddy et al., 2003; Saloojee et al., 2017; Sengupta et al., 2008; Spelman et al., 2007; Strassnig et al., 2007; Verma et al., 2009; Wu et al., 2013; Zhang et al., 2004, 2016). There appeared to be some overlap in the samples between two studies from Egypt (Fawzi and Fawzi, 2012; Fawzi et al., 2011), between three studies from the United States (Jindal et al., 2010; Reddy et al., 2003; Strassnig et al., 2007), and between two studies from China (Cai et al., 2012; Zhang et al., 2016). All studies reported BMI (patient group, n = 1311; HCs, n = 1252), nine reported WC (patient group, n = 558; HCs, n = 405) (Chen et al., 2016; Fawzi and Fawzi, 2012; Jensen et al., 2017; McEvoy et al., 2013; Padmavati et al., 2010; Saloojee et al., 2017; Sengupta et al., 2008; Spelman et al., 2007; Wu et al., 2013), and five reported WHR (patient group, n = 434; HCs, n = 349) (Chen et al., 2016; Fawzi et al., 2011; Sengupta et al., 2008; Wu et al., 2013; Zhang et al., 2004). There were no differences between the patient and HCs groups in terms of mean sample size, sex, and age in studies reporting BMI and WC (Table S1). There was a greater proportion of males in HCs compared to the patient group in studies reporting WHR.

A funnel plot and Egger's regression test (intercept = 0.36, standard error = 1.28, 95% CI = −2.31 to 3.04, t = 0.28, $P = 0.78$) demonstrated no publication bias in 23 studies for which SMDs in BMI between patient and HC groups were calculated (Fig. S1). There were insufficient studies to adequately assess publication bias among studies reporting WC and WHR.

Fourteen out of 23 studies (61%) showed a low risk of bias for all the included criteria (Fig. S2), with the remaining studies showing either unclear risk of bias (17%) or high risk of bias (22%).

3.2. Group differences in body mass index

BMI was lower in antipsychotic-naive and minimally treated patients with psychosis in comparison to HCs (SMD = −0.19, 95% CI = −0.34 to −0.05, $P = 0.009$) (Fig. 2). Significant heterogeneity ($I^2 = 65\%$) existed between the studies, and one-leave-out sensitivity



Abbreviations. AP, Antipsychotics; BMI, Body Mass Index; WC, Waist Circumference; WHR, Waist-to-Hip Ratio

Fig. 1. Search methodology for the inclusion of studies in the meta-analysis.

Table 1
Summary of included studies describing obesity measures in antipsychotic-naive and minimally treated patients with psychosis and healthy controls (n = 23).

Authors, year, journal	Study sample (n)	Mean age in years (S.D.)	Sex (%Male)	Psychiatric diagnosis	Illness severity	Antipsychotic status	Obesity measure(s)	Mean values of obesity measurements (S.D.)	Matching	Key findings
Arranz et al., 2004, J Clin Psychiatry	Psych = 50; HCs = 50	Psych = 25.2 (SEM = 0.6); HCs = 29.8 (SEM = 0.7)	Psych = 66.0%; HCs = 62.0%	Schizophrenia	N/A	Never received AP, antidepressants, mood stabilizers	BMI	Psych = 22.2 (SEM = 0.3) [kg/m^2]; HCs = 22.1 (SEM = 9.3) [kg/m^2]	None	Mean BMI higher in Psych group
Balotsev et al., 2017, Early Interv Psychiatry	Psych = 38; HCs = 37	Psych = 25.4 (0.89); HCs = 24.8 (0.86)	Psych = 55.3%; HCs = 43.2%	First Episode Psychosis	N/A	Never received AP	BMI	Psych = 22.55 (2.94) [kg/m^2]; HCs = 23.02 (3.05) [kg/m^2]	Not specified	Mean BMI lower in Psych group
Cai et al., 2012, J Proteome Res	Psych = 11; HCs = 11	Psych = 27.6 (9.50); HCs = 27.6 (9.5)	Psych = 54.5%; HCs = 54.5%	Schizophrenia	PANSS = 55.6 (16.8)	Never received AP	BMI	Psych = 21.0 (1.7) [kg/m^2]; HCs = 21.1 (0.7) [kg/m^2]	Age and Sex	Mean BMI lower in Psych group
Chen et al., 2013, Psych Res	Psych = 49; HCs = 30	Psych = 26.8 (8.1); HCs = 26.9 (3.9)	Psych = 28.6%; HCs = 33.3%	Schizophrenia	N/A	Never received AP or < 2 weeks of lifetime exposure	BMI	Psych = 21.6 (3.9) [kg/m2]; HCs = 21.4 (2.5) [kg/m2]	Not specified	Mean BMI higher in Psych group
Chen et al., 2016, Psychol Med	Psych = 172; HCs = 31	Psych = 28.7 (9.9); HCs = 26.9 (5.2)	Psych = 48.3%; HCs = 45.2%	Schizophrenia	N/A	Never received AP	BMI, WC, WHR	BMI: Psych = 21.8 (3.8) [kg/m^2]; HCs = 22.4 (3.5) [kg/m^2] WC: Psych = 76.8 (10.6) [cm]; HCs = 77.5 (9.8) [cm] WHR: Psych = 0.8 (0.1); HCs = 0.8 (0.1)	None	Mean BMI and WC lower in Psych group, no difference in WHR
Dasgupta et al., 2010, Prog Neuropsychopharmacol Biol Psychiatry	Psych = 30; HCs = 25	Psych = 32.53 (10.53); HCs = 35.68 (9.57)	Psych = 48.3%; HCs = 45.2%	Schizophrenia	N/A	Never received AP, antidepressants, mood stabilizers	BMI	Psych = 20.95 (3.07) [kg/m^2]; HCs = 21.01 (2.72) [kg/m^2]	Age and Sex	Mean BMI lower in Psych group
Emsley et al., 2015, Psych Res	Psych = 22; HCs = 23	Psych = 24.6 (6.1); HCs = 27 (8.9)	Psych = 86%; HCs = 65%	Schizophrenia or schizophreniform	PANSS = 83 (15)	Never received AP	BMI	Psych = 22.1 (3.5) [kg/m^2]; HCs = 20.5 (4.3) [kg/m^2]	Age, sex, ethnicity, and education	Mean BMI higher in Psych group
Fawzi et al., 2011, Psych Res	Psych = 108; HCs = 200	Psych = 27.2 (10.6); HCs = 28.8 (11.2)	Psych = 100.0%; HCs = 100.0%	Schizophrenia	PANSS = 69.2 (6.4)	Never received AP or psychotropic medications	BMI, WHR	BMI: Psych = 26.8 (3.5) [kg/m^2]; HCs = 26.4 (3.3) [kg/m^2] WHR: Psych = 0.91 (0.05); HCs = 0.89 (0.07)	Age, sex, and lifestyle characteristics (not specified)	Mean BMI and WHR higher in Psych group
Fawzi and Fawzi, 2012, Compr Psychiatry	Psych = 50; HCs = 50	Psych = 29.4 (10.2); HCs = 31.1 (10.8)	Psych = 58% HCs = 58%	Schizophrenia	N/A	Never received AP	BMI, WC	BMI: Psych = 27.1 (3.6) [kg/m^2]; HCs = 26.2 (3.5) [kg/m^2] WC: Psych = 90.7 (12.0) [cm]; HCs = 85.5 (10.8) [cm]	Age and Sex	Mean BMI and WC higher in Psych group
Jensen et al., 2017, J Clin Psychiatry	Psych = 57; HCs = 60	Psych = 15.87 (1.36); HCs = 15.69 (1.41)	Psych = 28.1% HCs = 30.0%	Schizophrenia and other psychotic disorders	PANSS = 77.28 (11.75)	Never received AP	BMI, WC	BMI Z scores: Psych = 0.51 (1.25); HCs = 0.44 (0.99). WC Z scores: Psych =1.41 (1.72); HCs = 0.42 (1.27)	Age, sex, and parental education	Mean BMI higher in Psych group
Jindal et al., 2010, Schiz Res	Psych = 24; HCs = 41	Psych = 22.4 (5.47); HCs = 22.31 (5.7)	Psych = 71% HCs = 61%	Schizophrenia, Schizoaffective, schizophreniform	SANS = 41.7 (10.41)	Never received AP	BMI	Psych = 5.08 (0.5)- sq. root transformed; HCs = 4.85 (0.48) - sq. root transformed	Age and Sex	Mean BMI higher in Psych group
Masopust et al., 2015, Neuropsychiatr Dis Treat	Psych = 50; HCs = 50	Psych = 27.4 (7.4); HCs = 27.0 (7.3)	Psych = 58% HCs = 58%	Schizophrenia, schizophreniform	PANSS = 97.7 (16.6)	Never received AP	BMI	Psych = 22.4 (4.2) [kg/m^2]; HCs = 23.7 (3.0) [kg/m^2]	Age and Sex	Mean BMI lower in Psych group

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Table 1 (*continued*)

Authors, year, journal	Study sample (n)	Mean age in years (S.D.)	Sex (%Male)	Psychiatric diagnosis	Illness severity	Antipsychotic status	Obesity measure(s)	Mean values of obesity measurements (S.D.)	Matching	Key findings
McEvoy et al., 2013, PLOS ONE	Psych = 20; HCs = 29	Psych = 27.0 (9.8); HCs = 41.0 (9.5)	Psych = 65.0%; HCs = 20.7%	Schizophrenia	BPRS = 34.8 (5.3)	Never received AP	BMI, WC	BMI: Psych = 23.4 (4.3) [kg/m^2]; HCs = 29.4 (7.0) [kg/m^2] WC Psych = 34.2 (5.0) [in]; HCs = 38.7 (7.1) [in]	Race	Mean weight, BMI and WC lower in Psych group
Padmavati et al., 2010, Schiz Res	Psych = 51; HCs = 51	Psych = 45.8 (10.7); HCs = 45.7 (10.9)	Psych = 58.8%; HCs = 58.8%	Schizophrenia	N/A	Never received AP	BMI, WC	BMI: Psych = 19.4 (3.7) [kg/m^2]; HCs = 22.7 (4.0) [kg/m^2] WC: Psych = 78.39 (19.51) [cm]; HCs = 80.59 (14.37) [cm]	None	Mean BMI and WC lower in Psych group
Reddy et al., 2003, Schiz Res	Psych = 31; HCs = 40	Psych = 28.5 (7.8); HCs = 27.9 (8.0)	Psych = 65%; HCs = 73%	Schizophrenia, schizoaffective	N/A	Never received AP	BMI	Psych = 23.3 (3.4) [kg/m^2]; HCs = 26.3 (4.8) [kg/m^2]	Age and Sex	Mean BMI lower in Psych group
Saloojee et al., 2017, Early Interv Psychiatry	Psych = 67; HCs = 67	Psych = 22.8 (3.7); HCs = 23.3 (2.6)	Psych = 71.6%; HCs = 71.6%	Schizophrenia, schizoaffective, bipolar	N/A	Never received AP or < 4 days of lifetime exposure	BMI, WC	BMI: Psych = 24.4 (3.5) [kg/m^2]; HCs = 24.6 (5.3) [kg/m^2] WC: Psych = 83.6 (8.9) [cm]; HCs = 80.0 (10.0) [cm]	Age, sex, ethnicity	Mean BMI lower and WC higher in Psych group
Sengupta et al., 2008, Schiz Res	Psych = 38; HCs = 36	Psych = 25.4 (5.6); HCs = 25.1 (5.3)	Psych = 86.8%; HCs = 77.8%	Schizophrenia spectrum	BPRS = 59 (11.9)	< 10 days of lifetime AP exposure	BMI, WC, WHR	BMI: Psych = 22.8 (3.2) [kg/m^2]; HCs = 23.9 (3.5) [kg/m^2] WC: Psych = 81.4 (9.6) [cm]; HCs = 82.7 (9.7) [cm] WHR: Psych = 0.86 (0.05); HCs = 0.82 (0.06)	Age, sex, ethnicity	Mean BMI and WC lower, and WHR higher in Psych group
Spelman et al., 2007, Diabetic Medicine	Psych = 38; HCs = 38	Psych = 25.2 (5.64); HCs = 25.2 (5.69)	Psych = 73.7%; HCs = 73.7%	Schizophrenia	BPRS = 44.4 (9.0)	Never received AP	BMI, WC	BMI: Psych = 22.8 (3.1) [kg/m^2]; HCs = 24.2 (2.9) [kg/m^2] WC: Psych = 84.9 (10.2) [cm]; HCs = 86.2 (7.9) [cm]	Age, sex, ethnicity, smoking status, alcohol intake	Mean BMI and WC lower in Psych group
Strassnig et al., 2007, Schiz Res	Psych = 98; HCs = 30	Psych = 27.2 (7.5); HCs = 21.3 (3)	Psych = 69.8%; HCs = 61.5%	Schizophrenia spectrum and affective psychosis	N/A	< 2 weeks of continuous AP exposure in lifetime	BMI	Psych = 23.9 (5.0) [kg/m^2]; HCs = 25.1 (4.6) [kg/m^2]	None	Mean BMI lower in Psych group
Verma et al., 2009, J Clin Psychiatry	Psych = 160; HCs = 200	Psych = 30.0 (6.5); HCs = 30.2 (5.2)	Psych = 54.5%; HCs = 50.0%	Schizophrenia spectrum, affective psychoses, other psychotic disorders	N/A	Never received AP or < 72 h of lifetime exposure	BMI	BMI: Psych = 21.2 (3.7) [kg/m^2]; HCs = 23.5 (4.4) [kg/m^2]	Age, sex, ethnicity	Mean weight and BMI lower in Psych group
Wu et al., 2013, Schiz Res	Psych = 70; HCs = 44	Psych = 24.49 (6.98); HCs = 26.20 (4.20)	Psych = 52.9%; HCs = 45.5%	Schizophrenia	PANSS = 92.04 (11.57)	Never received AP	BMI, WC, WHR	BMI: Psych = 19.63 (2.53) [kg/m^2]; HCs = 20.34 (2.72) [kg/m^2] WC: Psych = 70.42 (7.63) [cm]; HCs = 69.89 (10.10) [cm] WHR: Psych = 0.82 (0.06); HCs = 0.79 (0.06)	Age, sex, ethnicity	Mean BMI lower, and mean WC and WHR higher in Psych group
Zhang et al., 2004, Br J Psychiatry	Psych = 46; HCs = 38	Psych = 26.5 (6.6); HCs = 26.9 (50)	Psych = 58.7%; HCs = 57.9%	Schizophrenia	PANSS = 99.6 (16.1)	Never received AP	BMI, WHR	BMI: Psych = 20.5 (3.5) [kg/m^2]; HCs = 21.6 (2.3) [kg/m^2] WHR: Psych = 0.83 (0.07); HCs = 0.81 (0.07)	Age, sex	Mean weight and BMI lower, and mean WHR higher in Psych group
Zhang et al., 2016, Schiz Res	Psych = 31; HCs = 71	Psych = 25.6 (5.1); HCs = 30.2 years (5.0)	Psych = 48%; HCs = 45%	Schizophrenia	PANSS = 87.6 (12.5)	Never received AP	BMI	Psych = 22.5 (3.2) [kg/m^2]; HCs = 22.8 (1.7) [kg/m^2]	None	Mean BMI lower in Psych group

Abbreviation. AP, Antipsychotics; BMI, Body Mass Index; BPRS, Brief Psychiatric Rating Scale; HCs, Healthy Controls; PANSS, Positive and Negative Syndrome Scale; Psych; Patients with Psychosis; SD, Standard Deviation; SEM; Standard Error of the Mean; WC, Waist Circumference; WHR; Waist-to-Hip Ratio.

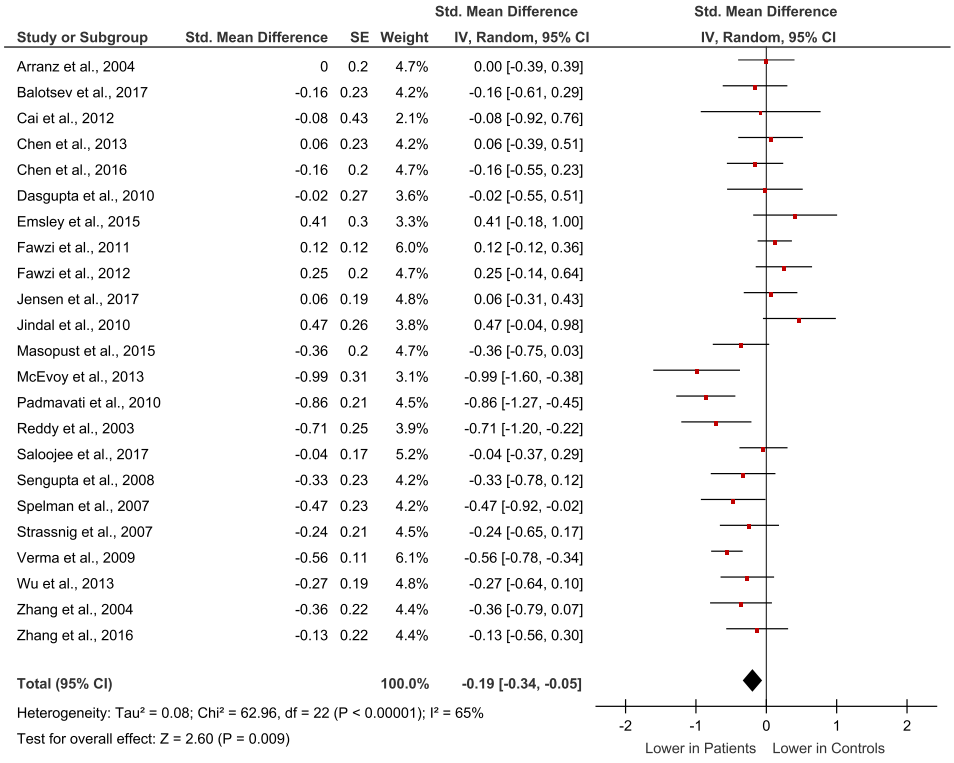

Fig. 2. Group differences in body mass index between antipsychotic-naive and minimally treated (≤2 weeks) patients with psychosis and healthy controls.

analysis indicated that no single study contributed to this heterogeneity. A sensitivity analysis examining studies in which patients were matched with HCs for age, sex, and ethnicity showed that BMI was lower in the patient group compared to HCs (SMD = −0.26, 95% CI = −0.51 to −0.00, $P = 0.05$). The exclusion of studies with patients who were treated with antipsychotics for up to 2 weeks revealed that BMI was lower in patients who had never received antipsychotics compared to HCs (SMD = −0.18, 95% CI = −0.35 to −0.00, $P = 0.05$). The analysis restricted to patients with schizophrenia-related non-affective psychotic diagnoses demonstrated lower BMI in this patient population compared to HCs (SMD = −0.19, 95% CI = −0.36 to −0.01, $P = 0.04$). Furthermore, the results remained significant after the analysis was restricted to studies (n = 14) with a low risk of bias (SMD = −0.19, 95% CI = −0.35 to −0.02, $P = 0.03$) and studies with non-overlapping samples (SMD = −0.22, 95% CI = −0.37 to −0.08, $P = 0.003$).

While 22 studies had non-obese patient (BMI range: 19.4 to 27.1 kg/m^2) and HC (BMI range: 20.34 to 29.4 kg/m^2) groups, one study had nearly obese HCs (BMI = 29.4 ± 7.0 kg/m^2) and normal weight patients (BMI = 23.4 ± 4.3 kg/m^2) (McEvoy et al., 2013). This study seems to drive some of the BMI results seen in our meta-analysis. However, BMI remained lower in patients after removal of the study from the main analysis (SMD = −0.16, 95% CI = −0.31 to −0.02, $P = 0.02$).

Meta-regression analyses (Fig. S3a) revealed a negative relationship between age and SMDs in BMI in the patient group (23 studies; patients, n = 1311; HCs, n = 1252; slope = −0.035; 95% CI = −0.051 to −0.018; $P = 0.00003$) (Fig. S3a). That is, older patients with psychosis had greater decrease in BMI. Positive non-significant trends were found between sex (%male) and SMD (Fig. S3b) and between PANSS total score and SMD (Fig. S3c).

3.3. Group differences in waist circumference

No differences in WC were observed between antipsychotic-naive and minimally treated patients with psychosis and HCs (SMD = −0.07, 95% CI = −0.17 to 0.32, $P = 0.55$) (Fig. S4). In the main analysis, significant heterogeneity ($I^2 = 69\%$) existed between the studies and one-leave-out sensitivity analysis indicated that no single study contributed to this heterogeneity. These results remained non-significant when sensitivity analyses were restricted to: patients matched with HCs for age, sex, and ethnicity (SMD = 0.08, 95% CI = −0.18 to 0.33, $P = 0.56$); patients who had never taken antipsychotics, after excluding those studies with patients who had up to 2 weeks of antipsychotic treatment (SMD = 0.05, 95% CI = −0.25 to 0.35, $P = 0.76$); and patients with schizophrenia-related non-affective psychotic disorders (SMD = −0.06, 95% CI = −0.28 to 0.17, $P = 0.63$). The results remained unchanged after the analysis was restricted to studies with a low risk of bias (SMD = 0.15, 95% CI = −0.07 to 0.37, $P = 0.18$) and studies with non-overlapping samples (SMD = 0.02, 95% CI = −0.24 to 0.29, $P = 0.85$).

3.4. Group differences in waist-to-hip ratio

WHR was elevated in antipsychotic-naive and minimally treated patients with psychosis compared to HCs (SMD = 0.34, 95% CI = 0.14 to 0.55, $P = 0.001$) (Fig. 3). In the main analysis, heterogeneity was not significant ($I^2 = 36\%$). All studies included in this analysis had non-overlapping samples of patients with schizophrenia-related disorders. After excluding studies in which patients were treated with antipsychotic, WHR remained elevated in patients who had never received antipsychotics compared to HCs (SMD = 0.28, 95% CI = 0.14 to 0.46, $P = 0.001$). The results remained significant after the analysis was restricted to studies with a low risk of bias (SMD = 0.37, 95% CI = 0.06 to 0.67, $P = 0.02$). There were insufficient studies to assess the effects of age, sex, and ethnicity.

4. Discussion

To our knowledge, this is the first meta-analysis to compare obesity measures (BMI, WC, and WHR) between antipsychotic-naive and minimally treated patients with psychosis and HCs. The main analyses revealed lower BMI and elevated WHR in the patient group compared to

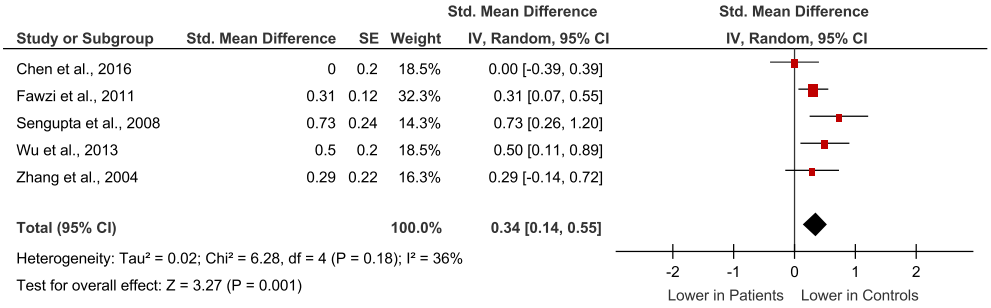

Fig. 3. Group differences in waist-to-hip ratio between antipsychotic-naive and minimally treated (≤2 weeks) patients with psychosis and healthy controls.

HCs. These differences remained after analyses were restricted to patients matched with HCs for age, sex, and ethnicity; patients who had never taken antipsychotics; and patients with schizophrenia-related disorders. Taken together, these results suggest that obesity measures are altered in never and minimally treated patients with psychosis, indicating that factors independent of antipsychotic effects may be contributing to obesity-related metabolic dysregulation seen in patients with schizophrenia and other psychotic disorders (Carney et al., 2016; Minichino et al., 2017; Vancampfort et al., 2010, 2015).

4.1. Analysis of reviewed studies

4.1.1. Differences in body mass index

Twenty-three studies reported BMI in patients with psychosis and HCs. Most of these studies (n = 18) had patients with first-episode psychosis, later confirmed to be schizophrenia or schizophrenia-related disorders. BMI differences in these studies were only assessed during the illness onset, so it is unclear how BMI would change over the course of the illness, independent of antipsychotic use.

BMI measures the ratio between weight and height, and individuals with scores above 30 kg/m^2 are generally considered obese (Wirshing, 2004). Twelve out of 23 studies only used BMI obesity measure (Arranz et al., 2004; Balotsev et al., 2017; Cai et al., 2012; Chen et al., 2013; Dasgupta et al., 2010; Emsley et al., 2015; Jindal et al., 2010; Masopust et al., 2015; Reddy et al., 2003; Strassnig et al., 2017; Verma et al., 2009; Zhang et al., 2016). All studies, except one (McEvoy et al., 2013), had non-obese patient and HCs groups using the BMI criterion. Consideration of BMI alone can lead to diagnostic inaccuracies as it is an indirect measure of body fat and does not take into account variables such as fat distribution, bone structure, and muscle mass that can affect the measure (Duren et al., 2008).

Meta-regression analyses showed that higher age of patients was related to lower SMDs in BMI. Although this was a significant relationship, one study (patients, n = 51; HCs, n = 51) (Padmavati et al., 2010) appeared to mainly drive this phenomenon.

4.1.2. Differences in waist circumference

Nine studies reported WC in patients with psychosis and HCs. Overall, studies showed mixed results in WC differences; and these inconsistencies may be related to multiple factors. First, the waist circumference measurement sites differed between the studies. While two studies measured WC midway between iliac crest and the ribcage (Chen et al., 2016; Saloojee et al., 2017), others measured it at the highest point of the iliac crest (Fawzi and Fawzi, 2012; Padmavati et al., 2010; Wu et al., 2013), and several studies provided no description on how WC was measured (Jensen et al., 2017; McEvoy et al., 2013; Sengupta et al., 2008; Spelman et al., 2007). Second, there may be varying degrees of measurement error between studies (Sebo et al., 2017; Verweij et al., 2013), likely indicative of differences in study protocols and training of research staff. Lastly, WC measurements could differ based on underlying medical conditions (e.g. enlarged liver) (Lee et al., 2017). In light of these limitations, more studies sharing similar methodologies are needed to draw definitive conclusions as to whether WC differs between antipsychotic-naive and minimally treated patients with psychosis and HCs.

4.1.3. Differences in waist-to-hip ratio

Five studies reported WHR measures. Of these, one found no difference in WHR between the patient and HC groups (Chen et al., 2016), whereas the remaining four showed elevated WHR in the patient group (Fawzi et al., 2011; Sengupta et al., 2008; Wu et al., 2013; Zhang et al., 2004). Similar to WC, WHR is also more susceptible to measurement error compared to BMI (Sebo et al., 2017; Verweij et al., 2013). Of note, one study used imaging (i.e. magnetic resonance imaging) to measure abdominal subcutaneous and visceral fat and found that although non-significant, these measures were elevated in antipsychotic-naive patients with schizophrenia in comparison to HCs (Zhang et al., 2004). Overall, the results suggest elevated WHR in antipsychotic-naive and minimally treated patients with psychosis compared to HCs.

4.2. Interpretation of study results

Lower BMI and elevated WHR in antipsychotic-naïve and minimally treated patients with psychosis compared to HCs may seem counterintuitive. However, these differences can be understood based on literature evidence, which suggests that BMI is poorly correlated with WHR (Deurenberg-Yap et al., 2000; Jee et al., 2002). WHR, a measure of abdominal body fat, is a better predictor of cardiovascular disease than BMI, which is a marker of overall body fat (Huxley et al., 2010). Not only are BMI and WHR measuring different dimensions of obesity, but they may have important differences in physiological processes and risk factors.

Importantly, given the small number of studies that reported WHR and the differing definitions of waist measurements among the included studies, the counterintuitive findings of lower BMI and higher WHR should be interpreted with caution. It is also possible that the difference in the directionality of BMI and WHR is a study artifact rather than a true phenomenon; however, this is questionable. Notably, the studies reporting WHR were a subset of the studies reporting BMI. When the BMI analyses were limited to the five studies that reported WHR, the results for BMI were not significant (SMD = −0.15, 95% CI = −0.36 to 0.06, $P = 0.15$). While this may suggest a bias in the studies that provided data for WHR, the findings were significant when we removed one (Fawzi et al., 2011) of the five studies that appeared to contribute to the observed heterogeneity (results after the study removal: BMI SMD = −0.27, 95% CI = −0.48 to −0.07, $P = 0.009$, $I^2 = 0\%$; WHR SMD = 0.37, 95% CI = 0.06 to 0.67, $P = 0.02$, $I^2 = 52\%$). The removed study appeared to have an unclear risk of bias in the selection of HCs because it was unclear whether individuals with resolved psychiatric illness or a family history of psychiatric illness were also included in the control group.

4.2.1. Lower body mass index

Many factors may contribute to a lower BMI in antipsychotic-naive and minimally treated patients with psychosis compared to HCs. One

explanation for this phenomenon could be that patients with psychosis are more likely to neglect basic needs, such as feeding themselves. For example, an individual with persecutory delusions of their food being poisoned may refuse to eat (Dadic-Hero et al., 2011). Another possible explanation could be related to dopaminergic dysfunction observed in schizophrenia. Specifically, patients demonstrate increased endogenous dopamine levels, as well as increased dopamine release, in the dorsal striatum compared to HCs (Caravaggio et al., 2015b; Fusar-Poli and Meyer-Lindenberg, 2013; Howes et al., 2012; Kegeles et al., 2010). This central dopaminergic dysfunction, combined with striatal dopamine's role in food reward and peripheral glucose metabolism, may modulate eating behaviours (Mahapatra, 2010; Singh, 2014). Indeed, greater dopamine signalling in the striatum has been associated with reduced BMI (Lee et al., 2018; Wallace et al., 2014; Wilcox et al., 2010) and greater insulin sensitivity (Caravaggio et al., 2015a; Ter Horst et al., 2018). Relatedly, the influence of the gut microbiota on body metabolism may mediate the link between obesity and neuropathology of schizophrenia (Dinan et al., 2014; Rogers et al., 2016).

4.2.2. Elevated waist-to-hip ratio

One plausible explanation for elevated WHR could be related to an inactive lifestyle. The prodromal and early stages of schizophrenia are generally characterized by negative symptoms such as reduced drive and motivation, in addition to increased isolation (Foussias and Remington, 2010; Gourzis et al., 2002). These symptoms may be linked to reduced physical activity and elevated risk of abdominal obesity. Notably, the influence of physical activity may be greater with respect to WHR versus BMI (Burke et al., 2012; Slentz et al., 2004), and therefore elevated WHR could be secondary to less active lifestyle observed in these patients. Higher WHR could also be related to stress caused by psychosis, contributing to increased cortisol and abdominal fat (Bjorntorp, 2001).

4.3. Future directions

Future studies should consider assessing clinical (e.g. illness severity), biochemical, and neuroimaging correlates of differences in obesity measures in antipsychotic-naive and minimally treated patients with psychosis. Along similar lines, assessing obesity measures as a function of illness progression, independent of the effects of antipsychotics, could help to understand the plausible intrinsic pathophysiological link between schizophrenia and obesity. However, ethical considerations related to withholding treatment make prospective studies of this sort unlikely. Further, it would be beneficial for future studies to investigate alterations in obesity measures by concurrently accounting for other confounders, such as diet and physical activity. Finally, future studies should consider investigating whether body fat alterations at illness onset can help to identify patients who are more likely to experience weight gain and other metabolic abnormalities following antipsychotic treatment.

4.4. Limitations of the present review

This review has a few limitations. First, we were unable to explore the impact of potential confounders (e.g. cultural factors, diet, physical activity, and socioeconomic status) relating to obesity due to the small number of studies that reported these variables. Therefore, we are unable to draw conclusions about the predictors of the differences in obesity that we identified. The heterogeneity of schizophrenia and other psychotic disorders further limits the interpretation of pooled data and may impact generalizability. Additionally, pooling data across different time periods and geographic locations may obscure interactions with time- and location-specific factors such as culture and population-based trends in obesity. Another limitation is the dependence on indirect measures of obesity, such as BMI and WC, which are prone to confounds and less specific than body fat percentage as measured by dual-energy x-ray absorptiometry (Duren et al., 2008). Similarly, the inclusion of obesity-related biomarkers (e.g. adiponectin, cytokines, orexin) could provide mechanistic insight regarding fat disposition and weight in this patient population; however, we were unable to assess these measures due to the small number of studies that reported them. Lastly, our sample size for WHR was small, which may have affected the study results.

4.5. Conclusions

The present meta-analysis found lower BMI and elevated WHR in psychiatric patients with minimal to no antipsychotic treatment compared to HCs. Future studies are required to explore the mechanisms underlying alterations in obesity measures in patients with psychosis, independent of antipsychotic effects. An improved understanding of these differences could guide strategies for monitoring weight gain in patients with schizophrenia.

Role of the funding source

The funding agencies did not contribute to the study design; in the data collection, analyses, and interpretation; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Conflict of interest

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CRediT authorship contribution statement

Parita Shah: Conceptualization, Investigation, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Yusuke Iwata:** Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Fernando Caravaggio:** Investigation, Writing - original draft, Writing - review & editing. **Eric Plitman:** Data curation, Writing - original draft, Writing - review & editing. **Eric E. Brown:** Investigation, Writing - original draft, Writing - review & editing. **Julia Kim:** Data curation, Writing - original draft, Writing - review & editing. **Nathan Chan:** Investigation, Writing - original draft, Writing - review & editing. **Margaret Hahn:** Investigation, Writing - original draft, Writing - review & editing. **Gary Remington:** Investigation, Writing - original draft, Writing - review & editing. **Philip Gerretsen:** Supervision, Investigation, Writing - original draft, Writing - review & editing. **Ariel Graff-Guerrero:** Funding acquisition, Supervision, Investigation, Writing - original draft, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.01.005.

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