CARDIOVASCULAR AND PHYSICAL HEALTH IN SEVERE MENTAL ILLNESS

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CARDIOVASCULAR AND PHYSICAL HEALTH IN SEVERE MENTAL ILLNESS

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EDITORIAL
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Editorial: Cardiovascular and Physical Health in Severe Mental Illness

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Keywords: severe mental illness, obesity, cardiovascular health, treatment, prevention

Editorial on the Research Topic

Cardiovascular and Physical Health in Severe Mental Illness

Severe mental illnesses (SMI) such as schizophrenia and bipolar disorder are associated with very high rates of metabolic disorders, including obesity, diabetes, and metabolic syndrome (1–3). There is a marked increase in standardized mortality ratios for both natural and unnatural causes of death in cases of SMI, much of which may be attributed to the increased prevalence of obesity and related coronary heart disease risk factors (4). Beyond cardiovascular risk, metabolic comorbidity has negative implications on other facets of clinical status, including cognitive performance (5–7), stigma (8), social engagement (9), quality of life (10), and adherence with treatment (11). The reasons driving these associations are complex, including contributing effects of illness-associated lifestyle factors, disease biology, and psychotropic treatments. Unfortunately, rates of non-treatment for these medical conditions are high in SMI, representing an unmet medical need (12–16). In this Research Topic, we discuss the relationship between SMI and metabolic dysfunction and provide novel perspectives from neurobiological, pathophysiological, and pharmacological points of view to improve the physical and mental well-being of vulnerable individuals suffering from SMI.

Several included papers have investigated the pathophysiological basis of this relationship. The role of inflammation in the etiopathogenesis of SMI and metabolic dysfunction and the effect of antipsychotics on these processes is an area of active inquiry, and articles in this issue reflect this (17–19). For example, Reponen, Dieset, et al. investigated the correlation between markers of systemic inflammation and dyslipidemia in patients with schizophrenia and bipolar disorder. They report higher levels of inflammatory markers, including high-sensitivity C-reactive protein (CRP) and myeloperoxidase and a correlation between inflammatory markers and atherogenic lipid ratios, suggesting that abnormal neutrophil activation may underlie increased metabolic risk in patients. In a subsequent paper, Reponen, Tesli, et al. have investigated if leptin, adiponectin, or their ratio could predict increased cardiovascular risk in SMI independent of other cardiometabolic risk factors. The group replicates previously documented elevations in leptin in SMI patients (20), but fails to find differences in adiponectin between patients and controls, or according to antipsychotic use. However, adiponectin emerges as a predictor of cardiovascular disease risk across cohorts, suggesting it may be a valuable marker for identifying individuals at higher

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cardiovascular disease risk. In an elegant preclinical study, Boyda et al. examined the effect of acute exposure to antipsychotics on peripheral catecholamines in female rats and found them to be increased in a manner consistent with their metabolic liability; the smallest increase was seen with haloperidol, followed by risperidone, olanzapine, whilst clozapine exposed rats showed the largest increase. Their findings align with a recent review of the evidence for autonomic dysfunction in schizophrenia where patients on antipsychotics with high-affinity muscarinic antagonism such as clozapine, olanzapine and quetiapine were noted to have the most significant autonomic dysfunction (21).

Delving further into the pathophysiological predictors of cardiovascular risk, Ward et al. combined genetic and metabolomic data to determine the relationship between folate pharmacogenomics, one-carbon metabolites, and insulin resistance. They found that pharmacogenomic variants that decrease the functional capacity of the Methylenetetrahydrofolate reductase (MTHFR) enzyme were associated with increased risk for cardiovascular disease. They also note that the increased presence of methyl-donating group containing molecules such as serine, glycine, and betaine might be inversely correlated with insulin resistance. Kim et al. investigated psychological characteristics associated with food cravings in patients with first-episode psychosis. In a study involving 182 patients (78 males and 104 females), they found that food cravings were, as expected, associated with weight gain. Interestingly, craving was influenced by perceived stress in females. The authors advocate for interventions aimed at reducing perceived stress in female patients with schizophrenia. Sneller et al. have summarized several of these aspects in a systematic review of clinical, biochemical, and genetic factors associated with metabolic syndrome among patients with SMI. They find that higher age, higher baseline BMI, higher current BMI, and male as well as female gender were positively associated with metabolic syndrome across all antipsychotics and suggest that this can form the basis for models that predict the risk of developing metabolic syndrome in patients with SMI who are being treated with antipsychotics.

Kumar et al. investigated the relationship between dietary glutamic acid and depressive symptomatology in patients with schizophrenia, stratified by obesity status, and report a possible correlation between dietary glutamic acid a depressive symptoms. Interestingly, this relationship was not seen in obese patients with schizophrenia supporting existing literature associating obesity, insulin resistance, and inflammation with depressive symptom severity, worse functional outcomes, and brain structural alterations (22). To further follow-up on this line of enquiry, two other studies in this issue addressed effects of metabolic dysfunction on brain structure and function, as measured by magnetic resonance imaging (MRI) across SMIs. Specifically, Kolenič et al. examined whether obesity could explain some of the heterogeneity in brain imaging findings in patients experiencing a first episode of psychosis (FEP). Their findings provide evidence for associations between higher BMI and lower cerebellar volume, raising the possibility that prevention and early mitigation of obesity and its related comorbidity could preserve brain structure in FEP. Taking this idea further, in a hypothesis paper, Calkin et al. have explored the potentially reversible impact of metabolic dysfunction on the brain in bipolar disorder. Leaning on recent findings from their group, they highlight growing evidence for a key role of insulin resistance in bipolar disorder pathophysiology and its relationship to shared inflammatory pathways. They posit that these modulations result in impaired blood-brain barrier (BBB) integrity and worse clinical outcomes and propose that reversing insulin resistance through lifestyle changes, vascular-protective drugs, or insulin-sensitizing medications could be a novel way forward for the prevention or treatment of bipolar disorder.

The special issue also includes two articles that have discussed antipsychotic-induced metabolic dysfunction in special contexts. Libowitz and Nurmi review the impact of this problem in pediatric populations, who represent one of the most vulnerable subgroups for metabolic adverse effects. They go on to propose underlying mechanisms and strategies to mitigate the impact of this large and difficult problem, along with future directions for research. Padmavati et al. have reviewed this problem from the point of view of a developing country, India, and identify strategies that need to be implemented at the clinic, community, and policy levels to understand and address the impact of cardiovascular diseases among persons with schizophrenia in developing countries.

Finally, two papers have discussed potential treatment strategies to address the enormous burden of metabolic dysfunction. García et al. have proposed a protocol to investigate whether implementing an individualized exercise program could improve overall functioning in patients with bipolar disorder. They propose to collect several clinical, biochemical, and imaging-based parameters at baseline, after a 4-month intervention period, and 6-month follow-up to investigate their hypothesis. Kanagasundaram et al. present the results of a large systematic review and meta-analysis assessing the effectiveness of pharmacological interventions in treating dyslipidemia in patients with schizophrenia. They report that antipsychotic switching, antipsychotic add-ons, and certain off label interventions might be effective in improving some but not all associated lipid parameters, highlighting that currently available lipid lowering agents may not work as well in this patient population.

Together, the special issue reviews the large body of work at the intersection of mental and physical health, and includes data from studies conducted across various settings and paradigms including fundamental research, clinical and intervention research, along with new hypothetical frameworks and protocols. It highlights recent advances in the field and that physical and mental well-being are closely interconnected. Concerted efforts to improve physical health are therefore likely to improve both quality of life and overall lifespan among individuals suffering from SMI.

AUTHOR CONTRIBUTIONS

SMA and MKH conceptualized the manuscript. SMA authored the first draft. All authors contributed to the writing and editing of the final manuscript.

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Atherogenic Lipid Ratios Related to Myeloperoxidase and C-Reactive Protein Levels in Psychotic Disorders

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Background: Cardiovascular disease (CVD) is a major cause of premature death in patients with psychotic disorders, where dyslipidemia occurs frequently. In the pathogenesis of these serious mental disorders, a low-grade inflammation seems to be a possible contributor. Concurrently, systemic inflammation and its interplay with dyslipidemia is a central driver in the pathogenesis of CVD. We hypothesize that evaluation of atherogenic lipid ratios together with inflammatory markers reflecting different inflammatory pathways with relevance for atherogenesis, could give novel information on immune-related mechanisms involved in early CVD risk in patients with psychotic disorders.

Methods: As a measure for CVD risk we calculated atherogenic lipid ratios using established sex-specific cut-offs: Total cholesterol/high-density lipoprotein; HDL-c (TC/HDL) and triglyceride/HDL-c (TG/HDL) were evaluated in 571 schizophrenia (SCZ) and 247 bipolar disorder (BD) patients, and in 99 healthy controls (HC). In addition, as a measure of low-grade inflammation, we measured fasting plasma levels of nine stable atherogenic inflammatory markers in patients (SCZ, BD) and in HC. The elevated inflammatory markers and CVD risk in patients, as reflected by TC/HDL and TG/HDL, were further assessed in multivariable analyses adjusting for comorbid cardio-metabolic risk factors.

Results: A markedly higher proportion (26%–31%) of patients had increased TC/HDL and TG/HDL ratios compared with HC. Plasma levels of high-sensitivity C-reactive protein (hs-CRP) and myeloperoxidase (MPO) were higher ($p<0.05$, $p<0.001$) in patients with psychotic disorders than in HC, and hs-CRP and MPO were independently associated with atherogenic lipid ratios in the multivariable analyses.

Conclusions: Our findings suggest that low-grade inflammation and abnormal neutrophil activation may cause increased CVD risk in patients with psychotic disorders. These mechanisms should be further examined to determine the potential for development of novel risk evaluation strategies.

Keywords: CVD risk, dyslipidemia, inflammatory biomarkers, schizophrenia, bipolar disorder

INTRODUCTION

Psychotic disorders are characterized by significant comorbid cardiometabolic risk (1, 2), and cardiovascular disease (CVD) mortality is elevated in patients with psychotic disorders. Compared with the general population, the risk of cardiovascular mortality is almost 2-fold in bipolar disorder and 2 to 3-fold in schizophrenia (3–5). Undiagnosed CVD prior to cardiovascular death is more common in psychotic disorders than in the general population (6).

Furthermore, dyslipidemia has frequently been reported in patients with severe mental disorders (1, 2). It is well known that second generation antipsychotic drugs (SGA) are associated with dyslipidemia and other metabolic side effects (7), but long-term antipsychotic treatment is contradictorily associated with reduced CVD mortality (8).

Atherogenic lipid ratios such as the total cholesterol/high-density lipoprotein; HDL-c (TC/HDL) and triglyceride/HDL-c (TG/HDL) have been shown to hold greater predictive value for CVD risk in individuals without symptomatic CVD than the isolated lipid parameters used independently (9, 10). Although increased TC and TG and reduced HDL-c have been reported (1, 2), these ratios have scarcely been investigated in psychiatric disorders.

It is well known that lipid accumulation together with low-grade inflammation lead to a chronic vascular remodeling and development of atherosclerosis in the arteries (11). An increasing number of novel inflammatory biomarkers that predict cardiovascular risk have recently been identified. These biomarkers are therefore relevant to investigate in patients with psychotic disorders, where a low-grade inflammation is a possible pathogenic contributor (12, 13).

Based on the emerging role of inflammation and its interaction with dyslipidemia in the progression of atherosclerotic disease, we hypothesize herein that evaluation of atherogenic lipid ratios together with inflammatory markers reflecting different inflammatory pathways with relevance for atherogenesis, could give novel information on immune-related mechanisms involved in the premature CVD risk in patients with psychotic disorders.

Our specific aims of this study were three-fold. Firstly, we evaluate whether the distribution of pro-atherogenic lipid ratios differ between a large cohort of patients with psychosis compared to healthy controls (HC). Secondly, we investigate whether the following inflammatory markers are dysregulated in patients with psychotic disorders versus HC:

- General down-stream markers of inflammation: High-sensitivity C-reactive protein (hs-CRP) (14) and glycoprotein 130 (gp130, a member of the interleukine-6 receptor family) (15).
- Markers of vascular inflammation, calcification, and endothelial function: Pentraxin 3 (PTX3) (16), osteoprotegerin (OPG) (17), and von Willebrand factor (vWF) (18).
- Markers related to fibrosis and extracellular matrix (ECM) remodeling: Galectin 3 (19) and Cathepsin S (20).
- Marker of neutrophil activation: Myeloperoxidase (MPO) (21).
- Marker of vascular apoptosis; Insulin-like growth factor-binding protein 4 (IGFBP4) (22).

Thirdly and lastly, we further investigate whether CVD risk as estimated by lipid ratios is associated with any upregulated inflammatory markers identified in the patient population. This study presents a detailed and thorough analysis of these three topics on a uniquely large cohort of patients with psychotic disorders.

METHODS

Design and Participants

The current study is part of the ongoing Thematically Organized Psychosis (TOP) Study at the Norwegian Centre for Mental Disorders Research (NORMENT). The TOP Study includes patients from both outpatient clinics and hospitals in the Oslo, Trondheim, and Lillehammer regions in Norway. Inclusion criteria in the TOP Study are: diagnosis of severe mental disorder, age between18–65 years and ability to give written informed consent. The healthy controls (HC), between 18–60 years old, were randomly selected from statistical records (www.ssb.no) in the Oslo region. All participants have given informed written consent. The study was approved by the Norwegian Scientific Ethical Committees and the Norwegian Data Protection Agency.

Sample

The sample used for the current cross-sectional study consists of 818 patients with severe mental disorders and 99 healthy controls

with fasting blood samples available, all included in the TOP Study from 2002 until 2013. In this sample, 571 patients had a schizophrenia spectrum disorder (SCZ: schizophrenia, schizoaffective disorder, schizophreniform disorder and psychotic disorder not otherwise specified), while 247 patients had a bipolar spectrum disorder (BD: bipolar I, bipolar II and bipolar disorder not otherwise specified). The SCZ and BD groups combined are hereafter referred to as the "all patients" group.

Participants with non-fasting blood samples, autoimmune or inflammatory diseases, on-going cancer, on-going infections, C-reactive protein (CRP) >20 mg/L of any reason, insulin levels >400 pmol/L, or participants receiving treatment with immune modulating drugs were excluded.

Clinical Assessments

All patients underwent a thorough diagnostic evaluation based on the Structured Clinical Interview in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) axis I Disorders (SCID-1). The Positive and Negative Syndrome Scale (PANSS), the Young Mania Rating scale (YMRS), and the Calgary Depression Scale for Schizophrenia (CDSS) were used for evaluations of the symtoms, and the functioning was assessed using the functioning score of the split version of the Global Assessment of the Functioning Scale (GAF-F). The inter-investigator diagnostic agreement has previously been evaluated to a satisfying level of 82%, with overall κ=0.77 (CI 0.60-0.94) (23).

Body mass index (BMI) (kg/m^2) was calculated based on height and weight measured by standard methods. For weight digitally calibrated weights were used. Blood pressure was measured using a manual device under standard conditions. The HC were interviewed using the Primary Care Evaluation of Mental Disorders (PRIME MD) to assess current or previous history of severe mental disorder themselves or in their family.

Blood Samples

The methodology used for drawing, processing and storage of blood samples have been described previously (24). Some of these biological markers have been reported previously by us in relation to other outcome measures (25–30).

Lipid Risk Factors

Plasma levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL-c), and low-density lipoprotein (LDL-c) were measured at the Department of Medical Biochemistry, Oslo University Hospital. TC, TG, and HDL-c were directly measured using an Integra 800 instrument from Roche Diagnostics, according to standard methods. LDL-c was calculated by Friedewald formula at the Department of Medical Biochemistry, Oslo University Hospital. This method changed during the study to direct measurement of LDL-c using an Integra 800 instrument from Roche Diagnostics.

Inflammatory Markers

Plasma levels of hs-CRP, gp130, PTX3, OPG, vWF, Galectin 3, Cathepsin S, MPO, and IGFBP4 were measured by enzyme immunoassays (EIA) in duplicate using commercially available antibodies (R&D Systems, Minneapolis, MN, USA) in a 384 format using a combination of a SELMA (Jena, Germany) pipetting robot and a BioTek (Winooski, VT, USA) dispenser/washer. Absorption was read at 450 nm with wavelength correction set to 540 nm using an ELISA plate reader (Bio-Rad, Hercules, CA, USA). Intra- and inter-assay coefficients of variation were <10% for all EIAs. For immunoassays blood was drawn using EDTA vials and the plasma was isolated the next working day and stored at -80°C. As plasma samples were collected over a long period, we evaluated potential degradation by comparing CRP measured continuously during samples collection and CRP measured during the bulk analysis of the other inflammatory markers. These CRP measurements correlated strongly (r=0.86) and both correlated similarly to time since sampling (r=0.17). Thus, the positive and similar association with sample time for CRP measured during sample collection and during bulk analysis argue against an effect of sample degradation during storage.

Insulin Resistance

Plasma levels of insulin and glucose were analyzed at the Department of Medical Biochemistry, Oslo University Hospital. Insulin was analyzed at the Hormone Laboratory by radioimmunoassay (RIA) using standard methods. Glucose levels were analyzed using standardized platforms from Roche Diagnostics. We estimated insulin resistance using the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) (31). As the calculation is valid only with insulin levels <400 pmol/L, participants with higher levels were excluded (N=11 patients).

Blood sampling was performed between 8 am and 11 am for most of the participants. All participants included in this study were fasting during blood collection.

Medication

Information on the use of prescribed medications including antipsychotics, immune modulating medication and statins used by patients was assessed by clinical interview and hospital records. "Defined daily dose" (DDD) was calculated according to the World Health Organization (WHO) principles. We calculated the individual total DDD based on antipsychotic polypharmacy. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults and provide a fixed unit of measurement independent of dosage form (http://www.whocc.no/atc_ddd_index/).

Statistical Analyses

All statistical analyses were done using the SPSS software package for Windows, version 25.0 (SPSS Chicago. USA). All analyses were two-tailed with a level of significance set at p<0.05. All skewed data was log-transformed prior to further analyses.

The cardio-metabolic risk was estimated using established atherogenic lipid ratios including TG/HDL and TC/HDL, with sex-dependent cut-offs established elsewhere (9, 10). Atherogenic lipid ratios were calculated, and enhanced cardio-metabolic risk was defined by (based on SI units, mmol/L): TC/HDL, male >5, female >4.5 (10); TG/HDL, male >1.53, female >1.09 (9). Differences in the proportion of individuals at risk between diagnostic groups were assessed using the chi-square test (unadjusted analysis). We then

adjusted for demographics (age, sex, BMI) in logistic regression analysis (adjusted analysis).

Differences in levels of inflammatory biomarkers between HC and diagnostic groups (i.e., SCZ and BD) were analyzed by multivariate analysis of covariance (MANCOVA) adjusting for demographics (age, sex, BMI).

Finally, in inflammatory markers that were elevated in patients (hs-CRP and MPO), the unadjusted and multivariable adjusted estimated atherogenic risk (i.e., based on lipid ratios) within the total patient population (i.e., SCZ and BD combined), and within diagnostic groups (i.e., SCZ and BD analyzed separately), were assessed using logistic regression. In these analyses, TC/HDL or TG/HDL were included as the dependent variable and hs-CRP or MPO were included as covariates in block 1 (unadjusted analysis). Further adjustments for conventional CVD risk factors; age, sex, BMI, insulin resistance, smoking, systolic blood pressure, and anti-psychotic treatment (DDD), were performed in block 2 (adjusted analysis). An example of a fully adjusted model is shown in **Figure 2C**.

RESULTS

Sample Characteristics

The clinical characteristics of the study population are shown in **Table 1**. The mean age and sex distribution in the patient group compared with HC were mainly the same when looking at the patient group as a whole. A subgroup analysis revealed that patients with BD were significantly older and more frequently female compared both to HC and patients with SCZ. The patients in general had significantly higher BMI, particularly so within SCZ. There was a higher proportion of non-European origin in patients compared to HC. The majority (78%) of patients received psychotropic drug treatment, with a higher DDD in SCZ than in BD.

Evaluation of lipids revealed a dysregulated profile with higher TC, LDL-c, and TG and lower HDL-c in the patients, and these differences were most prominent in patients with SCZ. Furthermore, patients, and in particular those with SCZ, had a higher degree of insulin resistance as estimated by HOMA-IR compared to HC (**Table 1**).

Pro-Atherogenic Lipid Ratios in Patients With Psychotic Disorders

To further evaluate the unfavorable lipid profile in patients with psychotic disorders, we calculated pro-atherogenic risk ratios based on lipid levels and assessed risk of CVD based on establish sex-specific cut-offs. Since indirectly measured LDL is derived from TC, and since TC/HDL ratio also is an established predictor of CVD risk, we focused the analyses on TC/HDL and TG/HDL. The patient group as a whole had a markedly higher proportion with enhanced TC/HDL (26.2%) and TG/HDL (30.5%) compared to healthy controls (9.2% and 8.2% for TC/HDL and TG/HDL, respectively). The unadjusted risk for an elevated TC/HDL was 3.35 [CI 1.65–6.80], p<0.001 in patients compared to controls, which persisted in age, sex, and BMI adjusted analysis, 2.69 [CI 1.29–5.60], p=0.008. Corresponding figures for TG/HDL were 4.77 [CI 2.27-10.01], p<0.001 in unadjusted and 3.16 [CI 1.47–6.80], p=0.003 in adjusted analysis.

Figure 1 shows the distribution of these lipid ratios according to diagnosis (BD, SCZ) and sex. Increased lipid ratios compared to HC were observed in both patient groups and sexes with a higher frequency in men and in patients with SCZ. Of note, the proportion of female patients with an elevated TG/HDL ratio was higher (23%–29%) than for TC/HDL (14%–21%), while these frequencies were similar in male patients (32%–34%).

Inflammatory Markers in Patients With Psychotic Disorders

Patients as a whole were characterized by higher levels of hs-CRP (f=3.19, p=0.042) than HC in age, sex and BMI adjusted multivariate analysis of covariance (MANCOVA), shown in **Table 2**, with the highest levels in patients with SCZ (f=4.62, p=0.032) compared to HC. Circulating MPO as marker of neutrophil activation was markedly higher in patients; both in SCZ (f=16.01, $p=7.1x10^{-5}$) and in BD (f=11.01, p=0.001) compared to HC. In contrast, we observed lower gp130 with a similar reduction in patients with BD (f=10.04, p=0.002) and SCZ (f=7.79, p=0.005) compared to HC. A similar association was observed for Galectin 3 in SCZ (f=40.5 $p=4.2x10^{-10}$) and in BD (f=62.8, $p=4.4x10^{-14}$) compared to HC, and for Cathepsin S in SCZ (f=6.91, p=0.009), and with the lowest levels in patients with BD (f=19.91, $p=1.1x10^{-5}$), compared to HC. No significant differences were observed for PTX3, OPG, IGFBP4, and vWF, although low vWF levels were noted in patients with BD (f=5.94, p=0.015) compared to HC. Within the patient population (where smoking status was available), there were no significant difference in levels of inflammatory markers between smokers and non-smokers, except with respect to vWF where smokers had higher levels (95 AU in non-smokers vs. 108 AU in smokers, p=0.025).

Association Between MPO, hs-CRP, and Atherogenic Lipid Ratios

Odds ratios (OR) were for these analyses based on log-transformed standardized values, and represent a one standard deviation (SD) increase in the analyzed marker. **Figure 2** shows unadjusted and adjusted logistic regression analysis for TC/HDL (**Figure 2A**) and TG/HDL (**Figure 2B**) ratios above the cut-off for CVD risk. Data are show for all patients and within diagnostic sub-groups (i.e., SCZ or BD).

As shown in **Figure 2**, unadjusted logistic regression analysis revealed a strong association between higher hs-CRP levels and CVD risk as reflected by elevated atherogenic lipid ratios, with OR 1.78 (95% CI 1.47–2.16, p<0.001) for TC/HDL (**Figure 2A**) and OR 1.91 (95% CI 1.58–2.30, p<0.001) for TG/HDL (**Figure 2B**). This association, although attenuated, remained significant in adjusted logistic regression analysis (OR 1.31 for TC/HDL and OR 1.40 for TG/HDL). Multivariable adjustment included insulin resistance (IR), smoking, anti-psychotic treatment (DDD), age, sex, BMI, hs-CRP (CRP), and MPO. The association was stronger in SCZ patients, where it remained significant in adjusted analysis with OR 1.49 (95% CI 1.14–1.96, p=0.004), while the association was not significant in BD following adjustment.

TABLE 1 | Demographics of the study population.

Clinical parameters	HC(n=99)	All patients(n=818)	BD(n=247)	SCZ(n=571)	Post hoc
	%(n)	%(n)	%(n)	%(n)	
Sex (male)	61.6 (61)	52.8 (432)	39.3 (97)	58.7 (335)	SCZ,HC>BD
Ethnicity (European)	98.0 (97)	82.2 (672)***	89.1 (220)	79.2 (452)	HC>BD,SCZ
Smoking status (daily use)	N/A	46.2 (367)	43.8 (106)	47.3 (261)	n.s.
Statin use	0 (0)	1.7 (14)	2.0 (5)	1.6 (9)	n.s.
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Anti-psychotic treatment (DDD)	N/A	0.96 (0.96)	0.5 (0.77)	1.13 (0.97)	SCZ>BD
Age	30 (8)	31 (11)	34 (12)	30 (10)	BD>SCZ,HC
Cardiometabolic risk factors					
HOMA-IR	2.7 (1.5)	3.7 (2.6)**	3.4 (2.2)	3.8 (2.7)	SCZ>BD,HC
HDL-c(mmol/L)	1.51 (0.46)	1.36 (0.43)**	1.46 (0.48)	1.31 (0.40)	HC,BD>SCZ
LDL-c (mmol/L)	2.85 (0.90)	3.14 (0.95)**	3.02 (0.90)	3.19 (0.96)	SCZ>BD,HC
Total-c (mmol/L)	4.70 (0.93)	5.10 (1.07)**	5.06 (1.06)	5.11 (1.08)	SCZ,BD>HC
Triglycerides(mmol/L)	1.04 (0.44)	1.46(1.10)***	1.39 (1.13)	1.49 (1.08)	SCZ,BD>HC
BMI	23.9 (3.2)	26.3 (5.0)***	25.7 (4.4)	26.5 (5.3)	SCZ,BD>HC
Symptom scores					
PANSS total	N/A	58 (17)	46 (11)	63 (17)	SCZ>BD
CDSS total	N/A	5.5 (4.8)	4.8(4.9)	5.7 (4.8)	SCZ>BD
YMRS total	N/A	4.8 (5.2)	3.9 (5.3)	5.3 (5.0)	SCZ>BD
GAF-S	N/A	46 (13)	56 (12)	42 (11)	BD>SCZ
GAF-F	N/A	46 (12)	53 (13)	44 (11)	BD>SCZ

*Analyzed with ANOVA for continuous variables and chi-square test for categorical variables. HC, healthy controls; BD, bipolar spectrum; SCZ, schizophrenia spectrum; n, number; DDD, defined daily dose; SD, standard deviation; HOMA-IR, homeostasis model assessment for insulin resistance; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; Total-c, total cholesterol; mmol/L, millimoles per liter; BMI, body mass index; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; YMRS, Young Mania Rating Scale; GAF-S, Global Assessment of Functioning-symptoms; GAF-F, Global Assessment of Functioning- functions; N/A, not applicable; n.s., not significant; *p<0.05 **p<0.01 ***p<0.001 vs. healthy controls.*

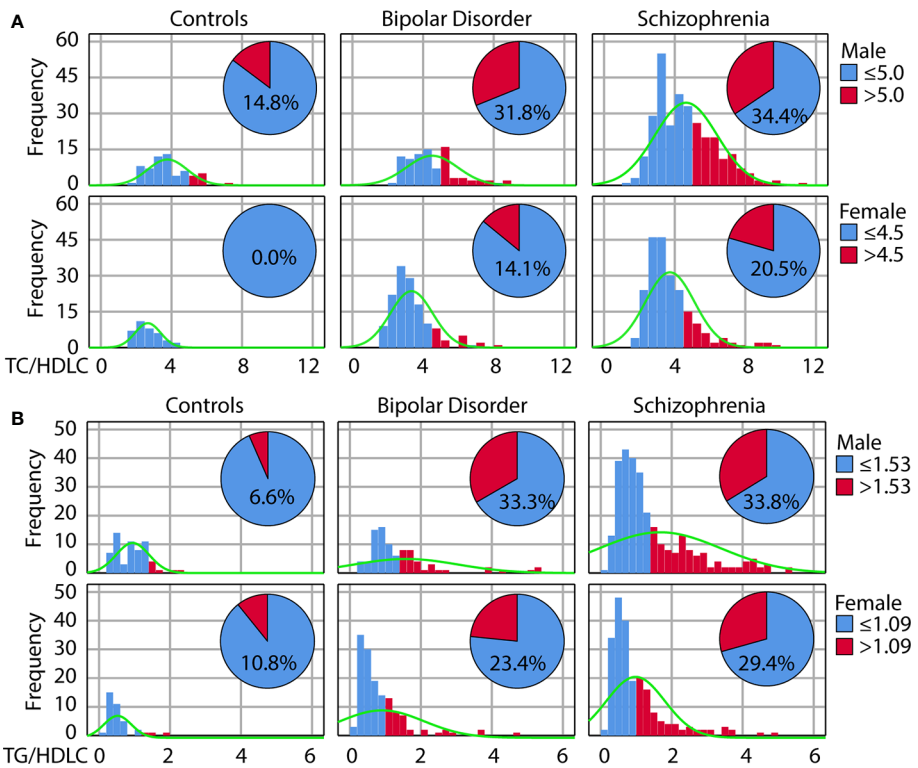

FIGURE 1 | Increased cardiovascular risk in psychotic disorders as reflected by atherogenic lipid ratios. Distribution of the total cholesterol/high-density lipoprotein (TC/HDL) **(A)** and triglyceride/HDL-c (TG/HDL) **(B)** ratios in healthy controls, patients with bipolar disorder or schizophrenia according to sex. The pie diagram shows the number of individuals with ratios above the risk cut-off.

TABLE 2 | Level of inflammatory markers (MANCOVA) after adjustment for age, BMI, and sex.

	HC(n=99)	All patients(n=818)	BD(n=247)	SCZ(n=571)
hsCRP (mg/L)	1.78 (1.44, 2.19)	2.18 (2.02, 2.36)*	1.96 (1.70, 2.26)	2.29 (2.09, 2.51)*
PTX3 (ng/ml)	2.97 (2.53, 3.49)	3.01 (2.84, 3.19)	3.03 (2.72, 3.37)	3.01 (2.80, 3.23)
OPG (ng/ml)	1.32 (1.24, 1.40)	1.35 (1.32, 1.38)	1.36 (1.31, 1.42)	1.35 (1.31, 1.38)
vWF (AU)	82.6 (70.8, 96.6)	72.8 (68.8, 77)	67.3 (60.7, 74.7)*	75.3 (70.4, 80.7)
gp130 (ng/ml)	234 (224, 243)	217 (214, 220)***	214 (208, 220)**	218 (214, 222)**
GAL3 (ng/ml)	5.47 (4.56, 6.56)	2.67 (2.50, 2.86)***	2.33 (2.06, 2.63)***	2.84 (2.62, 3.08)*** †
CatS (ng/ml)	5.99 (5.57, 6.41)	5.35 (5.19, 5.50)**	4.99 (4.71, 5.26)***	5.51 (5.32, 5.69)** †
MPO (ng/ml)	179 (148, 218)	275 (256, 295)***	294 (259, 335)***	266 (245, 290)***
IGFBP4 (ng/ml)	161 (151, 170)	165 (161, 168)	166 (160, 173)	164 (160, 168)

*Data are presented as estimated marginal means with 95% confidence interval. *p<0.05 **p<0.01 ***p<0.001 vs. healthy controls; †p<0.01 vs. bipolar disorder. MANCOVA, multivariate analysis of covariance; BMI, body mass index; n, number; hs-CRP, high sensitivity c-reactive protein; PTX3, pentraxin 3; OPG, osteoprotegerin; vWF, von Willebrand factor; gp130, glycoprotein 130; Gal3, galectin 3; CatS, cathepsin S; MPO, myeloperoxidase; IGFBP4, insulin-like growth factor-binding protein 4; mg/L, milligrams per liter; ng/mL, nanograms per milliliter; AU, arbitrary units.*

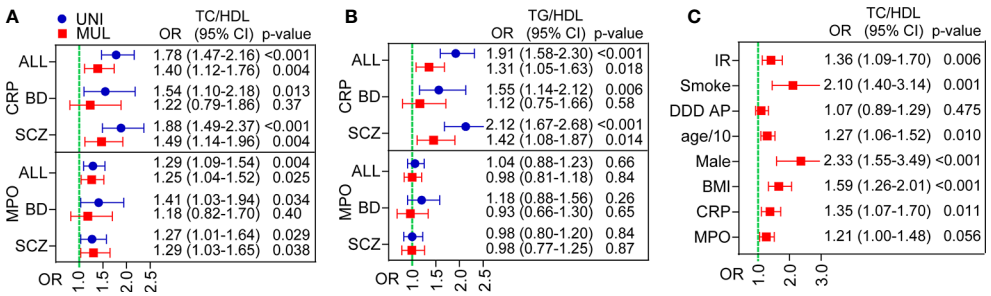

FIGURE 2 | Association between inflammatory markers and cardiovascular disease (CVD) risk as reflected by atherogenic lipid ratios in patients with psychotic disorders. Univariate (blue) and multivariable (red) logistic regression of hs-CRP (CRP) (top) and myeloperoxidase (MPO) (bottom) as predictors of dysregulated lipid ratios TC/HDL **(A)** and TG/HDL **(B)**. Multivariable adjustment for total cholesterol/high-density lipoprotein (TC/HDL) is shown in **(C)** and included insulin resistance (IR), smoking, antipsychotic treatment (DDD), age, sex, BMI, hs-CRP (CRP), and MPO. Odds ratios (OR) are expressed as log-transformed per SD change in marker.

The association between MPO and CVD risk in patients was more modest and only present for the TC/HDL ratio with OR 1.40 (95% CI 1.12–1.76 p=0.004), but persisted after multivariable adjustment with OR 1.25 (95% CI 1.04–1.52, p=0.025). The association appeared at the same level in SCZ and BD, but was more attenuated by adjustment in BD and thus only statistically significant in SCZ in adjusted analysis OR 1.29 (95% CI 1.03–1.65, p=0.038).

As both hs-CRP and MPO were associated with increased TC/HDL, we also evaluated these markers together. **Figure 2C** shows that both proteins were associated with an increased TC/HDL ratio in multivariable adjusted analysis.

DISCUSSION

Our study, evaluating a large number of relatively young (mean age = 31 years) patients with psychotic disorders, shows that this patient group is characterized by a markedly higher CVD risk. This is reflected by a larger proportion of individuals with elevated atherogenic lipid ratios among patients with psychotic disorders compared to HC, in particular in male patients and in patients with SCZ. Plasma levels of hs-CRP, a reliable downstream marker of inflammation, and MPO, a marker of neutrophil activation and oxidative stress, were higher in patients with psychotic disorders, and independently associated with unfavorable lipid ratios in multivariable analysis adjusting for conventional CVD risk factors. These data suggest that low-grade inflammation in combination with an atherogenic lipid profile may cause increased CVD risk in patients with psychotic disorders.

Dyslipidemia has frequently been reported in patients with severe mental disorders, in both medicated and drug naïve patients (32). We demonstrated relatively stable lipid levels during longitudinal testing (5 years follow-up) in patients with schizophrenia and schizoaffective disorders suggesting that lipid abnormalities may be related to core disease mechanisms (33) in addition to antipsychotic medication (7). Regardless of cause, dyslipidemia and metabolic abnormalities are closely associated with an enhanced risk of cardiovascular outcomes. In this regard, atherogenic lipid ratios such as the TC/HDL and TG/HDL hold greater predictive value in individuals without symptomatic CVD than the independent lipid parameters (10). We were unable to find age and sex distributed reference data on the prevalence of increased ratios in the general population.

However, the average TC/HDL ratio observed in healthy men and women in our study corresponded to the 50 percentile for 30 year-olds in a large contemporary population-based Dutch cohort study (34), suggesting that although limited in size the proportion of controls with increased lipid ratios in our study is comparable to similar European populations. This supports our data indicating a markedly enhanced CVD risk in this young population of patients with SCZ and BD, which may be related to the decreased life expectancy and plausibly increasing mortality due to cardiovascular causes in such patients (5, 35, 36). The higher proportion of patients with an elevated TG/HDL, compared to TC/HDL, (30.5% vs. 26.2%) in our study is compatible with the metabolic phenotype in these patients such as insulin resistance. Indeed, an increased TG/HDL ratio has been shown to closely correlate with insulin resistance in SCZ (37) as well as with the presence of small dense LDL particles which are particularly atherogenic (37, 38).

The interplay between dyslipidemia and chronic inflammation are hallmarks of atherosclerotic progression (39). CRP is the prototypical acute phase serum protein that rises rapidly in response to inflammation, but also represents the most robust marker of subclinical chronic inflammation. Chronic elevated levels have repeatedly been associated with persistent auto-inflammatory processes and an increased risk of future cardiovascular events in the general population (14, 40), and with CVD risk in patients with psychotic disorders (41–44). Our finding that elevated hs-CRP was associated with CVD risk as reflected by the TC/HDL and TG/HDL also in adjusted analysis including important cardio-metabolic risk factors, support these previous studies. Furthermore, this association was stronger and only significant after full multivariable adjustment in SCZ suggesting a stronger impact of inflammatory dysregulation on CVD risk in these patients. However, although hs-CRP by reflecting the general inflammatory burden related to important demographics such as insulin resistance and BMI (45, 46) represents a reliable risk marker of CVD, it is less useful in pinpointing specific dysregulation of inflammation that may be linked to CVD risk.

A major finding in our study was the markedly increased MPO levels in both SCZ and BD that were significantly associated with the TC/HDL ratio, also in adjusted analysis for SCZ. MPO is a reliable marker of neutrophil activation. These cells have recently received renewed interest with regard to atherosclerosis due to the variety of active substances they may release from granules, including reactive oxygen species promoting oxidation of lipoproteins, microparticles, and MPO that further are related to neutrophil extracellular traps (NETs). Aberrant neutrophil effector functions and increased circulating levels of inflammatory neutrophil effector peptides, such as alpha-defensins have been linked to SCZ pathogenesis (47) and may represent a bridging factor between atherosclerosis and inflammation (48). Indeed, elevated levels of MPO have been associated with coronary artery disease (CAD) (21) and predict risk in acute coronary syndromes (49). However, less is known on the role of MPO in individuals without symptomatic CVD, but epidemiologic studies demonstrate that MPO may predict future risk of coronary artery disease (50). Furthermore, elevated neutrophil counts have been reported in BD and SCZ (51–53) and based on the increased MPO levels observed in our study, it is tempting to speculate that abnormalities in neutrophil activation could represent an early event in the progression of CVD in patients with psychotic disorders. The stronger association with the TC/HDL compared to the TG/HDL, could suggest that the enhanced MPO is more directly linked to atherogenesis and not only a marker of this process.

We were unable to detect differences in a number of markers linked to vascular inflammation and CVD such as vWF (18), OPG (17), PTX3 (16), while levels of fibrosis and ECM remodeling markers such as Galectin 3 (19) and Cathepsin S (20) were lower, which may further support our hypothesis regarding dysregulated neutrophil effector functions and a consequent low-grade inflammatory "background". These markers have repeatedly been associated with risk of adverse cardiovascular outcomes, but have mainly been investigated in patients with stable atherosclerotic disease. However, the association with CVD risk in patients without established CVD may be different than in patients with symptomatic CVD concerning both the strength and potentially the direction of association (54). Based on the relatively young age of our population, vascular inflammation and ECM remodeling, which accelerate during atherogenesis, may not yet be activated. However, we are not able to conclude with respect to this without following the same patient group over time.

LIMITATIONS

This study had a cross-sectional design, making the causality described suggestive.

As fasting status can affect levels of the inflammatory markers, glucose, and lipid metabolism, we focused this study on fasting blood samples. This excluded 435 non-fasting controls and limited our control population to n=99, and gave uneven group size compared to the patient population (n=818). The relatively high portion of non-fasting participants in the initial control group was mostly due to their busy everyday lives, making it challenging to schedule blood sampling in the morning. These controls are used in other studies performed by the group. Furthermore, looking at differences between our patient group and HC, the majority of the healthy controls in the current sample are young and well-functioning, with a lower BMI than the patients, possibly underestimating the impact of lifestyle factors on dysregulation of some inflammatory markers. The smoking status is not available for our healthy controls. However, comparing inflammatory markers within the patient population, only vWF was significantly affected with higher levels in smokers. Also, while the effect of smoking on inflammation is less documented, the effect of smoking on CVD risk is known. Therefore, since we had smoking status in our patients, we were able to adjust for smoking when evaluating CVD risk. Future studies should include control groups that are better matched with the patient group in regard to their metabolic status. Finally, in our study, only 14 patients were using lipid-lowering agents, thus our sample was statistically underpowered to address the issue if these agents can be used as an early intervention to reduce CVD risk.

CONCLUSION

Patients with psychotic disorders have a markedly higher CVD risk compared to healthy controls as reflected by atherogenic lipid ratios, and the increased risk is associated with elevated hs-CRP and MPO reflecting subclinical inflammation and abnormal neutrophil activation in such patients. These findings support that low-grade inflammation may cause increased CVD risk in patients with psychotic disorders. These mechanisms should be further examined to determine the potential for treatment targets or development of novel risk evaluation strategies.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because sharing of data to external parties has not been approved by the ethics committee. Requests to access the datasets should be directed to e.j.reponen@medisin.uio.no.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional komite for medisinsk forskningsetikk, Øst-Norge (REK 1). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version. Each author specifically made the following contributions to this manuscript: ER: Data collection, literature search, statistical analysis, and manuscript editing. ID: Data collection, literature search, statistical analysis, and manuscript editing. MT: Data collection, literature search, statistical analysis, and manuscript editing. RM: Data collection, statistical analysis, and manuscript editing. MA: Data collection, statistical analysis, and manuscript editing. TV: Data collection and manuscript editing. EH: Data collection and manuscript editing. OD: Data collection and manuscript editing. NS: Data collection and manuscript editing. SH: Data collection, literature search, and manuscript editing. AS: Literature search and manuscript editing. SMG: Literature search and manuscript editing. KW-R: Literature search and manuscript editing. SD: Data collection, literature search, and manuscript editing. IM: Data collection and manuscript editing. PA: Data collection, literature search, and manuscript editing. OA: Data collection, literature search, statistical analysis, and manuscript editing. TU: Data collection, literature search, statistical analysis, and manuscript editing.

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BRIEF RESEARCH REPORT
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Higher Body-Mass Index and Lower Gray Matter Volumes in First Episode of Psychosis

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Background: Neurostructural alterations are often reported in first episode of psychosis (FEP), but there is heterogeneity in the direction and location of findings between individual studies. The reasons for this heterogeneity remain unknown. Obesity is disproportionately frequent already early in the course of psychosis and is associated with smaller brain volumes. Thus, we hypothesized that obesity may contribute to brain changes in FEP.

Method: We analyzed MRI scans from 120 participants with FEP and 114 healthy participants. In primary analyses, we performed voxel-based morphometry (VBM) with small volume corrections to regions associated with FEP or obesity in previous meta-analyses. In secondary analyses, we performed whole-brain VBM analyses.

Results: In primary analyses, we found that when controlling for BMI, FEP had lower GM volume than healthy participants in a) left fronto-temporal region (pTFCE = 0.008) and b) left postcentral gyrus (pTFCE = 0.043). When controlling for FEP, BMI was associated with lower GM volume in left cerebellum (pTFCE < 0.001). In secondary analyses, we found that when controlling for BMI, FEP had lower GM volume than healthy participants in the a) cerebellum (pTFCE = 0.004), b) left frontal (pTFCE = 0.024), and c) right temporal cortex (pTFCE = 0.031). When controlling for FEP, BMI was associated with lower GM volume in cerebellum (pTFCE = 0.004). Levels of C-reactive protein, HDL and LDL-cholesterol correlated with obesity related neurostructural alterations.

Conclusions: This study suggests that higher BMI, which is frequent in FEP, may contribute to cerebellar alterations in schizophrenia. As previous studies showed that obesity-related brain alterations may be reversible, our findings raise the possibility that improving the screening for and treatment of obesity and associated metabolic changes could preserve brain structure in FEP.

Keywords: obesity, schizophrenia, dyslipidemia, first-episode psychosis, low-grade inflammation, voxel-based morphometry

INTRODUCTION

Neurostructural alterations are frequently reported already early in the course of schizophrenia (SZ) and may contribute to worse psychiatric outcomes (1, 2). Participants in their first episode of psychosis (FEP) typically show smaller gray matter (GM) volumes in frontal, temporal, and insular lobes, although there is heterogeneity in the direction and location of findings between individual studies (3–5). The reasons for this heterogeneity and the origins of neurostructural alterations in FEP remain unknown. They may represent neurodevelopmental antecedents but may also reflect the presence or absence of certain clinical factors (6, 7). Better understanding of the clinical factors which contribute to brain alterations in FEP is important for interpretation of findings. It is also the first step toward prevention or treatment of neurobiological changes, which may contribute to functional impairment in FEP (1, 2). One potential source of neuroimaging abnormalities in FEP could be the comorbidity with medical conditions known to affect the brain. One such condition is obesity.

Almost 1 in 2 participants with SZ are obese or overweight (40%–60%), which is significantly more than in the general population (8, 9). Overweight or obesity are disproportionately frequent already in the earliest stages of illness (10–12) and affect about 20% of participants with FEP (13). There is a highly replicated evidence showing that obesity is negatively associated with brain structure in non-psychiatric, otherwise healthy participants and already in adolescence (14, 15). The most pronounced effects of obesity are observed in frontal, mesiotemporal/limbic regions and cerebellum, brain areas which are also implicated in SZ (5, 16–21). Yet, we know little about the effect of obesity on brain structure in SZ. There is a single previous study, which documented additive effects of psychosis and overweight/obesity on a composite index of brain structure (BrainAGE) in participants with FEP (22). However, no studies have investigated the localization of obesity related neurostructural alterations in SZ and whether these directly overlap with regions associated with psychosis.

To address this knowledge gap, we studied the effects of both, obesity and psychosis on regional brain volumes in a large sample of individuals with FEP and healthy subjects. Our *a priori* hypotheses were that BMI will be negatively associated with brain structure, when controlling for FEP and individuals with FEP will have lower regional brain volumes relative to controls, when controlling for BMI. We also hypothesized that both BMI and FEP will be additively associated with brain structure in some regions of interest. In exploratory analyses, we further explored the links between clinical or obesity related biochemical alterations and the brain changes associated with FEP or BMI.

METHODS

Sample Description

We analyzed a sample of 120 participants with FEP and 114 healthy participants (see **Table 1**). These analyses are a part of the Early Stages of SZ study (22, 23). To ensure generalizability, we recruited participants during their first hospitalization in a large general psychiatry hospital (1,200 beds), which serves the Prague and part of Central Bohemia regions—catchment area of over 1.5 million subjects. We focused on individuals with FEP, who met the following inclusion criteria: 1) were undergoing their first psychiatric hospitalization, 2) had the ICD-10 diagnosis of SZ (F20), or acute and transient psychotic disorders (F23) made by psychiatrist according to Mini-International Neuropsychiatric Interview (24), 3) had <24 months of untreated psychosis, and 4) were 18–35 years old. Participants with psychotic mood disorders were excluded from the study. As the diagnosis of SZ requires a minimal duration of symptoms, the retrospective diagnostic stability

TABLE 1 | Sample description.

	First-episode psychosis participants	Healthy participants	P
N	120	114	N/A
Sex, N (%) female	46 (38.33)	61 (53.51)	0.02
Age, mean (SD) years	27.00 (4.94)	25.70 (4.01)	0.03
Dg schizophrenia/acute polymorphic psychotic disorder N (%)	55(45.83)/65(54.17)	N/A	N/A
Duration of illness, mean (SD) months[a]	5.11 (5.43)	N/A	N/A
Duration of untreated illness, mean (SD) months[a]	3.12 (4.80)	N/A	N/A
Duration of antipsychotic treatment, mean (SD) months[a]	1.98 (2.92)	N/A	N/A
BMI, mean (SD; range)	23.32 (4.00; 16.0-42.5)	22.60 (2.93; 15.2–31.9)	NS
Overweight or obese, N (%)	38 (31.67)	23 (20.18)	0.045
LDL-cholesterol, mean (SD) mmol/l[b]	2.61 (0.73)	2.24 (0.56)	<0.001
HDL-cholesterol, mean (SD) mmol/l[b]	1.34 (0.37)	1.55 (0.38)	0.001
TG, mean (SD) mmol/l[b]	1.32 (0.56)	1.10 (0.45)	0.008
Total cholesterol, mean (SD) mmol/l[b]	4.56 (0.94)	4.29 (0.72)	0.05
CRP, mean (SD) mg/l[c]	2.16 (4.11)	1.18 (1.60)	NS
Glucose, mean (SD) mg/l[d]	4.45 (0.79)	N/A	N/A

BMI, body mass index; Dg, diagnosis; FEP, first-episode psychosis; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglycerides; CRP, C-reactive protein.
[a]*Data available from 116 FEP participants.*
[b]*Lipid levels were obtained in 73 FEP participants and 80 healthy participants.*
[c]*CRP levels were obtained in 68 FEP participants and 53 healthy participants.*
[d]*Three participants had glucose > 5.6 mmol/L, which in all instances normalized after re-testing; data available from 96 FEP participants.*

of SZ is low (0.6) (25). A significant number of individuals who are later diagnosed with SZ receive a different initial diagnosis. We wanted to recruit participants at the early stages of illness, to minimize the effects of illness and medications on brain structure. Thus, participants who were hospitalized before meeting the duration criteria for SZ are a particularly interesting group. These participants were included in the study and received the working diagnosis of acute and transient psychotic disorders, which is congruent with DSMIV brief psychotic disorder. This approach is in keeping with other studies of FEP (13, 25). Healthy participants, 18–35 years old, were recruited *via* advertisement, using the following exclusion criteria: 1) lifetime history of any psychiatric disorders, and 2) psychotic disorders in first or second-degree relatives. Additional exclusion criteria for both groups included history of neurological or cerebrovascular disorders and any MRI contraindications.

Within 1 week from scanning, we collected information about, weight, height, blood pressure, duration of untreated/treated psychiatric illness, current medications, and personal history of hypertension by direct assessment verified by chart review. On the day of scanning, we obtained symptom ratings (The Positive and Negative Syndrome Scale—PANSS) and where available (in 73 FEP participants and 80 healthy participants), also fasting blood samples for biochemical analyses (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides). In participants who were medication naive prior to hospitalization (N = 40) we calculated cumulative medication exposure until MRI, based on their prospective inpatient charts. Additionally, for exploratory analyses, we were able to obtain blood levels of C-reactive protein in 68 FEP and 53 healthy participants. To exclude diabetes in FEP, we collected personal history verified by review of medical records (where available complemented by fasting glucose blood levels form the hospitalization records, 96 FEP participants). Biochemical analyses were performed in a single clinical laboratory using Siemens ADVIA 1800 Clinical Chemistry systems and standard clinical methods. We measured body mass index (BMI) using the formula: BMI = weight (kg)/height (meters)^2. All diagnostic assessments and symptom ratings were performed by board certified psychiatrist using the Mini-International Neuropsychiatric Interview (24) and the PANSS (26).

The study was carried out in accordance with the latest version of the Declaration of Helsinki. The study design was reviewed and approved by the Research Ethics Board. Each participant received a complete description of the study and provided written informed consent.

MRI Methods

All data were acquired on the same scanner using the same imaging sequences.

Specifically, we acquired T1-weighted 3D MPRAGE scans (TR = 2,300 ms, TE = 4.63 ms, FOV = 256 × 256 mm, bandwidth 130 Hz/pixel, matrix 256 × 256, voxel size 1×1×1mm3) on 3T Siemens Trio MRI scanner equipped with standard head coil.

Voxel-Based Morphometry

We conducted FSL-VBM (27), http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM), optimized VBM protocol (28) carried out with FSL tools (29). First, structural images were brain-extracted and gray matter-segmented before being registered to the MNI 152 standard space using non-linear registration (30). The resulting images (GM volume probability maps) were averaged and flipped along the x-axis to create a left-right symmetric, study-specific GM template. Second, all native GM images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated GM images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Finally, voxel-wise general linear model (GLM) was used to compute associations between local GM volume as dependent variables, status - FEP versus healthy participants and BMI as predictors and age and sex as covariates of no interest; see *Statistical Analyses* for details). Permutation-based non-parametric testing, correcting for multiple comparisons across space, was applied. The threshold for primary analyses was set to $p < 0.05$ using threshold-free cluster enhancement (TFCE) and 5,000 permutations, as the cluster-based thresholding was developed to be more sensitive to finding true signal than voxelwise thresholding (31).

Statistical Analyses

We used two approaches (primary and secondary analyses) to 1) test *a priori* hypotheses using small volume correction, but also to 2) perform exploratory, whole brain analyses in order to investigate associations between FEP or BMI and brain regions not included in the primary analyses. We consider these approaches complementary. Using only the small volume correction, we could miss signal in additional regions. Using only the whole brain analyses would enforce a purely exploratory approach when in fact there is enough evidence formulate *a priori* hypotheses. Our analytical plan included the following steps.

Primary VBM Analyses

These analyses were carried out on a combined sample of FEP (N = 120) and healthy participants (N = 114). In order to maximize the sensitivity to our studied conditions, we performed VBM analysis with small volume corrections to regions which have been previously associated with FEP or obesity. To do this, we created a mask, which combined the results of a spatial meta-analysis of voxel based morphometry studies, which investigated: 1) association between FEP and GM volumes (5), and 2) association between BMI and GM volumes (18), see **Figure 2S**. Using GLM, we assessed the associations between diagnostic status (FEP versus healthy participants) and BMI as explanatory variables and regional GM volumes as the dependent variable, while controlling for age and sex as covariates of no interest. We also tested for status × BMI interaction and included it in the model only if significant. We used BMI as continuous variable, as this is preferable for statistical reasons and to increase sensitivity. In addition, this was the preferred approach in most previous studies (18). As BMI is also used clinically to define categories with increased risk of adverse outcomes, based on validated cut-offs (32) we also

repeated the analyses with BMI as a categorical variable. In these analyses we compared normal weight (BMI < 25) against overweight or obese participants (BMI >= 25). As our sample of FEP participants differed in age and sex compared to healthy participants, we also selected a subset of participants forming an age/sex-balanced dataset of 106 FEP and 107 healthy participants. We then performed sensitivity VBM analyses using the same approach as described above in this subsample.

Secondary Whole Brain VBM Analyses

These analyses were also carried out on a combined sample of FEP (N = 120) and healthy participants (N = 114). We conducted secondary whole brain VBM analysis and investigated the association between diagnostic status (FEP/healthy participants), BMI as explanatory variables, and local GM volumes, with sex and age as covariates of no interest. We tested for status × BMI interaction and included it in the model only if significant.

Additional Analyses

We explored the effects of clinical, treatment-related or metabolic variables on our VBM results among the FEP participants. Specifically, we tested for associations between average GM values from the voxels within the regions associated with FEP or BMI from the primary analyses and a) Duration of untreated psychosis; b) Duration of illness; c) PANSS positive subscale score; d) PANSS negative subscale score; e) PANSS global subscale score; f) Medication naive status before admission; g) Duration of antipsychotic treatment; h) chlorpromazine equivalent antipsychotic dose at MRI; i) cumulative medication exposure until MRI; j) Alcohol abuse history; k) THC history; l) Drug abuse diagnosis; m) Smoking at the time of MRI; n) HDL; o) LDL; p) TG; r) CRP; s) Glucose; t) Systolic blood pressure; u) Diastolic blood pressure; v) Age; and w) Sex. We used individual GM modulated, smoothed images (GM probability maps), and calculated average GM values from the significant clusters. For simple, robust and conservative exploration, we subsequently used Spearman's correlation coefficient and Mann-Whitney U test to explore the association between average GM values and continuous or categorical variables respectively. We reported nominal p-values for these hypotheses generating/exploratory analyses.

RESULTS

We analyzed a sample of 120 participants with FEP and 114 healthy individuals (see **Table 1** for description of the sample).

Primary VBM Analyses

When focusing on regions previously associated with FEP or obesity, we found lower GM volume in FEP versus healthy participants, while controlling for BMI, in a) cluster including left IFG-STG-temporal pole-insula-operculum (Cohen's d = 0.55; t_{max} = 4.19; pTFCE = 0.008; 395 voxels), b) left postcentral gyrus (Cohen's d = 0.43; t_{max}= 3.34; pTFCE = 0.043; 13 voxels). We also found a negative association between BMI and GM volume, when controlling for FEP, in the left cerebellum (Cohen's d = 0.74; t_{max} = 5.30; pTFCE < 0.001, 144 voxels); see **Figure 1**. We did not find interaction between diagnostic status (FEP vs. healthy participants) and BMI. The results remained essentially unchanged, when using BMI as categorical predictor (normal weight vs. overweight/obese; see **Supplementary Material**). Sensitivity analyses on the age/sex-balanced dataset (N = 213) showed similar results as our primary analyses (see **Supplementary Material** and **Figure 1S**).

Secondary Whole Brain VBM Analyses

At the whole brain level and when controlling for BMI, we found that FEP had lower GM volume than healthy participants in the a) right cerebellum (Cohen's d = 0.57; t_{max} = 4.39; p_{TFCE} = 0.004; 1242 voxels), b) left cerebellum (Cohen's d = 0.6, t_{max} = 4.59; pTFCE = 0.004, 1207 voxels), c) a cluster including left inferior frontal gyrus and superior temporal gyrus (Cohen's d = 0.62; t_{max} = 4.7, pTFCE = 0.024, 151 voxels), d) right temporal cortex (Cohen's d = 0.56; t_{max}= 4.25; pTFCE = 0.031, 110 voxels). When controlling for FEP, BMI was negatively associated with GM volume in the cerebellum (Cohen's d = 0.71; t_{max} = 5.1; p_{TFCE} = 0.004; 858 voxels); see **Figure 2**. We did not find interaction between diagnostic status (FEP vs. healthy participants) and BMI. Both FEP and BMI were negatively associated with GM in the left cerebellum, see **Figure 2**.

Additional Analyses: GM and Clinical/Treatment-Related/Metabolic Variables in FEP Participants

Average GM values from voxels associated with BMI from primary analyses were negatively associated with low density lipoprotein cholesterol - LDL (r_s = −0.255, p = 0.030), high sensitive C-reactive protein - CRP (r_s = −0.327, p = 0.006), positively associated with high density lipoprotein cholesterol - HDL (r_s = 0.269, p = 0.021). None of the other clinical/treatment-related/metabolic variables were associated with average GM values from the voxels within the regions associated with BMI or FEP, see supplementary material and **Table 1S**.

DISCUSSION

In this study, we found that both FEP and BMI were negatively associated with local GM volumes. When controlling for BMI, individuals with FEP had lower GM volumes relative to controls in frontotemporal areas and right cerebellum. In addition, we found a partial effect of BMI when controlling for the diagnosis of FEP in the left cerebellum. There was also a cluster of lower GM volumes in the left cerebellum additively associated with both FEP and BMI. Our results are congruent with our *a priori* hypotheses and expand our previous study demonstrating effects of BMI on BrainAGE, a composite measure of brain structure (22).

Our findings are in keeping with previous studies in FEP or obesity. Lower GM volume in frontal and temporal brain regions are among the most replicated findings in VBM studies of FEP participants (3–5, 33). Recent meta-analysis using automated segmentation also confirmed the importance of these brain areas

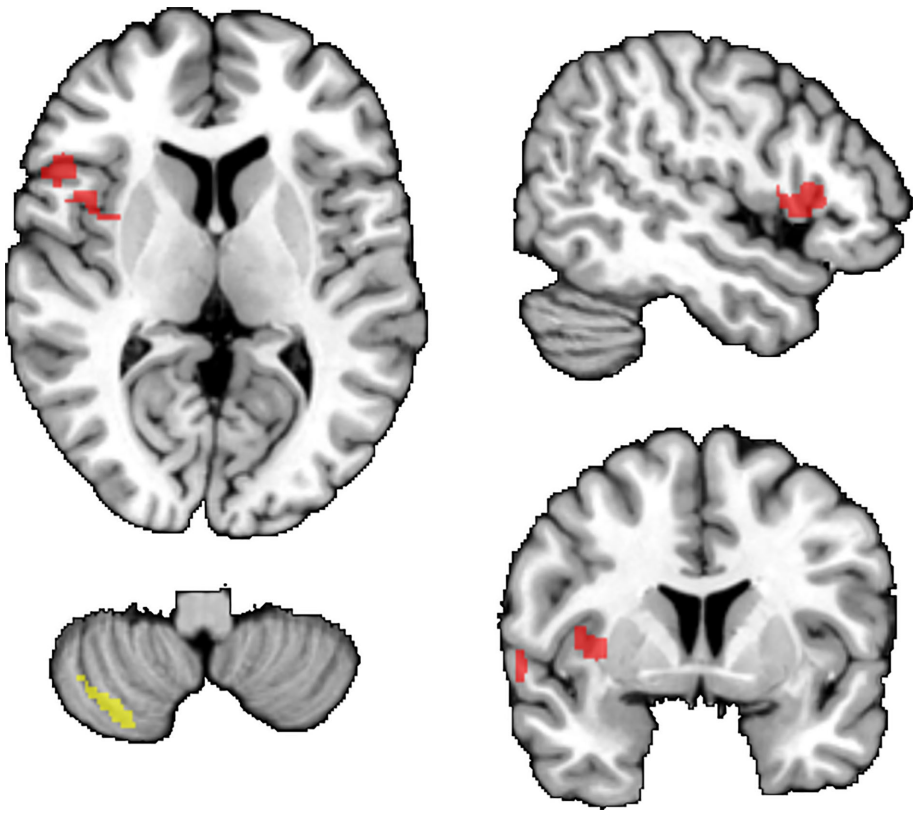

FIGURE 1 | Results of primary VBM analyses (small volume correction). Brain regions where FEP had lower GM volumes than healthy participants (red). Negative associations between BMI and GM volumes (yellow). TFCE corr. $p < 0.05$. Results are displayed superimposed on the Colin 27 T1 template.

in FEP (34). The associations between BMI and cerebellar regions are also in line with previous studies and meta-analyses in general population (18). Interestingly, even our whole brain results fell into regions, which showed smaller volumes in obesity in previous meta-analyses (18), thus providing strong replication and increasing the chance of true positive findings.

Previous neurostructural findings regarding cerebellum in FEP are less consistent. In keeping with our results, a number of individual studies reported lower GM volumes of cerebellum in all stages of SZ (35–41), including those at ultra-high risk (UHR) for psychosis (39, 42), FEP (40), or in the largest such study, a multisite mega-analyses of 983 participants and 1,349 healthy controls (19). However, cerebellar findings from meta-analyses exploring GM volume abnormalities in FEP are inconsistent, with some reports finding cerebellar alterations only in certain subgroups or not at all (3–5). Previous studies did not control for BMI, which appears to be negatively associated with cerebellar volume independent of the effects of psychosis. Perhaps, the uncontrolled presence of overweight/obesity may contribute to heterogeneity in cerebellar volumetric findings between studies in FEP.

As obesity is a complex phenomenon, it is important to explore which obesity associated factors are particularly relevant to the brain alterations found in obese/overweight participants. These may include low-grade systemic inflammation (43–45), HPA dysfunctions (46, 47), leptin-resistance (48), insulin resistance (49–51), or ceramide-induced DNA methylation (52). Our findings provide the strongest support for the role of dyslipidemia and systemic inflammation in these brain alteration. Specifically, among FEP participants, LDL levels were negatively and HDL levels were positively associated with GM within the cluster showing association with BMI. This is the first report suggesting that lipid abnormalities could contribute to brain alterations in FEP. Additionally, CRP was negatively associated with average GM values from the cerebellar cluster associated with BMI ($r_s = -0.327$, $p = 0.006$). These findings are in line with previous studies suggesting a role of low grade chronic inflammation in obesity related brain alterations, especially in cerebellum (53–55).

We did not find associations between clinical/treatment-related variables, including antipsychotic treatment and GM volumes. This is surprising, as previous studies described associations between cumulative exposure of antipsychotic medication and GM volumes (56) as well as pro-adipogenic effect of antipsychotics (57, 58). But, at the same time, participants in our study had on average only 1.99 month of antipsychotic treatment and BMI was not associated with cumulative antipsychotic exposure. We cannot rule out that following a longer antipsychotic treatment, their metabolic side effects would become more relevant for association between

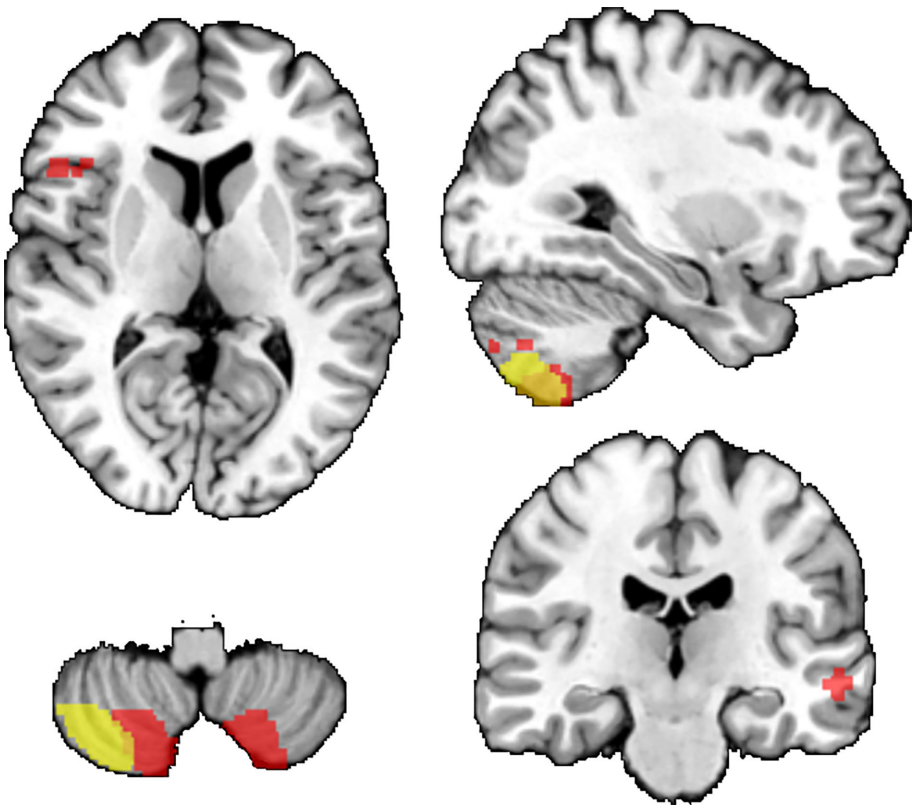

FIGURE 2 | Results of secondary VBM analyses (whole-brain). Brain regions where FEP had lower GM volumes than healthy participants (red). Negative associations between BMI and GM volumes (yellow). Overlap between the associations with FEP and BMI (orange). TFCE corr. $p < 0.05$. Results are displayed superimposed on the Colin 27 T1 template.

antipsychotics and GM volumes. The class of antipsychotic medication could also play a role. Almost all of the participants in our study received second generation antipsychotics. Previous meta-analysis of longitudinal studies found GM volume reduction mostly in participants treated with first generation antipsychotics (59). However, other studies and meta-analyses have found negative effects of antipsychotics on brain structure even in studies, which included participants treated with atypicals (33, 60, 61).

The results of negative associations between BMI and GM volume in FEP are clinically concerning, as overweight/obesity is disproportionately frequent in psychoses (8, 13), as also confirmed in this study. Identification of higher BMI or overweight/obesity as a potential risk factor for neurostructural alterations in FEP may be the first step toward their management. Lifestyle interventions focused on psychological well-being and weight management have proven to be effective in improving cognitive, clinical, and functional outcomes in many psychiatric syndromes (62–64). Obesity-related structural brain abnormalities might be reversible with dietary/lifestyle/surgical/medication interventions fostering weight loss and, especially in adolescents and young adults (65–69). Structural neuroimaging studies have reported increases in brain volumes following aerobic exercise in healthy subjects as well as in participants with SZ (70), which may be related to weight reduction (67, 71). Also medications targeting obesity may have neuroprotective effects. Promising results have been described using antidiabetic liraglutide (72), as also shown by our pilot trial in participants with bipolar disorder (73, 74). Other potential therapeutic options for future research include antiglucocorticoid mifepristone, which may improve cognitive dysfunction in participants with mood disorders (75) and showed also potential implications in reducing the risk of developing olanzapine/risperidone-induced weight gain (76, 77). Last but not least, protein deacetylase sirtuin1 (Sirt1) is protective against metabolic consequences of chronic exposure to a high-fat diet in animal models (78) and against signs of accelerated ageing in animal (79) as well as in human studies (80).

The results may have functional implications. Posterior cerebellar regions are connected to associative brain areas such as the prefrontal cortex and dysfunctions in the cortico-cerebellar-thalamo-cortical circuits could result in psychotic symptoms, as cerebellum acts as all-purpose modulator of movement as well as thought (81). Additionally, posterior cerebellum is involved in cognitive and mood regulation (82, 83). Therefore, cerebellar alterations could help explain the

pathoplastic effects of obesity on psychiatric outcomes, as previously documented (84–87).

Besides the clinical/functional implications, our results are relevant for methodological reasons. BMI is not usually controlled for in VBM studies of FEP, although the negative effects of obesity on brain structure are robust and replicated in both psychiatric and non-psychiatric participants (17, 18, 88, 89). Identification of relevant contributors to GM abnormalities in FEP is an important step toward the better understanding and interpretation of neurostructural studies.

With regard to limitations, only a prospective study could establish the direction of the association between obesity and GM volumes. It is possible that obesity is not the cause, but rather the consequence of brain imaging changes, which may render participants more impulsive (90–92). We were unable to quantify the effects of chronic stressors, life events, diet, or exercise. Only our primary VBM analyses were testing *a priori* hypotheses using preselected variables and regions of interest. Additional analyses exploring associations between metabolic and inflammatory markers were exploratory/hypothesis generating and their results should be interpreted with caution. The fact that the healthy group did not match the patients is another limitation. At the same time, matching on unseen variables, which are only obtained as a part of the study is difficult and thus, similar previous studies also showed between group differences in metabolic markers (93). In addition, when we performed analyses on a subgroup of age and sex balanced participants (N = 213, 106 FEP, 107 healthy participants), the results remained essentially unchanged.

The study has several advantages, including the sample size (N = 234), focus on clinically interesting group of FEP participants and quantification of metabolic health using both, anthropometric as well as biochemical measurements. The results have good face validity, as they replicate some of the previous findings. The effects of metabolic alterations on brain health are of major interest in diabetology, yet remain markedly understudied in psychiatry, despite the high prevalence of metabolic alterations in this population.

To conclude, we demonstrated that higher BMI, overweight/obesity and diagnosis of FEP were significantly associated with lower regional GM volumes and that dyslipidemia and elevated CRP could contribute to obesity related neurostructural alterations. The effects of psychosis were most pronounced in frontotemporal regions, whereas both psychosis and BMI were additively associated with lower GM in the cerebellum. This is highly clinically relevant, as FEP participants have an increased risk of metabolic disorders and brain structural alterations. The additive effects of FEP and BMI also suggest that comorbidity with obesity could contribute to heterogeneity of neuroimaging findings in psychosis. It remains to be tested, whether treatment of overweight/obesity, dyslipidemia, and low grade systemic inflammation might improve or preserve brain structure in FEP and whether this would have positive impact on psychiatric prognosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request and in compliance with the REB requirements.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of National Institute of Mental Health, Klecany, Czech Republic. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors met ICMJE criteria for authorship. Specifically, MK, TH, FŠ, and JH contributed to the conception and design of the study. MK, TH, FŠ, PK, AŠ, JR, and MM contributed to data collection and preprocessing. MK, TH, and JH contributed to the statistical analyses and checking the accuracy and integrity of the data. MK, TH, and JH contributed to interpretation of the results. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.556759/full#supplementary-material

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Functionality and Neurocognition in Patients With Bipolar Disorder After a Physical-Exercise Program (FINEXT-BD Study): Protocol of a Randomized Interventionist Program

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Introduction: Recent studies have shown that symptoms of psychiatric illness, functionality, and cognitive function improve with exercise. The aim of this study will be to investigate whether the implementation of an individualized exercise program will improve the functional status of patients with bipolar disorder (BD).

Methods: This longitudinal, interventional, randomized, controlled, simple-blind clinical trial will include 80 patients aged 18–65 years, all of them with BD diagnosis. Patients will be randomly assigned to a physical exercise intervention + Treatment-As-Usual (TAU) group and a non-intervention + TAU group. Patients will be assessed by an extensive battery of clinical tests, physical parameters (e.g., brain structure changes measured by optical coherence tomography, cardiorespiratory fitness) and biological parameters (inflammation, oxidative stress and neurotrophic factors) at baseline, after a 4-month intervention period, and 6-month follow-up.

Discussion: This is an innovative study aimed at gaining a deeper understanding of the physiopathology of BD and determining whether the prognosis and evolution of the disease can be improved through modifiable areas of the patient's lifestyle.

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Keywords: bipolar disorder, physical exercise, intervention program, neurocognition, functional capacity

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INTRODUCTION

Bipolar disorder (BD) is a mood disorder affecting about 400 million people worldwide (1). This psychiatric disease is a chronic disorder associated with cognitive dysfunction, increased mortality and intensive use of healthcare services (2, 3). The management of BD involves a combination of pharmacological therapies and psychosocial interventions including, but not limited to, cognitive-behavioral therapy, functional remediation, family psychoeducation, social skills training and protected employment (4). Despite therapies, the risk of recurrence is high, and patients often do not recover completely. Failure of current therapies to induce the remission of BD symptoms has led researchers to focus their efforts on developing more effective treatments (5).

In the search for new therapeutic strategies, physical exercise has been found to play a relevant role in the treatment of psychiatric disorders (6). Thus, physical exercise is not only effective in improving cardiorespiratory function, physical status, and metabolic syndrome (common comorbidities in BD), but it has also proven to reduce depressive symptoms and suicidal ideation (7).

Several studies have documented that moderate-to-vigorous physical exercise intensity programs influence the progression of mood disorders (8) and also improves cognitive performance and functionality in patients with schizophrenia (9). Concerning these results, at a biological level, physical exercise increases levels of neurotransmitters, cortisol, beta-endorphins, and neurotrophic factors such as BDNF (brain-derived neurotrophic factor) (8). It has been shown that serum levels of BDNF are reduced in persons with BD (10, 11) and major depressive disorder (12, 13). This neurotrophic factor plays a key role in neurological development, adult brain plasticity, neuron survival and differentiation, neuronal function, repair mechanisms of brain plasticity, and stimulates neurogenesis after the activation of its TrkB receptor (9). This receptor has two isoforms: a functional isoform with TrKB-FL activity, and a *truncated* isoform without TrkB-T activity (14). Elevated TrkB-T levels may induce neuronal death by the inhibition of the functional TrkB-FL isoform. In this line, patients with schizophrenia have been reported to exhibit increased levels of the *truncated* isoform in the prefrontal cortex (15). Indeed, TrkB-T levels in peripheral blood are more strongly associated with the early stages of psychosis than BDNF levels (14).

Physical exercise also modulates the body's response to stress and optimizes its antioxidant and anti-inflammatory capacity. Since BD patients have been reported to have an inflammatory state at the peripheral and central nervous system (16), the anti-inflammatory effects of physical exercise could play a relevant role in the physiopathology of the disease (17).

Interaction between the mechanisms described above explains how physical exercise can reduce symptoms of mood disorders and recurrence rates, thereby improving the quality of life and functionality of patients (18).

In line with the goal of better understanding the physiopathology of psychiatric diseases, brain imaging has been used for 15 years to assess brain alterations associated with these disorders. In BD patients, gray matter shrinks in the hippocampus, the fusiform gyrus, and the temporal lobe. The severity of brain alterations are related to symptoms and the number of episodes experienced by the patient (19). Patients with schizophrenia also show a loss of brain volume even since the first psychotic episode and in prodromal stages (20). Several authors have postulated that the retina could be an accessible marker of the structural and/or functional integrity of the brain (21–23). This hypothesis is grounded on the fact that the retina develops from the same embryonic layer as the brain. The retina and the brain are connected via the optic nerve, which would allow direct observation of the brain (22). Retinal alterations might be concomitant to the inflammatory and neurodegenerative processes and structural central nervous system alterations associated with BD (24). The retina is considered to be a part of the brain and contains several layers of neurons that are connected by synopses. The retinal nerve fiber layer (RNFL) is composed of unmyelinated axons of nodal cells. The ganglion cell complex contains the three innermost layers of the retina and comprises the retinal nerve fiber layer, the ganglion cell-inner layer, and the inner plexiform layer. Optical coherence tomography (OCT) is a non-invasive, no-contact, rapid imaging technique without known side effects that provides high-resolution and cross-sectional images of the retina, and measures RNFL (25). Some studies have reported OCT abnormalities such as retinal layer thinning (also in RNFL) associated with different neurological disorders with degenerative changes, including Parkinson's disease (26), Alzheimer's disease (27), and multiple sclerosis (28). Connecting with the growing interest in this technique for the diagnosis of neurodegenerative diseases, a recent study revealed that OCT demonstrated a thinning of retinal layers in patients with schizophrenia and schizoaffective disorder, as compared to a group of healthy individuals (29).

Previous studies have shown that physical exercise is an effective antidepressant intervention (30), but no studies have been able to provide a comprehensive overview of the mechanisms that produce these benefits in terms of patient prognosis. This fact led us to conduct a longitudinal comparative study to assess the impact on FunctIonality and Neurocognition of an individualized moderate-to-vigorous physical EXercise Training in a population of patients with BD (FINEXT-BD study).

We hypothesize that this intervention will improve the functional status of patients and this improvement will be reflected in physical and biological parameters. Thus, the primary aim of this study will be to investigate whether the implementation of an individualized moderate-to-vigorous physical exercise intensity program as adjuvant therapy to standard drug therapy will improve the functional status of patients with BD, as compared to a group of patients with BD without intervention. The specific secondary objectives of the study will be to: (1) investigate whether the implementation of this exercise program modifies the cognition, the clinical symptoms and incidence of comorbidities; (2) investigate whether the implementation of this exercise program induces changes in the levels of oxidative and inflammatory parameters

and these changes correlate with the evolution of clinical symptoms; (3) whether BDNF and TRkB-FL/TRkB-T ratio are associated with the evolution of the patient's functional and neurocognitive capacity, and (4) whether changes in the thickness of retinal layers as measured by OCT correlate with the functionality and neurocognitive function of BD patients.

METHODS AND ANALYSIS

Design

The FINEXT-BD study is a longitudinal, interventional, randomized, controlled, simple-blind trial conducted at the University Hospital of Araba in a cohort of BD patients divided into two groups: (1) physical exercise intervention + Treatment As Usual (TAU) (intervention group) and (2) patients with no intervention + TAU (TAU group). In addition, a gender-, race-, and age-matched healthy control group will be added to compare biological and physical parameters and the functional and neuropsychological status, with the cohort of BD patients.

Treatment As Usual will be defined as the prescribed pharmaceutical treatment by the clinician at the dose indicated for euthymic patients, with regular monthly visits that can be increased to weekly or biweekly sessions in the presence of prodromal symptoms or relapse.

Randomization and Blinding

FINEXT-BD patients will be randomly assigned to the groups (1:1) using Random Allocation Software version 1.0.0 software. Study evaluators will be blinded to the treatment branch. Patients will continue their usual treatment and will be treated by their reference psychiatrist, who will be informed of patient's participation in the interventionist program and will make sure that the appropriate clinical treatment is administered.

The flow diagram of the study can be seen in **Figure 1**.

Participants

Patients

The sample of patients with BD will be recruited by trained and experienced psychiatrists from patients treated in the Inpatient and Outpatient Unit of Psychiatry of the University Hospital of Alava.

Inclusion criteria will be:

1. Diagnosis of BD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (31), diagnosis based on semi-structured SCID-P interview (32). The study will involve patients with first-episode or multiple episodes of mania. Patients will be required to be euthymic at baseline, defined as no current diagnosis of an episode of mania, hypomania, or depression. Relapse during follow-up or presence of subsyndromal symptoms at any moment will not be exclusion criteria.
2. Age between 18 and 65 years.
3. Speak Spanish correctly.

Exclusion criteria will be:

1. Intellectual disability (assessed by DSM-V).
2. History of cranial trauma with loss of consciousness.
3. Physical diseases that cause mental health problems.
4. Pervasive developmental disorders.
5. Pregnancy or breastfeeding.
6. Be classified as "physically active" according to the Global Physical Activity Questionnaire (GPAQ) (33).
7. The presence of a severe or uncontrolled cardiovascular risk factor such as unstable coronary artery disease, uncontrolled hypertension, malignant ventricular arrhythmia, atrial fibrillation, exercise-induced ischemia, and ventricular failure during exercise.
8. Other significant medical conditions including, but not limited to chronic or recurrent respiratory, gastrointestinal, neuromuscular, or any musculoskeletal problems interfering with exercise.
9. The presence of inflammatory diseases.
10. Consumption of anti-inflammatory drugs during the week prior to blood extraction.

Controls

Controls will be recruited from friends of patients and healthcare personnel. If the established N is not reached, informative posters will be placed in different hospitals. In such case, posters will be sent to the CEIC for evaluation.

The inclusion criteria will be:

1. Age between 18 and 65 years.
2. Speak Spanish correctly.

The exclusion criteria will be:

1. Intellectual disability (assessed by DSM-V).
2. History of cranial trauma with loss of consciousness.
3. Physical diseases that causes mental health problems.
4. Pervasive developmental disorders.
5. Pregnancy or breastfeeding.
6. Consumption of anti-inflammatory drugs during the week prior to blood extraction
7. The presence of inflammatory diseases.
8. History of psychiatric episodes among first-degree relatives.

Assessments

Data collection will be based on an assessment protocol for gathering data on sociodemographic, physical, clinical, and biological variables. Patients from the two groups will be evaluated by blind raters at baseline (pre-intervention), after a 4-month intervention period, and 6-month follow-up period. Blood sampling for the analysis of biological parameters will be performed during the same visits. The control group will be evaluated only at baseline.

Sociodemographic Variables

Data on sociodemographic variables (age, sex, educational level, socioeconomic level, employment status, family history of psychiatric disorders, number of relapses, years of disease evolution, and number of manic episodes) will be collected at baseline.

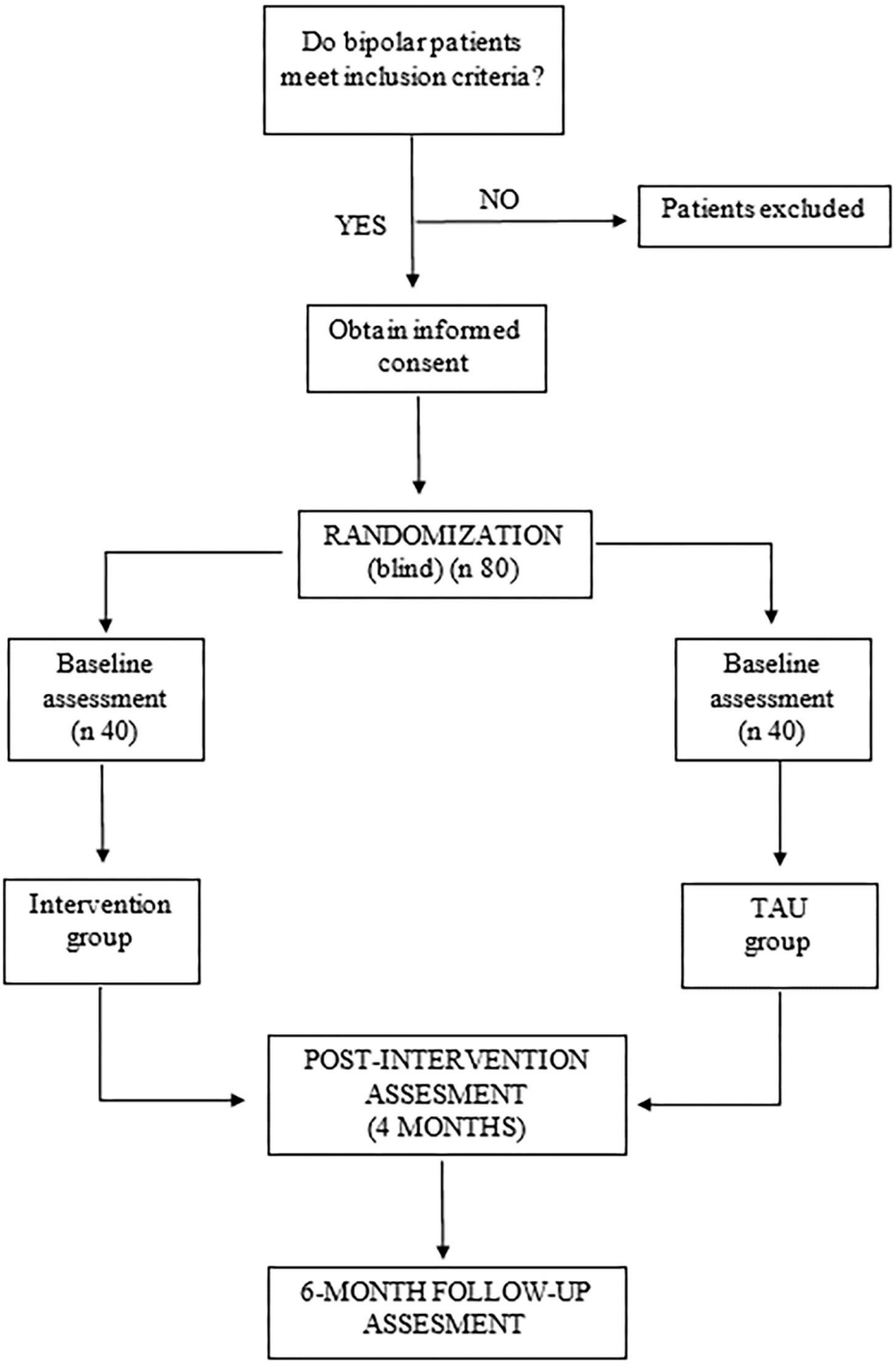

FIGURE 1 | FINEXT-BD study procedure.

Physical Parameters

The following physical parameters will be assessed at each of the three visits at the Psychiatric Service of the Alava University Hospital (HUA): body mass (kg) with individuals in light clothing and barefoot using a portable scan body composition and scale (Omron KARADA); height (cm) with participants in a standing position with no shoes using a measuring tape with shoulders in a relaxed position; body mass index will be calculated by dividing body mass to height (kg/m^2); waist circumference (cm) will be measured using a flexible anthropometric tape midway between

the iliac crest and lower rib margin; blood pressure (mm Hg) will be measured in the right arm with the patient in a seated and relaxed position by using a life-support monitor (General Electric carascape U100 Dinamap technology); and a blood sample will be drawn after 12 h overnight fasting to quantify serum levels of triglycerides, glucose and high-density lipoprotein cholesterol. With all this information, the diagnosis of metabolic syndrome will be documented in accordance with the National Cholesterol Education Program Adult Treatment Panel III (ATP III) (34). Thus, patients will have metabolic syndrome if they meet at least two of the following criteria: (1) waist circumference ≥ 102 cm in men or ≥ 88 cm in women; (2) serum triglycerides ≥ 150 mg/dl (8, 3 mmol/L); (3) cholesterol HDL <40 mg/dl (2, 2 mmol/L) in men and <50 mg/dl (2, 8 mmol/L) in women; (4) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg; (5) serum glucose ≥100 mg/dl (5, 6 mmol/L).

The Ophthalmology Service of the HUA will carry out the study of retinal layers by OCT (HRA+OCT Spectralis, version 6.0, Heidelberg Engineering, Germany): RNFL, GCL and IPL thickness in the two eyes, with each layer divided into segments: overall, temporal, nasal, superior and inferior. In the HUA cardiology service, patients will perform the cardiopulmonary exercise test (CPET) at the baseline visit and after the intervention. At these same visits, in the Nuclear Medicine Service of the HUA, a Dual-energy X-ray absorptiometry (Hologic QDR 4500 W) will be used to evaluate the body composition of participants. This whole-boy scan will be performed to analyze the amount of body fat and muscle mass of participants.

Physical Fitness

Physical fitness includes a peak, symptom-limited CPET. The CPET will be performed on a treadmill T-2100 (General Electrics Healthcare, Germany) in the cardiology department of the Alava University Hospital. The testing protocol will start with 1.6 km/h with a 0% slope, with gradual increments of 0.1 km/h and a 1% slope every 15 s to exhaustion with continuous electrocardiogram monitoring. During the test, participants will be verbally encouraged by the nurse in charge of the test. The expired gas analysis will be conducted using a commercially available system (Ganshorn, Germany) that will be calibrated before each test with a standard gas of known concentration and volume. Breath-by-breath gas exchange data will be measured continuously during exercise and averaged every 60 s. Peak oxygen uptake is defined as the highest oxygen uptake (VO_{2peak}) value attained toward the end of the test. Achievement of true peak effort can be assumed in the presence of two or more of the following criteria: (1) volitional fatigue (>18 on BORG scale), (2) peak respiratory exchange ratio (VCO2/VO2) ≥1.1, (3) achieving >85% of age-predicted maximum heart rate (HR), and (4) failure of VO_2 and/or HR to increase with further increases in work rate (35). A self-reported Borg rating of perceived exertion (6–20 scale) will be recorded at the end of the test. Blood pressure will be measured every 2 min throughout the test. Ventilatory thresholds (i.e., VT1 and VT2) will be assessed by standardized methods using the V-slope and ventilatory equivalents. First ventilatory threshold (VT1) will be identified as the point of transition in the carbon dioxide production (VCO_2) vs. VO_2 slope from <1 to >1, or VT1 is identified as the nadir of the ventilatory equivalent (VE) of VO_2 vs. work rate relationship. The second ventilatory threshold (VT2) is identifiable as the nadir of the VE/VCO_2 vs. work rate relationship (35). Absolute and relative indications for terminating the exercise test will be taken into account (36). The identification of the two VT will determine the three different exercise intensity domains or ranges for exercise design (R1, R2, R3): (R1) light to moderate exercise intensity with HR values below VT1; (R2) moderate to high or vigorous exercise intensity with HR values between VT1 and VT2, and (R3) high to severe intensity exercise intensity with HR values up to VT2 to peak intensity. When it is not possible to identify the VT2, exercise intensity domains are established taking into account percentages of HR reserve, i.e., moderate intensity is defined between 50 and 75% of HR reserve, high intensity from ≥76% to <95% of HR reserve (35).

Clinical Variables

Diagnosis

Patients will be diagnosed according to the DSM-5 criteria using the semi-structured SCID-P interview (32).

Analysis of the pre-morbid adjustment of patients as part of a determination of their prognosis will be made using an *abbreviated version of the Phillips Scale of Pre-morbid Adjustment* (37). This scale is an abbreviated version of the original five-section Phillips Pre-morbid Rating Scale and is composed of two parts: Part I (Abbreviated Pre-morbid Sexual Rating Scale) and Part II (Abbreviated Pre-morbid Personal-Social Rating Scale). This scale uses a 7-point scale (0–6) to evaluate each part.

Psychosocial functioning

The functioning of patients will be measured using *the Functioning Assessment Short Test (FAST*) (38). This scale is a brief instrument designed to assess functional impairment in psychiatric disorders. The scale comprises 24 items that cover six specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. Each item is scored in a 0–3 points range (0: no difficulty; 1: mild difficulty; 2: moderate difficulty; 3: severe difficulty) with total score ranging from 0 to 72 points (39).

The patient functionality will be assessed through the *Global Assessment of* Functioning (GAF) (40). This scale rates the level of functioning and severity of symptoms on a 0–100 scale, with higher values corresponding to better overall functionality.

Strauss-Carpenter scale (41). This scale will be employed to assess the psychosocial functioning of patients and consists of four items rated from 0 to 4 on a Likert-type scale and yields a total score that is calculated by the addition of all item scores: the higher the score is, the better the prognosis (42).

Neurocognition

- *The Stroop Color and Word Test (SCWT)* (43): is a neuropsychological test that will be used to assess selective attention and the impulsivity domain, executive subject's ability to inhibit cognitive interference that occurs when the processing of a specific stimulus feature impedes the

simultaneous processing of a second stimulus attribute, well-known as the Stroop Effect. Individuals are required to read three different tables as fast as possible. Two of them represent the neutral condition in which participants are required to read aloud a list of color name words printed in black ink and name different color patches. In contrast, in the third table, the conflict condition is provided by having color words written in an incongruous color of ink and participants are required to name the color of the ink instead of reading the word (44).

- The Complutense Verbal Learning Test (TAVEC) (45): The TAVEC is the Spanish version of the California Verbal Learning Test (CVLT) (46) and will be used for the assessment of different memory and learning processes, such as immediate recall, short and long term memory with and without semantic clues and recognition (47).
- The Computerized version of Wisconsin Card Sorting Test (WCST) (48): neuropsychological test that assesses individuals' executive function. WCST will be used to measure the subject's capacity to deduce concepts and apply a strategy to adapt behavior to changing conditions (49). This test consists of cards depicting simple geometric figures that vary in color, shape, and number. Examinees must sort cards in accordance with one of three viable rules: color, shape, or number of the depicted object(s) (50).

Clinical severity

- *The Clinical Global Impression Scale (CGI)* (51) will be used to assess symptom severity, global improvement and therapeutic response. This scale consists of two subscales that evaluate, respectively the clinical severity and the overall improvement in the patient's symptomatology. Each subscale has a single item scored between 0, not evaluated, and 7 which corresponds to the maximum severity (severity subscale) or to a state of no improvement and aggravated worsening of the symptomatology (improvement subscale).
- The presence of suicidal thoughts or behaviors will be assessed by means of *the Likert Clinical Global Impressions–Severity of Suicide scale (CGI-SS)* (52). This scale scores from 1 to 5 the patient's current risk of suicide.

Illness awareness

The illness awareness of patients will be measured using *the Scale to assess Unawareness in Mental Disorders (SUMD)* (53). This scale explores the thoughts and beliefs of patients regarding their illness and its pharmacological treatment. SUMD scale comprises nine items (current awareness of the following states): (1) a mental disorder; (2) consequences of a mental disorder; (3) effects of drugs; (4) hallucinatory experiences; (5) delusional ideas; (6) disorganized thoughts; (7) blunted affective; (8) anhedonia, and (9) lack of sociability. Each item is scored as follows: not applicable (response of "0" or missing data), aware (response of "1"), slightly aware/unaware (response of "2"), and seriously unaware (response of "3") (54).

Medication adherence

- Adherence to medication will be assessed using the *Morisky-Green scale*. This self-reported scale includes four yes/no questions rated on a 0–4 scale, considering patients who obtain 0 points as adherent and those who obtain a 1+ score as non-adherent (55).
- Response to lithium will be measured by the *Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder (Alda scale)* (56). This scale was specifically developed to evaluate the long-term mood stabilization effect under naturalistic conditions. Briefly, this scale quantifies the degree of improvement during the treatment (Criterion A), which is rated on a 0–10 scale, and weighs clinical factors that are considered to be relevant for determining if the observed improvement is a result of the treatment rather than a spontaneous improvement or an effect of additional medication (Criteria B1-B5), which are rated as 0, 1, or 2 points. The total score on the Alda scale is obtained by subtracting the B score from the A score (57).

Clinical symptomatology

- Depressive symptoms will be measured by *the Hamilton Rating Scale for Depression (HRSD*) (58). This scale consists of 17 items, each of which offers between 3 and 5 possible answers with values ranging from 0–2 or 0–4 points, respectively. The total score ranges from 0 to 52 points, and different cut-off points are used to classify the patient's depressive symptoms. Those who obtain scores of 0–7 are identified as non-depressed, minor depression 8–12, moderate depression 13–17, severe depression 18–29, and those who obtain scores above 30 are characterized as very severe depression (59).
- Manic symptoms will be measured using *the Young Mania Rating Scale (YMRS)* (60). This scale is composed of 11 items, each item consisting of 5 answer choices that are scored on a 0–4 scale, except four of the 11 items that are scored with double points (0, 2, 4, or 8 points). The total score ranges from 0 to 60, with the status of euthymia being classified as getting 6 or fewer points, hypomania as getting 12 or more points, and mania as getting between 20 and 60 points.

Quality of lifestyle

- *The World Health Organization Quality of Life-BREF (WHOQOL-BREF) instruments* will be used to measure the quality of life. It assesses the individual's perceptions in the context of their culture and value systems, as well as their personal goals, standards, and concerns. The WHOQOL-BREF instruments comprise 26 items that measure the following broad domains: physical health, psychological health, social relationships, and environment (61).
- The severity of substance addiction will be measured with the *European version of the Addiction Severity Index (EuropASI)*, a semi-structured interview, which measures the severity of addiction in different areas: medical, employment, alcohol consumption, use of other drugs, legal problems, family and social relationships, and psychological state (62).
- Chronobiological rhythms will be assessed with the *Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN)* (63). This scale contains 21 items designed to assess five domains related to biological rhythms: (1) Sleep, (2) Activities, (3) Social aspects, (4) Alimentation, based on the last 15 days,

and (5) predominant Rhythm (chronotype) based on the last year. The total score may range from 16 to 84, with the higher the score obtained, the greater the alteration of the biological rhythms (64).

Biological Variables

Venous blood samples (10 mL) will be collected between 8:00 and 9:00 after overnight fasting by the nursing staff in polypropylene EDTA-containing tubes. Fresh blood will be stored at 4°C until processing about 1 h. later. Blood will be centrifuged (652 g × 10 min, 4°C); the resulting plasma samples will be collected and stored at −80°C until use. The rest of the sample will be diluted 1:1 in culture medium (RPMI 1640, GIBCO) and a gradient with Ficoll-Paque (GE Healthcare) will be used to isolate peripheral blood mononuclear cells (PBMC) by centrifugation [800 g × 40 min, room temperature (RT)]. The PBMC layer will be aspired and suspended in RPMI and centrifuged at 1800 g for 15 min, RT. The supernatant will be removed and the PBMCs pellet will be stored at −80°C until analysis.

Biochemical measurements in plasma

- *Nitrite (NO_2^-):* The final and stable product of nitric oxide, will be measured in plasma using the Griess method (65). Briefly, in an acidic solution with 1% sulphanilamide and 0.1% N-(2-napthyl) ethylenediamine dihydrochloride (NEDA), nitrites will be converted into a pink compound that will be measured photometrically at 540 nm in a microplate reader (Synergy 2, BioTek).
- *Lipid Peroxidation (TBARS):* In the process of lipid peroxidation, there are several intermediate and final products due to the degradation of cell membranes, among which is malondialdehyde (MDA), used as a marker of cellular damage. The Thiobarbituric Acid Reactive Substances (TBARS) test is the most used for the measurement of this metabolite in plasma where thiobarbituric acid (TBA) reacts with malondialdehyde (MDA) under high temperature (95°C) and acidic conditions to produce a MDA-TBA complex that is measured photometrically at 530 nm (Synergy 2, BioTek) (66). The results obtained through this procedure will be expressed in μM of MDA.
- *Total Antioxidant Status (TAS):* This parameter reflects the cumulative effect of all antioxidants present in plasma and is determined by a standardized spectrophotometric assay. This assay is based on the ability of the antioxidants present in the sample to inhibit the oxidation of ABTS (2,2'-azino-bis-[3-ethylbenzothiazolin-6-sulfonic]) to the ABTS+ cation radical by the action of methemyoglobin (peroxidase). The concentration of this radical is measurable by spectrophotometry at 600 nm, the result of which is inversely proportional to the total antioxidant level of the sample (67).
- *Prostaglandin Levels*: PGE2 plasma levels will be measured by a competitive colorimetric immunoassay in which the PGE2 present in the sample competes with the PGE2-linked conjugate (provided by the kit) for binding to the anti-PGE2 antibody present in the wells of the plate. Then the substrate is added which triggers a measurable enzymatic reaction at 412 nm (Synergy 2, BioTek). Since the concentration of the conjugated is constant, the intensity of the bound yellow color is inversely proportional to the concentration of PGE2 in the sample.
- *Cytokine levels:* Plasma levels of IL-6 will be measured by enzyme immunoassays EIA kits, a technique based on recognition by specific antigen-antibody binding, both cytokines will be measured by spectrophotometry at 450nm in a microplate reader (Synergy 2, BioTek).
- *Glutathione peroxidase (GPx)* catalyzes the reduction of hydroperoxides, including H_2O_2, by reduced glutathione and functions to protect the cell from oxidative damage. The measure of GPx activity is based on a coupled reaction with glutathione reductase (GR). Oxidized glutathione (GSSG) produced upon reduction of hydroperoxide by GPx is recycled to its reduced state by GR and NADPH. The oxidation of NADPH to NADP+ is accompanied by a decrease in absorbance at 340 nm. Under conditions in which the GPx activity is rate-limiting, the rate of decrease in the absorbance is directly proportional to the GPx activity in the sample.
- *Glutathione (GSH)* serves as a nucleophilic co-substrate to glutathione transferases in the detoxification of xenobiotics and is an essential electron donor to GPx in the reduction of hydroperoxides. The oxidized GSH dimer (GSSG) is formed from GSH and H_2O_2 by the GPx. The detection of both forms, GSH and GSSG, could be detected using comercial kits, a colorimetric substance reacts with the free thiol group on GSH to yield a highly colored product that can be measured at 405 nm (Synergy 2, BioTek). On the other hand, by using 2-vinylpyridine to block any free GSH in the sample GSSG can be determined, because any sample that has not been treated with 2-vinylpyridine will yield Total GSH levels. Then, the free GSH concentration can be calculated from the difference between the total GSH and GSSG.
- *BDNF levels:* An *in vitro* enzyme-linked immunosorbent assay will be used for the quantitative measurement of human BDNF in plasma. This assay employs an antibody specific for human BDNF coated on a 96-well plate. Standards and samples are pipetted into the wells and BDNF present in a sample is bound to the wells by the immobilized antibody. A secondary antibody HRP-conjugated is used for the detection of bound BDNF. Then, a TMB substrate solution is added to the wells and color develops in proportion to the amount of BDNF bound, the absorbance is measured at 450 nm (Synergy 2, BioTek).

Biochemical measurements in PBMCs

To carry out all biochemical determinations, PBMC samples will be first fractionated in cytosolic and nuclear extracts. For the preparation of cytosolic and nuclear extracts, it will be used a modified procedure based on the Schreiber et al. (68). PBMC pellets will be homogenized in 150 μL of lysis buffer consisting of 10 mmol/L HEPES at pH 7.9, with a cocktail of proteases and phosphatase inhibitors (Roche), 1 mmol/L EDTA, 5 mmol/L NaF, 1 mmol/L NaVO4, 0.5 mol/L sucrose and 10 mmol/L Na2MoO4. After 15 min the detergent Nonidet P-40 (Roche, Mannheim, Germany) will be added at a concentration of 1%. The tubes will

be shaken for 30 s and the mixture will be centrifuged for 5 min at 8,000 g. The supernatant that constitutes the "cytosolic fraction" will be aspirated and the pellet will be resuspended in 50 μL of buffer supplemented with 20% glycerol and 0.4 M KCL. The mixture will be stirred for 30 min at 4°C, centrifuged for 5 min at 13.000 g and the supernatant, corresponding to the nuclear fraction, will be aspirated. Both fractions were stored at −80°C.

Protein Quantification Once the nuclear extracts have been obtained, protein quantification will be carried out. The Bradford© assay is one of the most popular methods to determine the concentration of a total protein in a sample. In this assay, proteins bind to Coomassie G-250 dye resulting in a color change from brown to bright blue and the formation of a protein-dye complex. The absorbance of the blue color produced is measured at 570–590 nm and is proportional to the protein concentration. Known bovine serum albumin concentrations with seven points between 0 and 0.8 mg/ml were used as the standard curve. For the measurements, the samples were diluted 1/20 and mixed with 10 μl of dilution or the standard with 200 μl of Bradford reagent and the absorbance was measured in the plate reader (Sinergy 2, BioTek, Germany).

TrkB-FL and TrkB-T receptors: Protein levels of receptors were quantified by Western blot analysis. In brief, 12.5 μg of cytosolic extracts were loaded onto electrophoresis gels. Protein samples were separated and transferred onto nitrocellulose membrane (Transfer Pack, Biorad) using a semi-dry transfer system and were blocked in 5% BSA for 1.5 h, and then the membranes were incubated overnight at 4°C with specific antibodies. Blots were imaged using an Odyssey® Fc System (Li-COR Biosciences) and quantified by densitometry (ImageJ®, NIH). We used β-actin as a loading control. All densitometry results are expressed as a percentage of the control. Given the counterbalancing effect of TrkB-T1 and TrkB-FL, we chose the ratio of TrkB-FL to TrkB-T expression (hereafter FL/T ratio) as our index variable for describing BDNF receptor expression.

Exercise Intervention Program

Previous investigations by the exercise specialists who will lead this research have already performed the exercise protocol (69, 70). In short, the experimental group will receive supervised physical exercise treatment by high-intensity interval training (HIIT), alternating high and moderate intensities (20 min). Participants will exercise two non-consecutive days per week for 16 weeks under the supervision of a coach at the facilities provided by the University Hospital of Araba. All the exercises sessions will start and finish with blood pressure monitoring and training intensity will be controlled by HR monitoring (Polar M200, Kempele, Finland) and through the rate of perceived exertion using the Borg's original scale (6–20 point). Each session will include a 10 min warm-up with joint mobility and coordination exercises with continuous leg movement to facilitate the venous return and a 10 min cool-down period with basic core strengthening exercises and passive stretching exercises on the floor to ensure a progressive return to the resting values of both blood pressure and HR. The main portion of the training session will consist of 20 min of aerobic exercises on the bike developing progressively intensity. Intensity will be individually tailored to HR at moderate or vigorous intensities, adjusting the power and speed on the bike, to achieve the planned target HR (**Table 1**). The exercise specialists will keep detailed records of all the exercise sessions reporting the HR and Borg scale values of every interval. The importance of targeting moderate and high intensity will be emphasized.

Several strategies will be implemented to maximize adherence, including music in all sessions, individualized attention at the intervention sessions and telephone calls following missed sessions.

The protocol of HIT will carry out a 5–10-min warm-up period on the bike. After that participants will cycle for 30 s at high-intensity (i.e., HR values up to VT2 to peak intensity) followed by 60 s at moderate-intensity (i.e., HR values between VT1 and VT2). Four repetitions (1 rep = 30 s high-intensity followed by 60 s moderate-intensity) will be initially performed and gradually increased to nine repetitions will be completed. The training session will end with a 5–10 min cool-down period at moderate-intensity.

Statistical Analysis

A general descriptive analysis of the sample will be performed to assess baseline homogeneity. The normality of quantitative variables will be assessed by the Kolmogorov-Smirnov test and results will be expressed as means and standard deviation or as median values and interquartile range in the case of non-normal distribution. Qualitative variables will be expressed as frequencies and percentages.

To respond to the main aim, analysis of covariance (ANCOVA) will be used to assess the improvement in functionality. The same test will be used to analyze the difference between the groups.

At baseline, an analysis of variance (ANOVA) will be performed to confirm that there is no difference between patient groups, but there is a difference with the control group.

Student's *t*-test for related samples will be used to assess changes after the physical exercise program between intervention patient groups, among normally distributed variables. Changes in the variables studied across the three visits will be assessed by an analysis of repeated measurements. The analysis of repeated measurements will be used to assess the evolution of the variables studied during the three visits. Non-normally distributed variables will be assessed using Wilcoxon test. Univariate and multivariate regression analysis will be performed to determine whether statistically significant differences are associated with the evolution of the functionality and clinical and cognitive symptoms. All statistical analyses were carried out using SPSS v23.0 and R v3.5.0 statistical software, with the significance level set at $p < 0.05$.

Sample Size

To calculate the sample size, a review of the literature related to the main topic of the study was carried out and using the Ene 2.0. computer program, it was determined that to obtain a power of 90% and an effect size of 0.65 with a significance of 5% and with possible losses to follow-up of 10% of the patients, it

TABLE 1 | Intervention program for the experimental group by High-intensity physical exercise program on the bike.

	Protocol			
	High-intensity interval		Moderate intensity interval	
Weeks	Volume (min)	Intensity (% heart rate reserve)	Volume (min)	Intensity (% heart rate reserve)
1–2	2	80	18	60
3–4	3	80	17	60
5–6	4	85	16	65
7–8	4:30	85	15:30	65
9–10	4:30	95	15:30	70
11–12	4:30	95	15:30	70
13–16	4:30	95	15:30	70

Volume and intensity progression.

is necessary to have a sample of at least 38 patients per group to detect differences between the means of the main variables (EEAG and FAST). Therefore, we have estimated a sample size of 40 per group.

ANTICIPANT RESULTS

This study anticipates that the patients belonging to the intervention group, at the end of the individualized physical exercise program, will show an improvement of their functional capacity, as compared to the TAU group. In addition a decrease in the clinical symptoms of the disease, as well as a better score on the neuropsychological scales is expected. Furthermore, completion of the intervention program will have greatly increased adherence to treatment in these patients. If we confirm our hypothesis, all these improvements will be reflected at the biological substrate level (decrease in oxidative and inflammatory parameters and increase in BDNF) and physical level (changes in retinal structure and anthropometrics) in the post-intervention and follow-up visits, compared to the control group.

Further, this program of physical exercise performed regularly for 16 weeks will provide patients with guidelines to improve their lifestyle and quality of life, which will be reflected in the post-intervention and follow-up visit at 6 months after the end of the intervention program.

DISSEMINATION

The final database obtained will be the property of the research team and shall not be shared without the principal investigator's permission. This protocol and the results obtained after the completion of the study will be presented at national and international conferences as well as published in scientific journals.

DISCUSSION

One of the most important objectives that Psychiatry is trying to address new strategies that improve clinical outcomes in patients. In this sense, the randomized single-blind intervention study described in this article aims to investigate whether the implementation of an individualized physical exercise program as an adjuvant therapy will improve the prognosis of patients with BD, by improving their functionality.

Previous studies have shown that physical exercise in people without psychiatric disease had protective effects against depression (71). In patients with major depression, it has been observed that physical exercise reduces symptoms of depression (72). In addition, in another study in these patients, spatial working memory improved with high-dose exercise, while other cognitive domains including attention, visual memory, and spatial planning improved regardless of the dose of exercise (73). Another research including a subset of patients with BD and schizophrenia found that intense circuit training improved memory, processing speed, and symptoms of depression (74). Therefore, there is broad variability in the response of individuals with psychiatric diseases to physical exercise and how it influences the prognosis of each patient (75). As functionality is related with cognition, and cognitive deficits are related with subthreshold depressive symptoms in BD patients (76), it is possible to hypothesize that positive effects of physical activity on functionality are related also with mood stabilization in patients with psychiatric disorders such as BD. That is why it is so important to study the effect of physical activity on functionality of patients diagnosed with BD and the real mechanisms by which exercise influences functionality, considering both clinical symptoms as subthreshold depressive, manic symptoms, and cognitive symptoms, and physiopathology. Other therapies have shown that non-pharmacological treatments improve functionality and cognition (77), and that BDNF is related with this improvement (78).

To our knowledge, no holistic studies have been performed so far to investigate how moderate-to-vigorous physical exercise influences cognitive deterioration and functional capacity in patients with BD using clinical scales, neuroinflammatory and oxidative stress parameters, and by the study of changes in brain structure.

Our study is subject to a limitation typical of longitudinal studies: loss of follow-up either by voluntary discontinuation of the participant or by a relapse of the patient during the study.

Nevertheless, the number of patients receiving treatment or with first episode BD who are lost to follow-up will be limited, as their treatment will involve regular follow-up visits at University Alava Hospital. Another aspect to consider is the representativity of the sample. The results obtained will only correspond to BD patients 18–65 years of age and in a sample of 40 participants per group. But, an advantage of the University Hospital of Alava is that it is the only emergency care center of the region, and also the only center that attends patients with episodes of BD. The severity of illness in patients with long-standing disease is heterogeneous, and they may be treated in Outpatient or Partial Inpatient units.

CONCLUSION

This is an innovative study aimed at gaining a deeper understanding of the physiopathology of BD and investigating how the prognosis and evolution of the disease can be improved through potential modifiable areas of patients' lifestyle. Moreover, with the results of this study it will be possible to provide patients with solid tools for managing their disease, making them co-managers of their own illness, which would also increase their awareness of the disease and ultimately their adherence to treatment.

ETHICS STATEMENT

This study was approved by the local Ethics Committee, the University Hospital of Alava Ethics Committee (September 20, 2019, Certificate No. 2019-036) in accordance with the Declaration of Helskinki II. After providing written and oral information about the study, informed consent was obtained from all participants. This study is registered with the international standard randomized controlled trial NCT04400630.

AUTHOR CONTRIBUTIONS

SG and AG-P wrote the first draft of the manuscript. AG-P, SG, and EG-C participated in the clinical design of the intervention. SM-M and IG-A participated in the design of the exercise intensities and the physical-exercise program. KM, JL, and SG participated in the design of the biochemical measurements. CB-A participated in the design of the statistical analysis. All authors participated in the drafting of the manuscript and all of them approved the final version.

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BRIEF RESEARCH REPORT
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Differential Effects of Acute Treatment With Antipsychotic Drugs on Peripheral Catecholamines

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Antipsychotic drugs represent the most effective treatment for chronic psychotic disorders. The newer second generation drugs offer the advantage of fewer neurological side-effects compared to prior drugs, but many cause serious metabolic side-effects. The underlying physiology of these side-effects is not well-understood, but evidence exists to indicate that the sympathetic nervous system may play an important role. In order to examine this possibility further, we treated separate groups of adult female rats acutely with either the first generation antipsychotic drug haloperidol (0.1 or 1 mg/kg) or the second generation drugs risperidone (0.25 or 2.5 mg/kg), clozapine (2 or 20 mg/kg), olanzapine (3 or 15 mg/kg) or vehicle by intraperitoneal injection. Blood samples were collected prior to drug and then 30, 60, 120, and 180 mins after treatment. Plasma samples were assayed by HPLC-ED for levels of norepinephrine, epinephrine, and dopamine. Results confirmed that all antipsychotics increased peripheral catecholamines, although this was drug and dose dependent. For norepinephrine, haloperidol caused the smallest maximum increase (+158%], followed by risperidone (+793%), olanzapine (+952%) and clozapine (+1,684%). A similar pattern was observed for increases in epinephrine levels by haloperidol (+143%], olanzapine (+529%), risperidone (+617%) then clozapine (+806%). Dopamine levels increased moderately with olanzapine [+174%], risperidone [+271%], and clozapine [+430%]. Interestingly, levels of the catecholamines did not correlate strongly with each other prior to treatment at baseline, but were increasingly correlated after treatment as time proceeded. The results demonstrate antipsychotics can potently regulate peripheral catecholamines, in a manner consistent with their metabolic liability.

Keywords: antipsychotic, norepinephrine, epinephrine, dopamine, catecholamine, rat, metabolic side effects

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INTRODUCTION

The second generation antipsychotic drugs (also known as the "atypical" antipsychotics, to differentiate them from the original first generation, "typical," antipsychotics) represent the most effective pharmacological treatment for chronic psychotic illnesses, which include the schizophrenia spectrum disorders (1). This class of drugs is also increasingly being used to treat

additional psychiatric indications, such as bipolar disorder, mood, and anxiety disorders (2–7). The widespread preference for the use of the second over the first generation antipsychotics is largely driven by the lower incidence of neurological side-effects in the former, which include extrapyramidal symptoms and tardive dyskinesia (8), as well as lower rates of neuroendocrine abnormalities such as hyperprolactinemia (9, 10). The second generation drugs, however, have been linked to their own serious side-effects as well. These most commonly include cardiometabolic side-effects, which significantly increase the risk of developing cardiometabolic disorders such as Type 2 diabetes mellitus (DM) and cardiovascular disease (11–19). Typically, Type 2 DM is preceded by the onset of the metabolic syndrome, which is characterized by weight gain, hypertension, hyperlipidemia, hyperglycemia, glucose intolerance, and insulin resistance (20–22). It is important to note, though, that these metabolic side-effects vary considerably between the different second generation antipsychotics, with some drugs having more severe metabolic effects than others (23, 24).

Currently, the physiological substrates that mediate the metabolic side-effects of the second generation antipsychotic drugs remain incompletely understood. As it is likely that invasive procedures will be required to fully elucidate the biochemical pathways involved, which may not be appropriate for application in humans, there is a key need to develop translational animal models of these drug side-effects. The use of preclinical paradigms offers the additional benefit of helping to disentangle the multifactorial causes of metabolic dysregulation in psychiatric illness, where variables such as diet, exercise, and drug use can all contribute to cardiometabolic dysregulation (25–27). Fortunately, the past 10–15 years has seen significant advances in animal models of the metabolic side-effects of antipsychotic drugs (28), which have demonstrated that many of these compounds cause acute glucose dysregulation and insulin resistance independent of weight gain (29–39).

The biochemical substrates involved are under examination, and important advances have been made. But the present perspective suggests a complex picture, as both central and peripheral mechanisms may be involved (40). It is also possible that multiple biochemical pathways may be affected, upstream, and downstream of each other. One physiological network that spans both central and peripheral systems, and that has been implicated in the metabolic side-effect of antipsychotic drugs in both animal and human studies, is the sympathetic nervous system. Under physiological conditions, an overactive sympathetic nervous system predicts an increase in metabolic abnormalities over time (41). Increased sympathetic activity; as evident by elevated plasma catecholamines, is a consistently reported effect of high metabolic-risk second generation antipsychotic drugs such as clozapine, whereas minimal effects on catecholamine levels are observed in patients treated with lower metabolic-risk drugs (42–44).

While animal studies also suggest a role for peripheral catecholamines (45, 46), a limitation of the literature is the absence of data on the impact of concurrent multiple different antipsychotics, including both first and second generation drugs (to capture the spectrum of metabolic liability), on peripheral catecholamine levels over repeated time points. To address this gap in the literature, we performed a head-to-head comparison of the effects of treatment with the first generation antipsychotic drug haloperidol—with low metabolic liability—against the second generation drugs risperidone, olanzapine and clozapine—which exert increasing metabolic effects. To increase the validity of the study, multiple doses of each drug were used, based on known metabolic effects reported by our laboratory previously (47–51). Animals were unanesthetized and freely moving, handled by a staff well-trained in stress-free phlebotomy, and catecholamine levels were measured with multiple blood draws over a 3-h period. Catecholamines were measured with a sensitive HPLC-ECD assay.

MATERIALS AND METHODS

Animals

One hundred twenty female, adult Sprague-Dawley rats (225–250 g) were obtained from the animal supplier (Charles River, Montreal, QC) and allowed to habituate in the UBC animal colony for at least 1 week before all experiments commenced. Females are used by our laboratory and many other groups because they exhibit more consistent metabolic abnormalities than males following antipsychotic drug treatment (28, 33, 52–54). Animals were housed in groups of 3–4 in large polycarbonate cages and given ad libitum access to food (Purina rat chow) and tap water. All rats were maintained on a 12-h light-dark cycle (lights on at 07:00 h) in a temperature-controlled colony at 22 ± 1°C. Experimental procedures were conducted during the light cycle, and in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The University of British Columbia's Animal Care and Use Committee approved all experimental methods.

Pharmaceutical Agents and Solutions

Doses of antipsychotic drugs were based on previous studies of the metabolic side-effects of antipsychotic drugs which we and others have demonstrated previously. A lower and higher dose were selected for each antipsychotic, spanning a 3–10-fold range. Doses for the present study included risperidone (0.25; 2.5 mg/kg), haloperidol (0.1; 1.0 mg/kg), clozapine (2; 20 mg/kg), and olanzapine (3; 15 mg/kg) [purchased from Toronto Research Chemicals Inc, Toronto, ON, Canada]. Dosing solutions were prepared fresh daily: risperidone, clozapine, and olanzapine were formulated in a vehicle composed of 50% polyethylene glycol 400, 40% distilled water, and 10% ethanol. Haloperidol was formulated in a vehicle of 0.3% tartaric acid. All other chemicals were commercially available and of reagent grade. Each rat received a 1 ml/kg intraperitoneal (IP) injection of the vehicle control or antipsychotic formulation. Animals were all experimentally naïve, and randomized to treatment group.

Treatment and Plasma Collection

Fasted animals [$n = 10$ per group] were weighed and allowed 1 h to acclimate. We used fasted animals, as this is the condition under which we typically assess the metabolic effects of antipsychotic drugs. Rats were then given a saphenous blood

draw (200 μL) prior to drug treatment to obtain a baseline measure of plasma catecholamines. Immediately following, animals were treated with their assigned antipsychotic drug or vehicle. Additional blood samples were then collected at 30, 60, 120, and 180 mins after drug treatment. Blood samples were centrifuged (10,000 RPM, 10 mins, 4°C) and stored at −80°C until analysis.

Determination of Plasma Catecholamine Concentration

Standard solutions of epinephrine, norepinephrine and dopamine (50–25,600 pg/ml) were prepared by dilution of a stock 1 mg/ml solution with standard diluent (ThermoFisher, Sunnyvale, CA) to generate a standard curve. The internal standard (IS) solution consisted of 20 ng/ml 3,4-dihydroxybenzylamine (DHBA). Samples were prepared by adding 90 μL of 3 M Tris-5% EDTA buffer, 10 μL of DHBA, and 50 μL of plasma or standard to a 0.6 ml centrifuge tubes containing 5.0 mg activated alumina oxide (Sigma Aldrich, St. Louis, MO). Samples were vortexed and placed on a rotary mixer for 10 mins at 4°C, followed by centrifugation and removal of supernatant. Addition of 400 μl of ultra-pure water followed by aspiration was performed three consecutive times, followed by centrifugation. Addition of 50 μl of 0.1 M perchloric acid was added and samples were mixed on the rotary mixer for 10 mins. Samples were vortexed, centrifuged, and the remaining supernatant was injected into the HPLC system.

HPLC-ECD

Catecholamine levels were analyzed by HPLC coupled to electrochemical detection (ECD). A Shimadzu series HPLC system, including an ESA Coulochem III electrochemical detector, separated analytes on a ESA HR-80 column (80 × 4.6 mm, 3 μm). Mobile phase contained 0.7% sodium phosphate, 3% sodium citrate, 0.02% EDTA, 0.2% diethylamine HCl, 0.1% 1-octanesulfonic acid, 5% acetonitrile, 0.2% dimethylacetamide and water, pH–adjusted to 3.1. A 20 μl injection was loaded at 0.4 ml/min. The ECD system contained an ESA 5020 guard cell (200 mV) and an ESA 5011 analytical cell ($E_1 = -150$ mV; $E_2 = 225$ mV) for acquisition of epinephrine, norepinephrine, dopamine, and IS plasma levels. Data were processed blind to treatment condition, with chromatogram peaks analyzed by the LCsolution software package.

Statistical Analysis

Data obtained included plasma levels of norepinephrine, epinephrine, and dopamine. All data were subjected to a repeated-measures analysis of variance (ANOVA), with drug treatment and dose as between group factors, and time as the within-subjects factor. Main effects or interactions were followed up with the LSD *post-hoc* test. Correlations were conducted using the Pearson correlation coefficient (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp).

RESULTS

Blood samples were successfully collected for all animals at all time points. Observation of the chromatograms demonstrated that peaks for norepinephrine, epinephrine, and dopamine (as well as the IS) were all well-separated and with no overlap (**Figure 1**). We also identified an unknown peak at ∼8–9 mins (peak "X," **Figure 1**), which we confirmed was not serotonin, and may represent a catecholamine metabolite.

Norepinephrine

When reviewing the data on norepinephrine levels, an analysis for outliers determined that two samples were strong outliers based on SPSS criteria (>3 × the interquartile range) and so were excluded from analysis and replaced with next observation carried backward (55). Analyzing each drug individually, risperidone demonstrated a significant effect of dose [$F_{(2,27)} = 31.44$, $p < 0.001$], time [$F_{(4,108)} = 29.23$, $p < 0.001$] and a dose × time interaction [$F_{(8,108)} = 13.71$, $p < 0.001$]. *Post-hoc* analysis revealed that both doses of risperidone caused a significant increase in norepinephrine levels by 30 mins compared to controls, but by 60 mins the lower dose of risperidone did not differ from controls, for the duration of the test (**Figure 2A**). By contrast, norepinephrine levels remained significantly elevated at all time points after treatment with the higher dose of risperidone compared to both the low dose of risperidone and controls.

For haloperidol, the ANOVA indicated a significant effect of dose [$F_{(2,27)} = 7.31$, $p < 0.005$], time [$F_{(4,108)} = 5.80$, $p < 0.001$] and a dose × time interaction [$F_{(8,108)} = 3.01$, $p < 0.005$]. *Post-hoc* analysis confirmed that levels of norepinephrine with the low dose of haloperidol did not differ at any time point from controls (**Figure 2B**). In contrast, the high dose of haloperidol was associated with a trend for increased norepinephrine levels compared to controls at 30 mins after treatment ($p = 0.06$), and then significantly higher between 60 and 120 mins ($p < 0.05$), but no longer at 180 mins ($p = 0.07$).

With clozapine, the ANOVA indicated a significant effect of dose [$F_{(2,27)} = 18.60$, $p < 0.001$], time [$F_{(4,108)} = 6.82$, $p < 0.001$] and a dose × time interaction [$F_{(8,108)} = 5.56$, $p < 0.001$]. *Post-hoc* analysis demonstrated that levels of norepinephrine with the low dose of clozapine did not differ at any time point from controls (**Figure 2C**). However, the high dose of clozapine evinced a large, highly significant increase in norepinephrine levels compared to both the controls and the low dose of clozapine at all time points after treatment ($p < 0.001$).

For olanzapine, analysis of the data by the ANOVA revealed a significant effect of dose [$F_{(2,27)} = 11.07$, $p < 0.001$], time [$F_{(4,108)} = 4.00$, $p = 0.005$] and a dose × time interaction [$F_{(8,108)} = 3.08$, $p < 0.005$]. Similarly to clozapine, the *post-hoc* analysis indicated that levels of norepinephrine with the low dose of olanzapine did not differ at any time point from controls (**Figure 2D**). In contrast, the high dose of olanzapine caused a large, significant increase in norepinephrine levels compared to both the controls and the low dose of clozapine at all time points after treatment ($p < 0.01$).

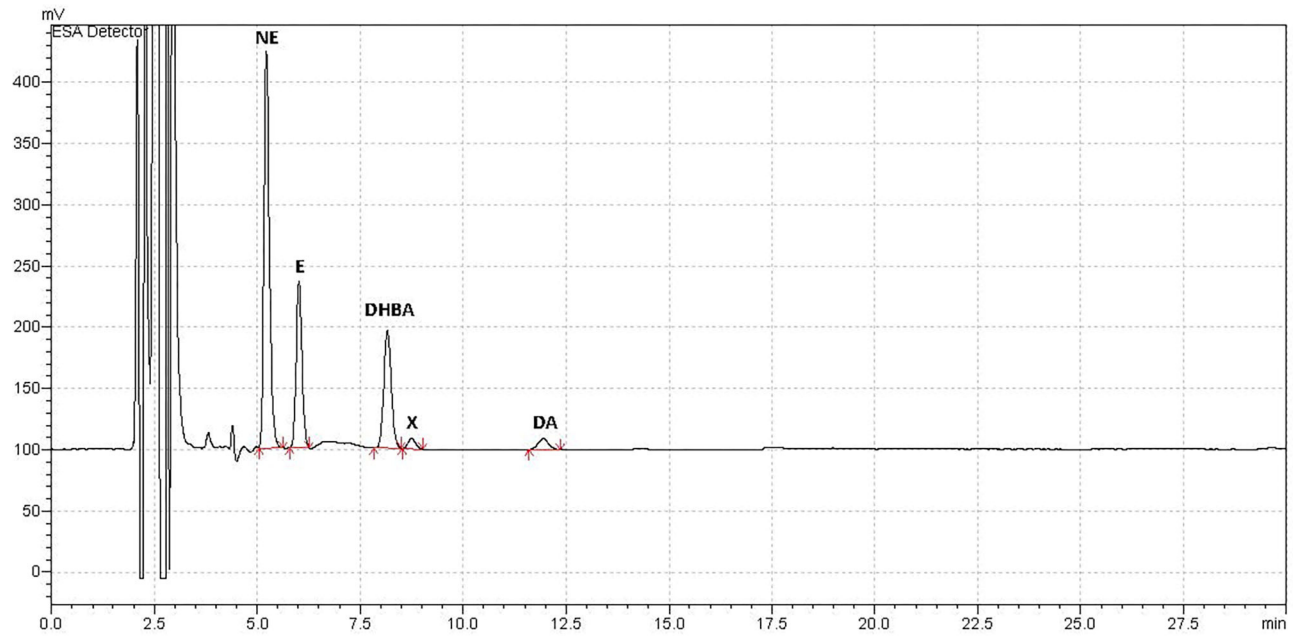

FIGURE 1 | Example Chromatograph. Example of typical chromatograph obtained using HPLC-ED for analysis of plasma catecholamine concentrations in a sample from adult female rats treated with an antipsychotic drug or vehicle. Catecholamine peaks were all well-separated with no peak overlap. Catecholamines measured were norepinephrine (NE), epinephrine (E), and dopamine (DA). The internal standard, added after plasma collection, was 3,4-dihydroxybenzylamine (DHBA). An unidentified peak ("X") occurred at ~8–8.5 mins, which correlated with catecholamine levels, and may have been a metabolite.

Epinephrine

Epinephrine levels were reliably measured with the HPLC-ED, with no samples below the limit of detection. Looking at each drug individually, the ANOVA noted that risperidone demonstrated a significant effect of dose [$F_{(2,27)} = 20.17$, $p < 0.001$], time [$F_{(4,108)} = 17.11$, $p < 0.001$] and a dose × time interaction [$F_{(8,108)} = 7.97$, $p < 0.001$]. The *post-hoc* analysis revealed that both doses of risperidone caused a significant increase in epinephrine levels by 30 mins compared to controls ($p \leq 0.01$), but by 60 mins the lower dose of risperidone did not differ significantly from controls, for the duration of the test (**Figure 3A**). By contrast, epinephrine levels remained significantly elevated at all time points after treatment with the higher dose of risperidone compared to both the low dose of risperidone and controls ($p \leq 0.005$).

Analysis of the results with haloperidol by ANOVA indicated a significant effect of dose [$F_{(2,27)} = 4.05$, $p < 0.05$], but no main effect of time or dose × time interaction. *Post-hoc* analysis of the dose effect showed that the low dose of haloperidol and controls did not differ at any time point (**Figure 3B**), but the high dose of haloperidol caused a significant increase in epinephrine levels compared to both other groups at 30, 60, and 180 mins ($p < 0.05$).

For clozapine, ANOVA indicated a significant effect of dose [$F_{(2,27)} = 14.15$, $p < 0.001$], time [$F_{(4,108)} = 8.14$, $p < 0.001$] and a dose × time interaction [$F_{(8,108)} = 5.27$, $p < 0.001$]. The *post-hoc* analysis confirmed that showed that the low dose of clozapine and controls did not differ at any time point in epinephrine levels (**Figure 3C**), but the high dose of clozapine had higher epinephrine levels than both other groups at all time points after drug treatment ($p < 0.01$).

With olanzapine, the analysis showed significant main effects of dose [$F_{(2,27)} = 14.05$, $p < 0.001$], time [$F_{(4,108)} = 6.51$, $p < 0.001$] and a dose × time interaction [$F_{(8,108)} = 3.77$, $p = 0.001$]. Follow-up *post-hoc* tests revealed that both doses of olanzapine caused a significant increase in epinephrine levels by 30 mins compared to controls ($p \leq 0.01$) (**Figure 3D**), but by 60 mins the lower dose of olanzapine did not differ from controls, for the duration of the test. Epinephrine levels with the higher dose of olanzapine remained significantly higher than both other groups from 60 through to 180 mins ($p < 0.005$).

Dopamine

Although dopamine levels were substantially lower than both norepinephrine and epinephrine, dopamine was reliably detected and above the limit of detection in all processed plasma samples. An analysis for outliers determined that three samples were strong outliers (> 3 × the interquartile range) and so were excluded from analysis and replaced with next observation carried backward (55). ANOVA indicated a main effect of dose of risperidone on dopamine levels [$F_{(2,27)} = 19.60$, $p < 0.001$], time [$F_{(4,108)} = 4.93$, $p = 0.001$], and a dose × time interaction [$F_{(8,108)} = 3.97$, $p = 0.001$]. Follow-up *post-hoc* tests showed that while low dose risperidone and vehicle-treated rats did not differ at any time point in dopamine levels, the levels were significantly higher in the high dose group compared to the low dose group at 30 and 60 mins ($p < 0.05$) (**Figure 4A**), with a strong trend

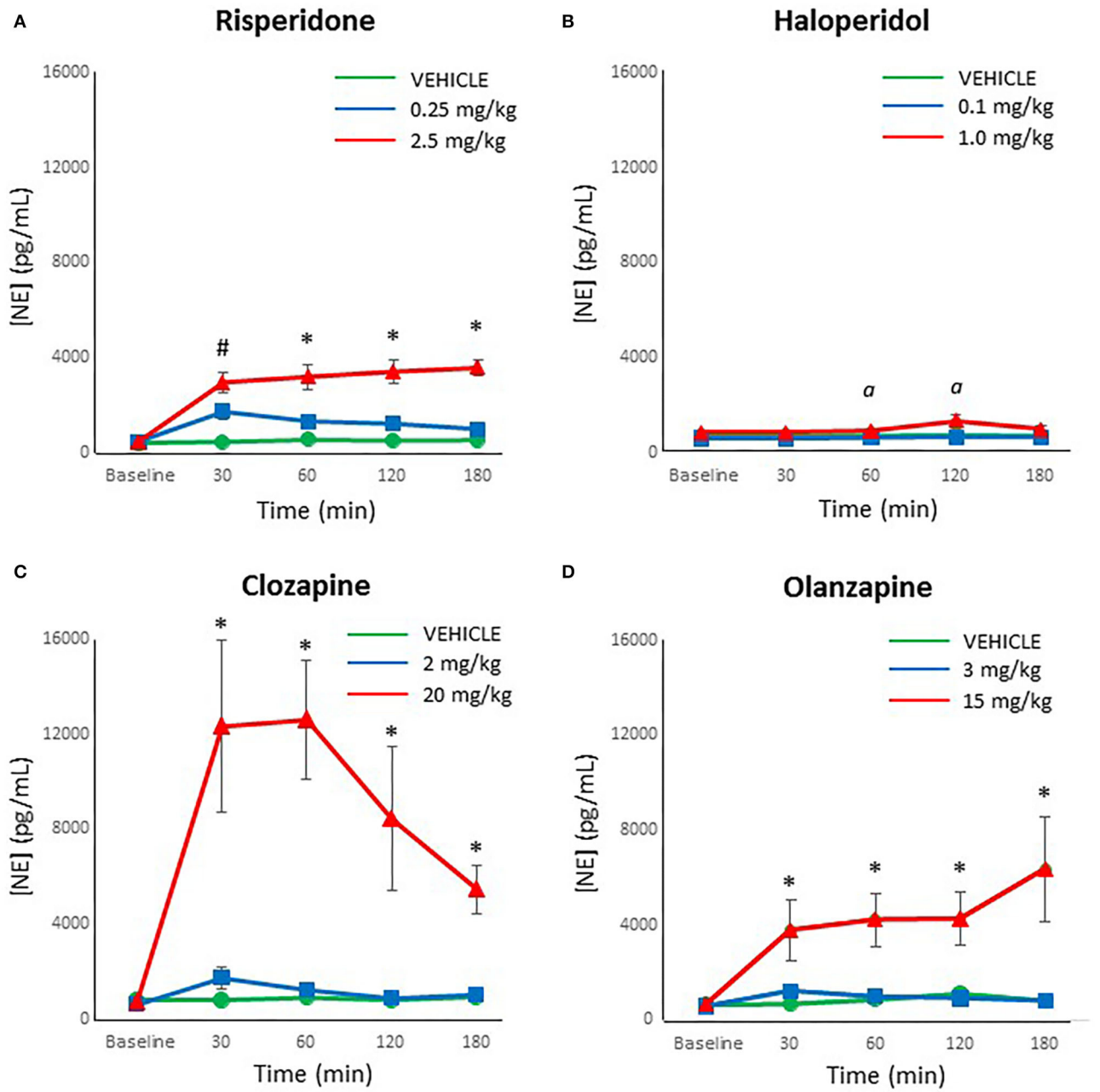

FIGURE 2 | Acute changes in plasma norepinephrine (NE) concentrations (pg/ml) after antipsychotic drug treatment in adult female rats. Animals ($n = 10$ per group) were given a single IP injection of **(A)** risperidone (0.25 or 2.5 mg/kg) or **(B)** haloperidol (0.1 or 1.0 mg/kg) or **(C)** clozapine (2 or 20 mg/kg) or **(D)** olanzapine (3 or 15 mg/kg) or vehicle. Values are expressed in group means ± SEM. Plasma samples were collected immediately prior to drug treatment (Baseline) and at 30, 60, 120, and 180 mins after treatment. #Statistically significant difference between both drug treated groups and vehicle, $p < 0.05$; *Statistically significant difference between high dose group and both other groups, $p < 0.05$; α Statistically significant difference between high dose group and vehicle, $p < 0.05$.

vs. controls ($p = 0.057$ and 0.072, respectively). By 120–180 mins, the high dose exhibited higher levels of dopamine than both other groups ($p \leq 0.001$).

For haloperidol, there was a main effect of time [$F_{(4,108)} = 2.51$, $p < 0.05$] but no effect of dose or dose × time interaction. This time effect reflected a gradual reduction of dopamine levels in all groups over time (**Figure 4B**).

With clozapine, the ANOVA indicated a main effect of dose [$F_{(2,27)} = 11.48$, $p < 0.001$], time [$F_{(4,108)} = 6.79$, $p < 0.001$] and a dose × time interaction [$F_{(8,108)} = 8.44$, $p < 0.001$].

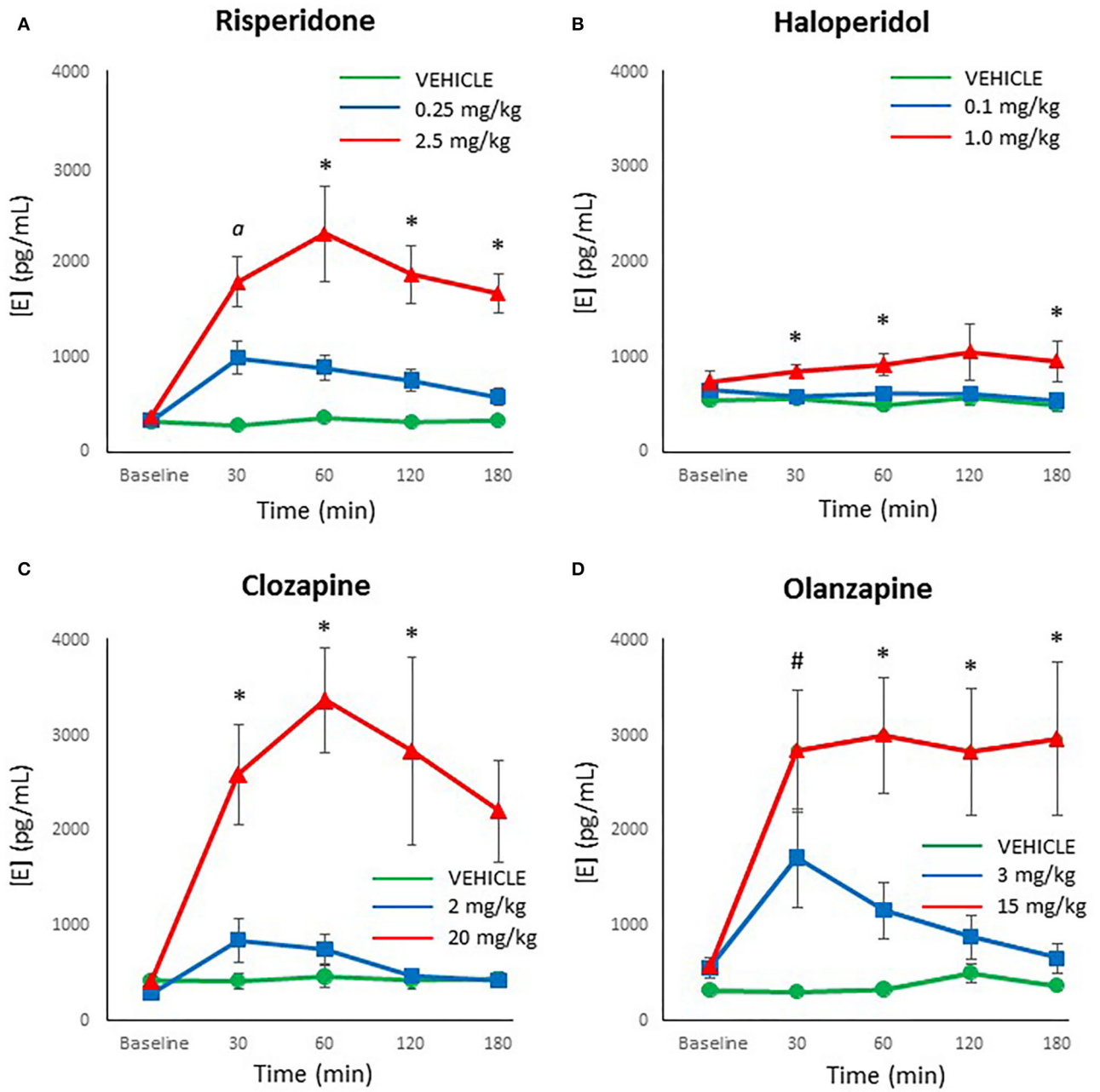

FIGURE 3 | Acute changes in plasma epinephrine (E) concentrations (pg/ml) after antipsychotic drug treatment in adult female rats. Animals ($n = 10$ per group) were given a single IP injection of **(A)** risperidone (0.25 or 2.5 mg/kg) or **(B)** haloperidol (0.1 or 1.0 mg/kg) or **(C)** clozapine (2 or 20 mg/kg) or **(D)** olanzapine (3 or 15 mg/kg) or vehicle. Values are expressed in group means ± SEM. Plasma samples were collected immediately prior to drug treatment (Baseline) and at 30, 60, 120, and 180 mins after treatment. α Statistically significant difference between all three groups, $p < 0.05$; *Statistically significant difference between high dose group and both other groups, $p < 0.05$; #Statistically significant difference between both drug treated groups and vehicle, $p < 0.05$.

Follow-up *post-hoc* tests revealed that low dose clozapine and controls did not differ at any time point (**Figure 4C**), but high dose clozapine demonstrated higher dopamine levels than both other groups at all timepoints after treatment ($p < 0.05$).

Analysis of olanzapine data by ANOVA indicated a main effect of dose [$F_{(2,27)} = 7.50$, $p < 0.001$] but no effect of time or dose × time interaction. Dopamine levels were higher in the high dose olanzapine group than both other groups from 60–180 mins ($p < 0.05$) (**Figure 4D**).

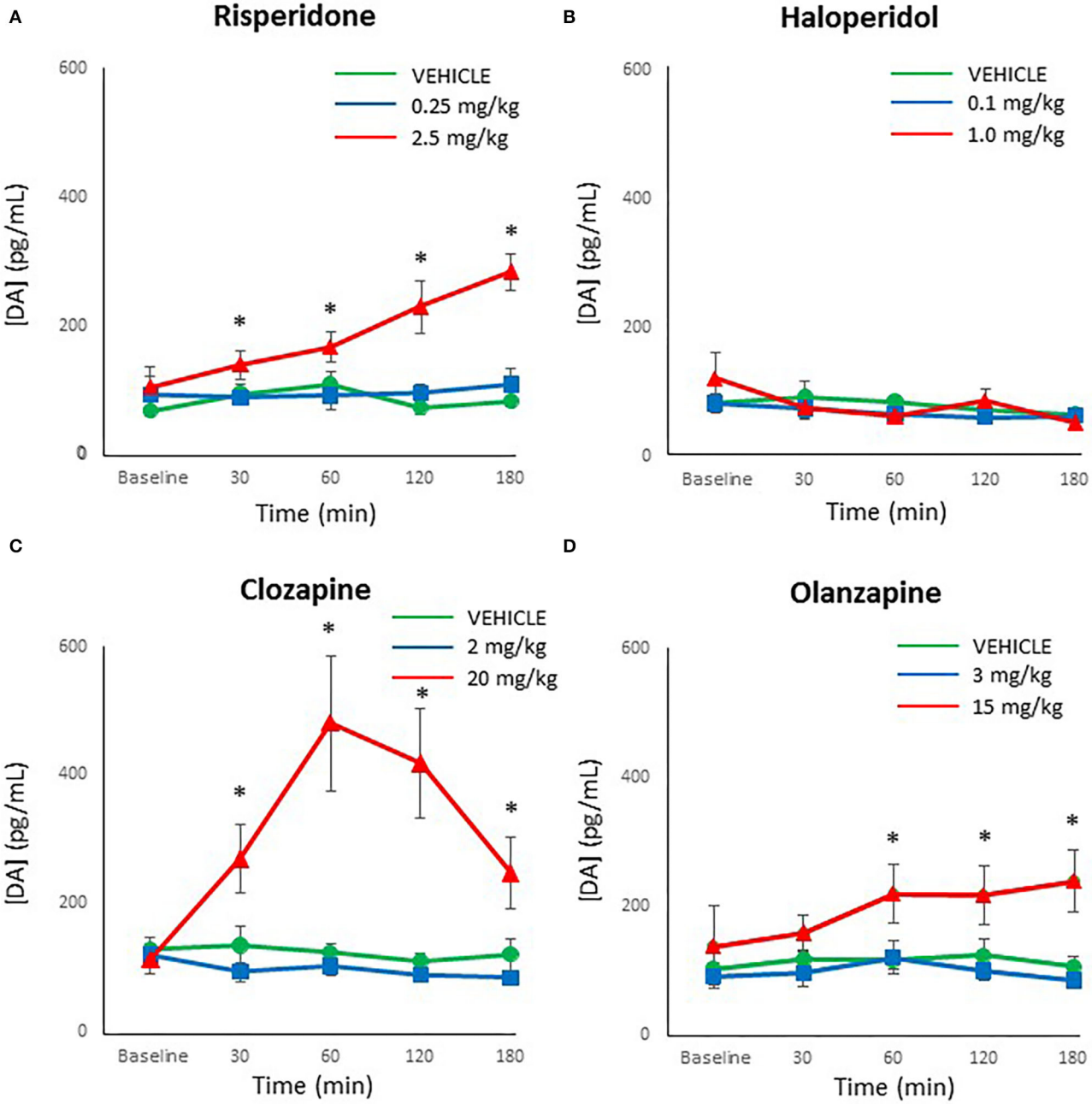

FIGURE 4 | Acute changes in plasma dopamine (DA) concentrations (pg/ml) after antipsychotic drug treatment in adult female rats. Animals ($n = 10$ per group) were given a single IP injection of **(A)** risperidone (0.25 or 2.5 mg/kg) or **(B)** haloperidol (0.1 or 1.0 mg/kg) or **(C)** clozapine (2 or 20 mg/kg) or **(D)** olanzapine (3 or 15 mg/kg) or vehicle. Values are expressed in group means ± SEM. Plasma samples were collected immediately prior to drug treatment (Baseline) and at 30, 60, 120, and 180 mins after treatment. *Statistically significant difference between high dose group and both other groups, $p < 0.05$.

Comparison Between Drugs

As the low doses of antipsychotics did not strongly affect catecholamine levels, we limited our head-to-head comparison of different drugs to the high doses. Baseline norepinephrine levels were included as a covariate for post-treatment norepinephrine levels. The ANOVA indicated a main effect of drug [$F_{(3,36)} = 10.02$, $p < 0.001$], no effect of time, and a drug × time interaction [$F_{(9,108)} = 2.75, p < 0.01$]. Follow-up analysis revealed that norepinephrine levels were higher in the clozapine group than all others from 30 to 60 mins ($p < 0.05$), and higher than haloperidol from 120 to 180 mins. Olanzapine had marginally higher levels than haloperidol at 180 mins ($p = 0.055$). For

epinephrine, ANOVA indicated a main effect of drug [$F_{(3,36)} = 4.65$, $p < 0.01$] and no effect of time or drug × time interaction. *Post-hoc* analyses demonstrated that risperidone, clozapine, and risperidone had higher epinephrine levels than haloperidol at all points after drug treatment. With dopamine, there were main effects of drug [$F_{(3,36)} = 8.34$, $p < 0.001$], time [$F_{(3,108)} = 6.12$, $p = 0.001$], and a dose × time interaction [$F_{(9,108)} = 5.54$, $p < 0.001$], whereby clozapine-treated animals had higher dopamine levels than all other groups from 30 to 120 mins, and all groups had higher levels than haloperidol at 180 mins.

Relationship Between Catecholamines

As an exploratory analysis, we examined the relationship between the three catecholamines at each time point (all treatment groups were combined). At pre-treatment baseline, there was a moderate correlation between norepinephrine and the other two catecholamines ($r = 0.31$–0.36, $p < 0.001$) while epinephrine and dopamine were not correlated ($r = 0.02$, NS). Following drug treatment at 30 mins, all catecholamine levels showed a large increase in their correlation with each other ($r = 0.50$–0.73, $p < 0.001$), which increased further at 60 mins ($r = 0.67$–0.88, $p < 0.001$), at 120 mins ($r = 0.59$–0.79, $p < 0.001$) and at 180 mins ($r = 0.70$–0.91, $p < 0.001$).

DISCUSSION

In the present study, we compared treatment in freely moving rats with multiple doses of four different antipsychotic drugs, over a 180-mins period, on levels of peripheral catecholamines. The drugs included the first generation antipsychotic drug haloperidol, as well as the second generation drugs risperidone, olanzapine and clozapine. Metabolic abnormalities in patients are most common with the latter two drugs (21, 56), although can occur with all antipsychotic medications, including first generation drugs (57). The key results of the study were that all antipsychotics caused an increase in plasma catecholamine levels. For norepinephrine, this varied considerably by drug, and maximal increases relative to baseline for risperidone were [low dose: +382%; high dose: +793%], haloperidol [low dose: no change; high dose: +158%], clozapine [low dose: +273%; high dose: +1,684%] and olanzapine [low dose: +212%; high dose: +952%]. A similar pattern was observed with epinephrine, where maximal changes relative to baseline for risperidone were [low dose: +299%; high dose: +617%], haloperidol [low dose: no change; high dose: +143%], clozapine [low dose: +293%; high dose: +806%] and olanzapine [low dose: +307%; high dose: +529%]. Increases in peripheral dopamine were smaller, showing no change with the low dose of each drug, and only moderate increases relative to baseline with the high dose for risperidone [+271%], haloperidol [no change], clozapine [+430%] and olanzapine [+174%]. Interestingly, levels of the catecholamines did not correlate strongly with each other prior to treatment at baseline, but were increasingly correlated after treatment as time proceeded.

Overall, these findings clearly demonstrate that antipsychotic drugs can increase peripheral plasma catecholamines in a dose- and drug-dependent manner. The smallest increases in catecholamines were caused by haloperidol, followed by risperidone/olanzapine, and largest by clozapine. These findings are in general agreement with the limited literature on the effects of antipsychotic drugs on peripheral catecholamine levels in animals and humans. An earlier study observed that intravenous treatment of rats with the first generation antipsychotic chlorpromazine resulted in a dose-dependent elevation of both norepinephrine and epinephrine to levels comparable to those observed in the present study with the second generation drugs (58). Of interest, chlorpromazine has been characterized as the first generation drug most likely to cause metabolic syndrome (59). More recently, a pair of studies by the same research group noted that intravenous olanzapine and clozapine both caused significant increases in plasma epinephrine, to a comparable degree to the present study (46, 60); norepinephrine and dopamine were not measured in their studies. Indirect evidence for elevated peripheral catecholamines following treatment with clozapine and chlorpromazine was provided by Savoy et al. (45), who demonstrated that the hyperglycemia caused by these two drugs could be decreased by treatment with the ganglionic blocker hexamethonium, which presumably worked by preventing the release of peripheral norepinephrine and epinephrine. Clinical studies of patients treated with antipsychotic drugs have also reliably observed increases in peripheral catecholamines with higher metabolic liability drugs, such as clozapine (42, 44, 61, 62). For example, plasma norepinephrine levels were ∼three times higher in patients treated with clozapine than in controls or patients treated with the first generation antipsychotics haloperidol and fluphenazine (42, 44). We are not aware of any studies that have measured the effects of antipsychotic drugs on peripheral dopamine, which may be due to the greater sensitivity of the assay needed.

While the link between elevated peripheral catecholamines and the metabolic effects of antipsychotics was not determined in this study (as we did not measure metabolic indices), norepinephrine and epinephrine are well-established as two of the most potent hormones involved in the regulation of blood glucose levels. They tightly control insulin release, glucagon secretion, hepatic gluconeogenesis, and glycogenolysis (41, 63), and elevated levels of these catecholamines are related to metabolic dysregulation and metabolic syndrome (64). As such, the observed increased in catecholamines provide a possible pathway to hyperglycemia that requires further study. However, the catecholamines may represent only part of the story. The present doses of drugs were based on prior studies by our laboratory, that observed effects on glucose intolerance and insulin resistance (32, 34, 47, 48). These doses were selected to produce metabolic effects comparable in magnitude to metabolic effects observed in humans treated with the same drugs (65, 66). Some of those doses, such as the high dose (1 mg/kg) of haloperidol and the low dose of clozapine (2 mg/kg), previously exerted pronounced effects in the glucose tolerance test (47), yet those same doses currently only produced very modest increases in catecholamines. Whether these are

sufficient to produce metabolic dysregulation will require additional experimentation. The role of peripheral dopamine also requires further evaluation; the hormone has diverse functions peripherally, and is mainly co-released from sympathetic nerve fibers with norepinephrine (67). There is considerable evidence to show that peripheral dopamine regulates body weight and glucose homeostasis via insulin release (68, 69), and so may represent an unexplored contributor to the metabolic effects of antipsychotics.

Importantly, the observed effects were all determined in fasted animals, as this is the condition under which we and many other groups typically assess the metabolic effects of antipsychotic drugs (28). Fasting is associated with decreased sympathetic activity (70), whereas carbohydrate and fat feeding causes increased sympathetic activity (71, 72). The present use of fasting animals therefore likely maximized the capacity to observe increases in catecholamines and reduced pre-treatment variability in catecholamine levels between animals.

The mechanism by which antipsychotics increase peripheral catecholamines remains unknown. One potential substrate is the α_2-adrenoceptor, which acts as an autoreceptor to decrease catecholamine release from nerve terminals (41, 73). Many antipsychotics have a strong affinity for the α_2-adrenoceptor, and clozapine (which caused the greatest increase of peripheral catecholamines) has the highest α_2 receptor load (74). However, high α_2 receptor loads are also associated with antipsychotics with minimal metabolic liability, such as asenapine (32, 74), suggesting that this may not be the main mechanism. We would posit that antipsychotic drugs may be acting centrally in brain regions such as the locus coeruleus (75) or the lateral and paraventricular nuclei of the hypothalamus (76), which serve to activate the sympathetic nervous system and have been implicated in the metabolic effects of antipsychotics (77). The possibility certainly remains, though, that antipsychotics could be exerting peripheral effects on the sympathetic nervous system, such as through their affinity for the monoamine transporters (78).

The current study has a number of limitations. The first of these is that antipsychotic drugs were only administered to female rats, and not to males. The basis for this decision was that female rats typically produce more reliable and robust metabolic effects than do male rats when treated with antipsychotic drugs (28, 52, 53), and so better model the human condition. However, the physiological basis for these sex differences remains incompletely understood, and could feasibly be related to sex differences in catecholamine release (79). This straightforward experiment therefore represents a logical next step in following up the present results. Another limitation of the present study is the acute nature of drug treatment, as animals were only given a single injection of the drug. We would predict that increases in catecholamine levels would not change with repeated treatment, as we have found the metabolic effects of antipsychotics to be stable in rats over time in longitudinal studies (34, 50), and reports of elevated catecholamines in antipsychotic-treated patients include subjects who have also been administered the drugs chronically (42, 44, 61, 62). Nevertheless, the current effects should be determined in rats treated over an extended period with antipsychotic drugs to confirm that the findings remain consistent, and thus better model clinical populations. It would also be informative to assess plasma antipsychotic drug levels in animals treated with the current doses of drugs. Finally, the present study did not concurrently measure both catecholamine release and metabolic dysregulation to confirm, at an individual level, the link between elevated catecholamines and glucose dysregulation. While this would have been informative, there was a conscious decision to progress in a step-by-step manner, which partly comes from a legitimate concern that additional blood draws, injections, and a glucose challenge could significantly have affected stress levels and thus modified catecholamine release. However, future studies will clearly be needed to determine whether these increased catecholamines are causal to metabolic dysregulation using well-designed experimental protocols.

In conclusion, the present results provide strong evidence that antipsychotic drugs exert potent stimulatory effects on peripheral catecholamines, which may be relevant to drug metabolic side-effects. The observation that even the first generation antipsychotic drug haloperidol can significantly increase catecholamine levels with a sufficient dose is consistent with the clinical observation that many first generation drugs are not metabolically neutral and may be associated with metabolic dysregulation (22, 80), albeit milder than most second generation drugs. To our knowledge, the present preclinical study is the first to compare multiple antipsychotics head-to-head, and is also the first to report effects on all three peripheral catecholamine levels. Time-series data collected from unrestrained, unanesthetized animals by a team experienced in stress-free phlebotomy increase the validity of the data. However, many questions remain regarding the direct relationship of these catecholamines to metabolic dysregulation, as well as the physiological pathways involved in catecholamine release, and so significant further research in required on this topic, including assessment of complementary indices of sympathetic activity.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by UBC Animal Care Committee.

AUTHOR CONTRIBUTIONS

HB, AH, and LT collected and processed data. AB designed and supervised the study. All authors contributed to the

writing and final draft of this manuscript and approve it for publication.

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The Psychology of Food Cravings in Patients With First-Episode Psychosis

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Objectives: Food cravings may cause weight gain in patients with schizophrenia. This study investigated psychological characteristics associated with food cravings in patients with first-episode psychosis.

Methods: This study analyzed data from a clinical cohort of first-episode psychosis patients taking antipsychotics for 3 months or less. The strength of food cravings was measured using the General Food Cravings Questionnaire-Trait (G-FCQ-T). Psychological characteristics and psychiatric symptoms were investigated with the Positive and Negative Symptom Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS), Social and Occupational Functioning Assessment Scale, Rosenberg Self-Esteem Scale (RSES), and Perceived Stress Scale (PSS). Clinical characteristics were compared according to significant weight gain (≥10% increase in body weight compared to baseline) over 3 months. Associations between the G-FCQ-T and other psychiatric scales were investigated. We conducted sex-stratified analyses.

Results: In total, 182 patients (78 males and 104 females) with first-episode psychosis were enrolled in this study. In females, the G-FCQ-T total score at baseline was associated with baseline body weight and significant weight gain over 3 months. The PSS scales were significantly associated the G-FCQ-T total and all subscale scores in female participants. Scores on the RSES and CDSS were significantly associated with the G-FCQ-T total score and with the preoccupation and loss of control subscale scores. The PANSS negative and general subscales were significantly associated with the positive outcome expectancy and loss of control subscales of the G-FCQ-T, respectively. In males, the only significant association was between the loss of control subscale and RSES scores. Linear regression analysis showed significant associations of PSS scores with the total and all subscale scores of the G-FCQ-T despite the loss of significance for other variables.

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Conclusion: These results indicate that the food cravings in patients with first-episode psychosis, which were associated with weight gain, were influenced by perceived stress in females. To reduce food cravings in female patients with schizophrenia, interventions aimed at perceived stress should be considered.

Keywords: weight gain, food craving, schizophrenia, First-Episode Psychosis (FEP), stress, depression

INTRODUCTION

The relative risk of obesity in patients with schizophrenia is 1.5–2 times higher than that in the general population (1). Patients with schizophrenia also have higher rates of diabetes, hypertension, and hyperlipidemia (1–3). A meta-analysis of 77 publications found that the prevalence of metabolic syndrome in patients with schizophrenia was 32.5% (4). This rate is quite high compared to that in the general population; the International Diabetes Federation (IDF) estimated that the global prevalence of metabolic syndrome was 25% (5). In Korea, the prevalence of metabolic syndrome in patients with schizophrenia was reported to be higher (35–43%) (6–8) than that in the general population (20.3%) (9). These chronic physical diseases and metabolic syndrome can adversely impact mortality and general health.

Maintenance treatment with antipsychotics is essential for patients with schizophrenia, although those who are also obese are twice as likely to discontinue using their medication (10). Several studies have also indicated that high body mass index (BMI) (11, 12) and weight gain (13) are associated with a poor quality of life in patients with schizophrenia. Weight gain in patients with schizophrenia is a major public health issue associated with significant health and economic costs (14). There is growing recognition of the need for interventions to address obesity and weight gain in patients with schizophrenia (15–18). It is critical to explore the factors that lead to weight gain in this population in detail.

Antipsychotic treatment has a significant effect on weight gain (19–21). However, several groups have suggested that schizophrenic patients are liable to develop metabolic abnormalities even in the absence of antipsychotic medication (22, 23). Unhealthy eating habits, such as consuming instant meals instead of fresh groceries, have been reported in patients with schizophrenia (24). It remains uncertain whether antipsychotics cause weight gain directly, by decreasing metabolism, or indirectly via increased appetite and decreased activity (25). Therefore, non-drug factors are also important to consider with respect to weight gain in patients with schizophrenia.

In the general population, certain eating habits, food cravings, and psychological factors are associated with body weight and weight gain (26, 27). High levels of perceived stress are associated with a poor diet (28), increased consumption of snack foods (29, 30), decreased consumption of fruit (29, 30), binge eating (31), and increased disinhibition (32), all of which can lead to weight gain. Depression and anxiety have also been shown to increase cravings for palatable foods (33).

Most previous studies on weight gain in patients with schizophrenia have focused on biological factors, including the type of antipsychotics used, rather than on psychosocial and behavioral factors. In addition, weight gain in patients with schizophrenia occurs early in the disease course (34). However, many studies on the eating habits of patients with schizophrenia have been conducted in chronic patients, and the potential confounding effect of the type of antipsychotic medication has not been ruled out.

This study hypothesized that (i) food cravings are associated with weight gain in patients with first-episode psychosis, and (ii) various psychological factors can contribute to food cravings. To minimize confounding factors, only patients with first-episode psychosis, and those using antipsychotics with a low to moderate propensity to cause gain weight, were included in this study. In addition, we conducted sex-stratified analyses to account for possible sex differences in eating patterns.

METHODS

Study Design

This study analyzed the data of an early-psychosis cohort enrolled in the Gwangju Early Treatment and Intervention Team (GETIT) study (35). The GETIT cohort included patients with a duration of treatment for psychotic symptoms of $\leq$2 years who met the criteria for "Schizophrenia Spectrum Disorder and Other Psychotic Disorders," according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (36). The patients included in in this study were experiencing first-episode schizophrenia, schizophreniform disorder, or another schizophrenia spectrum disorder. To minimize confounding effects of the type or duration of antipsychotic medication, only patients who took aripiprazole, amisulpride, or paliperidone (risperidone) for 3 months or less were included. Patients with a substance- or medication-induced psychotic disorder, psychotic disorder due to another medical condition, or severe neurological or medical disorder were excluded. This study was conducted from September 2015 to December 2019 and was approved by the Chonnam National University Hospital Institutional Review Board. All subjects provided written informed consent before participation.

Study Population and Measures

Baseline sociodemographic and clinical data included age, sex, diagnosis, type of antipsychotics taken, dosage of chlorpromazine equivalent dosage (37), duration of treatment, and the duration of untreated psychosis (DUP), which was defined as the time between the appearance of the first psychotic symptoms and the

start of antipsychotic treatment (38). Body weight was measured at the start of the study and after 3 months.

The strength of food cravings was measured using the General Food Cravings Questionnaire-Trait (G-FCQ-T), which is a 21-item self-report measure of the general "desire for food" or "desire to eat." (39) and formally standardized in Korean version (40). The General Food Cravings Questionnaire (G-FCQ), a modified version of the Food Craving Questionnaire (FCQ) (41), was developed by Nijs et al. (39) and consists of two subscales: the G-FCQ-T and General Food Cravings Questionnaires-State (G-FCQ-S). The G-FCQ-T measures the frequency and intensity of general food cravings, while the G-FCQ-S measures the intensity of momentary food cravings. The G-FCQ-T consists of four subscales, and includes six items on preoccupation with food (i.e., obsessively thinking about food and eating), six items on loss of control (i.e., the tendency toward disinhibited eating behavior when exposed to food cues), five items on positive outcome expectancy (i.e., believing eating to be positively or negatively reinforcing), and four items on emotional craving (i.e., the tendency to crave food when experiencing negative emotions). Each item was scored on a six-point Likert scale (1 = strongly disagree, 6 = strongly agree).

Other psychological characteristics and psychiatric symptoms were investigated using the Positive and Negative Syndrome Scale (PANSS) (42), Calgary Depression Scale for Schizophrenia (CDSS) (43), Social and Occupational Functioning Assessment Scale (SOFAS) (44), Rosenberg Self-Esteem Scale (RSES) (45), and Perceived Stress Scale (PSS) (46). All psychiatric scales were completed at baseline.

Statistical Analysis

Comparisons of clinical characteristics according to "clinically significant weight gain," defined as a $\geq$10% increase in body weight after 3 months compared to baseline, were conducted using the chi-square test for categorical variables, independent *t*-tests for normally distributed variables (tested by the Kolmogorov-Smirnov test), and Mann-Whitney U tests for non-normally distributed variables, as appropriate. All clinical scales submitted to statistical analyses were measured at baseline. A two-way analysis of variance (ANOVA) with interactions was conducted to compare participants' clinical scale scores according to sex and significant weight gain. Then, statistical analyses were separately conducted in males and females. Scores on the G-FCQ-T and psychiatric scales were compared between the two groups divided by significant weight gain using an analysis of covariance after controlling for baseline body weight. Associations between G-FCQ-T scores and psychiatric scales were investigated using Pearson's correlation test for normally distributed variables and Spearman's correlation test for non-normally distributed variables. Age and variables that were significantly associated with G-FCQ-T scores at the $p < 0.05$ level were entered into linear regression analysis to control for confounding effects. Non-normally distributed variables were entered into the regression model after log transformation. The sample size calculated using GPower for a correlation test with a power of 0.80 and an alpha of 0.05 for a medium effect size (0.3) was 84 for each sex. All statistical tests were two-tailed and $p < 0.05$ was taken to indicate statistical significance. The statistical analysis was performed using SPSS software (version 25.0; IBM Corp., Armonk, NY, USA).

RESULTS

A total of 182 patients (78 males and 104 females) with first-episode psychosis were enrolled in this study. The media (interquartile range) age at baseline was 25.5 (21.0–32.0) years. The median (interquartile range) duration of treatment and DUP were 1 (0.6–1.5) and 3 (1–12) months, respectively. There were no significant sex differences in these variables. The scores on the G-FCQ-T did not differ significantly between sexes. The scores on the emotional craving subscale of the G-FCQ-T tended to be higher in females than in males, but the difference was not statistically significant ($t = -1.891$, $p = 0.060$). Aripiprazole, amisulpride, and paliperidone were prescribed in 36 (19.8%), 57 (31.3%), and 89 patients (48.9%), respectively. Scores on the G-FCQ-T were not significantly associated with type and chlorpromazine equivalent dosage of antipsychotic medication (all $p > 0.1$, data not shown).

Pearson correlation coefficients between the G-FCQ-T scores and baseline body weight were significant only for the loss of control subscale and total scores in female patients ($r = 0.346$ and 0.251, $p = 0.002$ and 0.013, respectively). A total of 150 patients (82.4%) completed the 3-month follow-up evaluation of weight gain. Clinically significant weigh gain was found in 44 patients (29.3%). **Table 1** shows demographic and clinical characteristics, including G-FCQ-T scores, according to the clinically significant weight gain status in the total population. No significant group difference in age, sex, DUP, duration of treatment, or type of antipsychotics and their chlorpromazine equivalent dosage were observed. Scores on the preoccupation subscale score of the G-FCQ-T, the PANSS general and total, and the SOFAS were significantly higher in the group with significant weight gain.

A two-way ANOVA revealed no significant sex × weight gain interaction except for the RSES ($F = 4.582$, $p = 0.034$). The RSES score was lower in the weight gain group than in the non-weight gain group for females, and it was higher in the weight grain group than the non-weight gain group for males; the results of separate analyses in each sex were not statistically significant (**Table 2**). **Table 2** shows comparisons of psychiatric scale scores according to clinically significant weight gain status for each sex, adjusted for baseline body weight. In female patients, the total G-FCQ-T score and the preoccupation and loss of control subscale scores were significantly higher in the group with significant weight gain. The SOFAS score was significantly lower in patients with significant weight gain.

Spearman correlation analysis showed that the G-FCQ-T total score was significantly associated with age in the female population ($r = -0.222$, $p = 0.023$). Spearman correlation analyses showed no significant associations among G-FCQ-T scores, DUP, and duration of treatment (all $p > 0.1$, data not shown). **Table 3** shows Pearson or Spearman correlation coefficients between G-FCQ-T scores and clinical

TABLE 1 | Demographic and clinical characteristics according to clinically significant weight gain status.

	Weight gain ≥ 10% (*n* = 44, 29.3%)	Weight gain < 10% (*n* = 106, 70.7%)	Statistical value*	*p*-value
Sex, *n* (%):				
Male	22 (32.8)	45 (67.2)	0.717	0.397
Female	22 (26.5)	61 (73.5)		
Age, years, med (IQR)	24.5 (21.0–30.0)	25.0 (20.0–32.0)	−0.409	0.682
Duration of Untreated Psychosisd, months, med (IQR)	2.0 (1.0–9.5)	2.6 (1.0–15.5)	−0.335	0.738
Duration of treatment, months, med (IQR)	1.0 (0.6–1.0)	1.0 (0.6–1.5)	−1.259	0.208
Type of Antipsychotics, *n* (%)			0.352	0.839
Aripiprazole	8 (28.6)	20 (71.4)		
Amisulpride	15 (32.6)	31 (67.4)		
Paliperidone	21 (27.6)	55 (72.4)		
Bodyweight at baseline, kg, M (SD)	59.6 (10.1)	62.8 (12.1)	−1.565	0.120
Bodyweight at 3 months, kg, M (SD)	67.7 (10.5)	64.6 (12.4)	1.434	0.154
Weight gain for 3 months, kg, M (SD)	8.1 (1.7)	1.8 (2.6)	17.512	**<0.001**
CPZ Eq. dosage, mg/day, med (IQR)	345 (200–630)	400 (200–600)	−0.717	0.473
General Food Cravings Questionnaires-Trait, M (SD)				
Preoccupation	15.9 (6.5)	13.4 (6.1)	2.201	**0.029**
Loss of control	18.3 (6.2)	17.0 (6.9)	1.137	0.257
Emotional craving	13.3 (4.7)	11.7 (5.2)	1.780	0.077
Positive outcome expectancy	17.9 (5.1)	17.1 (5.5)	0.826	0.410
Total	65.4 (19.8)	59.2 (20.7)	1.704	0.090
Positive And Negative Syndrome Scale, M (SD)				
Positive	16.3 (5.1)	15.4 (4.7)	1.009	0.314
Negative	17.9 (4.9)	16.4 (4.3)	1.856	0.066
General	37.1 (8.0)	33.6 (7.2)	2.604	**0.010**
Total	71.3 (15.3)	65.5 (14.2)	2.233	**0.027**
Calgary Depression Scale for Schizophrenia, med (IQR)	3.0 (0.3–8.0)	4.0 (1.0–8.0)	−0.945	0.345
Social and Occupational Functioning Assessment Scale, M (SD)	56.5 (11.0)	60.5 (8.8)	−2.319	**0.022**
Perceived Stress Scale, M (SD)	21.2 (5.8)	20.1 (6.9)	0.918	0.360
Rosenberg Self-Esteem Scale, M (SD)	22.0 (6.9)	21.9 (3.0)	−0.211	0.833

**Statistical tests are chi-square test, independent t-tests, or Mann-Whitney U tests, respectively. Statistical values are T, Z, or χ^2, respectively. Values in bold show statistical significance. M, mean; SD, standard deviation; med, median; IQR, Interquartile range; CPZ Eq., chlorpromazine equivalent.*

variables at baseline. In males, a significant association was only found between the loss of control subscale and RSES scores. In females, the PSS scales were significantly associated the G-FCQ-T total and all subscale scores. Scores on the RSES and CDSS were significantly associated with the total G-FCQ-T scale score and with the preoccupation and loss of control subscales. The PANSS negative and general subscales were significantly associated with the positive outcome expectancy and loss of control subscales on the G-FCQ-T, respectively.

Table 4 shows results of the linear regression analyses in females adjusted for the confounding effects of variables that were significantly associated with the G-FCQ-T in correlation analyses. PSS scores were significantly associated with all subscales and the total score for the G-FCQ-T even after adjusting for other variables. The PANSS negative subscale was significantly inversely associated with positive outcome expectancy on the G-FCQ-T.

DISCUSSION

Weight gain in patients with schizophrenia begins in the early stage of the disease and rapidly worsens; thus, early intervention is important. In this study, we found that significant weight gain was prevalent in patients who recently started taking antipsychotic medications. Additionally, body weight and weight gain during treatment were significantly associated with food cravings in female patients with first-episode psychosis, but not in males. Associations between food cravings and psychological variables, such as perceived stress, were also prominent in females. There was no significant difference in the degree of food cravings or weight gain according to the type and dosage of antipsychotic drug being taken. To reduce food cravings and uncontrolled eating in patients with schizophrenia, and particularly in females, interventions aimed at perceived stress should be considered. To our knowledge, this is the first study to identify sex-specific associations among food craving,

TABLE 2 | Comparisons of psychiatric scale scores according to significant weight gain status for each sex.

	Female			Male		
	Weight gain ≥10% (*n* = 22)	Weight gain <10% (*n* = 61)	*p**	Weight gain ≥10% (*n* = 22)	Weight gain <10% (*n* = 45)	*p**
	M (SD)	M (SD)		M (SD)	M (SD)	
General Food Cravings Questionnaires-Trait						
Preoccupation	17.5 (6.3)	13.7 (6.2)	**0.013**	14.4 (6.5)	13.1 (6.1)	0.365
Loss of control	20.0 (5.2)	16.9 (6.9)	**0.027**	16.7 (6.9)	17.1 (7.0)	0.890
Emotional craving	14.1 (4.0)	12.3 (5.4)	0.140	12.5 (5.2)	10.9 (4.9)	0.188
Positive outcome expectancy	18.5 (5.0)	17.4 (5.3)	0.365	17.3 (5.1)	16.7 (5.9)	0.624
Total	70.0 (17.3)	60.2 (20.8)	**0.035**	60.9 (21.3)	57.7 (20.8)	0.445
Positive And Negative Syndrome Scale						
Positive	16.3 (5.8)	15.7 (5.1)	0.688	16.4 (4.3)	15.2 (4.2)	0.277
Negative	17.8 (5.3)	16.3 (3.8)	0.180	18.0 (4.6)	16.7 (4.9)	0.707
General	37.9 (9.2)	34.1 (6.7)	0.055	36.3 (6.8)	33.0 (7.7)	0.151
Total	72.0 (18.3)	66.0 (13.6)	0.139	70.7 (12.1)	64.8 (15.2)	0.229
Calgary Depression Scale for Schizophrenia	4.9 (4.9)	4.6 (3.7)	0.686	3.7 (3.6)	5.1 (4.2)	0.274
Social and Occupational Functioning Assessment Scale	54.5 (12.6)	61.0 (8.3)	**0.012**	58.6 (8.9)	59.8 (9.5)	0.851
Perceived Stress Scale	22.5 (3.1)	21.8 (2.9)	0.096	19.9 (5.5)	20.9 (6.6)	0.577
Rosenberg Self-Esteem Scale	25.7 (5.3)	28.0 (5.6)	0.096	27.3 (5.4)	25.0 (6.4)	0.149

**Adjusted for baseline body weight. All values of scales are described as mean (standard deviation). Values in bold show statistical significance.*
M, mean; SD, standard deviation; CDSS, Calgary Depression Scale for Schizophrenia; SOFAS, Social and Occupational Functioning Assessment Scale.

TABLE 3 | Correlation coefficients between the General Food Cravings Questionnaires-Trait scores and clinical characteristics for each sex.

	PANSS_P	PANSS_N	PANSS_G	PANSS_T	CDSS	SOFAS	PSS	RSES
Female								
Preoccupation	0.029	−0.049	0.191	0.094	**0.208***	−0.163	**0.346*****	**−0.212***
Loss of control	0.119	−0.008	**0.259****	0.171	**0.288****	−0.154	**0.400*****	**−0.274****
Emotional craving	−0.111	−0.189	0.016	−0.083	0.108	−0.053	**0.323****	−0.061
Positive outcome expectancy	−0.006	**−0.209***	0.012	−0.055	0.119	−0.065	**0.310****	−0.089
Total	0.019	−0.119	0.154	0.051	**0.220***	−0.134	**0.405*****	**−0.197***
Male								
Preoccupation	0.065	0.157	0.120	0.134	0.012	−0.011	0.145	−0.189
Loss of control	0.030	0.022	0.022	0.028	0.084	0.054	0.123	**−0.256***
Emotional craving	0.018	−0.038	0.138	0.067	0.117	−0.042	0.056	−0.140
Positive outcome expectancy	−0.046	−0.032	0.029	−0.009	0.220	0.067	0.050	−0.145
Total	0.022	0.037	0.085	0.064	0.109	0.022	0.112	−0.215

Values are Pearson correlation coefficients except those for the CDSS, which are Spearman correlation coefficients. Values in bold show statistical significance.
**p-value < 0.05; **p-value < 0.01; ***p-value < 0.001.*
PANSS_P, Positive symptom subscale of Positive And Negative Syndrome Scale; PANSS_N, Negative symptom subscale of PANSS; PANSS_G, General psychopathology subscale of PANSS; PANSS_T, Total score of PANSS; CDSS, Calgary Depression Scale for Schizophrenia; SOFAS, Social and Occupational Functioning Assessment Scale; PSS, Perceived Stress Scale; RSES, Rosenberg Self-Esteem Scale.

weight gain, and psychological factors in patients with first-episode psychosis.

This study results were consistent with previous studies on the general population showing that food cravings were associated with body weight (47) and weight gain (26). In this study, food cravings were associated with significant weight gain at the 3-month follow-up, in the female participants. Considering that the participants had a median length of 1 month and a median DUP of 3 months, baseline body weight was also likely influenced by weight gain after treatment and food cravings to enrolment in the study.

Sex differences in eating patterns have been noted in the general population, with women usually showing higher levels of dietary restraint and disinhibition than men (48). In addition, women usually partake in more comfort eating than men (49). Women have been found to be more likely to have more food cravings (50), and greater food consumption (51), appetite (52) and weight gain (52), in association with negative emotions.

TABLE 4 | Linear regression analysis to investigate correlates of the General Food Cravings Questionnaires-Trait (G-FCQ-T) after adjusting for age and other psychiatric scales in female population.

	G-FCQ-T total		Preoccupation		Loss of control		Emotional craving		Positive outcome Ex.	
	beta	*p*	beta	*p*	beta	*p*	beta	*p*	beta	*p*
Perceived Stress Scale	0.386	**<0.001**	0.318	**0.003**	0.312	**0.003**	0.328	**0.001**	0.352	**<0.001**
RSES	−0.013	0.905	−0.063	0.565	−0.078	0.458	–	–	–	–
CDSS	0.034	0.750	0.009	0.933	0.060	0.581	–	–	–	–
PANSS-Negative	–	–	–	–	–	–	–	–	−0.242	**0.010**
PANSS-General	–	–	–	–	0.080	0.423	–	–	–	–
Age	−0.169	0.066	−0.153	0.106	−0.196	**0.032**	−0.128	0.180	−0.089	0.339
R^2	0.220		0.168		0.247		0.139		0.179	

RSES, Rosenberg Self-Esteem Scale; CDSS, Calgary Depression Scale for Schizophrenia; PANSS_N, Negative symptom subscale of Positive And Negative Syndrome Scale; PANSS_G, General psychopathology subscale of PANSS; Ex., expectancy.
Values in bold show statistical significance.

Among our patients with schizophrenia, the females were also more likely to show an increase in food cravings due to psychological factors such as perceived stress.

The stress response is generated by activity in two interacting pathways: the sympathetic adrenal medullary system, in which the release of catecholamines is typical during periods of acute stress (53), and the hypothalamic–pituitary–adrenal (HPA) axis. Acute stress-related sympathetic arousal and glucocorticoid release promote fight-or-flight reactions, which support energy mobilization and gluconeogenesis. Stress-related sympathetic arousal results in redirection of blood flow from the gastrointestinal tract to skeletal muscle and the brain (54). Under an acute stress reaction, suppression of appetite and food intake may occur (55, 56). However, repeated and uncontrollable stress can lead to dysregulation of the HPA axis, which, if chronically activated, can alter glucose metabolism, promote insulin resistance, and influence multiple appetite-related hormones and hypothalamic neuropeptides (57, 58). Moreover, individuals under chronic stress tend to eat more under acute stress conditions and show consume more hyperpalatable, energy-dense "comfort food." (55, 59) These comfort foods can alleviate stress-related negative affect, as a form of self-medication, via inhibition of hypothalamic corticotropin-releasing factor (CRF) secretion (58, 60), or via temporary normalization of the dopaminergic reward circuit (61–63). Some previous studies have reported correlations between a high level of perceived stress, comfort eating, and decreased HPA activity (64, 65). Repeated stimulation of the reward pathways by palatable foods may lead to neurobiological adaptations that eventually increase food intake in association with food cravings (66–68).

Moreover, depressive symptoms, usually accompanied by chronic stress, are associated with a preference for snack/fast food and sweet food (30, 69), and food addiction (70). Increased intake of convenience food and physical inactivity, accompanied by negative emotional states, are predisposing factors for weight gain (71–73). A meta-analysis of 15 studies (74) showed that depression increased the risk of obesity by 58%. In this study, perceived stress and depression in female patients with first-episode psychosis was associated with food cravings, which could lead to weight gain. However, the effect of depression was not significant in regression analyses, although perceived stress was, suggesting mediating effects of stress on the association between depression and food cravings. The effects of perceived stress and concurrent negative mood on food cravings seen in the general population may also apply to females with early psychosis.

In this study, negative symptoms were inversely associated with positive outcome expectancy relative to food cravings. This finding indicates that negative symptoms such as avolition and anhedonia might inversely affect food cravings in a manner opposite the positive associations found between food cravings and emotional factors such as perceived stress and depression.

Low self-esteem and negative affect have frequently been hypothesized as key features of binge eating, including in the cognitive-behavioral model of bulimia nervosa (75), escape theory (76), emotional regulation theory (77), and schematic models of binge eating (78). These theories posit that individuals showing high self-awareness and negative self-evaluation eventually experience emotional distress, including anxiety and depressed mood, and use binge eating to try and resolve these emotional problems. This study on the relationships among depressive mood, perceived stress, and food craving suggests that these cognitive structures are also present in patients with first-episode psychosis. Furthermore, an association of low self-esteem with uncontrolled eating was seen. Uncontrolled eating has been associated with reward sensitivity and poor cognitive control, which are associated with impulsivity and maladaptive behaviors (79, 80). These traits might also mediate low self-esteem in patients with early psychosis.

This study had a few limitations. First, in this study, patients taking antipsychotics with a low to moderate propensity to cause weight gain (81) were selected, to control the influence of type of antipsychotic on weight gain and food cravings. Although the effect of antipsychotic type on food cravings was controlled, caution is required when generalizing the present findings to patients taking other types of antipsychotics associated with greater weight gain. Second, food intake was measured subjectively. Nevertheless, we found that weight gain, which frequently occurs in patients with schizophrenia, was affected not only by the type of antipsychotic, but also by self-reported food cravings. Finally, cultural differences

should also be considered when assessing the association between food cravings and weight gain in Western patients with schizophrenia.

Our study suggests that psychological mechanisms mediating weight gain in patients with schizophrenia may differ according to sex. Food cravings associated with weight gain in female patients with first-episode psychosis were influenced by emotional factors such as perceived stress. Interventions targeting perceived stress may be necessary to promote control of eating behaviors. Psychological factors and eating habits merit more attention, particularly in female patients with schizophrenia, to prevent weight gain. We believe that our findings can contribute to the development of effective interventions to prevent weight gain in patients with schizophrenia.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Chonnam National University Hospital Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Y-HK, MK, MJ, and S-WK have contributed to the conception and design of the study. S-WK and Y-CC organized the database. S-WK performed the statistical analysis. Y-HK wrote the first draft of the manuscript. SR, H-JN, J-YL, J-MK, and MS critically revised the draft. All authors read and approved the submitted version.

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Dietary Glutamic Acid, Obesity, and Depressive Symptoms in Patients With Schizophrenia

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Introduction: Schizophrenia is a lifelong condition associated with several comorbid conditions such as physical illnesses like obesity, as well as co-occurring psychiatric symptoms such as depression. Research regarding susceptibility to some of these comorbidities has primary focused on genetic risks or neurotransmitters and very little work has been done to understand environmental factors such as diet. In particular, understanding the role of dietary glutamic acid consumption on co-morbidities in patients with schizophrenia is important, as evidence suggests that glutamic acid consumption may directly influence glutamatergic neurotransmission; a key neurotransmitter related to schizophrenia, its associated co-morbidities, and depression. Therefore, the aim of this study was to examine the potential relationship between dietary glutamic acid and depressive symptomatology in patients with schizophrenia, stratified by obesity status, due to its relationship with inflammation, antipsychotic use, and depressive symptoms.

Methods: Subjects included in this analysis, were part of a parent cross-sectional study in which included three dietary recalls analyzed using protocols outlined as part of the National Health and Nutrition Examination Surveys (NHANES) standardized criteria. Additionally, body mass index (BMI), and Beck Depression Inventory were obtained at this visit. Subjects with a BMI $\geq$ 30 kg/m^2 were included in the obesity group, and the relationship between glutamic acid consumption and BDI scores was analyzed after controlling for age, race, sex, antidepressant and antipsychotic use, and animal and vegetable protein intake which provide natural forms of dietary glutamic acid.

Results: A total of 168 participants were included in this study, of which 42.5% were female and 52.9% were White. The mean BMI for the group as a whole was 33.5 $\pm$ 8.7 (kg/m^2) and the mean BDI was 14.5 $\pm$ 10.2 (range 2–50). No differences were found between obesity groups, other than a greater hyperlipidemia, hypertension, and lower waist to hip ratio. Overall, no relationship was found between dietary glutamic acid and BDI scores, However, for non-obese participants, diets higher levels of glutamic acid were associated with greater depression symptomatology ($p = 0.021$).

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Conclusion: These preliminary results indicate a possible correlation between dietary glutamic acid a depressive symptoms in non-obese patients with schizophrenia, although further research is needed to specifically examine this relationship.

Keywords: glutamate, diet, depression, schizophrenia, obesity

INTRODUCTION

For those diagnosed with a serious mental illness, such as schizophrenia, co-morbid psychiatric and physical illnesses are commonplace. In fact, the prevalence of depressive symptoms within this patient population is ∼40%, whereas the prevalence of obesity contributing to cardiovascular disease is upwards of 50% (1, 2). Why these conditions commonly co-occur is not fully understood, however genetic risk factors as well as common neurotransmitter pathways, have been identified (3, 4). Recently, research has focused on the role of glutamate, which acts primarily thorough the N-Methyl-D-aspartate (NMDA) receptor. Data shows that over activation of the NDMA receptors by glutamate can be neurotoxic and result in cell death (5). Additionally antipsychotics, like olanzapine and clozapine, used for the treatment of psychotic symptoms seen in persons with schizophrenia, can attenuate hyperglutamateric states resulting in their therapeutic effect, while also contributing to the occurrence of obesity and cardiovascular disease (6, 7). For depression, glutamate is also a neurotransmitter of interest, however its role is not as clearly understood (8, 9). Most work regarding glutamate's role has come from data showing that ketamine, a NMDA acting medication, is effective in the treatment of refractory depression, however, the mechanisms this therapeutic effect is not fully known (8).

In addition to glutamate neurotransmission, epigenomic relationships between obesity, cardiovascular disease, psychosis, and depressive symptoms have been reported (10). In particular, hypermethylation of genes common to known obesity and depression pathways [i.e., Brain Derived Neurotropic Factor (BDNF)] may trigger various inflammatory cascades, which link diet, obesity, and depressive symptoms (10–12). This work also supports findings reported by our group examining gene specific methylation differences between schizophrenia and cardiovascular risk factors (13–15). Thus, taken as a whole, the field needs to better understand the impact of environmental factors in patients with psychosis, as work regarding diet in schizophrenia spectrum disorder, and the occurrence of co-morbid disorders such as obesity, cardiovascular disease, and depressive symptoms is fairly limited (16–18).

The newly emerging field of nutritional psychiatry may provide some answers regarding this relationship as groups, such as ours, begin to examine the relationships between diet, obesity, and depression symptomatology. Key to this investigation is work that has focused on the role of dietary monosodium glutamate (MSG) in relation to psychiatric symptoms, pain response, and obesity. Emerging evidence suggests that MSG may directly influence glutamatergic neurotransmission, which underlies the pathophysiology of mental illnesses, including schizophrenia, and depressive disorders (8).

Chemically, glutamic acid is an amino acid necessary for the biosynthesis of glutamate, a key neurotransmitter. In a healthy diet, most glutamic acid is obtained through the consumption of meats, poultry, fish, eggs, and dairy products, as well as a few high protein vegetable sources. Monosodium glutamate (MSG) is the mono sodium salt form of glutamic acid, which is used as a food additive in commercially processed foods (19). Physiologically, both animal, and vegetable protein sources of glutamic acid, as well as the intake of MSG through processed foods, are key compounds used for the biosynthesis of glutamate. Glutamate is necessary for the functionality of key neurotransmitters and the body cannot distinguish between glutamic acid originating from animal and/or vegetable sources or MSG sources from processed foods. Thus, for individuals with diets high in processed foods, high MSG consumption may result in an abundance of glutamic acid, leading to hyperglutamatergic neurotransmission possibly contributing to psychiatric symptoms such as depressive symptoms (20).

Most research regarding the impact of MSG on mental health symptomatology comes from *in vitro* animal studies that have demonstrated a link between MSG consumption and the occurrence of anxiety and depression symptoms, as well as the occurrence of pain (21, 22). Briefly, rats exposed to MSG during early life are more likely to have behavioral patterns in line with animal models of depression and anxiety. Furthermore, limited data suggests that MSG administration in these rats leads to changes in brain morphology as seen by increased microglial cell density in the motor cortex, which occurred in a dose dependent manner (23). The authors hypothesized that these findings were indicative of hyperglutamateric neurotoxicity secondary to MSG administration.

In addition, MSG consumption is also linked to the occurrence of obesity, as studies have shown that rats exposed to MSG through subcutaneous injection during the first 10 days of life developed 20–42% higher body weights when compared to the control group (24). To add to this evidence, MSG has been used to induce obesity and diabetes in animals for further study (25). For human studies however, conflicting relationships have been observed between MSG consumption, body weight, and obesity (19, 26). Thus, further studies need to be done, especially given that other groups have reported preliminary relationships between MSG consumption and pain (27, 28), in patients diagnosed with myofascial temporomandibular disorders or fibromyalgia. Additionally, other groups have found that in healthy individuals, MSG consumption was also associated with 6-fold greater incidence of pain symptoms when compared

to ingestion of an equivalent amount of sodium chloride (27–29).

Therefore, overall very little is known regarding dietary MSG and the occurrence of psychiatric symptoms in humans, and how obesity may alter patterns of association. Thus, with this in mind, the primary purpose of this investigation was to evaluate the relationship between dietary glutamic acid consumption, and depressive symptoms in obese and non-obese patients with psychotic disorders. We hypothesized that overall, there would be a positive association between dietary glutamic acid consumption and increasing depressive symptoms for schizophrenia subjects, and that this relationship would vary by obesity status.

METHODS

Participants

Study participants included in this investigation, were part of a larger cross-sectional study that has been described elsewhere (30). Briefly subjects were included if they met the following inclusion criteria (i) aged 18–90 years; (ii) had a diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, psychosis not otherwise specified (NOS), using the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria; and (iii) had been treated with an antipsychotic for 6 months. Participants were excluded if they were (i) unable to give informed consent or unwilling to participate; (ii) had an active substance dependence diagnosis; or (iii) had a documented history of type 2 Diabetes Mellitus prior to the antipsychotic use. Participants were recruited from outpatient clinics in the Southeastern Michigan region. The study was approved by the University of Michigan Medical School Institutional Review Board, the Washtenaw County Health Organization, the Ann Arbor Veterans Affairs Medical Center, and the Detroit Wayne County Community Mental Health Agency. The following assessments were collected as part of the parent study, and were used in this analysis.

Assessments

All participants included in this analysis, provided written informed consent at their first study visit followed by a clinical interview, which included a psychiatric diagnostic assessment using the structured clinical interview for DSM-IV (SCID) (31). The Beck Depression Inventory (BDI) was used as the primary assessment for depressive symptomatology as this scale has demonstrated to be a reliable and valid measure of depressive symptoms in patients with schizophrenia (32). Subjects also answered questions regarding current and past medications, as well as current and previous medical history, which included information regarding comorbid conditions (i.e., hypertension, diabetes, and hyperlipidemia). These data were confirmed through review of each subjects' electronic health record. To standardize antipsychotic use/exposure, chlorpromazine (CPZ) equivalents were calculated for every participant using standardized methods (33, 34). Subjects also underwent a brief physical assessment which included height, weight, and hip and waist circumference. Both the height and weight measurements were used to calculate Body Mass Index (BMI). Subjects with a BMI $\geq$ 30 kg/m^2 were considered obese while those with a BMI below this threshold were placed in the non-obese group.

Additionally for the parent study, subjects were asked to complete a 24 h food recall, conducted by the study's registered dietician, where each subject was guided in recalling all foods eaten within the 24 h before their study visit. This assessment was then repeated twice by phone on random occasions within 10 days after the in-person study visit, for a total of three recalls assessments. The dietary staff used standard protocols outlined as part of the National Health and Nutrition Examination Surveys (NHANES) training and used standard measuring guides to help the patients remember the volume and dimensions of food they consumed in the previous 24 h. Nutritional data from this information was calculated using the Nutrition Data Systems for Research (NDSR) software developed by the Nutrition Coordinating Center (NCC) at the University of Minnesota (35). For the current analysis, data were averaged across the three dietary recall occasions in terms of nutrient values. As the nutritional output from this assessment does not specifically measure MSG content, dietary intake related to glutamic acid, was used as a surrogate measure of MSG consumption, controlling for animal and vegetable protein intake, in each analysis, in order to determine excessive glutamic acid consumption.

Statistical Analysis

Analyses were done using SPSS Statistics version 23 to analyze the relationship between dietary intake of glutamic acid and BDI scores in all subjects, as well as subjects stratified by obesity status (BMI $\geq$ 30 kg/m^2; 24). Differences in baseline subject characteristics between the obese and non—obese groups were conducted using a chi—squared analysis to compare categorical variables and a *t*-test for continuous variables. A hierarchical regression tested the independent association between dietary intake of the glutamic acid, and depression symptoms assessed using the BDI, controlling for age, sex, race, antidepressant usage, CPZ equivalents, as well as animal and vegetable protein intake.

RESULTS

The study sample included 168 patients with baseline characteristics described in **Table 1**. Overall, the sample was 45.2% female and primarily White (52.9%). The mean BMI for the group as a whole was 33.5 $\pm$ 8.7 (kg/m^2) and the mean BDI 14.5 $\pm$ 10.2, indicating mild depressive disturbances, however the range was 2–50. In terms of demographic differences between the obese and non-obese groups, on average, the obese group was older, had a higher proportion of women, included more White subjects, and had higher rates of hypertension and hyperlipidemia, and lower waist to hip ratio indicating greater central adiposity (**Table 2**). There were no significant differences in mean dietary glutamic acid and mean vegetable protein, but the mean animal protein consumed was significantly higher in the obese group (~58 grams) compared to the non—obese group (~49 grams). There were no differences in BDI scores or antidepressant use between the two groups.

TABLE 1 | Baseline subjects characteristics.

Baseline characteristics ($N = 168$) [Mean ± Standard Deviation]	
Mean age (years) (range)	45.4 ± 11.9 (19–71)
Female (%)	76 (45.2)
Mean body mass index (BMI) (kg/m^2) (range)	33.5 ± 8.7 (20–58)
Waist/hip ratio (range)	0.96 ± 0.08 (0.78–1.17)
White/caucasian (%)	89 (52.9)
Black/african american (%)	74 (44.3)
Total beck depression inventory (BDI)	14.5 ± 10.2 (2–50)
Diabetes (%)	38 (22.6)
Hyperlipidemia (%)	66 (39)
Hypertension (%)	66 (39)
Current antidepressant use (%)	118 (70)
Chlorpromazine (CPZ) equivalent (mg)	642.2 ± 1249.7 (180–2,000)
Energy (kcal/day) (range)	2,035 ± 763 (1,918–4,793)
Glutamic acid intake (grams/day) (range)	15.5 ± 6.7 (6.06–40.9)
Vegetable protein intake (grams/day) (range)	25.5 ± 11.9 (5.9–61.5)
Animal protein intake (grams/day) (range)	54.4 ± 27.7 (18.1–199.2)

Overall, when examining the entire subject group, glutamic acid was not associated with BDI scores after controlling for age, sex, race, antidepressant use, CPZ equivalents in normal control populations or other sources of dietary glutamic acid (i.e., vegetable and animal protein sources) ($p = 0.42$). However, in the models stratified by obesity status, higher glutamic acid level was correlated with higher BDI scores after controlling for animal and vegetable protein sources of glutamic acid ($B = 2.389$, s.e. $= 1.04$, $p = 0.021$), whereas this was not found for the obese subjects ($B = -0.438$, s.e. $= 0.65$, $p = 0.662$). For both of these analyses, age, race, sex, CPZ equivalents and antidepressant use, were controlled for in an effort to reduce variability. Each of these analysis had ∼a $\beta = 0.7$.

DISCUSSION

Overall, the results of this investigation showed a correlation between greater dietary intake of glutamic acid and increased depressive symptoms among non—obese participants with a schizophrenia spectrum diagnosis. Of note, the participants' level of depressive symptoms, indicating mild mood disturbances, was similar between the two groups, as was current use of antidepressants. Regardless, these results add to the growing evidence regarding the role of dietary additives such as MSG within the field of psychiatry, food additives constitute the highest source of glutamic acid following food, and vegetable protein sources (36). To our knowledge, this is the first investigation to examine the relationships between dietary intake of glutamic acid and depressive symptoms within patients with psychosis, stratified by obesity status.

In examining our subjects' diets, mean glutamic acid consumption was 15.5 grams (range 6–41) which translates in to ∼0.2 grams/kg. This is significantly higher than the average of 12 grams/day, commonly seen in a general westernized diet, which is ∼0.15 grams/kg for an 80 kg person (37, 38). Physiologically, serum glutamate concentrations have been shown to increase by 250–500% compared to baseline after bolus administration and these elevations are maintained for sustained periods of time, although this is dose dependent (39, 40). Therefore, sustained glutamate serum concentrations due to continuous administration during meals, may be a contributing factor to the occurrence of co-morbid conditions such as obesity and/or depressive disorders. However, it is often difficult to extrapolate results between different subject groups, which necessitates investigations specific to patients with mental illness.

Currently, most data regarding the neuropsychiatric effects of MSG consumption has focused on the occurrence of pain in patients with fibromyalgia or temporomandibular disorders (27, 28, 41). However, while pain did increase in these subjects compared to controls, MSG administration also resulted in more depressive symptomology, specifically greater difficulty concentrating (60 vs. 39%), problems sleeping (83 vs. 53%), impaired attention span (48 vs. 43%), or overall brain fog (61 vs. 48%) (28). Thus, the clinical adverse effects seen may have occurred due to the high risk for psychiatric co-morbidity associated with their neuropsychiatric conditions, similar to our patients with their schizophrenia spectrum diagnosis. Thus, while dietary MSG consumption in general is associated with no or few adverse effects, some patients populations may be at greater risk for significant adverse effects, or may be unknowingly consuming higher doses of glutamic acid which may contribute to these adverse effects (20).

Mechanistically, dietary glutamic acid may be exerting these clinical effects through serotonergic and HPA dysfunction, as animal research has found significantly higher serum levels of cortisol and ACTH, and increased 5-HT uptake in cerebral cortices of rats following MSG administration compared to placebo (21, 42, 43). Additionally, these effects in animals have been found to be reversed by 7,8-dihydroxyflavone, a brain-derived neurotrophic factor/tropomyosin receptor kinase B (BDNF/TrkB) agonist, which mechanistically may reverse glucocorticoid receptor phosphorylation (44). This finding in particular is important to this investigation, as BDNF hypermethylation has been previously reported as a link between obesity and depression in addition to its role in schizophrenia pathophysiology (10, 12, 45). Taken together then, these data suggest that the both the metabolic and behavioral effects of MSG may occur through epigenomic modulation potentially impairing the hypothalamic-pituitary-axis (HPA) feedback inhibition.

Therefore, the results of our study add to the literature regarding the role of dietary glutamic acid concentrations and depressive symptoms in patients diagnosed with schizophrenia spectrum disorder. Although overall, we did not find a relationship between dietary glutamic acid and depressive symptoms overall, we did find differences in the non—obese subject group. The effect seen in this group may be due to fewer cardiovascular risk factors contributing to depression in these individuals, resulting in a greater impact regarding dietary glutamic acid consumption. Additionally, as previously discussed, the role of co-occurring conditions such as obesity,

TABLE 2 | Subject demographics stratified by obesity.

	Non-obese (<30 kg/m^2) (*N* = 60)	Obese (≥ 30 kg/m^2) (*N* = 108)	*P*-value
Demographics (means ± standard deviation)			
Age in years	42.8 ± 12.5 (19–70)	46.7 ± 11.2 (22–71)	0.038
Total number of female subjects (%)	21 (35)	53 (49)	0.045
Total number of white subjects (%)	21 (35.5)	53 (49)	0.32
Total beck depression inventory (BDI)	13.2 ± 10.6 (2–43)	15.2 ± 10.0 (3–50)	0.23
Comorbid conditions			
Waist/hip ratio	0.92 ± 0.08 (0.78–1.14)	0.98 ± 0.08 (0.83–1.17)	<0.0001
Diabetes (%)	10 (16.7)	28 (25.9)	0.129
Hyperlipidemia (%)	16 (26.7)	50 (46.3)	0.023
Hypertension (%)	14 (23.3)	52 (48.2)	0.001
Medications			
Chlorpromazine (CPZ) equivalents (mg)	548 ± 618 (200–1,800)	695 ± 1,483 (180–2,000)	0.473
Current antidepressant use (%)	38 (63.3)	81 (74.8)	0.12
Dietary parameters			
Total caloric intake (kcals/day) (range)	2,062 ± 749 (1,096–4,793)	2,027 ± 791 (1,110–4,436)	0.70
Glutamic acid intake (grams/day)	14.30 ± 4.97 (6.75–25.4)	16.14 ± 7.37 (7.8–37.8)	0.086
Vegetable protein intake (grams/day)	24.79 ± 11.14 (16–54.7)	25.84 ± 12.29 (12–58.4)	0.583
Animal protein intake (grams/day)	48.56 ± 20.48 (25–126)	57.61461 ± 30.63 (23–199)	0.042

which potentially influences differing inflammatory cascades due to epigenomic modulations, may have also impacted this relationship and mask any correlations between glutamic acid consumption and depressive symptomatology in our obese subjects (46, 47).

Regardless, these relationships should be considered preliminary as future research needs to directly examine the role diet and in particular, MSG consumption on not only depressive symptomatology, and psychotic symptoms in patients with a schizophrenia spectrum diagnosis, but also epigenomic mechanisms behind these potential relationships.

LIMITATIONS

Given the exploratory nature of this study, a few limitations to this work need to be addressed. First, glutamic acid was used as a surrogate measurement for MSG since we were unable to directly measure MSG intake as part of this study. Currently, the Food and Drug Administration (FDA) requires that foods containing MSG note monosodium glutamate as part of their ingredient panel, but it is not currently necessary to quantify the amount of MSG included (21). This limitation is not unique to this investigation, and speaks to the need to continue research examining the relationship between dietary glutamic acid consumption and health effects. In order to overcome this limitation, many studies will place subjects on controlled MSG free diets, or give subjects supplementary doses of MSG. However, for individuals with mental illness, these interventions may be associated with an increased risk of symptom relapse and therefore might not be appropriate. Furthermore, although this study did not measure serum glutamate levels, previous work shows that MSG administration in humans leads to variable changes in serum glutamate concentrations due to unknown reasons (48). Thus, this variability, and our lack of glutamate serum concentrations may also partly explain why our primary significant finding were only seen in the non-obese group, as the mg/kg "dose" of MSG consumed in the obese group would have been smaller. Thus, future work will need to take this under consideration as we examine the relationship between MSG consumption, serum glutamate, and psychiatric symptomatology. We also need to acknowledge that the use of a 24 h food recount in patients with schizophrenia spectrum disorders may be a limitation due to memory recall issues. Lastly, the lack of a control group in the analysis, as well as the small sample size, and in particular the small number of subjects within the non-obese group, are also limitations of this work.

Despite these limitations, this study also exhibited a few strengths, such as the use of the 24 h food frequency questionnaire given on three separate occasions, as this dietary recall data is considered the gold standard and the same methodology used as part of the National Health and Nutritional Examination Study (NHANES) (49). Previous work examining diet has used dietary diaries or 1 day of diet data, resulting in limited validity, particularly among patients with psychotic, and mood disorders who may have memory deficits (50–52).

CONCLUSION

In summary, this current study found a correlation between greater dietary intake of glutamic acid and greater depressive symptoms in non-obese adults with a schizophrenia spectrum diagnosis. In contrast, there was no correlation between dietary glutamic acid and depressive symptomology in obese participants. These preliminary

observational findings warrant replication and add to the growing evidence on the role of environmental factors, such as diet modifications, as adjunctive non-pharmacological approach for reducing psychiatric symptoms in serious mental illness.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: contain protected heath information. Requests to access these datasets should be directed to Vicki Ellingrod, vellingr@med.umich.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Michigan IRBMED. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PK, AK, and VE: study design, data collection and analysis, and manuscript preparation. AP and AR: data analysis and manuscript preparation. All authors contributed to the article and approved the submitted version.

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REVIEW
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The Burden of Antipsychotic-Induced Weight Gain and Metabolic Syndrome in Children

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Antipsychotic medications are critical to child and adolescent psychiatry, from the stabilization of psychotic disorders like schizophrenia, bipolar disorder, and psychotic depression to behavioral treatment of autism spectrum disorder, tic disorders, and pediatric aggression. While effective, these medications carry serious risk of adverse events—most commonly, weight gain and cardiometabolic abnormalities. Negative metabolic consequences affect up to 60% of patients and present a major obstacle to long-term treatment. Since antipsychotics are often chronically prescribed beginning in childhood, cardiometabolic risk accumulates. An increased susceptibility to antipsychotic-induced weight gain (AIWG) has been repeatedly documented in children, particularly rapid weight gain. Associated cardiometabolic abnormalities include central obesity, insulin resistance, dyslipidemia, and systemic inflammation. Lifestyle interventions and medications such as metformin have been proposed to reduce risk but remain limited in efficacy. Furthermore, antipsychotic medications touted to be weight-neutral in adults can cause substantial weight gain in children. A better understanding of the biological underpinnings of AIWG could inform targeted and potentially more fruitful treatments; however, little is known about the underlying mechanism. As yet, modest genetic studies have nominated a few risk genes that explain only a small percentage of the risk. Recent investigations have begun to explore novel potential mechanisms of AIWG, including a role for gut microbiota and microbial metabolites. This article reviews the problem of AIWG and AP metabolic side effects in pediatric populations, proposed mechanisms underlying this serious side effect, and strategies to mitigate adverse impact. We suggest future directions for research efforts that may advance the field and lead to improved clinical interventions.

Keywords: child psychiatry, pediatrics, antipsychotics, antipsychotic-induced weight gain, adverse drug effects, metabolic syndrome

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INTRODUCTION

In the 1950s the first antipsychotic (AP) medication, chlorpromazine, became available for adults. These first-generation antipsychotic (FGAs) drugs made it possible to stabilize severe mental illness that previously required long-term institutionalization. While FGAs revolutionized the practice of psychiatry, serious motor adverse effects were common (1). This prompted the introduction of the first atypical antipsychotic (second-generation antipsychotic, SGA), clozapine, in 1990. SGA

prescriptions soon dominated due to their reduced motor side effects and benefit in treating negative symptoms compared to FGAs (2, 3). SGAs also cause considerable morbidity, however, predominantly through antipsychotic-induced weight gain (AIWG) and metabolic dysfunction (1). Nevertheless, SGAs continue to represent the standard of care (93% of AP prescriptions as of 2008) (4), including for children and adolescents (age $\leq$ 19) (5).

The already dire prevalence of pediatric obesity and metabolic syndrome (6) is compounded by increasing global trends in pediatric AP prescribing, with children potentially accumulating risk over decades of pharmacotherapy. The mechanisms underlying these adverse effects are poorly understood, and consequently, few mitigating or alternative options are available to clinicians. This review will first outline AP exposure in the pediatric population, metabolic health consequences of pediatric AP treatment, and moderators of risk for adverse events (AEs). Next, an overview of proposed mechanistic pathways will be provided. Finally, we will summarize strategies to mitigate adverse impacts of these necessary therapeutics and synthesize a decision support algorithm for clinicians. We will conclude with future directions for research and treatment. An understanding of the biological underpinnings of metabolic AP effects is crucial to preventing negative physical and mental outcomes of youth in need of AP therapy and to designing new targeted treatments without burdensome side effects.

SEARCH STRATEGY, SELECTION CRITERIA, AND DEFINITION OF TERMS

In this narrative review, we attempted to limit bias and ensure comprehensiveness through broad search strategies. We searched PubMed, using the search terms "antipsychotic-induced weight gain," "metabolic syndrome," "cardiometabolic," "pediatric OR adolescents OR child OR children," "obesity," "diabetes," "second generation antipsychotics," "neurohormone," and "neuroendocrine." Our search included articles published on PubMed through October 30th 2020. Publications were selected based on relevance, with priority given to publications from human research on antipsychotic-induced weight gain and metabolic effects from the past 10 years. We prioritized data from pediatric populations and provided adult data when this was lacking. With regard to treatment studies, we prioritized randomized controlled trials, systematic reviews and meta-analyses. With regard to genetic studies, we prioritized unbiased genome-wide studies. We also searched the reference list from articles and reviews identified by this strategy to select additional relevant titles. We supplemented the search with reviewer recommendations.

We use the following terms as defined by the American Association of Child and Adolescent Psychiatry (AACAP): "child" or "children" will refer to patients ages 5 to 12 years (or zero to 12 when specified), "adolescent(s)" to those between the ages of 13–17 years (inclusive) and "youth" to patients between ages 5 and 18 (7).

ANTIPSYCHOTIC EXPOSURE IN YOUTH

Prescription rates of psychotropic medications vary by country, with US utilization exceeding that in Europe (8). A 2019 analysis of international data revealed that the highest prevalence estimates ($\sim$3%) for AP prescriptions in children and adolescents (age $\leq$ 19) occur in Taiwan and the US (9). A 2014 survey revealed that AP prescription rates are higher in publicly (2%) vs. privately (0.7%) insured US children and adolescents (0–19 years) (10). In the outpatient setting, the SGA most frequently prescribed to children aged 0-13 is risperidone (42.1%), followed by aripiprazole (28.0%), quetiapine (19.2%), and olanzapine (4.4%) (11).

Despite their name and primary use in treating psychosis, AP treatment is supported by evidence for a range of psychiatric disorders. Aggression, and not psychosis, is the most common symptom targeted by AP administration to youth (12–17). The National Ambulatory Medical Care Survey reported that from 2005–2009, APs were prescribed in 31.3% of outpatient visits for youth (age $\leq$ 20, $n = 527$) with mood disorders (11). The Food and Drug Administration has approved SGAs for use in children and adolescents with schizophrenia, type I and II bipolar disorder, Tourette disorder, and irritability related to autism spectrum disorder. Prescribing trends have shown an increase in SGA prescriptions for younger children (5, 18–24), including off-label use for childhood ADHD and depression for which AP therapy has limited evidence-base (22).

The typical reported duration of pediatric AP treatment varies. In a cohort of Australian patients <15 years of age prescribed APs ($n = 901$), the average duration of overall AP use was 2.4 years (25). The AP with the longest duration of use for this cohort was haloperidol followed by risperidone, chlorpromazine, olanzapine, quetiapine, aripiprazole, and lastly amisulpride. The most prescribed AP for this age group, risperidone, had a mean use of 2.25 years. In a Canadian Cohort of pediatric patients prescribed an SGA the most common diagnosis was ADHD, Mood Disorder, Conduct Disorder, or Psychotic Disorder. The median duration of risperidone, the most prescribed SGA for this cohort, was 179, 334, and 408 days for children aged 1–6 ($n = 1{,}341$), 7–12 ($n = 17{,}356$), and 13–18 ($n = 32{,}604$), respectively (26). A Medicaid-insured birth cohort examining trends in psychotropic prescription rates and medication use found that among 7-year-old children prescribed APs, 50.6% continued use for 6 months or more (27). Median duration of AP use increased with age, from 57 days in children aged 3 ($n = 9$) to 193 days in children aged 7 ($n = 193$). In this cohort only 15% of those prescribed an AP had a diagnosis of autism spectrum disorder, schizophrenia or bipolar disorder, revealing a trend of off-label AP prescriptions.

Weight gain is commonly reported by patients and physicians as an important factor in non-adherence (28–30). Discontinuation of pediatric AP treatment is common and determining the long-term severity of AEs after discontinuation is a concern (28–33). Both a naturalist study of (29) first-episode psychosis ($n = 110$, age range = 9–17, mean age = 15.3) treated with olanzapine, clozapine, or quetiapine and a controlled study (28) of early-onset schizophrenia spectrum disorder ($n = 116$,

age range = 8–19) treated with olanzapine, risperidone, or molindone found that discontinuation of AP use within 12 months is the norm. In both studies, the main reasons cited by patients for discontinuation were insufficient response and AEs such as weight gain.

METABOLIC EFFECTS OF ANTIPSYCHOTICS IN YOUTH

Metabolic syndrome is a cluster of signs and symptoms, including insulin resistance, dyslipidemia, and hypertension, that increases subsequent risk of type 2 diabetes, heart disease, and stroke (**Figure 1**). APs can adversely impact metabolic function through direct effects on lipids and insulin sensitivity and indirect effects on these parameters as a result of AIWG and obesity (34–36). AIWG can be substantial, with average weight gain over a 12-month period measured at 5 kg, corresponding to a BMI increase by 1.5 in children and adolescents (mean age = 12, age range = 6–18, n = 200) (37). Importantly, AIWG increases the risk of obesity, which is predictive of both adult type 2 diabetes and adult metabolic syndrome (38). The International Childhood Cardiovascular Cohort Consortium consisting of 5,803 participants found a 2.4-fold increased risk for adult metabolic syndrome in children that are overweight with metabolic metrics above the 75th percentile from 5 years of age onward (39). Additionally, this study found increased risk (risk ratio = 2.6–4.1) for type 2 diabetes for children 8 years and older that were overweight and met 2 metabolic syndrome criteria.

Several studies have indicated that SGAs are associated with increased risk for metabolic symptoms. Results of a 2018 systematic review of 126 studies report AEs of APs in pediatric populations showed that compared to placebo, SGAs were associated with elevated triglyceride levels, weight gain, increased risk of type 2 diabetes, and unfavorable lipid changes (34). While this included only subjects under 18 years of age, the mean age across the studies was > 8 years, reducing its applicability to younger children. The SATIETY cohort (age range 4–19, mean age = 13.9, n = 205) study observed mean level increases in serum total cholesterol (15.6 mg/dL: both low-density lipoprotein, high density lipoprotein) and triglyceride (24.3 mg/dL) levels to increase with just a median of 10.8 weeks of exposure to SGAs (40). Further, patients developed dyslipidemia (17.1%), insulin resistance (8.6%), and metabolic syndrome (1.6%). In a mixed diagnosis comparison study of metabolic changes in adolescents (N = 179, age range = 12–18, mean age = 15.8) vs. adults (N = 4,280) receiving at least 24 weeks of olanzapine treatment, adolescents were found to have greater mean increases in fasting total cholesterol, LDL and triglyceride levels as compared to adults, while increases in fasting glucose levels were similar (41). Despite greater vulnerability, children and adolescents are less likely than adults to have their metabolic parameters monitored during AP treatment (37).

Type 2 diabetes has been implicated as a long-term AE of AP treatment in children and adolescents (42–45), as well as in adults (42, 43, 46). Studies examining this association are inconsistent. A retrospective study (47) evaluated South Carolina medical and pharmacy claims of children/adolescents receiving AP monotherapy (n = 30) or AP plus antidepressant treatment (n = 274) with type 2 (or misclassified type 1) diabetes did not attribute psychotropic medication as an explanatory factor of diabetes; however, causality cannot be inferred with a retrospective design and final group sizes are underpowered for most comparisons. Another retrospective cohort study (48) of outpatients (mean age 41.9, SD = 21.5) administered SGAs (n = 10,265), FGA (n = 4,607), antidepressants (n = 60,856), or antibiotics (n = 59,878) and a systematic review (n = 258,597 aged 0–5, n = 294,722 aged 6–11, and 331,339 aged 12–17) attributed risk of diabetes to non-specific factors given similar rates of diabetes with both APs and antidepressants (48, 49). A final retrospective national cohort study (age range = 10–18, 59.8% age 10–14, 40.2% age 15–18, n = 107,551) of youth receiving AP treatment reported higher risk of type 2 diabetes when antidepressants are used concomitantly with APs (45). Studies are also contradictory with regard to the relationship between risk for diabetes and age, with some reporting greater risk in older adolescents (44, 50) and others in younger patients (42). Although, there have been inconsistent findings for pediatric AP treatment and subsequent type 2 diabetes, data is strong enough to warrant regular physician monitoring of glucose levels (42, 44, 51).

RISK FOR ANTIPSYCHOTIC-RELATED METABOLIC EFFECTS

Negative metabolic consequences and AIWG affect up to 60% of patients receiving APs, with the highest risk to children (40, 52–57). A multicenter naturalistic observational study (ETAPE) performed a 12-month follow up of AEs for 200 youth (mean age = 12, 92% prescribed SGAs) and found that the overall AE incidence rate was 11.52 AEs per person-years (37). For the AEs attributable to APs, 12.2% were related to metabolic or neuroendocrine parameters and included elevated cholesterol (>170 mg/dl) and triglycerides (≥100 mg/dl) (36.3%), hyperprolactinemia (>25 ng/ml) (38.5%), vitamin D deficiency (<30 ng/mL) (36.6%), hyperphagia (67.4%), and diabetes (7%). For the AEs recorded, more than half had incidence during the first 3 months of treatment. Moreover, children are more vulnerable to both the adverse physical and emotional effects of SGAs (24). As a result of this increased vulnerability, non-adherence in youth is prompted by changes in their physical appearance leading to body image issues (58) and negative peer perception (59).

Studies have shown that adverse health effects in youth increase with duration of treatment (60, 61) and that a younger age of AP use is associated with increased AIWG vulnerability (62), as well as AEs associated with obesity such as cardiovascular and metabolic complications (62–65). As research shows that most pediatric AIWG occurs within the first 12 weeks of administration (40, 65, 66), even relatively short-term treatment can result in considerable weight gain. First-episode psychosis is also a risk factor for greater weight gain, likely due to multiple factors (40, 67–69) such as younger age, lack of previous antipsychotic exposure, and less established

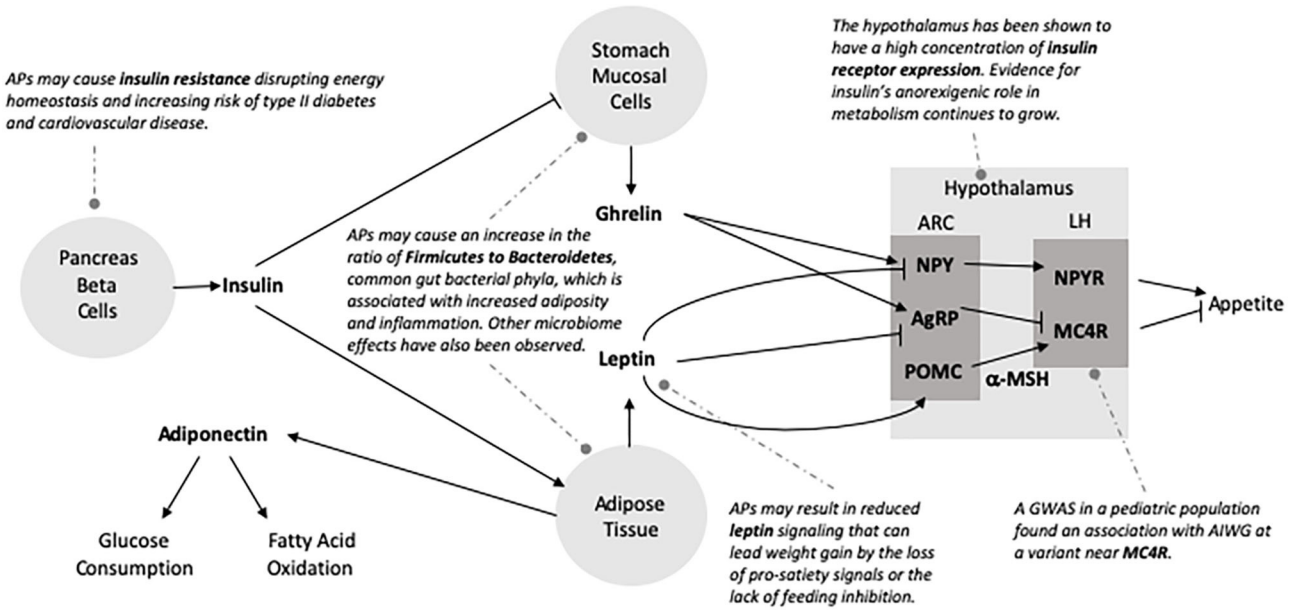

FIGURE 1 | The associated burden of pediatric antipsychotic treatment. Antipsychotic use is associated with weight gain, increased fasting lipids (total cholesterol, LDL, and triglyceride levels), and impaired glucose tolerance in pediatric patients. Subsequently, this population is at an increased risk of obesity, metabolic syndrome and type 2 diabetes. Although pediatric patients are more vulnerable to these adverse side effects, they are less likely to have their metabolic parameters monitored during AP treatment.

participation in psychiatric treatment. Regular monitoring of adverse cardiometabolic effects for pediatric patients prescribed APs is standard of care (21, 70–77). Given accumulating risk over time and earlier age of initiation, longitudinal studies for pediatric AP use are highly warranted.

Propensity for weight gain and metabolic effects varies among AP agents. A 2018 network meta-analysis of 28 studies of pediatric AIWG (mean age = 14.41, 58% male) (78) found that molindone, lurasidone, and ziprasidone were relatively benign while clozapine, quetiapine, and olanzapine resulted in the greatest weight gain. Paralleling the adult literature, clozapine demonstrated both the greatest efficacy and side effect burden in youth. Importantly, medications touted to be weight neutral in adults behave differently in children. Aripiprazole, for example, has been noted to produce weight gain equivalent to or greater than risperidone in 2 pediatric studies (79, 80). The relationship of AP dose to AIWG remains unclear and may vary with time and across specific APs (81–83). Concomitant medications can also alter risk in either direction; for example, stimulants have been associated with attenuated (83) and mood stabilizers with compounded (84) risk for AIWG.

Diagnostic differences in weight gain have also been examined. A systematic review of children receiving AP treatment ($n = 3{,}048$) found that children diagnosed with autism spectrum disorder had higher propensity for weight gain, but this could be a result of younger age at treatment or lack of previous exposure to APs (66). Additionally, in a cohort of youth with schizophrenia or schizoaffective disorder, the Treatment of Early-Onset Schizophrenia Spectrum Disorders Study found that schizoaffective diagnosis predicted greater weight gain for risperidone prescribed youth ($n = 119$, age range = 8–19, $p = 0.004$) (85).

Considerable variability in weight gain and metabolic effects exists between individuals (86), though this variability is poorly understood. As previously discussed, young and antipsychotic-naïve patients are at particularly high risk, gaining 3–4-fold more weight irrespective of the specific AP (67). Few other patient-specific moderators of AIWG have been confirmed. Both higher and lower baseline BMI have been reported to predict AIWG in children (83, 87), which is complicated by confounding with age, AP exposure, and the expectation that extreme BMI values will regress toward the mean (83, 88). Reports of sex effects are also inconsistent, with studies claiming female (46, 89–91), male (63, 92), or equal (80) predominance of weight gain; though boys are prescribed APs more frequently than girls, paralleling male preponderance of many indications for AP administration (autism, Tourette, aggression). While AIWG and metabolic AEs appear to be a worldwide phenomenon, ethnicity and socioeconomic status may influence risk magnitude (92–94). APs are disproportionately prescribed more frequently to those in foster care (95) and to those with public insurance (96, 97).

Only a few studies have addressed the reversibility of AIWG (30–33). Two of these studies reported that AIWG in children and/or adolescents was reversible but are limited by small sample size ($n = 14$, mean age = 11.5; and $n = 18$, mean age = 9.68) and the inclusion of subjects who did not gain weight during AP treatment (31, 33). More moderately-sized studies showed contradicting results (30, 32). In a secondary analysis of AIWG

in a pediatric placebo-controlled, cross-over study (age range = 5–17, mean age = 11.1, $n = 527$) of risperidone treatment of disruptive behavior disorders, those receiving placebo after 12 weeks of treatment underwent an average decrease of 0.2 kg (*SD* = 2.2 kg) over 6-months compared to an average of 3.2 kg (*SD* = 2.49 kg) gained during the treatment period (32). Upadhyay et al. (30) performed the most robust study to date, which showed only a fraction of weight gained during AP treatment is lost (average of +7.85 kg during treatment and−3.39 kg after 12-months discontinuation). This study limited its analysis to individuals who experienced any weight gain after AP treatment for a bipolar diagnosis before the age of 18 ($n = 146$). To date, it is unclear the extent to which pediatric AIWG is reversible. It is essential that future studies investigate the persistence of long-term metabolic outcomes in the context of AP discontinuation.

MECHANISMS UNDERLYING ANTIPSYCHOTIC-RELATED METABOLIC SYNDROME AND AIWG

Multiple mechanisms have been hypothesized to influence pediatric AIWG and metabolic effects of APs. It is likely that AEs are due to a combination of these mechanisms including AP influence on neurohormone receptor signaling and hormone mediation of APs, predisposition due to genetic risk factors, and AP effects on the gut microbiome. This review will summarize the main aspects of these mechanisms, as each has been thoroughly reviewed by other authors.

Neurotransmitter Receptor Signaling

APs bind, with various affinities, to serotonin (5-HT), dopamine, histamine, adrenergic, and muscarinic cholinergic receptors (98–102). Several extensive reviews are available on neurotransmitter signaling as a potential mechanism in AIWG (**Table 1**) and metabolic effects of APs (101, 102, 112).

Serotonin Signaling

Compared to FGAs, SGAs have greater affinity for 5-HT receptors than for dopamine receptors, conferring their reduced extrapyramidal side effects and superior efficacy in treating negative psychotic symptoms (2, 3) leading to preferential use in children (101, 113). Of the 5-HT receptors, SGA blockade of the serotonin 2C receptor (5- HT_{2C}R) has been the most comprehensively studied. Rat models have shown reduced mRNA expression of 5- HT_{2C}Rs in the hypothalamus, striatum, nucleus accumbens and amygdala with long-term clozapine administration (114). SGAs have shown high 5-HT receptor occupancy in neuroimaging studies (115), and there is longstanding evidence for the association of increased 5-HT levels and satiety (116). SGAs act to block 5-HT receptors including those in the hypothalamus, which play a central role in satiety signaling, and thus have been implicated as a candidate mechanism in AIWG (102, 112). Olanzapine and clozapine act as inverse agonists at the 5- HT_{2C}R (117, 118) with lower affinity than aripiprazole, a partial agonist (119), but show greater AIWG (101). This evidence highlights the likely complex role of multiple mechanisms in AIWG.

Histamine Signaling

Three histamine receptors are expressed in the brain (H1, H2, and H3). Histaminergic neurons originating in the posterior hypothalamus project throughout the brain and the H1 receptor, specifically, has been described to have a role in feeding behavior. In a study screening FGAs and SGAs, AP binding to the H1 receptor was most strongly associated with weight gain (99). In animal studies investigating clozapine and olanzapine, weight gain is associated with H1 receptor blockade, whereas agonist such as betahistine reduced olanzapine-induced weight gain (120, 121) Further, H1 antagonism by olanzapine and clozapine is proportional to the activation of AMP-activated protein kinase (AMPK) (122, 123), which has been shown to reduce the anorexigenic effects of leptin (124). These associations should be interpreted with caution, as both clozapine and olanzapine have high affinity for multiple receptors.

Other Neurotransmitter Signaling

SGAs result in lower occupancy of dopamine D2 receptors (D2R) as compared to FGAs but still bind these receptors as antagonists (98–100, 125). AP administration results in decreased striatal D2R availability (102, 126) and it has been hypothesized that overeating compensates for reduction of D2-regulated reward circuits resulting in increased caloric intake (126–128). SGAs also act as antagonists at D4 and agonists at D1 receptors (98). Many APs have strong affinity for adrenergic receptors which have been more heavily implicated in metabolic effects of APs due to α1 and α2 receptor association with glucose control (101) and the ratio of α2 to β3 in adipocyte hyperplasia (129, 130). SGAs have high affinity for cholinergic muscarinic receptors and blockade of M3 has been proposed to disrupt insulin homeostasis (131), but there is lack of data for a role in AIWG. Of the early hypotheses related to AP effects on neurohormone signaling based on genetic candidate gene data, none of the genetic associations with AIWG have been strengthened by concurrent evidence from unbiased genome studies.

Neuroendocrine Signaling

Metabolic effects associated with APs could result from direct changes to neuroendocrine signaling or occur secondary to weight gain. AP effects on adiponectin, ghrelin, insulin, and leptin (**Figure 2**) have been examined as potential mediators of AP-related changes in energy homeostasis (132). These signaling molecules impact various levels of energy balance including appetite and feeding, energy expenditure and metabolic rate. Insulin and leptin modulate expression of neuropeptides in the hypothalamus, which regulate feeding behavior and are considered the most important agents in regulating weight gain and energy homeostasis (133).

Leptin Signaling

A review published by Endomba et al. (134) provides an excellent overview of the potential influence of APs on leptin metabolism. In brief, leptin acts on neurons of the lateral arcuate

TABLE 1 | Second generation antipsychotic neurotransmitter receptor binding profiles.

	Second generation antipsychotic								
Receptor	**ZPD**	**LRD**	**APZ**	**ASN**	**RSP**	**PPD**	**QTP**	**CLZ**	**OLZ**
5-HT_{1A}	+++	+++	+++	+++	+	+	++	+	–
5-HT_{1B}	+++		+	+++	++	++		+	+
5-HT_{2A}	++++	+++	++	++++	++++	++++	++	++	+++
5-HT_{2C}	**++++**	**+**	**++**	**++++**	**++**	**++**	**+**	**++**	**++**
5-HT_{6}	++		+	++++	–	–	+	++	+++
D1	+	+		+++	+	+	+	+	++
D2	**+++**	**+++**	**+++**	**+++**	**+++**	**+++**	**+**	**+**	**++**
D3	+++		+++	++++	+++	+++	+	+	++
D4	++		+	+++	+++	+++		++	++
M1							+	+++	++
M3	–	–	–		–	–	+	++	++
H1	**++**	**–**	**++**	**+++**	**+++**	**++**	**+++**	**+++**	**+++**
H2				+++	+	+		+	++
H3									+
α1	++	++	++	+++	+++	+++	++	+++	++
α2A	**+**	**++**	**++**	**+++**	**++**	**+++**	**+**	**++**	**+**
α2B	++		++	++++	++	+++	+	++	++
α2C	++	+++	++	+++	+++	+++	++	++	++

Antipsychotic-Induced Weight gain

Inhibition constants (Ki) indicated as follows: ++++ (1 > Ki), +++ (1 < Ki < 10), ++ (10 < Ki < 100), + (100 < Ki < 1,000), –(1,000 < Ki), gray box indicates lack of data; data derived from (98–100, 103–111). Second Generation Antipsychotics are listed from left-to-right in order of increasing antipsychotic-induced weight gain; data derived from (78). This table does not provide an exhaustive receptor profile but focusses on receptors hypothesized to relate to metabolic effects. Those with the most evidence are bolded. ZPD, ziprasidone; LRD, lurasidone; APZ, aripiprazole; ASN, asenapine; RSP, risperidone; PDD, paliperidone; QTP, quetiapine; CLZ, clozapine; OLZ, olanzapine.

nucleus within the hypothalamus inhibiting the expression of neuropeptide Y (NPY) and agouti-related peptide (AgRP) and stimulating proopiomelanocortin (POMC) (135–137). POMC is modified to α-melanocyte-stimulating hormone, which can then stimulate melanocortin receptor 3 (MC3R) and 4 (MC4R), suppressing food intake (137). Mouse models have shown that structural MC4R alterations and decreased MC3R expression are associated with leptin resistance and obesity (137, 138). In addition to NPY and AgRP, leptin also acts to inhibit neurons in the ventromedial arcuate nucleus that express gamma-amino butyric acid (GABA), which induce feeding (139). Thereby, reduced leptin signaling can lead to obesity by the loss of pro-satiety signals or the lack of feeding inhibition (135). Yet, the overall effects of APs on leptin remain unclear despite extensive investigation. For example, increased leptin levels have been associated with SGA treatment in patients with schizophrenia (140). It has been proposed that leptin metabolism can be affected by AP treatment independent of AIWG (141–146), or conversely, only secondary to AIWG rather than by direct effects (147–152).

Insulin Signaling

APs have been shown to increase insulin resistance (40). Insulin is produced in the pancreas by beta cells and binds to receptors in the arcuate nucleus aiding in energy homeostasis. Insulin resistance occurs when the activity of insulin is blunted in liver, muscle and adipose tissue and is linked to intra-abdominal fat (153). Childhood-onset insulin resistance increases risk for type 2 diabetes and cardiovascular disease (154, 155). AP actions on histamine and muscarinic receptors have been shown to reduce acetylcholine-induced insulin secretion (156, 157) and result in the failure of leptin signaling (158), which may contribute to insulin resistance. More recently, the hypothalamus has been shown to have a high concentration of insulin receptor expression and insulin concentration *in vitro* (159). In post-mortem studies receptor expression has been revealed to be greatest in the cerebellum and hypothalamus (160). Insulin has been shown to play an anorexigenic role in the brain and brain imaging studies have revealed a reduced neural response in patients with obesity upon exogenous insulin administration (160, 161). Insulin produced by the pancreas enters the brain via the bloodstream through an insulin-receptor mediated pathway initiating the phosphoinositide 3-kinase pathway that plays a crucial role in controlling metabolism (160). Additionally, insulin is involved in the stimulation of leptin secretion (162), and reciprocally, leptin plays a role in the regulation of circulating insulin (153). Human imaging studies have revealed that central insulin modulates the activity of mesocorticolimbic dopaminergic circuitry (163–165). In psychiatric patients, the development of type 2 diabetes and adverse metabolic effects may be facilitated by insulin resistance in the brain (166). **Figure 2** depicts aspects of insulin's role in the CNS. For a more comprehensive review of the role insulin plays in the

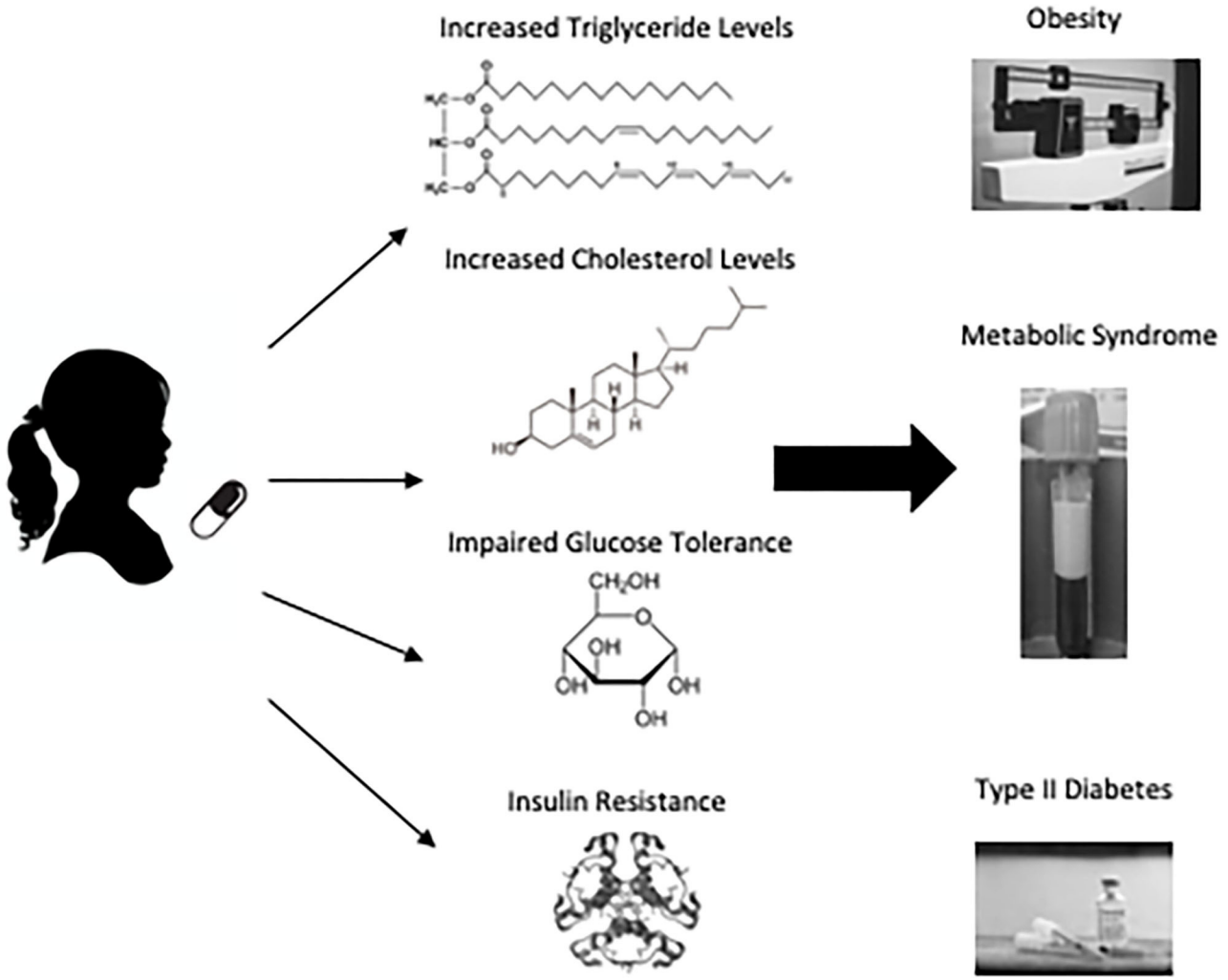

FIGURE 2 | Possible mechanisms of antipsychotic adverse metabolic effects. The energy homeostasis pathway is complex and provides numerous possible mechanisms that might explain AP-related weight gain and metabolic effects. Arrow at end of line indicates activation of pathway and perpendicular bar denotes inhibition. Neuroendocrine signaling molecules are bolded. Potential AP inputs are italicized and represented by dotted lines. ARC, arcuate nucleus; LH, lateral hypothalamus; NPY, neuropeptide Y; AgRP, agouti-related peptide; POMC, pro-opiomelanocortin; NPYR, neuropeptide Y receptor; MC4R, Melanocortin 4 Receptor; α-MSH, alpha-Melanocyte-stimulating hormone.

central nervous system as it relates to metabolism see Kullmann et al. (160).

Other Neurohormone Signaling

Adiponectin is secreted by adipose tissue and increases fatty acid oxidation and glucose uptake in muscle thereby contributing to weight regulation (167). Decreased adiponectin serum levels have been associated with insulin resistance, dyslipidemia, obesity and type 2 diabetes (168, 169). Meta-analysis found that SGA-treatment in patients with schizophrenia was associated with decreased levels of adiponectin (170). Ghrelin is a peptide hormone secreted in the stomach that has orexigenic effects by increasing food intake and fat deposits. Insulin has been evidenced to decrease ghrelin levels (171). Paradoxically, meta-analysis has provided some evidence that olanzapine-associated weight gain is associated with reduced ghrelin levels but associations with increased ghrelin in the context of SGA treatment has been reported as well (172–174). The circadian and immune regulator, melatonin, also plays a role in energy metabolism (175). Increased weight and visceral adiposity in olanzapine-treated rats is inversely proportional to nocturnal circulating melatonin (176) and daily melatonin supplementation ameliorates this effect (176, 177). More longitudinal studies with greater sample size are necessary to determine the relationship of AP treatment and these neurohormones.

Genetic Predisposition

Genetic risk factors likely play an important role in the extent to which an individual experiences AIWG. In a study of

monozygotic twins and siblings receiving SGAs, the influence of genetic factors on AIWG was reported to be between 60 and 80% (178). Candidate gene studies have focused on neurotransmitter receptors including 5-HT_{2C}R *(HTR2C)* (142, 148, 179–183), D2R *(DRD2)* (184–188), α2-adrenergic receptor *(ADRA2A)* (189–193) and cannabinoid 1 receptor *(CNR1)* (194–197); energy balance regulators including *MC4R* (198–201), leptin *(LEP)* (145, 202–205) and transcription factor *SREBP* (206–209); and growth and synaptic genes like brain-derived neurotrophic factor *(BDNF)* (210–215) and synaptosomal associated protein *SNAP25* (216). For a comprehensive review of the candidate gene studies associated with AIWG and metabolic effects of APs see Li et al. (217).

Candidate gene studies have exploratory value but are weakened as they are based on functional hypotheses with inherent bias (218–220). The genetics field has agreed that candidate gene studies should be interpreted with extreme caution (221). Large unbiased genome-wide studies, such as genome wide association studies (GWAS), are thus necessary to reveal replicable genetic risk factors for complex phenotypes. The common variation model postulates that susceptibility to complex disease is driven by a combination of common alleles that each carry a small disease risk, such as can be revealed in large-scale GWAS analyses. For example, genetic risk for AIWG at *MC4R* was first identified in the only GWAS study of weight gain in pediatric patients (age $\leq$ 19, $n = 139$) taking quetiapine, risperidone, olanzapine, or aripiprazole for any diagnosis (222). This GWAS study revealed a single nucleotide polymorphism (SNP) at locus rs489693 located downstream from the *MC4R* gene. Independent studies investigating SNPs near *MC4R* subsequently replicated this finding (198–201). MC4R plays a central role in energy balance. As described above, leptin stimulates hypothalamic POMC neurons, resulting in the production of α-MSH, which in turn stimulates anorexigenic effects by binding MC4R and inhibiting AgRP, an MC4R antagonist (102). 5-HT_{2C}R has upstream inputs to this pathway (223), and BDNF has been suggested to have effects downstream of MC4R, as its infusion in MC4R-deficient mouse models reduces food intake (224).

Several GWAS of AIWG have been performed in adult samples receiving APs to treat schizophrenia. Two studies utilized data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (225), both failing to detect genome-wide significant signals. The first also reported trends in SNPs upstream of opioid growth factor receptor *OGFRL1* (226), and the second highlighted enrichment of nominally associated SNPs in energy balance pathway genes by hypothesis-driven pathway enrichment analysis (227). A SNP (rs10977144) located in the protein tyrosine phosphatase, receptor type D gene *(PTPRD)* (228) was associated with AIWG in a GWAS of Chinese patients with schizophrenia ($n = 524$, mean age = 26.4). *PTPRD* deficient mice were shown to have insufficient weight gain postnatally due to feeding difficulties, arguing for a role in energy balance (229). A replication GWAS of European and African ancestry ($n = 201$, mean age = 37) treated primarily with clozapine or olanzapine did not confirm the lead SNP, which may be explained by unmatched ancestry, but notably did detect nominal significance at other SNPs within the *PTPRD* gene (230). This same GWAS found only marginal association ($p < 0.05$) at a SNP located near the *MC4R* gene. In an additional study of this cohort, a SNP (rs1525085) in the lipid biosynthesis gene, diacylglycerol kinase beta *(DGKB),* was found to be significantly associated with AIWG (231). The study notes that *DGKB* variants have been associated with insulin clearance (232) and, by interaction with insulin secretion, increased risk for type 2 diabetes (233). When limiting analyses to the European subset, a SNP (rs62097526) downstream of *CIDEA*, a regulator of lipolysis and thermogenesis in mice, was nominally associated with AIWG (231). *CIDEA* variants have also been shown to associate with metabolic syndrome in Swedish, Japanese and Chinese population cohorts as well as obesity risk in a Han-Chinese cohort (234, 235). The most recent GWAS (236) examining AIWG analyzed 339 subjects (Age Range = 15-45, mean age = 26.4) with first-episode psychosis derived from The Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) (237) cohort. This study identified the intergenic SNP rs78310016 near *SEPP1*, a hepatic protein involved in selenium transport, and growth hormone receptor (GHR) that was significantly associated with AIWG but not replicated in follow-up analyses. Providing face validity to this finding, SEPP1 and GHR have been implicated in metabolic phenotypes (238–243). Another possible functional link was identified by *in silico* analysis, which predicted a chromatin interaction of the lead SNP with the HMG-CoA synthase 1 gene *(HMGCS1)*. HMGCS1 is highly expressed in the brain and liver and involved in the regulation of cholesterol biosynthesis (244).

Overall, while candidate gene studies may provide mechanistic clues in pediatric AIWG and metabolic effects of APs, large GWAS studies are required to definitively identify risk genes. Currently, a few GWAS samples exist but are underpowered and difficult to harmonize given different ages and ancestries. Moreover, only one study examined pediatric participants (222). Existing studies are derived almost entirely from treatment studies of schizophrenia, which due to time and expense are generally limited to hundreds of patients. Sample sizes consisting of thousands of patients will be necessary to comprehensively capture genetic contributions of common variants to AIWG. Data from electronic medical records, national registries, and commercial genetic profile industries may represent fruitful avenues for future study.

The Microbiome

SGAs have been associated with perturbations of the gut microflora that may contribute to weight gain (245–248). The mechanism underlying alterations in the microbiome during SGA treatment and the link between these changes and weight gain are only beginning to be explored.

Several distinct observations have emerged from recent work including evidence that microbiome changes are necessary for AIWG rather than the reverse. AP administration in rodents and humans (249–252) results in an increase in the ratio of *Firmicutes* to *Bacteroidetes* (F:B), two common bacterial phyla. This observation parallels findings in obesity; however, systematic reviews in pediatric (253) and adult (254) populations identify

inconsistencies. Preclinical studies have demonstrated that gut bacteria are necessary for AIWG (245, 249–251). In fact, AIWG is absent in germ-free mice but can be induced by microbiome transplant (251). Similar F:B changes, increased adiposity, and inflammation were reported in olanzapine-treated rats (249). In a follow-up study, these effects could be prevented by co-administration of an antibiotic cocktail that effectively sterilized the gut (250). Similarly, mice receiving risperidone developed AIWG, an effect that was mediated by decreased energy expenditure and transferrable by fecal transplant (245). Small studies investigating risperidone treated children substantiated these preclinical findings. Risperidone treated children ($n = 18$, age range = 9–15, mean age = 12.2) were observed, cross-sectionally, to have an elevated F:B ratio and a host of differences in the metabolic potential of the gut microbiota (252). In an independent longitudinal study published in the same report, children ($n = 5$, age range = 9–13, mean age = 11.7) were enrolled within days (mean = 3.2, $SD = 5.2$) of starting risperidone (252). Within 1–3 months of risperidone initiation, the F:B ratio had begun to increase, appearing to plateau by about 5–6 months. Importantly, the F:B ratio was positively correlated with the magnitude of AIWG. An overall increase in putative "obese gut microbiota" was seen for these adolescents, and interestingly an enrichment in microbiota genes related to serotonin signaling and short chain fatty acid metabolism was reported.

Additional microbiota alterations associated with AP treatment include changes in *Actinobacteria*, although both increases (245, 255) and decreases (249) in the phylum has been reported. Risperidone-treated mice display increased abundance of the *Erysipelotrichaceae* (256) family and *Mollicutes* (257) class but decreases in *Alistipes* and *Akkermansia* species, which are considered lean gut microbiota (258, 259). Reduced diversity and stability of the microbiome of children compared to adults could explain the increased sensitivity to AIWG seen in youth (65, 260, 261). Lower microbiota species diversity is associated with obesity (255) dysbiosis in youth may mediate subsequent adult obesity (65). Childhood microbiota composition has also been shown to be instrumental for brain and immune system development and function (262). Therefore, given their lower baseline microbiota population diversity, long-term disturbance of brain and immune system development as a result of SGA-associated with changes in gut microbiota should be examined. Lastly, a study that investigated 117 adult patients with bipolar disorder ($n = 49$ treated with an AP, $n = 68$ non-treated) a greater AP-related reduction in bacterial diversity was seen in females vs. males treated with an AP (263), suggesting that sex differences must also be considered.

PHARMACOLOGICAL AND LIFESTYLE INTERVENTIONS TO ADDRESS METABOLIC AEs OF APs

Current strategies to prevent or treat AIWG and the metabolic effects associated with AP use are inadequate. Unfortunately, the two most effective SGAs on the market, clozapine and olanzapine, also have the highest reported AIWG (78). Clinicians should understand and weigh the benefits and risks of SGA treatment for each individual patient. In some situations, it may be possible to avoid APs if behavioral strategies or medications with less AEs are implemented. Nevertheless, in children with acute psychosis or mania, there are often few other appropriate options. In cases where benefit outweighs risk, it is crucial to warn patients and families about AIWG and metabolic effects and useful to discuss strategies to reduce harm. The most conservative approaches to metabolic side effects, which can also be safely employed for prevention, are non-pharmacologic interventions, which include lifestyle modification and dietary supplementation, including pre- and probiotic supplements. When these approaches are insufficient, switch to an AP with less propensity for weight gain may be warranted or adjunctive medications may be added to manage weight gain. The most effective pharmacologic interventions, however, will likely be supported by a healthy lifestyle.

Non-pharmacological Treatments

There is a paucity of data examining lifestyle interventions for AIWG in children (264). A 52-week study found that standard ($n = 102$) or intense behavioral weight interventions (n = 103) did not reduce AEs of APs for adolescents (age range = 13–17, mean age = 15.8) with schizophrenia or bipolar I disorder receiving olanzapine (265). A 16-week intensive weekly family-based behavioral weight loss intervention in AP-treated youth ($n = 19$, mean age = 13.35), compared to treatment as usual, resulted in decreased adiposity ($p = 0.01$) and hepatic fat ($p = 0.04$) that could support beneficial impacts on AIWG with long-term behavioral intervention (266). There is a need for large-scale pediatric studies to determine the most effective lifestyle interventions for weight gain and metabolic symptoms. As childhood obesity continues to present a major health challenge, a robust research literature exists on effective lifestyle interventions for obese youth. A comprehensive review of such integrative approaches was recently published (267) describing potential dietary, physical activity, sleep, and stress management interventions. Nutritional supplements with data in pediatric obesity, though not yet tested in the context of AP treatment, are also reviewed. The interventions with the best support in reducing childhood obesity and subsequent metabolic symptoms include an increased level of physical activity, improved sleep, and a diet consisting of fruits, vegetables, whole grains, and fish oil supplementation (267). Generalizing from healthy populations must be done with caution, however, as psychiatric diagnoses and psychosocial stressors may result in poorer outcomes of lifestyle interventions. Future development of lifestyle programs targeting AIWG should be designed for and tested in relevant psychiatric populations. Mixed data supports the effectiveness of lifestyle interventions in adults receiving AP treatment. A recent meta-analysis, however, reported a significant reduction in body weight after exercise initiation with a large effect size (SMD = −0.96), concluding that lifestyle interventions remain the most effective method to improve physical health outcomes in patients with schizophrenia (268). Compared to adults, pediatric patients present some unique

challenges and advantages. Youth may not cognitively appreciate risk, may be less self-motivated to comply with prevention measures, and may be resistant to lifestyle interventions. On the other hand, caregivers are in a position to exercise considerable influence over diet, nutrition, and lifestyle factors.

As SGAs may directly affect gut microbiota populations (245, 249–252, 269, 270) probiotics, prebiotics, and fecal transplants have been proposed as potential therapies to reduce adverse AP effects. Prebiotics have been shown to promote the growth of beneficial microbiota in humans resulting in suppressed appetite in youth ($n = 42$, age range = 7–12) (271), and probiotics are associated with improved gastrointestinal function in patients with schizophrenia (272, 273). While a promising and novel strategy, further research efforts are necessary to explore specific gut microflora that could alleviate AP side effects. Animal models have aided in this effort. Probiotics were able to reverse weight gain and metabolic dysfunction resulting from olanzapine treatment in mice (247). The prebiotic B-GOS prevented weight gain in rats (274), and a prebiotic mixture reduced weight gain and decreased the putative obesogenic F:B ratio in mice (246). Fecal transplants from mice treated with risperidone have also been shown to reduce basal metabolic rate and increase weight gain in control mice (245). Nevertheless, to develop effective and safe interventions, preclinical studies and clinical trials in human subjects will be crucial. An exploratory study comparing children ($n = 30$, age range = 4–17) with extreme risperidone-induced weight gain vs. those without AIWG uncovered bile acid changes resulting from AP treatment and distinct bile acid profiles in subjects with vs. without weight gain (275, 276). Preliminary evidence suggests a potential link between bile acid changes and the gut microbiota. Interestingly, a similar mechanism was suggested by studies of metformin effects in diabetes (277).

Pharmacological Treatments

Metformin, the most commonly used adjunctive medication targeting AIWG, is supported by the strongest evidence, but several other strategies have shown promise including glucagon-like peptide 1 receptor and histamine 1 receptor agonists. Unfortunately, most studies have been small and follow-up periods rarely exceed 6 months. Medications used to treat obesity in the general population have also been tried, and represent reasonable options, but these are often limited by intolerability of unpleasant side effects in psychiatric populations (278). In youth with metabolic abnormalities, insulin resistance, hyperglycemia and dyslipidemia, these medical sequelae are typically be managed by a pediatrician or endocrinologist. Studies have shown benefits of standard treatments, such as metformin and statins, in adults with antipsychotic related metabolic syndrome (279).

Metformin

Metformin, an anti-diabetic, has been studied extensively as a potential alleviator of AIWG and metabolic effects. Metformin has been shown to reduce metabolic effects in patients with schizophrenia spectrum disorders by decreasing hepatic gluconeogenesis, insulin resistance (i.e., improving insulin sensitivity) and total cholesterol (264, 268). Regulation of leptin sensitivity and hypothalamic signaling are also affected by metformin (280). Therefore, metformin may play a role in reducing caloric intake and fat storage (280). A 2014 meta-analysis of 40 studies on pharmacological interventions to combat adverse AP effects concluded that metformin should be the first choice for pharmacological treatment if non-pharmacological interventions have failed and switching to an AP with reduced potential for AIWG is not feasible (281). This meta-analysis was not focused on pediatric populations, but there have been several studies that have examined metformin adjunctive treatment in youth. In the Improving Parameters in Antipsychotic Child Treatment (IMPACT) trial of AIWG interventions, overweight youth ($n = 127$, age range = 8–19, mean age = 13.7) with a primary diagnosis of bipolar spectrum disorder, schizophrenia spectrum disorder, or psychotic depression were randomized to metformin treatment; AP switch to aripiprazole, perphenazine, or molindone; or continued current AP treatment (264). Both the metformin (moderate to large effect size 0.68) and AP switch (large effect size 0.81) group had significant reductions in BMI z-scores compared to the continued treatment control. More gastrointestinal complaints, however, were reported in the metformin group than the AP switch and control groups. Several additional studies support the benefit of metformin for pediatric SGA treatment. A randomized controlled trial ($n = 61$, age range = 6–17, mean age = 12.8) reported that metformin attenuated weight gain but did not affect metabolic measures (282), though given that no metabolic abnormalities were observed in either group, this is not surprising. Two small open label metformin trials reported weight loss in 5 out of 11 (age range = 10–18, mean age = 14) (283) and 15 out of 19 (age range = 10–18, mean age = 14.1) (284) patients. An open-label extension of one of the trials (282) found that this effect on anthropometric measures but not metabolic measures persists over long-term treatment, although they did note a non-significant decrease in hemoglobin A1c in both trial phases (285). One Iranian study failed to demonstrate a significant impact of metformin on AIWG prevention over a 12-week treatment period but did note significant effects over the first 4-weeks of treatment and a positive trend at 12 weeks ($n = 49$, mean age = 10.1) (286). Authors acknowledge that lower doses of metformin were used compared to other studies, which may explain conflicting results. Metformin may be more effective in first-episode psychosis patients in comparison to those receiving chronic treatment (287). Some have proposed that timing is critical and early use of metformin may improve outcomes through prevention rather than correction of weight gain (288). Lessons learned from metformin's modest efficacy may spur the testing and development of new approaches in the future.

Glucagon-Like Peptide 1 Receptor Agonists (GLP1RA)

GLP1RAs, another medication class borrowed from diabetes treatment and associated with weight loss, have been examined as potential adjuncts to reduce AIWG and metabolic dysfunction (289). This approach is supported by evidence that serum GLP1

increases with SGA treatment (290) and is associated with both hyperglycemia as well as insulin resistance (291). A meta-analysis of 3 trials of adults receiving adjunctive GLP1RA along with an AP demonstrated reduced HbA1c, fasting blood glucose and BMI (292). This meta-analysis only consisted of 164 patients, underscoring the need for larger trials. Pediatric trials of efficacy in AIWG are lacking but warranted given promising effects of GL1RA treatment in adolescents with severe obesity (293). Until recently, GLP1RAs have been limited by a subcutaneous formulation, but the 2019 approval of an oral agent, semaglutide, could drive an expanded role for this medication class in the future.

Betahistine

Betahistine, an agonist of the H1 histamine receptor has been shown to reduce or attenuate olanzapine-induced AIWG in adults (121, 294, 295), as discussed previously. Many APs are antagonists at the H1 receptor, especially those with high propensity to cause AIWG. To our knowledge, only one study (296) has included pediatric patients ($n = 12$ of 51 total patients, age range 12-17). In this sample, betahistine tempered weight gain in participants receiving the strongly antihistaminergic APs olanzapine and clozapine, but not for those taking other APs with lower H1 potency. The study found no moderating effect of age (i.e., adolescent vs. adult) but did not analyze the adolescent population separately. Mechanistic queries of protective effects against AIWG conferred by potent H1 antagonists have been explored in several animal models (294, 297–302). The exact mechanism underlying beneficial effects is unclear, however, since adjunctive treatment with betahistine attenuates H1-NPY, H1-AMPK, and H1-POMC signaling and increases H3-mediated release of histamine. Further, in a rat model, betahistine was shown to reverse the upregulated dopamine D2R expression that typically results from olanzapine treatment, while not interfering with AP effects at serotonergic receptors in brain regions associated with AP efficacy (302). Thus, betahistine may reduce the increased D2 sensitivity associated with AP treatment but its potential interference with AP efficacy requires thorough investigation.

Other drugs that have been tested to reduce AIWG, largely in adults, include reboxantine, topiramate, and amantadine. When combined with betahistine, reboxantine, a norepinephrine reuptake inhibitor was shown to be effective in attenuating olanzapine-induced weight gain (294) and appetite (24) in adults. A meta-analysis of 10 studies of adjunctive topiramate (an antiepileptic drug known to reduce appetite) for AIWG, found topiramate mitigated weight gain in AP-treated adults (303). In a medical record review, there was an overall reduction in BMI for 47 child and adolescent psychiatric patients (mean age = 13.4) receiving topiramate and another anticonvulsant, zonisamide (304). Future efforts are needed to investigate these anticonvulsant adjunctive treatments to combat AIWG in pediatric patients.

The "natural," over-the-counter supplement with the best evidence to mitigate AIWG and metabolic effects is melatonin. As discussed previously, melatonin plays a key role in energy homeostasis as well as central and peripheral insulin action (305). Reduction in melatonin production has been associated with insulin resistance, glucose intolerance, and metabolic disease (305). A recent meta-analysis of both adult and adolescent studies supported clinical use of melatonin and melatonin receptor agonists as adjuncts to mitigate AIWG and metabolic effects (175). In adolescents ($n = 38$) diagnosed with bipolar disorder receiving olanzapine and lithium combination therapy, melatonin as compared to placebo attenuated increases in cholesterol level and systolic blood pressure (306). In a smaller cohort ($n = 19$, mean age ~14), although not reaching significance, melatonin as compared to placebo reduced weight gain in the context of olanzapine and lithium combination therapy (307). Because of its role in the regulation of circadian rhythms (308), it is possible that positive metabolic effects may be secondary to beneficial effects on sleep, which has been show to play a role in obesity (309). Interestingly, co-administration of melatonin appears more effective with risperidone and quetiapine, agents with intermediate risk of AIWG, compared to olanzapine and clozapine, agents with the highest risk (175). If confirmed in larger studies, melatonin represents a relatively benign pharmacological intervention for youth.

CLINICAL GUIDELINES FOR THE ASSESSMENT, PREVENTION, AND TREATMENT OF METABOLIC ADVERSE EFFECTS OF ANTIPSYCHOTIC MEDICATIONS IN YOUTH

Clinical practice guidelines are published by various groups, organizations, and experts. We present an overview of those guidelines most relevant to pediatric psychiatry, the AACAP Practice Parameters for Schizophrenia (7) and Aggression (14), supplemented with additional recommendations from the American Psychiatric Association (70, 82) and other adult sources (86, 278). The AACAP guidelines emphasize a comprehensive baseline assessment and treatment plan (**Figure 3A**) followed by responsible regular monitoring and follow-up (**Figure 3B**).

If initial psychiatric evaluation prompts the consideration of AP therapy, further baseline assessment should include expanded history (personal and family history of diabetes, hyperlipidemia, or previous response or adverse events associated with APs), physical exam (vital signs including blood pressure and heart rate, weight and BMI with determination of pediatric growth chart percentiles, and waist circumferences) and baseline laboratory measurements (fasting lipids, glucose and hemoglobin A1C).

The risks, benefits and alternatives of an AP should be assessed, weighed, and discussed (and informed consent obtained) with the guardian(s) and child/adolescent if possible. Even if an AP is a first-line treatment for the patient's diagnosis, behavioral treatments, psychosocial interventions, and medication alternatives should be considered. Behavioral and psychosocial approaches can improve outcomes and potentially reduce AP burden. Expected duration of therapy may also influence treatment planning, as it may be possible to minimize

A

Decision Support for The Use of Antipsychotics in Youth:
INITIAL ASSESSMENT & PLAN

ASSESSMENT

- Conduct psychiatric diagnostic evaluation

Decision Support: Is an AP first-line for the diagnosis?

1. Does the evidence-base strongly support APs as a first-line treatment for the diagnosis?
2. Consider alternative options with less AE potential and weigh risks and benefits:
   - Mania: mood stabilizers, family focused therapy
   - Autism: behavioral treatments, parent-training, stimulants, α2-agonists, mood stabilizers, SSRIs, others
   - Aggression: behavioral treatments, parent-training, stimulants, α2-agonists, mood stabilizers, SSRIs, others
   - Tourette: habit reversal therapy, alpha-2 agonists, others

- Conduct expanded baseline health screening if AP will be considered

History	Exam	Labs
• Personal history of metabolic dysfunction	• Weight & BMI -> Growth Chart Percentiles	• Fasting glucose & hemoglobin A1C
• Family history of metabolic dysfunction	• Waist circumference	• Fasting lipids
• Assess other modifiable risk factors (nutrition, exercise, habits)	• Vital signs: Blood pressure & heart rate	
	• Physical exam by pediatrician	

- Weigh risks versus benefits of AP treatment

Decision Support: Do the benefits of an AP outweigh the risks?

1. Does the child have a high risk for weight gain and metabolic AEs based on personal/family history and baseline exam/labs?
2. Are there viable non-AP alternatives for the diagnosis and specific patient factors?
3. Could APs be used for short-term stabilization with a plan to switch to a safer alternative once stable?
4. Do the patient's psychosocial situation and level of functioning support the ability to adhere to lifestyle preventive measures?
5. Could an AP with lower propensity for weight gain be prioritized?

TREATMENT PLAN

- Discuss options with patient/guardian(s) explaining health risks of AP therapy
- Incorporate patient/guardian(s) preferences in treatment decision and obtain informed consent from guardian(s) & ideally child as well
- Prescribe best-evidence AP considering decision support factors above and patient/guardian preference
- Implement preventive measures (healthy lifestyle education and program referrals)
- "Start low & go slow" approach to titration to minimize risk
- Add psychosocial interventions/support and complementary psychotherapy/behavioral approaches to minimize AP use
- Minimize polypharmacy
- Implement regular monitoring plan and follow-up

FIGURE 3 | Continued

B

Decision Support for The Use of Antipsychotics in Youth: FOLLOW-UP ASSESSMENT & PLAN

ASSESSMENT

- Review monitoring metrics

3 Month Follow-up	Quarterly	Annually
Weight & BMI -> Growth Chart Percentiles	Weight & BMI -> Growth Chart Percentiles	Physical exam by pediatrician
Assess lifestyle factors & review preventive plan	Patient/caregiver report of AEs	Consider healthy lifestyle program booster
Exam • Waist circumference • Blood pressure & heart rate	Assess lifestyle & other risk factors	***Exam*** • Waist circumference • Blood pressure & heart rate
Labs • Fasting glucose & hemoglobin A1C • Fasting lipids	Review & troubleshoot preventive plan	***Labs*** • Fasting glucose & hemoglobin A1C • Fasting lipids

- Significant weight gain? (AACAP definition: weight gain exceeding 90th percentile BMI for age or a change of five BMI units in previously obese youth)

Decision Support: Management of AIWG and/or metabolic dysfunction

Consider	Possible Action
Has the AP been effective for psychiatric symptoms?	Consider alternative treatments
Are there non-AP alternative treatments?	Weigh risks & benefits of switch to a different medication class or psychosocial treatment
Has the preventive plan been followed & what are barriers?	Interventions to enhance effectiveness of non-pharmacologic strategies
Are APs with less potential for AIWG an option?	Weigh risks & benefits of switch to an alternative AP
Is the addition of an adjunctive medication targeting weight gain warranted?	Consider addition of metformin or other evidence-based options as appropriate

- Assess need for continued treatment

Decision Support: Appropriate Treatment Duration

1. Is the diagnosis potentially time-limited (aggression, substance-induced, tics, psychotic depression, acute mania that could be managed with a mood stabilizer in the long-term)? Consider options with less risk.
2. Have the psychosocial factors or comorbidities improved allowing for more conservative medication management? Consider treatment options with less risk.
3. Has the patient been psychiatrically stable for a year or more? Consider careful AP taper if appropriate.

TREATMENT PLAN

- Incorporate patient/guardian(s) preferences in treatment decision and obtain informed consent from guardian(s) & ideally child as well
- Continue regular monitoring plan and follow-up

FIGURE 3 | (A,B) Clinical guideline and decision support for the assessment, prevention, and treatment of metabolic adverse effects of antipsychotic medications in youth. Adapted from the American Academy of Child and Adolescent Psychiatry (7) and American Psychiatric Association and American Diabetes Association Guidelines (70). **(A)** Initial Assessment and Plan. **(B)** Follow-up Assessment and Plan.

long-term AP use by switching to a safer medication or non-pharmacological treatment once an acute crisis has passed. If it is determined that benefits of an antipsychotic outweigh risks, the use of an AP with lower AIWG potential may be appropriate depending on diagnostic and patient-specific factors.

Once an AP is selected, a standard "start low and go slow" approach should be implemented. The administration of multiple concomitant psychotropic medications should be minimized, especially avoiding the concurrent use of multiple APs. Education and counseling on healthy lifestyle choices as preventive measures against weight gain and metabolic effects should be provided. Formal referral to a dietician or healthy lifestyle program may be warranted in higher risk or already overweight patients. An AACAP Facts for Families Sheet on "Weight Gain from Medication: Prevention and Management" is available on the AACAP website at https://www.aacap.org/AACAP/Families_and_Youth/Facts_for_Families/FFF-Guide/Preventing-and-Managing-Medication-Related-Weight-094.aspx.

Given the high risk of AIWG in youth taking APs, frequent monitoring of AEs must occur. Monitoring for AIWG in psychiatric patients using self-reported awareness is less effective than objective measurement (310). AACAP advises following the joint consensus recommendations of the American Diabetes Association and the American Psychiatric Association (**Figure 3B**) to monitor BMI quarterly and blood pressure, fasting blood glucose and fasting lipid profiles at 3 months and then annually thereafter (70). Since BMI distribution varies over typical development, BMI should be normed with respect to age and translated to percentiles. Developmentally normed growth charts can be found at the Center for Disease Control website (www.cdc.gov/growthcharts), and/or percentile calculators can be found online or in mobile app form. Despite strong guidelines, a 2016 review estimates that 70% of patients taking APs in the US fail to be screened or treated for metabolic AEs (311). The continued need for AP treatment should be regularly evaluated, as the appropriateness of long-term use will vary based on the severity of symptoms, psychosocial environment, availability of safer evidence-based options, and the natural course of the illness being treated.

Consideration of weight management interventions and increased regularity of blood glucose and lipid levels should be implemented if AIWG exceeds 90th percentile BMI for age, or a change occurs of 5 BMI units in patients already obese at baseline. Other contributors to weight gain and metabolic syndrome should be explored (312). A review and troubleshooting of lifestyle interventions may be adequate to curb weight gain, but in cases where lifestyle modification is insufficient, 2 main strategies exist for pharmacological intervention. First, a switch from an AP with higher to lower weight gain potential may be appropriate with careful attention to the risk of psychiatric relapse. The effectiveness of the current AP is an important factor. As reviewed previously, an AP switch strategy is supported by studies in both youth (264) and adults (313, 314); however, methodological problems, including high incidence of drug discontinuation and study attrition compounded by the use of per protocol data analysis, confound many of these trials and limit their application. Prior to switching, patients/families should be informed of the potential risk of relapse. Gradual cross-taper over several weeks is recommended to minimize this risk. If a switch to a lower risk AP is not appropriate or preferred, addition of an evidence-based adjunctive medication is a reasonable option with relatively low risk. As discussed above, metformin is currently the agent with the best support; however, several promising leads and novel alternatives are being developed and tested.

CONCLUSIONS AND FUTURE DIRECTIONS

SGA prescription has become the standard of care for children and adolescents with psychotic disorders as well as a frequent therapeutic employed, both with FDA-approval and off-label, for a range of psychiatric disorders. These APs have proven to be effective to reduce psychiatric symptoms but result in AEs, chiefly AIWG and metabolic effects. Despite robust research efforts to reveal underlying mechanisms, it is unclear how to maintain AP efficacy while reducing serious side effects.

The pharmacological interventions that have been proposed and investigated to date are limited. Interventions such as anti-diabetic and anti-convulsant medications are not biologically targeted treatments but rather repurposed based on incidental observations of weight loss or metabolic improvement when these medications are used for other conditions. Thus, these serendipitous positive effects may simply balance metabolic dysfunction rather than directly correct the underlying lesion driving these AEs. Additionally, drugs targeting obesity in the general population may be relevant to AIWG. Promising drugs that warrant further testing in AIWG include 5-HT_{2C}R agonist lorcaserin (315), fat absorption blocker orlistat (316), and melanin concentrating hormone receptor 1 antagonists (317), as well as combination treatment of naltrexone and bupropion to curb craving (318). While obesity drugs are a Big Pharma priority, lack of mechanistic clarity underlying obesity and frequent prohibitive AEs have stalled progress. Future studies should take care to use high-quality study designs, including randomized controlled trials with intent-to-treat analysis, and provide effect sizes in addition to significance measures to convey the clinical utility of potential treatments.

Efforts to reduce AEs for pediatric patients undergoing SGA treatment will require mechanistic studies that illuminate a clearer, definitive conception of their biological underpinnings. Progress in neuroendocrine, genetic, and microbiome related mechanisms of AIWG lay a foundation for developing interventions to combat unwanted AEs. Manipulation of energy balance pathways in animal models can reveal potential avenues for human translation. Large-scale genomic and microbiome studies in both adult and pediatric patients can also yield links to biology. Further understanding of a healthy gut microbiome and effective manipulation strategies may expand psychotherapeutic modalities. Epigenetic changes produced by

AP exposure, exploration of which remains rudimentary, may also contribute to compounding of genetic and environmental risk. A mechanistic appreciation of metabolic AEs will not only inform interventions to reduce or prevent side effects, but ultimately drive the design of specific therapies that can target psychiatric symptoms without inflicting harm.

The ever-expanding development of new technologies has the potential to considerably advance both discovery and intervention. Computational analysis of electronic medical records and machine learning approaches will generate and test new data-driven hypotheses. Similarly, wearable devices can collect objective data, such as patterns of activity, speech, sleep and biological metrics, that will facilitate clinician monitoring and feed big data approaches. Wearable devices and mobile apps can also be used to enhance patient engagement and motivation with lifestyle interventions and improve treatment adherence.

These diverse approaches can eventually explain the large, individual variability in risk for AIWG and metabolic effects and fuel precision medicine algorithms. The precision psychiatry model of the future seeks to incorporate demographic, genetic, epigenetic, biomarker, psychosocial, and other information to achieve a molecular diagnosis and a personalized risk assessment. This approach can match the individual patient with a data-driven treatment plan, thus boosting adherence, preventing AEs, and optimizing patient outcomes.

AUTHOR CONTRIBUTIONS

ML performed the primary literature search and prepared the first and final draft of the manuscript, figures, and table. EN defined the scope of the topic, authored the abstract, and edited the manuscript, figures, and tables.

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SYSTEMATIC REVIEW
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Pharmacological Interventions to Treat Antipsychotic-Induced Dyslipidemia in Schizophrenia Patients: A Systematic Review and Meta Analysis

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Introduction: Antipsychotic-induced dyslipidemia represents a common adverse effect faced by patients with schizophrenia that increases risk for developing further metabolic complications and cardiovascular disease. Despite its burden, antipsychotic-induced dyslipidemia is often left untreated, and the effectiveness of pharmacological interventions for mitigating dyslipidemia has not been well-addressed. This review aims to assess the effectiveness of pharmacological interventions in alleviating dyslipidemia in patients with schizophrenia.

Methods: Medline, PsychInfo, and EMBASE were searched for all relevant English articles from 1950 to November 2020. Randomized placebo-controlled trials were included. Differences in changes in triglycerides, HDL cholesterol, LDL cholesterol, and VLDL cholesterol levels between treatment and placebo groups were meta-analyzed as primary outcomes.

Results: Our review identified 48 randomized controlled trials that comprised a total of 3,128 patients and investigated 29 pharmacological interventions. Overall, pharmacological interventions were effective in lowering LDL cholesterol, triglycerides, and total cholesterol levels while increasing the levels of HDL cholesterol. Within the intervention subgroups, approved lipid-lowering agents did not reduce lipid parameters other than total cholesterol level, while antipsychotic switching and antipsychotic add-on interventions improved multiple lipid parameters, including triglycerides, LDL cholesterol, HDL cholesterol, and total cholesterol. Off label lipid lowering agents improved triglycerides and total cholesterol levels, with statistically significant changes seen with metformin.

Conclusion: Currently available lipid lowering agents may not work as well in patients with schizophrenia who are being treated with antipsychotics. Additionally, antipsychotic switching, antipsychotic add-ons, and certain off label interventions might be more

effective in improving some but not all associated lipid parameters. Future studies should explore novel interventions for effectively managing antipsychotic-induced dyslipidemia.

Registration: PROSPERO 2020 CRD42020219982; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020219982.

Keywords: schizophrenia, antipsychotics, dyslipidemia, systematic review, meta-analysis

INTRODUCTION

Dyslipidemia refers to abnormalities in lipid levels such as increases in total and low-density lipoprotein (LDL) cholesterols, low concentrations of high-density lipoprotein (HDL) cholesterols, and high triglyceride levels. This metabolic abnormality causes almost a third of ischemic heart disease and a fifth of global cerebrovascular disease (1). Patients with schizophrenia are at an increased risk of developing cardiovascular disease in part due to the illness itself (2–7), as well as a higher prevalence of well-known lifestyle factors that promote cardiovascular disease risk, namely sedentary lifestyle, poor diet, and smoking (8, 9). Antipsychotics are the cornerstone of treatment in schizophrenia and are widely prescribed across other psychiatric conditions (10). However, their use is associated with severe metabolic adverse effects, including weight gain, dyslipidemia, insulin resistance, and risk of type 2 diabetes mellitus (T2D) in a population burdened with premature cardiovascular mortality.

While the prevalence of dyslipidemia and consequent effects on morbidity and mortality are high worldwide among the general population, particular subgroups may be at a greater risk. In particular, patients with schizophrenia are at an increased risk of dyslipidemia and its associated influence on cardiovascular disease and metabolic dysfunction (11, 12). Despite its high prevalence and associated cardiovascular risk, dyslipidemia often goes untreated among patients with schizophrenia. Reported rates for non-treatment are almost 90% (13–15), and patients with schizophrenia are often medically underserved and disadvantaged in their physical health care (16–18). As shown by results from a study by the National Institute of Mental Health, namely the Recovery After an Initial Schizophrenia Episode–Early Treatment Program (RAISE-ETP), at baseline more than half of patients (161/394 or 56.5%) had dyslipidemia and only 0.5% were receiving treatment (16).

Previous discussions addressing antipsychotic-induced metabolic abnormalities in patients with schizophrenia have largely focused on weight gain or metabolic syndrome, and not dyslipidemia *per se* (19–21). Only a few studies have investigated approved lipid lowering agents for treating dyslipidemia in schizophrenia (22–30). More commonly, as reported in a 2014 review by Tse et al. a wide variety of pharmacological agents have been investigated to treat dyslipidemia in patients with schizophrenia, including treatment with omega-3 fatty acids, fluvoxamine, topiramate, metformin, sibutramine, telmisartan, ramelteon, and valsartan (31). Antipsychotic switching and adding aripiprazole have also been evaluated as strategies to improve lipid outcomes in patients with schizophrenia (32–38). Given the variety of approaches used to address dyslipidemia in this patient population, as well as the absence of clear clinical guidelines, it is important to summarize the available evidence and guide clinical decision making. Hence, we performed a systematic review and meta-analysis of randomized controlled trials to compare the effects of pharmacological interventions vs. placebo treatment in antipsychotic-induced dyslipidemia in patients with schizophrenia.

METHODS

The protocol for the review is registered on PROSPERO (PROSPERO 2020 CRD42020219982; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020219982). PRISMA guidelines were used for study design and reporting.

Search

We searched for studies published between 1950 and November 2020 using Medline, PsychInfo and EMBASE databases, with the following search string: *psychotic disorder* OR *schizophrenia* OR *schizoaffective* OR *schizophreniform* OR *psychosis* OR *first episode* AND *hyperlipidemia* OR *triglycerides* OR *cholesterol* OR *lipid* OR *LDL cholesterol* OR *VLDL cholesterol* OR *HDL cholesterol.* The search was limited to studies conducted in human participants and published in English. References cited in previously published literature reviews and meta-analyses pertaining to interventions for metabolic disturbances in the schizophrenia population were reviewed for additional studies.

Inclusion Criteria

Articles were initially screened using title and abstract, based on the study's relevance to our meta-analysis. Thereafter, articles were further screened to ensure that studies met the following inclusion criteria: (a) randomized placebo-controlled trial; (b) diagnosis of schizophrenia spectrum disorders comprising the majority (>50%) of study populations; (c) patients with current metabolic abnormalities; (d) an active pharmacological intervention used to improve metabolic abnormalities or an antipsychotic switching/add-on method if the antipsychotic change is aimed to improve metabolic parameters; and (e) primary outcome listed as lipids or other metabolic measures if lipid outcomes were included in the list of metabolic measures.

Studies were excluded from analysis during the final screening stage if (a) not aimed at improving metabolic measures; (b) comparing different modes of antipsychotic administration (i.e., deltoid, sublingual, gluteal etc.); (c) comparing effectiveness between different antipsychotics; (d) evaluating non-pharmacological intervention (e.g., behavioral

interventions, dietary modulations etc.); or, (e) evaluating strategies to prevent dyslipidemia (i.e., patients did not have metabolic abnormalities or dyslipidemia at baseline).

Outcomes Extracted

The primary outcomes included the following lipid parameters: total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, and very low-density lipoprotein cholesterol (VLDL) cholesterol. Additional secondary outcome data were also extracted including body weight, body mass index (BMI), waist circumference, waist to hip ratio, fasting blood glucose, fasting insulin, hemoglobin A1c (HbA1c), diastolic blood pressure, systolic blood pressure, the homeostatic model assessment of insulin resistance (HOMA-IR), and total positive and negative symptom scale (total PANSS). Outcomes were extracted for both the intervention and placebo groups, where the placebo groups were used as comparators. Outcomes were extracted by two authors (PK and KC-D) and were checked by authors, FP and JL. For studies that examined multiple doses of the same intervention, the data pertaining to the higher dose were extracted.

Data Analysis

Review Manager 5.4 (Revman 5.4.0 (Mac Version) Cochrane Collaboration, Oxford) was used to analyze the data extracted from the final list of included articles. Continuous outcomes were reported using mean differences (MD) with 95% confidence intervals (CIs), following the inverse variance statistical method and random effects model to account for study heterogeneity. Missing standard deviations (SDs) were calculated using other available statistics that were reported. Endpoint data were primarily used unless not available, in which case mean change data were used. Endpoint and change data were combined during the analysis, as we used mean difference rather than standardized mean difference (39). For Emsley et al. which was a double-blind trial with an open-label extension (27), data were extracted at the endpoint of the double-blind phase. Study heterogeneity was calculated using the I^2 statistic, with significant heterogeneity being classified as $I^2 \geq 50\%$. Significant statistical differences were classified as $p < 0.05$. Changes in lipid profiles (i.e., HDL cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides, and total cholesterol) were assessed for all interventions pooled and for the following 4 subgroups: lipid lowering agents; antipsychotic switching or antipsychotic add-on interventions; the off-label lipid lowering agent metformin; and other off-label lipid lowering agents.

All included studies were judged for risk of bias in random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias using the Cochrane Risk of Bias tool (40). Studies were judged to have either a low, high, or unclear risk of bias. Sensitivity analyses were conducted after removing studies found to be at high risk of bias to examine their impact on findings.

RESULTS

Of the 244 full-text articles screened, 48 articles ($n = 3{,}128$) met criteria for inclusion (**Figure 1**, **Supplementary Table 1**). Forty-three studies were double-blind, 2 were open-label, one had blinding but did not specify level, and the remaining 2 studies did not provide information on blinding. All studies included adult populations (18 years or older). The average age (±SD) of participants receiving interventions was 40.1 (±12.8) years, vs. 40.6 (±9.6) for those receiving placebo. A total of 74% of participants in both the intervention and placebo groups were male, with 89.2% diagnosed with schizophrenia. Trials were 4–24 weeks long, with a mean duration (±SD) of 13.1 (±5.7) weeks. Studies comprised a total of 29 interventions. Lipid lowering agents included omega-3 fatty acids [(26–28, 30), $N = 4$, $n = 250$] and pravastatin [(29), $N = 1$, $n = 49$]. Antipsychotic switching or add-on interventions included the following: switching to quetiapine [(41), $N = 1$, $n = 133$]; adding aripiprazole [(33, 34, 38), $N = 3$, $n = 322$]; and, switching to aripiprazole [(35–37), $N = 3$, $n = 390$]. Off label lipid modulating agents included the following: metformin [(42–47), $N = 6$, $n = 565$], reboxetine [(48), $N = 1$, $n = 54$], nizatidine [(49), $N = 1$, $n = 54$], atomoxetine [(50), $N = 1$, $n = 29$], combination of metformin and sibutramine [(51), $N = 1$, $n = 28$], rosiglitazone [(52, 53), $N = 2$, $n = 47$], ramelteon [(54), $N = 1$, $n = 20$], telmisartan [(55), $N = 1$, $n = 43$], vitamin D and probiotic combination [(56), $N = 1$, $n = 60$], sibutramine [(17, 57), $N = 2$, $n = 55$]; dehydroepiandrosterone [DHEA; (58), $N = 1$, $n = 43$], exenatide [(59), $N = 1$, $n = 40$], orlistat [(60), $N = 1$, $n = 63$], vitamin D [(61), $N = 1$, $n = 47$], liraglutide [(62), $N = 1$, $n = 97$], intranasal insulin [(63), $N = 1$, $n = 39$], minocycline [(64), $N = 1$, $n = 55$], fluvoxamine [(65, 66), $N = 2$, $n = 153$], naltrexone and bupropion combination [(67), $N = 1$, $n = 21$], melatonin [(68, 69), $N = 2$, $n = 80$], pioglitazone [(70), $N = 1$, $n = 52$], Liuyu decoction, traditional Chinese medicine [(71), $N = 1$, $n = 154$], a combination of celery, dill, and green tea [(72), $N = 1$, $n = 60$], naltrexone [(73, 74), $N = 2$, $n = 47$], Konjac powder [(75), $N = 1$, $n = 59$], and resveratrol [(76), $N = 1$, $n = 19$]. Baseline antipsychotic use by participants included olanzapine ($N = 27$), clozapine ($N = 25$), risperidone ($N = 11$), quetiapine ($N = 8$), aripiprazole ($N = 5$), ziprasidone ($N = 2$), paliperidone ($N = 2$), haloperidol ($N = 1$), fluphenazine ($N = 1$), flupenthixol ($N = 1$), clopenthixol ($N = 1$), and sulpiride ($N = 1$), chlorpromazine ($N = 1$), perphenazine ($N = 1$), zuclopenthixol ($N = 1$), chlorprothixene ($N = 1$), amisulpride ($N = 1$), sertindole ($N = 1$), and sulpiride ($N = 1$).

Primary Outcomes: Lipid Profile

Compared to placebo, pharmacological interventions were associated with a pooled mean difference of −13.08 mg/dL (CI: −20.82, −5.33; $p = 0.0009$) for triglycerides (**Figure 2**), 0.43 mg/dL (CI: −0.85, 1.70; $p = 0.51$) for HDL (**Figure 3**), −4.19 mg/dL (CI: −7.71, −0.67; $p = 0.02$) for LDL cholesterol (**Figure 4**), −3.27 mg/dL (CI: −7.38, 0.84; $p = 0.12$) for VLDL cholesterol (**Figure 5**), and −7.96 mg/dL (CI: −11.14, −4.77; $p < 0.00001$) for total cholesterol (**Figure 6**). Heterogeneity was low to moderate for most outcomes: $I^2 = 71\%$ for HDL, $I^2 = 60\%$

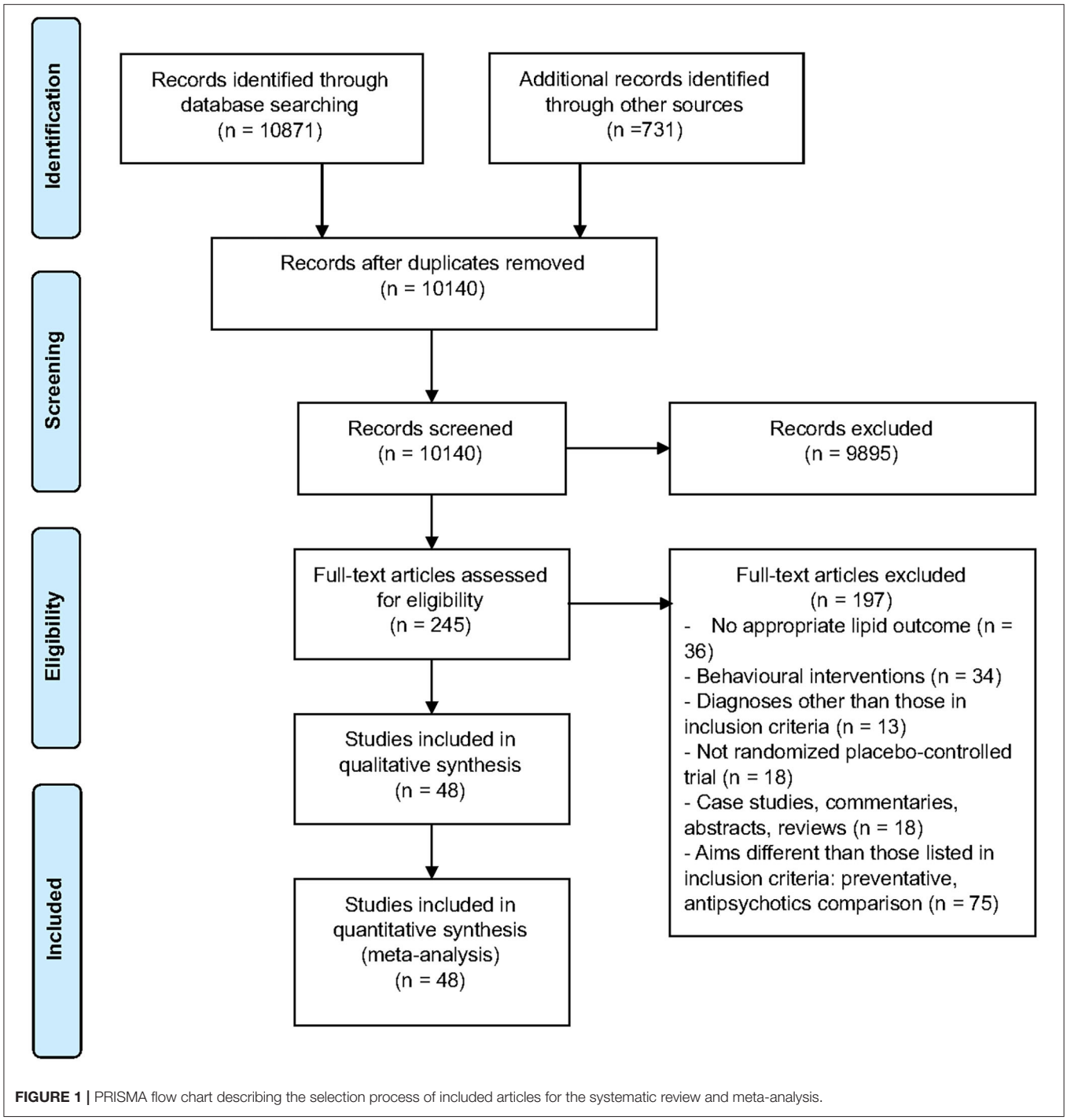

FIGURE 1 | PRISMA flow chart describing the selection process of included articles for the systematic review and meta-analysis.

for LDL cholesterol, $I^2 = 0\%$ for VLDL cholesterol, $I^2 = 52\%$ for triglycerides, $I^2 = 37\%$ for total cholesterol.

Lipid Lowering Agents

Lipid lowering agents were associated with significant reductions in total cholesterol compared to placebo (**Figure 6**; $N = 4$, $n = 227$; WMD $= -11.52$ mg/dL, CI: -15.51, -7.53; $p < 0.00001$; $I^2 = 0$). There were no significant differences in triglycerides (**Figure 2**; $N = 4$, $n = 243$; $I^2 = 56$), HDL cholesterol (**Figure 3**; $N = 5$, $n = 299$; $I^2 = 81$), and LDL cholesterol (**Figure 4**; $N = 4$, $n = 227$; $I^2 = 56$) levels. None of the lipid lowering agent studies examined VLDL cholesterol.

Antipsychotic Switching/Add-on Interventions

Antipsychotic switch/add-on strategies were associated with significant decreases in triglycerides (**Figure 2**; $N = 7$, $n = 800$;

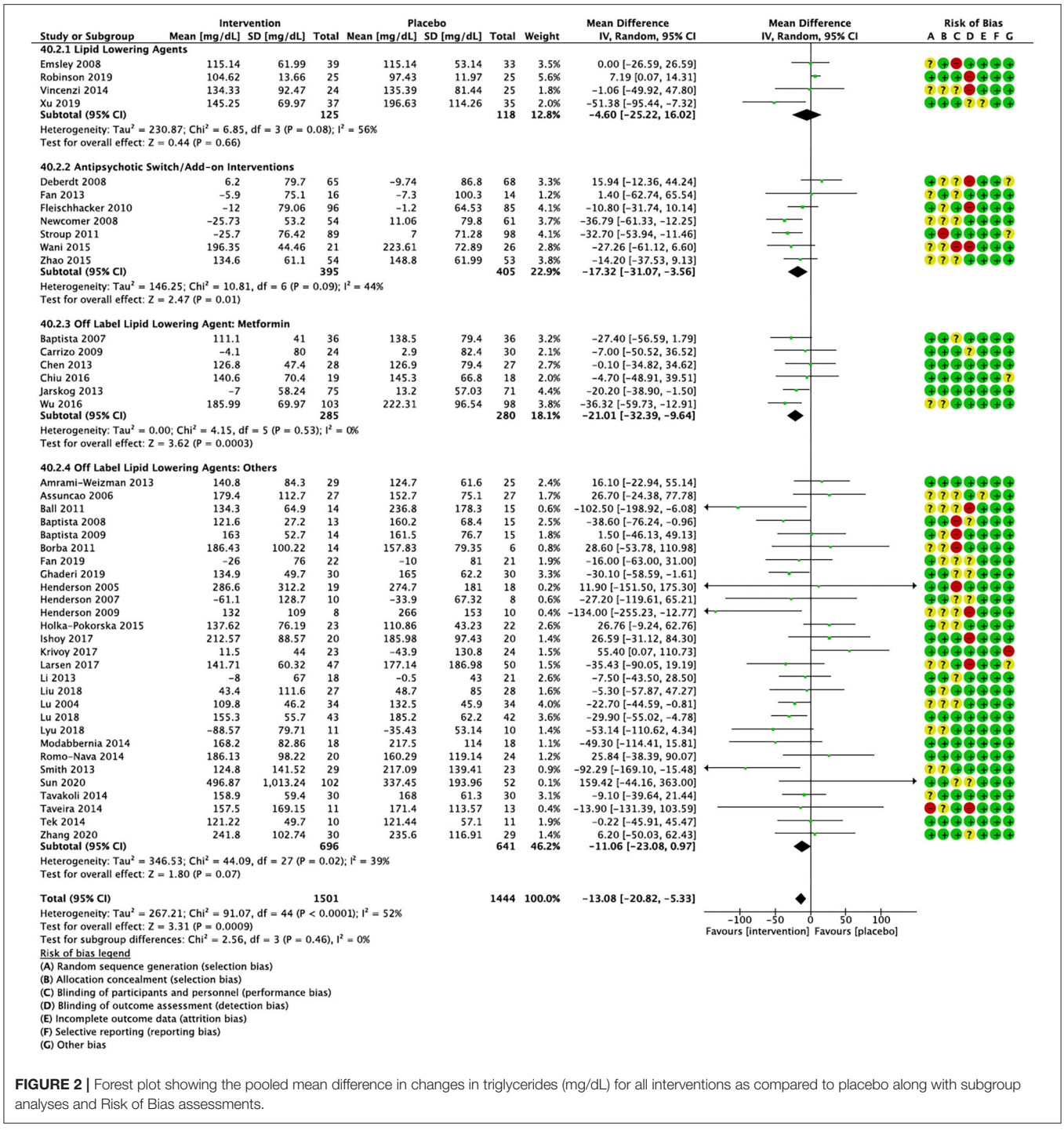

FIGURE 2 | Forest plot showing the pooled mean difference in changes in triglycerides (mg/dL) for all interventions as compared to placebo along with subgroup analyses and Risk of Bias assessments.

WMD = −17.32 mg/dL, CI: −31.07, −3.56; $p = 0.01$; $I^2 = 44$), LDL cholesterol (**Figure 4**; $N = 5$, $n = 689$; WMD = −6.45 mg/dL, CI: −12.83, −0.07; $p = 0.05$; $I^2 = 55$), and total cholesterol levels (**Figure 6**; $N = 6$, $n = 798$; WMD = −8.83 mg/dL; CI: −13.91, −3.74; $p = 0.0007$; $I^2 = 32$) in comparison to placebo. A significant increase was noted for HDL cholesterol level (**Figure 3**; $N = 7$, $n = 844$; WMD = 1.72 mg/dL; CI: 0.06, 3.39; $p = 0.04$; $I^2 = 58$). None of the antipsychotic switching/add-on studies examined VLDL cholesterol.

Off Label Lipid Lowering Agent: Metformin

Metformin was associated with significant reductions in triglycerides (**Figure 2**; $N = 6$, $n = 565$; WMD = −21.01 mg/dL, CI: −32.39, −9.64; $p = 0.0003$; $I^2 = 0$) and total cholesterol

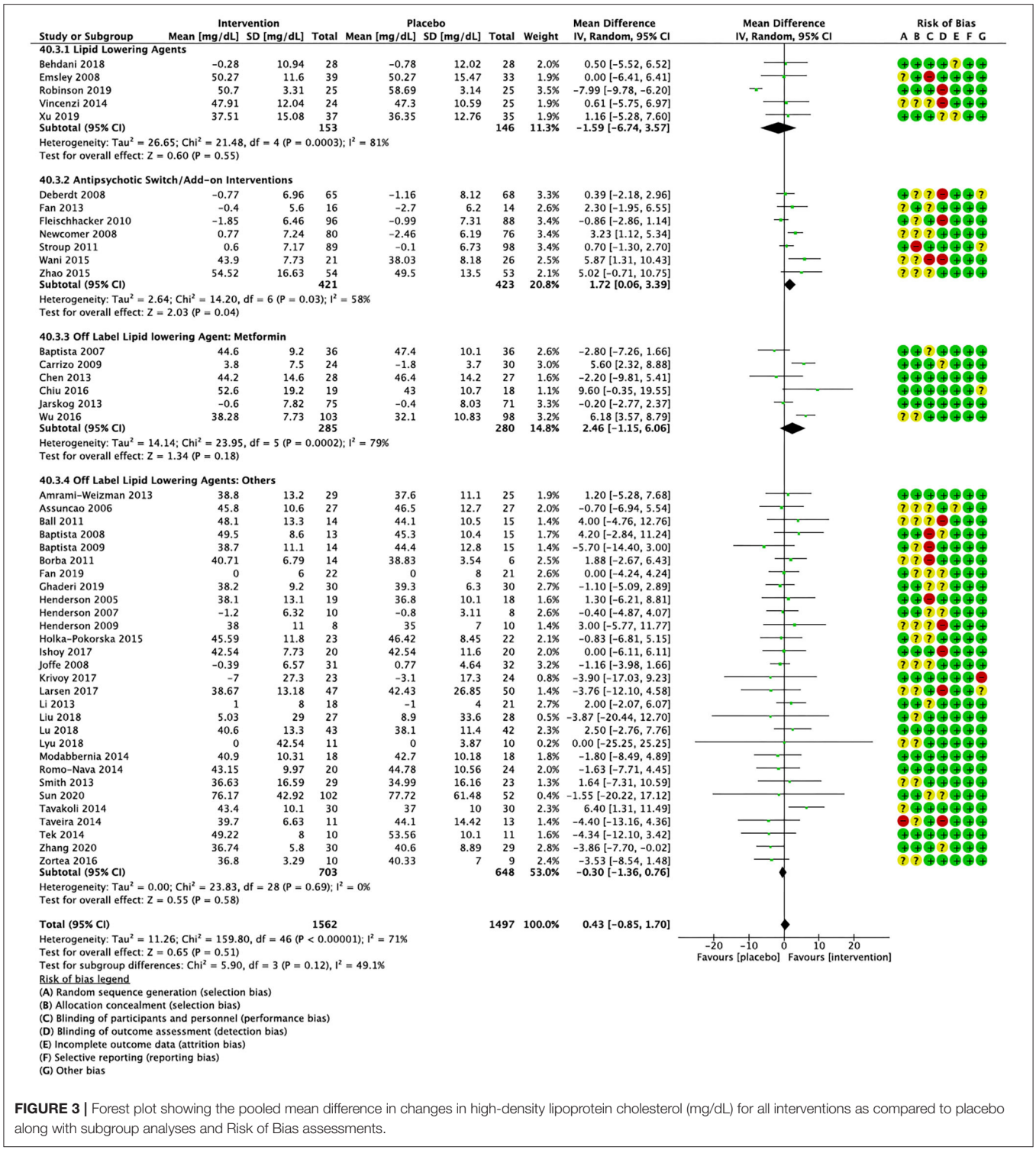

FIGURE 3 | Forest plot showing the pooled mean difference in changes in high-density lipoprotein cholesterol (mg/dL) for all interventions as compared to placebo along with subgroup analyses and Risk of Bias assessments.

(**Figure 6**; $N = 3$, $n = 419$; WMD = −14.40 mg/dL; CI: −26.51, −2.28; $p = 0.02$; $I^2 = 47$) compared to placebo. No significant changes were noted for HDL cholesterol (**Figure 3**; $N = 6$, $n = 565$; $I^2 = 79$) and LDL cholesterol (**Figure 4**; $N = 3$, $n = 419$; $I^2 = 89$). None of the metformin studies examined VLDL cholesterol.

Off Label Lipid Lowering Agents: Others

For other off label lipid lowering agents, there was a statistically significant reduction in total cholesterol levels (**Figure 6**; $N = 27$, $n = 1{,}322$; WMD = −5.18 mg/dL, CI: −10.31, −0.05; $p = 0.05$; $I^2 = 41$) along with a decreasing trend in levels of triglycerides

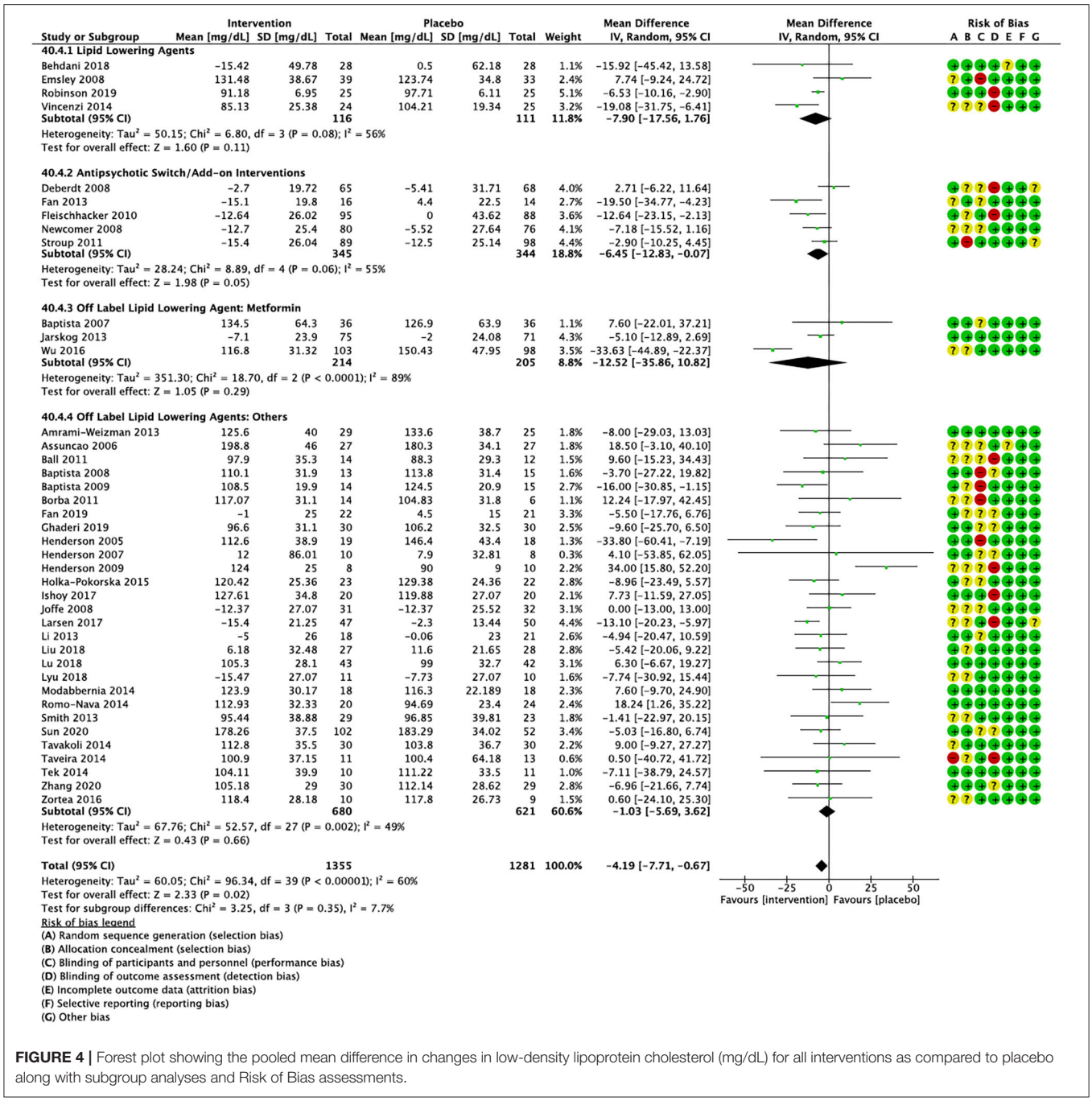

FIGURE 4 | Forest plot showing the pooled mean difference in changes in low-density lipoprotein cholesterol (mg/dL) for all interventions as compared to placebo along with subgroup analyses and Risk of Bias assessments.

that was nonsignificant (**Figure 2**; $N = 28$, n = 1,337; WMD = −11.06, CI: −23.08, 0.97; $p = 0.07$; $I^2 = 39$). There were no significant differences for LDL cholesterol (**Figure 4**; $N = 28$, $n = 1{,}301$; $I^2 = 49$), HDL cholesterol (**Figure 3**; $N = 29$, $n = 1{,}351$; $I^2 = 0$), and VLDL cholesterol (**Figure 5**; $N = 4$; $n = 223$; $I^2 = 0$).

Secondary Outcomes: Additional Metabolic Measures

Cumulatively, the pharmacological interventions reviewed in this paper were associated with significant reductions in body weight (**Supplementary Figure 1**; $N = 38$, $n = 2{,}380$; WMD = −1.13 kg, CI: −2.18, −0.08; $p = 0.03$), BMI (**Supplementary Figure 2**; $N = 36$, $n = 2{,}174$; WMD = −0.42 kg/m^2, CI: −0.85, 0.01; $p = 0.05$), and waist circumference (**Supplementary Figure 3**; $N = 29$, $n = 1{,}532$; WMD = −1.34 cm, CI: −2.34, −0.34; $p = 0.009$) compared to placebo. As for glucose-related parameters, interventions led to significant decreases in blood insulin (**Supplementary Figure 4**; $N = 24$, $n = 1{,}636$; WMD = −1.64 mIU/mL, CI: −2.76, −0.52; $p = 0.004$) and HOMA-IR (**Supplementary Figure 5**; $N = 16$, $n = 867$; WMD = −0.52, CI:

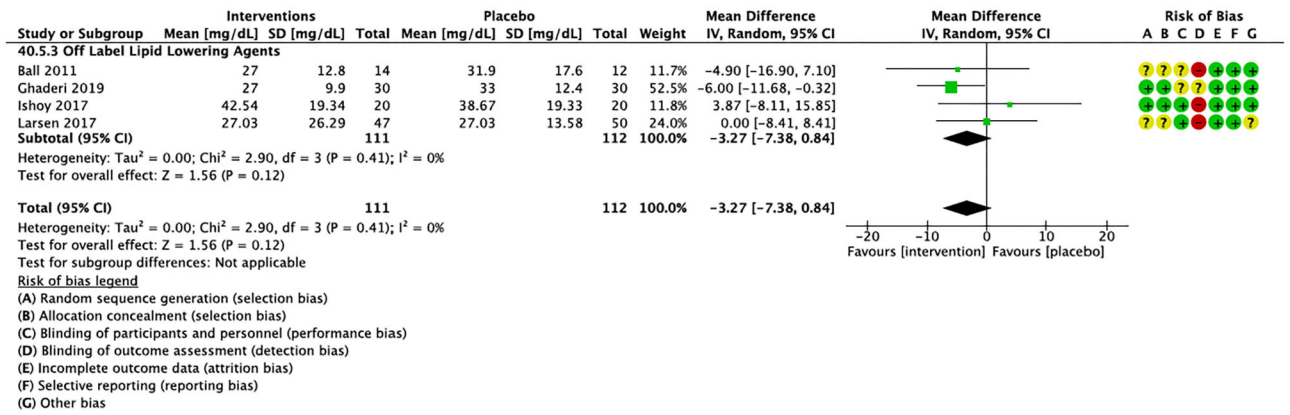

FIGURE 5 | Forest plot showing the pooled mean difference in changes in very low-density lipoprotein cholesterol (mg/dL) for all interventions as compared to placebo and Risk of Bias assessments.

−0.89, −0.15; $p = 0.005$) compared to placebo. Blood glucose levels showed a decreasing trend, but the difference was not significant (**Supplementary Figure 6**; $N = 46$, $n = 3{,}048$; WMD = −1.17 mg/dL, CI: −2.44, −0.11; $p = 0.07$). Differences in HbA1c levels were also not significant (**Supplementary Figure 7**; $N = 19$, $n = 1{,}097$). Total PANSS scores showed a trend toward improvement in the intervention group, but the difference again was not statistically significant (**Supplementary Figure 8**; $N = 13$, $n = 1{,}005$, WMD = −2.15; CI: −4.45, 0.16; $p = 0.07$). Finally, there were no significant differences in systolic blood pressure (**Supplementary Figure 9**; $N = 16$, $n = 892$) and diastolic blood pressure (**Supplementary Figure 10**; $N = 15$, $n = 845$).

Risk of Bias

Risk of bias in random sequence generation was deemed to be low in 29 studies, high in 1, and unclear in 18 (**Supplementary Figure 11**). Outcomes did not change significantly after the study with high risk of bias was removed.

DISCUSSION

In this systematic review and meta-analysis, we examined different pharmacological interventions used to treat antipsychotic-induced dyslipidemia in schizophrenia spectrum disorders. The 29 pharmacological interventions analyzed were cumulatively effective in lowering total cholesterol, LDL cholesterol, and triglycerides, while increasing HDL cholesterol. However, improvements were not significant with VLDL cholesterol. Amongst the subgroups analyzed, we found that antipsychotic switching/add-on proved most effective in improving lipid parameters commonly dysregulated in schizophrenia, namely triglycerides and HDL cholesterol (77). Notably, the off-label lipid lowering agent metformin was more promising than approved lipid lowering agents in decreasing triglycerides and total cholesterol levels. However, other off label agents only showed a trend in improving lipid parameters.

Our findings suggest that off label strategies can be effectively employed to ameliorate antipsychotic-induced dyslipidemia. In particular, metformin shows considerable promise, improving lipid parameters and showing consistent association with a decrease in triglycerides and total cholesterol levels. Similar findings for triglycerides and total cholesterol levels were previously demonstrated in a review by Jiang et al. (78), and in the context of schizophrenia would benefit through evidence specific to long-term outcomes. Prior studies indicate that a 40 mg/dL reduction in LDL cholesterol and triglycerides translates into a 20% and 4–5% decrease in risk for developing cardiovascular disease, respectively, independent of baseline risk (79). Given this, our review suggests that the available strategies for targeting dyslipidemia are inadequate, reinforcing the need for novel, more effective interventions. Furthermore, while our findings provide strong evidence for antipsychotic switch/add-on interventions, study duration ranged from 6 to 24 weeks, which does not provide adequate time to assess the long-term effects of these treatments on dyslipidemia. While aripiprazole and quetiapine are both second generation antipsychotics with less severe metabolic side-effects compared to others like olanzapine and clozapine, they have their own metabolic burden that cannot be ignored and needs to be better understood over the longer term (80, 81). Similarly, while our findings suggest that lipid lowering agents are not effective in improving dyslipidemia, these results may have been limited by the short duration of the included studies. The small number of studies also did not permit examination of the possible effects of dose of lipid-lowering agents.

Current studies provide general support for the potential effectiveness of pharmacological interventions, but further research is warranted to refining recommendations pertaining to individual treatments. Currently in many studies, lipid management was not a primary focus; of the 48 reviewed studies, only 26 identified lipid profile as a primary outcome measure, in contrast to 22 where it was positioned as a secondary outcome. More studies focused on this area of research sets the stage for additional insights and the increased power necessary to detect not only beneficial outcomes, but also the elucidation of specific variables contributing to effective

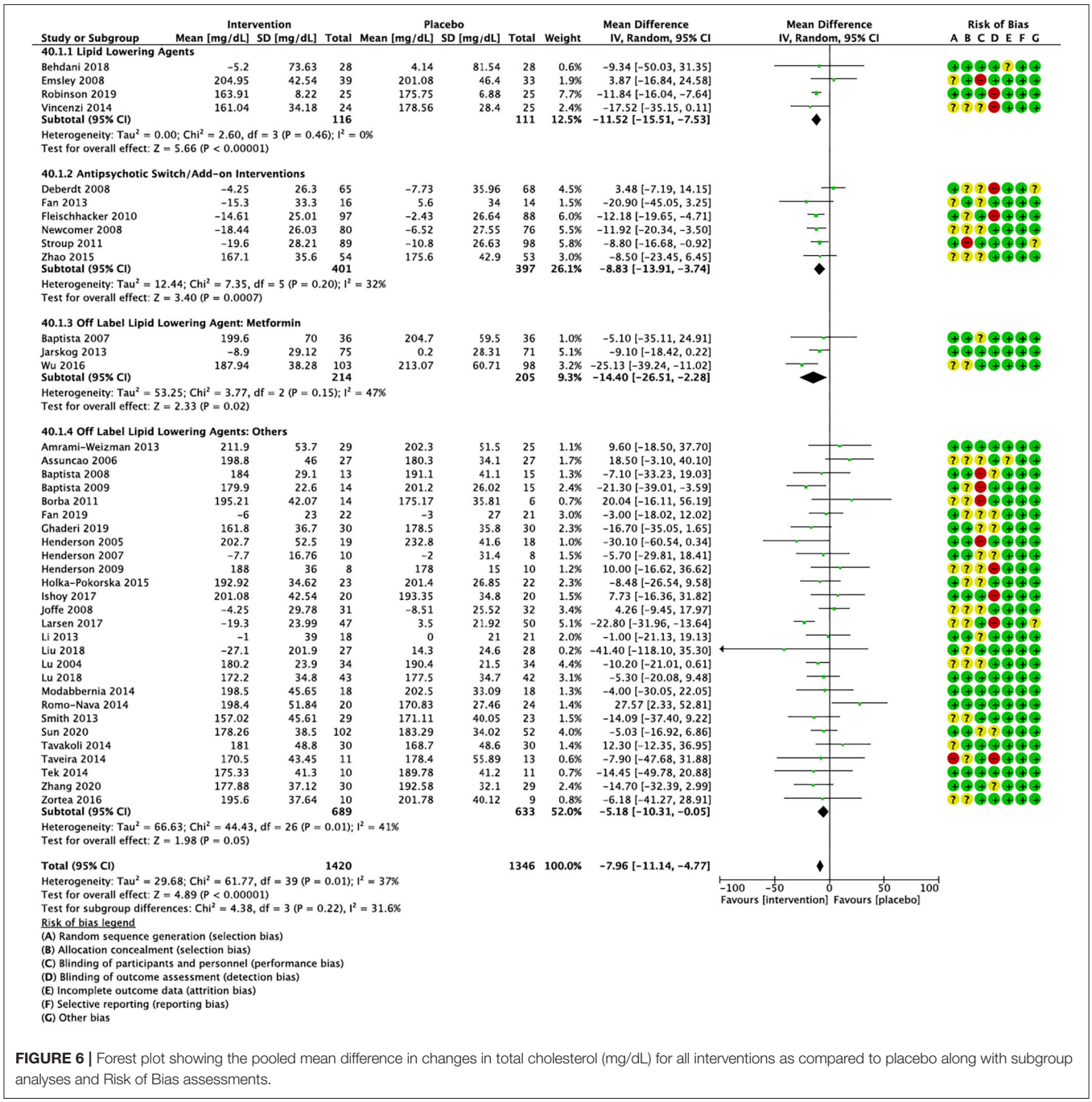

FIGURE 6 | Forest plot showing the pooled mean difference in changes in total cholesterol (mg/dL) for all interventions as compared to placebo along with subgroup analyses and Risk of Bias assessments.

treatment. At present, the significant heterogeneity among studies within intervention categories limit generalizations that can be made with respect to mechanisms or interacting variables. Factors affecting outcomes may include specific antipsychotic treatment, diagnosis and stage of illness, co-morbid health conditions, concomitant medications, and duration of antipsychotic and/or lipid intervention treatment. Differential pharmacological interventions may, in fact, vary as a function of patient population. Moreover, to date, many interventions are confined to a single study, precluding pooled data or comparisons between interventions. Our review restricted the population to schizophrenia patients, even though antipsychotics are used to treat patients with other psychiatric illnesses such as affective disorders who also share the metabolic burden (82) and may benefit from the reviewed interventions. Finally, while behavioral and lifestyle interventions remain first-line treatments for dyslipidemia, our review restricted the search to pharmacological interventions.

Given the prevalence of dyslipidemia in schizophrenia, along with the associated increased risk of metabolic complications

and cardiovascular disease, it is imperative that such studies be undertaken. At present, dyslipidemia is often left untreated (13–15); indeed, the physical health of this population is generally overlooked while the focus is directed to managing psychotic symptoms (83, 84). The integration of psychiatric and medical care falls short at present (85); however, this overview of dyslipidemia, its prevalence and current treatment underscores the need to ensure a more comprehensive model of care be implemented.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

PK, SMA, and MKH contributed to developing the original protocol. PK and KC-D contributed to the original screening, data extraction, risk of bias assessments, and writing the first draft of the manuscript (introduction, methods, and results). FP and JL wrote and registered the protocol with PROSPERO, re-ran the search, updated study selection and risk of bias, and contributed to final data extraction and synthesis prior to manuscript submission, as well as updating the first draft. LH assisted with editing and writing the final draft. SMA was involved in supervising all aspects of the review. GR and MKH contributed to editing the final draft. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.642403/full#supplementary-material

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SYSTEMATIC REVIEW
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Clinical, Biochemical and Genetic Variables Associated With Metabolic Syndrome in Patients With Schizophrenia Spectrum Disorders Using Second-Generation Antipsychotics: A Systematic Review

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Background: Individuals with severe mental illness experience increased morbidity and mortality compared to the general population. Adverse effects of antipsychotics, including weight gain, may contribute to the development of metabolic syndrome (MetS), which is associated with increased risks of all-cause and cardiovascular disease mortality. We aim to provide a comprehensive overview of clinical, biochemical and genetic factors associated with MetS among patients with schizophrenia spectrum disorders using second-generation antipsychotics (SGA).

Methods: A literature search was performed in Pubmed and Embase to identify all cohort studies, cross-sectional studies and clinical trials investigating associations with MetS in patients with schizophrenia spectrum disorders using SGAs. We extracted and enumerated clinical, biochemical and genetic factors reported to be associated with MetS. We defined factors associated with MetS as factors being reported as associated with MetS in two or more studies.

Results: 58 studies were included in this review (n = 12,123). In total, 62 factors were found to be associated with increased risk of MetS. Thirty one out of 58 studies investigated factors that were reported as associated with MetS in two or more studies. With regard to clinical factors, we found gender, higher age, concomitant use of mood stabilizers, higher baseline and current BMI, earlier SGA exposure, higher dose, longer duration of treatment, psychosis and tobacco smoking to be significantly associated with MetS. Furthermore, the biochemical factors hypo-adiponectinemia, elevated levels of C-reactive protein (CRP) and higher white blood cell (WBC) count were identified as factors associated with MetS. Among pharmacogenetic factors, the rs1414334 C-allele of the HTR2C-gene was associated with MetS in patients using SGA.

Conclusion: In this systematic review investigating clinical, biochemical and genetic factors associated with MetS in patients using SGAs we found that higher age, higher baseline BMI, higher current BMI and male as well as female gender were positively associated with MetS across all antipsychotics. This study may set the stage for the application of clinical, biochemical and genetic factors to predict the risk of developing MetS in patients using SGAs. Future research is needed to determine which patients using SGAs are at risk to develop MetS in clinical practice.

Keywords: metabolic syndrome, antipsychotics, psychotic spectrum disorder, schizophrenia, systematic review

INTRODUCTION

Patients with psychotic spectrum disorders have a markedly reduced life expectancy compared to the general population. For instance, patients with schizophrenia have a reduced life span of 15–20 years compared to the general population and also have more somatic co-morbidities (1, 2). This is partially due to the development of the metabolic syndrome (MetS). MetS is a combination of risk factors that can lead to increased mortality and morbidity such as cardiovascular disease and diabetes (3). According to The US National Cholesterol Education Programme Adult Treatment Panel III (ATP III), MetS is diagnosed when a person fulfills at least three of the following criteria: waist size of at least 102 cm for males and at least 88 cm for females; triglycerides of at least 150 mg/dl; HDL cholesterol level of <40 mg/dl for males and <50 mg/dl for females; a blood pressure of more than 130 mmHg systolic or 85 mmHg diastolic; and a fasting glucose of more than 100 mg/dl (4). The International Diabetes Federation (IDF) applies similar criteria but requires the presence of an increased, ethnicity specific waist size plus two or more of the abovementioned factors (5).

Rates of MetS vary significantly between populations. Genetic and geographical environmental differences are known to affect metabolic risk factors. For Europeans the age-adjusted rates are 18.4% for men and 14.4% for women while in South Asians the occurrence in men is 28.8 and 31.8% for women, based on the ATP III MetS definition (6). In Japan, the rate of MetS is 14.2% in the general population (7) while in the United States, the age-adjusted weighted prevalence is 34.3% (8). Compared to the general population, patients with schizophrenia have a 2- to 3-fold increased prevalence of MetS varying per country (9, 10). Given the higher prevalence of MetS among these schizophrenia patients, the syndrome poses a greater health risk to this population. It has a significant impact on morbidity and mortality due to the increased risk of diabetes mellitus type 2 (DM2) and cardiovascular disease (3). Explanations for this higher prevalence are a poor diet, cigarette smoking (11, 12), lack of exercise (12), stress and abnormalities in the hypothalamic-pituitary-adrenal axis (13). On top of this, SGA use is associated with metabolic abnormalities and may exacerbate this condition by causing weight gain, glucose and lipid metabolism deregulation (6, 14–18). Antipsychotics can influence metabolic parameters within 2 weeks of treatment (19). However, the existing body of research suggests that the degree of metabolic dysregulations varies considerably between different SGAs (19). Evidence for weight gain was found for clozapine, zotepine, olanzapine, and sertindole, iloperidone, quetiapine, risperidone and paliperidone, and brexpiprazole. SGA are also associated with glucose abnormalities and development of DM2 (9, 20–23). Pillinger et al. (24), performed a large meta-analysis to compare and rank antipsychotics based on their metabolic side-effects and to identify predictors of antipsychotic-induced metabolic dysregulation. Increased baseline weight, male sex, and non-white ethnicity were found to be predictors of susceptibility to antipsychotic induced metabolic change (24). Increase in fasting-glucose was associated with a higher risk of (cardio)vascular disease and was especially evident in olanzapine, zotepine, and clozapine use (24). Furthermore, several studies have demonstrated lipid disturbances following SGA-use (25). Evidence was found that quetiapine, olanzapine, zotepine, and clozapine are negatively correlated with triglyceride alterations (24). Finally, research indicates that patients using SGA have increased cholesterol levels (26), especially in patients using quetiapine, olanzapine, or clozapine (24). Clozapine is the most effective treatment to improve symptom severity and to reduce the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder (27, 28). Meanwhile, together with olanzapine, it is also associated with the highest increases in weight, body mass index (BMI) and total cholesterol, suggesting that the greatest metabolic disturbances are caused by the most efficacious antipsychotics (16, 24, 29).

Qualitative research shows that patients have concerns about the negative long-term effects of antipsychotics on their physical appearance and physical health (30, 31). Multiple studies show that patients using antipsychotic medication consider weight gain, possibly leading to overweight and obesity, as one of the most disturbing adverse events and therefore one of the major reasons for non-adherence to therapy (32, 33). Taking this into consideration, elucidating factors that contribute to the occurrence of MetS in specific antipsychotics is useful for clinical practice.

Although the use of SGA is thus clearly associated with increased risk to develop MetS, specific factors that increase this risk have remained largely elusive. Apart from the effects accounted for by lifestyle and antipsychotic medication, research hints at a shared underlying pathophysiology between schizophrenia and cardiovascular disease (34). The high

interindividual variability in the occurrence of MetS suggests that genetic factors influence its risk (35). In previous studies, factors associated with MetS among patients with psychotic spectrum disorders who use SGA have been examined (36–38). These factors, however, have been discussed in isolation and findings remain inconclusive. Furthermore, in the analysis by Pillinger et al. (24), MetS was not examined as an outcome measure; only isolated factors (e.g., dislipidemia, hypercholesteremia) were investigated. We chose to perform a systematic review in which we included only studies that took MetS (the combination of risk factors) as an outcome measure. Since people with MetS have a reduced life span of 15–20 years compared to the general population and also have more somatic co-morbidities (39), we reasoned there would be added value in considering MetS as a conglomerate of factors, instead of its isolated components. Finally, in the study of Pillinger et al. (24), limited clinical and biochemical factors and no genetic factors were investigated, which we here expanded on. Thus, we conducted a systematic review of factors associated with MetS during treatment with SGAs (4, 5).

METHODS

Search Strategy

The systematic review was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (40). Articles were identified through searches in PubMed and Embase from inception until July 25, 2020. Synonyms of the following search terms were used: (schizo* OR psychos*) AND ("metabolic syndrome(s)" OR "syndrome X") AND (antipsychotic OR [generic/branded antipsychotic names]). The search strategy is described extensively in the **Appendix** (p. 29). We included all cohort studies, cross-sectional studies and clinical trials investigating factors associated with MetS among patients with psychosis spectrum disorders using clozapine, olanzapine, quetiapine, risperidone, aripiprazole, ziprasidone, lurasidone, asenapine, zotepine, and paliperidone (**Appendix**, p. 1–5).

Inclusion and Exclusion Criteria

The following studies were included: (i) studies which reported factors associated with MetS; (ii); studies which were cohort studies, cross-sectional studies or clinical trials; (iii) studies that have been written in English or Dutch; (iv) studies with full text availability; (v) studies that were conducted in adult human participants (≥18 years, with no upper age limit) with a diagnosis of psychotic spectrum disorders classified according to DSM-5 criteria (schizophrenia, schizophreniform disorders, schizoaffective disorders, delusional disorders, short-term psychotic disorders and catatonia) and; (vi) studies that investigated the outcome MetS using ATP III, ATP III-A or IDF criteria (4, 5). Presence of MetS in the individual studies was considered only if defined according to one of the following accepted criteria, meaning either the IDF criteria or the National Cholesterol Education Programme's Adult Treatment Panel III criteria (NCEP/ATP III), or the modified IDF and modified NCEP/ATP III criteria with Asian cutoffs for BMI and waist circumference, or the American Heart Association/National Heart, Lung and Blood Institute (AHA/NLHBI) criteria. When the full text of an article was not available through our University library, librarians tried to retrieve the article from other sources. Studies were excluded from the review if they were: (i) animal studies and (ii) reviews/meta-analyses.

Data Extraction and Reporting of Results

Articles were included or excluded based on title and abstract. In case of doubt, the full text of the articles was screened. The snowball method was used by checking the references of the retrieved articles, including reviews, on potential additional literature for the current review. Article screening and data extraction was performed by S.E., M.S. and M.H.S. Of all included studies author, year of publication, study type, antipsychotics, factors, outcomes, prevalence of MetS, *p*-values, odds ratios (OR), confidence interval (CI), follow-up time, origin of population, sample size (*n*), male/female ratio, mean age and mean duration of SGA treatment were gathered. A factor was considered as significant in this review when authors named it as significant. It was decided not to use $p = 0.05$ as the limit for significance, because the number of factors investigated influences the interpretation of the p-value due to a higher chance of type 1 errors. For our systematic review, we enumerated the clinical, biochemical and genetic factors reported as significantly associated with MetS in the studies as outcome measure. Only factors that were found to be associated with MetS in two or more studies were included. Studies on factors that were not found to be associated, or factors that were found to be associated in only one study, were included in **Supplementary Material** (see **Supplementary Tables 1–3** for study characteristics and **Supplementary Tables 4–11** for results on investigated factors). Solely data on subjects with complete metabolic profile is included. Results on associated factors are presented separately for studies investigating a SGA individually and for studies investigating a pooled group of antipsychotics.

Quality Assessment

The quality of the articles was assessed using the Quality In Prognosis Studies (QUIPS) checklist (41). When using this method, articles are scored on: Study Participation, Study Attrition, Prognostic Factor Measurement, Outcome Measurement, Study Confounding and Statistical Analysis and Reporting by marking them as low risk, uncertain risk and high risk of bias. Study Participation addresses the representativeness of the study sample for the source population. Studies with low participation rates, considerable differences in age and sex distribution or very selective eligibility criteria were considered to have a high risk of bias, while studies with high participation and a study sample comparable to the entire population had a low risk of bias. Study Attrition addresses the possible bias with regards to participants who do not complete the study. Studies with high withdrawal rates and inconclusive follow-up information have a high risk of bias, while studies with complete follow-up data, or evidence of participants missing at random, have a low risk of bias. The Prognostic Factor Measurement and Outcome Measurement domain addresses the clarity of outcome

definition, the validity and reliability of measurement and the similarity of measurements. Differential measurements between groups are considered to contribute to a high risk of bias, while similarity and reliability of measurements are considered to have a low risk of bias. Study Confounding addresses the risk of bias with regards to the possibility of confounding factors that might contribute to the outcome. Adequate measurement of potential confounding variables and correction for these factors lowers the risk of bias. Finally, the Statistical Analysis and Reporting domain addresses the suitability of the statistical analysis and the completeness of reporting in a study. The risk of bias in this domain is considered low if the analysis is appropriate for the data, statistical requirements are met and all primary outcomes are reported. Thus, generally we used the QUIPS checklist to evaluate the risk of bias. Studies that scored high risk of bias in more than four categories were excluded from our systematic review.

RESULTS

Search Results

The study selection process for this systematic review is summarized in **Figure 1**. The initial search identified 2,053 research articles. The snowball method resulted in an additional 8 articles. After removing duplicates, 683 unique articles were screened for suitability for inclusion, utilizing the search criteria defined above, by reading the titles and abstracts. Of these, 108 articles were extracted for further evaluation to assess the full-text of these articles for potential eligibility. The references of these full-text articles were also scrutinized to identify additional eligible publications. Fifty articles were excluded because they: did not provide data on schizophrenia diagnosis ($n = 5$), did not perform a relevant intervention ($n = 3$), did not use MetS as outcome measure ($n = 18$), were in a different domain ($n = 1$), did not investigate risk factors (14) or solely provided conference abstracts ($n = 9$). These studies reported p-values, odds ratios and F-values (**Tables 2**, **3**). All steps resulted in 58 studies meeting the selection criteria.

Study Characteristics

The 58 included studies were made up of eight cohort studies, 44 cross-sectional studies, five case-control studies and one clinical trial. Of the 58 studies, 26 investigated a single SGA and 32 multiple SGAs. The studies were conducted in: China (11), United States (9), Taiwan (7), the Netherlands (5), Korea (3), India (2), Croatia (2), Turkey (2), Serbia (2), Ireland (1), Australia (1), Venezuela (1), Brazil (1), Thailand (1), Sudan (1), Sweden (1), Finland (1), United Kingdom (1), Germany (1), Malaysia (1), Denmark (1), Romania (1), Chile (1), and Italy (1). Thus, 23 out of 58 studies (40%) had been conducted in low- and middle-income countries (2 and 21 studies, respectively). Twenty-seven of the studies were performed in Asian countries. The number of participants per study varied from 24 to 621. The total number of participants was 12.123 (excluding overlap of sample size). The most commonly studied antipsychotics were: clozapine (5,739 participants); olanzapine (2,081 participants), risperidone (1,875 participants), quetiapine (233 participants), aripiprazole (110 participants) and paliperidone (79 subjects). Two hundred and sixty-four participants received polytherapy. Regarding the studies that investigated single SGAs, clozapine was the most prevalent (21 studies), followed by olanzapine (six studies), risperidone (one study) and aripiprazole (one study). The mean duration of SGA treatment ranged from 10 to 209 months. The MetS prevalence ranged from 28.4 to 64%. Forty-four of the 58 studies were cross-sectional, which limits the ability to draw valid conclusions about possible causality because the presence of risk factors and outcomes are measured simultaneously. See **Supplementary Tables 1–3** for the study characteristics of all included studies.

Quality Assessment

Quality assessment was conducted based on the reporting and methodological quality of the studies. There was a high risk of bias regarding study participation in 18 studies, 16 had an unclear risk of bias and 20 a low risk of bias regarding study participation (**Table 1**). Most of the studies had a low risk of bias with regards to study attrition. Only four were considered to have a high risk of bias regarding study attrition, while three had an uncertain risk of bias. The domain of prognostic factor measurement was found to have a high risk of bias in three studies, while the other 55 were not considered to have a risk of bias in this domain. The outcome measurement was clearly defined and established in all studies and was therefore considered to have low risk of bias in this category. Most of the studies were cross-sectional studies that, due to the nature of their design, were more prone to confounding. The risk of bias due to study confounding was therefore considered to be high in 45 of the studies; seven had an uncertain risk of bias, while six had a low risk of bias. Finally, the risk of bias regarding statistical analysis and reporting was considered high in 13 studies, while 45 were considered to have a low risk of bias. Thus, generally studies that had high risk of bias in three or more of the QUIPS categories were excluded from the analysis. None of the identified studies had a high risk of bias in more than four categories, therefore all 58 were included in this systematic review.

Clozapine

Nine clinical factors were found to be related to MetS (**Table 2**). Three studies found an association between male gender and MetS in patients treated with clozapine (47, 86, 92). In three other studies of clozapine, an association between female gender and MetS was found (62, 81, 84). The use of concomitant mood stabilizers was reported to be a risk factor for MetS in two studies (81, 85, 94). Bai et al. (94) and Josiassen et al. (84), found higher age at initiation of clozapine treatment to be associated with MetS. Brunero et al. (86), Lamberti et al. (22), and Bai et al. (94), found higher age to be a risk factor associated with MetS. Higher baseline BMI was reported to be associated with MetS in two studies (84, 94). In four other studies, it was shown that higher current BMI is also a risk factor for MetS in patients treated with clozapine (22, 78, 86, 92). Clozapine dose also seems to affect the occurrence of MetS, as was found by Josiassen et al. (84) and Brunero et al. 2009 (86). Finally, the duration of

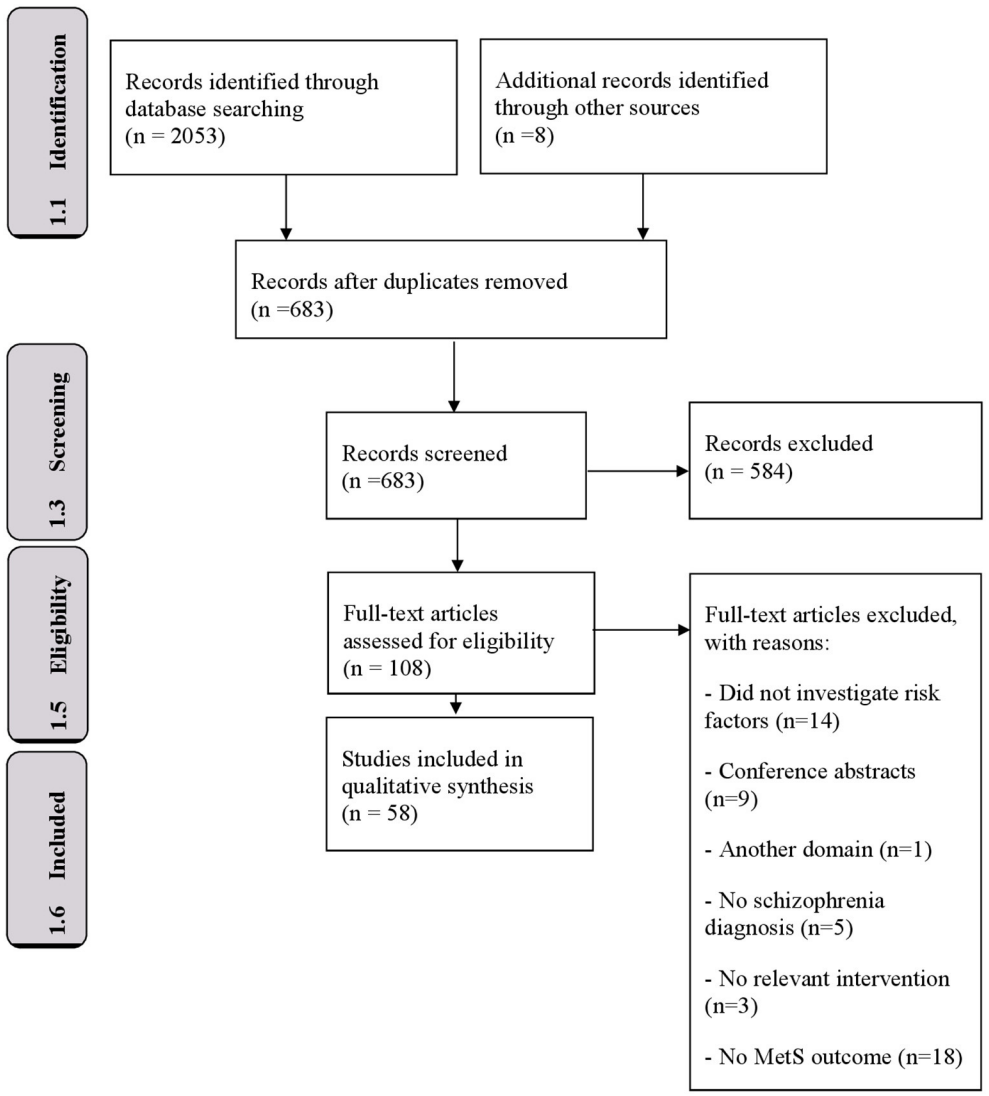

FIGURE 1 | Flow diagram of the review selection process.

clozapine treatment was found to be associated with MetS in two studies (22, 84).

Risperidone, Olanzapine, and Aripiprazole

Eight studies investigated the association between clinical, biochemical or genetic factors and the occurrence of MetS in patients treated with either risperidone, olanzapine or aripiprazole. All reported factors were only found to be associated in single studies (**Supplementary Tables 6–9**).

Pooled Results of SGAs

The majority of the studies on risk factors associated with MetS analyzed antipsychotics in pooled groups, consisting of several antipsychotics. Sixteen factors were found to be risk factors for MetS (**Table 3**). Hypo-adiponectinemia was reported to be associated with MetS in two studies (51, 85). Kraemer et al. (76) and Miller et al. (64), investigated the association of CRP in their patient sample and found values of ≥3 mg/L to be correlating with the occurrence of MetS. Higher total WBC count was found to be associated in two studies (64, 80). Three studies reported male gender to be associated with MetS (46, 74, 76), while four studies found female gender to be a risk factor for MetS (54, 71, 89, 91). Several studies reported a higher age of patients treated with antipsychotics to be significantly associated with the development of MetS (43, 46, 55, 73, 74, 85, 87, 91). Grover et al. (71), found age >35 to be associated with MetS. Ethnicity was not found to be a clear risk factor for MetS.

Various studies reported BMI to be a significant risk factor for MetS. Higher baseline BMI was found to be associated with MetS (85). Medved et al. (83), Saatcioglu et al. (57), and Hagg et al. (95), reported higher current BMI to be significantly correlating with MetS in their subjects (57, 83,

TABLE 1 | Quality assessment of the included studies.

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Mohamed et al. (42)	?	+	+	+	+	+
Ventriglio et al. (43)	?	+	+	+	−	+
Iruretagoyena et al. (44)	−	+	+	+	−	+
Dehelean et al. (45)	−	+	+	+	−	+
Chen et al. (46)	+	+	+	+	−	+
Puangpetch et al. (47)	+	+	+	+	−	+
Pinto et al. (48)	+	+	+	+	−	−
Lu et al. (49)	+	+	+	+	−	+
Larsen et al. (50)	−	+	+	+	−	+
Chen et al. (51)	−	+	+	+	−	+
Zhang et al. (52)	−	+	+	+	−	+
Zhang et al. (53)	?	+	+	+	−	+
Kraal et al. (54)	?	−	+	+	−	+
Yang et al. (55)	−	+	−	+	−	+
Yang et al. (56)	−	+	+	+	−	+
Saatcioglu et al. (57)	?	+	?	+	−	+
Popovic et al. (58)	?	+	+	+	−	+
Yang et al. (59)	−	+	+	+	+	−
Popovic et al. (60)	?	?	+	+	?	+
Lin et al. (61)	−	+	+	+	−	+
Zhang et al. (62)	−	+	+	+	?	+
Roffeei et al. (63)	?	+	+	+	−	+
Zhang et al. (53)	−	+	+	+	−	+
Miller et al. (64)	−	+	+	+	−	−
Lott et al. (65)	−	+	+	+	−	−
Liou et al. (66)	−	+	+	+	?	+
Lee et al. (67)	+	?	+	+	?	+
Chen et al. (68)	−	+	+	+	?	+
Risselada et al. (69)	−	+	+	+	−	−
Liou et al. (70)	−	+	+	+	−	+
Grover et al. (71)	+	+	+	+	−	+
Fernandez et al. (72)	−	+	+	+	−	+
Ellingrod et al. (73)	?	?	+	+	−	+
Lee et al. (74)	−	+	+	+	−	−
Kuzman et al. (75)	+	+	+	+	−	−
Kraemer et al. (76)	−	−	+	+	−	−
Kang et al. (77)	?	+	+	+	−	+
Grover et al. (78)	?	+	+	+	−	+
Van Winkel et al. (79)	+	+	+	+	−	+
Fan et al. (80)	+	+	+	+	+	+
Steylen et al. (81)	+	+	+	+	−	+
Patel et al. (19)	?	+	−	+	−	+
Mulder et al. (82)	+	+	+	+	−	−
Medved et al. (83)	?	+	+	+	−	+
Josiassen et al. (84)	+	+	−	+	−	−
Bai et al. (85)	+	−	?	+	−	−
Brunero et al. (86)	?	+	+	+	−	+
Yevtushenko et al. (87)	+	−	+	+	−	+
Ojala et al. (88)	+	+	+	+	+	+
Lee et al. (89)	−	+	+	+	+	+

(Continued)

TABLE 1 | Continued

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Ellingrod et al. (90)	?	+	+	+	–	–
Boke et al. (91)	+	+	+	+	+	+
Ahmed et al. (92)	?	+	+	+	–	+
Mulder et al. (93)	+	+	+	+	–	+
Bai et al. (94)	?	+	+	+	–	+
Lamberti et al. (22)	+	+	+	+	–	+
Hägg et al. (95)	+	+	+	+	?	+
Kato et al. (96)	+	+	+	+	?	–

[–/red], high risk of bias; [?/yellow], uncertain risk of bias; [+/green], low risk of bias.

TABLE 2 | Factors associated with MetS in clozapine users reported by ≥2 studies.

Factor	Study/studies	MetS prevalence (%)	Test statistics reported in the included studies	*N*
Male gender	(92)	46.6	OR = 11.18 ($P = 0.013$)	84
	(86)	61.6	$P = 0.009$	73
	(47)	36	OR = 4.33 ($P = 0.02$)	50
Female gender	(84) (#1)	64	F = 4.9 ($P < 0.05$)	25
	(62)	43.2	$P = 0.04$	468
	(81)	61	$P = 0.012$	62
Concomitant use of mood stabilizers	(94)	28.4	OR = 2.642 ($P = 0.041$)	188
	(81)	61	$P = 0.023$	62
(Higher) age at initiation of clozapine treatment	(94)	28.4	OR = 1.056 (P =0.049)	188
	(84) (#1)	64	Statistical trend	25
(Higher) age	(94)	28.4	P =0.009	188
	(86)	61.6	OR = 1.083 (#2) ($P = 0.007$)	73
	(22)	53.8	$P < 0.001$	93
(Higher) baseline BMI	(94)	28.4	OR = 1.226 ($P < 0.001$)	188
	(84) (#1)	64	F = 16.12 ($P < 0.005$)	25
(Higher) current BMI	(92)	46.6	OR = 1.38 ($P = 0.001$)	84
	(78)	47	$P = 0.001$	100
	(22)	53.8	$P < 0.0001$	93
	(86)	61.6	$P = 0.001$	73
Higher clozapine dose	(84)	64	Statistical trend	25
	(86) (#1)	61.6	$P = 0.03$	73
(Longer) clozapine duration	(84) (#1)	64	F = 5.97 ($P < 0.01$)	25
	(22)	53.8	Statistical trend ($P = 0.06$)	93

#1: Half (8 of 16) of the subjects already met MetS criteria during first-generation antipsychotic treatment.
#2: When controlling for the variables of gender, clozapine dose, duration of clozapine treatment, and concomitant use of mood stabilizers and other antipsychotics.

95). A BMI >25 was found to be associated with MetS by Grover et al. (71), while Lin et al. (61) and Yang et al. (55), reported this association for BMI >24. Higher antipsychotic dose was reported to be associated with MetS in two studies (43, 89). Duration of psychosis was found to be a risk factor for the development of MetS (45, 57). Three studies reported a significantly higher prevalence of MetS in tobacco smoking patients (73, 76, 87). One genetic factor, carriership of the variant rs1414334 C-allele, was found to increase the prevalence of MetS (69, 93).

DISCUSSION

In this systematic review that examines the clinical, biochemical and/ or genetic factors associated with MetS in patients using SGAs, we found male and female gender, higher age (at initiation of treatment), concomitant use of mood stabilizers, higher baseline BMI, higher current BMI, higher dose and longer duration of treatment to be positively associated with MetS in patients treated with clozapine. In studies with pooled antipsychotics, hypo-adiponectinemia, elevated CRP (≥ 3 mg/L),

TABLE 3 | Results regarding factors which were associated with MetS in pooled SGAs.

Factor	Study/studies	Antipsychotics	MetS prevalence (%)	Test statistics reported in the included studies	*N*
Hypo-adiponectinemia	(85)	CLO/OLA/RIS	23.8	$P < 0.0001$	567
	(51)	CLO/OLA	33.2	$P = 0.005$	262
CRP ≥ 3 mg/L	(76)	CLO/OLA/RIS	49.6	OR = 2.00, 95% CI = 1.22 – 3.30 ($P = 0.0062$)	476
	(64)	CLO/OLA/RIS/ ARI/QUE/ PAL/HAL/ZIP*	32.2	$P = 0.04$	59
Higher total WBC count	(64)	CLO/OLA/RIS/ ARI/QUE/PAL/ HAL/ZIP*	32.2	$P = 0.001$	59
	(80)	OLA/RIS*	53.8	OR = 47.2, 95% CI = 3.4 – 658.7 ($P = 0.004$)	199
Male gender	(74)	OLA/RISP/ARI	31.7	OR = 2.09, 95% CI = 1.49–2.70 ($P < 0.05$)	145
	(46)	CLO/ARI/AMI/ ZIP/HAL	31.2	OR = 1.45, 95% CI = 1.16–4.65 ($P < 0.05$)	
	(76)	OLA/RIS/QUE	49.6	OR = 0.56, 95% CI = 0.34 – 0.91 ($P = 0.0185$)	476
Female gender	(74)	OLA/RISP	14.7	OR = 2.914, 95% CI = 1.373 – 4.454 ($P < 0.01$)	75
	(54)	QUE/RISP/ ILO/PAL*	41.1	$P = 0.05$	112
	(91)	N/A	32.0	OR = 4.60, 95% CI = 2.20 – 9.64 ($P = 0.005$)	231
	(71)	CLO/OLA/RIS/ QUE	43.6	OR = 1.81, 95% CI = 1.07 – 3.08 ($P = 0.027$)	227
Higher age	(74)	OLA/RISP/ARI	31.7	$P = 0.02$	145
	(43)	CLO/OLA/RIS/ ARI/QUE/ PAL/HAL	31.8	OR = 1.03, 95% CI = 1.01 –1.07 ($P = 0.029$)	151
	(46)	CLO/ARI/HAL/ AMI/ZIP	31.2	OR= 1.03, 95% CI = 0.98 –1.09 ($P < 0.05$)	157
	(73)	CLO/OLA/RIS/ QUE/PAL	41	$P < 0.001$	237
	(85)	CLO/OLA/RIS	23.8	$P = 0.007$	567
	(55)	OLA/RIS*	37.8	OR = 1.939, 95% = 1.078 – 3.485 ($P = 0.012$)	357
	(91)	N/A	32.0	$P = 0.026$	231
	(87)	CLO/OLA/RIS*	38.3	$P = 0.003$	120
Age > 35	(71)	CLO/OLA/RIS/ QUE	43.6	OR = 3.37, 95% CI = 1.94 – 5.86 ($P < 0.001$)	227
(Higher) baseline BMI	(85)	CLO/OLA/RIS	23.8	$P = 0.007$	567
(Higher) current BMI	(83)	OLA/RISP	27	95% CI = 1.201–1.686 ($P < 0.001$)	40
	(57)	CLO/OLA*	42.2	OR = 1.389, 95% CI = 1.210 – 1.595 ($P = 0.018$)	116
	(95)	CLO/OLA*	34.6	$P < 0.001$	269
(Higher) BMI increase after initiation of antipsychotic treatment	(85)	CLO/OLA/RIS	23.8	$P = 0.007$	567
BMI > 25	(71)	CLO/OLA/RIS/ QUE	43.6	OR = 5.64 ($P < 0.001$)	227
BMI > 24	(61)	CLO/OLA/RIS/ ARI/QUE/ ZOT/AMI/ZIP	23.7	OR = 6.084, 95% CI = 3.207–11.540 ($P < 0.001$)	329
	(55)	OLA/RIS*	37.8	OR = 3.999, 95% CI = 2.482–6.442 ($P < 0.001$)	357
(Higher) dose	(89)	OLA/RISP	14.7	$P < 0.01$	75
	(43)	CLO/OLA/RIS/ ARI/QUE/ PAL/HAL	31.8	OR = 1.003, 95% CI = 1.001–1.005 ($P = 0.028$)	151

(Continued)

TABLE 3 | Continued

Factor	Study/studies	Antipsychotics	MetS prevalence (%)	Test statistics reported in the included studies	*N*
Longer duration of psychosis	(45)	OLA/RIS	58.4	$P = 0.027$	77
	(57)	CLO/OLA*	42.2	OR = 1.053, 95% CI = 1.009–1.099 ($P = 0.018$)	116
Tobacco smoking	(87)	CLO/OLA/RIS*	38.3	$P = 0.047$	120
	(73)	CLO/OLA/RIS/QUE/PAL	41	$P < 0.001$	237
	(76)	OLA/RIS/QUE	49.6	OR = 0.6, 95% CI = 0.37–1.00 ($P = 0.049$)	476
HTR2C rs1414334 C-allele	(69)	CLO/OLA/RIS/ARI/QUE/	35	OR, 4.09, 95% CI, 1.41–11.89 ($P = 0.015$)	162
	(93)	CLO/OLA/RIS*	25	OR = 4.09, 95% CI = 1.41–11.89 ($P = 0.01$)	112

Patients with cumulative exposure to antipsychotics ≤2 weeks were categorized as the Minimal Antipsychotic Exposed Group, and the remainder were classified as the Antipsychotic Exposed Group.
Moderate risk group.
**Also other AP used in this study.*
Age >40 years risk factor for MetS.
The main oral drug treatments were clozapine (n = 21), olanzapine (n = 31) and risperidone (n = 16); depot medication was received by 27 patients. No further details on AP that were being used.

higher WBC count, female and male gender, older age, higher baseline BMI, higher current BMI, BMI >24, higher dose, longer duration of psychosis, tobacco smoking and HTR2C polymorphism were found to be positively associated with MetS. Overall, higher age, higher baseline BMI, higher current BMI and male as well as female gender were the only factors associated with MetS across all antipsychotics.

A large meta-analysis by Pillinger et al. (24), found male gender to predict greater vulnerability to antipsychotic-induced metabolic dysregulation. In this systematic review gender was also found to be a factor associated with MetS in patients treated with clozapine and in the pooled antipsychotics group. However, the results on this factor are not unequivocal since some studies found male gender while other studies found female gender to be associated with MetS. One possible explanation for these contradictory findings is related to age. In the general population, the risk of MetS increases with age in a gender-specific manner: under 50 years of age the risk is slightly higher in men, while over the age of 50 the risk is higher in women (97). In addition to gender, age was found to be a risk factor in the clozapine studies, as well as in the pooled groups. Given the fact that with older age the risk of MetS in the general population increases, this is not surprising. Due to variations in MetS prevalence between different countries, we expected to find an association between ethnicity and MetS. However, no clear association was found. It cannot be excluded that this incongruence is compounded by socio-economic factors.

Another factor associated with the development of MetS in studies including clozapine and SGAs was higher antipsychotic dosage. It has been suggested that not all SGA have the same propensity to induce metabolic disturbances, whereby clozapine and olanzapine appear to have concentration-dependent metabolic effects (98). Interestingly, drugs with high affinity for the H_1-histamine, muscarinic, and α-adrenergic receptors, also seem to exhibit the strongest off-target metabolic effects, especially with higher doses (98).

As expected, considering the clinical role of CRP as cardiovascular risk indicator, elevated CRP (≥3 mg/L) was found to be positively associated with MetS. The finding of higher WBC, another inflammatory marker, is consistent with previous literature, however, the underlying mechanism explaining this association remains unclear (80). Furthermore, the association between concomitant use of mood stabilizers and MetS in patients treated with clozapine is in line with previous studies showing a higher MetS prevalence in patients receiving polypharmacy vs. monotherapy and studies reporting weight gain and MetS following treatment with mood stabilizers (10, 99–101). Our findings regarding hypoadiponectinemia support results from previous studies (102). Adiponectinemia is thought to have a normalizing effect on metabolic dysregulations (103).

Literature suggests that nicotine can reduce food intake and body weight (104) and might therefore reduce the risk of MetS (46, 74). Interestingly, in our systematic review, tobacco smoking was found to be positively associated with MetS. Tobacco smoking is known to cause upregulation of CYP1A1, CYP1A2, CYP2E1 and UGT, enzymes that are known to be involved in, among others, antipsychotic metabolism (105, 106). Smoking patients therefore would have lower plasma concentrations when comparing to non-smoking patients with the same dose. Nevertheless, physicians might prescribe these patients higher doses in order to reach the same plasma level, which could explain our finding (54, 89, 100).

Previous studies evaluating genetic factors observed inconsistent results on whether certain polymorphisms increase risk of MetS (**Supplementary Tables 10, 11**). To our knowledge, only the rs1414334 C allele of the HTR2C gene has been associated with MetS in multiple studies, although in pooled groups of antipsychotics. Although the mechanism of action

is unclear, Mulder et al. (107), reported this polymorphism also to be significantly related to an increased risk of obesity in psychiatric patients treated with antipsychotics (107). This strengthens the idea that this polymorphism could be relevant.

One of the constituents of MetS is waist circumference (WC). A normal waist circumference differs for specific ethnic groups due to differences in cardiometabolic risk. For example, the relationship between WC and risk factors is such that men and women of South Asian descent present with a more severe metabolic risk profile than those of European descent at the same WC (108). As ethnic descent influences the relationship between WC and metabolic risk factors, current WC data derived from studies in European populations cannot be directly extrapolated to Asians. Furthermore, Asians have increased cardiometabolic risk with lower waist circumferences than other populations (109). Therefore, ethnic background should be considered when using WC as a marker of cardiovascular risk.

Naturally, several limitations may have influenced the results and interpretation of this systematic review. First, the included literature largely consisted of cross-sectional studies. Due to the nature of these studies, no definite conclusions regarding potential causal relationships may be made. Second, the antipsychotic agents used prior to the treatment drug were not recorded in most cross-sectional studies. If these antipsychotics included atypical antipsychotics, the associated factors could not be attributed to the SGA alone. For example, olanzapine prior to the initiation of clozapine leads to adverse metabolic consequences impacting weight, glucose and cholesterol (110). Besides, especially in the pooled groups of antipsychotics, the variation between SGA with their differing propensities to cause metabolic disturbances might have skewed the results. Third, a relatively large part of the studies was conducted in Asian countries. The results of these studies may therefore not be directly extrapolated to the European patient population since there are important metabolic differences partially related to lifestyle and diet between Asian and Caucasian patients on SGA (24). Twenty-seven studies were performed in Asian countries. Furthermore, a substantial number of the studies (40%) was performed in low- or middle-income countries (2 and 21, respectively), which may influence the generalizability of the results. More importantly, the inclusion of studies investigating different ethnicities is a problem regarding the genetic factors. The Chinese population can differ widely in genetic makeup compared to Europeans. This will have clinical implications for genotyping patients based on genetic findings that may not be relevant to the clinical population of interest. Fourth, several factors found to be associated with MetS (see **Supplementary Tables 4–11**) were only reported in a single study and thus excluded, while other factors were consistently identified in multiple studies. The results of the current study should therefore be interpreted with caution. Finally, we only included studies that used MetS as outcome measure to compare studies adequately. During the suitability screening in our literature search, we noticed that the majority of the initially identified studies investigated the effect of antipsychotics on one or more separate metabolic disturbances, instead of the MetS definition using ATP III, ATP III-A or IDF criteria. For example, the large meta-analysis by Pillinger et al. (24) investigated the effects of various antipsychotics on individual metabolic abnormalities, but not the syndrome as a whole. Therefore, these studies fell outside the scope of this systematic review. Potentially, this influenced the validity of this systematic review, leading to ambiguous and incomplete results.

Despite these limitations, the findings of this study are a promising first step toward the application of using clinical, biochemical and genetic information in personalized medicine. Evidence shows that MetS is highly prevalent among schizophrenia patients. Possibly, several factors interact to increase this risk in schizophrenia patients, including effects of SGAs, unhealthy lifestyle, and genetic and pathophysiological vulnerability. Further research is needed to elucidate how individual risk factors operate to increase this risk as well as how risk factors may interact to further increase MetS risk. Further research is also required to examine whether the contributions of these factors geographically differ. In this context, both clinical and preclinical studies may prove useful in the future to ascertain underlying pathophysiological mechanisms. Further risk factor management strategies are also required, involving pharmaceutical and nonpharmaceutical lifestyle interventions to try and counter the effects of such risk factors on MetS risk profiles in schizophrenia patients.

However, before applying these factors in clinical practice, by determining which patients have a high risk at developing MetS during SGA use, more research is required. Studies are needed using machine learning techniques to identify the exact molecular basis of the identified factors and to individually predict the risk to develop MetS in clinical practice. In this way, the discrepancy between life expectancy of patients with psychotic spectrum disorders and the general population may be reduced.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MS and SE performed the literature search. All authors contributed to the writing of the systematic review and read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.625935/full#supplementary-material

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Insulin Resistance and Blood-Brain Barrier Dysfunction Underlie Neuroprogression in Bipolar Disorder

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Bipolar disorder (BD) often progresses to a more chronic and treatment resistant (neuroprogressive) course. Identifying which patients are at risk could allow for early intervention and prevention. Bipolar disorder is highly comorbid with metabolic disorders including type II diabetes mellitus (T2DM), hypertension, obesity, and dyslipidemia. Our studies have shown that insulin resistance (IR) is present in over 50% of patients with BD and that IR might underlie the progression of BD. While no confirmed predictors exist for identifying which patients with BD are likely to develop a more chronic course, emerging evidence including our own studies suggest that IR and related inflammatory pathways lead to impairments in blood-brain barrier (BBB) functioning. For the first time in living psychiatric patients, we have shown that the severity of BBB leakage is proportional to BD severity and is associated with IR. In this hypothesis paper we (i) highlight the evidence for a key role of IR in BD, (ii) show how IR in BD relates to shared inflammatory pathways, and (iii) hypothesize that these modulations result in BBB leakage and worse outcomes in BD. We further hypothesize that (iv) reversing IR through lifestyle changes or the actions of insulin sensitizing medications such as metformin, or optimizing BBB function using vascular protective drugs, such as losartan, could provide novel strategies for the prevention or treatment of neuroprogressive BD.

Keywords: bipolar disorder, blood-brain barrier, insulin resistance, neuroprogression, vascular damage, inflammation

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INTRODUCTION

Bipolar disorder is a mood disorder affecting up to 5% of the population, leading to significant morbidity and premature mortality. Mood dysregulation occurs in conjunction with symptoms affecting sleep, energy, interests/motivation, appetite/weight, concentration, speech, thought process, and judgment. Patients experience episodes of mania with or without depressive episodes in bipolar I disorder and recurrent episodes of hypomania and depression in bipolar II disorder. Treatment-resistant disease progression (neuroprogression) is not uncommon in bipolar patients and includes a shift toward more severe, prolonged and frequent mood episodes, including rapid cycling (a minimum of 4 discrete mood episodes yearly) (**Figure 1A**), and poor functional outcomes (1, 2). Until now there have been no validated predictors for which patients will progress to this advanced course and there are no corresponding treatments. Increasing evidence suggests

that comorbid metabolic dysregulation, and specifically IR might underlie the progression of BD (3). We have found that those with comorbid T2DM or IR were more likely to develop a chronic course of BD, more rapid cycling, and were less likely to respond to lithium compared to those without metabolic dysregulation (4). Similarly, poor outcomes in BD with comorbid IR have been reported, including worse cognitive decline (5), memory impairment (6), and poor response to mood stabilizers in general (7). Understanding mechanisms underlying these findings could lead to novel therapeutic or adjunctive treatment strategies.

Insulin resistance is an inflammatory state which affects the vasculature and can lead to endothelial changes in the BBB (8) (**Figure 1B**). We have recently examined the potential role of BBB dysfunction (BBBD) in BD using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). We found that BD patients with extensive BBB leakage had a more chronic course, greater severity of depression and anxiety, and poorer overall functioning compared with BD patients with normal BBB permeability (9). Further, we found that all patients with extensive BBB leakage also had IR. Expanding on our earlier hypothesis that IR plays a role in the development of neuroprogression in BD (3), we now propose that *both* IR and BBBD are biomarkers for neuroprogression and advancement of the illness process. We suggest that neuroprogression in patients with BD may be the *result* of comorbid IR and its effect on the integrity of the BBB, as mediated through shared inflammatory pathways (**Figure 1B**).

METABOLIC DYSREGULATION IN BD

Patients with BD are symptomatic almost half of their lives (10). The leading cause of death in BD is cardiovascular disease with a 2.3-fold increased risk in patients with BD compared to the general population (11). Rates of cardiovascular risk factors including obesity, hypertension, dyslipidemia, metabolic syndrome and T2DM are all higher in patients with BD (12–14), and bipolar patients with comorbid T2DM have higher rates of hypertension, obesity, and a more chronic course (15). Obesity is a chronic, proinflammatory state, and adipose tissue secretes cytokines and inflammatory mediators (16) (**Figures 1B,C**) leading to further subsequent systemic inflammation and worsening obesity. This eventually results in an inadequate increase in insulin in response to plasma glucose, leading to IR with progression to glucose intolerance and eventually T2DM (17). We have reported that BD patients with comorbid obesity also have a more chronic course of illness and poor response to lithium (18). Similarly, worse outcomes in BD have been reported with comorbid IR, including worse cognitive decline (5).

Insulin resistance is present in more than half of all bipolar patients and is associated with a three times higher likelihood of a chronic course of illness with significantly more mood episodes including rapid cycling compared to those without metabolic dysregulation (4). These findings remained significant after controlling for the potential effects of age, body mass index (BMI), and lifetime exposure to antipsychotic medication (4). This is important, given that many medications used to treat BD can also lead to the development of metabolic dysfunction (19), although the association between BD and metabolic dysregulation was described as early as 1921, well before the advent of psychotropic medications (20, 21). We have also reported that psychiatric morbidity in BD increases 12-fold following the onset of IR, and we have identified IR as an early manifestation or possible predictor of progression of BD (22).

Insulin resistance might also be useful in predicting poor response to treatment. In a 2015 study, we found that bipolar patients with either T2DM or IR were 8.4 times more likely to have a poor response to lithium (the gold-standard treatment) than bipolar patients with normal glucose metabolism (4). An inverse relationship between IR and response to lithium was demonstrated, such that as IR progressed, a poorer response to lithium was found (4). Similarly, Steardo et al. (7) found that bipolar patients with comorbid IR/T2DM were 4.3 times more likely to fail treatment with *any* mood stabilizer, including lithium. Furthermore, we found that IR *preceded* neuroprogression of BD (22), highlighting the potential to modify BD trajectory through early treatment of IR. Together, these findings stress the importance of monitoring IR in BD patients (23, 24) for early identification of neuroprogression and targeted treatment strategies. Targeting IR in bipolar patients may not only facilitate BD remission; but could also decrease the risk for T2DM, cardiovascular disease and dementia (3).

HYPOTHALAMIC PITUITARY ADRENAL (HPA) DYSFUNCTION LEADS TO SYSTEMIC INFLAMMATION

We identify the key role of the HPA axis in the development of both BD and IR (25–27), via induction of sustained hypercortisolemia (**Figure 1B**). Sustained hypercortisolemia causes the body to mount an immune response (25, 28), leading to systemic inflammation (29, 30), obesity, and increased risk of IR. Bipolar disorder is also associated with abnormalities of HPA axis activity, including increased levels of cortisol and adrenocorticotropic hormone (ACTH) (26, 27) along with disruption in the normal diurnal variation of cortisol. Specifically there is an absence of expected cortisol troughs at night (31) and higher than usual daytime elevations (32), contributing to circadian rhythm dysfunction. Bipolar patients also have altered sleep and cortisol levels even when euthymic (33) and poor sleep initiation and frequent nighttime awakenings increase risk for IR/T2DM (34).

SYSTEMIC INFLAMMATION LEADS TO NEUROINFLAMMATION AND NEUROPROGRESSION

We further propose that systemic inflammation and IR increase the risk of endothelial injury, dysfunction of the BBB and subsequent neuroinflammation (8) (**Figure 1B**).

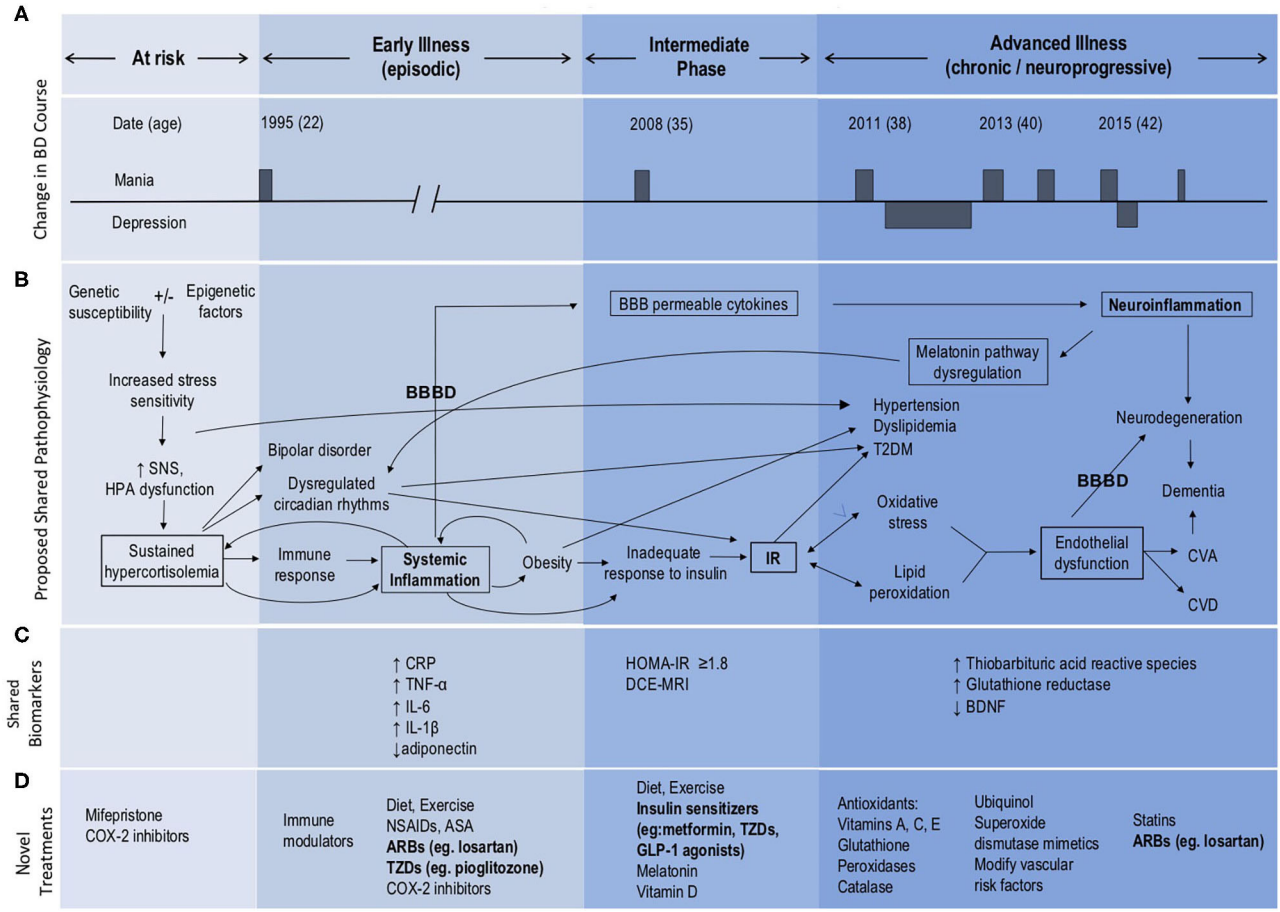

FIGURE 1 | Model of BD neuroprogression mediated by IR and BBBD. ARBs, Angiotensin II receptor blockers; ASA, acetylsalicylic acid; BBB, blood-brain barrier; BBBD, blood-brain barrier dysfunction; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; COX-2 inhibitors, Cyclooxygenase-2 inhibitors; CRP, C-reactive protein; CVA, cerebrovascular accident; CVD, cardiovascular disease; GLP, glucagon-like peptide; HOMA-IR, Homeostatic Model Assessment—Insulin Resistance; HPA, hypothalamic pituitary adrenal; IL, interleukin; IR, insulin resistance; NSAIDs, Non-steroidal anti-inflammatory drugs; SNS, sympathetic nervous system; TNF, tumor necrosis factor; T2DM, type 2 diabetes mellitus; TZDs, thiazolidinediones. This figure has been modified from the original published figure by Calkin C V., Insulin resistance takes center stage: a new paradigm in the progression of bipolar disorder, published in Annals of Medicine. Taylor and Francis Ltd; 2019.

Neuroinflammation then further amplifies BBBD, creating a self-reinforcing positive feedback loop that exacerbates BD, and contributes to its progression. In addition, hyperglycemia and hyperinsulinemia activate the renin-angiotensin system (RAS) which contributes to the development of hypertension and endothelial dysfunction Endothelial dysfunction results in microvascular and macrovascular changes, which when occurring within the brain lead to impairments in BBB functions. Given that even mild hyperglycemia can lead to profound dysfunction of the BBB (8), it is possible that early intervention with lifestyle and dietary changes (35) at the IR stage prior to the development of hyperglycemia could prevent or mitigate these effects on the BBB and development of neuroprogression. Further, targeting factors such as hypercortisolemia, sleep disturbances, IR, BBBD and/or neuroinflammation may offer novel therapeutic avenues for the management of BD and in preventing neuroprogression (**Figure 1D**).

SYSTEMIC INFLAMMATION IN BD AND IR

Mood disorders are understood to develop from a combination of genetic and environmental factors, which ultimately lead to a broad spectrum of clinical presentations. While the pathophysiology of these processes remains largely elusive, increasing evidence supports a key role of inflammatory cascades in BD (36, 37). Inflammation is defined as a non-specific state, known to be caused by both internal and external factors and may represent the body's response as a defense to a perceived threat (25, 37). Patients with systemic autoimmune diseases have an increased propensity for the development of BD, and several increased peripheral proinflammatory mediators have been reported in BD (38). Further, markers of neuroinflammation are present in the cerebrospinal fluid of living patients with BD (39), and post-mortem studies have demonstrated increased inflammatory markers in the

frontal cortex (40). Along with BD, it is generally accepted that a mild inflammatory state occurs in major depressive disorder (MDD) and schizophrenia (41). Long-term exposure to cytokines can lead to depressive episodes in euthymic patients receiving immune therapy with INF-alpha (42–44). Similarly, the administration of pro-inflammatory cytokines may lead to depressive symptoms in healthy controls (45–47). Blockade of TNF-type cytokines in depressed subjects with comorbid diseases including rheumatoid arthritis, psoriasis, and cancer was found to significantly *reduce* depressive symptoms (48, 49). Additionally, improvement in psychiatric symptoms has been demonstrated in schizophrenia patients treated with anti-inflammatory drugs for other indications (50).

The most prominent cytokines associated with mood disorders include: interleukin-1 beta (IL-1ß), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-alpha), and C-reactive protein (CRP) (51) (see **Figure 1C**). Interleukin-6 was shown to be increased in BD patients when unwell. Interestingly, levels of IL-6 were decreased following 6 weeks of mood stabilizing treatment (52). Indeed, increased activity of pro-inflammatory cytokines and an imbalance with anti-inflammatory cytokines have been implicated in the development of BD and neuroprogression (51–53) and (see **Figure 1C**). Of particular interest, varying cytokine profiles have been identified in distinct mood states of BD, including in mania, depression, euthymia and in healthy controls (54, 55). Specifically, manic episodes are associated with a prominent pro-inflammatory profile state (38). It has also been shown that inflammatory markers positively correlate with symptom severity in BD (29, 56, 57). In late-stage BD more extreme elevations in these serum markers have been found, especially TNF-alpha. As underscored by Benedetti et al. (58), increased inflammation has been linked to other known hallmarks of BD, including white matter changes and structural alterations in the prefrontal cortex, hippocampus, and amygdala (59, 60).

Practically, inflammatory profiles could prove to be useful in predicting treatment response to antidepressants in depressed states. The presence of neuroinflammation has been shown to result in a decreased response to some antidepressants (61). Specifically, in a systematic review, the presence of an inflammatory state (raised serum CRP and IL-6) in MDD patients correlated with poor outcome and poor response to predominantly serotonergic antidepressants (61). A better response to antidepressant regimes was demonstrated with add-on noradrenergic, dopaminergic, or glutamatergic action (61). In rats with a depression-like phenotype, augmentation with acetylsalicylic acid (ASA), a non-selective cyclo-oxygenase (COX) inhibitor and anti-inflammatory, enhanced the efficacy of fluoxetine (62). Levels of immunological markers could also help to predict the efficacy of some medications in BD, such as lithium response (29, 63–65). Overall evidence suggests that an activated inflammatory response is associated with treatment resistance in general and is possibly indicative of a different (i.e., neuroprogressive) disease phase. This draws a similarity to our findings of treatment resistance in bipolar patients with comorbid IR and thus, possibly, indicates a shared inflammatory mechanism.

Over years of research, various signaling pathways have been associated with mood disorders, including alterations in 5-hydroxytryptamine (5-HT) receptor functioning, neurotrophins, and the HPA axis (25, 28, 30). Immune dysregulation has also become a focused area of this research. However, the general framework regarded immune alterations as an association or *consequence* of mood disorders, as opposed to a causative factor. A growing body of research has questioned this framework. Indeed, genetic studies have shown that immune alterations are detectable even before the onset of BD (58). Moreover, inflammatory serum markers are also elevated in adolescents with BD prior to the development of a clear illness course (66). A recent systematic review by Mucci et al. (51) highlights inflammatory processes as the mechanism contributing to the onset of mood disorders following a stressful stimuli.

It has also been found that an increased production of cortisol in Cushing's disease leads to depressive and manic symptoms and neurocognitive deficits, and affects various central nervous system (CNS) regions (67). In addition to other commonalities, increased oxidative stress has been identified in both BD and T2DM. Insulin resistance initially stimulates an increase in metabolic activity, resulting in elevated production of reactive oxygen species (ROS), and a subsequent increase in inflammatory cytokines, such as TNF-alpha, Interleukin Beta (IL-ß), and monocyte chemoattractant protein-1 (MCP-1) (68). Importantly, oxidative stress markers such as nitric oxide (NO) and ROS have also been suggested to play a role in the pathophysiology of BD (57). Since oxidative stress and inflammation may contribute to both BD and IR, IR-related inflammation could underlie and precede BD neuroprogression, triggering a transition into a more chronic and treatment-resistant course of illness (3, 69, 70) (see **Figures 1A,B**). Utilizing a growing body of research, we further propose that alterations in BBB functions play a critical role in this pathogenic cascade. Specifically, we suggest that: (i) IR and associated inflammation underlie microvascular injury and BBB dysfunction; and (ii) that high BBB permeability to serum components facilitates further neuroinflammation and dysfunction of the neurovascular unit—including neuronal networks, that underlie the chronic and neuroprogressive course of BD.

BLOOD-BRAIN BARRIER DYSFUNCTION IN BD

The BBB is a complex structural and functional interface tightly regulating molecular exchange between the circulation and brain tissue. The BBB is formed by endothelial cells, linked together by tight junction proteins, and surrounded by pericytes, and astroglial foot processes (71, 72). This complex structure restricts harmful molecules in the blood from entering the brain, while facilitating the entry of essential nutrients and removal of waste products (73, 74). The BBB is integral to healthy brain functioning, and pathological BBB has been associated with autoimmune diseases (75) and common neurological conditions (76–79). Increase in BBB permeability can be inferred indirectly, by measuring whether a patient's

CSF has a high concentration of molecules that are normally excluded from the brain, for example, albumin or urate (80). High levels of these BBBD markers have been associated with MDD in elderly women, as well as suicidality in unipolar MDD patients (81–83)—supporting a possible role for BBBD in mood disorders. Post-mortem evidence of BBBD has been demonstrated in neuropsychiatric disorders such as dementia (84) and depression (85). Recent advances in MRI techniques have allowed direct assessment of BBB functionality in living patients, demonstrating BBBD in pathological conditions such as traumatic and ischemic injuries (86, 87), epilepsy (77), dementia (78) multiple sclerosis (79), and systemic lupus erythematosus (SLE) (75).

The understanding of the molecular mechanisms involved in BBBD had been largely derived from experimental animal models. This growing body of evidence suggests that: (i) systemic inflammation is associated with injury to brain (and other organs) microvasculature, resulting in BBBD (88), and (ii) BBBD allows leakage of serum macromolecules into the brain, resulting in glial activation, neuro-inflammation, network reorganization and delayed neurodegeneration as well as further BBBD (71, 73, 89).

One widely studied example of a serum macromolecule that leaks into the brain following BBB dysfunction is albumin (80)—the most abundant protein in the blood. Once leaking into the brain, albumin has been shown to trigger glial transformation, by activation of the pro-inflammatory transforming growth factor beta (TGF-ß) pathway (80, 89, 90), leading to cytokine secretion, synaptogenesis and neurodegeneration (77, 87, 88). In mouse models of social defeat, stress was also linked to increased BBB permeability and subsequent leakage of molecules into the brain (91). Specifically, the tight junction protein claudin-5 was downregulated and promoted peripheral IL-6 passage across the BBB (91). Claudin-5 expression was similarly downregulated in depressed patients (92). Using immunohistochemistry and qRT-PCR, (92) a key role for claudin-5 which was reduced in the hippocampus in post-mortem human brain tissues in people diagnosed with MDD or schizophrenia was also demonstrated. Interestingly, levels of claudins including expression of claudin-5 correlated with disease duration and age of psychiatric disorder in these post-mortem studies (92). Indeed, BBB associated tight junction disruption could be a major step in the development of various psychiatric pathologies. This is further supported by post-mortem analysis of patients with MDD, showing reduced astrocytic coverage of the BBB in the orbitofrontal cortex (85). Notably, post-mortem studies in human patients with BD have also demonstrated neuroinflammatory changes, microglial activation, and oligodendrocyte dysfunction (93). To add to the animal and post-mortem studies linking BD, neuroinflammation, and BBBD, our group has recently conducted the first ever BBB imaging study in living bipolar patients (9). Using DCE-MRI, we have demonstrated that extensive BBB leakage affects 28% of BD patients (9), and that these patients had greater psychiatric morbidity, compared to BD patients with normal BBB function. Extensive BBB leakage was found to be associated with worse depression, anxiety and socio/occupational dysfunction, chronic illness course with more frequent and/or severe manic/depressive episodes (9). Importantly, all bipolar patients with extensive BBB leakage also had IR, supporting the hypothesis that IR-related inflammation may contribute to BBBD and BD progression. Our results suggest BBBD could indeed be a mechanistic link between systemic inflammation, IR and BD neuroprogression. Moreover, repair of the BBB may, thus, prove to be a novel and effective approach for maintaining brain health and facilitating BD remission.

IR AND BLOOD-BRAIN BARRIER DYSFUNCTION

Our finding that all BD patients with extensive BBB leakage also had IR (9), highlights a potential causal link between IR and BBBD. While animal and human studies suggest that inflammation is the likely mechanism connecting IR and BBBD, the direct mechanistic link between IR and BBBD in BD patients has yet to be studied. Evidence for the role of IR in BBBD can be found in animal studies of hyperglycemia, showing that hyperglycemia causes inflammation and damage to the BBB (8). Notably, numerous overlapping pathways are involved in the inflammatory states of both IR and BBBD, including vascular endothelial growth factor (VEGF) and protein kinase C (PKC) (94). Further evidence supporting a possible link between BBBD and IR comes from studies of BBBD in T2DM. Impairment of the BBB is now accepted as one of the key mechanisms leading to diabetic encephalopathy (95). The structural integrity and transport function of the BBB is compromised in T2DM, through pathways of oxidative stress and chronic inflammation (95). BBBD in T2DM has also been suggested to play a role in neuronal dysfunction (96), and cognitive impairment (95). Further, both human and animal studies have demonstrated a role for insulin in synaptic viability, dendritic spine formation, cerebral bioenergetics and suggest that insulin dysregulation can lead to diseases of pathological aging (97). Specifically, a relationship between IR in the periphery and the brain in Alzheimer's disease suggests that peripheral IR might precede accumulation of amyloid ß protein in Alzheimer's (97). Applying this concept to the current body of evidence in IR and BD, we postulate that BBBD is likely to be a key mechanism contributing to BD neuroprogression, as *mediated by* IR and shared inflammatory pathways (**Figure 1B**).

INTRACELLULAR MECHANISMS SUPPORTING A LINK BETWEEN IR, INFLAMMATION, BBBD, AND NEUROPROGRESSION

In this paper we present a framework for development of BD neuroprogression (**Figure 1B**), centered around the transition from systemic inflammation to neuroinflammation via the BBB. We identify HPA dysfunction as an early stage of a pathological cascade that leads to sustained hypercortisolemia and circadian dysregulation that may underlie the parallel development of

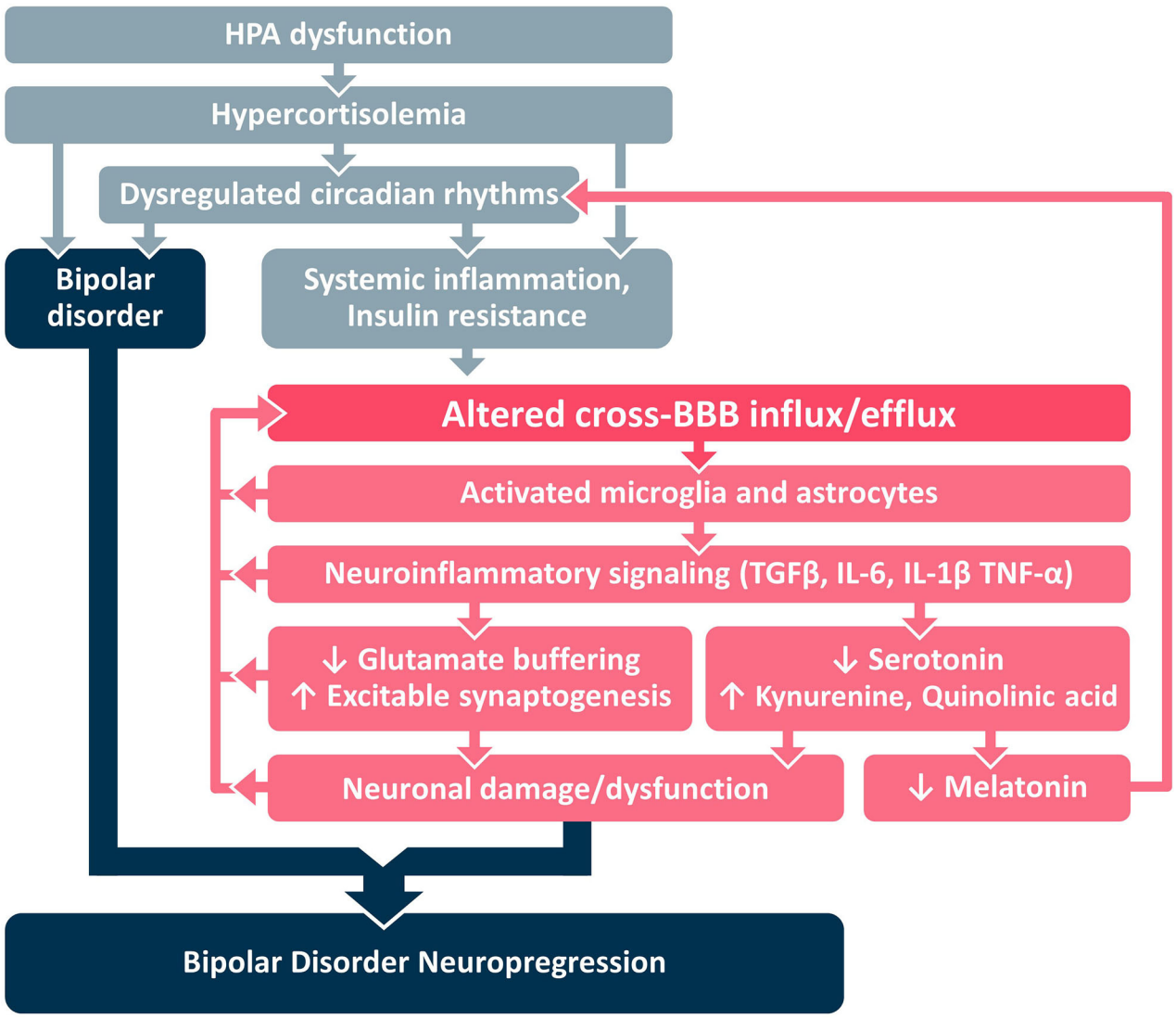

FIGURE 2 | Proposed mechanistic framework. BBB, blood-brain barrier; HPA, hypothalamic pituitary adrenal; IL, interleukin; TGFβ, Transforming Growth Factor Beta; TNF, tumor necrosis factor.

both (a) BD and (b) systemic inflammation and IR (**Figure 2**). Systemic inflammation and IR leads to neuroinflammation via cross-BBB infiltration of systemically-secreted cytokines (e.g., IL1, IL-6, or TNF-α) and/or damage to the BBB's endothelium mediated by hyperinsulinemia/hyperglycemia (8, 17, 98, 99). Once the BBB is breached, the brain's microglial and astrocytic cells undergo a neuroinflammatory transformation, involving TGFβ pathway activation and further cytokine secretion. The astrocytic TGFβ cascade results in reduced buffering of extracellular glutamate (100), and generation of new excitatory synapses (91). Together these changes result in a reorganization of the neural network, a shift favoring hyperexcitation, and glutamate-mediated neuronal damage (101). Notably, each step of the neuroinflammatory cascade can contribute to further BBBD, creating a self-reinforcing positive feedback loop that may also amplify the subsequent neuronal dysfunction. We hypothesize that the processes mediated by BBBD and neuroinflammation may impair the function of the affected brain regions, and contribute to the severity of BD and its responsiveness to available mood-stabilizing treatments. Interestingly, neuroinflammatory signaling cascades may also amplify the circadian dysregulation in BD patients, by favoring the production of kynurenine (and quinolinic acid) over serotonin (and melatonin) (102–104). Together, these pathways demonstrate the tight interplay between HPA activity, systemic inflammation, BBBD, neuroinflammation and BD neuroprogression, with the BBB being the interface between systemic and CNS processes/manifestations.

CAN TREATING IR AND/OR REPAIRING BBBD HALT BD NEUROPROGRESSION?

Thus far, we have reviewed evidence suggesting that: (i) BBBD in bipolar patients might be caused by inflammatory processes such as IR, and (ii) BBBD may contribute to BD neuroprogression, that is more common in bipolar patients with IR. Research into manipulation of the BBB is becoming an area of growing interest, with several groups developing therapeutics targeting the repair of the BBB and/or inhibition of neuroinflammatory processes subsequent to BBBD (105–107). Given that BBBD in bipolar patients may be caused by systemic inflammation and IR, the question follows whether reversal of inflammation or IR could facilitate BBB repair and the remission of neuroprogression.

While some studies suggest that anti-inflammatory treatment or TNF inhibitors may *reduce* depressive symptoms (48, 49), whether they can repair the BBB remains unclear. A study in patients undergoing cardiac surgery suggests that treatment with the potent anti-inflammatory prednisone does not reduce post-operative BBBD (108). While this is perhaps far removed from BD, conceptually, this suggests that treating systemic inflammation alone may not be sufficient to repair the BBB.

Studies in animals suggest that reversal of IR may be a more promising therapeutic target for BBB repair. Specifically, metformin—regarded as the safest and most effective insulin-sensitizing drug—has been reported to reduce BBBD in a mouse model of stroke (109). In a mouse model of systemic inflammation using peripheral injection of bacterial lipopolysaccharide (LPS), metformin was shown to downregulate neuroinflammation and improve exploratory behavior (110). In this model, LPS was shown to cause neuroinflammation (elevated levels of TNF-α and IL-6 in the brain), BBBD and significant lethargy and illness (88, 110). Remarkably, pre-treatment of mice with metformin significantly reduced systemic and CNS inflammation, LPS-induced oxidative stress, and neurobehavioral symptoms of illness (110). In humans, metformin has also been shown to enact antioxidant and anti-inflammatory effects, and to reduce cardiovascular complications, stroke, certain cancers, thyroid diseases, and polycystic ovarian syndrome (111–113).

Metformin is generally understood to exert its effects on the liver and peripheral tissues, by decreasing glucose output from the liver and increasing glucose utilization at peripheral tissues, including the musculature. This process requires the activation of adenosine monophosphate-activated protein kinase (AMPK) which reduces energy expenditure at the cellular level (112). However, metformin may offer further benefits beyond reversing IR. Metformin is also thought to suppresses the action of matrix metalloproteinase-9 (MMP-9)—an enzyme that degrades components of the BBB (114). MMP-9 has been widely implicated in conditions such as cancer, MS, migraines, neuropsychiatric disorders (115, 116), and complications of coronary artery disease (116), atherosclerosis (117), and hypertension (118). Furthermore, increased levels of MMP-9 were demonstrated in bipolar depression (119), suggesting that MMP-9 could contribute to BBB degradation and disease progression of bipolar patients. Metformin has been shown to suppress MMP9 in human breast cancer cell lines, and is gaining focus as a potential anticancer drug (120).

An additional mechanism by which metformin may exert its neuroprotective effect is through activation of the peroxisome proliferator-activated receptor (PPAR) (121). PPAR is thought to mediate the insulin-sensitizing action of metformin, by modulating the insulin-like growth-factor (IGF) axis (121). In animal studies, PPAR agonists (thiazoladinediones, such as rosiglitosone) have been shown to protect the BBB; reduce neuro-inflammation, oxidative stress and neuronal injury (120, 122); and improve neurological outcomes of CNS injury/disease (123). Elegantly, PPAR-γ antagonists lead to an opposite effect (122). These findings were further confirmed in a monolayer of human microvascular endothelial cells (122), suggesting that activation of PPAR signaling may be a promising neuroprotective target, and further highlighting the therapeutic potential of metformin and the thiazolidinedione class of drugs. Targeting the BBB directly, may indeed provide a promising approach in other CNS diseases, such as epilepsy which is also associated with BBBD (77). The angiotensin II receptor antagonist, losartan is vascular protective and has potential implications for protecting BBB integrity though action on TGF-ß. In a rat model of vascular injury, losartan prevented acquired epilepsy via TGF-ß signaling suppression when administered prior to injury and may become the first available treatment for the prevention of epilepsy (105).

We conclude that treatment of IR and potential repair of the BBB with metformin, thiazolidinediones or vascular protective drugs, such as losartan may prove to be effective strategies for treatment resistant or neuroprogressive bipolar disorder (**Figure 1D**). Further research is needed to investigate the mechanisms underlying the effects of these agents on MMP9 and PPAR pathways in particular. By more directly targeting the BBB, a shift in focus toward *prevention* of BD neuroprogression could emerge.

EVALUATING IR AND BBBD TO IDENTIFY BD PATIENTS WITH NEUROPROGRESSION

Insulin resistance can be easily estimated using concurrent FPG and FSI levels and the HOMA-IR equation: HOMA-IR = FPG (mmol/L) × FSI (μU/ml)/22.5 (124), and the HOMA-IR cut-off value of ≥1.8 (since metabolic syndrome becomes clinically significant at this value) (125). Once it is determined that a patient is insulin resistant, DCE-MRI could be used to quantify and localize BBB leakage. While DCE-MRI is clinically available and there are algorithms to analyze and interpret images for BBBD, this has only been used for research. Standardizing abnormal BBB permeability cut-off values between different types of MRI scanners is required and feasible, but calls for large sample sizes, controls and further validation before it can be brought widely into clinical use. As our group is currently doing this work, we expect BBB imaging to be available for clinical use

in the future. We suggest that utilizing these two biomarkers (IR, and BBBD once clinically available) will be important in identifying bipolar patients with neuroprogression and for following treatment response.

DISCUSSION

We have highlighted the evidence for a key role for IR and shared inflammatory pathways leading to BBBD and neuroprogression of BD. We have outlined the rationale for our expanded hypothesis that these modulations result in BBB leakage and worse outcomes in BD. We have further connected this body of evidence with key known treatments for IR. Indeed, reversing IR could provide a novel strategy for the prevention or treatment of a neuroprogressive course of BD. This could be accomplished through the actions of widely used diabetic medications, such as metformin or thiazolidinediones or vascular protective agents, like losartan, that target BBBD more directly. While there is currently a lack of evidence to clearly determine whether treating IR or BBBD is of value in BD neuroprogression, our group has a number of studies under way. We are hopeful that data from our completed TRIO-BD quadruple-masked randomized clinical trial comparing metformin to placebo in improving outcomes in treatment resistant bipolar depression will soon help provide answers. Further research is needed in terms of replicating completed studies and investigating novel new treatments for BD neuroprogression, targeting IR and BBBD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

CC contributed intellectual concepts, hypotheses, writing, and editing. CM synthesized these concepts and hypotheses in the writing of the manuscript and provided the literature search. LK, KC, and AF contributed to intellectual content, writing, and editing. All authors contributed to the article and approved the submitted version.

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Genetic and Metabolite Variability in One-Carbon Metabolism Applied to an Insulin Resistance Model in Patients With Schizophrenia Receiving Atypical Antipsychotics

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Background: Patients with schizophrenia are at high risk of pre-mature mortality due to cardiovascular disease (CVD). Our group has completed studies in pharmacogenomics and metabolomics that have independently identified perturbations in one-carbon metabolism as associated with risk factors for CVD in this patient population. Therefore, this study aimed to use genetic and metabolomic data to determine the relationship between folate pharmacogenomics, one-carbon metabolites, and insulin resistance as measured using the homeostatic model assessment for insulin resistance (HOMA-IR) as a marker of CVD.

Methods: Participants in this pilot analysis were on a stable atypical antipsychotic regimen for at least 6 months, with no diabetes diagnosis or use of antidiabetic medications. Participant samples were genotyped for *MTHFR* variants rs1801131 (*MTHFR* A1298C) and rs1801133 (*MTHFR* C677T). Serum metabolite concentrations were obtained with NMR. A least squares regression model was used to predict log(HOMA-IR) values based on the following independent variables: serum glutamate, glycine, betaine, serine, and threonine concentrations, and carrier status of the variant alleles for the selected genotypes.

Results: A total of 67 participants were included, with a median age of 47 years old (IQR 42–52), 39% were female, and the median BMI was 30.3 (IQR 26.3–37.1). Overall, the model demonstrated an ability to predict log(HOMA-IR) values with an adjusted R^2 of 0.44 and a p-value of <0.001. Glutamate, threonine, and carrier status of the *MTHFR* 1298 C or *MTHFR* 677 T allele were positively correlated with log(HOMA-IR), whereas glycine, serine, and betaine concentrations trended inversely with log(HOMA-IR). All factors included in this final model were considered as having a possible effect on predicting log(HOMA-IR) as measured with a p-value < 0.1.

Conclusions: Presence of pharmacogenomic variants that decrease the functional capacity of the MTHFR enzyme are associated with increased risk for cardiovascular disease, as measured in this instance by log(HOMA-IR). Furthermore, serine, glycine, and betaine concentrations trended inversely with HOMA-IR, suggesting that increased presence of methyl-donating groups is associated with lower measures of insulin resistance. Ultimately, these results will need to be replicated in a significantly larger population.

Keywords: pharmacogenomics, metabolomics, folate, one-carbon metabolism, cardiovascular disease, antipsychotics, insulin resistance

INTRODUCTION

The rate of mortality due to cardiovascular disease (CVD) is 2–3 times higher in patients with severe mental illness, such as schizophrenia and bipolar disorder, when compared to the general adult population (1, 2). Among risk factors for CVD, insulin resistance is important as an early, defining feature of diabetes and metabolic syndrome (3, 4). Meta-analyses have demonstrated that diabetes and metabolic syndrome occur at higher rates in patients with schizophrenia, and that these rates are higher yet among patients exposed to antipsychotic drug therapy (5, 6). However, the mechanisms underlying increased rates of insulin resistance and CVD are poorly understood and likely due to a complex interplay of genetic and environmental influence such as medication use and cigarette smoking.

One potential mechanism of CVD in patients with schizophrenia is aberrant one-carbon metabolism (7). One-carbon metabolism includes a network of pathways such as the folate cycle, methionine cycle, and the transsulfuration pathway that are involved in critical processes such as methylation, DNA synthesis, and protein synthesis (8). These pathways include essential one-carbon metabolite sources and products such as serine, choline, betaine, threonine, glutamate, and methionine (**Figure 1**). Additionally, within the folate cycle, genetic variants in the gene coding for the methylenetetrahydrofolate reductase (MTHFR) enzyme have been given particular attention based on studies associating carrier status with increased rates of CVD risk factors, such as metabolic syndrome (10–12). This enzyme plays an important role in the folate cycle by converting dietary folate to the active form, L-methylfolate (5 methyl-THF; **Figure 1**) (13). The functional impact of decreased MTHFR activity is accumulation of homocysteine and decreased synthesis of neurotransmitters (14, 15). Two genetic variants in the gene coding for the MTHFR enzyme that have been associated with decreased enzyme activity are *MTHFR* C677T and *MTHFR* A1298C. The presence of either variant leads to amino acid base pair changes that ultimately reduce enzyme activity, and variant carrier status has been linked to risk of metabolic syndrome in patients treated with antipsychotics (11, 16–19). Variants within the *MTHFR* gene have also been studied in patients without serious mental illness, and associations with variant carrier status and inflammation, adverse metabolic outcomes, and cardiovascular events have been inconsistent and in some studies dependent on population, age, or folate serum levels (20–22).

Metabolomics is the science of small molecule profiling in biological samples, and in relation to the other "omics" approaches, it reflects downstream activities of the genome, transcriptome, and proteome (23–25). This makes metabolomics useful for identifying mechanisms of treatment and disease. In an NMR metabolomics experiment, our group identified that metabolites attributable to one-carbon metabolism differentiated patients with schizophrenia on antipsychotics based on fasting insulin concentration (26). Ultimately, our group has completed genetic and metabolomics analyses that have independently identified an association between variable one-carbon metabolism and CVD risk when identified as metabolic syndrome and variable fasting insulin (10, 11, 26). Here, we expand upon these findings by combining metabolomics and genomics to predict CVD risk using the homeostatic model assessment of insulin resistance (HOMA-IR) as a surrogate CVD risk measure (27). HOMA-IR has been studied extensively as a minimally invasive, clinically accessible method to assess insulin resistance and beta-cell function that correlates well with values obtained using the hyperinsulinemic euglycemic clamp technique (28).

Therefore, the aim of this study was to determine the extent to which genetic variants in the *MTHFR* gene and metabolites important in one-carbon metabolism could predict insulin resistance in patients with schizophrenia that were not diagnosed with diabetes or treated with diabetes medications. We hypothesized that the aforementioned metabolites and *MTHFR* variant carrier statuses would contribute to a model that would be able to predict log(HOMA-IR) concentration as determined by a p-value of <0.05.

METHODS

Participants

Participants included in this analysis were selected from a large, observational, cross-sectional study investigating CVD in patients diagnosed with a schizophrenia spectrum disorder or bipolar disorder per the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (29). The parent study's inclusion criteria included use of an antipsychotic for at least 6 months prior to enrollment, with no antipsychotic regimen changes within the previous 8 weeks. Additional inclusion criteria were ages between

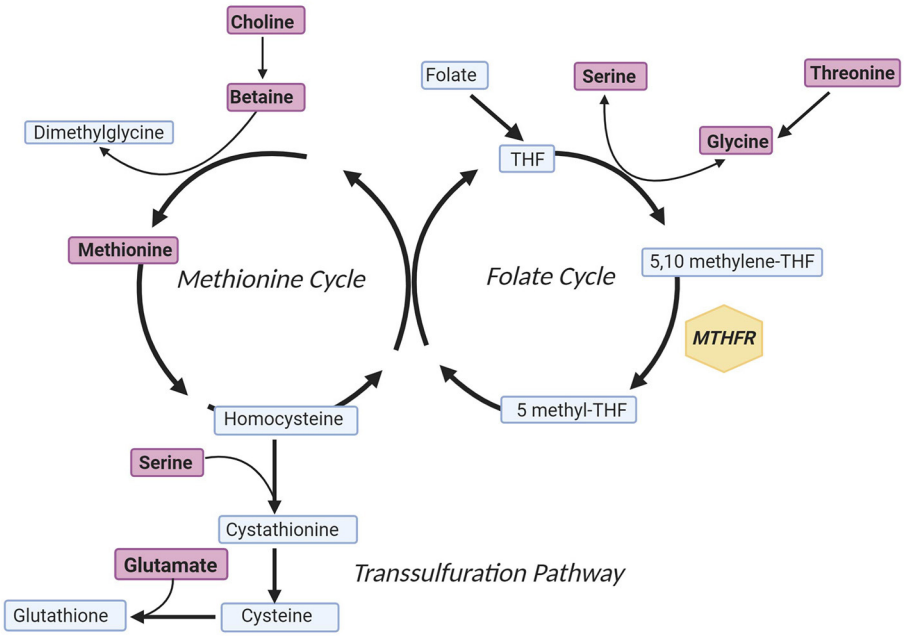

FIGURE 1 | Simplified One-Carbon Metabolism. Metabolites included in the model predicting log(HOMA-IR) concentration are indicated in purple, and the gene of interest is annotated within a yellow hexagon. In brief, the methionine cycle is involved in methyl-transferase reactions, the folate cycle is involved in purine synthesis, and the transsulfuration pathway culminates with formation of the antioxidant glutathione (9). The figure was created with Biorender.com. MTHFR, methylenetetrahydrofolate reductase; THF, tetrahydrofolate.

18 and 90 years old and no diabetes diagnosis prior to starting an antipsychotic. To be included in this analysis participants were restricted to those using an atypical antipsychotic for the treatment of a schizophrenia spectrum disorder, and no diagnosis of diabetes or use of medications that impact blood glucose regulation, such as metformin. Furthermore, subjects had to have had prior metabolomics profiling as part of a previous investigation (26). Atypical antipsychotic chlorpromazine equivalents were calculated using methods previously described by Andreasen et al. (30) and Woods (31).

Demographics, clinical histories, fasting blood draws and anthropometric measurements were performed at the University of Michigan's Clinical Research Unit (MCRU; http://www.michr.umich.edu/services/mcru). Members of the study team collected data from participants on the course of their disease and treatment (for example time since diagnosis and antipsychotic medication trials). HOMA-IR was calculated according to Matthews et al. (27) utilizing fasting insulin and fasting glucose values. The study protocol received Institutional Review Board (IRB) approval from the University of Michigan (IRBMED HUM00017774) and the following local organizations: the Detroit-Wayne County Community Mental Health Agency (DWCCMHA), Washtenaw County Health Organization (WCHO), and the Ann Arbor Veterans Affairs Medical Center. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Genotyping

A salt precipitation technique was used to extract DNA from fasting whole blood samples (32). The variants analyzed were two single nucleotide polymorphisms (SNPs) in the gene coding for the methyltetrahydrofolate reductase (MTHFR) enzyme: (rs1801131/*MTHFR* A1298C and rs1801133/*MTHFR* C677T). For both variants, Assay Design 2.0 software with Pyrosequencing™ Technology (Qiagen, Valencia, CA) was utilized for primer design for polymerase chain reaction (PCR) primers and pyrosequencing sequencing primers as previously described (17). Briefly, PCR was used to amplify short segments of DNA containing the SNPs of interest with Thermo Scientific™ TaqMan™ Master Mix. After visualization of the PCR product using a 1.2% agarose gel with ethidium bromide or GelRed® (Biotium) dye, the PCR product was then used for genetic sequencing with a PyroMark MD sequencer with Qiagen pyrosequencing reagents (Qiagen, Valencia, CA) following their recommended protocols. In any instance of uncertain genotype assignment, the sequencing was repeated. When a sequencing genotype could not be identified conclusively for any given variant, it was excluded from the analysis. Pyrosequencing, as a method of genotyping, has been described in detail previously (33).

Metabolomics

We obtained quantified metabolomics data from a previously completed study (26). Briefly, these data were generated from fasting (10 h) blood samples that were extracted into hydrophilic

and hydrophobic metabolite fractions. The hydrophilic fraction was lyophilized and then re-suspended in deuterated water, with the addition of the internal standard formate, prior to NMR analysis by the University of Michigan's NMR Biochemical Core Laboratory. Among all identified metabolites in the previously completed study, only those involved in one-carbon metabolism were included in this analysis. When the samples were thawed for the metabolomics analysis, a small fraction was delivered to the Michigan Diabetes Research Center (http://diabetesresearch.med.umich.edu/) for fasting insulin and fasting glucose quantification in order to compute HOMA-IR.

Statistical Analysis

Statistical analyses were completed with JMP Pro® 14.2.0 (SAS Institute Inc., Cary, NC). Demographic data were described as the mean and standard distribution, medians and interquartile range, or percentages of the study cohort, as appropriate. HOMA-IR was log transformed to address heteroscedasticity in the original model residual plot and its observed deviation from normality. Least squares regression was used to predict log(HOMA-IR) concentration as a function of the following quantified one-carbon metabolites: serine, choline, betaine, threonine, methionine, glutamate, and variant carrier status. *MTHFR* C677T TT or A1298C CC carriers were not considered separately in the model due to small numbers (3 and 5 participants for each genotype, respectively).

Ultimately, we proceeded with two models utilizing genomic and metabolomics factors to predict log(HOMA-IR). The first model included all the genetic and metabolite variables above followed by a second model only including variables with a possible effect ($p < 0.1$). Corrected Aikaike's Information Criterion (AICc) values were provided to compare models, and a model p-value < 0.05 was considered statistically significant (34).

Of note, a number of potential confounding variables, specifically age, BMI, race (simplified as Caucasian and non-Caucasian), smoking status, and chlorpromazine equivalents were added to the final regression model to assess for independent variable contribution from non-metabolomic and genomic factors. This was also done for use of clozapine or olanzapine when considering that these medications are known to be associated with a higher risk of adverse metabolic events (35).

RESULTS

Participant Demographics

Participant demographic details are provided in **Table 1**. Of the 67 included participants, ∼28% were currently treated with antipsychotics considered to have the highest risk of weight gain and glucose disturbance (i.e., olanzapine and clozapine) and the average CPZ equivalents was 558 mg in our sample. Despite the parent study allowing for enrollment of patients up to 90 years of age, the oldest participant in this secondary analysis was 60 years old. Finally, there was no significant departure from Hardy-Weinberg equilibrium for either *MTHFR* variant ($p > 0.05$).

TABLE 1 | Participant demographics.

Participant demographics ($N = 67$)	
Age (IQR)	47 (42–52)
Sex (% female)	38.8
BMI (IQR)	30.3 (26.3–37.1)
Fasting insulin μU/mL (IQR)	16.6 (10.6–26.4)
Fasting glucose mg/dL (SD)	94.6 (12.0)
Log(HOMA-IR) (SD)	0.63 (0.29)
Use of clozapine or olanzapine (% yes)	28.4
MTHFR 677 T carrier (%)	28.8
MTHFR 1298 C carrier (%)	48.5
Race (% non-caucasian)	41.8
Smoker (% yes)	53.7
CPZ equivalents, AAP only in mg (IQR)	558.0 (367.0–727.2)
Total antipsychotic medication trials (IQR)	5 (3–6)
Atypical antipsychotic medication trials (IQR)	2 (2–4)
Typical antipsychotic medication trials (IQR)	2 (1–3)
Time since diagnosis in years (IQR)	19.0 (14.0–30.0)

For continuous data, demographics were provided as means and standard deviations (SD) when values were normally distributed, otherwise as medians and interquartile ranges (IQR). CPZ, chlorpromazine; AAP, atypical antipsychotic.

Regression Analyses

Results of the least squares regressions analyses are provided in **Tables 2** and **3**. In **Table 2**, it is apparent that two metabolites within the one-carbon cycle (choline and methionine) do not significantly contribute to the prediction of log(HOMA-IR) despite a significant overall model ($p = 0.001$). These metabolites were removed from the analysis, and the final parameters are shown in **Table 3**. Decreasing the number of predictive factors improved the AICc, from 13.15 to 7.52 and the model remained significant ($p = 1.622$ E-5). With our participant sample size of 67, this allows for a power level of 0.8, assuming an effect size of 0.25 and an α of 0.05. Furthermore, the model remains significant when applying a Bonferroni correction as the p-value is below 0.007. For the two *MTHFR* SNPs, carrier status (i.e., carriers for reduced function enzymes) was associated with an increased log(HOMA-IR) value. In an exploratory analysis not shown here, when including the interaction of variant carrier status of the two *MTHFR* SNPs in the final model (described in **Table 3**) the interacting factor was not a significant contributor to predicting log(HOMA-IR) (p-value for the factor was 0.60).

In the analysis of potential confounding factors, the independent factors based on medication (clozapine or olanzapine use and chlorpromazine equivalents), race, and smoking were not independent predictors of log(HOMA-IR) using the criterion of a p-value of >0.1. Although age and BMI were significant by this estimate (each had a p-value of <0.1), none of the potential confounding factors were highly correlated with each other (correlation coefficients smaller than 0.8), one carbon metabolism metabolites or genetic variants, and were left out of the final model to limit the number of independent model factors and maintain power of the model described in **Table 3**. Results of the regression analysis including potential

TABLE 2 | Least squares regression model parameters for initial input including all detected metabolites within one-carbon metabolism.

Term	Estimate	Std. error	Prob > |t|
Regression model 1 (*N* = 67)			
MTHFR 677 T Carrier	−0.06627	0.035263	0.07
MTHFR 1298 C Carrier	−0.07146	0.03099	0.03
Glycine	−0.00121	0.000469	0.01
Serine	−0.00347	0.001669	0.04
Choline	−0.00088	0.016049	1.00
Betaine	0.00841	0.003633	0.02
Threonine	0.004593	0.001968	0.02
Methionine	0.001833	0.005933	0.76
Glutamate	0.002866	0.000687	0.0001

$R^2 = 0.44$, $p = 0.001$, AICc = 13.15.
AICc, Corrected Aikaike's Information Criterion.

TABLE 3 | Final least squares regression model parameters.

Term	Estimate	Std. error	Prob > |t|
Regression model 2 (*N* = 67)			
MTHFR 677 T Carrier	−0.0667	0.034556	0.06
MTHFR 1298 C Carrier	−0.07195	0.030423	0.02
Glycine	−0.00122	0.000434	0.007
Serine	−0.00344	0.001625	0.04
Betaine	−0.00841	0.003569	0.02
Threonine	0.004801	0.00163	0.005
Glutamate	0.002878	0.000654	<0.0001

$R^2 = 0.44$, $p < 0.001$ (1.622E-5), AICc = 7.52.
AICc, Corrected Aikaike's Information Criterion.

confounders, and the table of correlation estimates are provided in the **Supplementary Material**.

DISCUSSION

The results of this study suggest that in middle-aged patients with schizophrenia, who are stable on an atypical antipsychotic medication regimen, metabolite concentrations and genetic variants within one-carbon metabolism (**Figure 1**) are capable of predicting log(HOMA-IR) and thus may contribute to the development of CVD. Among the independent factors in our analysis, *MTHFR* variant carriers trended toward higher concentrations of HOMA-IR. Variant carriers have reduced conversion of 5,10-methyl tetrahydrofolate to 5-methyl tetrahydrofolate for subsequent creation of methionine. Despite this association, methionine, which is downstream of *MTHFR,* was not a significant predictor of log(HOMA-IR) in our model which could be attributable to variation in either methionine synthase (*MTR*) expression or activity, neither of which was measured. All metabolites, except threonine and glutamate, were negatively associated with HOMA-IR concentration suggesting that reduced concentrations of one-carbon donors are associated with increased insulin resistance (36, 37). All of these metabolites, except glutamate, are involved in one-carbon metabolism as sources of one-carbon units. Glutamate is also thought to be involved in insulin secretion, which aligns with the observation of increased insulin in this population (38).

Compounding Data Points to a Role of One-Carbon Metabolism

Our findings support past work that demonstrates a potential link between antipsychotics, anti-oxidant levels, one-carbon metabolism and cardiovascular disease mortality in psychiatric patients (39). Furthermore, changes in one-carbon metabolism are also important for the production of methyl groups for various reactions in the cell including that of DNA methylation. To this end, our group has identified associations between DNA methylation and antipsychotic treatment in more than one tissue as well as the impact of folate (a source of one-carbon) supplementation on gene methylation and some metabolic side effects in patients treated with antipsychotic medications (40–42). Taken together, these findings suggest a strong role for one-carbon metabolism in antipsychotic-induced metabolic side effects and the subsequent increased risk for cardiovascular death in this patient population.

Glutamate and Inflammatory Pathways

Glutamate, serine, and glycine are required for the synthesis of the antioxidant glutathione within the transsulfuration pathway (43). Glutamate is involved in the rate-limiting step of glutathione synthesis, prior to the addition of glycine (43). In our study, glutamate trended positively with increasing HOMA-IR, whereas glycine and serine concentrations trended negatively with HOMA-IR. This agrees with the recent work of Vangipurapu et al., that identified increased concentrations of glutamate and decreased concentrations of glycine as significantly associated with worsening insulin sensitivity over time in a longitudinal study of ∼5,000 men without diabetes at baseline (44). Considering that glutamate is involved in a variety of reactions, including brain-derived neurotrophic factor (45), and elevated serum levels have been associated with a number of inflammatory diseases (46), it is possible that glutamate-derived formation of glutathione within the transsulferation pathway is likely not the key mechanism by which it exerts its role in insulin resistance.

The positive correlation between threonine and HOMA-IR is somewhat discordant with the shared negative relationship between the other metabolites in our predictive model and HOMA-IR. Although threonine is a source of one-carbon groups, it is first metabolized to glycine before entering the folate cycle (**Figure 1**). Unlike glutamate, variable serum threonine concentrations have not been found to be associated with inflammatory disease states or insulin sensitivity (47).

Genetic Associations of the Folate Cycle

When considering the contribution of the *MTHFR* genetic variants in our model, we determined that carrier status of either variant trended with higher HOMA-IR values. These results generally agree with other studies in patients with severe mental

illness, demonstrating that patients who carry variants that decrease MTHFR enzyme activity have higher rates of metabolic risk factors for CVD (10–12, 18, 48). Our group previously identified that carriers of the *MTHFR* 677 T allele were associated with significantly higher rates of metabolic syndrome diagnosis and that variant carrier status was also associated with increased HOMA-IR value (10, 11). While additional investigators have found that the *MTHFR* 677 T allele was associated with higher rates of metabolic syndrome (12), other studies have found a lack of association with the *MTHFR* 677 T allele (9, 48). In some instances when both variants were studied, there was a lack of association with the *MTHFR* 677 T variant, but the *MTHFR* 1298 C variant (or CC homozygote) was associated with metabolic syndrome prevalence (48) or the development of worse metabolic outcomes following 3 months of atypical antipsychotic treatment (18). Cumulatively, results from our group and others demonstrate that variants within the *MTHFR* gene known to cause reduced enzyme function are associated with higher risk of cardiovascular disease.

LIMITATIONS

We acknowledge that there are several limitations of our study. As a pilot investigation with a small sample size, we recognize that this model will need to be tested in larger, independent populations to validate the ability of metabolomics and genetic variants within one-carbon metabolism to predict HOMA-IR. Nevertheless, despite this limitation, our study cohort consisted of well-characterized schizophrenia patients on long-term antipsychotic therapy with targeted profiling of both genetic and metabolite factors in the one-carbon pathway. Another limitation of our study that may impact external validity is the variable past and current medication exposure. Meta-analyses have demonstrated that CVD risk increases after the first exposure to antipsychotics when compared to similar treatment naïve patients (6), and that olanzapine and clozapine are known to be associated with higher risk of metabolic complications (34). Our model did not identify a relationship between current medication use and HOMA-IR, which may be due to the cross-sectional nature of the study and inability to associate medication changes with metabolite variability. In future studies it will be important to test associations between genetic variants, metabolites, and medication use over time to assess whether these relationships are consistent depending on extent and type of medication exposure. It will also be important to consider, in larger samples sizes, additional pharmacogenetic markers that are associated with antipsychotic outcomes, as well as serum medication concentrations. As an example, select variants in CYP1A2 are known to lead to lower-than-anticipated serum concentrations of clozapine and greater risk of treatment failure in the presence of enzyme inducers (49). Finally, the cross-sectional nature of this study limits drawing any conclusions about the impact of environmental factors over time, such as prior smoking and how that relates to the ability of metabolite concentrations, in concert with genetic data, to predict HOMA-IR concentrations.

CONCLUSIONS

In summary, a least squares regression model including metabolite concentration data of primarily one-carbon unit donors within one-carbon metabolism, and genetic variants in *MTHFR*, are able to predict HOMA-IR. This is clinically important as elevated HOMA-IR has been associated with increased risk of developing diabetes, and future cardiovascular disease. Cumulatively, these results should be interrogated further in larger, prospective studies to determine precisely how variations in this complex metabolic and genetic network relate to mechanisms underlying the development of CVD risk in patients with severe mental illness, such as schizophrenia, or in patients who are otherwise healthy. Ideally, future precision health research will work toward leveraging an understanding of genetic and environmental markers of metabolism to identify opportunities for tailoring antipsychotic prescribing, or supplementation with adjunctive therapies, to decrease the risk of metabolic side effects in patients with serious mental illness.

DATA AVAILABILITY STATEMENT

The genetic datasets presented in this article are not readily available because they contain protected health information. Requests to access the datasets should be directed to Dr. Vicki Ellingrod. The metabolomics data used in this study are accessible through the Metabolomics Workbench: https://www.metabolomicsworkbench.org/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Study Protocol received Institutional Review Board (IRB) approval from the University of Michigan (IRBMED HUM00017774) and the following local organizations: the Detroit-Wayne County Community Mental Health Agency (DWCCMHA), Washtenaw County Health Organization (WCHO), and the Ann Arbor Veterans Affairs Medical Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KW, VE, AZK, and KB contributed to the study design. KW, KB, AJ, CM, LY, AK, and KS contributed to the metabolomics and genomics analyses. KW, KB, and AJ drafted the initial manuscript. All authors contributed to critical revision of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.623143/full#supplementary-material

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Adiponectin Is Related to Cardiovascular Risk in Severe Mental Illness Independent of Antipsychotic Treatment

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Background: Schizophrenia (SCZ) and bipolar disorder (BD) are severe mental illnesses (SMI) associated with elevated cardiovascular disease (CVD) risk, including obesity. Leptin and adiponectin are secreted by adipose tissue, with pro- and anti-inflammatory properties, respectively. The second generation antipsychotics (AP) olanzapine, clozapine, and quetiapine have been associated with high leptin levels in SMI. However, the link between inflammatory dysregulation of leptin and adiponectin and CVD risk in SMI, and how this risk is influenced by body mass and AP medication, is still not completely understood. We investigated herein if leptin, adiponectin or their ratio (L/A ratio) could predict increased CVD risk in SCZ, BD, and in subgroups according to use of antipsychotic (AP) treatment, independent of other cardio-metabolic risk factors.

Methods: We measured fasting plasma levels of leptin and adiponectin, and calculated the L/A ratio in $n = 1{,}092$ patients with SCZ and BD, in subgroups according to AP treatment, and in $n = 176$ healthy controls (HC). Differences in the levels of adipokines and L/A between groups were examined in multivariate analysis of covariance, and the correlations between adipokines and body mass index (BMI) with linear regression. CVD risk was defined by total cholesterol/high-density lipoprotein (TC/HDL) and triglyceride/HDL (TG/HDL) ratios. The adipokines and L/A ratios ability to discriminate individuals with TG/HDL and TC/HDL ratios above threshold levels was explored by ROC analysis, and we investigated the possible influence of other cardio-metabolic risk factors on the association in logistic regression analyses.

Results: We observed higher leptin levels and L/A ratios in SMI compared with HC but found no differences in adiponectin. Both adipokines were highly correlated with BMI. The low adiponectin levels showed a fair discrimination in ROC analysis of individuals

with CVD risk, with AUC between 0.7 and 0.8 for both TC/HDL and TG/HDL, in all groups examined regardless of diagnosis or AP treatment. Adiponectin remained significantly associated with an elevated TC/HDL and TG/HDL ratio in SMI, also after further adjustment with other cardio-metabolic risk factors.

Conclusions: Adiponectin is not dysregulated in SMI but is associated with CVD risk regardless of AP treatment regime.

Keywords: leptin, adiponectin, L/A ratio, CVD risk, antipsychotic treatment, schizophrenia, bipolar disorder

INTRODUCTION

Schizophrenia (SCZ) and bipolar disorder (BD) are severe mental illnesses (SMI) that are associated with an increased cardiovascular disease (CVD) risk (1). Obesity occurs frequently in patients with SCZ and BD and contributes to the elevated cardiovascular risk (2). The prevalence of elevated body-mass index (BMI) in patients with SCZ and BD is estimated to be 3–5 times higher compared with the general population (2, 3).

A pro-inflammatory state of the adipose tissue is supposed to accelerate CVD in obese and overweighed subjects and is characterized by augmented production of inflammatory cytokines (4). Thus, leptin and adiponectin are cytokines primarily secreted by adipose tissue (adipokines) with pro- and anti-inflammatory properties, respectively (5). These proteins may have direct effects on atherogenesis in CVD, and experimental studies have demonstrated that leptin promotes, whereas adiponectin attenuates atherosclerosis (6), although a dual role on endothelial cells has recently been described for adiponectin (7). Furthermore, numerous clinical studies implicate dysregulated leptin and adiponectin levels in the progression of CVD (8–11). Thus, both hyperleptinemia and hypoadiponectinemia have been shown to be independently associated with increased fat tissue and CVD risk in the general population. Due to the opposite metabolic effects of leptin and adiponectin, the leptin/adiponectin ratio (L/A ratio) has been proposed as a useful marker for metabolic disease, and may be more strongly associated with CVD risk than leptin or adiponectin alone (12, 13).

Schizophrenia and related disorders are associated with dysregulated adipokine levels (14) and we and other have demonstrated that use of antipsychotic (AP) medication (15), especially the 3 s generation antipsychotics olanzapine, clozapine, and quetiapine (16, 17) may enhance the leptin as well as the L/A ratio (15) in SMI. However, the link between dysregulation of the leptin-adiponectin axis and CVD in SMI, and how this risk is modified by body mass and AP medication, have scarcely been examined. Herein vi investigate whether leptin, adiponectin or their ratio (L/A ratio) could be associated with increased CVD risk in SCZ and BD, and in subgroups according to AP treatment, independent of other established cardio-metabolic risk factors.

Our specific aims of this study were 4-fold. Firstly, we evaluate whether the distribution of leptin and adiponectin and their ratio differ between patients with SMI (SCZ or BD) compared to healthy controls (HC), and between subgroups of AP medication, and secondly if this difference is mitigated by BMI. Thirdly, we investigate if these adipokines or their ratio can discriminate individuals with or without pro-atherogenic lipid ratios above threshold levels, and fourthly, if any association with these lipid ratios is independent or modified by other established cardio-metabolic risk factors: age, sex, BMI, C-reactive protein (CRP), insulin resistance (HOMA-IR), smoking, and anti-psychotic, anticonvulsant, and lithium treatment dose (DDD). As a measure of CVD risk we calculated pro-atherogenic lipid ratios total cholesterol/high-density lipoprotein; HDL-c (TC/HDL) and triglyceride/HDL-c (TG/HDL), based on our previously published results (18).

We hypothesize to find significantly higher leptin levels and significantly lower adiponectin levels in SCZ and BD compared to healthy controls, mitigated by BMI. We expect the dysregulated adipokine levels and particularly L/A to independently predict elevated atherogenic lipid ratios in all groups, and in particular in patients using AP treatment, and in patients using olanzapine, clozapine or quetiapine.

METHODS

Design and Ethics

This cross-sectional study is a part of the large ongoing Thematically Organized Psychosis (TOP) Study at the Norwegian Centre for Mental Disorders Research (NORMENT). Patients in the TOP study are included from hospitals and outpatient clinics in the Oslo, Trondheim, and Lillehammer regions in Norway. The sample for this current study consists of patients and healthy controls included from year 2002 until 2015, all with fasting blood samples available. Both the patients and the HC have given written informed consent, and the study was approved by the Norwegian Scientific Ethical Committees and the Norwegian Data Protection Agency.

Sample

Patients

In the current study, 701 patients with schizophrenia spectrum disorder and 391 patients with bipolar spectrum disorder were included, with age between 18 and 65 years.

The diagnostic evaluation of the patients was based on the SCID-1 (Structured Clinical Interview in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) axis I Disorders) [The inter-investigator diagnostic agreement has previously been evaluated to a satisfying level of 82%, with overall $\kappa = 0.77$ (CI 0.60–0.94) (19)]. Symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS), and

the Calgary Depression Scale for Schizophrenia (CDSS), and patient medication records and smoking habits were registered.

A diagnosis of schizophrenia spectrum disorder (SCZ) included the diagnoses of schizophrenia, schizoaffective disorder, schizophreniform disorder, and psychotic disorder not otherwise specified, while a diagnosis of bipolar spectrum disorder (BD) included the diagnoses of bipolar I, bipolar II, and bipolar disorder not otherwise specified.

In this study, SMI is defined as the SCZ and BD groups combined. The subgroups according to antipsychotic treatment were defined as follows: those patients with SMI receiving second generation AP treatment with olanzapine, clozapine or quetiapine were the $AP^{O/C/Q}$ ($n = 522$) group, those receiving other, first or second generation, AP treatment were the AP ($n = 269$) group, and those patients who did not receive antipsychotic treatment were the AP- ($n = 301$) group.

Healthy Controls

The current study included 176 healthy controls (HC), between 18 and 65 years old. The HC were randomly selected from statistical records (www.ssb.no) in the Oslo region. Exclusion criterion for HC was current or previous SMI in index persons or their family members, assessed with the clinical interview Primary Care Evaluation of Mental Disorders (PRIME MD).

The Exclusion Criteria

The exclusion criteria for all participants in the study were: on-going infections, C-reactive protein (hs-CRP) >20 mg/L of any reason, on-going autoimmune or inflammatory diseases, on-going cancer, treatment with immune modulating medication of any reason, or insulin levels <400 pmol/L (for valid calculation of insulin resistance). As we investigated atherogenic lipid ratios in our study, a diabetic profile or other dysregulated metabolic parameters were not an exclusion criteria.

Body Mass Index

All participants were weighed on calibrated digital weights under standard conditions, height was measured with standard methods and body mass index (BMI) (kg/m^2) calculated.

Defined Daily Dose for Antipsychotics, Anticonvulsants, and Lithium

Information on the use of prescribed antipsychotics, anticonvulsants, and lithium was assessed by clinical interview and hospital records. "Defined daily dose" (DDD) of the medication was calculated according to the World Health Organization (WHO) principles. For antipsychotic or anticonvulsant medication, we calculated the individual total DDD based on polypharmacy. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults and provide a fixed unit of measurement independent of dosage form (http://www.whocc.no/atc_ddd_index/).

Blood Samples

Fasting blood samples were collected between 8 am and 11 am for the most participants. Blood samples were drawn into EDTA tubes, stored at room temperature for 45 min and placed in refrigerator at 4 degrees C. They were then transported to the Biobank the following workday, where 2 x 9 ml EDTA tubes were centrifuged at 1,800 g for 15 min. Plasma was collected and stored at −80 degrees C in multiple aliquots (20).

Biochemistry

Plasma levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL-c), and low-density lipoprotein (LDL-c) were measured on an Integra 800 instrument from Roche Diagnostics, according to standard methods. Leptin, adiponectin and C-reactive protein (CRP) were analyzed using standardized platforms from Roche Diagnostics. All analyses were performed at the Department of Medical Biochemistry, Oslo University Hospital.

Insulin Resistance

Glucose and insulin were analyzed at the Department of Medical Biochemistry, Oslo University Hospital. Glucose levels were analyzed using standardized platforms from Roche Diagnostics. Insulin was analyzed at the Hormone Laboratory by radioimmunoassay (RIA) using standard methods. We estimated insulin resistance using the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) (21). As the calculation is valid only with insulin levels <400 pmol/L, participants with higher levels were excluded ($n = 11$).

Cardiovascular Risk

Cardiovascular risk was estimated calculating established pro-atherogenic lipid ratios including TG/HDL and TC/HDL, with sex-dependent cut-offs established elsewhere (22, 23).

Statistical Analyses

All statistical analyses were done using the SPSS software package for Windows, version 26.0 (SPSS Chicago. USA). All analyses were two-tailed with a level of significance set at $p < 0.05$. All skewed data was log-transformed prior to further analyses. Demographics of the study population were analyzed with analysis of covariance (ANOVA) for continuous variables and chi-square test for independence for categorical variables.

Differences in levels of adipokines, between HC and diagnostic groups (i.e., SCZ and BD) were analyzed by multivariate analysis of covariance (MANCOVA), adjusting stepwise for age, sex, duration of illness, and BMI. The same analysis model was then repeated for the AP, AP-, and $AP^{O/C/Q}$ subgroups. Further adjustment included mood stabilizers; anticonvulsive, and lithium treatment dose (DDD) as well as duration of AP treatment. We then analyzed correlations with linear regression analysis between BMI and leptin, adiponectin or L/A ratio across the studied groups.

To evaluate if adipokines or their ratio could discriminate individuals with or without pro-atherogenic lipid ratios (TG/HDL and TC/HDL) above threshold levels, we then performed receiver operating characteristics (ROC) analysis of leptin, adiponectin, and L/A ratio.

Finally, we evaluated the association between adipokine levels and pro-atherogenic risk using logistic regression with different

adjustment levels to assess if the associations were independent or modified by other cardio-metabolic risk factors in BD, SCZ and HC. The same analysis model was then repeated for the AP, AP-, and $AP^{O/C/Q}$ subgroups. Multivariable adjustment included age, sex, BMI, C-reactive protein (CRP), insulin resistance (HOMA-IR), smoking, anti-psychotic, anticonvulsive, and lithium treatment dose (DDD), duration of AP treatment and duration of illness.

RESULTS

Sample Characteristics

The clinical characteristics of the study population according to AP treatment are shown in **Table 1** and the clinical characteristics according to diagnostic groups are shown in **Supplementary Table 1**. Patients with SMI were of a similar age compared to HC, but when looking at the diagnostic groups, patients with BD were older than SCZ and had a longer duration of illness. Patients were less frequently male and of European origin than HC. Patients with SCZ received more often anti-psychotic treatment than BD but less anticonvulsants and lithium. Comparing a range of cardio-metabolic risk factors including HOMA-IR, CRP, BMI and lipids revealed a generally higher burden in patients with SMI was revealed, especially in SCZ compared with HC. Focusing on pro-atherogenic lipid ratios, patients with SMI had a 2- and 3-times higher proportion of individuals with TC/HDL and TG/HDL above threshold limits, respectively. Evaluated within the diagnostic groups, particularly SCZ patients had elevated ratios. These findings are similar to our previously published results on pro-atherogenic lipid ratios in a partly overlapping sample (18).

Evaluation of demographics according to antipsychotic (AP) treatment revealed a lower proportion of male patients that did not receive AP treatment (AP-). In general, patients using AP (including $AP^{O/C/Q}$) had a higher metabolic burden compared with those not receiving AP (both AP- and HC). The highest proportion of dysregulated pro-atherogenic lipid ratios (i.e., TC/HDL and TG/HDL) were observed in patients using AP (including $AP^{O/C/Q}$) followed by those not using AP (AP-), and then HC.

Adipokine and L/A Ratio Levels in SMI and Between AP Subgroups

As shown in **Figure 1A**, patients as a whole were characteriz1ed by markedly higher leptin levels compared to HC ($p = 0.005$) in age-, sex-, and duration of illness adjusted analysis. Further, patients using AP (both AP and $AP^{O/C/Q}$), had markedly higher leptin levels compared to patients not using AP (AP-), ($p < 0.01$ for both AP groups vs. AP-) and HC ($p < 0.01$ for both AP groups vs. HC), in analysis with further adjustment for AP treatment duration, and treatment with mood stabilizers (anticonvulsants and lithium). The same pattern of higher leptin levels was observed when evaluating the diagnostic groups SCZ or BD according to AP use (**Supplementary Figure 1A**).

As shown in **Figure 1B** and in **Supplementary Figure 1B**, no significant differences in adiponectin levels was observed between HC and SMI or according to AP use with similar findings within SCZ and BD.

As shown in **Figure 1C** and in **Supplementary Figure 1C**, the L/A ratio mirrored leptin levels although the differences between groups were somewhat attenuated. Thus, patients with SMI have an elevated L/A ratio compared to HC ($p = 0.041$), and AP users had a higher ratio than non-AP users ($p < 0.002$ for both AP groups) with a similar pattern, but larger confidence intervals attenuated significance, in diagnostic SCZ and BD groups.

Leptin was correlated with duration of illness ($r = 0.11$, $p < 0.001$) and duration of AP treatment ($r = 0.18$, $p < 0.001$. DDD for anticonvulsive therapy correlated modestly with adiponectin levels ($r = 0.15$, $p < 0.001$) and the L/A ratio ($r = -0.09$, $p = 0.004$). DDD for lithium correlated modestly with leptin levels ($r = 0.11$, $p < 0.001$) and the L/A ratio ($r = -0.09$, $p = 0.002$). No other correlation between adipokine levels DDD for lithium and anticonvulsive therapy or duration of illness or AP treatment were detected.

Adipokine Distribution by BMI

As shown in **Figure 1A**, leptin and BMI were strongly positively correlated in all groups ($p < 0.001$) and no interaction between BMI and AP group (i.e., group*BMI) was observed. Accordingly, the marked differences observed in age- and sex-adjusted analysis were largely mitigated by BMI adjustment and no differences in leptin levels between SMI, HC or AP, AP- and $AP^{O/C/Q}$ groups were observed after this adjustment.

As shown in **Figure 1B**, adiponectin correlated negatively with BMI ($p < 0.001$ for all groups), but correction for BMI did not reveal differences between the studied groups.

As shown in **Figure 1C**, the L/A ratio was strongly positively correlated with BMI ($p < 0.001$ for all groups) and the differences between diagnostic and between sub-groups according to AP use were diminished following BMI adjustment.

Discriminating Power of Adipokines on Atherogenic Lipid Ratios

Figure 2A shows ROC analysis of leptin, adiponectin, and L/A ratio levels ability to discriminate individuals with or without pro-atherogenic lipid ratios above treshold levels. The leptin levels were poor in identifying patients with elevated pro-atherogenic as reflected by the area under the curve (AUC) < 0.7 for TC/HDL and TG/HDL across the groups analyzed. The adiponectin levels showed a fair discrimination of individuals with elevated atherogenic ratios. The reciprocal values of the ROC analysis (i.e., inverse) indicated AUC between 0.7 and 0.8 with no major differences in HC, SMI or according to AP treatment. Notably, the best discrimination was observed in the AP- group with an AUC of 0.78 (inverse of 0.22). The L/A ratio was better than leptin but still poor in identifying individuals with elevated TC/HDL ratio (AUC < 0.7) but somewhat better in identifying individuals with an elevated TG/HDL ratio (AUC > 0.7). This pattern was seen across all groups studied but was notably poorer in the AP- group vs. TG/HDL (AUC = 0.65).

TABLE 1 | Demographics of the study population.

	HC	SMI	AP-	AP	APO/C/Q	*Post-hoc*
N	176	1092	301	269	522	
Sex (male)	113 (64)	576 (53)**	139 (46)	141 (52)	296 (57)	HC, APO/C/Q>AP-
Age	32 ± 8	32 ± 11	33 ± 12	31 ± 10	31 ± 10	
Ethnicity (European)	173 (98)	893 (82)***	254 (84)	209 (78)	430 (82)	HC>AP-,AP,APO/C/Q
Duration of illness, years	N/A	9.9 (8.9)	12.0 (9.8)	8.9 (8.1)	9.1 (8.5)	AP-> AP,APO/C/Q
Daily smoking	N/A	492 (46)	120 (41)	135 (52)	237 (46)	
Statin use	0 (0)	15 (1.5)	1 (0.3)	9 (3.3)	6 (1.1)	AP>AP-
Antipsychotics (DDD)	N/A	0.88 (0.96)	0 (0)	0.93 (0.69)	1.35 (1.01)	APO/C/Q>AP>AP-
Duration of AP treatment, months	N/A	9.7 (24.6)	0 (0)	11.6 (29.4)	14.2 (27.1)	
Anticonvulsants (DDD)	N/A	0.14 (0.35)	0.17 (0.39)	0.10 (0.29)	0.14 (0.35)	AP-> AP
Lithium (DDD)	N/A	0.08 (0.30)	0.09 (0.33)	0.05 (0.22)	0.09 (0.32)	APO/C/Q>AP
Cardiometabolic Risk Factors						
HOMA-IR	1.2 ± 0.7	1.7 ± 1.0***	1.4 ± 0.8	1.7 ± 0.9	1.8 ± 1.1	APO/C/Q,AP>AP-,HC
CRP (mg/L)	1.6 ± 2.2	2.3 ± 2.8***	2.0 ± 2.5	2.6 ± 3.3	2.4 ± 2.7	APO/C/Q,AP>AP->HC
BMI	24.2 ± 3.6	25.8 ± 4.6***	24.8 ± 4.3	26.3 ± 5.0	26.0 ± 4.5	APO/C/Q,AP>AP-,HC
HDL-c(mmol/L)	1.47 ± 0.39	1.38 ± 0.43*	1.48 ± 0.45	1.35 ± 0.41	1.34 ± 0.42	HC,AP->AP,APO/C/Q
LDL-c (mmol/L)	2.94 ± 0.88	3.13 ± 0.95*	3.01 ± 0.90	3.05 ± 0.89	3.24 ± 0.99	APO/C/Q>HC,AP-,AP
Total-c (mmol/L)	4.70 ± 0.95	5.07 ± 1.07***	4.97 ± 1.07	5.03 (1.02)	5.16 ± 1.09	AP-,AP,APO/C/Q>HC
Triglycerides (mmol/L)	1.07 ± 0.78	1.39 ± 0.99***	1.19 ± 0.71	1.48 ± 1.19	1.45 ± 1.00	AP,APO/C/Q>HC,AP-
Total-c/HDL-c	21 (12)	257 (24)	50 (17)	65 (24)	142 (27)	APO/C/Q,AP>AP->HC
Triglycerides/HDL-c	17 (10)	301 (28)	58 (19)	85 (32)	158 (30)	APO/C/Q,AP>AP->HC
Symptom scores						
PANSS total	N/A	0.22 ± 0.13	0.22 ± 0.12	0.24 ± 0.12	0.22 ± 0.13	
CDSS total	N/A	5.3 ± 4.7	5.7 ± 4.4	5.5 ± 5.2	5.0 ± 4.6	

*Analyzed with ANOVA for continuous variables and chi-square test for categorical variables. HC, healthy controls; SMI, severe mental illness; AP-, patients not using antipsychotic treatment; APO/C/Q, patients using olanzapine, clozapine or quetiapine; AP, patients using other AP; n, number; DDD, defined daily dose; HOMA-IR, homeostasis model assessment for insulin resistance; CRP, C-reactive protein; mg/L, milligrams per liter; mmol/L, millimoles per liter; BMI, body mass index; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; Total-c, total cholesterol; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; N/A, not applicable; n.s., not significant, *p < 0.05 **p < 0.01 ***p < 0.001 vs. HC.*

Association Between Adipokine Levels and Atherogenic Lipid Ratios

We next evaluated the association between adipokine levels and elevated pro-atherogenic ratios using logistic regression with different adjustment levels to assess if the associations were independent or modified by other cardio-metabolic risk factors, mood stabilizers (anticonvulsants and lithium), duration of illness, and duration of AP treatment. Odds ratios (OR) were for these analyses based on log-transformed standardized values, and represent a one standard deviation (SD) increase in the analyzed marker. Based on the poor performance of leptin in the ROC analysis, we focused on adiponectin and the L/A ratio. The results of these analyses are presented in **Figure 2B** and **Supplementary Tables 2, 3**. As presented in **Figure 2B**, the OR for adiponectin and the L/A ratio was largely comparable in age- and sex-adjusted analysis in identifying individuals that had an elevated TC/HDL or TG/HDL ratio with overlapping CI's between all groups. The numeric for this analysis as well as for the diagnostic groups and subgroups according to AP use are presented in **Supplementary Tables 2, 3**.

The OR's were somewhat attenuated upon addition of BMI but both the L/A ratio and in particular adiponectin, remained significantly associated with an elevated TC/HDL and TG/HDL ratio, also after further adjustment with other cardio-metabolic risk factors (i.e., CRP, smoking, HOMA-IR, DDD for AP), mood stabilizers, duration of illness, and duration of AP treatment to the models. The lack of significance in the HC population is largely due the lower frequency of dyslipidemia in this group as reflected by large CI's but comparable point estimates (OR) were observed in HC compared to the other groups. Altogether, the L/A ratio and in particular adiponectin were independently associated with atherogenic risk in all diagnostic groups and treatment modalities.

DISCUSSION

We investigated dysregulation of the prototypical adipokines leptin, adiponectin, and leptin/adiponectin ratio in a large clinical sample of patients with SMI, associations with elevated atherogenic lipid ratios, and whether these associations were dependent on antipsychotic treatment. We found that (i) patients with SMI displayed markedly elevated leptin levels and L/A ratio, with particularly high levels observed in AP users while adiponectin was comparable in all groups, that (ii) all markers correlated strongly with BMI with similar associations in all diagnostic groups and AP treatment regimes, and that (iii) low adiponectin and a high L/A ratio were associated with elevated lipid ratios, and (iv) the association with elevated lipid ratios was independent of other cardio-metabolic risk factors; BMI, CRP, insulin resistance and smoking, with comparable

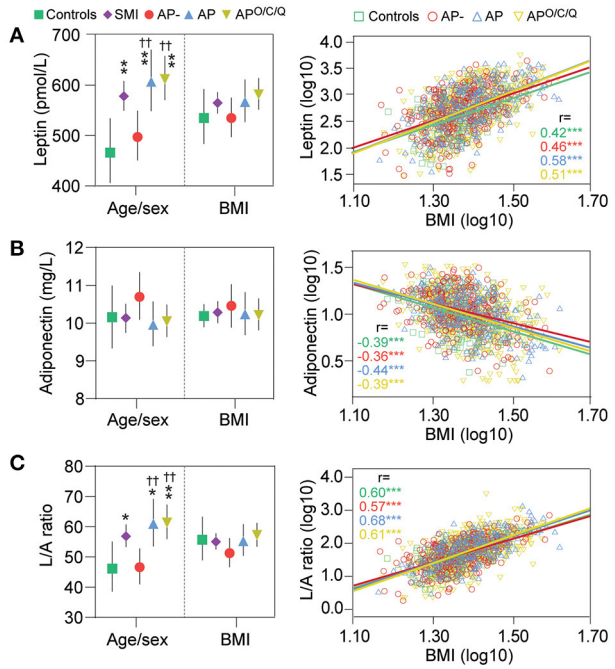

FIGURE 1 | Leptin, adiponectin and their ratio (L/A) in severe mental illness (SMI) and according to antipsychotic (AP) treatment. To the left: multivariate analysis of covariance with dependent variable: leptin **(A)**, adiponectin **(B)** or L/A **(C)**, with adjustment for age, sex, duration of illness, mood stabilizers (DDD), duration of AP treatment and additional adjustment with body mass index (BMI). $^{*}p < 0.05$ $^{**}p < 0.01$ $^{***}p < 0.001$ vs. healthy controls; $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, $^{\dagger\dagger\dagger}p < 0.001$ vs. AP-. To the right: correlation between log-transferred leptin, adiponectin or L/A, and BMI. Numbers indicate the regression coefficient. $^{***}p < 0.001$.

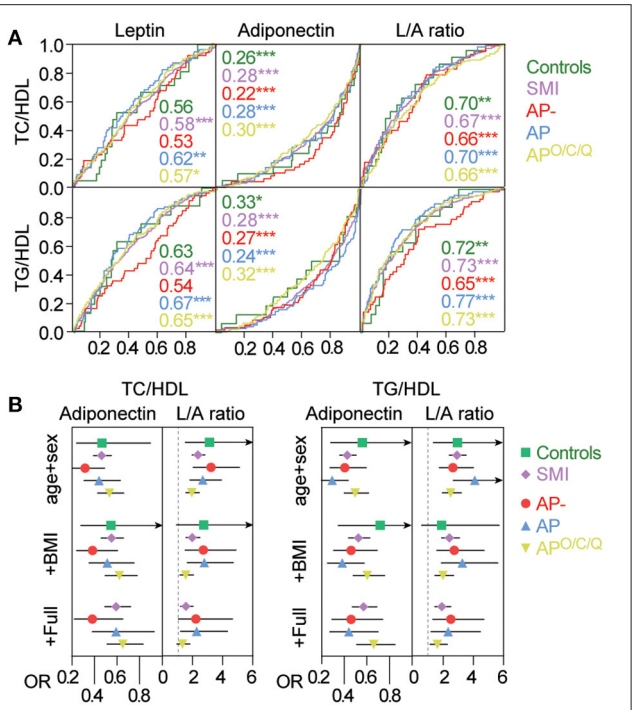

FIGURE 2 | Association between Adiponectin and the L/A ratio and atherogenic risk. **(A)** Association between Adiponectin or the L/A ratio, and having a TC/HDL or TG/HDL above threshold levels as assessed by the area under the receiver-operating characteristics curve (ROC). Numbers indicate the AUC in the different groups. $^{*}p < 0.05$ $^{**}p < 0.01$ $^{***}p < 0.001$. **(B)** Association between adiponectin and L/A levels and cardiovascular risk (TC/HDL, TG/HDL) using logistic regression with adjustment levels for a. Age and sex b. a+BMI c. b+C-reactive protein (CRP), insulin resistance (HOMA-IR), smoking, and anti-psychotic treatment dose (DDD), duration of illness, mood stabilizers (DDD), duration of AP treatment. Odds ratios (OR) are expressed as log-transformed per SD change in marker. Odds ratios with 95% Confidence interval are given in **Supplementary Tables 2, 3**.

associations with risk according to AP use. Altogether, elevated leptin in SMI was largely driven by BMI and not strongly associated with elevated lipid ratios. In contrast, adiponectin was not dysregulated, however, low levels were strongly and independently associated with the elevated lipid ratios. We were unable to detect that any adverse effect of AP treatment on elevated lipid ratios is conveyed by these adipokines as reflected by their circulating levels.

Obesity and overweight are frequent in SMI and are associated with increased leptin levels, closely correlated with BMI and AP treatment, as confirmed in the present study and shown previously in numerous other studies (14, 24). Increased fat mass is accompanied by infiltration of various myeloid immune cells (such as neutrophils, monocytes and macrophages) in adipose tissue, and altered secretion of adipokines including reduced expression of the insulin sensitizing adiponectin (25–27). Furthermore, AP treatment has been shown to promote monocyte infiltration, macrophage effector functions and inflammation in adipose tissue in experimental studies (28–30), as well as to regulate adiponectin expression and secretion (30). Thus, dysregulated adiponectin levels could be expected to be particularly low in AP treatment users. However, in line with recent meta-analyses, adiponectin levels were similar in SMI and HC (31, 32). Except for somewhat higher adiponectin levels in AP-, we did not find the levels to be significantly modified by AP use. While several studies report low levels of adiponectin with AP use, and in particular in patients receiving second generation AP treatment (30, 32), few of these studies compare with HC which in our study showed similar levels as in SMI. The differences in L/A ratio between SMI and HC in our study largely reflect leptin levels, since no major dysregulation in adiponectin was detected. Importantly, leptin and adiponectin were closely correlated with BMI in all diagnostic and treatment groups, with comparable regression coefficients and no interactions between group and BMI, suggesting similar production of these adipokines per unit change in BMI. This argues against a more inflamed adipose tissue in SMI, where augmented or antagonized secretion of leptin and adiponectin would be expected, although regional fat distribution would be more informative in this regard.

Obesity in patients with SCZ and BD may contribute to elevated CVD risk, which may be further augmented by AP treatment use (1). Indeed, atherogenic lipid ratios were markedly enhanced as previously shown (18), especially in SCZ and in AP users in our study. Leptin and adiponectin could contribute

to enhanced CVD risk through metabolic pathways related to obesity and insulin resistance, but could have independent effects as well. Adiponectin has been shown to directly affect HDL and TG metabolism, independent of fat mass, insulin resistance and dyslipidemia (33, 34) in non-psychiatric patients, and may modulate signaling pathways in response to inflammatory stimuli in several cell types (35). Thus, adiponectin seems to diminish the inflammatory response in endothelial cells to mechanical injury (36) and modulated macrophages to acquire an anti-inflammatory phenotype and inhibited foam cell transformation (37). Adiponectin has recently been demonstrated to have two forms with opposing actions in endothelial cells (7). However, in line with a protective anti-inflammatory role, we found an inverse association between adiponectin and atherogenic lipid ratios in SMI patients. Furthermore, the association with lipid ratios was markedly stronger than for leptin, and persisted following full adjustment for important cardio-metabolic factors.

Focusing on non-psychiatric patients with metabolic disturbances, numerous clinical studies have shown that dysregulated leptin and adiponectin levels (38, 39) are strongly associated with dyslipidemia. However, as in the present study, studies on these adipokines and CVD are often cross-sectional using surrogate endpoints for CVD such as lipid ratios (40) or coronary artery calcium (41). There are fewer prospective studies evaluating the association between these adipokines and incident CVD or CVD related outcomes in patients with metabolic distrubances. Shanker et al. demonstrated that low adiponectin and high leptin were associated with incident events in patients with coronary artery disease (42). Low adiponectin was associated with future coronary heart disease in type 2 diabetes (43) as well as CV mortality (44). In contrast, high adiponectin was associated with cardiovascular events in patients with hypertension (45), and in older adults (46). Thus, the association between these adipokines and incident CVD or outcomes seem to depend on the degree of metabolic disturbances.

Evaluating diagnostic groups revealed overall stronger associations in BD compared to SCZ. Thus, despite quite similar levels, a unit decrease of adiponectin in BD was associated with a larger risk of having an atherogenic lipid profile than SCZ possibly indicating a more anti-atherogenic effect of adiponectin in BD. As we measured total adiponectin, evaluation of high molecular weight (HMW) adiponectin could have given different results (47). Possibly, different distribution of sub-fractions could also explain the stronger association with CVD risk in BD but we were unable to find any studies evaluating this. Adipose tissue has been shown to sense and respond to emotional stress through peroxisome-profilator activated receptor γ (PPARγ)-adiponectin interactions (48), that are also linked to immunometabolic regulation and systemic inflammation (49), but future studies are needed to evaluate how or if this is relevant in BD.

Increased risk of adverse cardiac events has been associated with AP use, and in particular second generation AP including olanzapine, clozapine, and quetiapine (50). However, we did not observe any clear differences in pro-atherogenic lipid ratios associated with low adiponectin or high L/A ratio, that were dependent on AP use. We found a lower risk of having elevated lipid ratios per unit decrease in adiponectin in users of these 3 s generation AP, arguing against any adverse effects of these drugs acting through the adiponectin signaling pathway, at least as reflected by circulating levels in a cross-sectional setting. Adverse effects of AP could still be mediated by other pathways, both inflammatory [e.g., activated leukocytes in adipose tissue enhancing inflammation (4)], and non-inflammatory [e.g., effects on lipogenesis and lipolysis (51)].

LIMITATIONS

Since fasting status effects the levels of adipokines and other confounding cardiovascular variables, a non-fasting status was an exclusion criteria for this study, thus excluding 520 non-fasting available healthy controls, limiting the size of the HC population. This gave different group sizes of HC vs. SMI. We also excluded 60 non-fasting BD and 158 non-fasting SCZ patients. The patients with a lower function level can find it challenging to fast over night. Many participants, both controls and patients, have busy everyday lives and were not able to schedule blood sampling in the morning. The non-fasting participants are included in other studies in the overall TOP-study.

For the HC in our study smoking status is not available. Although the effect of smoking on inflammation is less documented, the effect of smoking on CVD risk is known. Therefore, since we had smoking status in our patients, we were able to adjust for smoking when evaluating the association between adiponectin and L/A ratio and CVD risk in logistic regression analysis.

Patients with major depression with psychotic symptoms were not included in this study due to small sample size and thus limited statistical power.

We were unable to investigate the possible effect of lipid lowering medication (statins) on CVD risk as only 15 patients in our sample were using these agents. Finally, the design of this study is cross-sectional, limiting our ability to conclude on causality of the associations shown.

Furthermore, as our study is associative by nature, cause–effect relationships would have to be shown in a prospective controlled study.

STRENGTHS AND CLINICAL IMPLICATIONS

To our knowledge, this is to date the largest study evaluating dysregulation of leptin, adiponectin, and leptin/adiponectin ratio in patients with SMI. The patient population was well-characterized allowing us to adjust our regression models with relevant cardio-metabolic risk factors as well as use of other mood stabilizers and duration of both illness and AP treatment.

As lifespans in people with SMI are markedly reduced frequently due to CVD, there is a need for treatment options that target modifiable metabolic risk factors. Circulating adiponectin represents a modifiable risk factor that can be efficiently targeted by lifestyle modifications, mainly weight loss and dietary changes (52). Thus, low adiponectin could be used to identify and monitor patients that could benefit from such modifications as well as in increasing awareness of increased CVD risk in these individuals.

CONCLUSION

In a large clinical sample of patients with SMI we show that adiponectin is not dysregulated in patients compared to HC, but low levels of adiponectin are associated with enhanced CVD risk regardless of AP treatment regime. Our findings support an anti-atherogenic role for adiponectin and suggest it could be further evaluated in novel CVD risk prediction strategies in SMI.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because sharing of data to external parties has not been approved by the ethics committee. Requests to access the datasets should be directed to e.j.reponen@medisin.uio.no.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional committees for medical and health research ethics, East Norway (REK 1). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ER and TU contributed to data collection, literature search, study design, statistical analysis, and manuscript editing. MT contributed to data collection, literature search, statistical analysis, and manuscript editing. ID and TV contributed to data collection, literature search, and manuscript editing. NS, MW, SL, IJ, LR, and OA contributed to data collection and manuscript editing. AS contributed to literature search and manuscript editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.623192/full#supplementary-material

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REVIEW
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Cardiovascular Diseases and Schizophrenia in India: Evidence, Gaps, and Way Forward

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Background: The importance of physical health among persons with schizophrenia is well-established. Studies from developed and developing countries indicated a strong association between cardiovascular diseases and schizophrenia, while evidence from India is scattered and in its infancy. Hence, the aims of the study were to collate available studies from India on cardiovascular diseases among persons with schizophrenia, identify knowledge gaps and challenges, and discuss recommendations to improve clinical care and research on cardiovascular diseases among persons with schizophrenia in India.

Materials and methods: A comprehensive literature review of Indian studies on cardiovascular diseases and schizophrenia was conducted to collate and synthesise available knowledge.

Results: Several risk factors for cardiovascular disease predominated among persons with schizophrenia. Metabolic syndrome and obesity were the key factors that were reported. Knowledge gaps were identified with respect to the prevalence of cardiovascular diseases among persons with schizophrenia. Sparse research in interventions to prevent and reduce the impact of cardiovascular diseases among persons with schizophrenia was noted.

Conclusion: Targeted efforts are needed at the clinic, community, and policy levels to understand the impact of cardiovascular diseases among persons with schizophrenia. Robust and feasible interventions targeting cardiovascular diseases and its varied risk factors in persons with schizophrenia, that can be implemented in tertiary mental health services, need to be developed and tested.

Keywords: cardiovascular diseases, risk factors, interventions, India, schizophrenia

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INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality in India (1). Serious mental disorders (SMD), comprising of schizophrenia spectrum disorders and bipolar disorders, also contribute as major causes of morbidity worldwide (2) and in India (3). Among the serious mental disorders, CVD morbidity and mortality is more pronounced among schizophrenia spectrum disorders. In the National Mental Health Survey in 2016, the prevalence of schizophrenia spectrum disorders was found to be 0.8% in India (4). This translates to a huge number of people being affected by schizophrenia spectrum disorders in India.

While global literature has shown a strong association between cardiovascular diseases and schizophrenia, evidence from India is scattered and still in its infancy. Hence, the aims of this paper were to: (1) To comprehensively review the available literature on the interface of cardiovascular health and schizophrenia from India; and (2) To use the information from this scoping review to identify gaps and put forth evidence-informed recommendations to improve management of cardiovascular health among persons with schizophrenia in India.

MATERIALS AND METHODS

Search Strategy

We conducted a scoping review for published articles, up to October 2020. The electronic databases used were PubMed and Google Scholar, using Medical Subject Headings (MESH) terms in combinations: schizophrenia OR psychosis AND "cardiovascular disease" OR "metabolic syndrome" OR diabetes OR hypertension AND India OR Indian, to identify the relevant research publications. Cross references from the articles were retrieved and grey literature were also screened for relevant articles (**Figure 1**).

Study Selection

In this scoping review, we included peer reviewed studies, including original research and reviews, that reported on: (1) Prevalence/incidence of cardiovascular disorders in persons with schizophrenia; (2) Etiological and risk factors associated with cardiovascular disorders among persons with schizophrenia; and (3) Intervention/management of cardiovascular disorders among

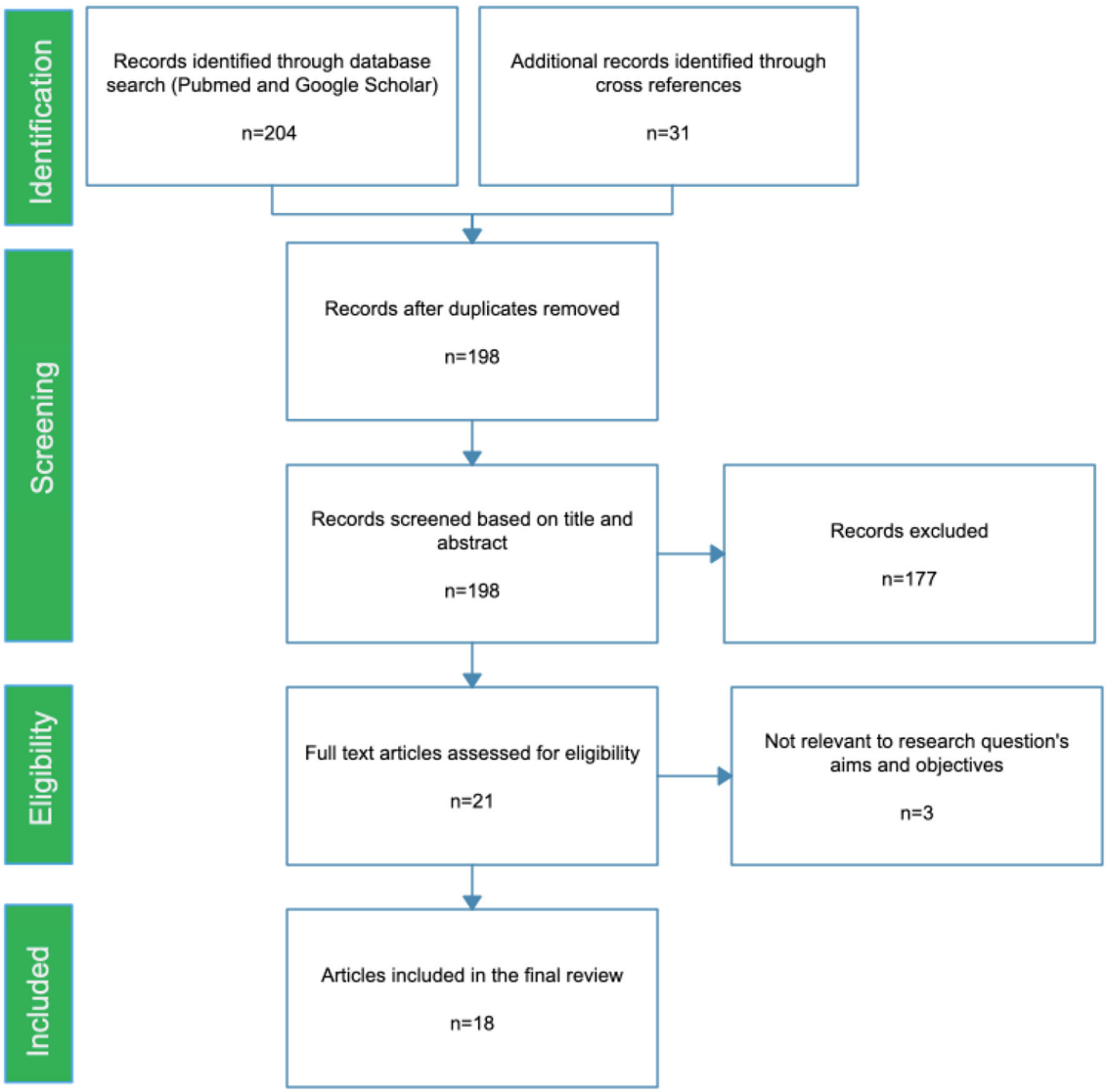

FIGURE 1 | PRISMA flow diagram of the scoping review.

persons with schizophrenia. The inclusion criteria were: (1) Articles on cardiovascular disease and metabolic syndrome—prevalence, risk factors, and interventions for persons with schizophrenia, and studies conducted in India. Commentaries and perspectives were excluded from this review.

Data Analysis

The research studies obtained from electronic databases were screened according to the inclusion and exclusion criteria. The selected studies were then categorised under relevant sub-headings pertaining to cardiovascular risk.

RESULTS

Studies Included

The search Identified 198 unique articles. Of these, 177 articles were excluded as they were not found to satisfy the inclusion and exclusion criteria during the title and abstract search. The remaining 21 research articles were reviewed as full text articles 18 articles were found to be eligible to be included in the current review. All of the studies included in this review, along with their main findings, are given in **Table 1**.

Major Findings

Search results indicate that there is a dearth of studies on the interface of CVD and schizophrenia from India, the majority of the studies have examined the prevalence of metabolic syndrome and its association with CVD and the clinical outcomes in persons with schizophrenia.

Metabolic Syndrome Among Persons With SMD

Reported literature indicates that standard methods of defining metabolic syndrome have been adopted in the studies, facilitating the comparison and generalizability of the findings. The prevalence of metabolic syndrome among persons with schizophrenia varies in studies from India. In a study conducted in Assam, 78.7% of persons with schizophrenia were found to have metabolic abnormalities (9).There is a higher prevalence amongst persons with mental illness than healthy controls (21). In a recent review by Ganesh et al., pooled prevalence of metabolic syndrome in persons with schizophrenia was 29.83%, and the meta-analysis showed an OR = 3.03 for prevalence in persons with schizophrenia when compared to normal controls and drug-naïve persons had a pooled prevalence of 11.86% (10).

Modifiable lifestyle factors seem to contribute largely by affective quality of life, self-esteem, and increasing distress to the occurrence of metabolic syndrome (16). Some risk factors identified were female gender, antipsychotic use, high BP in men, age > 30 years (13), fasting blood sugar, and triglycerides (18, 23).

Monitoring of metabolic parameters was indicated to be inadequate (17). In drug naïve persons with schizophrenia, high density lipoprotein cholesterol, BMI, and low density lipoprotein were indicated to be risk factors for metabolic syndrome (18).

The presence of metabolic syndrome was also found to impact multiple factors such as neurocognition of persons with schizophrenia (7), while lipid fractions were found to be associated with levels of impulsivity, suicidality, and aggression (15) in persons with schizophrenia. It is further indicated that the presence of mental illness with co-morbid CVD is found to lead to productivity loss (24).

Olanzapine was found to have the greatest weight gain, followed by risperidone and haloperidol (5.1, 4.1, and 2.8 kg), respectively (6). Though other factors contribute to the onset of metabolic changes, clozapine use contributed largely, as after starting clozapine the prevalence of metabolic syndrome increased from 23 to 38.5% and after 6 months increased to 46.2% (12). A study from north India indicates that obstructive sleep apnoea may be a mediating factor for metabolic syndrome with persons on second generation antipsychotics (14). At the same time, Padmavati et al. found low prevalence of obesity and metabolic syndrome among never treated persons with schizophrenia (22). Similarly, the proportion of persons with metabolic syndrome did not increase significantly in this rural cohort, despite the fact that nearly three-fourths of the persons were initiated on second-generation antipsychotics (8).

Prevalence of Obesity Among Persons With SMD

The prevalence of overweight individuals was 22.7% and obesity at 31.8%. It was found that at times the difference of prevalence of metabolic syndrome is up to 30 times greater in persons with mental illness when compared to controls (6).

Interventions for CVD Among Persons With SMD

Some methods to reduce weight gain due to medications that were proven to be effective were—reducing body mass index, reducing waist circumference, lower blood glucose levels, and interventions by dieticians and nurses (19).Other facilitators to improve healthy lifestyle behaviours were increased self-confidence, social support, and conducive environment; level of self-motivation; encouragement from health professional, and availability of health services (20).

DISCUSSION

The aims of our study were to synthesise the available information on the interface of schizophrenia and cardiovascular diseases in India through a scoping review of available studies from India, to understand the gaps in the understanding of cardiac diseases in the Indian context and to discuss a potential way forward to improve clinical care and research for CVD among persons with schizophrenia.

Two important risk factors identified have been metabolic syndrome and obesity, both of which could be intervened with. Most of the studies from India have concentrated on the risk factors for CVD such as metabolic syndrome and anti-psychotic medications among persons with schizophrenia (10). There is sparse research on interventions that can prevent the syndrome or manage the components after they manifest (25), despite evidence of effective management using therapeutic lifestyle approaches and targeted pharmacological interventions in the general population (26).

TABLE 1 | Studies on cardiovascular diseases among persons with schizophrenia from India.

References	Study type	Variables studied	Major findings
Joshi et al. (5)	Case control	Schizophrenia, cardiovascular disease	• Metabolic syndrome prevalence−28.8% • 51.1%higher compared to control group
Saddichha et al. (6)	RCT	Schizophrenia, weight, BMI	• Prevalence of overweight-22.7%; obesity-31.8% • Prevalence of obesity is over 30 times as that of the matched healthy control group
Grover et al. (7)	Cross-sectional	Schizophrenia, neurocognition, metabolic syndrome	• Metabolic syndrome was indicated to have an effect on the neurocognition of those with schizophrenia- cognitive processing and selective attention, auditory and verbal memory, and executive functions
Bijjal et al. (8)	Prospective cohort	Schizophrenia, metabolic syndrome	• Proportion of persons with metabolic syndrome did not increase significantly in this rural cohort
Das et al. (9)	Cross-sectional	Schizophrenia, metabolic syndrome	• 78.7% were found to have metabolic abnormalities • Risks identified were female gender, smoking, anti-psychotic use, f/h/o chronic lifestyle disorder
Ganesh et al. (10)	Review	Schizophrenia, metabolic syndrome	• Community based studies highlight a significantly lower prevalence
Rawat et al. (11)	Cross-sectional	Schizophrenia, metabolic syndrome, antipsychotics	• 31.8%persons and 28.9% controls were found to have metabolic syndrome • Risk factors were female gender and antipsychotic use
Grover et al. (12)	Cross-sectional	Schizophrenia, metabolic syndrome adolescents	• After starting clozapine the prevalence metabolic syndrome increased from 23 to 38.5% and after 6 months increased to 46.2% • Though other factors prior to onset of medications contribute, Clozapine contributes to half the risk of onset of metabolic changes in adolescence
Anjum and Bathla (13)	Cross-sectional	Schizophrenia, metabolic syndrome	• More than 1/5th psychiatric persons are affected by metabolic syndrome
Rohatgi et al. (14)	Preliminary study	Schizophrenia, metabolic syndrome sleep apnoea, antipsychotic	• Metabolic syndrome in participants taking second-generation antipsychotics is mediated through obstructive sleep apnoea
Kavoor et al. (15)	Case control	Schizophrenia, lipids	• In persons the HDL, LDL levels were found to be lower • Lipid fractions were found to be contributing to levels of impulsivity, suicidality and aggression among persons with schizophrenia
Malhotra et al. (16)	Cross-sectional	Schizophrenia, metabolic syndrome	• Metabolic syndrome was found to be associated with lower scores on health responsibility and nutrition habit, physical activity and stress • Obesity was found to be associated with poor self-esteem and excessive personal distress
Poojari et al. (17)	Retrospective cohort	Schizophrenia, metabolic syndrome antipsychotic	• Age >50 years (OR = 2.00) and duration of antipsychotic treatment>5 years (OR = 1.55) were found to be risk factors • Documenting metabolic changes was inadequate
Anjum et al. (18)	Cross-sectional	Schizophrenia, metabolic syndrome	• Most common metabolic abnormality was low HDL in 76.6%; High TGs in 26.6%; High SBP ≥ 130 mm Hg in 16.67%; DBP>85 mm Hg in 13.33%; High FBS 10% of the persons. In risk assessment strongest risk factors for metabolic syndrome were high waist circumference, FBS, and TGs • In-drug naïve persons, High Density Lipoprotein cholesterol, BMI, and Low Density Lipoprotein were indicated to be risk factors
Gurusamy et al. (19)	Review	Schizophrenia, metabolic syndrome psychoeducation, diet and physical activity interventions	• Non pharmacological management—psychoeducation, diet, and physical activity were proven to be effective in reducing anti-psychotic induced weight gain
Gandhi et al. (20)	Qualitative study	Schizophrenia, metabolic syndrome healthy lifestyle	• Four major themes as facilitators; increased self- confidence, social support and conducive environment; level of self-motivation; encouragement from health professional and availability of health services
Grover et al. (21)	Cross-sectional	Schizophrenia, metabolic syndrome CVD	• Prevalence of metabolic syndrome among healthy controls was 6%, significantly less than persons with SMI • Persons with bipolar disorder had a greater risk for metabolic syndrome
Padmavati et al. (22)	Case control	Schizophrenia, obesity, metabolic syndrome	• Schizophrenia in the absence of antipsychotics was not indicated to contribute to the onset of metabolic syndrome

Obesity is a critical factor associated with an increased risk of developing cardiovascular disease. Several meta-analyses have documented the increased prevalence of obesity in persons with mental disorders in general (27).

In India, a large proportion of the population is affected by obesity (28) and the prevalence of obesity in India varies due to various socio-demographic factors. According to an ICMR-INDIAB study in 2015 (29), the prevalence rate of obesity

and central obesity varies from 11.8 to 31.3% and 16.9 to 36.3%, respectively. Several meta-analyses have documented the increased prevalence of obesity in persons with mental disorders in general (27) but very few studies from India. This implies the need for more data on obesity, especially central obesity. This becomes important given that there are few intervention studies that cite body weight and patterning as outcome variables in the general population (30) and virtually none in persons with schizophrenia.

Global literature recognises that over three quarters of deaths from heart disease happen in LMIC with 4–5 persons dying of a heart attack or a stroke (31). These outcomes would be avoidable if there was more awareness of the conditions and the ways to control risk factors through lifestyle interventions and drug treatment where necessary (32). In the Indian context too, cardiovascular diseases are the leading cause of mortality, the estimated prevalence being 54.4 million (33). CVDs with ischemic heart disease and stroke responsible for >80% are the cause of one in four deaths (34). These diseases tend to affect persons in the most productive years of their lives and result in catastrophic social and economic consequences.

Gaps

The gaps in the current knowledge of the status of cardiac health in persons with schizophrenia need to be explored in depth. The association between cardiac disease and mental illnesses has been well-documented with the existing world literature providing relevant insights (35).

The scoping review that we undertook however, demonstrates the limited literature in the Indian context. This finding needs to be understood from several angles. First, it appears that the focus of research has been related largely to metabolic syndrome—taking into context the role of psychotropic medications. Secondly, mental health services are largely delivered in mental health settings, limiting the scope of physical health screening, although the incorporation of psychiatric services at a general hospital psychiatric unit has been documented historically and is within the scope of the National Mental Health program (36). However, despite making mental health services more accessible, several limitations bring about inadequate utilisation of this facility for general medical care for the persons. With increasing emphasis on the primary care provider's role in promoting preventive care, lifestyle changes, and patient self-management, services for the chronically mentally ill persons from the mainstream has become more marginalised (37). Thirdly, there is sufficient evidence that people with schizophrenia are less likely to be screened for lifestyle factors, insufficiently tested for baseline physical parameters or receive standard levels of care for chronic diseases (38). Other factors that limit treatment for cardiac and other physical comorbidities include stigma and diagnostic overshadowing (39). This also limits the possibility of undertaking collaborative research for the study of medical morbidity in persons with severe mental illnesses, explaining the sparse data that is available, despite the increased prevalence of chronic disease and mental illnesses.

Existing literature has several implications. Persons, clinicians and the health care system all play a role in mitigating the multiple factors that are associated with poor physical health in persons with serious mental illnesses. Most persons with schizophrenia receive psychiatric services as out-persons. While many receive medication, social, and rehabilitative services, most either do not receive or access medical care. For persons with serious mental illness, negotiating a separate, complex, medical health care system can be challenging (40). While integrated services offering both mental and medical care at the same location, sometimes even by the same clinician, can overcome systems-based barriers, it also implies that the mental health service system must be able to recognise the comorbidity early and take steps to manage it through referral pathways or collaborative care.

Recommendations

Clinical

Various factors have been identified to contribute to poor cardiovascular health from previous studies. One of the major factors contributing to poor physical health among persons with SMD is lifestyle risk factors (41). Persons with SMD are more likely to smoke, even after comparison with lower socioeconomic status (42). Persons with SMD are also less likely to exercise (43), have diets higher in fat and lower in fibre (44), and are more prone to substance misuse (45). Depressive symptoms (46) and antipsychotic medications (47) have also been implicated to play a role towards poor physical health among persons with SMD. Previous research has highlighted that the mental health professionals are poor in identifying and treating physical health disorders including cardiovascular diseases in persons with SMD (48–50). Improper recording of cardiovascular risk factors and inadequate action are done to intervene to improve these risk factors (49). The stigma of mental illness may be another hurdle that prevents persons from receiving the appropriate and timely treatment (50).

In the recent World Health Organization (WHO) guidelines on managing physical health conditions in persons with severe mental disorders, recommendations are suggested to address important areas such as tobacco cessation, weight management, substance use disorders, cardiovascular disease and cardiovascular risk, diabetes mellitus, HIV/AIDS, and other infectious diseases (tuberculosis, hepatitis B/C) (51).

Physical health screening such as historical review of physical health symptoms and existing chronic disease status and review and follow up of weight, waist circumference, and body mass index are highly recommended to identify CVD risks and diseases early in persons with SMD (52). The recent India Hypertension Control Initiative (IHCI) advocates for regular blood pressure checking for all the persons and caregivers visiting any health facility and initiation of medications at the facility itself rather than referring to experts to prevent delay and drop-out from taking medications (53). Guideline based laboratory assessment of blood glucose, lipid profile, renal functions and ECG monitoring are to be added (51).

As mental health professionals are found to be less involved in the physical health care of persons with SMD (54), additional training to the mental health professionals are needed with respect to advice on safe exercises and diet. At the systems level,

TABLE 2 | Challenges and recommendations to improve cardiovascular health and diseases among persons with schizophrenia.

Challenges	Recommendations
Patient related	
Health beliefs	• Effective communication to clarify/change beliefs
Lifestyle factors—Diet and Physical activity	• Assess capability and opportunities for physical activity and healthy diet • Set realistic measurable goals • Lifestyle counselling • Culturally appropriate
Comorbidities—substance use and depression	• Adequate and appropriate treatment for the comorbidities
Weight gain due to antipsychotics	• Change to weight neutral psychotropics • Adjunct Metformin can be considered
Stigma	• Community based interventions • Awareness programmes • Integrating treatment of mental health disorders and NCDs
Health professionals related	
Attitudes of health professionals towards mentally ill persons	• Adequate orientation and training on mental health for all health professionals • Continued education programs on regular basis
Lack of Skills to assess and manage risk factors of CVD	• Training to develop skills and provide standardised assessment frameworks • Essential equipment for a physical assessment
Health system related	
Lack of integration	• Documentation of NCD related data and maintenance of medical records • Holistic approach for non-communicable disorders
Lack of resources	• Training of primary care health professionals
Evidence related	
Paucity of research	• Identification and conduct of locally relevant research questions pertaining to CVD in SMD
Lack of collaborative research	• Development of appropriate interventions involving multiple stakeholders

efforts must be made to record history of mental illnesses in the data base of the National Hypertension control program (55), to bring in a holistic care for non-communicable disorders in India.

Research

Though literature indicates a well-established need for focus on physical health in persons with mental illness, little progress has been made in understanding the implementation barriers in a developing country such as India. The economic disparity in our nation coupled with lack of awareness may contribute largely to multiple comorbid physical problems that may easily go undetected. Due to cultural barriers in India, persons often do not report their concerns freely unless probed by a professional. Due to their difficulty to verbalise their ailments, their pain behaviour, discomfort may often be overshadowed by their psychiatric ailments.

There are a dearth of trained mental health professionals in India, which results in the existing professionals being over burdened with patient load. This may often lead to an oversight while attending to a patient whose physical ailments are not reported specifically by a patient or caregiver. There is a lack of access to medical records across health care professionals which further widens the gap and hinders collaborative care.

Healthy lifestyle behaviours are not common knowledge in rural parts of India. With the easy availability of fast foods and low priced packaged food there has also been an increase in consumption of fatty foods across the nation (56). This coupled with the existing diet in underdeveloped areas which often lack nutritive value may facilitate poor physical health (57). Sedentary lifestyles are perpetuated by a lack of education regarding exercising, lack of access to parks, gymnasiums etc. (58). Non pharmacological interventions to improve motivation and lifestyle behaviours may not suffice unless the model is tailored for rural areas, as implementation barriers are specific and vary widely from region to region (59).

Economic difficulties often dictate the quality of care, time of reaching out for health care (60), urgency of care, and implementation of the health care plan (61). Even when diagnosed an asymptomatic individual with a comorbid SMI often does not implement a regimented care plan due to economic constraints (16). When individuals from underprivileged sectors are faced with economic constraints, there is often a trade-off made between immediate respite from their fatiguing lives and long term investment for health care. Often the latter is neglected till the health concern is of imminent nature. This may also stem from their health beliefs and lack of knowledge of the trajectory of illness. Various challenges and recommendations to improve cardiovascular health and diseases among persons with serious mental disorders is provided in **Table 2**.

Strengths and Limitations

This study, through a comprehensive review on cardiovascular health and diseases among persons with serious mental disorders from India, outlines the knowledge gaps and recommendations based on the existing evidence. At the same time, this study is

not without limitations. Most of the studies from India on CVD and schizophrenia are heterogenous and have compared various parameters. Given the limited number of studies providing adequate information on CVD and schizophrenia, risk of bias and high heterogeneity, the review findings are unlikely to be valid among different settings in India. Further, a lack of studies from communities and wide age groups could skew our results.

CONCLUSION

The high incidence of cardiovascular diseases among persons with schizophrenia are a major public health concern worldwide and in India. Better understanding of the magnitude of the problem and various biological, psychological, and social factors contributing in the interplay between cardiovascular diseases and schizophrenia is much needed from India to develop cost-effective, scalable, and culturally appropriate interventions to prevent and/or reduce the impact of cardiovascular disease among persons with schizophrenia.

AUTHOR CONTRIBUTIONS

RP and VR planned, designed the manuscript, and wrote the first draft of the manuscript. SB did the scoping review of the manuscript and wrote the review section. SK and VR did secondary data analysis. SK and SB commented on the draft and contributed to the subsequent drafts. All authors approved the final manuscript and agreed to submit for publication.

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