BRAIN-METABOLIC CROSSROADS IN SEVERE MENTAL DISORDERS – FOCUS ON METABOLIC SYNDROME

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BRAIN-METABOLIC CROSSROADS IN SEVERE MENTAL DISORDERS – FOCUS ON METABOLIC SYNDROME

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EDITORIAL
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Editorial: Brain-Metabolic Crossroads in Severe Mental Disorders—Focus on Metabolic Syndrome

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Keywords: insulin, metabolic syndrome (MetS), cognition, metabolism, brain

Editorial on the Research Topic

Brain-Metabolic Crossroads in Severe Mental Disorders—Focus on Metabolic Syndrome

A large body of evidence shows that patients with severe mental illnesses are more frequently affected by metabolic disorders such as diabetes and the metabolic syndrome, which contribute to cardiovascular morbidity and reduced life expectancy (1). In addition, we are learning more about the effects of metabolic pathways and key metabolic hormones on the functioning of the brain. For example, even though insulin is not necessary for the neuronal uptake and utilization of glucose in the brain, it has multiple roles in central nervous system, from acting as a growth factor to directly influencing cognitive functions such as memory formation (2). It is thus not surprising that patients with type 2 diabetes display cognitive impairments, even in the absence of macrovascular complications. They are at an increased risk for accelerated brain aging and dementia. Furthermore, diabetes in major psychiatric disorders is not only associated with worse somatic health, but also with poor psychiatric outcomes, poor response to psychiatric medications, and with greater extent of neurostructural and neurochemical brain alterations (3, 4).

Besides insulin, other mediators such as total and HDL cholesterol levels play key roles in the brain and were found to have pathoplastic effects on psychiatric disorders: the former has been repeatedly associated with suicide risk (5), the latter with higher prevalence of negative symptoms in schizophrenia (6). Considering the role of these metabolic pathways on the functioning of the brain, it is not surprising that metabolic syndrome, which is highly prevalent in patients with bipolar disorders and schizophrenia (7) and tends to increase over time (8), contributes to cognitive decline (9) and brain ageing (10) in schizophrenia and even interferes with the efficacy of cognitive remediation therapy (11).

The scope of the present Research Topic, then, was to collect papers investigating the complex interplay between brain/cognitive/psychopathological and metabolic disturbances in severe mental disorders. Several eminent researchers contributed to this collection, which includes seven original research articles and three literature reviews. These studies contribute to our knowledge about the interrelationship between cognitive and metabolic disturbances in severe mental illnesses. They highlight the need to rethink psychiatry as a branch of medicine deeply intertwined with physical health.

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The observation that severe mental illnesses are associated with adverse metabolic profiles draws back to the pre-pharmacological era. As far back as in late 19th century, the British psychiatrist Henry Maudsley noted that "diabetes is a disease that often shows itself in families where insanity prevails" (12). More than one century later the association is further confirmed, among others, by the work of Toma et al., who reported a more frequent family history of cardiovascular disease in families of subjects with bipolar disorder than in families of healthy controls. Moreover, the authors reported for the first time that the risk of cardiovascular disease increased in families with a family history for bipolar disorder, suggesting common pathogenetic pathways to be investigated in genetic studies.

Besides the common genetic factors, the comorbidity between mental and metabolic disorders may also be explained by common environmental factors. Stress can both influence the expression and severity of mental disorders and contribute to the development of insulin resistance and metabolic syndrome. To address this, Sun et al. conducted a cutting-edge study correlating levels of childhood abuse with glucose metabolism and resting-state functional connectivity in a sample of overweight adolescents with depression. The authors found that high level of abuse was associated with dysfunctional connectivity between amygdala, precuneus, and nucleus accumbens. This connectivity pattern was, in turn, associated with decreased levels of glycemia and insulinemia, possibly reflecting a compensatory response in early age. Interestingly, other studies found association between insulin resistance and early life trauma in depressed individuals (13), so we need more research to clarify the existence and directions of these associations and the factors that may mediate/moderate them.

In another article by Knytl et al., cortisol and other neurosteroids did not qualify as endophenotypes in schizophrenia: although cognitive functions were impaired in patients versus siblings and controls, stress hormone cortisol and other steroids were neither different between the groups nor found to mediate the association with cognitive function. It should be noted, however, that the high number of comparisons and the small sample size lowered the statistical power. It would still be interesting to investigate the effects of neurosteroids on cognition in larger samples.

Increased stress hormones, pro-inflammatory mediators, and alterations in insulin signaling, seem nevertheless to convey increased risk for both metabolic and mental disorders, as Lyra e Silva and colleagues comprehensively describe in their review. The authors concluded their work by discussing which medications used to treat metabolic disorders also exert positive effects on cognition or psychopathology. To this end, liraglutide, an agonist at GLP-1 receptor used to control type 2 diabetes, is one of the most promising drugs. Liraglutide improved overall cognitive performances in a group of subjects with mood disorders (14), and several trials testing its effect on Alzheimer's dementia are ongoing. In this Research Topic, Cuomo et al. evaluated its efficacy in reducing weight in severely obese patients with depressive and bipolar disorders. In their study, liraglutide was effective in 50% of the treated patients, who lost an average of 10 kg during the 6 months of treatment. Since liraglutide is still a very expensive antidiabetic medication, studying whether it also has pro-cognitive or pathoplastic effects might create an even stronger impetus for its use in participants with severe mental disorders.

Aside from these other factors, antipsychotic medications are among the strongest contributors to weight gain and diabetes in subjects with psychiatric illnesses. Some antipsychotics were also thought to contribute to worse cognition in patients with schizophrenia (15), although it is challenging to disentangle the effects of medications from the effects of illness. The review by Mackenzie et al. comprehensively summarizes the interplay between antipsychotic use, metabolic effects, and cognition in schizophrenia. Early in the course of illness, antipsychotics seem to convey benefits to cognition by countering the detrimental effects of mental disorders. However, in the long run, as their effect on metabolism grows, their continuous use may start to negatively affect cognitive functioning.

Attempts to reduce the metabolic impact of antipsychotics are thus warranted. In their retrospective analysis of a cohort of veterans, Chipchura et al. assessed for the first time the impact of time of administration on the metabolic profile of aripiprazole. Interestingly, nighttime administration led to a worse metabolic profile in terms of reduced HDL cholesterol. According to the authors, the effect might be mediated by the blocking of pancreatic D2/D3 receptors, leading to a disinhibition of insulin release during nighttime, eventually reducing lipolysis and altering the lipid profile.

In contrast to antipsychotics, antidepressant medications have usually been regarded as neutral in their effects on metabolism. The review by Gramaglia et al. indeed does not find an association between antidepressants and metabolic syndrome, with the notable exception of anti-histaminergic antidepressants such as the tricyclics or mirtazapine, which had previously been associated with abdominal obesity and reduction in HDL levels (16).

The impact of treatment on metabolic markers has been extensively studied. More recently, researches have started to examine how metabolic disorders can affect the psychopathological or cognitive outcomes in major mental disorders. For instance, insulin resistance is associated with resistance to treatment with lithium salts (17). In keeping with this trend, Soontornniyomkij et al. showed that in schizophrenia, insulin resistance was associated with a preponderance of negative symptoms. In a large sample of suicide attempters, Aguglia et al. added further evidence about the association between low total cholesterol blood levels and suicide attempts. For the first time, they also showed that low total cholesterol may be linked with a higher lethality of the suicide attempt. This may perhaps be related to the reduction of serotonin transporters in subjects with low cholesterol levels, eventually resulting in higher levels of impulsive behaviors.

Taken together, the high-quality contributions gathered in this Research Topic covered several aspects of the reciprocal influences between metabolism and cognition/psychopathology

in severe mental illness, and constitute a step ahead in this intriguing and expanding area of research.

AUTHOR CONTRIBUTIONS

VS and TH equally contributed to designing and writing the manuscript, and approved it for publication.

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ORIGINAL RESEARCH
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Neuroactive Steroids and Cognitive Functions in First-Episode Psychosis Patients and Their Healthy Siblings

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Background: Neuroactive steroids (NAS) affect neurotransmitter systems and cognition; thus, they play role in etiopathogenesis of psychiatric disorders.

Aims: The primary aim was to examine cognition and effects of NAS on cognitive functioning in first-episode psychosis patients and in their healthy siblings. The secondary aims were to verify whether cognitive deficit is an endophenotype of psychosis and whether higher NAS levels represent a high-risk factor for psychosis.

Methods: Studied participants were 1) patients with first episode of psychosis, 2) healthy siblings of the patients, and 3) matching healthy controls. Study procedures included administration of a battery of neuropsychological tests assessing six cognitive domains and examination of NAS plasma levels [cortisol (CORT), 11-deoxycorticosterone (DOC), testosterone (TEST), dehydroepiandrostendione (DHEA), dihydrotestosterone (DHT), and progesterone (PROG)].

Results: A total of 67 subjects were analyzed (16 patients, 22 siblings, and 29 controls). Significant group differences were found in most of the cognitive domains; the patients had the lowest scores. The Kruskal–Wallis test revealed significant group differences in CORT levels ($p < 0.01$), TEST ($p < 0.01$), and DHT ($p < 0.001$); no difference was found in PROG, DHEA, and DOC. All cognitive domains, except for attention, were affected by the NAS levels. CORT levels of patients correlated with speed of processing ($r = 0.55$) and working memory ($r = 0.52$), while PROG levels correlated with abstraction ($r = –0.63$). In siblings, there was a negative correlation between TEST levels and verbal memory ($r = –0.51$) and PROG with attention ($r = –0.47$).

Conclusions: Our results verified that individual domains of cognitive deficit (abstraction and verbal memory) can be considered as an endophenotype of psychosis. Higher levels of cortisol and testosterone in siblings are consistent with high-risk states for psychosis. Multiple interactions between NAS and cognitive functioning, particularly memory functions, were observed. Study limitations (small sample size and administration of antipsychotic medication) did not allow us to establish unequivocally NAS as an endophenotype.

Keywords: neuroactive steroids, cognition, endophenotype, siblings, psychosis

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INTRODUCTION

Complex etiopathological mechanisms of schizophrenia are still poorly understood and their key features are yet to be identified. The widely cited dopaminergic theory (1) seems to be just an ending point of several pathophysiological processes in which other neurotransmitter systems (e.g., glutamatergic, GABAergic, and serotoninergic) are involved, as well (2–4).

In addition to other factors, neurotransmission is significantly affected by steroid substances synthetized in the central nervous system (CNS), labeled as "neurosteroids" (5, 6). A more general term, "neuroactive steroids" (NAS) is used for all substances that interact with the CNS in two different modes. First, genomically, through binding with intracellular steroid receptors, NAS can change gene expression. Second, interacting with membrane neurotransmitter receptors, NAS can modulate psychopathology of psychiatric disorders (7, 8). NAS may exhibit therapeutic potential, and their antidepressant, anxiolytic, and antipsychotic effects have been reported (9–11). Targeting NAS metabolism is considered as a novel therapeutic approach (12–14). Alterations of NAS are currently being studied intensively to investigate their role in the pathophysiology of schizophrenia, with an accumulating amount of evidence suggesting their involvement (12, 15, 16). However, the findings are not consistent, mostly due to the treatment, age, or gender effects (17–19).

Studies showed that early intervention can improve outcome of schizophrenia patients (20, 21). Therefore, prodromal phases of psychotic disorders are the focus of current research efforts (22). Healthy siblings of schizophrenia patients are a well-defined population at higher risk of developing illness (23). One promising approach on how to investigate etiopathogenesis of psychiatric disorders is through endophenotypes (24). Endophenotypes are state independent, observed in actively manifested illness or in remission and are present in healthy relatives of patients, but not in the general population.

Various candidate endophenotypes of schizophrenic disorder have been proposed, e.g., structural changes of the white and grey brain matter, biochemical blood markers, neurophysiological measures, or impairment of cognitive and social functioning (25). Cognitive deficit was also consistently observed in a population at risk of psychosis (26). A recent meta-analysis found a correlation between cognitive impairment and metabolic syndrome, suggesting an effect of metabolic alteration on cognition (27).

Several studies linked NAS to cognitive functioning of schizophrenia spectrum patients (28). NAS were also examined as candidate adjunctive agents for treatment of cognitive impairment in schizophrenia (29, 30). However, there are so far no data on the relationship of NAS and cognition among high-risk individuals.

The primary aim of our study was to examine the differences in cognitive performance of first-episode patients with psychosis, their siblings, and healthy controls. The secondary goal was to examine the effect of NAS on cognition, in order to verify whether cognitive deficit is an endophenotype of psychosis and whether higher levels of NAS represent a high-risk factor for psychotic disorder.

MATERIALS AND METHODS

Study Sample

The study was conducted at the National Institute of Mental Health, Czechia. The study sample consisted of three groups of subjects: (1) first-episode psychosis patients; (2) their unaffected siblings; and (3) matching healthy controls. Patients met the *International Statistical Classification of Diseases and Related Health Problems*, 10th revision (*ICD-10*), criteria for schizophrenia (F20.x), acute psychosis (F23.x), or schizoaffective disorder (F25.x), first episode (31). Siblings and the control group were assessed with the Mini International Neuropsychiatric Interview (MINI) to rule out any current or past psychiatric disorders. Exclusion criteria in all groups were organic brain disorder, neurological or endocrine disease, substance dependence, intellectual disability, motor or perceptual handicap, and incapacity to provide informed consent. The study protocol was approved by the local ethical committee, and all subjects signed an informed consent form.

Study Procedures

Basic demographic and clinical data, sex, age, education, medical history, family history, and duration of untreated psychosis were recorded. Severity of psychotic symptoms in the patient group was assessed with the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI). Patients were assessed during the non-acute phase of their illness (CGI $\leq$ 4). The MINI was used to examine psychiatric comorbidity among patients and to verify the absence of psychiatric disorder in siblings and healthy controls.

Cognitive tests were administered by trained psychologists, using both pencil-paper and computer methods. Composition of the neuropsychological battery was based on the expert consensus and our previous research (32, 33). The battery evaluated cognitive functions in the following six domains: psychomotor speed/speed of processing [tested with Verbal Fluency Test; Stroop Test: word, color; Trail Making Test (TMT) A; Wechsler Adult Intelligence Scale (WAIS-III): digit–symbol coding]; attention (Continuous Performance Task); working memory/flexibility [WAIS-III: digit span; WAIS-III: letter–number sequencing; Wechsler Memory Scale (WMS-III): spatial span; TMT-B; Stroop Test: color word]; verbal memory (Auditory Verbal Learning Test, WMS-III: logical memory); visual memory (Rey–Osterrieth Complex Figure Test), and abstraction (WAIS-III: similarities; WAIS-III: comprehension; Picture arrangement; Wisconsin Card Sorting Test; Tower of London). For a detailed description and calculation of the composition and consistency of cognitive domains, see Rodriguez et al. (33). Participants were tested in two consecutive sessions with a break in between, and maximum time of psychological assessment was 120 min.

All subjects had their blood samples taken after 12 h of fasting; females were in the follicular phase of their menstrual cycle. NAS that previously showed an impact on the cognition of schizophrenia patients were assessed (28, 34–38). Plasma levels of cortisol (CORT), 11-deoxycorticosterone (DOC), testosterone (TEST), dehydroepiandrostendione (DHEA), dihydrotestosterone (DHT), and progesterone (PROG) were

analyzed with liquid chromatography and mass spectroscopy in laboratories of the University of Chemistry and Technology in Prague.

Statistical Analysis

Fisher's exact test was used to detect possible differences in distribution of sex and education between the groups. Non-parametric Kruskal–Wallis test and epsilon squared as effect size were used to assess the age differences to compare cognitive performance between the groups and for the group comparison of the NAS levels. The Dunn test was used for the *post hoc* multiple comparison; *p*-values were adjusted with the Benjamini–Hochberg method. Non-parametric version of analysis of covariance (ANCOVA) was used to examine possible differences in the NAS levels between the groups in relation to cognitive performance. For statistical analyses, R software version 3.3.2 was used.

RESULTS

Study Sample

The total number of enrolled subjects was 74 (22 patients, 23 siblings, and 29 controls). Six patients and one sibling were excluded from the analyses due to the following reasons: manifested psychotic symptoms during cognitive testing, non-native Czech speaker, history of multiple episodes, and incorrect diagnosis. Analyzed study sample included 67 subjects: 16 first-episode patients, 22 siblings, and 29 healthy controls. There was no significant group difference in sex ratio (Fisher's exact test: $p = 0.535$; Cramer's $V = 0.14$), education (Fisher's exact test: $p = 0.09$; Cramer's $V = 0.32$), or age [Kruskal–Wallis test: $H(2) = 2.95$, $p = 0.23$; $\varepsilon^2 = 0.05$]. For details, see **Table 1**.

Data on the patients' psychiatric history (duration of illness, duration of untreated psychosis, length of antipsychotic treatment, and drug dosage in chlorpromazine equivalents) are shown in **Table 2**. Except for one patient, all of them were treated with antipsychotic medication. Fourteen were given oral monotherapy (for 7 subjects olanzapine 10–30 mg p.d.; 4 risperidone 3–4.5 mg p.d.; 1 aripiprazole 15 mg p.d.; 1 clozapine 175 mg p.d.; and 1 patient quetiapine 500 mg p.d). Four patients were prescribed a combination of two oral drugs (olanzapine 25 mg + haloperidol 6 mg; olanzapine 30 mg + aripiprazole 30 mg; and aripiprazole 15 mg + clozapine 150 mg), and four subjects were administered long-acting injectable antipsychotics (for 2 patients paliperidone 150 mg monthly; 1 olanzapine 300 mg biweekly; and 1 flupenthixol 40 mg monthly).

Cognition

Mean and median values of *Z*-scores for each of the cognitive domains are summarized in **Table 3**. Significant group differences were found in most of the cognitive domains, with the exception of attention. Kruskal–Wallis test: visual memory [$H(2) = 12.67$, $p < 0.01$, $\varepsilon^2 = 0.19$]; verbal memory [$H(2) = 15.38$, $p < 0.001$, $\varepsilon^2 = 0.24$]; abstraction [$H(2) = 10.09$, $p < 0.01$, $\varepsilon^2 = 0.15$]; psychomotor speed [$H(2) = 6.66$, $p < 0.05$, $\varepsilon^2 = 0.1$]; working memory [$H(2) = 8.75$, $p < 0.05$, $\varepsilon^2 = 0.13$]; attention [$H(2) = 1.39$, $p > 0.05$, $\varepsilon^2 = 0.02$].

Results of the *post hoc* Dunn test with the Benjamini–Hochberg correction (median values listed in **Table 3**) revealed that visual memory performance of controls was statistically superior to that of patients ($p < 0.05$), performance of siblings was significantly better than that of patients ($p < 0.05$), and no difference between siblings and controls was observed. In verbal memory, controls performed significantly better than patients ($p < 0.001$) and siblings ($p < 0.01$), but no difference was detected between patients and siblings. In abstraction, controls performed significantly better than patients ($p < 0.05$) and siblings ($p < 0.05$), but no difference was found between patients and siblings. In psychomotor speed/speed of processing, control subjects outperformed significantly patients ($p < 0.05$), while no significant difference was observed between controls and siblings or between patients and siblings. In working memory/flexibility, control subjects performed significantly better than patients ($p < 0.05$), but no significant differences were detected between controls and siblings and between patients and siblings.

Neuroactive Steroids

Mean and median values of plasma levels of the analyzed NAS (CORT, DOC, TEST, DHEA, DHT, and PROG) are summarized in **Table 4**. Kruskal–Wallis test revealed significant differences between the groups in CORT levels [$H(2) = 11.77$, $p < 0.01$, $\varepsilon^2 = 0.18$], TEST [$H(2) = 11.57$, $p < 0.01$, $\varepsilon^2 = 0.18$] and DHT

TABLE 1 | Study sample, demographic characteristics.

		Patients ($n = 16$)	Siblings ($n = 22$)	Controls ($n = 29$)	All ($n = 67$)
Sex	Male (%)	8 (50)	15 (68)	17 (59)	40 (60)
	Female (%)	8 (50)	7 (32)	12 (41)	27 (40)
Age (years)	Mean (SD)	25.81 (5.56)	29.27 (7.32)	29.38 (6.48)	28.49 (6.65)
	Median	26.5	29	29	28
Education	Elementary (%)	3 (19)	0 (0)	1 (3)	4 (6)
	Secondary, without graduation (%)	3 (19)	6 (27)	2 (7)	11 (16)
	Secondary, graduated (%)	4 (25)	11 (50)	15 (52)	30 (45)
	University (%)	6 (37)	5 (23)	9 (31)	20 (30)
	College (%)	0 (0)	0 (0)	2 (7)	2 (3)

TABLE 2 | Psychiatric history of the patients.

	Mean (SD)	Median
Duration of illness (months)	8.70 (8.81)	5
Duration of untreated psychosis (months)	3.17 (4.45)	1
Length of antipsychotic treatment (months)	5.21 (8.68)	1.38
Antipsychotic dosage (chlorpromazine equivalents in mg/day)	330 (220.30)	297

TABLE 3 | Descriptive characteristics of cognitive domains (z-scores).

		Mean (SD)	Median
Visual memory[a]	Patients	–0.74 (0.55)	–0.84
	Siblings	0.13 (0.8)	0.34
	Controls	0 (0.73)	0.02
Verbal memory[b]	Patients	–1.34 (1.33)	–0.85
	Siblings	–0.67 (0.84)	–0.8
	Controls	0 (0.79)	–0.01
Abstraction[a]	Patients	–1.17 (1.58)	–0.46
	Siblings	–0.7 (0.9)	–0.78
	Controls	0 (0.74)	0.03
Psychomotor speed/speed of processing[c]	Patients	–0.7 (0.99)	–0.53
	Siblings	–0.14 (0.92)	0
	Controls	0 (0.57)	0.13
Attention	Patients	–0.22 (0.8)	0.09
	Siblings	0.08 (0.62)	0.25
	Controls	0 (0.74)	0.16
Working memory/flexibility[c]	Patients	–0.96 (1.48)	–0.6
	Siblings	–0.42 (0.94)	–0.31
	Controls	0 (0.57)	–0.08

Group differences: [a]$p < 0.01$; [b]$p < 0.001$; [c]$p < 0.05$.

TABLE 4 | Plasma levels of the selected neuroactive steroids (ng/ml).

		Mean (SD)	Median
Cortisol (CORT)[a]	Patients	174.17 (85.1)	181.17
	Siblings	236.07 (86.22)	245.73
	Controls	153.65 (59.46)	153.74
Testosterone (TEST)[a]	Patients	3.78 (4.21)	1.64
	Siblings	8.13 (6.03)	8.61
	Controls	4.45 (3.93)	4.71
Progesterone (PROG)	Patients	0.12 (0.1)	0.11
	Siblings	0.14 (0.06)	0.12
	Controls	0.13 (0.1)	0.14
Dehydroepiandrostendione (DHEA)	Patients	10.71 (5.28)	11.72
	Siblings	13.53 (6.77)	13.05
	Controls	16.63 (10.09)	14.81
Dihydrotestosterone (DHT)[b]	Patients	0.45 (0.28)	0.41
	Siblings	1.07 (0.56)	0.93
	Controls	0.68 (0.31)	0.64
11-Deoxycorticosterone (DOC)	Patients	0.08 (0.04)	0.08
	Siblings	0.06 (0.02)	0.05
	Controls	0.05 (0.04)	0.05

Group differences: [a]$p < 0.01$; [b]$p < 0.001$.

[$H(2) = 16.69$, $p < 0.001$, $\varepsilon^2 = 0.25$]. No differences were found in levels of PROG [$H(2) = 0.30$, $p > 0.05$, $\varepsilon^2 = 0.005$], DHEA [$H(2) = 3.66$, $p > 0.05$, $\varepsilon^2 = 0.06$], and DOC [$H(2) = 5.19$, $p > 0.05$, $\varepsilon^2 = 0.08$].

Post hoc multiple comparisons (Dunn test) and adjustments with the Benjamini–Hochberg correction (median values listed in **Table 4**) found that CORT levels were significantly higher in siblings than in controls ($p < 0.01$), while no differences in CORT were detected between patients and siblings and between patients and controls. TEST levels were significantly higher in siblings than in both controls ($p < 0.01$) and patients ($p < 0.01$), but no difference was observed between patients and controls. Levels of DHT were significantly higher in siblings than in controls ($p < 0.05$) and in patients ($p < 0.001$), but DHT levels were significantly higher in controls than in patients ($p < 0.05$).

Effect of Neuroactive Steroids on Cognition

The relationship of NAS with cognition across the study groups was tested with non-parametric ANCOVA. For CORT, equality was rejected for verbal memory (test of equality: $p = 0.0185$), visual memory ($p = 0.0374$), and working memory ($p = 0.0179$) but not for speed of processing ($p = 0.0744$), abstraction ($p = 0.1991$), and attention ($p = 0.2856$). Parallelism was rejected for verbal memory (test of parallelism: $p = 0.0097$) and working memory ($p = 0.012$) but not for visual memory ($p = 0.1092$).

In TEST analysis, equality was rejected for verbal memory ($p = 0.0303$), visual memory ($p = 0.0109$), and abstraction ($p = 0.0118$) but not for speed of processing ($p = 0.1636$), working memory ($p = 0.0563$), and attention ($p = 0.4698$). Parallelism was rejected for verbal memory ($p = 0.0177$), visual memory ($p = 0.0108$), and abstraction ($p = 0.0095$) but not for speed of processing ($p = 0.1096$) and attention ($p = 0.4976$).

In PROG, equality was rejected for visual memory ($p = 0.027$) and abstraction ($p = 0.0108$) but not verbal memory ($p = 0.1665$), speed of processing ($p = 0.25$), working memory ($p = 0.3633$), and attention ($p = 0.8943$). Parallelism was rejected for abstraction ($p = 0.0076$) but not visual memory ($p = 0.0736$).

In DHEA, equality was rejected for verbal memory ($p = 0.0456$) and visual memory ($p = 0.016$) but not for speed of processing ($p = 0.593$), abstraction ($p = 0.0814$), attention ($p = 0.5217$), and working memory (0.6568). Parallelism was rejected for verbal memory ($p = 0.0445$) and visual memory ($p = 0.024$).

In DHT, equality was rejected for verbal memory ($p = 0.0055$), visual memory ($p = 0.0149$), speed of processing ($p = 0.0146$), abstraction ($p = 0.0063$), and working memory ($p = 0.022$) but not for attention (0.5326). Parallelism was rejected for verbal memory ($p = 0.0054$), visual memory ($p = 0.0143$), speed of processing ($p = 0.0115$), abstraction ($p = 0.0066$), and working memory ($p = 0.0112$).

In DOC, equality was rejected for verbal memory ($p = 0.0095$) and visual memory ($p = 0.024$) but not for speed of processing ($p = 0.1703$), abstraction ($p = 0.1164$), attention ($p = 0.524$), and working memory (0.793). Parallelism was rejected for verbal memory ($p = 0.0081$) and visual memory ($p = 0.044$).

Significant positive correlations of NAS with cognition in patients were found between the cortisol levels and speed of processing ($r = 0.55$), and working memory ($r = 0.52$), and negative correlations were found between progesterone and abstraction ($r = -0.63$) (**Table 5**). In siblings, there was a negative correlation between testosterone and verbal memory ($r = -0.51$) and between progesterone and attention ($r = -0.47$) (**Table 6**). No significant correlation was observed in healthy controls.

TABLE 5 | Correlations between neurosteroid levels and domains of cognition—patients.

	CORT	TEST	PROG	DHEA	DHT	DOC
Verbal memory	–0.003	–0.19	–0.47	0.09	–0.45	0.25
Visual memory	0.19	0.22	–0.25	–0.12	0.40	0.25
Processing speed	0.55*	–0.08	–0.14	0.02	–0.15	–0.20
Abstraction	0.02	0.06	–0.63*	–0.26	–0.25	–0.12
Attention	0.32	0.25	–0.17	–0.45	0.05	0.39
Working memory/flexibility	0.52*	0.37	0.21	–0.24	–0.20	0.05

*CORT, cortisol; TEST, testosterone; PROG, progesterone; DHEA, dehydroepiandrostendione; DHT, dihydrotestosterone; DOC, 11-deoxycorticosterone. *Significant correlation.*

TABLE 6 | Correlations between neurosteroid levels and domains of cognition—siblings.

	CORT	TEST	PROG	DHEA	DHT	DOC
Verbal memory	–0.095	–0.51*	–0.02	–0.19	–0.12	0.15
Visual memory	0.021	–0.06	–0.31	–0.35	–0.10	–0.10
Processing speed	0.038	–0.24	–0.32	–0.07	–0.30	–0.19
Abstraction	0.024	0.01	–0.36	–0.02	–0.30	–0.12
Attention	–0.09	0.13	–0.47*	–0.09	0.02	–0.38
Working memory/ flexibility	–0.10	–0.28	–0.28	–0.29	–0.33	–0.07

*CORT, cortisol; TEST, testosterone; PROG, progesterone; DHEA, dehydroepiandrostendione; DHT, dihydrotestosterone; DOC, 11-deoxycorticosterone. *Significant correlation.*

DISCUSSION

Our results confirmed the presence of global cognitive deficit in first-episode schizophrenia patients (FES). This finding, impaired cognition across all studied domains, as compared with healthy controls, is in full agreement with published research (39, 40). Additionally, functional correlates of cognitive deficit in FES have been reported recently (41). Cognitive dysfunction, albeit less pronounced than in patients, has been previously described among healthy first-degree relatives as well (42). Cognitive functioning is therefore considered as one of the most consistent endophenotypes of psychotic disorders (43).

Notably, our results strongly suggest that the endophenotype is not the global cognitive functioning but more likely individual, specific domains of cognition. We found verbal memory and abstraction significantly impaired in both patients and siblings compared with controls. Moreover, the performance in verbal memory and abstraction did not differ between patients and siblings; thus, both domains can be viewed as candidate intermediate endophenotypes (26, 44). The results further corroborate findings of other authors who identified executive control functions (i.e., abstraction and flexibility) and verbal memory as the most impaired cognitive domains that did not differ between unaffected siblings and patients with psychotic or bipolar disorder (42, 45, 46).

Analysis of NAS revealed significantly higher plasma levels of cortisol, testosterone, and dihydrotestosterone in siblings as compared with healthy controls. Siblings also had higher levels of testosterone and dihydrotestosterone than had patients. Somewhat surprisingly, no difference in NAS between patients and controls was observed, except for the higher levels of DHT in controls. Since all FES were already treated with antipsychotics, an effect of medication on steroid levels cannot be completely ruled out. Previous studies demonstrated the impact of second-generation antipsychotics on NAS levels in rodent models (17, 47). Decreased testosterone in our FES group can hence be related to administration of antipsychotic drugs (48). While the small number of patients in our study and the heterogeneity of drugs used do not allow more detailed analysis of the impact of specific antipsychotics on the NAS levels, it should be acknowledged that the length of drug treatment was in fact very short (median 1.38 months).

Observed higher levels of testosterone and its active metabolite dihydrotestosterone among healthy siblings seem to be in contrast to previously reported data (49). Nonetheless, in some models, high testosterone has been associated with a hyperdopaminergic state, a presumptive high-risk state for development of psychosis (50, 51). A recent meta-analysis also confirmed higher testosterone levels in FES (15). Increased levels of cortisol in siblings are consistent with published literature, since higher cortisol levels have been repeatedly found among high-risk populations (52, 53) and are associated with higher transition rate into psychosis (54).

Cognition is a very intricate and complex neural process, based on synaptic plasticity, connectivity, and density. Various agents, including neurosteroids, can affect its neurodevelopment (55). It has been discussed that particularly DHEA and its sulfate conjugate play an important role in the development, neuroprotection, and restoration of neuronal characteristics through aging, although the studies with supplementation demonstrated only a small effect (56).

Despite the small sample size, we were able to identify several interactions between the cognitive performance and neurosteroids. The only cognitive domain not affected by steroid levels was attention. The most notable impact of NAS was on all domains of memory functions: Verbal memory was significantly influenced by CORT, TEST, DHEA, DHT, and DOC; visual memory by CORT,

TEST, PROG, DHEA, DHT, and DOC; and working memory by CORT and DHT. Abstraction interacted with TEST, PROG, and DHT, and speed of processing interacted only with DHT. Similarly, other authors consistently reported positive effects of testosterone on memory function (including enhancement of hippocampal plasticity), and the effects of progesterone differ according to acute or chronic administration (55, 57).

While no significant correlation was observed in healthy individuals, cortisol levels in patients were associated with better performance in processing speed and working memory, which is in contrast with previous findings that associated higher CORT levels with poorer cognitive performance (34, 35, 58). Progesterone levels in patients were negatively associated with abstraction. In siblings, testosterone correlated negatively with verbal memory and progesterone with attention. The role of progesterone is rarely investigated; a single study identified a correlation between PROG and cognitive functioning in male schizophrenia patients (38).

Previous findings in healthy subjects underlined the higher impact of NAS on cognition in men than in women (59). For example, the role of testosterone in cognitive impairment has been discussed in male patients with schizophrenia only (37). Clearly, the effects of NAS levels on cognitive functioning should be interpreted according to gender. Due to the limited sample size, we were not able to analyze the gender difference in study groups.

In summary, we were able to endorse cognitive deficit as an endophenotype of psychotic disorder. While the results are still preliminary, the major finding is the observation that most likely not a global dysfunction but individual domains of cognition (i.e., abstraction and verbal memory) might be the foundation of cognitive endophenotype. Impairment in specific cognitive domains is shared by both first-episode patients and their healthy siblings and distinguishes them from the general population.

There are several study limitations (primarily small sample size, cross-sectional design without follow-up, and patients who were not drug naive) that prevent us from any generalization of neurosteroid data and do not allow for their plasma levels to be established unequivocally as an endophenotype of schizophrenia. We were not able to verify or reject steroid metabolome as a diagnostic tool, as suggested previously (60). Nevertheless, higher levels of cortisol and testosterone in siblings are consistent with high-risk states for psychosis, and cortisol levels are associated with higher transition rates to fully develop psychosis. Finally, our study results revealed in both patients and siblings multiple interactions between NAS and cognitive functioning, especially memory functions. If replicated in a larger study sample, this observation could have potential implications for timely therapeutic interventions in high-risk individuals, prodromal phases, and early phases of psychotic disorders.

ETHICS STATEMENT

The study protocol was approved by the Ethical Committee of the National Institute of Mental Health, Czechia. All study subjects signed an informed consent form.

AUTHOR CONTRIBUTIONS

PK collected clinical and biochemical data, recruited subjects, and drafted the manuscript. VV collected and analyzed neuropsychological data and recruited subjects. AD and PS collected neuropsychological data. MR designed neuropsychological testing and interpreted cognitive data. AC performed statistical analyses. EK and MK analyzed biochemical samples. ZK designed neuropsychological testing. SC collected clinical data. PM drafted the study design, interpreted the results, and drafted the manuscript.

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Clinical Correlates of Insulin Resistance in Chronic Schizophrenia: Relationship to Negative Symptoms

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Higher prevalence of physical comorbidity and premature mortality in persons with schizophrenia (PwS) results primarily from heightened cardiovascular and metabolic risks. The literature suggests that insulin resistance precedes the development of obesity, smoking, and use of antipsychotic medications, although these likely play a compounding role later in the course of the disorder. It is thus important to discover the clinical characteristics of PwS with high insulin resistance, as these individuals may represent an etiopathologically distinct subgroup with a distinct course and treatment needs. We conducted a cross-sectional study and compared insulin resistance between 145 PwS and 140 nonpsychiatric comparison (NC) participants, similar in age, sex, and race distribution. In addition, we examined correlates of insulin resistance in PwS. As expected, PwS had higher levels of insulin resistance [Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)] and body mass index (BMI) compared to the NC participants. HOMA-IR in the PwS was most associated with negative symptoms, BMI, and non-White race/ethnicity. The mechanistic relationships between insulin resistance and negative symptoms in schizophrenia patients warrant further investigation, and future studies should examine outcomes of PwS with this cluster of physical and mental symptoms and determine how management of insulin resistance might improve health of these individuals.

Keywords: body mass index, cognitive function, depression, hemoglobin A1c, psychosis, antipsychotics

INTRODUCTION

The mortality gap between persons with schizophrenia (PwS) and the general population is driven, to a large extent, by cardiovascular disease-related deaths (1). Metabolic abnormalities and metabolic syndrome, which are highly prevalent among PwS, are strong independent predictors of cardiovascular-related mortality (2–4). Compared with healthy subjects, schizophrenia patients are more likely to have metabolic comorbidities, including obesity, impaired glucose homeostasis, and metabolic syndrome (5–8). Thus, understanding individual differences among PwS in the degree of metabolic dysfunction could help to identify subgroups who may have an accelerated course of aging and who may be good candidates for preventative measures to reduce morbidity and mortality.

An important contributor to metabolic comorbidities is insulin resistance, which has been shown to precede the cumulative effects of antipsychotic medications, sedentary behaviors, unhealthy diet, and smoking (9–15). In a systematic review and meta-analysis by Pillinger et al. (16), impaired glucose homeostasis, including insulin resistance (Homeostatic Model Assessment of Insulin Resistance or HOMA-IR), was documented in antipsychotic-naive patients with first-episode schizophrenia. Several studies have shown elevated HOMA-IR levels in antipsychotic-naive patients with first-episode psychosis compared with age- and gender-matched controls with similar mean BMI values (17–21). Thus, altered insulin resistance may be part of a whole-body syndrome that manifests in the behavioral disorder of schizophrenia. Consistent with this view is growing evidence that schizophrenia phenotypes may share overlapping genetic loci with metabolic phenotypes (22, 23), and a Mendelian randomization study showing specifically that a genetic predisposition to higher fasting plasma insulin levels is causally linked to an increased risk of schizophrenia (24).

Little is known about the specific demographic and clinical features that characterize PwS who have elevated insulin resistance. Most studies to date have focused on correlates of more general metabolic abnormalities, such as metabolic syndrome and diabetes mellitus (DM). A study by Sicras-Mainar et al. (25) showed that, among 1,120 schizophrenia outpatients on antipsychotic treatment, the prevalence of metabolic syndrome was significantly higher in the patients with one or more negative symptoms (43.9%) than in those without any negative symptoms (34.9%). In a meta-analysis of 12 studies, Bora et al. (26) reported that metabolic syndrome and DM were both associated with more severe cognitive impairment. A focus on the correlates of insulin resistance, which seems to be among the earliest metabolic abnormalities and perhaps intrinsically linked to the pathophysiology of the disorder, may reveal a distinct subgroup of PwS who may have a unique course and could respond differently to treatments.

Our group has examined relationships between metabolic abnormalities and antipsychotic use. One study randomized middle-aged and older patients to one of four atypical antipsychotic medications and tracked metabolic and other adverse outcomes in middle-aged and older adults with schizophrenia and other psychiatric illnesses over 2 years (27). It showed that all the commonly used atypical antipsychotics carried similar high risk of metabolic pathology. The current study is a naturalistic evaluation of the association of other clinical factors (in addition to antipsychotic medication use) possibly related to metabolic dysfunction in a broader age group of PwS, using a multivariate approach. This type of information has considerable potential value for developing targeted interventions to reduce insulin resistance in PwS. This study presents findings from a large sample with extensive clinical phenotyping—allowing us to examine the relationships of insulin resistance with a number of key psychopathological, cognitive, and functioning measures, using multivariate methods to assess the relative contributions of different factors to metabolic abnormalities. PwS often have many risk factors for metabolic abnormalities: lifestyle habits, medications, and underlying biological mechanisms including inflammation and oxidative stress. Treatment and prevention of metabolic abnormalities in PwS can be particularly challenging due to these multiple risk factors (28–32). This study aims to better understand the factors most highly associated with metabolic dysfunction in this high-risk group.

In the present cross-sectional study, we aimed to compare insulin resistance between adults with chronic schizophrenia and nonpsychiatric comparison (NC) subjects, with similar age, sex, and race/ethnicity distribution. Furthermore, within the PwS we examined the relationships between insulin resistance and psychopathology, cognition, and everyday functioning. We performed targeted statistical analyses using the least absolute shrinkage and selection operator (LASSO) method to see what group of factors were most associated with insulin resistance in PwS. These findings will help us better understand what patient characteristics and clinical factors would predict response to interventions to prevent or treat diabetes in PwS. This knowledge would help develop preventive and therapeutic interventions to reduce insulin resistance in schizophrenia and thereby reduce some of the excess morbidity and mortality that characterizes this serious mental and physical illness. We hypothesized that PwS would have worse insulin resistance compared to NCs. We also hypothesized that HOMA-IR would be related to worse psychopathology, cognitive performance, and everyday functioning within the schizophrenia group, even while controlling for BMI and other clinical covariates.

MATERIALS AND METHODS

Study Participants

We recruited 145 persons with chronic schizophrenia receiving outpatient psychiatric treatment and 140 NCs from the greater San Diego area, ranging in age from 26 to 65 years. Analyses on subsets of these data have been reported previously (33–37). The Human Research Protections Program at University of California San Diego approved the study protocol. All participants provided written informed consent prior to participation. The Structured Clinical Interview for *the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition–Text Revision* (DSM-IV-TR, SCID) was used to determine schizophrenia diagnosis (38). The Mini-International Neuropsychiatric Interview (MINI) (39) was used to screen NC participants who did not have major neuropsychiatric disorders. Exclusion criteria were as follows: 1) other current DSM-IV-TR Axis I diagnoses; 2) alcohol or other substance use disorders (except nicotine or caffeine) within prior 3 months; 3) diagnosis of dementia, intellectual disability disorders, or other major neurological disorders; and 4) any medical disability affecting the ability to complete study procedures. Trained research staff interviewed the study participants, reviewed available medical records, and administered standardized physical and psychological assessments in person.

Sociodemographic Variables

Demographic features included in the present analysis included age, sex, race/ethnicity, education, and cigarette smoking (**Table 1**).

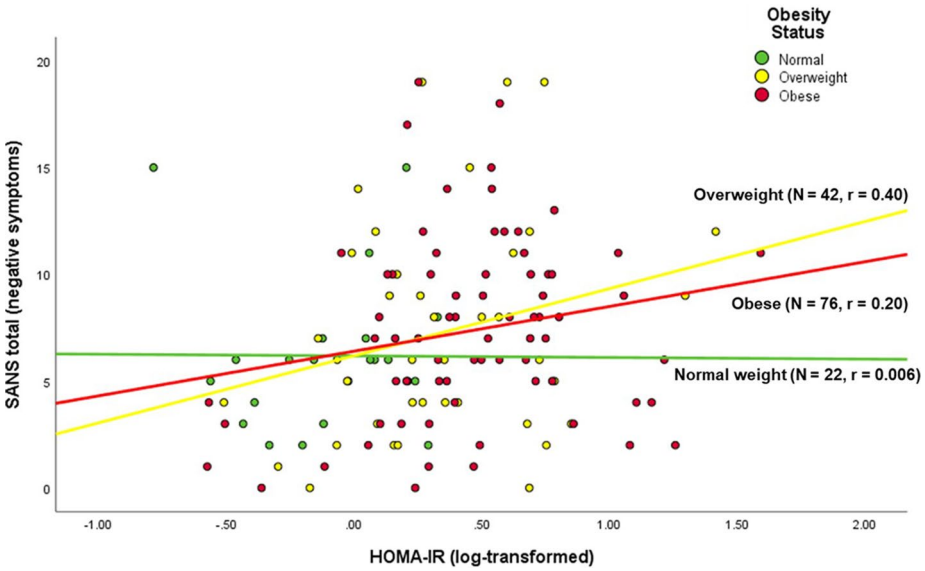

FIGURE 1 | Correlation of negative symptoms with insulin resistance in persons with schizophrenia, stratified by BMI status.

Psychopathology

Dose equivalents of antipsychotics were based on the defined daily dose (DDD; the assumed average maintenance dose per day for a drug used for its main indication in adults) presented by the World Health Organization Collaborating Centre for Drug Statistics and Methodology (40). Duration of illness was assessed for all PwS.

Positive symptoms were measured by using the Scale for the Assessment of Positive Symptoms (SAPS) (41). Negative symptoms were measured by using the Scale for the Assessment of Negative Symptoms (SANS) (41, 42).

Depressive symptoms were assessed with the nine-item Patient Health Questionnaire (PHQ-9, total score range 0–27) (43). Perceived stress was measured with the 10-item Perceived Stress Scale (PSS-10, total score range 0–40); and higher scores indicated more severe perceived stress (44).

Cognitive Performance, Quality of Life, and Everyday Functioning

All cognitive testing was done in face-to-face interviews. Global cognitive functioning was evaluated with the Telephone Interview for Cognitive Status–Modified (TICS-M, 12-item, total score range 0–50), performed during an in-person assessment using the phone script (45–48). TICS-M has been shown to have high sensitivity (82.4%) and specificity (87.0%) for detecting amnestic mild cognitive impairment in community-dwelling older adults (46). Executive functioning was assessed with selected subsets of the Delis-Kaplan Executive Function System (D-KEFS) (49, 50), including Trail Making Letter-Number Sequencing, Color Word Inhibition (Switching), and Letter Fluency (FAS total). We used standardized z-scores from these D-KEFS subtests in order to create a composite score of executive functioning, as previously described by Palmer et al. (51). Mental health-related quality of life was measured with the 36-item Short Form Health Survey, Mental Component Summary (SF-36 MCS) (52, 53). UCSD Performance-Based Assessment-Brief (UPSA-B) is a test of everyday functioning across a variety of community-based tasks (54, 55). In all these measures, higher scores indicated better functioning.

Metabolic Measures

The body mass index [BMI = bodyweight (kg)/height $(m)^2$] was also assessed based on standard measurements.

Fasting venous blood was used for biochemical assays including plasma glucose (mmol/L) and plasma insulin (mU/L). Both assays were conducted in the Altman Clinical and Translational Research Institute (ACTRI) laboratory at University of California San Diego. The level of insulin resistance was estimated with the homeostatic model assessment of insulin resistance {HOMA-IR = [fasting plasma insulin (mU/L) × fasting plasma glucose (mmol/L)]/22.5, giving normal HOMA-IR of 1} (56, 57). HOMA-IR, a steady-state basal test, was validated as a surrogate marker of insulin resistance with reference to standard stimulated-state tests of insulin resistance such as the hyperinsulinemic-euglycemic clamp (57).

Statistical Analysis

All variables were assessed for violation of distribution assumptions (skew and kurtosis) and, if appropriate, were log-transformed. The schizophrenia and NC groups were compared using independent samples t-test (continuous variables) or Spearman's rho (categorical variables).

In the PwS and NC groups, pairwise associations of insulin resistance to clinical, medical, and psychological (continuous) variables were assessed with Spearman's rho. The null of common

Spearman's correlation between the schizophrenia and NC groups was tested by comparing two independent Spearman's correlations.

We performed multiple regression analyses, aided by LASSO variable selection, to identify the best multivariable model for HOMA-IR. In the multiple regression analysis, regression coefficients were made commensurate by standardizing each variable. Independent variables were ranked by the order in which they entered the LASSO regression. LASSO overcomes various limitations of classic variable selection procedures such as multicollinearity to provide reliable selection of independent variables (58). Independent variables selected by LASSO were entered into the linear model for further trimming using backward elimination, as univariate analysis may also miss significant predictors, and such models may be biased (59). Multicollinearity of the independent variables was assessed using variance inflation factor (VIF) (60).

For all analyses, unadjusted two-tailed *p*-values were considered significant at $p < 0.05$. Significance was defined as Type I error alpha = 0.05 (two-tailed) for all analyses, and false discovery rate (FDR) was used to account for multiple comparisons to ensure overall Type 1 error at alpha = 0.05. The statistical analyses were conducted using the IBM SPSS Version 25 (IBM Corp., Armonk, New York, USA) and R.

RESULTS

Group Comparisons

Characteristics of the schizophrenia and NC groups and group differences in the measured variables are presented in **Table 1**. The two groups were similar in the distribution of age, sex, and race/ethnicity, although PwS had fewer years of education and longer duration of cigarette smoking ($p < 0.001$, both). As expected, the PwS endorsed worse depressive symptoms and perceived stress and had worse cognitive functioning, quality of life, and everyday functioning ($p < 0.0005$, all).

The schizophrenia group had higher levels of insulin resistance (HOMA-IR, $t_{258} = -4.66$, $p < 0.001$); in addition, BMI was higher ($t_{277} = -5.38$, $p < 0.001$). In terms of diabetes treatment, 6% of NCs and 23% of PwS reported current use of diabetes medications. HOMA-IR levels were significantly higher among the PwS on diabetes medications, compared to those not taking medications [5.67 (SD = 6.0) vs. 3.12 (SD = 4.6), t47.0 = −2.75, $p = 0.009$].

TABLE 1 | Comparison of study participants with and without schizophrenia.

	Nonpsychiatric comparison group			Schizophrenia group						
	N	Mean	SD	N	Mean	SD	t or χ^2	df	p	Cohen's d
Sociodemographic variables										
Age (years)	140	48.7	11.2	145	48.3	10.1	0.27	283	0.79	0.03
Sex (% female)	140	54		145	46		1.85	1	0.17	
Race/ethnicity	140			145			4.93	2	0.09	
Non-Hispanic White (%)		58			45					
Hispanic (%)		24			30					
Other (%)		18			25					
Education (years)	140	14.5	2.3	145	12.4	2.3	8.16	283	<0.001	0.97
Cigarette use (packs per day)	140	0.02	0.09	145	0.38	0.50	−8.49	283	<0.001	−1.01
Psychopathology										
Antipsychotic daily dose[1]				145	1.85	1.56				
Duration of illness (years)				142	25.0	11.1				
Positive symptoms (SAPS)				145	6.52	4.20				
Negative symptoms (SANS)				145	7.21	4.35				
Depression (PHQ-9)	130	1.95	2.81	138	7.80	6.59	−9.37	266	<0.001	−1.16
Perceived stress (PSS)	130	10.9	6.04	141	18.7	6.20	−10.5	269	<0.001	−1.28
Cognitive performance, quality of life, and everyday functioning										
Global functioning (TICS-M)	138	37.4	4.22	141	31.0	6.02	10.2	277	<0.001	1.23
Executive functioning (D-KEFS)	140	0.39	0.61	145	−0.57	0.75	11.8	283	<0.001	1.40
Quality of life (SF-36)	131	54.7	5.83	141	42.8	11.26	10.8	270	<0.001	1.32
Everyday functioning (UPSA-B)	140	84.2	9.9	139	67.7	18.1	9.50	277	<0.001	1.14
Metabolic measures										
Body mass index	139	27.6	6.64	140	32.2	7.35	−5.38	277	<0.001	−0.64
Insulin resistance (HOMA-IR)	126	1.74	1.57	134	3.73	5.07	−4.66	258	<0.001	−0.58

For all measures (except the depression and perceived stress), lower scores suggest worse functioning. D-KEFS, Delis-Kaplan Executive Function System (49, 50); HOMA-IR, Homeostatic Model Assessment of Insulin Resistance (56, 57); PHQ-9, Patient Health Questionnaire-9; measure of depression (43); PSS, Perceived Stress Scale; measure of perceived stress (44); SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; SF-36, Medical Outcomes Survey—Short Form 36; measure of mental and physical functioning (61); TICS-M, Telephone Interview for Cognitive Status—Modified (45, 46); UPSA-B, UCSD Performance-Based Assessment-Brief (54, 55).

[1]Antipsychotic medication daily dosages were converted to WHO average daily doses based on published standards (40).

TABLE 2 | Spearman's correlations of insulin resistance (HOMA-IR) in participants with and without schizophrenia.

	Nonpsychiatric comparison group			Schizophrenia group			Test for equal correlations	
	N	rho	p	N	rho	p	*z*	*p*
Sociodemographic variables								
Age (years)	126	0.10	0.29	134	–0.18	0.04	2.25	0.02
Education (years)	126	–0.16	0.08	134	–0.04	0.62	–0.97	0.33
Cigarette use (packs per day)	126	0.12	0.19	134	–0.16	0.06	2.25	0.02
Psychopathology								
Antipsychotic daily dose[1]				134	0.07	0.42		
Duration of illness (years)				131	–0.06	0.49		
Body mass index	126	0.55	<0.001	132	0.53	<0.001	0.22	0.83
Positive symptoms (SAPS)				134	0.04	0.69		
Negative symptoms (SANS)				134	0.23	0.007		
Depression (PHQ-9)	117	0.15	0.10	128	0.17	0.06	–0.16	0.87
Perceived stress (PSS)	116	0.18	0.05	131	0.15	0.09	0.24	0.81
Cognitive performance, quality of life, and everyday functioning								
Global functioning (TICS-M)	125	–0.35	<0.001	130	–0.28	0.02	–0.61	0.54
Executive functioning (D-KEFS)	126	–0.29	0.001	134	–0.06	0.46	–1.90	0.06
Quality of life (SF-36)	117	–0.15	0.11	131	–0.23	0.01	0.64	0.52
Everyday functioning (UPSA-B)	126	–0.13	0.16	130	–0.21	0.02	0.65	0.52

For all measures (except the depression and perceived stress), lower scores suggest worse functioning. D-KEFS, Delis-Kaplan Executive Function System (49, 50); HOMA-IR, Homeostatic Model Assessment of Insulin Resistance (56, 57); PHQ-9, Patient Health Questionnaire-9; measure of depression (43); PSS, Perceived Stress Scale; measure of perceived stress (44); SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; SF-36, Medical Outcomes Survey—Short Form 36; measure of mental and physical functioning (61); TICS-M, Telephone Interview for Cognitive Status—Modified (45, 46); UPSA-B, UCSD Performance-Based Assessment-Brief (54, 55).

[1]Antipsychotic medication daily dosages were converted to WHO average daily doses based on published standards (40).

Pairwise Correlates of Insulin Resistance

Among the PwS, worse insulin resistance (HOMA-IR) was associated with younger age, higher BMI, worse negative symptoms, worse global cognitive performance, worse quality of life, and worse everyday functioning (**Table 2, Figure 1**). Antipsychotic dose, duration of illness, and positive symptoms were not associated with HOMA-IR within the PwS.

Regression Analyses

The best-fit regression model for HOMA-IR had the following factors emerge as significantly associated with higher HOMA-IR: worse negative symptoms, higher BMI, and non-White race/ethnicity (**Table 3**). Collinearity was minimal with VIF < 1.2 for all variables.

DISCUSSION

Consistent with our hypothesis, we found that insulin resistance was worse in PwS compared to the NC group. We also found that HOMA-IR was related to several variables when considered individually, but the best-fit linear model found non-White race/ethnicity, higher BMI, and worse negative symptoms to be associated with higher HOMA-IR levels in PwS. Positive symptoms, antipsychotic dosage, and duration of illness were not associated with HOMA-IR levels in the PwS. Several measures that were significantly associated individually with HOMA-IR, such as age, quality of life, cognitive performance, and everyday functioning, did not emerge in the multivariate models.

TABLE 3 | Best-fit general linear models of insulin resistance within persons with schizophrenia (N = 145).

Variable	B	SE	FDR-adjusted *p*
Race/ethnicity (Hispanic)	0.18	0.09	0.05
Race/ethnicity (other)	0.19	0.09	0.05
Body mass index	0.02	0.005	<0.001
Negative symptoms (SANS)	0.02	0.008	0.01

SANS, Scale for the Assessment of Negative Symptoms.

Similar to other published studies (5–8), the sample of PwS studied in the present study had worse psychopathology, cognitive performance, and everyday functioning, as well as higher HOMA-IR and BMI compared with NCs of similar age, sex, and race/ethnicity distribution (26, 62–67). Thus, the findings presented here are likely generalizable to other groups of adults with chronic schizophrenia.

We found an association of insulin resistance (HOMA-IR) with negative symptoms (SANS) in a model that also included BMI and race/ethnicity as significant predictors. Previous observational studies reported associations of metabolic comorbidities such as fasting plasma glucose levels (68), DM (26), and metabolic syndrome (25, 26) with specific psychological symptoms in chronic schizophrenia patients. In antipsychotic-naive patients with first-episode schizophrenia, Chen et al. (19) found that patients with impaired glucose tolerance (assessed with the 75-g oral glucose tolerance test, $n = 43$) had more severe negative symptoms [assessed with the Positive and Negative Syndrome Scale (PANSS)] than those without ($n = 129$) after controlling for age and age of illness onset. In contrast, in another study of antipsychotic-naive patients with

first-episode schizophrenia, Steiner et al. (20) found no significant correlation between the level of insulin resistance (HOMA-IR) and the severity of negative symptoms (PANSS). However, in this study of acute schizophrenia (20), the level of insulin resistance (HOMA-IR) was relatively low (given normal HOMA-IR of 1) and the sample size was small {median [interquartile range (IQR)] HOMA-IR = 0.72 [0.38, 2.28], $n = 24$}, as compared with those parameters in our present study of chronic schizophrenia (median [IQR] HOMA-IR = 2.08 [1.21, 4.66], $n = 134$). It is conceivable that the relationship between insulin resistance (HOMA-IR) and negative symptoms of schizophrenia is dependent on the chronicity and severity of illness.

PwS with negative symptoms have been shown to have more severe overall psychopathology, worse cognition, poorer every day functioning, and lower physical activity (69, 70). Negative symptoms may impede help-seeking behaviors and healthcare utilization (71). Thus, PwS with higher levels of negative symptoms may have worse lifestyle behaviors resulting in poorer physical health including greater insulin resistance.

The exact biological processes underlying the relationship of negative symptoms with insulin resistance are unclear. However, dysregulated hypothalamic–pituitary–adrenal (HPA) axis responses and dopamine D2 receptor activity are involved in both psychopathology of schizophrenia and insulin resistance (72, 73). Unexpectedly, PwS with significant negative symptoms were reported to have higher HDL cholesterol levels, which may reflect altered lipid metabolism at the neuronal and systemic levels (74), as well as different patterns of cerebral metabolic activity (75). Adjunctive medications that improve metabolic side effects of antipsychotic medications (e.g., topiramate and pioglitazone) have been shown to also improve negative symptoms (76, 77), possibly through the AMPA/KA receptor antagonism and inhibition of NF-κB expression, respectively. Similarly, exercise has been shown to improve negative symptoms, possibly through increasing serum brain-derived neurotrophic factor and insulin-like growth factor-1 levels (78). Thus, there is a biological basis for our findings. The relationships between insulin resistance and negative symptoms warrant further investigation, especially when targeting interventions for metabolic problems and psychopathology for persons with chronic schizophrenia.

The present study had some limitations. Data on exogenous insulin therapy in our study participants were not available, although we did assess current use of diabetes medications. There are multiple possible contributors to metabolic pathology in schizophrenia. These include lifestyle factors such as physical activity, diet, and sedentary behavior, atypical antipsychotics, and biology of schizophrenia itself (37, 79, 80). In this study, we did not assess lifestyle factors in a systematic way and, therefore cannot comment on their role in the association between negative symptoms and insulin resistance. We found higher HOMA-IR levels among the PwS on diabetes medications, compared to PwS not taking medications. The use of HOMA-IR to assess insulin resistance in individuals specifically on insulin therapy warrants further investigation (57, 81). Furthermore, this is an examination of cross-sectional data to examine insulin resistance, which is highly dependent on longitudinal factors—duration of illness, age, exposure to antipsychotic medications, and other issues. Thus, causality cannot be inferred, though we did include certain time-related factors (duration of illness, daily dose of antipsychotic medications) into our multivariate analyses. Finally, the schizophrenia group consisted of outpatients with a chronic and relatively stable course of illness. The results of the present study may not be generalized to antipsychotic-naive patients with first-episode or acute schizophrenia or hospitalized severely ill patients.

In conclusion, we found that PwS who have higher insulin resistance also have worse negative symptoms as well as higher BMI. Thus, efforts to prevent metabolic comorbidities and subsequent cardiovascular disease and death among chronic patients should focus on PwS with this clinical profile. Our cross-sectional study was not able to discern the temporal relationship among these factors. It is possible, for example, that heightened insulin resistance could be the consequence of unhealthy lifestyle secondary to sedentary behaviors associated with greater negative symptoms in the prodrome or throughout the course of illness (8, 68, 82–85). However, it is also possible, given evidence that insulin resistance exists early in the course of the illness and is linked to genetic risk for the disorder, that glucose dysregulation is a part and parcel of the schizophrenia syndrome, at least for some patients. If so, it may be that a subsyndrome exists in those with high negative symptoms, high BMI, and high insulin resistance.

AUTHOR CONTRIBUTIONS

VS conducted and interpreted data analyses and wrote the manuscript. EL and HJ interpreted data analyses and revised the manuscript. AM conducted the study procedures, interpreted data analyses, and revised the manuscript. RD managed data and revised the manuscript. JL supervised statistical analyses and revised the manuscript. XT supervised statistical analyses, interpreted data analyses, and revised the manuscript. LE designed the study and revised the manuscript. DJ designed the study, supervised data management, and revised the manuscript. All authors read and accepted the final version of the manuscript.

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The Association Between Dyslipidemia and Lethality of Suicide Attempts: A Case-Control Study

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Evidence supports the existence of an association between dyslipidemia, psychiatric disorders, and suicide risk due to the effects of altered lipid profiles on serotoninergic neuron membranes. The aim of this study was to investigate the differences in c-reactive protein (CRP), thyroid functioning, total cholesterol, high lipoprotein density cholesterol (HDL-c), low-lipoprotein density cholesterol (LDL-c), and triglycerides (TG) serum levels in low lethality (LLSA) vs. high lethality suicide attempters (HLSA) within 24 h from the suicide attempt and inpatients who never attempted suicide (NAS). After attempting suicide, subjects were admitted to the emergency ward of the IRCCS Ospedale Policlinico San Martino and later to the section of Psychiatry from 1st August 2013 to 31st July 2018. Socio-demographic and clinical characteristics, serum lipids profile, CRP, and thyroid functioning were collected. The sample consisted of 133 individuals with a HLSA, 299 subjects with LLSA, and 200 patients NAS. HLSA subjects were more likely to be males and diagnosed as having a bipolar disorder. Furthermore, HLSA subgroup showed significantly lower total cholesterol and LDL-c levels and higher CRP serum levels compared to LLSA and control group, respectively. LLSA subgroup showed higher HDL-c levels compared to HLSA subgroup (no differences between HLSA and control group were observed). Additionally, the control group reported higher triglycerides levels compared to patients admitted to psychiatric ward for a suicide attempt. Only male gender, having a diagnosis of bipolar disorder, lower total cholesterol, and higher CRP serum levels predicted HLSA. Investigating the relation between dyslipidemia and the severity of suicide attempts may contribute to reveal the complex determinants underlying at-risk behaviors such as suicide, thus playing a relevant role in the possible prevention of this disabling phenomenon.

Keywords: suicide, lethality, dyslipidemia, cholesterol, -c reactive protein, metabolic profile, inflammation

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INTRODUCTION

Suicide and non-fatal suicidal behaviors are major causes of mortality and morbidity worldwide. The World Health Organization (1) estimated that ∼800,000 people die from suicide each year and a number from 10 to 20 times higher of individuals attempt suicide, indicating that both suicide and non-fatal suicidal behaviors need to be addressed as a real health priority. The variability in rates

of suicidal behaviors within and between countries has been attributed to both population and individual risk factors, including economic status and cultural differences (2) that may significantly affect suicide risk.

Different explanatory models were developed in order to reveal the complex interplay between neurobiological factors such as genetic risk variables, altered serotonergic functioning, and stress responses potentially leading to suicidal behaviors (3, 4). Interestingly, two major dietary lipid classes, cholesterol, and polyunsaturated fatty acids (PUFAs), were significantly associated with higher suicide risk (5, 6). Consistent with the inflammation-related hypothesis of depression and suicidal behavior, C-reactive protein (CRP) blood levels were directly associated with the enhanced risk of attempting and committing suicide (7–9), suggesting that CRP may be a trait marker of suicidal behavior due to its pro-inflammatory effect together with its growing levels during acute inflammation (10). From a genetic perspective, genome-wide association studies (GWAS) identified a region on 2p25 that influences risk for attempting suicide and contains the ACP1 gene (11, 12) and polymorphisms in ACP1 which were found to modulate both protection and predisposition to dyslipidemia (13).

The association between low total cholesterol and cholesterol metabolites serum levels with higher suicide risk has been reported since 1990, when Muldoon et al. initially showed that treatments able to reduce cholesterol levels may attenuate the excess of suicidal behaviors and injury deaths in their sample (14). These results were confirmed by a wide body of literature showing significant associations between altered lipid profiles and higher suicide risk both in patients with specific psychiatric disorders as well as in non-clinical populations (15–21). Recently, Wu et al. conducted a large meta-analysis on 65 epidemiological studies, involving 510.392 participants, and investigated the association between serum lipid levels and "suicidality" subjects defined as individuals presenting suicidal ideation, suicide attempt, having threatened suicide, or death by suicide. Their findings showed that total cholesterol (TC) and low density lipoprotein cholesterol (LDL-c) levels were lower in suicidal patients than non-suicidal patients and healthy controls, high density lipoprotein cholesterol (HDL-c) levels were lower in suicidal patients relative to healthy controls, and triglycerides (TG) levels were lower in suicidal when compared to non-suicidal patients, respectively. Importantly, when the three groups were pooled, lower serum TC was associated with a 112% higher risk of suicidal behaviors (22).

Moreover, subjects who attempted suicide within a month from the blood tests had significantly lower TG and higher HDL-c levels than lifetime suicide attempters and those who never attempted suicide, with TG levels that were negatively associated with current suicidal behavior (23). However, other studies investigating a sample of inpatients with type 1 bipolar disorder and other psychiatric conditions failed to confirm these findings reporting no significant differences in lipid profiles between suicidal and non-suicidal subjects (24–26).

Recent studies investigated the role of cholesterol levels in violent vs. non-violent suicide attempts and showed that the former was significantly associated with lower cholesterol serum levels of ∼30% than the latter (27–29). Moreover, two post-mortem studies showed significantly lower cholesterol levels in the pre-frontal-cortex (PFC) of violent suicide attempters and significantly higher cholesteryl-ester-hydrolase (LIPA) expression in violent suicide attempters when compared with non-violent suicide attempters (30, 31).

Given this background, in this study we investigated the differences in CRP, thyroid functioning, TC, HDL-c, LDL-c, and TG serum levels between low-lethality (LLSA) vs. high-lethality suicide attempts (HLSA) within 24 h from the suicide attempt and inpatients who never attempted suicide (NAS).

According to this main objective, we tested the following hypothesis: (a) lower total cholesterol, HDL-c, LDL-c, and TG serum levels determine HLSA instead of LLSA and NAS; (b) CRP levels are higher in HLSA instead of LLSA and NAS.

MATERIALS AND METHODS

Sample

The present study was conducted in a sample of patients who were recruited at the section of Psychiatry of the IRCCS Ospedale Policlinico San Martino—Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal, and Child Health, University of Genoa, Italy, from 1st August 2013 to 31st July 2018.

The inclusion criteria were: (a) hospitalization in an emergency psychiatric ward for a suicide attempt; (b) aged over 18 years old; (c) the willingness to participate in the study by signing a written informed consent. The exclusion criteria were: (a) pregnancy or having just given birth; (b) having a positive history of acute neurological injury, such as neurodegenerative illnesses, mental retardation, loss of consciousness related to the presence of severe neurological conditions; (c) the assumption of lipid-lowering agents; (d) the refusal or inability to provide a valid consent prior to participate in the study.

A control group was also included in the sample and it was represented by admitted patients without a history of current and/or lifetime suicide attempts. The control group was matched for age, gender, occupational/marital status, and diagnosis to avoid any bias. We initially screened a sample of 703 patients; however, only 632 subjects voluntarily accepted to participate in the study by signing a written informed consent, the remaining individuals were lost due to lack of serum data or because they did not sign the required informed consent.

The study design was reviewed and approved by the local ethic committee.

Assessments and Procedures

Socio-demographic and clinical characteristics of the recruited patients were investigated during hospitalization through the standardized clinical chart and lifetime computerized medical record, used in Psychiatric Unit. The following patients' domains: age, gender, marital and occupational status, education level, suicide attempts, and suicide method were carefully investigated.

All available information have been cross-referred.

Psychiatric diagnoses were evaluated and set according to Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM 5) (32). Clinical evaluations were carried out by

expert clinicians and carefully reviewed by a senior psychiatrist (with at least 10 years of clinical experience in inpatient clinical setting). If patients had more than one psychiatric diagnosis, the principal psychiatric condition as diagnosed by the treating psychiatrist, was recorded. According to previous published studies (33, 34), we grouped the diagnosis in four main categories: bipolar and related disorders, depressive disorders, schizophrenia, and related disorders, other psychiatric disorders.

Based on Schrijvers et al., we considered suicide as a process, for which suicidal behaviors can be broken down chronologically into "component parts," beginning with the development of suicidal ideation, that progresses to planning, then putting thoughts and plans into action via attempts, and, if successful, culminating in completed suicide (35).

The term "suicidal lethality" has not yet been defined outside health literature. Beyond one publication describing suicide lethality as the lethality of the chosen suicide method (36), some theorists like Shneidman and Joiner conceptually identified suicide lethality "as a key ingredient of serious suicidality" (37, 38). We adopted Joiner's definition of suicide lethality, defined as "the acquired ability to enact lethal self-injury" (38). Within suicide lethality, the only individual intent is to perish as a result of the lethality of self-inflicted actions. Methods of suicide attempt were dichotomized in terms of lethality. Therefore, a high-lethality suicide attempt was defined as a suicide attempt that warranted hospitalization for at least 24 h and either treatment in a specialized unit (including intensive care unit, hyperbaric unit, or burn unit), surgery under general anesthesia, or extensive medical treatment (beyond gastric lavage, activated charcoal, or routine neurological observations), including antidotes for drug overdoses, telemetry, or repeated tests or investigations. Conversely, a low-lethality suicide attempt was defined as a suicide attempt that did not meet these criteria (39–46).

A routine blood examination was usually performed at hospital admission for all patients as a part of the clinical management routine. Blood samples were taken between 7:00 and 8:30 a.m. after patients had fasted for at least 10 h and after a psychiatric evaluation; patients who were not fasting were rescheduled. Blood exams included TC, TG, HDL-c, LDL-c, CRP serum levels, and TSH Reflex. Blood samples were drawn during the hospitalization in the Psychiatric Clinic and examined in the laboratory analysis of IRCCS Ospedale Policlinico San Martino, Genoa, Italy.

Statistical Analysis

All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) with the value of statistical significance which was set at $p < 0.05$.

Socio-demographic and clinical characteristics of the subjects were represented as mean and standard deviation (SD) for continuous variables and as frequency and percentage regarding categorical variables. The Kolmogorov-Smirnov test was conducted to confirm whether all the investigated sample variables followed the normal distribution.

Firstly, the sample was divided in two subgroups according to the presence/absence of current suicide attempt. A statistical comparison between patients with and without current suicide attempt was performed to examine whether there were differences in terms of socio-demographic and diagnostic features. Thus, in order to avoid statistical bias, the two subgroups were matched for age, gender, marital/occupational status, and psychiatric diagnoses.

Subsequently, the subgroup of patients admitted for a current suicide attempt was divided according to the lethality of suicide attempts, identifying a subgroup with high-lethality of suicide attempts and a subgroup with low-lethality of suicide attempts. In order to analyze differences between these three subgroups, we used the Pearson $\chi 2$ test with Yates correction for the comparison of categorical variables, and ANOVA for continuous variables.

Lastly, a multinomial regression model was performed to detect the variables associated with the lethality of suicide attempt (dependent variable) and each of the other independent variables previously found associated in the statistical analyses. The probability of entering the equation was set at 0.05.

RESULTS

In our study we recruited a total sample of 632 patients, with a mean age of 49.69 ± 18.97 years old. Of the total sample, 478 subjects were females (75.6%) with an educational level of 11.06 ± 3.28 years. Four hundred and thirty-two subjects were recruited in the case-group and 200 in the control group. There were no statistically significant differences in socio-demographic and clinical characteristics (i.e., gender, age, marital status, educational level, working status, psychiatric diagnoses and pharmacological treatment) between the subgroup of patients who attempted suicide and the subgroup of patients who never attempted suicide (control group). Socio-demographic and clinical characteristics of the included subjects are summarized in **Tables 1**, **2**.

Regarding patients admitted for a suicide attempt, 133 individuals (30.8%) committed a HLSA while 299 subjects (69.2%) carried out a LLSA, respectively. The prevalence of the method used to attempt suicide is shown in **Table 3**.

Considering socio-demographic and clinical features within the three subgroups, the HLSA subgroup was significantly associated with male gender (38.3 vs. 16.1 vs. 27.5%, $p < 0.001$) and diagnosis of bipolar disorder (41.4 vs. 29.1 vs. 32.0%, $p = 0.007$), compared to LLSA, and control group, respectively.

When the three subgroups were compared, the HLSA subgroup showed significantly lower total cholesterol levels (151.08 ± 40.90 vs. 184.40 ± 43.21 vs. 189.41 ± 33.88, $p < 0.001$) and LDL-c levels (99.55 ± 33.25 vs. 119.15 ± 38.30 vs. 126.15 ± 31.52, $p < 0.001$), and higher CRP serum levels (24.18 ± 38.69 vs. 8.78 ± 19.66 vs. 4.37 ± 5.61, $p < 0.001$) compared to LLSA and control group, respectively.

Furthermore, the LLSA subgroup showed higher HDL-c levels compared to HLSA subgroup (54.64 ± 16.59 vs. 46.31 ± 17.82, $p < 0.001$) (no differences between HLSA and control group were observed). Additionally, the control group reported higher triglycerides level compared to patients admitted for a suicide attempt. No differences in triglycerides levels between HLSA and LLSA were found). Additional differences are shown in **Table 4**.

TABLE 1 | Socio-demographic characteristics in the total sample and in the two subgroups.

	Total sample (*N* = 632)	Suicide attempt (*N* = 432)	No suicide attempt (*N* = 200)	*t*/*χ2*	*df*	*p*
Gender (female), *N (%)*	478 (75.6)	333 (77.1)	145 (72.5)	1.558	1	0.212
Age (years), *mean* ± *SD*	49.69 ± 18.97	49.13 ± 20.16	50.89 ± 16.11	1.086	630	0.278
Education level, *mean* ± *SD*	11.06 ± 3.28	11.15 ± 3.27	10.86 ± 3.30	−1.046	630	0.296
MARITAL STATUS, *N (%)*						
Single	296 (46.8)	195 (45.1)	101 (50.5)	4.672	3	0.197
Married	131 (20.7)	93 (21.5)	38 (19.0)			
Divorced	147 (23.3)	98 (22.7)	49 (24.5)			
Widowed	58 (9.2)	46 (10.6)	12 (6.0)			
Working status, *N (%)*	177 (28.0)	121 (28.0)	56 (28.0)	0.000	1	0.998

TABLE 2 | Clinical characteristics in the total sample and in the two subgroups.

	Total sample (*N* = 632)	Suicide attempt (*N* = 432)	No suicide attempt (*N* = 200)	*t*/*χ2*	*df*	*p*
DIAGNOSIS, *N (%)*						
Bipolar and related disorders	206 (32.6)	142 (32.9)	64 (32.0)	4.434	3	0.218
Schizophrenia and related disorders	63 (10.0)	37 (8.6)	26 (13.0)			
Depressive disorders	202 (32.0)	146 (33.8)	56 (28.0)			
Others	161 (25.4)	107 (24.7)	54 (27.0)			
PHARMACOLOGICAL TREATMENT, *N (%)*						
Antipsychotics	252 (58.3)	175 (40.5)	77 (38.5)	0.230	1	0.631
Mood stabilizers	303 (70.1)	202 (46.8)	101 (50.5)	0.766	1	0.381
Antidepressants	165 (38.2)	110 (25.5)	55 (27.5)	0.294	1	0.588
Others	108 (25.0)	82 (19.0)	26 (13.0)	3.452	1	0.063
Drug-free	55 (12.7)	40 (9.3)	15 (7.5)	0.533	1	0.466
Total Cholesterol, *mean* ± *SD*	178.97 ± 42.50	174.14 ± 45.17	189.41 ± 33.86	4.257	630	<0.001
LDL Cholesterol, *mean* ± *SD*	117.23 ± 36.47	113.11 ± 37.88	126.15 ± 31.52	4.235	630	<0.001
HDL Cholesterol, *mean* ± *SD*	51.55 ± 17.11	52.08 ± 17.39	50.43 ± 16.50	−1.128	630	0.260
Tryglicerides, *mean* ± *SD*	122.63 ± 69.07	114.32 ± 57.38	140.58 ± 86.73	4.514	630	<0.001
TSH reflex, *mean* ± *SD*	2.33 ± 1.92	2.30 ± 1.89	2.40 ± 1.99	0.629	630	0.529
CRP, *mean* ± *SD*	10.63 ± 23.63	13.52 ± 27.86	4.37 ± 5.61	−4.599	630	<0.001

When the multinomial regression was performed, male gender, diagnosis of bipolar disorder, lower total cholesterol level, and higher CRP serum levels predicted HLSA (**Table 5**).

DISCUSSION

The present study tested the association between lipid profile, CRP levels, and thyroid functioning in a relatively large sample of psychiatric inpatients who committed HLSA (133 subjects) vs. psychiatric inpatients who carried out LLSA (299 subjects) and a control group of psychiatric inpatients who never attempted suicide (200 subjects).

HLSA were more likely to be males and affected by bipolar disorder. This is consistent with previous findings showing that subjects with bipolar disorder presented a higher risk for attempting and committing suicide (47–49) and supported the higher lethality suicide among males irrespective from their psychiatric diagnosis (46, 49–51).

Our study showed that HLSA was clearly associated with lower total cholesterol and LDL-c, and higher CRP levels when compared with LLSA and controls. To the best of our knowledge, no previous studies investigated the association between suicide lethality and lipid profiles, though our results may be explained in the light of previous evidence showing that violent methods to attempt suicide were associated with lower total cholesterol levels (27).

The well-known cholesterol-serotonin hypothesis (52) may help to explain these results as lower total cholesterol levels may foster higher central neuroinflammation, thus altering the serotonergic system and leading to higher aggressiveness and impulsivity, especially among males (53). In the central nervous system, serotonin plays a role in the suppression of aggressive and harmful behaviors. There are several theories that may

TABLE 3 | Type of suicide according to lethality.

	Total sample (*N* = 432)
Suicide Attempt, *N (%)*	432 (68.4)
High lethality	133 (30.8)
Low lethality	299 (69.2)
TYPE OF SUICIDE ATTEMPT (*N* = 432), *N (%)*	
Drug intoxication	284 (65.7)
Defenestration	40 (9.3)
Drowning	1 (0.2)
Weapon	2 (0.3)
Stabbing	9 (2.1)
Burn/Gas/Caustic	26 (6.0)
Strangling	11 (2.5)
Cuts	59 (13.7)

explain the potential effect of serum lipid profile (in particular cholesterol levels) on violent conduct and suicide risk. The most blamed mechanism is the reduction of brain serotonergic activity which is associated with the risk of attempting suicide. It has been hypothesized that cholesterol levels are associated with the lipid micro viscosity of serotonin receptors and transporters. Since reliable evidence shows that circulating levels of cholesterol—those that may be detected by routine blood tests as those used on the patients in the study—correlate with the role of stabilizer of cellular membrane functioning (6), and membrane cholesterol exchanges freely with cholesterol in the surrounding medium, low membrane cholesterol decreases the number of serotonergic receptors through the decreased lipid micro viscosity of the serotonergic receptor on the neuronal membrane (53, 54). This process could lead to a poorer suppression of impulsive and violent behaviors, such as suicidal behaviors (54). As a matter of fact, cholesterol is crucial for membrane stability and neurotransmission that include the alteration of membrane lipid raft structure by the proportions of cholesterol and n-3 PUFAs, affecting the functioning of membrane-bound proteins including serotonin receptors and transporters, and toll-like receptors (6, 55). Therefore, low levels of cholesterol might be responsible of increased n-6:n-3 PUFA ratio, thereby promoting neuroinflammation as n-3 PUFAs tend to exert anti-inflammatory properties, while n-6 PUFAs levels tend to show a pro-inflammatory activity, and disinhibit, albeit indirectly, two inflammatory intermediates such as nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) and peroxisome proliferator activated receptors (PPARs), respectively (56). The abnormal monoaminergic neurotransmission as well as neuroinflammation are two leading mechanisms which are evoked as biological pathways underlying suicidal behavior (6, 9, 55). Lower cholesterol levels are associated with greater impulsivity of suicide attempts and violent methods due to their effects on the serotonergic system. Indirect evidence suggests an association between attempt lethality and low-cholesterol levels on the basis of the relation between lethality and the choice of violent methods to attempt suicide (29).

Although, to the best of our knowledge, no studies investigated directly the association between CRP, cholesterol, and cholesterol metabolites serum levels and lethality of suicide attempts, interestingly, a recent study hypothesized a bridge between the well-known cholesterol metabolism process with its associated molecular pathways and the neurobiological underpinnings of suicide risk, by showing that the relation between total unesterified cholesterol and suicide risk was significantly mediated by ABCA-1-specific cholesterol efflux capacity (57).

Conversely, our results show no differences in total cholesterol and LDL-c levels between LLSA and controls, although ANOVA did not confirm these findings. The lack of differences concerning lipid profiles of LLSA and controls could be explained in the light of the method lethality used to attempt suicide. For instance, Lalovic et al. (30) reported no significant differences in cholesterol content between suicide victims and controls in specific brain regions such as the frontal cortex, amygdala, and hippocampus. However, when suicides were classified as violent or non-violent according to the used method, violent suicides were found to have lower gray-matter cholesterol content in the frontal cortex compared to non-violent suicides. Other authors (58), albeit in a small sample, reported no difference in the levels of total cholesterol and triglycerides among attempters and non-attempters.

Our findings show that TG were significantly higher in the control group than in LLSA and HLSA subgroups, among which no significant differences were reported. This is consistent with previous studies showing lower TG levels among suicide attempters when compared with controls without a positive history of suicide attempts (17, 20–22). Lower TG levels were reported in subjects who attempted suicide in the month before the survey compared with subjects who had suicidal ideation in the month before the survey and never suicidal controls (23).

Moreover, our findings do not show any differences regarding TG levels in LLSA and HLSA subgroups; to date, no previous studies investigated the possible association between the lethality of suicide attempts and TG levels. There are studies in the current literature that reported no differences in TG levels among violent vs. non-violent suicide attempts, though they did not consider the lethality of suicide attempts (25, 59).

Our study should be considered in the light of the following limitations; firstly, this is a cross-sectional study, and we cannot assess whether a decrease in TC or TG may have caused a mood episode with active suicidal ideation leading to suicide attempts, or if the presence of a mood episode originated a loss of appetite and a consequent loss of weight altering lipid profiles. Thus, given the main nature of this study, we could not evaluate the direct causal relation between suicidal behaviors and lipid profile. Moreover, our results could not be adjusted for the psychopharmacological medications that both cases and controls were taking when assessed and this may have influenced our findings. However, subjects taking lipid-lowering agents were not included in the sample. Thirdly, a detailed medical history, including careful information about the body mass index (BMI) was not available. Neither blood pressure nor glycaemic values were collected and, consequently, included in the analysis.

TABLE 4 | Comparison among three subgroups according to the lethality of suicide attempt.

	High lethality (*N* = 133)	Low lethality (*N* = 299)	Controls (*N* = 200)	*F*	*p*	*post-hoc* (Bonferroni)
Gender (male), *N (%)*	51 (38.3)	48 (16.1)	55 (27.5)	26.380	<0.001	
Age (years), *mean* ± *SD*	49.62 ± 20.69	48.91 ± 19.95	50.89 ± 16.11	0.653	0.521	H=L=C
Education level, *mean* ± *SD*	10.93 ± 3.15	11.24 ± 3.32	10.86 ± 3.30	0.963	0.382	H=L=C
MARITAL STATUS, *N (%)*						
Single	62 (46.6)	133 (44.5)	101 (50.5)	5.477	0.484	
Married	30 (22.6)	63 (21.0)	38 (19.0)			
Divorced	29 (21.8)	69 (23.1)	49 (24.5)			
Widowed	12 (9.0)	34 (11.4)	12 (6.0)			
Working status, *N (%)*	36 (27.1)	85 (28.4)	56 (28.0)	0.085	0.959	
DIAGNOSIS, *N (%)*						
Bipolar and related disorders	55 (41.4)	87 (29.1)	64 (32.0)	17.603	0.007	
Schizophrenia and related disorders	16 (12.0)	21 (7.0)	26 (13.0)			
Depressive disorders	41 (30.8)	105 (35.1)	56 (28.0)			
Others	21 (15.8)	86 (28.8)	54 (27.0)			
Total Cholesterol, *mean* ± *SD*	151.08 ± 40.90	184.40 ± 43.21	189.41 ± 33.88	41.921	<0.001	L=C>H
LDL Cholesterol, *mean* ± *SD*	99.55 ± 33.25	119.15 ± 38.30	126.15 ± 31.52	23.600	<0.001	L=C>H
HDL Cholesterol, *mean* ± *SD*	46.31 ± 17.82	54.64 ± 16.59	50.43 ± 16.50	11.946	<0.001	L>H=C
Triglycerides, *mean* ± *SD*	122.13 ± 59.78	110.84 ± 56.03	140.58 ± 86.73	11.480	<0.001	C>H=L
TSH reflex, *mean* ± *SD*	2.04 ± 1.89	2.42 ± 1.88	2.40 ± 1.99	1.988	0.138	H=L=C
CRP, *mean* ± *SD*	24.18 ± 38.69	8.78 ± 19.66	4.37 ± 5.61	32.808	<0.001	H>L=C

TABLE 5 | Relationship between potential explanatory variables and lethality of suicide attempts: results from the logistic regression analysis.

Step	Variables	T	E.S.	Wald	df	*p*	Exp(B)	95% CI for EXP
Step 1	Gender	−0.684	0.274	6.250	1	0.012	0.504	0.295–0.863
Step 2	Diagnosis	0.498	0.252	3.903	1	0.048	1.645	1.004–2.695
Step 3	Total cholesterol	−0.022	0.006	15.377	1	<0.001	0.979	0.968–0.989
Step 4	LDL cholesterol	0.004	0.006	0.479	1	0.489	1.004	0.992–1.017
Step 5	HDL cholesterol	−0.014	0.008	3.483	1	0.062	0.986	0.971–1.001
Step 6	Triglycerides	0.004	0.002	3.099	1	0.078	1.004	1.000–1.008
Step 7	c-reactive protein—CRP	0.017	0.005	13.844	1	<0.001	1.017	1.008–1.026
	Constant	3.388	0.759	19.950	1	<0.001		

However, we only included those subjects with stable clinical conditions apart from what was related to suicide attempts.

CONCLUSIONS

Our data suggest that low total cholesterol serum levels may increase the risk of HLSA and low triglycerides serum levels increase suicide risk—as well as low TC levels do—but they do not influence the lethality of the attempt. To the best of our knowledge, no previous studies have investigated TC and TG levels in respect to the lethality of suicide attempt. Therefore, further studies should focus on this association in order to confirm these preliminary results and shed light on the complex neurobiological mechanisms underlying suicidal behaviors.

AUTHOR CONTRIBUTIONS

AA: supervision data collection, writing protocol, statistical analyses, writing original draft; PS: writing original draft, designed the study; GG: writing protocol, conceived, and designed the study; MC, CC, and MR: data collection, revision of data literature; EA and MA: review and editing of the original draft, scientific advisor of the project; GS: designed the study, review, and editing of the original draft. All authors approved of the final draft of the manuscript before submission.

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MINI REVIEW
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Insulin Resistance as a Shared Pathogenic Mechanism Between Depression and Type 2 Diabetes

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Neuropsychiatric disorders and type 2 diabetes (T2D) are major public health concerns proposed to be intimately connected. T2D is associated with increased risk of dementia, neuropsychiatric and mood disorders. Evidences of the involvement of insulin signaling on brain mechanisms related to depression indicate that insulin resistance, a hallmark of type 2 diabetes, could develop in the brains of depressive patients. In this article, we briefly review possible molecular mechanisms associating defective brain insulin signaling with reward system, neurogenesis, synaptic plasticity and hypothalamic-pituitary-adrenal (HPA) stress axis in depression. We further discuss the involvement of tumor necrosis factor α (TNFα) promoting defective insulin signaling and depressive-like behavior in rodent models. Finally, due to the high resistant rate of anti-depressants, novel insights into the link between insulin resistance and depression may advance the development of alternative treatments for this disease.

Keywords: depression, type 2 diabetes, insulin resistance, inflammation, synaptic plasticity, hippocampus, HPA axis, dopamine

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INTRODUCTION

Depressive disorders, type 2 diabetes (T2D) and obesity are among the top causes of years lived with disability, a widely accepted measure of disease burden on society (1). Major Depressive Disorder represents the highest burden among mental disorders, with a significant impact on individuals, their families and the community at large. The World Health Organization estimates that more than 300 million people suffer from depressive disorders (2). In parallel, T2D has been estimated to afflict >400 million adults worldwide (2). T2D is characterized by peripheral insulin resistance that culminates in hyperglycemia (3). While T2D has precise diagnostic parameters, that includes fasting serum glucose levels and glycated hemoglobin blood levels; depression diagnoses is based on the persistence of some of the following symptoms for >2 weeks: sad/anxious mood, hopelessness, helplessness, decreased energy, appetite/weight changes, headaches, sleep changes, feelings of guilt, loss of interest, decreased concentration, psychomotor retardation and suicide attempts (4).

T2D is a risk factor not only for the development of cardiovascular diseases, but also to neurological and psychiatric disorders, including Alzheimer's disease (AD) (5, 6). Some clinical reports and meta-analyses indicate a correlation between T2D and depression with a bi-directional increased risk between both conditions (6–9). Albeit evidences correlating T2D and depression, confounders implicated in epidemiological studies hamper the temporal order assessment of those co-morbid cases. As a result, the association between both diseases is still unclear (8, 10, 11).

Insulin signaling play a role in neuronal dysfunction and cognitive decline in AD (12, 13) and it emerged as a possible mechanism underlying alterations in the brain and in behavior in mood disorders (14). In children, the severity of depressive symptoms predicted the development of insulin resistance (15) and a recent report demonstrated that worst insulin resistance correlated with more pronounced depressive symptoms and dysfunction of the anterior cingulate cortex-hippocampal motivational network in a cohort of obese depressed youths (16).

In this minireview, we highlight a possible role of decreased insulin signaling in the brain, as a result of metabolic dyshomeostasis, in mechanisms involved with depressive behavior.

MOLECULAR LINKS BETWEEN DEPRESSION AND DIABETES

Brain Insulin Resistance

Insulin has been implicated with diverse central roles, like modulating feeding behavior and energy maintenance by the hypothalamus, as well as memory-related processes by the hippocampus (13, 17–19). Insulin receptors are expressed throughout the brain, including regions classically involved with mood regulation, such as the nucleus accumbens (NAc), the ventral tegmental area (VTA), the amygdala, and the raphe nuclei (20, 21). The knockdown of insulin receptors in the hypothalamus of rats triggered depressive and anxiety-like behaviors in mice (22). Anxiety and depressive-like behaviors were further reported in mice with neuronal-specific knockout of insulin receptors (NIRKO). NIRKO mice also exhibited mitochondrial dysfunction, oxidative stress and increased monoamine oxidase expression and dopamine turnover in the mesolimbic system (23). Interestingly, altered behavior was detected in 17-month-old NIRKO mice, but not in younger animals (23). It is important to note that by this age, these animals display increased white adipose tissue and plasma leptin concentration (17), raising the possibility of the behavior response being a secondary effect to the absence of insulin signaling in neurons.

A recent study demonstrated that the knockdown of insulin receptors in astrocytes also generates anxiety and depressive-like behavior in mice, via decreased purinergic signaling and altered dopamine release (24). A recent *post-mortem* analysis in the brain of patients diagnosed with mental illness has observed a correlation between gene expression of proteins involved with both the dopaminergic system and the insulin signaling (25), supporting the idea that insulin could regulate the dopaminergic response. Oppositely, another report observed that deleting insulin receptors from dopaminergic neurons had no impact on anxiety or depressive-like behavior in young adult mice (26). The absence of altered behavior in this model counteracts the idea of insulin regulating the dopaminergic system. Other possibilities to explain this phenotype are the development of compensatory mechanisms, or that, similar to what is observed in the NIRKO mice, altered behavior would be detected in older animals.

Defective brain insulin signaling in T2D patients has been associated with impaired transport of the hormone across the blood-brain barrier (27). Markers of impaired insulin signaling are present in the brain of *db/db* mice, a transgenic model for T2D that lacks the long isoform of the leptin receptor (28). These mice also exhibit increased immobility time in the forced swim test as early as 5 weeks of age, coinciding with an initial metabolic dysregulation, including hyperglycemia, increased food and water intake and body weight (29–31). This animal model also presents with progressive anxious and psychosis-like behavior that progress with age (30). Interestingly, since most metabolic parameters are also aggravated with aging in the *db/db* mice, it hinders an accurate determination of the major player influencing the behavior. High-fat diet (HFD) promotes T2D symptoms, as well as anxiety and depressive-like behavior in wild-type mice associated with impaired brain insulin signaling (32). Parallelly, HFD disrupts brain reward system of mice, by altering dopamine-related proteins in the VTA, NAc and dorsolateral striatum (32). Overall, further studies designed to investigate a direct correlation between brain insulin dysfunction and depressive-like behavior are needed in the field.

Neurogenesis and Synaptic Plasticity

Hippocampal neurogenesis, a process in which neural progenitors from the subgranular zone differentiate into new neurons at the dentate gyrus, is proposed to be involved with depression and to be impaired in diabetes (33, 34). HFD impairs cell proliferation, insulin signaling and the Akt/glycogen synthase kinase 3β (GSK3β) activation promoted by serotonin in the dentate gyrus of the hippocampus. Interestingly, replacing HFD by chow diet recovered depressive symptoms and Akt/GSK3β response to insulin, even without a complete recovery of body weight. Neurogenesis was partially recovered by a chow diet replacement, suggesting that it was not the only mechanism implicated with the beneficial effect promoted by the regular diet (35). Other hormones like Insulin-like growth factor I (IGF-I) and leptin activate Akt and GSK3β pathway and mediate hippocampal neurogenesis (36–39). Interestingly, downregulation of those hormones are observed in the hippocampus of rodent models of T2D, being other possible targets to the link between T2D and depression (40, 41). Neurogenesis is also proposed to be impaired in T2D due to mitochondrial dysfunction (42). Peroxisome proliferator-activated receptor gamma (PPARγ) agonists increase central insulin sensitivity, mitochondrial biogenesis and prevent depressive-like behavior in rats through facilitation of hippocampal neurogenesis (43, 44).

Defective synaptic plasticity may lead to impairment of stress adaptation, prompting the onset of depression (45). In the food reward circuitry, insulin actions modulate synaptic plasticity in a concentration, time and brain region -dependent manner [for a review see (46)]. For instance, insulin promotes long-term depression of glutamatergic afferent connections into the VTA (47), but increases the activity of striatal cholinergic interneurons, elevating dopamine release into the NAc (48). Downregulation

of insulin receptors in the hippocampus of rats impaired proper long-term potentiation response mediated by high frequency stimulation and decreased glutamate receptors levels (19). This approach also worsened learning behavior in a similar fashion to what is observed in T2D rodent models (19). Altogether, data indicate that brain insulin resistance can impair physiological mechanisms of reward and learning that would ultimately elicit depressive symptoms.

Hypothalamic-Pituitary-Adrenal (HPA) Axis

Chronic psychological stress is associated with neuropsychiatric diseases, including depression and also with T2D (49–51). A well-supported theory of depression and T2D pathophysiology involves allostatic load on the hypothalamic-pituitary-adrenal (HPA) axis, a key mediator of the stress response regulating the secretion of glucocorticoids by the adrenal gland (52, 53). In an allostatic model, constant input throughout the life course of an individual will generate learning and adaptive responses, but it may promote ablation of the HPA axis and the emergence of diseases (14). Supporting this idea, variation of cortisol level is observed in the blood of depressive and patients with T2D compared to healthy control participants (54, 55).

Physiologically, insulin elevates adrenocorticotropin and corticosterone hormone levels, promoting HPA axis activation in rats (56). Also, insulin receptor knockdown at the arcuate nucleus of the hypothalamus led to reduced vasopressin response to restraint stress, suggesting that brain insulin resistance could cause disturbances in the HPA axis (14, 56). The hippocampus is proposed to exert negative feedback regulation on the HPA axis (57). Chronic unpredictable stress modulates glucocorticoid and serotonin receptors in the hippocampus of rats, similar to what was observed in the hippocampus of suicidal victims with medical history of depression (58). Interestingly, diabetic rats show decreased expression of hippocampal glucose-dependent type 1 glucocorticoid receptor (59) and lower HPA axis regulation by insulin with decreased response of corticosteroid receptor expression by the hippocampus (60). Collectively, results suggest that brain insulin signaling dysfunction could impair the HPA axis normal response to stress, possibly facilitating the development of depression.

Tumor Necrosis Factor α (TNFα)

T2D patients have elevated circulating levels of pro-inflammatory markers, in particular of the cytokine tumor necrosis factor α (TNFα) (61). Clinical studies indicate that blood concentrations of the pro-inflammatory cytokine tumor necrosis factor α (TNFα) correlates with depression and impaired performance on memory tests (62, 63). In a Bavarian cohort with history of depression elevated blood levels of TNFα, two isoforms of the soluble TNFα receptor and diabetes were commonly observed (64). In mice, intracerebroventricular administration of TNFα induced depressive-like behavior in the forced swim and tail suspension tests, effects that were counteracted by the ablation of the TNFα receptor 1 (TNFR1) (65). On the other hand, a recent study demonstrated that TNFR1 was involved with anxiety-like behavior analyzed by the open-field test, but not with more related depression tests like the forced swim test (66).

TNFα was shown to contribute to depressive states by modifying the serotonin system. For instance, this cytokine can activate the enzyme indoleamine 2,3-dioxygenase degrading the precursor molecule tryptophan and indirectly decreasing brain serotonin levels (67, 68). This cytokine also promotes blood-brain barrier (BBB) disruption in patients with T2D and in a mouse model of depression (69, 70), which could ultimately lead to loss of the BBB transport regulation of other inflammatory signals, and exacerbate allostatic load to the HPA axis, leading to its dysregulation (71–74).

TNFα promotes insulin resistance by the phosphorylation of insulin receptor substrate 1 (IRS1) on serine residues, via the activation of cellular stress-response kinases, including IκB kinase β (IKKβ), c-Jun N-terminal kinase (JNK), and protein kinase RNA-activated (PKR) (12, 75–78). Increased levels of IRS1 phosphorylated at serine residues are observed in the hippocampus and in the hypothalamus of AD mouse models. In the AD context, activation of stress-response kinases was shown to regulate brain insulin signaling impairment and memory behavior tests (12, 13, 75, 78). TNFα further activates the nuclear factor κ B (NFκB), a transcriptional factor that regulates neuronal survival and the transcription rate of other cytokines, that will convey on insulin signaling impairment (79, 80). The NAc of HFD mice have reduced insulin signaling and increased expression of TNFα. Interestingly, both measures plus depressive-like behavior were counteracted by the administration of probiotics (81).

Depressive-like behavior was also reported in these models and it was dependent of TNFα signaling and activation of microglial Toll-like receptor 4 (TLR4) (82). Interestingly, TLR4 expression correlates with depression in humans (83, 84) and followed anxiety and depressive-like behavior in mice fed a high-cholesterol diet (85). Since this receptor can be activated by saturated fatty acids (86),which are associated with higher risk of developing T2D (87), a pathway involving TLR4, TNFα, and insulin resistance could be a mechanistic link between T2D and depression yet to be explored (**Figure 1**).

ANTIDEPRESSANT ASPECTS OF ANTIDIABETIC DRUGS

Due to the heterogeneity of depression and the lack of specific biomarkers, the management of this condition in the primary care setting remains challenging (88, 89) and treatment frequently involves trial and error experimentation. Different types of antidepressants are applied in clinical practices, usually directed to neurotransmitters reuptake and monoamine oxidase inhibition. However, response rates to treatments remain low, with more than 30% of patients with depressive disorders failing to respond to four different antidepressant therapies (90). It is not uncommon to observe cases of treatment-resistant depression despite adequate dosing and duration of antidepressants (91). More effective treatments are required, and some overlapping mechanisms between T2D and depression, suggested above, opens up new avenues for the identification of novel pharmacological targets for the treatment of those comorbid disorders. Regarding this topic, anti-depressant effects

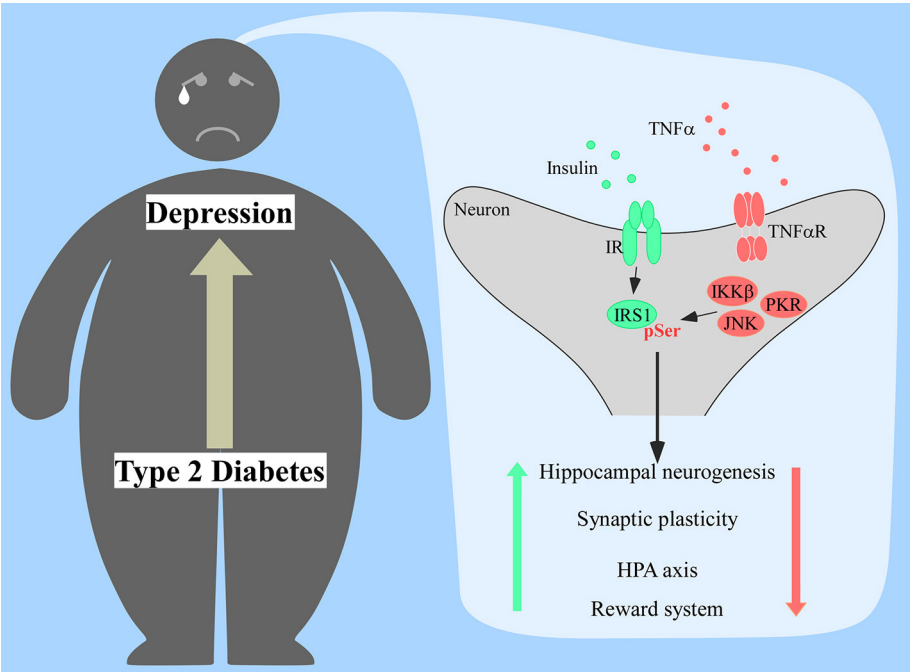

FIGURE 1 | Proposed mechanism of insulin resistance in the brain of diabetic patients prompting the onset of depression. Increased production of tumor necrosis factor α (TNFα) would activate several stress kinases in the brain, including IκB kinase β (IKKβ), c-Jun N-terminal kinase (JNK), and protein kinase RNA-activated (PKR). Activation of those stress pathways leads to the phosphorylation of insulin receptor substrate 1 (IRS1) at serine residues, impacting proper insulin signaling response. Lack of proper central insulin signaling would affect hippocampal neurogenesis, synaptic plasticity, hypothalamic-pituitary-adrenal (HPA) axis response, and the reward system.

of anti-diabetic and anti-inflammatory medications are currently being explored in the field.

Insulin based medications can be considered first-line treatments in T2D in cases of severe basal hyperglycemia or elevated serum glycated hemoglobin. Clinical studies administering intranasal insulin in healthy human subjects have reported improvements in mood and memory (92), as well as better HPA axis response to a social stress test, assessed by decreased saliva and plasma cortisol levels (93). But when evaluated in a cohort of depressive patients, intranasal insulin had no improvements on the depressive scores and neurocognition indexes applied compared to the placebo group (94). Lack of effective response to insulin amongst patients could be related to an intracellular insulin resistance (**Figure 1**), suggesting that approaches that bypass the first steps of the insulin signaling might show better results.

Liraglutide, another anti-diabetic medication, is an incretin analog that binds to the Glucagon-like peptide 1 receptor and ameliorates insulin signaling. This injectable anti-diabetic medication is capable of crossing the blood-brain barrier (95) and shows positive effects on brain insulin signaling and memory performance on animal models of AD (78, 96, 97). When tested in animal models of depression, liraglutide also had beneficial effects (98, 99). Clinical trials using this drug as a treatment for neurodegenerative diseases, like Alzheimer's disease are ongoing (ClinicalTrials.gov Identifiers: NCT01843075; NCT01469351; NCT02140983). A 4-week pilot study adding liraglutide as a treatment for patients with mood disorders observed better scores on measures of cognitive function compared to baseline (100). But more robust trials involving liraglutide and a placebo group in depressive patients are still warranted.

Metformin is a commonly used treatment for T2D with mechanisms of action not fully understood, but it involves key regulators of cellular energy status, including mitochondrial proteins and the AMP kinase (AMPK) (101, 102). In a cohort of patients with comorbid depression and T2D, metformin was reported to ameliorate depressive behavior when compared to baseline (103). Nonetheless, in a study involving overweight participants with impaired glucose tolerance, metformin had no effect on the Beck Depression Inventory score when compared to the placebo group (104). The effects of metformin in the antidepressant response to sertraline in a group of obese people is currently being evaluated in a phase 4 clinical trial (ClinicalTrials.gov Identifier: NCT00834652).

PPARγ receptor agonists such as thiazolidinediones enhances insulin sensitivity and are used as anti-diabetic drugs (105). Rosiglitazone administration provides antidepressant-like effects in mouse models of depression and T2D (31, 106). Pioglitazone has been evaluated in several clinical trials involving depressed

patients and analysis indicated that the drug was more effective in patients with insulin resistance (107–110). Interestingly, pioglitazone effectiveness was age-dependent, being more efficacious in younger subjects (107).

Recent studies have also shown that immunosuppressive agents can improve outcomes in depression. Etanercept and infliximab neutralize TNFα and are currently being used in the treatment of auto-immune disorders (111). In regard to brain diseases, pilot studies administering TNFα inhibitors via intrathecal and perispinal routes had beneficial effects on cognitive measures in AD patients (112–114). But, when delivery subcuteously, etanercept had no beneficial effects on cognition (115), possibly due to restricted transport across the blood-brain barrier (116). A randomized double-blind placebo-controlled trial using an indwelling catheter to deliver infliximab in depressed patients showed no significant changes in Hamilton-Depression (HAM-D) score when compared with the placebo group. However, in patients with a higher inflammatory state, indicated by serum C-Reactive protein (CRP) concentration higher than 5 mg/L, infliximab improved HAM-D scores compared to placebo (117). Since the treatment decreased circulating CRP levels within the responder vs. the non-responder group, and the limitation of infliximab to reach the brain, the beneficial effect of the drug might have been driven by an overall decrease of peripheral inflammatory markers.

Finally, changes in the gut microbiota are associated with stress disorders (118). Probiotics can modulate the HPA axis (119), neurotransmitters (120), inflammatory markers and, as previously mentioned, insulin signaling in the brain (81). Probiotics are emerging as promising treatments for depression, showing positive results in different clinical studies [for a systematic review see (121)].

CONCLUSION

The association between depression and diabetes is supported by several evidences, but the mechanistic links between both diseases are still emerging. The development of brain insulin resistance is a possible candidate connecting both diseases, but further studies focusing on this issue are warranted in the field. Unraveling this connection is a matter of a great value in order to pursue alternative treatments or to optimize anti-depressants response.

AUTHOR CONTRIBUTIONS

NL: development of the subject matter, drafting of the article, conception, and design of the figure, critical revision of the article, final approval of the version to be published; ML: development of the subject matter, drafting of the article, critical revision of the article, final approval of the version to be published; CS and DM: critical revision of the article, final approval of the version to be published; RM and FD: development of the subject matter, drafting of the article, critical revision of the article, final approval of the version to be published.

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Elevated Familial Cardiovascular Burden Among Adolescents With Familial Bipolar Disorder

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Background: Bipolar disorder (BD) is one of the most heritable medical conditions, and certain phenotypic characteristics are especially familial in BD. BD is also strongly associated with elevated and premature cardiovascular disease (CVD) morbidity and mortality. Thus, far, little is known regarding the familiality of cardiovascular risk in BD. We therefore examined the extent of CVD-related conditions among relatives of: adolescents with BD with a family history of BD (familial BD), adolescents with BD without a family history of BD (non-familial BD) and healthy controls (HC).

Materials and Methods: The sample included 372 adolescents; 75 with familial BD, 96 with non-familial BD, and 201 HC. Parents of the adolescents completed the CARDIA Family Medical History interview regarding the adolescents' first- and second- degree adult relatives. We computed a "cardiovascular risk score" (CRS) for each relative, based on the sum of the presence of diabetes, hypertension, obesity, dyslipidemia, stroke, angina, and myocardial infarction (range 0–7). Primary analyses examined for group differences in mean overall CRS scores among first and second- degree relatives combined, controlling for age, sex, and race. Secondary analyses examined first- and second-degree relatives separately, controlling for age, sex, and race.

Results: There were significant between-group differences in CRS in first- and second- degree relatives combined, following the hypothesized ordering: CRS was highest among adolescents with familial BD (1.14 ± 0.78), intermediate among adolescents with non-familial BD (0.92 ± 0.79) and lowest in HC (0.76 ± 0.79; $F = 6.23$, $df = 2$, $p = 0.002$, $\eta_p^2 = 0.03$). There was a significant pairwise difference between adolescents with familial BD and HC ($p = 0.002$, Cohen's $d = 0.49$). A similar pattern of between-group differences was identified when first-degree and second-degree relatives were examined separately.

Limitations: familial cardiovascular burden was determined based on parent interview, not evaluated directly.

Conclusions: Adolescents with BD with a family history of BD have elevated rates of CVD-related conditions among their relatives. This may be related to genetic overlap between BD and CVD-related conditions, shared environmental factors that contribute to both BD and CVD-related conditions, or a combination of these factors. More research is warranted to better understand the interaction between familial risk for BD and CVD, and to address this risk using family-wide preventive approaches.

Keywords: bipolar, metabolic, family history, cardiovascular, adolescents

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INTRODUCTION

Bipolar Disorder (BD) is a chronic mood disorder with a strong genetic contribution (1). Studies have estimated that heritability of BD is 0.8, although the exact pattern of heritability and implicated genes are not yet elucidated (2). In addition to an 8–20 fold increase in risk of developing BD, relatives of those with BD are at higher risk for other psychiatric conditions such as depressive disorders, anxiety disorders, attention deficit hyperactivity disorder (ADHD), and substance use disorders (3, 4). Studies have also reported neurocognitive differences between unaffected relatives of BD probands and controls, potentially related in part to obesity in the unaffected relatives (5–7). Furthermore, in those with BD with a family history of BD (familial BD), several characteristics, and markers of severity such as substance use disorders, psychosis, suicidality, and level of social functioning may be shared by BD probands from the same family, suggesting that certain phenotypes may congregate in familial BD (8).

There is a known link between BD and cardiovascular disease (CVD) risk, with excessive and premature morbidity and mortality replicated in samples from various countries (9–15). CVD and its complications are the leading cause of mortality in BD, and the most common medical conditions in BD (16, 17). In comparison to healthy controls (HC) individuals with BD have an adjusted CVD mortality rate ratio of 1.5–2.5 and CVD mortality 10 years earlier than in the general population (16, 18). In addition, the age of onset of new CVD was found to be up to 17 years premature in BD (19). Metabolic syndrome and its components of obesity, hypertension, high cholesterol levels and type II diabetes are also elevated in those with BD (20–22). This association between CVD and BD is in excess of what can be explained by psychotropic medication, lifestyle behaviors and even traditional CVD risk factors (11, 19, 23–25).

There is a paucity of studies on the topic of cardiovascular burden in unaffected relatives of BD probands. One study found lower plasma high-density lipoprotein (HDL) cholesterol and increased omega-6 fatty acids in adult unaffected first-degree relatives of adults with BD in comparison to controls (26). A second study found increased prevalence of cardiovascular-related conditions (diabetes, hypertension, hyperlipidemia, and coronary artery disease) with a risk rate ratio of 4.8 in affected and unaffected adult first-degree relatives of probands with schizophrenia, schizoaffective disorder, bipolar subtype, and BD with psychotic symptoms in comparison to controls (27). Adult offspring of BD subjects were included. There was no effect of the specific psychiatric diagnosis of the proband on cardiovascular risk in the relative (27). A third study examining first-, second- and third-degree relatives of subjects with BD within a large extended family did not find differences in the rate of metabolic syndrome or obesity rates in BD relatives vs. HC, but found higher total cholesterol, LDL and triglycerides, lower HDL, and abnormal glucose in BD relatives (28). An analysis of children and adolescents with a second- or third-degree family history of BD (mean age 11.6 years old) in contrast to HC (mean age 7.8 years old), controlling for age, found higher rates of elevated LDL in the BD relatives than in HC, although there were higher rates of elevated triglycerides and low HDL in the HC group (28).

Importantly, there is a strong familial aggregation of metabolic syndrome and its components in non-psychiatric samples (29–31). A large study in psychiatrically healthy young adults found anomalous blood pressure (BP), cholesterol and glucose profiles in those with parental history of CVD-related conditions including myocardial infarction, stroke, diabetes, hypertension and obesity (32). In the only study on the topic, a family history of type II diabetes was associated with metabolic abnormalities such as insulin resistance, fasting blood glucose, higher body mass index (BMI), and waist circumference in adult women with BD, and the impact of a family history of type II diabetes was greater in those with BD than in controls (33).

Given the paucity of research on this important topic, particularly in relation to early-onset BD, we compared the cardiovascular burden among adolescents, and hypothesized that cardiovascular burden would be highest among adolescents with familial BD, followed by adolescents with non-familial BD, followed by HC adolescents.

MATERIALS AND METHODS

This study included 372 adolescent participants (171 BD, 201 HC) between the ages of 13–20 years old. Adolescents with BD-I, -II, or -Not Otherwise Specified (NOS) were recruited from a tertiary subspecialty clinic in an academic health sciences center in Toronto, Canada, and HC were recruited from the community via advertisements in the Greater Toronto Area. All participants were English-speaking. HC had no lifetime history of mood or psychotic disorders, or substance use disorders within the preceding 3 months. In addition, HC did not have a first- or second-degree family history of BD or psychotic disorders. HC were also excluded if they had a history of cardiac, autoimmune or inflammatory illness, neurological or cognitive impairment or were treated with anti-inflammatory, anti-platelet, anti-lipidemic, anti-hypertensive, or hypoglycemic agents including insulin and metformin.

Adolescent psychiatric diagnoses were made using the Schedule for Affective Disorders and Schizophrenia for School Age Children, Present, and Life Version (K-SADS-PL) (34), a semi-structured interview completed with adolescents and parents to ascertain current and lifetime history of psychiatric disorders. The KSADS Depression Rating Scale (DRS) (35) and the KSADS Mania Rating Scale (MRS) (36) were used in place of the mood section in the K-SADS-PL. Diagnoses were confirmed by a child-adolescent psychiatrist. BD-NOS was defined using criteria previously operationalized by the Course and Outcome of Bipolar Illness in Youth (COBY) study group (37): Elevated and/or irritable mood, plus (1) two *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. (DSM-IV) (38) manic symptoms (3 if only irritable mood is reported), (2) change in functioning, (3) mood, and symptom duration of at least 4 h during a 24 h period, and (4) at least four cumulative 24 h periods of episodes over the participants' lifetime that meet the mood, symptom severity, and functional change criteria. Overall, the

participants' general level of functioning was evaluated using the Children's Global Assessment Scale (CGAS) (39), which was administered as an interview. Socio-economic Status (SES) was evaluated using the Hollingshead Four Factor Index (40).

Family psychiatric history in all first- and second-degree relatives was evaluated using the Family History Screen interview (41). The Coronary Artery Risk Development in Young Adults Study (CARDIA) Family Medical History was completed as an interview with adolescents and their parents, regarding adolescents' first- and second-degree adult relatives (42). Adolescents and a parent were interviewed and provided information on second-degree relatives of the adolescent, including aunts, uncles and grand-parents. These second-degree relatives were not directly interviewed, nor were their medical records accessed. The current study focused on family history of diabetes, hypertension, obesity, dyslipidemia, stroke, angina, and myocardial infarction. A "Cardiovascular Risk Score" (CRS) was computed for each relative based on the sum of the number of these conditions present (score of 0–7). Given the young age of participants' siblings, first-degree relatives included only parents. Familial mean CRS scores were calculated for parents and for combined first- and second-degree relatives.

All participants, as well as one parent or guardian, provided written informed consent prior to study participation. The study was approved by the local research ethics board.

Anthropomorphic Variables

Measures of height and weight were available for 339 adolescents, and systolic blood pressure (SBP) and diastolic blood pressure (DBP) were available for 344 adolescents. Body mass index (BMI) was computed by dividing weight in kilograms (kg) by height in meter squared (m^2) as previously described (43). Percentiles were determined using the BMI-for-age percentile based on Centers for Disease Control (CDC) growth charts, applicable for youth under the age of 20 (44).

Statistical Analysis

Analyses were performed using SPSS, version 24 (IBM Corp., Armonk, N.Y., USA). Participants were divided into three groups: BD adolescents with family history of BD (familial BD), BD adolescents without family history of BD (non-familial BD), and HC adolescents. Group differences were evaluated using one-way ANOVA for dimensional measures and chi-square tests for dichotomous measures. To test our primary hypothesis, a one-way ANCOVA (controlling for age, sex, and race) was used to compare CRS across the three groups. Omnibus tests comparing CRS across the groups were followed by *post-hoc* pairwise comparisons of CRS.

RESULTS

Demographic and Clinical Characteristics

Table 1 presents demographic and clinical variables for all study participants; descriptive statistics are presented for BD participants in **Table 2**. The sample included 372 adolescents: 75 with familial BD, 96 with non-familial BD, and 201 HC. 372 parents were interviewed (one for each adolescent participant) and provided information regarding their own medical history along with that of co-parents and second-degree relatives. In total, information regarding medical history was obtained regarding 2,797 second degree relatives, among which 561 were relatives of adolescents with familial BD, 691 were relatives of adolescents with non-familial BD, and 1,545 were relatives of healthy adolescents. There were significant differences between the adolescent groups in terms of age, sex, and race. A total of 19.9% of the HC group had at least one lifetime psychiatric diagnosis, including anxiety disorders (8.5%), ADHD (11.1%), obsessive compulsive disorder (OCD; 1%), and oppositional defiant disorder (ODD; 1%). Furthermore, 1% of HC had a lifetime history of antidepressant use, and 4% had a lifetime history of stimulant use.

Anthropomorphic variables are presented in **Table 3**. There were significant between-group differences in BMI percentile ($F = 4.40$, $p = 0.01$, $\eta^2_p = 0.03$). When controlling for age, sex and race, average systolic, and average diastolic BP were also significantly higher in the BD groups in comparison to HC (respectively $F = 4.85$, $p = 0.008$, $\eta^2_p = 0.03$; $F = 6.86$, $p < 0.001$, $\eta^2_p = 0.04$).

Cardiovascular Risk Score (CRS)

Overall familial CRS (i.e., first and second-degree relatives combined) differed significantly across groups in the hypothesized direction: highest among familial BD (1.14 ± 0.78), intermediate among non-familial BD (0.92 ± 0.79), and lowest among HC (0.76 ± 0.79) (see **Table 2**) ($F = 6.23$, $p = 0.002$, $\eta^2_p = 0.03$). Planned pair-wise comparisons indicated a significant difference between the familial BD and HC groups ($p = 0.002$, Cohen's $d = 0.49$), and non-significant differences between the familial BD and non-familial BD relatives ($p = 0.19$; Cohen's $d = 0.28$) as well as between the non-familial BD and HC relatives ($p = 0.34$; Cohen's $d = 0.20$).

CRS among only first-degree relatives (i.e., parents) followed the same pattern: highest among familial BD (0.65 ± 0.60), intermediate among non-familial BD (0.48 ± 0.60), and lowest among HC (0.32 ± 0.61) (see **Table 2**) ($F = 8.63$, $p < 0.001$, $\eta^2_p = 0.05$). Planned pair-wise comparisons indicated a significant difference between familial BD and HC ($p < 0.001$; Cohen's $d = 0.56$) but not between familial BD and non-familial BD ($p = 0.11$; Cohen's $d = 0.30$) or between non-familial BD and HC ($p = 0.15$; Cohen's $d = 0.26$).

Finally, CRS among only second-degree relatives also followed the same pattern: highest among familial BD (0.67 ± 0.47), intermediate among non-familial BD (0.57 ± 0.47), and lowest among HC (0.49 ± 0.48) (see Table 2) ($F = 3.96$, $p = 0.02$, $\eta^2_p = 0.02$). Planned pair-wise comparisons indicated a significant difference between familial BD and HC ($p = 0.02$, Cohen's $d = 0.38$) but not between familial BD and non-familial BD ($p = 0.45$, Cohen's $d = 0.21$) or between non-familial BD and HC ($p = 0.58$, Cohen's $d = 0.17$).

DISCUSSION

This study found that cardiovascular risk, based on a score defined by the combination of diabetes, hypertension, obesity,

TABLE 1 | Demographic and clinical variables among 372 adolescents.

	Participants			Statistics		
	Familial BD ($n = 75$)	**Non-familial BD ($n = 96$)**	**HC ($n = 201$)**	***F*/ χ^2**	**Cramer's V/ ηp^2**	***P*-value**
Age, years (±SD)	16.5 ± 1.46	16.8 ± 1.50	16 ± 1.82	7.68	0.04	<0.001
Females (%)	48 (64%)	66 (68.8%)	104 (51.7%)	8.88	0.15	0.012
Race (%Caucasian)	63 (84%)	75 (78.1%)	112 (55.7%)	26.82	0.27	<0.001
SES (±SD)	49.19 ± 12.08	48.95 ± 14.18	52.36 ± 11.13	3.41	0.02	0.034

BD, Bipolar Disorder; HC, Healthy Controls; SES, Socio-economic Status; SD, Standard Deviation.

TABLE 2 | Clinical characteristics among 171 adolescents with bipolar disorder.

Age at onset (±SD)	14.66 ± 2.73
BD subtype (%)	
BD-I	45 (26.3%)
BD-II	65 (38%)
BD-NOS	61 (35.7%)
Lifetime comorbidity (%)	
Substance use disorder	59 (35.5%)
ADHD	79 (47.6%)
Anxiety disorder	132 (79.5%)
OCD	29 (17.5%)
ODD	54 (32.5%)
Lifetime medication use (%)	
SGA	92 (55.4%)
Lithium	28 (16.9%)
Antimanic/Anticonvulsant	13 (7.8%)
Antidepressant (SSRI)	62 (37.3%)
Stimulants	37 (22.3%)
Clinical scores (±SD)	
Mania score-current	18.43 ± 12.44
Mania score-lifetime most severe	29.60 ± 9.05
Depression score-current	19.86 ± 12.84
Depression score-lifetime most severe	31.59 ± 10.21
CGAS—Current episode	52.99 ± 10.57
CGAS—Highest past	60.21 ± 11.58
CGAS—Lowest past	42.29 ± 8.73

ADHD, Attention Deficit/Hyperactivity Disorder; BD, Bipolar Disorder; CGAS, Children's Global Assessment Scale; OCD, Obsessive Compulsive Disorder; ODD, Oppositional Defiant Disorder; SD, Standard Deviation; SGA, Second Generation Antipsychotics; SSRI, Selective Serotonin Reuptake Inhibitor.

dyslipidemia, stroke, angina, and myocardial infarction, was highest in relatives of adolescents with familial BD, followed by relatives of adolescents with non-familial BD, followed by relatives of HC adolescents. Whereas, familial CRS differed significantly between adolescents with familial BD and HC, familial CRS among adolescents with non-BD did not differ significantly from the other groups. A similar pattern, including the ordering effect and between-group effect sizes, was found for combined first- and second-degree relatives, and for first- and second- degree relatives examined separately.

In addition to the known link between BD and cardiovascular risk, the limited number of prior studies on the topic of cardiovascular burden in adult BD relatives also found elevated rates of dyslipidemia and insulin resistance, including those unaffected by BD, in comparison to HC relatives (20, 26–28). The current study extends prior findings by showing that relatives of adolescents with BD have particularly elevated cardiovascular risk in the context of a family loading of BD, which has not been previously described. Relatives of adolescents with non-familial BD were intermediate between the other groups. This ordering effect could reflect differential loading of genetic and/or environmental risk for CVD-related conditions. Our findings could be due to familial BD being a more severe phenotype, shared genetic factors or biological processes such as inflammation, familial psychiatric burden, or environmental influences such as patterns of exercise and substance use (45–48). However, the current study was not designed to evaluate these hypotheses.

Family history of BD or other mood disorders has been associated with an earlier age of onset of BD, higher rates of psychiatric comorbidities and an overall more severe course of illness among people with BD (8, 45, 49, 50). More severe course of BD, in turn, is associated with increased risk of CVD and CVD mortality (19, 51–53). Relatedly, prior cross-sectional studies found that CVD risk factors, including metabolic syndrome and its components, are associated with increased functional impairment, suicide attempts and symptom severity in BD (54–56). Taking together prior findings and current findings, it appears that there is an interweaving of psychiatric and cardiovascular burden in BD, and that this interweaving is familial.

Prior studies provide context for the potential genetic contributions to current findings. Independently, BD and metabolic syndrome are each known to have a strong familial aggregation, yet little is known about their interaction (1, 29–31). A study found that susceptibility gene TCF7L2 conferred an increased risk of BD in the presence of elevated BMI, suggesting an interaction between an interaction between obesity and BD risk (57). Furthermore, genetic variants thought to be implicated in BD such as BDNF, MTHFR, GNAS, and CACNA1C/D, have been hypothesized to overlap between BD and CVD, conferring risk of mood disorders in addition to risk of hypertension, type 2 diabetes, obesity, and dyslipidemia (46, 58). Dysregulation of the inflammatory system with increased pro-inflammatory markers such as cytokines, especially during acute mood episodes has been well-described in BD, and may comprise a familial trait in BD pedigrees (59–63).

TABLE 3 | Anthropomorphic variables among adolescents.

	Participants			Statistics		
	Familial BD	**Non-familial BD**	**HC**	F/χ^2	Cramer's V/ ηp^2	***P*-value**
BMI percentile ($n = 336$)	62.67 ± 27.67 ($n = 65$)	66.07 ± 26.08 ($n = 77$)	56.01 ± 26.88 (n=194)	4.4	0.03	0.013
Systolic blood pressure ($n = 344$)	115.70 ± 19.07 ($n = 67$)	114.72 ± 16.44 ($n = 79$)	110.04 ± 13.63 ($n = 198$)	4.85	0.03	0.008
Diastolic blood pressure ($n = 344$)	72.75 ± 9.40 ($n = 67$)	70.87 ± 11.01 ($n = 79$)	67.5 ± 7.68 ($n = 198$)	6.86	0.04	0.001

BD, Bipolar Disorder; HC, Healthy Controls; SES, Socio-economic Status; SD, Standard Deviation.

It is well-recognized that immune dysfunction and chronic inflammation are associated with CVD and related risk factors (64–66). It has been proposed that a genetic predisposition to inflammation could be linked to both BD and CVD-related conditions (67).

Similar to putative genetic contributions, prior studies also provide context for the potential environmental contributions to current findings. For example, obesity and metabolic syndrome have been associated with pregnancy complications such as gestational hypertension or preeclampsia, as well as future risk of obesity and heart disease in the offspring (68, 69). Maternal cardiovascular risk factors during pregnancy have been linked with an increased risk of ADHD, autism spectrum disorder, eating disorders, and psychosis in offspring (70, 71). Although studies have yet to link maternal gestational cardiovascular risk factors with risk of BD in offspring, it is known that these risk factors are increased among pregnant women with BD, which one can speculate is also relevant to the transmission of BD to the offspring, and to the cross-risk of CVD-related conditions and BD (72).

Another environmental factor that may underlie our findings is lifestyle. For example, an individual's physical activity is associated with physical activity among relatives (73, 74) and some studies have found that adults with BD tend to be less physically active than the general population (75–79). Similarly, there is also evidence that adolescents with BD are less likely to engage in moderate-vigorous physical activity than controls (80). Sedentary lifestyle has been associated in the general population with metabolic syndrome and CVD morbidity and mortality (47, 81). While there are genetic factors that contribute to physical activity, reduced physical activity in relatives also comprises an environmental factor that influences behavior (82, 83). Similar considerations apply to other CVD risk factors such as cigarette smoking (84–87). Furthermore, adverse childhood experiences such as poverty, family conflicts, maltreatment, neglect, or peer victimization have been linked with both cardiovascular burden and psychopathology, and this association is thought to be mediated by both psychological and neurobiological factors (11, 88, 89) Indeed, there is a hypothesized synergistic interaction between genetic predisposition, epigenetic factors such as DNA methylation in the presence of early adversity, health behaviors and subsequent risk for mood disorders and CVD (88, 90–92).

LIMITATIONS

Several limitations may have impacted our findings. First, the data collected from adolescents and their parents is indirect and based on their knowledge of family history. The absence of direct assessment of the relatives' cardiovascular health or access of their medical records is a major limitation of this study. Future studies would benefit from directly examining medical records and directly evaluating for psychiatric disorders and directly measuring cardiovascular risk factors. Given known disparities in the recognition and treatment of CVD-related conditions among people with BD and other severe psychiatric conditions, our findings may be biased toward lower CRS scores. Second, although we have controlled for key demographic variables, the study methods and sample size do not allow us to address questions regarding the effect of BD independent of variables such as psychiatric comorbidities and lifestyle. Nonetheless, prior epidemiologic studies in predominantly untreated samples have verified that the BD-CVD link is independent of these important considerations (19, 25). Finally, the CRS was computed as a sum score of conditions that are inter-related, and includes cardiovascular risk factors (e.g., hypertension) alongside fully manifest vascular disorder (e.g., myocardial infarction). Larger samples would enable alternative proxies for cardiovascular burden, and would allow for evaluation of fully manifest vascular disorder while controlling for cardiovascular risk factors (as has been done in studies evaluating cardiovascular risk among those with BD). Counter-balancing these limitations is the importance of gaining insights regarding the BD-CVD link; to this end, the current study is the first on the topic that is focused on adolescents, and the first study in any age group to evaluate the link between familiality of BD and familiality of cardiovascular risk.

FUTURE DIRECTIONS

In addition to the aforementioned future directions within the limitations section, studies are warranted that examine for correlation between probands and their relatives regarding cardiovascular burden, and that evaluate whether these correlations differ across groups (i.e., familial BD, non-familial BD, HC). Because of the very large samples required to evaluate low-frequency "hard" endpoints, such as myocardial

infarction and stroke, administrative database studies based on large population samples would provide complementary information to that available in clinical cohort studies. As with any observational study, prospective design would offer advantages with regard to causal inferences and mechanisms. Studies that include genetic markers and biomarkers beyond glucose and lipids (e.g., inflammatory markers, neurotrophic factors, oxidative stress markers) would enable further evaluation of potential bridges linking BD and CVD-related conditions. Finally, it will be important to move toward modifying assessment and treatment approaches that are informed by the BD-CVD link. For example, treatment approaches for those with BD may benefit from the assessment of medical and psychiatric family history and identification of those at higher risk. In addition, future studies evaluating behavioral and pharmacological approaches to prevention and treatment of CVD-related conditions in BD could benefit from incorporating familial considerations.

CONCLUSIONS

In conclusion, we found that adolescents with BD with a family history of BD have elevated rates of CVD-related conditions among their relatives. This may be related to genetic overlap between BD and CVD-related conditions, shared environmental factors that contribute to both BD and CVD-related conditions, or a combination of these factors. More research is warranted to better understand the interaction between familial risk for BD and CVD. The possible interaction between BD familial loading and CVD loading opens the opportunity to integrate familial medical and psychiatric history during assessment, and opens the opportunity to use this information to inform prevention and treatment strategies. Involvement of family members may be beneficial due to the shared environmental factors and familial nature of BD and cardiovascular risk.

ETHICS STATEMENT

Sunnybrook Health Sciences Center Research Ethics Board Written consent.

AUTHOR CONTRIBUTIONS

LF and ST performed the analyses. ST primarily wrote the manuscript. All authors participated in iterative revisions of the manuscript and participated in the conception and design of the analysis.

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frontiers in Psychiatry

BRIEF RESEARCH REPORT
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Feasibility, Adherence and Efficacy of Liraglutide Treatment in a Sample of Individuals With Mood Disorders and Obesity

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Background: Liraglutide is a once-daily injectable medication approved for the treatment of obesity. Hereby we report the feasibility, adherence and efficacy of liraglutide treatment in a sample of individuals with mood disorders and obesity.

Methods and Sample: Twenty-nine patients with Bipolar or Major Depressive Disorder received liraglutide once daily subcutaneously at a dose gradually titrated from 0.6 to 3 mg. All patients were obese and had previously failed multiple healthy lifestyle interventions, including exercise and diet programs. Patients' weight was recorded before liraglutide treatment (T0) and then 1 (T1), 3 (T3), and 6 months (T6) following T0.

Results: Mean baseline (T0) weight was 110.54 Kg (±24.95). Compared to baseline, the percentage of weight loss was 3.37% at T1, 7.85% at T3, and 10.20% at T6. Thirty-one percent ($n = 9$) of patients had no side effects, 34.48% ($n = 10$) had one, 24.14% ($n = 7$) had two, and 10.34% ($n = 3$) had three side effects. All 29 subjects were still on liraglutide at T1; 79.31 and 48.28% were on liraglutide at T3 and T6. No significant relationship was found between liraglutide dose and likelihood to continue the medication. No patient showed a worsening of the psychiatric condition due to liraglutide treatment. Acceptability and satisfaction with treatment were good for the 48% that completed the study.

Conclusions: Liraglutide treatment was efficacious, accepted and tolerated by ∼50% of our sample, followed up for a period of 180 days. Larger, longer, controlled, prospective studies are warranted.

Keywords: liraglutide, mood, obesity, bipolar, depression, depressive disorder

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INTRODUCTION

Several studies have pointed to a link between cardiovascular diseases, obesity or metabolic syndrome among patients suffering from severe psychiatric disorders (1).

For instance, patients suffering from depression, bipolar disorder and schizophrenia have 53% higher chance of cardiovascular disease, comparing to persons without psychiatric disorders, and

their life expectancy is decreased by at least one or two decades (2). In addition, Weiner and associates found that the risk of cardiovascular mortality is twice as larger among persons with diagnosed bipolar disorder compared to general population (3).

The high prevalence of obesity, metabolic syndrome and cardiovascular disease among patients diagnosed with major psychiatric disorders may be a result of genetic factors, inadequate lifestyles, such as poor dietary habits, lack of physical activity and tobacco smoking, adverse effects of psychotropic drugs, and environmental factor (4). Patients with psychiatric diseases may also have poorer access to care, which may affect the prevalence and severity of physical illnesses (5).

Liraglutide is an agonist of the acylated human Glucagon-Like-Peptide-1 (GLP-1) receptor with 97% of sequence homology with naturally produced GLP-1. This medication is the first once-daily injectable derivative of the human incretin glucagon-like peptide-1 recently approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) for the treatment of obesity (adults with a BMI $\geq$ 30 kg/m^2), as well for adults with a BMI of 27 kg/m^2 or greater who also have one or more complications related to their weight, such as type 2 diabetes, high blood pressure, high cholesterol or obstructive sleep apnea (6, 7). Liraglutide reduces body weight as well fatty mass through mechanisms that decrease the need for food and energy intake. This agent also improves glycemic control by reducing sugar levels in patients with type 2 diabetes mellitus (8). Liraglutide stimulates the secretion of insulin and reduces the excessive elimination of glucagon, based on glucose concentration. When glucose level is high, insulin release is stimulated and glucagon release inhibited. Conversely, during hypoglycemia, liraglutide decreases the release of insulin, without affecting glucagon release.

We recently reported on the development, acceptability and efficacy of a standardized healthy lifestyle intervention in recurrent unipolar and bipolar depression (9). Our lifestyle intervention includes modules dealing with energy balance, physical exercise, nutritional education and other strategies to lose weight with physical exercise and to not relapse into bad eating habits and sedentary life. Among other findings, we observed a significant reduction in BMI in patients who received the intervention, compared to controls. However, while conducting the trial above, and during our daily practice, we observed that–for a considerable number of patients- a lifestyle behavioral intervention may not be sufficient to achieve the necessary improvement in metabolic parameters. To this end, we decided to test the feasibility, adherence, weight effects and tolerability of liraglutide treatment, administered for a period of 6 months in a sample of patients with mood disorders.

MATERIALS AND METHODS

This was a retrospective study involving individuals with bipolar or major depressive disorder who received liraglutide. All study participants had previously failed multiple standardized healthy lifestyle interventions, including physical exercise and diet programs. Patients weight and BMI were registered at four different time-points: baseline, i.e., when liraglutide was started (T0), and then after 1 (T1), 3 (T2), and 6 months (T3).

Data were analyzed using STATA15 (Stat Corp., College Station, Texas, USA). Descriptive statistics, Wilcoxon signed-rank test and Fisher exact test were performed. The statistical significance was set at level of 5% ($p < 0.05$). All study data was collected retrospectively and no exam was specifically conducted for the purposes of this study. For the reasons previously mentioned, the study was exempt from informed consent. The retrospective study was approved by the Regione Toscana–Area Vasta Sud Est Ethical Committee Board.

RESULTS

Sample Characteristics

The sample included 29 patients diagnosed with mood disorders and treated at University of Siena Medical Center, Italy. There were almost four times more female patients (F = 80% of the sample). Mean age was 53.48 $\pm$ 12.75 years and half of participants (51.72) were employed. Twenty-one percent were smokers. The vast majority was physically inactive and all participants were obese. Four patients were in treatment with second generation antipsychotics: 2 with risperidone, 1 with olanzapine and 1 with aripiprazole. Hyperlipidemia and systolic hypertension were the most frequent physical comorbidities (**Table 1**).

Weight and BMI

At T1 (i.e., 1 month after liraglutide was started), a significant weight loss was observed ($p < 0.001$) and the mean weight decreased from 110.54 ($\pm$24.95) kg at baseline (T0) to 106.81

TABLE 1 | Sample characteristics.

Patients' sociodemographic characteristics		Frequency (%)
Total number of participants		29
Gender	Female	23 (79.31)
	Male	6 (20.69)
Marital Status	Single	11 (37.93)
	Married	18 (62.07)
Educational Background	Primary/Middle School	8 (27.59)
	High School Diploma	13 (44.83)
	Bachelor	8 (27.59)
PATIENTS' LIFESTYLE		
Smoking tobacco		6 (20.69)
Physical activity		5 (17.24)
Diet	Between meals	23 (79.31)
	At meal time	6 (20.69)
PATIENTS' BMI		
Obesity Class I (BMI 30–34, 9 kg/m^2)		4 (13,79)
Obesity Class II (BMI 35–39, 9 kg/m^2)		25 (86,21)
PATIENTS' COMORBIDITIES		
Type 2 diabetes		6 (20.69)
Impaired glucose tolerance		7 (24.14)
Hyperlipidemia		16 (55.17)
Hypertension		13 (44.83)

(±24.43) kg at T1 (**Table 2**). On average, patients lost 3.37% of their baseline weight. Only two patients did not lose weight in the first 1 month of treatment, and they both decided to discontinue liraglutide. At the 3-month time point (T3), the weight loss compared to baseline (T0) remained significantly lower ($p = 0.0001$). Mean weight at T3 was (101.84 ± 17.92 kg) (**Table 2**). On average, subjects lost 7.85% of their baseline weight. Six patients discontinued liraglutide because of the following reasons: pancreatic enzymes (lipase and amylase) increase ($n = 1$), bariatric surgery ($n = 1$), no declared reason ($n = 1$), treatment ineffectiveness ($n = 2$); lost to follow up ($n = 1$).

At the 6 months' time-point (T6) a significant weight loss compared to baseline (T0) ($p = 0.0010$) was recorded as well. Mean weight at T6 was 99.26 (±20.53) (**Table 2**). On average, patients lost 10.2% of their baseline weight. However, only 14 patients, out of the original 29, were still taking liraglutide. The reasons for discontinuation among 15 study participants who did not complete 90 day of treatment were primarily due to treatment ineffectiveness and/or undesirable side effects related with liraglutide use.

Tolerability

The following undesirable side effects were recorded: amylase and lipase increase, nausea, vomiting, diarrhea, and constipation. Nine of the 29 patients (31%) reported no side effects, ten (34%) reported one side effect, seven (24.14%) reported two side effects, and 3 (10%) reported three side effects.

No significant relationship was observed between liraglutide dose and number or severity of side effects. Similarly, no relationship between physical comorbidities and side effects was noted.

DISCUSSION

To our knowledge, only few studies have evaluated the feasibility and safety of liraglutide treatment in patients with mood disorders. For instance, Mansour and colleagues evaluated the ability of liraglutide to improve cognitive function in 19 subjects with mood disorders and found that liraglutide was well-tolerated and had beneficial effects on cognitive function. The study was a 4-week pilot, open-label trial, and 17 of the 19 participating subjects completed the trial (10). In patients with schizophrenia spectrum, Larsen et al. (11) conducted a double-blind trial involving 103 overweight/obese individuals who were prediabetic. Study subjects were randomized to a 16-week treatment with either liraglutide or placebo, while receiving clozapine or olanzapine. Fifty-two individuals received liraglutide. Five of these patients did not complete the 16-week treatment, because of thyrotoxicosis ($n = 1$), worsening of psychiatric disorder ($n = 2$), discontinuation or dose reduction of olanzapine or clozapine ($n = 2$), death ($n = 1$). The Authors showed that liraglutide treatment administered for 16 weeks significantly reduced glucometabolic disturbances and body weight in overweight or obese and pre-diabetic patients with schizophrenia-spectrum disorders, receiving clozapine or olanzapine. Patients were then followed for 1 year after discontinuing liraglutide. Although body weight reduction was partially sustained, the improvements in other metabolic variables returned to the levels that had been recorded before starting the 16-week treatment with liraglutide (12). In our study, liraglutide was continued for at least 6 months and proved efficacious in about 50% of the study sample (14 out of 29) whereas the remaining 50% discontinued the medication before completing a 6 months treatment period, primarily because of inefficacy or side effects. Among the latter, nine participants asked to discontinue the medication (5 due to inefficacy; 4 due side effects), five dropped out without presenting at the following appointments, and one discontinued the treatment in agreement with the treating physician (because of bariatric surgery). The rate of persistence with liraglutide treatment was lower than the rate observed in liraglutide trials involving subjects that were not selected based on their psychiatric diagnosis (13, 14), this suggesting the possibility that patients with mood disorders may be less likely to adhere to liraglutide treatment, possibly because of their mental disorder. This rate was also lower than the trials in patients with mental illness mentioned above, which however were conducted in different settings and for different periods. Nonetheless, we find it interesting that ∼50% of our sample was able to tolerate, continue and respond to liraglutide for a 6-month period. Neuropsychiatric safety of treatment with liraglutide was evaluated pooling data from the liraglutide weight-management programme, with no between-treatment imbalances being noted for depression or suicidal ideation/behavior (15). Consistently with this study, no neuropsychiatric side-effects nor any liraglutide related worsening of the pre-existing mental condition were noted in our study. However, our research has several limitations that should be acknowledged, including: (1) the small sample size, which clearly does not permit to consider our sample as representative of all patients with mood disorders; (2) the retrospective and non-randomized design; (3) the absence of a placebo-control group; (4) the relatively short duration (6 months) of the observation period. Larger, longer, controlled, prospective trials including measures of metabolic parameters, quality of life, daily functioning and course of the psychiatric disease are warranted.

TABLE 2 | Weight, weight loss (%), BMI and BMI loss (%) of patients at T0, T1, T3, and T6.

	N	Average weight ± SD (kg)	%	*p*
Baseline	29	110.54 (±24.95)	–	–
1 month (T1)	29	106.81 (±24.43)	−3.37	$p < 0.01$
3 months (T3)	23	101.84 (±17.92)	−7.85	$p < 0.01$
6 months (T6)	14	99.26 (±20.53)	−10.20	$p < 0.01$
	N	**Average BMI ± SD (kg/m^2)**	**%**	
Baseline	29	41.28 (±7.63)	–	–
1 month (T1)	29	39.90 (±7.22)	−3.34	$p < 0.01$
3 months (T3)	23	40.65 (±11.43)	−1.53	$p < 0.01$
6 months (T6)	14	38.4 (±6.57)	−6.98	$p < 0.01$

N, Number of patients.

AUTHOR CONTRIBUTIONS

AC, SB, and AG: contributed to study design, data collection, data analysis, data interpretation, and manuscript drafting. CC: contributed to study design, data collection, data interpretation, and manuscript drafting. BB, GM, GR, EF, CM, NG, VV, and AF: contributed to study design, data interpretation, and manuscript drafting.

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Neural and Endocrine Correlates of Early Life Abuse in Youth With Depression and Obesity

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Depression and insulin resistance are becoming increasingly prevalent in younger populations. The origin and consequence of insulin resistance in depressed youth may, in part, be rooted in exposure to environmental stressors, such as early life abuse, that may lead to aberrant brain motivational networks mediating maladaptive food-seeking behaviors and insipient insulin resistance. In this paper, we aimed to investigate the impact of early life abuse on the development of insulin resistance in depressed and overweight youth aged 9 to 17 years. We hypothesized that youth with the greatest burden of early life abuse would have the highest levels of insulin resistance and corresponding aberrant reward network connectivities. To test this hypothesis, we evaluated sixty-nine depressed and overweight youth aged 9 to 17, using multimodal assessments of early life abuse, food-seeking behavior, and insulin resistance. Based on results of the Childhood Trauma Questionnaire (CTQ), we separated our study participants into two groups: 35 youth who reported high levels of the sum of emotional, physical, or sexual abuse and 34 youth who reported insignificant or no levels of any abuse. Results of an oral glucose tolerance test (OGTT) and resting state functional connectivity (RSFC), using the amygdala, insula, and nucleus accumbens (NAcc) as seed-based reward network regions of interest, were analyzed for group differences between high abuse and low abuse groups. High abuse youth exhibited differences from low abuse youth in amygdala-precuneus, NAcc-paracingulate gyrus, and NAcc-prefrontal cortex connectivities, that correlated with levels of abuse experienced. The more different their connectivity from of that of low abuse youth, the higher were their fasting glucose and glucose at OGTT endpoint. Importantly, level of abuse moderated the relation between reward network connectivity and OGTT glucose response. In contrast, low abuse youth showed hyperinsulinemia and more insulin resistance than high abuse youth, and their higher OGTT insulin areas under the curve correlated with more negative insula-precuneus connectivity. Our findings suggest distinct neural and endocrine profiles of youth with depression and obesity based on their histories of early life abuse.

Keywords: pediatric depression, obesity, insulin resistance, early life stress, abuse, resting state functional connectivity, diabetes

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INTRODUCTION

Depression is a common psychiatric disorder that significantly impacts youth worldwide (1, 2). In parallel, rates of obesity among youth are also rising, resulting in the common co-occurrence of these conditions that may lead to an increased risk of cardiovascular disease, type 2 diabetes mellitus, and all-cause mortality (3, 4). Indeed, multiple studies have demonstrated a clear relation between depression and insulin resistance (5), which is the precursor to diabetes when cells fail to respond to the normal actions of insulin (6–8). Specifically, a bidirectional relation between depressive symptoms and diabetes is evident, in which the presence of one increases the incidence and severity of the other (9). In pediatric populations, this bidirectional relation has, in part, been linked to a dysregulated stress system (10).

Stress exposure in early childhood arises in different types of adverse childhood experiences, each with unique consequences on brain and biological development (11). Indeed, recent studies distinguish the effects of inadequate input (such as neglect and deprivation) from the effects of harmful input (such as abuse and trauma) on brain structure and function, as well as on psychopathology, cortisol metabolism, and epigenetic changes (12–14). Among these various maltreatment inputs, childhood abuse has been shown to worsen depression course (15), and emotional abuse in particular has been shown to best predict psychiatric symptomatology in children compared to other maltreatment types (16). Importantly, childhood abuse can increase the risk of developing insulin resistance in adulthood (17, 18). Contributing to this literature, we here focus principally on exposure to childhood abuse and its specific neural and endocrine correlates.

Independent studies in pediatric populations affected by depression, insulin resistance, and childhood abuse converge on impairment in a common reward network. This mesolimbic reward circuit consists primarily of the prefrontal cortex (PFC), nucleus accumbens (NAcc), ventral tegmental area (VTA), amygdala, and hippocampus (19). In depression, a dysregulated reward network can lead to reward hyposensitivity and contribute to the motivational deficits of anhedonia (20). With regards to insulin resistance, multiple insulin receptors are found in key reward centers of the brain (21, 22), exerting their central actions through aiding the release of dopamine (23–25) and the inhibition of GABA (26). Youth with insulin resistance show dysfunction in limbic and striatal subregions of this reward network (27–29). Finally, several studies suggest that youth with early childhood adversity experience dysfunction of the prefrontal-limbic (30, 31) and basal ganglia portions of the reward network leading to blunted reward responses (32, 33).

Previous studies that investigated different combinations of depression, insulin resistance, and childhood abuse also implicated dysregulation of the mesolimbic reward network (34–36). Our prior study presented a potential neural link between depression and insulin resistance through dysregulation of the neural reward network, as overweight youth with depression and insulin resistance had higher levels of dysconnectivity between the anterior cingulate cortex and hippocampus, as well as reduced volumes of these regions (37). It is unknown whether childhood abuse mediates altered regulation of the neural reward network in these youth, leading to the potential for either resilient or lifelong depression and diabetes outcomes.

In this study, we evaluated 69 children between the ages of 9 to 17 with depression and a BMI at or above the 85th percentile. We hypothesized that higher levels of early childhood abuse would be associated with higher levels of insulin resistance, as demonstrated by higher fasting insulin levels, higher fasting glucose levels, and a persistently elevated glucose curve after an oral glucose tolerance test (OGTT) (38, 39). We also hypothesized that youth with depression and obesity who had higher compared to lower levels of abuse would have more dysfunctional connectivity in the reward neural network. We selected the amygdala, insula, and nucleus accumbens (NAcc) as regions of interest due to their central roles in the reward network common to depression, insulin resistance, and childhood abuse literatures (21, 22, 30).

MATERIALS AND METHODS

Study Participants, Screening Procedures, and Analytic Approach to Behavioral Correlates of Insulin Resistance

Sixty-nine overweight or obese youth between the ages of 9 to 17 years with currently untreated depressive symptoms were recruited for this study. All participants provided written assent and at least one parent or legal guardian provided written informed consent prior to all study procedures. This study was approved by Stanford University's Institutional Review Board. Participants were recruited from pediatric mood and weight control programs and community advertisements.

Youth were included if their body mass index (BMI) was at the 85th percentile or higher for their age and sex based on the Center for Disease Control and Prevention BMI calculator for children and teens (https://nccd.cdc.gov/dnpabmi/calculator.aspx). During the screening visit, height (with accuracy of 0.1 cm) and weight (with accuracy of 0.1 kg) were measured with the Seca 284, an electronic measuring station, after the removal of shoes and jackets. Two measures of height were obtained and averaged. We assessed Tanner stage using the youth self-reported Pubertal Development Scale (40) in conjunction with a clinician's physical examination of secondary sex characteristics to confirm the self-reported rating. Participants were also evaluated on levels of depression severity using the Children's Depression Rating Scale-Revised (CDRS-R) (41) administered separately to parents and youth by a study clinician or trained coordinator. Participants were included if their raw CDRS-R summary scores were greater than 35, signifying at least moderate levels of depression severity at the time of enrollment. All youth in this sample were treatment-seeking for active unremitted symptoms, but unmedicated, and were generally early in the course of their depressive illness.

Individuals were assessed for current and lifetime psychiatric disorders with the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (KSADS-PL) (42). Youth were excluded if they were already being treated for a

mood disorder when evaluated at the screening visit. Youth were also excluded if they had type 1 or type 2 diabetes, were taking medication that affected their mood, weight, or metabolism at the time of screening, had a contraindication for an MRI (e.g., metal in their body or anterior-posterior diameter > 46 cm), or if their Full-4 IQ score on the Wechsler Abbreviated Scale of Intelligence (WASI) (43) was <70.

The Childhood Trauma Questionnaire (CTQ) was used as our primary clinical assessment of early childhood abuse. The CTQ is a 28-item scale of childhood trauma self-reported by youth participants (44). The CTQ separates trauma into five categorical scores with five questions per category: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. We secondarily used the Multidimensional Peer Victimization Scale (PVS) to understand other environmental forms of abuse, such as bullying, that are commonly experienced by youth outside of the home (45). This scale is a 16-item self-report measure with 4 subscales, to assess physical victimization, verbal victimization, social manipulation, and property attacks. We used a totaled PVS score in our linear models to adjust for the possible confounding effect of peer victimization on the relation between abuse and neural and endocrine outcomes, as childhood bullying has been shown to predict systemic inflammation and being overweight in early adulthood (46, 47). We used the Three-Factor Eating Questionnaire (TFEQ) (48) in youth to contexualize neural findings with behavioral measures of food-seeking behavior, including the constructs of cognitive restraint, uncontrolled eating or eating disinhibition, and emotional eating. Finally, we assessed socioeconomic status by the Hollingshead Four-Factor Index of Social Status and reported participants' raw scores (49).

Assessment of Insulin Resistance

After the screening visit, eligible youth were assessed for insulin resistance. Serum markers of insulin resistance were assessed using a 2-h oral glucose tolerance test (OGTT). After a 10-h fasting period and an initial fasting blood draw, participants consumed 75 g of oral glucose and had their blood drawn every 30 min for 2 h to measure insulin and glucose (37). Insulin values were measured by immunoassay.

Insulin response to OGTT was determined by calculating the area under the serum insulin curves, plotted at each time point during the OGTT. Graphing plasma glucose levels vs. time and finding the area under the curve similarly calculated glucose response to OGTT. Insulin resistance was determined by fasting insulin measure and by HOMA-IR, which was calculated using the equation fasting insulin (mU/mL) × fasting glucose (mg/dL)/405 (50).

Childhood Trauma Questionnaire (CTQ) Groupings

Using the cumulative CTQ categories of emotional abuse, physical abuse, and sexual abuse, we grouped participants into "high abuse" and "low abuse" groups. Here, we focused on abuse rather than emotional or physical neglect, due to previous findings of childhood abuse as risk factors for metabolic outcomes such as prediabetes and diabetes (51, 52), and due to the demonstrated role of emotional abuse in predicting psychopathology (16). We classified participants as highly abused if they met the threshold for "low to moderate" abuse, as defined by the CTQ manual, for at least one of the three aforementioned categories. We used the following "high abuse" cutoff scores: an emotional abuse categorical score > 9; a physical abuse categorical score > 8; and a sexual abuse categorical score > 6. We also totaled the three abuse scores for a total CTQ abuse score that we used as a continuous variable in linear modeling. In order to be included in the "low abuse" group, youth could not endorse abuse above any of the cut-off scores for the three CTQ categories of abuse. Using such criteria, we were able to define with confidence a "low abuse" group of youth who did not report any significant early life stress from childhood abuse.

Neuroimaging Data Acquisition

We used neuroimaging to investigate neural connectivity group differences at resting state, assessing for neural markers of approach motivation. Using functional MRI data of a subset of our participants ($n = 47$), we seeded three different regions that have been implicated in reward and depression: amygdala, insula, and nucleus accumbens (NAcc). After participants were familiarized with the scanning environment in an MRI simulator, whole-brain images were acquired on a 3T GE Signa Excite (General Electric Co., Milwaukee, WI) scanner equipped with an 8-channel head coil. Functional images were collected at rest using a spiral pulse sequence with the following parameters: repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, flip angle (FA) = 80°, field of view (FOV) = 22 cm, number of slices = 30 slices in the axial plane, and slice thickness = 4 mm with a gap of 1 mm. The first four volumes of each resting state scan were discarded at the scanner to allow for stabilization of longitudinal magnetization. High-order shimming was used before acquisition of resting state data to improve field inhomogeneity. High-resolution structural images were also collected to assist in registration of functional data to standard space using a fast spoiled gradient recalled (3D FSPGR) pulse sequence with the following parameters: TR = 8.5 ms, TE = 3.32 ms, TI = 400 ms, flip angle = 15°, field of view(x) = 25.6 cm, matrix of 256 × 256, number of slices = 186 slices in the axial plane, and a slice thickness of 1 mm.

Functional MRI Pre-Processing

Pre-processing of resting-state data was carried out using FEAT Version 6.00 within FSL (FMRIB's Software Library; www.fmrib.ox.ac.uk/fsl). The 210-volume functional dataset for each participant was realigned to compensate for small head movements using MCFLIRT (53), skull-stripped using the Brain Extraction Tool (BET) (54); spatially smoothed using a Gaussian kernel of 5 mm FWHM, intensity normalized by a single multiplicative factor, and band-pass filtered to correct for baseline drift and high frequency noise (high-pass temporal filter: Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s; low-pass temporal filter: Gaussian with sigma = 2.8 s). Functional images were registered to corresponding high-resolution T1-weighted structural images and then normalized to Montreal Neurological Institute (MNI)

space using a 12-parameter transformation. Masks of white matter and cerebrospinal fluid (CSF) generated from anatomical images were applied to the functional data to extract white matter and CSF time-series. These time-series were used together with 6 motion parameters as nuisance regressors in a voxel-wise regression of the fMRI data. Data scrubbing was also performed following the method of Power et al. (55), excluding any volume in which either the value for DVARS (the root mean squared change in BOLD signal from the prior volume) or the value for framewise displacement exceeded the upper boxplot threshold (the 75th percentile plus 1.5 times the interquartile range), along with the previous volume and the 2 following volumes. Forty-Seven out of sixty-nine participants in the resting state analysis had <33% of the volumes requiring removal, enabling inclusion in this analysis. Subjects included in the RSFC analysis did not differ from subjects excluded due to motion ($P > 0.05$ on all demographic, clinical, and OGTT-related variables). Similarly, high and low abuse groups did not differ in number of censored volumes [$t_{(47)} = 0.403$, $P = 0.689$]. Residuals of the voxel-wise regression were used in subsequent seed-based connectivity analyses.

Resting State Functional Connectivity Analysis

A seed-based intrinsic connectivity approach was used to examine resting state functional connectivity (RSFC) with the bilateral amygdala, NAcc, and insula in three separate whole brain analyses. Seed regions were anatomically defined using probabilistic maps from the Harvard-Oxford Subcortical Structural Atlas (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases), incorporating voxels that had 25% or greater probability of being labeled as the amygdala (left: 3,456 mm^3, right: 3,936 mm^3), the NAcc (left: 1,088 mm^3, right: 1,016 mm^3) or the insula (left: 9,928 mm^3, right: 10,080 mm^3). Amygdala, NAcc, and insula ROIs were registered from the MNI template to each participant's preprocessed fMRI data, and the mean time-series of voxels in the right and left hemispheres for each of these regions were extracted for each participant for use as primary regressors in a GLM analysis of all other voxel time-series, resulting in individual whole-brain amygdala, NAcc, and insula RSFC maps. Talairach Daemon Labels (http://www.talairach.org) were used to find corresponding Brodmann areas.

Group differences in bilateral amygdala, bilateral NAcc, and bilateral insula RSFC were examined in separate voxel-wise *t*-tests, covarying age and sex. Subjects included in the RSFC analysis showed no difference in Full-4 IQ scores by abuse group ($P > 0.05$), so we did not include IQ as a covariate in the imaging subanalyses. Resulting statistical maps were thresholded with a height threshold of $z > 2.3$ and an extent threshold of $P < 0.01667$ (Bonferroni-corrected to control for multiple comparisons with three seeds), using Gaussian random field theory to correct for multiple comparisons. Parameter estimates (proportional to fMRI signal change) of BOLD signal response were extracted separately for each cluster and for each participant using featquery (fsl.fmrib.ox.ac.uk/fsl/fsl4.0/feat5/featquery.html) and analyzed in separate GLMs in SPSS (v.22; www.ibm.com/analytics/us/en/technology/spss/) that modeled the parameter estimate as the dependent variables and age, sex, and group as independent variables.

Statistical Analyses

All statistical analyses were carried out using R version 3.5. *t*-Tests were used to test the association between abuse group and demographic, clinical, metabolic, and behavioral characteristics. Linear regression models were performed to test for association between abuse and OGTT-derived measures of insulin and glucose. Specifically, totaled CTQ abuse score was included in linear models as a predictor of area under the OGTT insulin curve, insulin at OGTT time points of 90 and 120 min, and glucose at OGTT 120 min. To account for various possible confounders and mediators, we included age, sex, BMI percentile, IQ, pubertal development (assessed by Tanner stage), depression severity, and total Peer Victimization Scale score as covariates in subsequent linear regression analyses.

Statistical assumptions for linear regression models were tested using regression diagnostics, including tests of normality of residuals, heteroscedasticity, linearity, and collinearity. While performing regression diagnostics, we found that insulin measures, including area under the OGTT insulin curve, were not normally distributed across all study participants. We performed log transformations and checked with the Shapiro-Wilk test that log-transformed area under the insulin curve met the normality assumption for linear regression. We also identified one subject as a statistical outlier in the association between totaled CTQ abuse score and glucose at OGTT endpoint. By reviewing Cook's distance and leverage statistics, we determined the subject's T+120 glucose level to exert undue influence on the regression, and we removed the subject from this and subsequent linear regression analyses with T+120 glucose.

Following our linear regression analysis, to determine if food-seeking behavior mediated the differences in OGTT insulin response between abuse groups, we used *t*-tests to investigate group differences in eating behavior.

Finally, with the connectivities that we identified with RSFC analysis as significantly different between abuse groups, we performed an interaction analysis between totaled abuse score and parameter estimates of BOLD signal response. These included (1) the interaction between abuse and amygdala-precuneus connectivity on fasting glucose, (2) the interaction between abuse and insula-precuneus connectivity on area under insulin curve, (3) the interaction between NAcc-prefrontal connectivity on fasting glucose, and (4) the interaction between abuse and NAcc-paracingulate gyrus connectivity on T+120 glucose.

RESULTS

Demographic and Clinical Characteristics

Demographic and clinical characteristics of the 69 participants are summarized in **Table 1**. Fifty-nine percent of the youth in this sample were female, with diverse ethnic backgrounds (55% Caucasian), with above average IQ (102.46 ± 14.14), with an average BMI in the obese range (29.95 ± 6.17), and with

TABLE 1 | Demographic and clinical characteristics for participants overall and by abuse group.

	All participants (*N* = 69)	CTQ high abuse (*N* = 35)	CTQ low abuse (*N* = 34)
Age (*)	14.60 ± 2.06	15.08 ± 2.18	14.11 ± 1.83
Female sex	41 (59%)	23 (66%)	18 (53%)
Caucasian race	38 (55%)	16 (46%)	22 (65%)
Intellectual quotient (IQ) (*)	102.46 ± 14.14	98.54 ± 13.30	106.50 ± 14.03
Body mass index (BMI)	29.95 ± 6.17	31.01 ± 6.71	28.87 ± 5.44
Tanner stage (*)	3.68 ± 0.99	3.91 ± 0.92	3.44 ± 1.02
Socioeconomic status (SES) (Hollingshead Index raw score)	45.60 ± 13.78	44.43 ± 13.57	46.81 ± 14.10
Depression severity (Children's Depression Rating Scale-Revised raw score)	54.19 ± 11.28	55.91 ± 11.58	52.41 ± 10.84
Childhood trauma questionnaire (*)	39.59 ± 10.84	46.80 ± 9.97	32.18 ± 5.28
Emotional abuse (*)	10.36 ± 4.78	13.97 ± 4.02	6.65 ± 1.54
Physical abuse (*)	6.07 ± 1.86	6.74 ± 2.33	5.38 ± 0.74
Sexual abuse (*)	5.67 ± 2.30	6.31 ± 3.11	5.00 ± 0.00
Emotional neglect (*)	10.35 ± 4.25	12.17 ± 4.47	8.47 ± 3.07
Physical neglect	7.15 ± 2.17	7.60 ± 2.46	6.68 ± 1.74
Peer victimization scale	9.71 ± 7.98	10.37 ± 8.54	8.96 ± 7.39
Physical victimization	1.00 ± 2.03	1.00 ± 2.08	1.00 ± 2.00
Verbal victimization	3.96 ± 2.93	4.13 ± 2.90	3.78 ± 3.00
Social manipulation	2.53 ± 2.62	2.90 ± 2.78	2.11 ± 2.40
Attacks on property	1.89 ± 2.31	2.00 ± 2.51	1.78 ± 2.12
Three factor eating questionnaire	23.37 ± 8.39	23.76 ± 7.89	22.97 ± 8.97
Cognitive restraint	9.47 ± 4.94	9.74 ± 4.97	9.21 ± 4.97
Disinhibition scale	7.18 ± 3.69	7.38 ± 3.48	6.97 ± 3.93
Hunger	6.72 ± 3.66	6.65 ± 3.68	6.79 ± 3.69

Values reported are mean ± SD or N (%). (*) P < 0.05.

moderate to severe depression severity (CDRS-R Raw Score = 54.19 ± 11.28). By grouping the participants by high or low levels of abuse (see Methods), we noted significant differences in age, IQ, and Tanner stage, so we adjusted for these variables in all subsequent linear modeling. We also examined how OGTT insulin and glucose measures varied by participants' level of abuse (**Table 2**). Participants in the high abuse group had significantly lower insulin levels at the 2-h time point ($P = 0.015$) and almost significantly lower areas under the insulin curve ($P = 0.083$). Glucose levels at the 2-h time point were also significantly different between the two abuse groups ($P = 0.049$), but the difference between abuse groups in areas under the glucose curve was not significant ($P = 0.280$). We found no mediating effect of food-seeking behavior in our analysis, as the results showed no significant group differences in self-reported eating behaviors or significant associations with OGTT measures.

TABLE 2 | Baseline metabolic characteristics from OGTT by abuse group.

	CTQ high abuse	CTQ low abuse	*P*
T+120 insulin	69.94 ± 51.06	116.68 ± 95.13	0.015
T+120 glucose	114.17 ± 33.85	128.90 ± 27.04	0.049
Area under insulin curve	9841.29 ± 5519.2	13002.35 ± 8924.0	0.083
Area under glucose curve	15691.97 ± 3501.7	16515.84 ± 2748.5	0.280
Fasting insulin	13.23 ± 8.56	14.74 ± 9.94	0.503
Fasting glucose	92.87 ± 8.64	92.33 ± 9.17	0.801
HOMA-IR	3.69 ± 2.21	4.29 ± 3.41	0.391

T+120 insulin, insulin at time 120 min after glucose challenge; T+120 glucose, glucose at time 120 min after glucose challenge; HOMA-IR, Homeostatic Model Assessment-Insulin Resistance; CTQ, Childhood Trauma Questionnaire.

Abuse Group Differences in Serum Insulin and Plasma Glucose Levels During OGTT

In order to evaluate differences in insulin and glucose response to OGTT between the two abuse groups, we visualized each abuse group's mean serum insulin and mean plasma glucose at time point during the oral glucose tolerance test, creating metabolic response curves. A more elevated insulin response to the oral glucose challenge was observed in participants who reported a low level of abuse (**Figure 1A**). Insulin and glucose shapes varied between groups; mean insulin curve in the high abuse group showed earlier peak and decline, whereas the curve for the low abuse group was elevated for a sustained period. Mean glucose curves showed more similarity between the two groups (**Figure 1B**). Peaks for both curves were observed at the 30-min time point, followed by declines in plasma glucose.

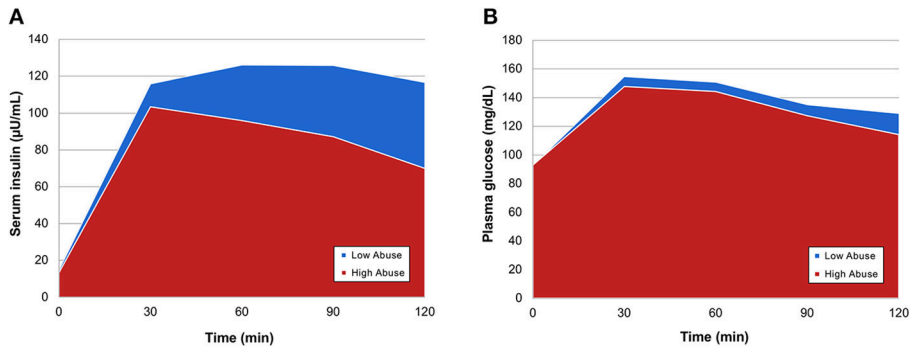

FIGURE 1 | Mean OGTT curves by abuse group for **(A)** serum insulin and **(B)** plasma glucose.

TABLE 3 | Linear regression model parameter estimates for total level of abuse in additive models predicting OGTT insulin (log-transformed) and glucose values.

	Insulin curve area (log-transformed)		T+90 insulin (log-transformed)		T+120 insulin (log-transformed)		T+120 glucose	
	ß	*P*	ß	*P*	ß	*P*	ß	*P*
CTQ total abuse score	−0.0107	0.039	−0.0090	0.175	−0.0127	0.070	−1.475	0.005
Add age, sex, Tanner stage, race, SES, IQ	−0.0112	0.060	−0.0087	0.260	−0.0115	0.146	−1.379	0.011
Add BMI percentile	−0.0126	0.034	−0.0109	0.150	−0.0126	0.118	−1.364	0.013
Add CDRS-R depression severity	−0.0131	0.030	−0.0111	0.152	−0.0132	0.106	−1.484	0.007
Add PVS total score	−0.0169	0.020	−0.0187	0.047	−0.0158	0.116	−1.252	0.049

Values reported for the model predicting T+120 glucose are after removal of one outlier. CTQ, Childhood Trauma Questionnaire; SES, Socioeconomic Status; IQ, Intelligence Quotient; BMI, Body Mass Index; CDRS-R, Children's Depression Rating Scale-Revised; PVS, Peer Victimization Scale.

Linear regression modeling showed that insulin and glucose response was associated with level of abuse (**Table 3**). Totaled CTQ abuse scores significantly correlated with log-transformed area under the insulin curve, insulin at 90 min, and glucose at OGTT endpoint. We found that age, sex, race, IQ, and depression severity did not confound or mediate the relationship between abuse and OGTT measures. On the other hand, BMI percentile and Peer Victimization Scale (PVS) total score were identified as possible negative confounders of the association between abuse and log-transformed insulin curve area ($\Delta ß = +12.5\%$ adjusting for BMI; +29% adjusting for PVS), as well as between abuse and log-transformed T+90 insulin ($\Delta ß = +68.5\%$ adjusting for PVS). In other words, adjusting for BMI percentile and peer victimization accentuated the significant effect of abuse on insulin response. Whereas we found significant differences in T+120 insulin between abuse groups when we treated abuse as a categorical variable, our linear modeling with totaled CTQ abuse as a continuous variable did not show correlations with insulin at OGTT endpoint.

Abuse Group Differences in Amygdala, NAcc, and Insula RSFC

Group differences in bilateral amygdala, bilateral NAcc, and bilateral insula RSFC were examined in separate voxel-wise *t*-tests, co-varying age, and sex. After correcting for multiple comparisons, we found a significant main effect of group between the bilateral amygdala and precuneus ($k = 644$ voxels, peak x/y/z MNI coordinate = 14/−58/24, $z = 3.56$, $P = 0.000594$, Brodmann areas 7, 23, 31) (**Figure 2A**). We also found a significant main effect of group between the bilateral insula and precuneus ($k = 566$ voxels, peak x/y/z MNI coordinate = 10/−66/34, $z = 4.05$, $P = 0.002$, Brodmann areas 7, 31) (**Figure 2B**). For both of these main effects, the high abuse group showed reduced negative connectivity to the precuneus compared to the low abuse group.

We also found significant group differences in connectivity between bilateral NAcc and two regions: a prefrontal cluster which included the left dorsolateral prefrontal cortex (DLPFC), precentral gyrus, and inferior frontal gyrus (IFG) ($k = 597$ voxels, peak x/y/z MNI coordinates = −54/4/30, $z = 3.46$, $P = 0.0013$, Brodmann areas 6, 9, 45, 46) and a cluster encompassing the bilateral paracingulate gyri in the medial prefrontal cortex (mPFC) ($k = 386$ voxels, peak x/y/z MNI coordinates = −12/48/−4, z = 3.89, $P = 0.023$, Brodmann areas 10, 32) (**Figures 2C,D**). In the high- compared to low- abuse group, there was increased negative connectivity between NAcc and the prefrontal cluster, and reduced positive connectivity between NAcc and the paracingulate gyrus cluster.

We extracted parameter estimates of BOLD signal response for these four connectivity clusters showing abuse group differences. Taking total abuse score as a continuous variable, we explored a dose relation between level of abuse and connectivity

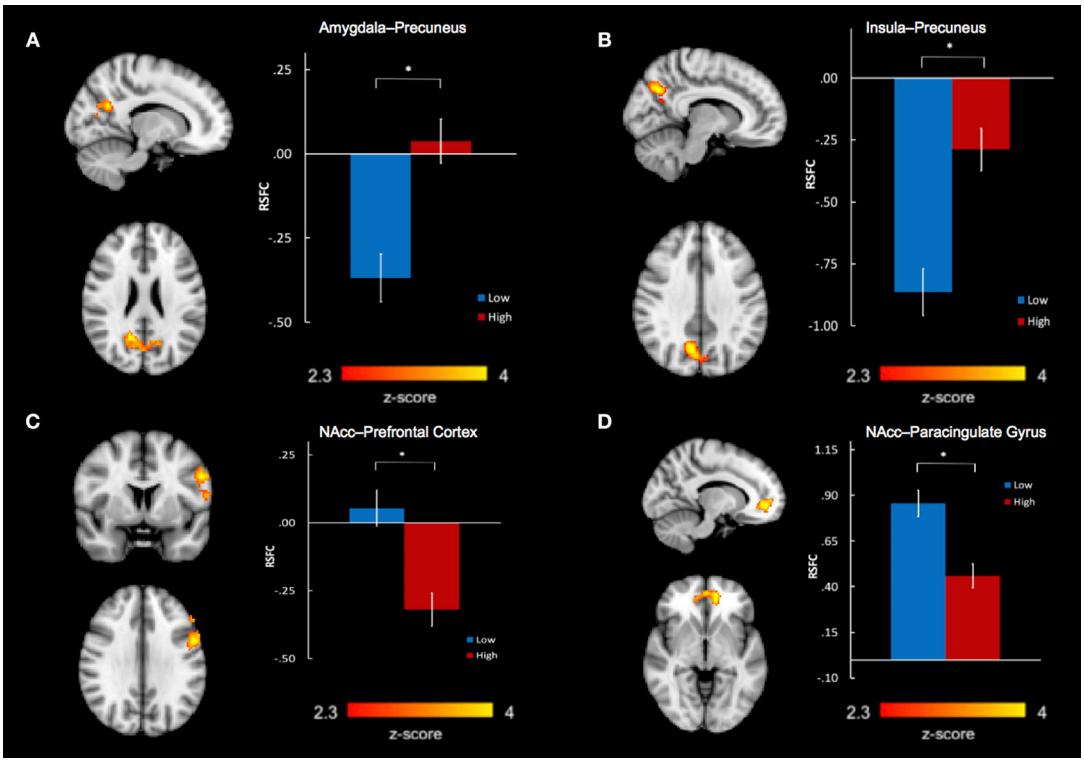

FIGURE 2 | Abuse group differences in resting state functional connectivity between **(A)** bilateral amygdala and precuneus, **(B)** bilateral insula and precuneus, **(C)** bilateral nucleus accumbens and left prefrontal cortex, including the left dorsolateral prefrontal gyrus, precentral gyrus, and inferior frontal gyrus, and **(D)** bilateral nucleus accumbens and bilateral paracingulate gyri in the medial prefrontal cortex. *$P < 0.01667$.

values that was significant for insula-precuneus ($P = 0.0032$, $r = 0.421$), NAcc-prefrontal ($P = 0.0035$, $r = -0.418$), and NAcc-paracingulate gyrus ($P = 0.0046$, $r = -0.406$) connectivities, and near significant for amygdala-precuneus connectivity ($P = 0.064$, $r = 0.272$).

Abuse Level Moderates the Relation Between RSFC and OGTT Insulin and Glucose Response

With extracted neural connectivity values from the four connectivity group differences shown above, we explored associations between connectivity estimates and OGTT measures of insulin and glucose. We made scatterplots with least-squares lines for each abuse group and found that the two groups had visibly different correlations between the insulin or glucose response and brain connectivity (**Figure 3**). The high abuse group showed correlations between OGTT measures and amygdala-precuneus, NAcc-prefrontal cortex, and NAcc-paracingulate gyrus connectivity, while the low abuse group did not (**Figures 3A,C,D**). On the other hand, the low abuse group showed a negative correlation between area under the insulin curve and insula-precuneus connectivity, while the high abuse group did not (**Figure 3B**). Adjusting for age, sex, BMI, and peer victimization, we found a significant negative correlation across all participants between log-transformed area under the insulin curve and bilateral insula-precuneus connectivity ($P = 0.041$), as well as between log-transformed T+120 insulin and bilateral amygdala-precuneus connectivity ($P = 0.019$).

Mediation analysis using connectivity values and abuse scores as covariates in linear models of OGTT measures, both study-wide and by separated abuse group, did not show significant mediation by connectivity of the effect of abuse on insulin or glucose. However, when we performed moderation analysis to see if abuse moderated the association between connectivity estimates and OGTT measures, we found that each of the four identified connectivity differences interacted with abuse in predicting OGTT measures, in line with our scatterplot findings. Cumulative CTQ abuse score as a continuous variable moderated the associations between: amygdala-precuneus connectivity and fasting glucose (interaction term $P = 0.043$), insula-precuneus connectivity and log-transformed area under the insulin curve (interaction term $P = 0.037$), and NAcc-prefrontal connectivity and fasting glucose (interaction term $P = 0.0005$) (**Tables 4–6**). We also found moderation by cumulative CTQ abuse score of the association between NAcc-paracingulate gyrus connectivity and T+120 glucose, trending toward significance (interaction term $P = 0.114$) (**Table 7**).

DISCUSSION

Our findings suggest that depressed and overweight youth with high abuse exposure have different neural and endocrine

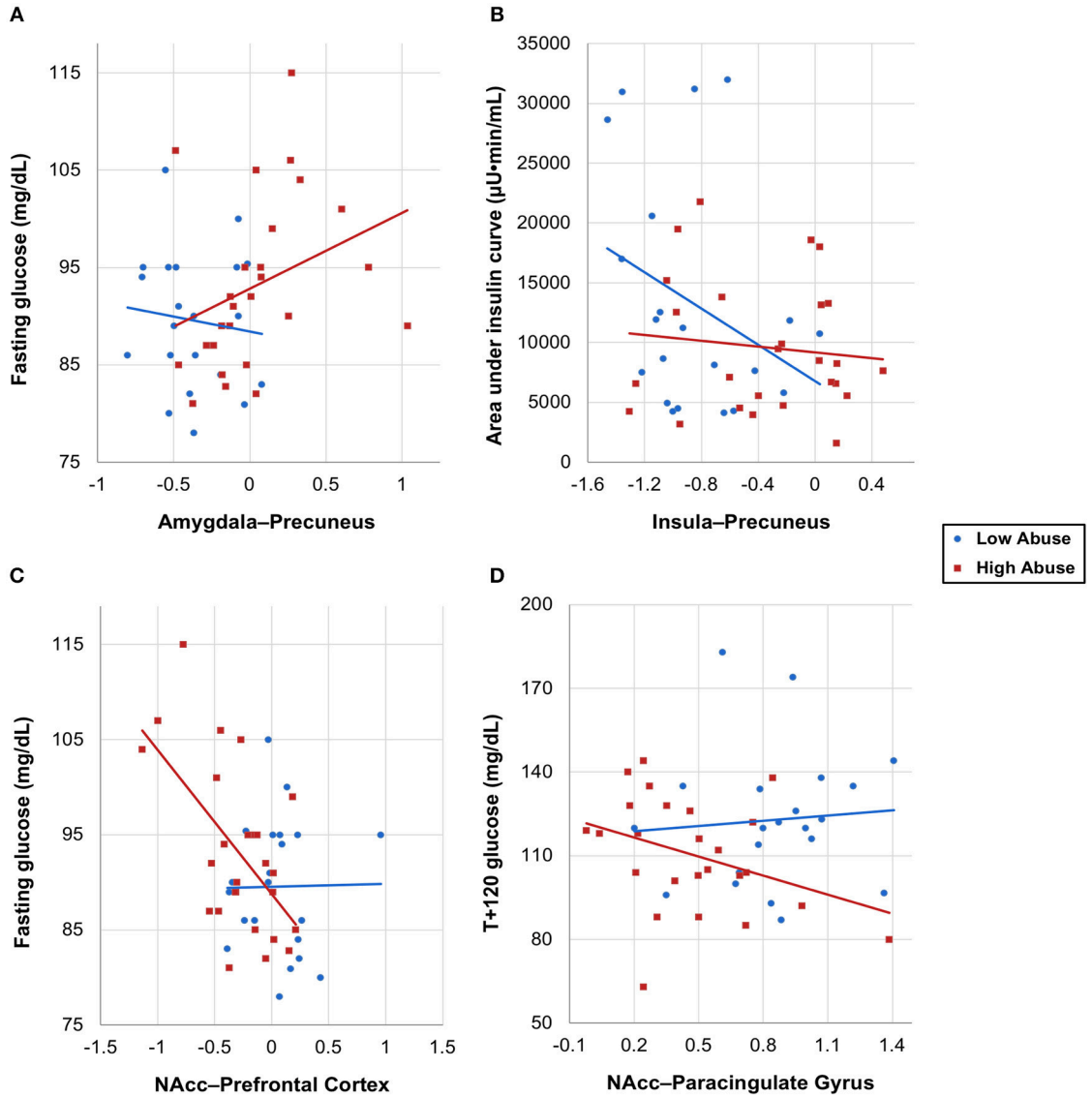

FIGURE 3 | OGTT insulin and glucose measures vs. neural connectivity values by abuse group, with group-specific least-squares lines. **(A)** Fasting glucose vs. amygdala–precuneus connectivity, **(B)** area under the insulin curve vs. insula–precuneus connectivity, **(C)** fasting glucose vs. NAcc–prefrontal connectivity, **(D)** T+120 glucose vs. NAcc–paracingulate gyrus connectivity, with one outlier removed.

characteristics compared to low abuse-exposed counterparts. Further, levels of abuse seem to be related to levels of hyperglycemia and insulin resistance. However, contrary to our hypotheses, lower levels of abuse were associated with post-glucose challenge hyperglycemia, hyperinsulinemia, and a persistently elevated glucose response. Neurally, the low abuse group showed more negative bilateral insula-precuneus connectivity than the high abuse group. More negative insula-precuneus connectivity was associated with higher area under the insulin curve and hyperinsulinemia. In contrast, overweight and depressed youth with high abuse showed dysfunctional connectivities between the amygdala-precuneus, NAcc-paracingulate gyrus, and NAcc-prefrontal networks at rest. Their levels of connectivity in these networks correlated with fasting and post-glucose challenge glucose levels. These unexpected results suggest possible compensatory or group-independent mechanisms that may be unique to our cohort and merit replication with larger sample sizes and broader comparison groups.

Although brain connectivity varied between abuse groups, glucose response to OGTT varied independently of abuse. The insignificant difference in glucose response between abuse groups was not unexpected, as previous literature has suggested the same. Specifically, in youth with insulin resistance, blood glucose levels may appear normal, as pancreatic beta-cell reserves may mount compensatory hyperinsulinemic responses (39). However, the significant difference in insulin response between high and low abuse groups was surprising. We propose two

TABLE 4 | Adjusted interaction effect of abuse and amygdala-precuneus connectivity on fasting glucose.

Predictor	ß	SE	*P*
(Intercept)	73.119	41.883	0.093
Age	−0.093	1.562	0.953
Male sex	3.321	3.536	0.356
Tanner stage	1.284	3.706	0.732
Non-Hispanic race	−1.835	3.624	0.617
SES	−0.278	0.146	0.068
IQ	0.056	0.135	0.683
BMI percentile	0.043	0.398	0.915
Depression severity	0.097	0.114	0.404
Peer victimization total score	0.101	0.182	0.583
CTQ total abuse score	0.492	0.277	0.088
Amygdala-precuneus connectivity	−28.857	15.630	0.076
CTQ total abuse score × Amygdala-precuneus connectivity (*)	1.439	0.675	0.043

(*) $P < 0.05$. Model $P = 0.067$, $F = 2.00$, adjusted $R^2 = 0.241$. SES, Socioeconomic Status; IQ, Intelligence Quotient; BMI, Body Mass Index; CTQ, Childhood Trauma Questionnaire; SE, Standard Error.

TABLE 5 | Adjusted interaction effect of abuse and insula-precuneus connectivity on log-transformed area under insulin curve.

Predictor	ß	SE	*P*
(Intercept) (*)	3.3409	1.4317	0.028
Age	−0.0118	0.0526	0.824
Male sex	−0.1271	0.1388	0.368
Tanner stage	0.0063	0.1381	0.964
Non-Hispanic race	0.0670	0.1388	0.633
SES	−0.0053	0.0057	0.366
IQ	−0.0100	0.0051	0.060
BMI percentile	0.0214	0.0130	0.113
Depression severity	0.0007	0.0045	0.878
Peer victimization total score	−0.0129	0.0073	0.088
CTQ total abuse score	0.0016	0.0141	0.908
Insula-precuneus connectivity (*)	−1.040	0.4581	0.032
CTQ total abuse score × Insula-precuneus connectivity (*)	0.0421	0.0191	0.037

(*) $P < 0.05$. Model $P = 0.140$, $F = 1.644$, adjusted $R^2 = 0.169$. SES, Socioeconomic Status; IQ, Intelligence Quotient; BMI, Body Mass Index; CTQ, Childhood Trauma Questionnaire; SE, Standard Error.

possible explanations for this finding. First, highly stressed children may experience insulin deficiency due to beta cell dysfunction as a result of their exposure to abuse. This is supported by previous studies that showed early life stress increases the risk of type 1 diabetes (56). It also is supported potentially by a central brain mechanism, as illustrated by our neuroimaging results which link aberrant resting state brain connectivity with lower insulin and higher glucose responses. However, the average glucose curve for our high abuse group was not observed to be more elevated than that of our low abuse group, as would be expected. An alternative explanation may be that hyperinsulinemia in the high abuse group is a transient compensatory response to high stress, arising through sympathetic overdrive (57, 58). This transitory hypersensitivity may be supported by the slightly lower glucose curve for our highly abused participants. In either case, this finding suggests an early form of metabolic dysfunction in youth in the high abuse group that may be evolving but not yet fully realized.

The group differences in resting state brain connectivity demonstrate the impact of abuse on neural function in depressed and obese youth, specifically in correlated brain regions that form a network to process emotion and self-perception (59), as well as motivation, reward, and executive control over emotion and reward (60). In our investigation of the amygdala and insula as common denominator regions in depression and obesity, our data implicate the precuneus for both, highlighting the importance of self-referential thinking in high abuse-exposed youth. We observed less negative amygdala-precuneus connectivity in high abuse compared to low abuse youth with depression and obesity, which may result in impaired emotion processing and regulation (61, 62), problems with self-reflection (63, 64), and lower self-esteem in these youth (65). Indeed, less negative amygdala-precuneus connectivity has been described in adults with a history of childhood trauma (66). Our findings also showed decreased negative (toward more positive) connectivity between the insula and precuneus in the high abuse compared to the low abuse group. Childhood abuse has similarly been shown to be associated with an increase toward more positive connectivities in both the precuneus and insula within each of their neural networks (67). In the context of maltreatment, the insula has been reported to play an additive role with the precuneus toward dysfunctional self-awareness and emotional processing (68). Thus, our findings provide a neural network basis for the emotion dysregulation and negative self-concept commonly characterized in youth with depression and obesity (69, 70), which our data suggest may be compounded by high levels of abuse.

Emerging literature suggests that altered self-awareness due to dysfunctionally increased precuneus connectivity may be observed in addicted populations (71). Given the conditioned response to food cues that forms the basis of addictive behaviors in youth with co-occurring depression and obesity, we investigated regions correlated at rest within the brain's reward network. The NAcc is a critical region in the reward network, sending dopaminergic neurons to other components of the network (19). Decreased inhibitory control over food-seeking behaviors is a central feature of obesity, which is frequently represented by positive intrinsic7 connectivity between reward networks and the prefrontal cortex (72–74). Although we did not find differences in eating behavior between abuse groups, we did find that the high abuse group had increased *negative* connectivity between the NAcc and key regulatory subregions in the left prefrontal cortex, including the left DLPFC, IFG, and precentral gyrus. The prefrontal cortex is important for executive control of emotion and reward, processing behavioral rules in reward (75). Greater negative connectivity between NAcc and

portions of the prefrontal cortex including the DLPFC has been reported in individuals with alcohol abuse (67), depression (76), and with exposure or vulnerability to abuse across species (77–79), implicating this aberrant connectivity pattern in addiction and stress. Recent manipulation of NAcc-prefrontal network connectivity through transcranial magnetic stimulation to treat depression (80) and through dietary intervention to treat obese individuals (81) illustrates the robust replicability and utility of this neural system as a treatment target. Similarly, the high abuse group also showed reduced negative connectivity between the NAcc and paracingulate gyrus compared to the low abuse group. The paracingulate gyrus has been shown to be less activated in major depressive disorder during anticipation of monetary rewards (82), just as the subgenual portions of the anterior cingulate is less connected to the default mode network in abuse-exposed youth with higher levels of behavioral activation system sensitivity (83). Interventions that bolster behavioral activation may protect against the development of stress-related disorders by modifying the central neural circuit implicated in rumination. Indeed, the disruption between the NAcc and paracingulate gyrus in the high abuse group supports that abuse is associated with atypical regulation of the reward network, possibly through a decoupling mechanism.

We speculate that this decoupling of the frontostriatal network in high abuse youth may influence dopamine release in the VTA, which may further influence insulin sensitivity toward developmental adaptation. Studies on non-obese adults demonstrate that acute dopamine depletion leads to increased fasting insulin levels in diabetic and healthy individuals (84, 85). Consistently, increasing striatal dopamine levels by deep brain electrical stimulation reduces fasting insulin levels (85), suggesting the apparent link between striatal function and systemic insulin sensitivity, as demonstrated in our sample. Moreover, children who have experienced physical or sexual abuse exhibit higher striatal dopamine synthesis when they reach adolescence and young adulthood (86), and reduced dopamine levels have not been observed in depressed adults. Therefore, the lower insulin levels in our high abuse group may be a developmental adaption related to decreased regulation of NAcc connectivity, leading to increased striatal dopamine levels that improve insulin sensitivity. In other words, high abuse youth show better metabolic functioning, suggesting potentially better NAcc and dopamine functioning, which requires less prefrontal connectivity and consequent regulation. Alternatively, inhibition of the prefrontal cortex by high abuse may lead to a lack of regulation of NAcc connectivity, requiring greater levels of striatal dopamine synthesis. Regardless, this unique finding is confirmed by our moderation analysis, which yields correlations between NAcc connectivity and OGTT measures that are significant for high but not low abused youth.

We had hypothesized that deregulation of reward network connectivity may relate to a deregulation of eating behavior that mediates insulin resistance in youth. A preclinical mouse model of hyperinsulinemia in which insulin does not induce an expected synaptic depression of ventral tegmental dopamine neuron activity, raises one possibility that reward circuit function may be related to the disruption in typical insulin-glucose function, that may, in turn, be related to increased feeding behavior (87). However, our data did not show OGTT response differences in high and low abuse groups due to differences in eating behavior. Our finding is more consistent with the mixed and non-standardized evidence in humans regarding how dopamine release, endogenous dopamine levels, and dopamine D2 receptor expression in the NAcc and VTA are related to eating behavior (88–90).

We propose an alternative hypothesis that abuse may effect change on signaling between the brain and the pancreas. If abuse

TABLE 6 | Adjusted interaction effect of abuse and NAcc-prefrontal connectivity on fasting glucose.

Predictor	ß	SE	*P*
(Intercept)	60.741	31.203	0.062
Age	1.971	1.127	0.092
Male sex	−0.093	2.684	0.973
Tanner stage	−2.701	2.812	0.346
Non-Hispanic race	0.877	2.840	0.760
SES (*)	−0.258	0.121	0.042
IQ	−0.033	0.102	0.752
BMI percentile	0.345	0.278	0.226
Depression severity	−0.016	0.093	0.862
Peer victimization total score	−0.011	0.146	0.941
CTQ total abuse score	−0.281	0.216	0.206
NAcc-prefrontal connectivity (*)	26.256	8.743	0.006
CTQ total abuse score × NAcc-prefrontal connectivity (*)	−1.368	0.343	0.0005

(*) $P < 0.05$. Model $P = 0.002$, $F = 3.95$, adjusted $R^2 = 0.482$. SES, Socioeconomic Status; IQ, Intelligence Quotient; BMI, Body Mass Index; CTQ, Childhood Trauma Questionnaire; NAcc, Nucleus accumbens; SE, Standard Error.

TABLE 7 | Adjusted interaction effect of abuse and NAcc-paracingulate gyrus connectivity on T+120 glucose.

Predictor	ß	SE	*P*
(Intercept) (*)	261.149	119.17	0.038
Age	−1.806	4.061	0.660
Male sex	10.813	9.726	0.277
Tanner stage	−3.235	9.819	0.745
Non-Hispanic race	18.523	9.947	0.074
SES (*)	−0.913	0.429	0.043
IQ	−0.203	0.354	0.571
BMI percentile	−1.091	0.945	0.259
Depression severity	0.572	0.335	0.100
Peer victimization total score	0.051	0.570	0.929
CTQ total abuse score	0.409	1.471	0.784
NAcc-paracingulate gyrus connectivity	69.102	44.543	0.133
CTQ total abuse score × NAcc-paracingulate gyrus connectivity	−2.982	1.820	0.114

(*) $P < 0.05$. Model $P = 0.116$, $F = 1.75$, adjusted $R^2 = 0.1951$. One outlier removed. SES; Socioeconomic Status; IQ, Intelligence Quotient; BMI, Body Mass Index; CTQ, Childhood Trauma Questionnaire; NAcc, Nucleus accumbens; SE, Standard Error.

were to impact an intermediary between brain connectivity and insulin production, then it would also cause downstream effects on the neural and pancreatic targets of that intermediary. One potential intermediary is cortisol, which has been shown to be lowered by childhood abuse (91, 92). Cortisol is a glucocorticoid secreted by the hypothalamic-pituitary-adrenal (HPA) axis and has been shown to influence insulin levels and to correlate with amygdala resting state functional connectivity (93–95). Similarly, inflammatory mediators influence frontolimbic and frontostriatal circuits in such a way as to predispose individuals toward self-medicating behaviors such as consumption of high fat diets (96). Further studies are warranted to investigate the intriguing roles of cortisol and inflammatory markers in mediating relations among abuse, insulin secretion and sensitivity, and brain connectivity.

We should note four study limitations. First, we had a modest sample size for the multilevel assessments conducted. For our sample of youth with combined depression and obesity, and with varying levels of abuse histories, there were no referent effect sizes for group differences in resting state connectivity. Still, a comprehensive neurobiological assessment of the magnitude of impact of abuse on insulin resistance in youth with co-occurring depression and obesity has not been presented in the literature before, and is an important hypothesis-generating starting point in a growing population of youth. Second, our cross-sectional design without a typically developing comparison group made it difficult to assess degree of insulin resistance on OGTT, and to interpret our functional connectivity findings as markers of neural vulnerability or resilience. Comparing youth in our study to non-obese, non-depressed, or non-obese and depressed groups may more fully capture the range, level, and degree of insulin resistance and reward network dysregulation in these youth. Prior studies of non-obese youth with depression have shown increased amygdala-precuneus intrinsic connectivity compared to controls (97). In contrast, non-depressed youth with obesity have shown reduced insula-anterior cingulate and middle-temporal gyrus-cuneus intrinsic connectivity compared to controls (98). However, to our knowledge, no study has examined varying levels of abuse history in youth with both depression and obesity. Third, though our study focused on childhood abuse as measured by the CTQ, there may be other sources of early life stress that may contribute to the findings presented but were beyond the scope of the current study. Our results suggest that peer victimization may moderate the relation between abuse and insulin response after covarying for socioeconomic status. Indeed, prior studies report that both overweight (99) and low social status (100) children are more likely to be bullied. Further, both obesity and reduced social status have been associated with reduced dopamine D2 receptor expression in adults (101–104). Future studies that look at the neural and endocrine correlates of peer victimization—covarying for both socioeconomic status and childhood abuse—may provide further insights into the effects of early life stress. Finally, though our study focused on insulin resistance, many endocrine abnormalities may coincide with obesity. Our ongoing analyses of these other endocrine contributors were beyond the scope of the aims of this study.

Our results suggest a unique interaction between abuse, depression, and obesity in youth in terms of neural connectivity patterns and metabolic function. By characterizing the neural and endocrine impact of abuse in youth with depression and obesity, our findings can create better profiles for children with psychiatric disorders based on histories of early childhood stress exposure. Identifying these profiles can promote early intervention (105) and possibly interrupt trajectories toward chronic conditions (106). Future studies to further characterize high and low abuse groups will include longitudinal analysis of insulin resistance and changes in brain connectivity over the course of development. These prospective studies will help determine whether exposure to early childhood adversity predicts the expected progression of insulin resistance and depression outcomes. In addition, further research differentiating peer victimization from abuse derived from family settings can refine these neural and endocrine profiles by delineating specific early life stress factors and their impact.

AUTHOR CONTRIBUTIONS

MS conceptualized and received funding for the study and executed the study protocol. MS, KS, SA, BB, and AG contributed to the analyses and writing of the manuscript including the figures and tables. SL contributed to the analysis of imaging data. KW and NR assisted with the analysis of data and contributed to the final draft of the manuscript.

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Antipsychotics, Metabolic Adverse Effects, and Cognitive Function in Schizophrenia

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Cognitive impairment is a core symptom domain of schizophrenia. The effect of antipsychotics, the cornerstone of treatment in schizophrenia, on this domain is not fully clear. There is some evidence suggesting that antipsychotics may partially improve cognitive function, and that this improvement may vary depending on the specific cognitive domain. However, this research is confounded by various factors, such as age, duration/stage of illness, medication adherence, and extrapyramidal side effects that complicate the relationship between antipsychotics and cognitive improvement. Furthermore, antipsychotics—particularly the second generation, or "atypical" antipsychotics—can induce serious metabolic side effects, such as obesity, dyslipidemia and type 2 diabetes, illnesses which themselves have been linked to impairments in cognition. Thus, the inter-relationships between cognition and metabolic side effects are complex, and this review aims to examine them in the context of schizophrenia and antipsychotic treatment. The review also speculates on potential mechanisms underlying cognitive functioning and metabolic risk in schizophrenia. We conclude that the available literature examining the inter-section of antipsychotics, cognition, and metabolic effects in schizophrenia is sparse, but suggests a relationship between metabolic comorbidity and worse cognitive function in patients with schizophrenia. Further research is required to determine if there is a causal connection between the well-recognized metabolic adverse effects of antipsychotics and cognitive deficits over the course of the illness of schizophrenia, as well as, to determine underlying mechanisms. In addition, findings from this review highlight the importance of monitoring metabolic disturbances in parallel with cognition, as well as, the importance of interventions to minimize metabolic abnormalities for both physical and cognitive health.

Keywords: schizophrenia, antipsychotics, metabolic syndrome, cognitive dysfunction, mechanism, inter-relationship

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INTRODUCTION

Schizophrenia is a severe psychiatric disorder characterized by a wide range of symptoms. These include positive symptoms, such as hallucinations and delusions, negative symptoms, such as apathy and amotivation, and impaired cognition (1). From the advent of chlorpromazine in the 1950s, the first antipsychotic (AP) for the treatment of schizophrenia, to today, APs uniformly alleviate positive symptoms with minimal effect on negative symptoms (2). Treatment with APs may be associated with a modest positive impact on cognitive functioning but there are many caveats to this finding (3). Furthermore, most APs, led by clozapine and olanzapine, cause serious metabolic side effects including weight gain, insulin resistance, and dyslipidemia. Independent studies suggest that about 50% of patients treated with APs develop metabolic complications (4, 5). These rates are even higher in young, first episode patients (6, 7). Cognitive impairment and metabolic aberrations have important functional and physical consequences. Schizophrenia continues to be associated with severe disability, owing largely to cognitive impairments (2), while metabolic illness contributes to decreased patient lifespan by about 20 years due to cardiovascular disease (8). In addition, these two critical domains of health and functioning might interact, as metabolic dysregulation is associated with impaired cognition in both patients with schizophrenia (9), as well as, the non-psychiatrically ill (10). The inter-relationships between cognition and metabolic side effects are therefore complex, and this review aims to examine them in the context of schizophrenia and AP treatment.

Cognition and Schizophrenia

Cognition is broadly defined as the ability to accurately perceive, attend to, process and remember information (2). An impairment in cognition is a hallmark symptom experienced by individuals with schizophrenia, and has been postulated to be a core aspect of the disorder (11). Important work over the last couple of decades has informed our understanding of the nature and properties of these deficits and has been extensively reviewed elsewhere (3, 12, 13). The field, however, is characterized by heterogeneous findings and many unanswered questions. This has been fueled, in part, by heterogeneity in the clinical profiles of the participants recruited and the methods used for cognitive testing. However, there are certain broad points of agreement that are briefly summarized below.

Cognitive deficits are observed in the majority of patients with schizophrenia, and this deficit is robust with a large effect size (3, 13). However, inter-subject variability is also an important aspect of this impairment. There is both a generalized impairment of cognition, as well, as impairment in several specific areas of functioning (14). These specific domains include speed of processing, attention, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition (15). The deficits are present pre-morbidly and tend to persist throughout the course of the illness (12). The course of these deficits is not completely clear, however, but in general have a weak relationship with positive symptoms, and a stronger association with the severity of negative symptoms (16). These impairments are also seen in unaffected relatives, albeit to a lesser degree, suggesting genetic underpinnings and shared risk among family members of schizophrenia patients (17). As will be reviewed, emerging evidence suggests that impairment in cognitive functioning may be exacerbated in the presence of metabolic comorbidity, which may in part be caused by the main-stay treatment for psychosis (i.e., AP medications) (9). Cognitive impairments are of fundamental importance since they substantially change the way individuals interact with their environment and have been linked directly and robustly to social and vocational functioning outcomes (2). This impact on functional outcomes makes it imperative that we understand fully the effect of treatment with AP medications on cognitive functioning. This includes consideration of medication-associated metabolic side effects and whether these may limit treatment efficacy in this critical illness domain.

Antipsychotics and Cognition

Given that antipsychotics are the cornerstone of schizophrenia treatment, the interaction of APs with cognitive impairment is of critical importance when looking at treatment outcomes. In spite of the large number of studies evaluating this relationship, however, the effects of AP medications on cognition remains controversial (13). Historically, the so-called "first generation" or "conventional" class of APs (FGA) was considered to have neutral or even detrimental effects on cognitive functioning. The introduction of so called "atypical," or second-generation APs (SGA) spawned hope that these newer medications would improve cognitive functioning relative to their "first generation" counterparts. Indeed, soon after the introduction of the newer APs, several studies seemed to suggest that treatment with these compounds could improve cognitive functioning in schizophrenia patients (18, 19). For example, multiple studies have shown that SGAs improved set shifting ability (1–3), a component of cognitive flexibility. Clozapine has shown large positive effects in attention and verbal fluency with modest improvements in executive functioning (20) and delayed recall (21). Olanzapine has also demonstrated significant improvement in vigilance, selective attention, delayed recall, as well as, verbal learning and memory, verbal fluency, and executive functioning (20, 21). Risperidone has generally shown more modest effects in comparison to the aforementioned medications, demonstrating moderate improvements in working memory, executive functioning, attention (20, 21), and delayed recall (21). Aripiprazole has been shown to improve reaction time with correct responses to stimuli (22), as well as, verbal cognitive functioning (23) while quetiapine has been shown to improve global cognitive functioning in the early stages of treatment (24–26) and verbal short-term memory (27).

While there is strong support for the effect of SGAs and their impact on cognition, more recent work has challenged the finding that they are superior to FGAs in this regard. Results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which included a large sample size of chronic schizophrenia patients and sample characteristics considered reflective of the general schizophrenia population, indicated that

APs are very similar in their action across chemical classes, and this similarity extends to the effects APs have on cognition. Additionally, the effect size for improvement in cognition was found to be small (28), with questionable clinical significance (29). The debatable superiority of SGAs on cognitive functioning was also highlighted by a meta-analysis that suggested that "older" drugs did, in fact, have a moderate beneficial effect on cognition (30). Two recent network based meta-analyses have shed further light on this question (31, 32). When nine studies investigating long-term (>6 months) effect of APs were meta-analyzed, olanzapine and quetiapine emerged superior (32), but when all studies longer than 8 weeks were considered, there were no clear differences between antipsychotics (31). Furthermore, short follow-ups and methodologies that do not allow for a confident discounting of practice effects raise questions over the claim that APs significantly improve cognition, as practice effects may contribute to the modest gains seen across treatments (12, 28).

There are several confounders that likely have a bearing on this relationship including general symptom improvement, the stage, and duration of the illness, dose of the AP, adherence to treatment, medication-related sedation, and anticholinergic side effects. Many of these aspects have been investigated and reviewed in detail elsewhere (33–37), and are summarized briefly here.

General Symptom Improvement With AP Treatment in Relation to Cognition

The degree to which general symptom improvement contributes to the changes in cognitive outcomes seen with AP treatment is an important consideration (38). More specifically, it is important to think about how different symptom domains interact (i.e., positive, negative, cognitive) and whether improvement of some symptoms relates to improvement in others. Studies differ with respect to their findings in this area. For example, multiple studies have demonstrated that although positive (and to some degree negative) symptoms may improve with AP use, these changes do not interact with executive functioning (27, 39–41). This also speaks to the notion that certain aspects of cognitive deficits (i.e., cognitive flexibility) may be inherent to the illness of schizophrenia, occurring independently of positive or negative symptomatology (40–42). Conversely, there is also evidence to suggest that improvements in cognition correlate with improvements in symptomology. For example, improvement in processing speed has been found to relate to negative symptom improvement, where improvement in negative symptoms occurred alongside improvements in processing speed after 24 weeks of treatment with a second generation antipsychotic (43). Taken together, the possibility arises that symptoms impact specific facets of cognition, rather than impacting global cognitive function.

Illness Course and Stage of Intervention in Relation to Cognitive Improvement

It may also be important to consider the stage at which treatment begins when looking for interactions between improvement in specific symptom domains and subsequent cognitive improvement. A recent review suggests that the small cognitive improvement seen after AP treatment initiation is possibly due to an improvement in psychotic symptoms, and that there is not much further improvement in cognitive outcomes beyond the first 1–2 years of treatment (12). This is in agreement with studies that have evaluated cognition in patients either over the course of illness or at varied time points. In first-episode patients, significant improvement in cognition has been reported across many studies and small but significant cognitive improvements related to AP treatment have been seen in first-episode patients as early as 3 months into treatment, in correlation with positive symptom alleviation (44). Significant improvements also continue to be seen in this population at three (45) and 5-years follow-up (46), supporting the idea that if treatment is adequate in the early stages of psychosis, greater improvements in cognition are evident without later decline (45). These outcomes are different than what has been observed in chronic schizophrenia. Studies in chronically ill patients often show little improvement in cognitive symptoms with AP treatment; one study which looked at patients with chronic schizophrenia found no cognitive improvement at 6-months follow-up, and found that this lack of improvement was independent of positive symptom alleviation, as rated on the Positive and Negative Syndrome Scale (PANSS) (47). Cognitive functioning in the chronic stage of the illness is sometimes described as static, as even at a minimum of a year follow-up, no significant improvements are evident (48). Therefore, it appears that the potential cognitive gains with AP treatment are most prominent during the early stages of the illness.

Antipsychotic Dose and Adherence in Relation to Cognitive Improvement

There are several other factors that may impact the extent to which APs augment cognitive outcomes. The dose of AP medication may have an effect on cognition, with higher AP doses, as well as, AP polypharmacy, reported to be associated with worse cognitive functioning (49, 50). Further to this point, it has been reported that when AP dose is reduced, cognition significantly improves in several domains, including memory, visuospatial, language, attention, and delayed memory (51–54). There may also be a relationship between dose and length of time receiving treatment with high vs. low AP dose. One study has shown that with higher doses of APs taken over the long term, verbal learning and recall performance decline significantly over time, independently of age of illness onset or severity of illness. Interestingly, there were no significant differences in cognitive decline observed between low-dose cases and non-psychiatric controls over the 9-years naturalistic follow up (50). Conversely, in a meta-analysis of older schizophrenia patients, medication status or dosing according to chlorpromazine equivalence failed to demonstrate a significant association with cognition over 1–6 years of follow-up (55).

Medication adherence also contributes to the relationship between AP and cognitive functioning. In studies where medication adherence was considered, those who were adherent, not surprisingly, have been reported to show greater improvements in cognition compared to those who did

not take their medications regularly (37). However, whether poor adherence leads to a lack of improvement in cognition or inherent cognitive deficits related to the diagnosis of schizophrenia lead to poor medication adherence remains an unanswered question. Further to this point, a recent review has shown that long acting injectable (LAI) agents show superiority in terms of efficacy when compared to oral agents (56), with reported improvement in general cognitive performance in individuals switching from oral to injectable agents (57). In a direct comparison between risperidone in LAI vs. oral form, it was found that white matter and myelination increased with LAI use while it declined in oral risperidone use (58). This was attributed to adherence to medication (58) and suggests that perhaps adherence to treatment may impact the extent to which cognitive benefits are seen.

Extrapyramidal Adverse Effects and Cognition

Extrapyramidal symptoms (EPS) represent one of the more well-known side-effects of AP medications. While these side-effects have been found to be correlated with impaired cognitive abilities, such as set-shifting (59), it appears that cognitive impairments may be associated with EPS even in the absence of active antipsychotic treatment (35). This raises the question of whether the apparent impairment in cognition is a result of the medication or inherently linked to the illness and its premorbid cognitive dysfunction. Interestingly, with the introduction of SGAs less focus has been given to EPS and studies generally do not report significant correlations with cognition (60–62).

With this said, in cases where EPS is present, it is also critical to account for the role of anticholinergic treatments adjunct and inherent within antipsychotics when evaluating cognitive outcomes. Recent reviews have found that co-treatment with anticholinergic medications have a negative effect on cognition (36, 63), with individuals with schizophrenia particularly susceptible to these effects (64). The aspects of cognition which are most commonly impaired include memory and attention (64). Of note, cognition improves when anticholinergic treatment is discontinued (36, 63).

While each of the above-mentioned factors are important, another facet of AP effects that has not received adequate attention is the effect of AP-induced metabolic dysfunction on cognition. This presents a potentially modifiable therapeutic target (i.e., metabolic syndrome), the management of which can potentially lead to better clinical outcomes.

Antipsychotics and Metabolic Dysregulation

Although "atypical" or SGAs, as a class were associated with higher metabolic risk than first-generation antipsychotics, a more nuanced understanding of this "class" [which in itself has become a topic of controversy (65, 66)], has shown that there is a differential metabolic liability [i.e., olanzapine = clozapine > sertindole > risperidone > = quetiapine > = amisulpride > ziprasidone, lurasidone, aripiprazole (33, 67)] among the different constituent medications classified as an SGA. More recent work, however, suggests that all AP drugs are associated with early significant weight gain (68), particularly in young AP-naïve patients (69–72). The effect on weight gain is also of FGAs, which have historically been considered to be metabolically neutral; haloperidol has been found to cause significant weight gain in AP-naïve patients, with an average 3.8 kg weight gain within the first 3 months of treatment (70). Interestingly, while long-term prospective trials examining AP-induced weight gain are lacking, it has been demonstrated that when drug-naïve first episode patients are followed over the long-term (>2 years), the differences between individual antipsychotic agents disappear (70). This may suggest that treatments differ more by pattern of weight gain, rather than amount.

Similar to the trends seen with weight gain, studies published recently show concerning rates of prediabetes (>15%) in first episode patients within 6 months of AP exposure (73), and significantly higher cumulative risk and incidence of type two diabetes (T2D) (74). A recent population-wide national registry estimated that APs, irrespective of whether they were FGAs or SGAs increased the risk of diabetes 3-fold in patients with schizophrenia (75). Moreover, while overweight and obesity represent leading risk factors for diabetes, work in animals and humans consistently demonstrates that APs can directly induce insulin resistance and glucose dysregulation even in absence of weight or adiposity changes (76). Notably, initial concern with metabolic side-effects linked to these agents was focused primarily on cardiometabolic morbidity and mortality (5). These concerns have been extended to quality of life, self-esteem, medication adherence (77), and most recently, as will be reviewed in detail, potentially to cognitive functioning.

Metabolic Dysregulation and Cognition in Non-psychiatrically Ill Populations

The term metabolic syndrome (MetS) refers to the presence of multiple, interrelated cardiovascular risk factors occurring simultaneously (78, 79). While specific criteria for MetS differ according to different guidelines, in general, three out of the five following criteria must be met: increased waist circumference, elevated triglycerides, reduced high-density lipoprotein (HDL), cholesterol, elevated blood pressure, and elevated fasting glucose (78, 80). There is a large body of data demonstrating impairments in cognition as a result of MetS in psychiatrically non-ill individuals (10, 81–85) and a recent literature review found a strong link between MetS and specific deficits in memory, visuospatial abilities, executive function, processing speed, and intellectual function (86). There are also significant correlations between specific components of MetS and cognition. For example, patients with hypertension performed significantly worse on executive functioning tasks, which was correlated with reduced frontal lobe volume and impaired glucocorticoid feedback (87). Moreover, high body mass index (BMI) has been found to correlate with lower cognition scores (12, 95).

An accumulating body of evidence suggests a mechanistic relationship between cognitive decline, obesity, MetS, diabetes, and Alzheimer's disease (88, 89) with shared neuropathological characteristics and insulin resistance, oxidative stress, and a

persistent inflammatory state as the core pathology. These lines of evidence suggest a tight link between cognitive and metabolic processes and outcomes, which would be predicted to extend to patients with schizophrenia as well. If this association does hold in patients with schizophrenia, an additional intriguing question is also the role of AP-related metabolic perturbations in the context of AP-related effects (or lack there-of) on cognitive function. Thus, focus must be turned to: (1) the association between MetS and cognitive deficits in schizophrenia, and, (2) whether AP-related metabolic dysfunction could, in part, mediate this association.

Metabolic Dysregulation and Cognition in Schizophrenia

MetS occurs in ∼33.5% of patients with schizophrenia (90). There are multiple factors which contribute to the elevated prevalence rate of MetS in the schizophrenia population, including lifestyle factors, such as smoking (91), poor eating habits and sedentary behavior (see Ringen (92) for an in-depth review). Biological and genetic factors inherent to the illness of schizophrenia and treatment response also overlap with genes related to metabolic function (93). For example, genes associated with the illness of schizophrenia have independently been linked to regulation of fat mass, leptin signaling (94), insulin signaling, glucose metabolism, and inflammation (95, 96). In addition, as reviewed here, antipsychotic medications are well-established to contribute to cardiometabolic risk in this already metabolically vulnerable population. Some of these agents are also implicated in cognition. The serotonin receptor gene 5HT2A has been found to influence both lipid levels and glucose intolerance (94), as well as, attention span and cognitive flexibility (97). As well, the methylenetetrahydrofolate reductase (MTHFR) gene is believed to increase the susceptibility of developing MetS in patients with schizophrenia (94), and is also implicated in poorer verbal recall and cognitive flexibility (98). Thus, it appears that the genes implicated in poor metabolic outcomes for individuals with schizophrenia could also be associated with cognitive outcomes.

Taken together, it is perhaps not surprising that the majority of studies in schizophrenia suggest that the relationship between MetS and cognitive dysfunction is similar among schizophrenia patients as it is to non-psychiatrically ill individuals. MetS has a negative impact on cognition, and indeed schizophrenia patients with MetS have been reported to perform worse on measures of cognition than those with schizophrenia in the absence of MetS (9, 99, 100). Performance appears to be negatively impacted on tasks measuring processing speed, memory, attention, and reasoning in those with co-morbid MetS as compared to those with schizophrenia alone (9, 99, 100). Furthermore, this impairment has been shown to develop post-morbidly (101), suggesting that there could be an active mechanism in the developmental course of the disorder that may impair cognition as one's metabolic health declines.

With that said, not all studies have found a relationship between MetS and cognitive impairment in schizophrenia. As reviewed by Bora and colleagues, the CATIE trial stands out as the largest study which failed to find an association (102). Other studies, which may have failed to find an association between MetS and cognitive dysfunction have however found that specific aspects of MetS (i.e., hypertension) were correlated with lower cognitive scores, whereas other factors, such as increased waist circumference and dyslipidemia were less consistently associated with general impairments in cognition in schizophrenia (49, 103). Other factors, which constitute a poor metabolic profile, such as high BMI, have also not consistently been found to predict poor cognitive functioning across several cognitive domains (104). Furthermore, in one study, hyperglycemia was actually found to predict better verbal memory performance (49).

The discrepancy in the schizophrenia literature examining associations between metabolic comorbidity and cognitive deficits could, in part, be attributable to the amalgamation of diverse metabolic aberrations under the common umbrella of MetS (i.e., considering MetS as merely a binary factor) and suggest value in considering cognition alongside individual metabolic symptoms. Indeed, studies that failed to find a relationship between metabolic aberrations and cognitive functioning, such as CATIE study (102), also did not examine effects of individual components of MetS in relation to cognition. This suggests that individual metabolic outcomes might interact independently with cognitive abilities and should be studied as distinct entities to understand the relationship between metabolic and cognitive parameters better (102).

Disentangling Antipsychotic-Induced Metabolic Dysregulation in Relation to Cognition in Schizophrenia

Cognition is a core area of impairment in schizophrenia and the impact of APs on cognition is not fully clear. Also, there appear to be associations between cognition and metabolic parameters that are being gradually understood. In summary, independent relationships exist between APs, metabolic outcomes, and cognition: (i) APs might influence cognition (with benefits more consistently seen early on in illness, possibly in relation to improvements in other domains of psychopathology); (ii) APs cause metabolic dysregulation, and (iii) metabolic dysregulation has been linked to cognitive dysfunction, with the predominance of evidence suggesting this association applies to patients with SCZ. However, the majority of existing studies have looked at individual associations between these factors, leaving more complex interactions between these factors largely unexplored. Here, we attempt to identify and extrapolate associations between these three factors in the presence of schizophrenia.

There have been a small number of studies investigating the interaction of APs, metabolic factors, and cognition in schizophrenia (**Supplementary Table 1**). A study by Chen and colleagues examined metabolic side effects and cognition in first-episode patients to establish whether a cognitive impairment related to metabolic dysfunction would be observed in the early stages of illness and AP treatment (105). In first-episode, newly medicated patients, there was a generally worse metabolic profile and poorer cognitive performance compared to their healthy

counterparts; however, the effect size was small. Chen et al. also demonstrated that an inverse relationship between cognition and metabolic symptoms within the newly medicated patients was present but that it was relatively small (105). The specific contribution of AP medications on metabolic comorbidity in relation to cognition was not examined in this cross-sectional design. In another study by Li and colleagues (99), cognitive performance of two groups of chronic schizophrenia patients, according to presence or absence of MetS was cross-sectionally compared, with secondary analyses considering relationships with disease course and antipsychotic medications. In the MetS group, cognition was significantly worse, as has been replicated in similar studies examining the interaction between APs, cognition, and metabolic outcomes (9). In the study by Li and colleagues, this association was attributed to higher fasting triglycerides and systolic blood pressure. Interestingly, however, the course of disease was significantly longer in the MetS compared to non-MetS group. Both duration of disease and use of FGAs (as compared to SGAs) were independently correlated with lower cognitive scores. The caveat here was that the most commonly prescribed FGA was chlorpromazine, which has been established to have a similar metabolic risk profile to higher metabolic liability SGAs, such as clozapine. Thus, while interpretation of specific contributing effects of APs according to predicted metabolic liability was not possible, duration of illness leading to cumulative effects of metabolic comorbidity appeared to emerge as a key predictive factor for worse cognitive function. Similar results were also seen in a study by Boyer et al, who found that longer disease duration was correlated with increased rates of MetS, and this was subsequently correlated with worse cognitive impairment, which was particularly robust in individuals taking second generation APs (106). Taken together, illness duration appears to be the more consistent factor linked to cognitive impairments.

Furthermore, specific components of MetS also appear to be differentially related to cognition in studies which considered the presence of AP medications. Hypertension has been shown to correlate with lower verbal cognition scores, including memory and fluency (49). Triglycerides have also been shown to correlate with poorer cognition scores (100), however this effect has been shown to cease to exist when cholesterol is controlled for (107). As for waist circumference (i.e., abdominal obesity), there is discord in the literature on whether it has an effect on cognition (100, 104) or if it does not (49).

From the evidence presented above, perhaps as illness course and treatment continues metabolic comorbidities accumulate and become more severe (in association with illness duration which is invariably linked in the majority of cases with longer exposure to medications); we subsequently see cumulative effects play out on cognition more clearly. This may explain why the relationship between cognitive performance and metabolic indicators appears to be more robust in patients with longer duration of illness. The accretion of structural changes in the brain (with illness progression, treatment, and metabolic abnormalities) may also contribute to this relationship, as cognitive performance has been shown to be associated with lower gray matter volume (108, 109).

Potential Mechanisms Underlying Cognitive Functioning and Metabolic Risk in Schizophrenia

While there is a paucity of literature examining the interrelation among APs, cognition, and metabolic disturbances in schizophrenia, the existing literature points to a number of potential mechanistic influences to explain the effects of APs on cognition and metabolic disturbances.

i. Direct receptor action: While all antipsychotics bind to the dopamine, D_2 receptor, a majority of them bind to multiple other receptors including the histamine, serotonin, muscarinic and adrenergic receptors. Antagonism of each these receptor systems is independently known to affect cognition, as well as, metabolic outcomes, such as weight gain, insulin and glucose dysregulation, and dyslipidemia. Hence, it is quite plausible that the effects of APs on cognition and metabolic measures are really two sides of the same coin: as binding to a given receptor leads to downstream effects on both domains (110). For instance, acute dopamine depletion in humans and rodents reduces peripheral insulin sensitivity (111, 112), purportedly via central dopamine effects in the striatum. Moreover, reduced insulin sensitivity and obesity are associated with reduced dopamine synthesis capacity and endogenous dopamine levels in the striatum (112–114). These neurochemical alterations in turn may be associated with poor cognition. Thus, it is plausible that central dopamine receptor blockade by antipsychotics in schizophrenia may produce both peripheral insulin resistance and poor cognition. Interestingly, evidence suggests that acute antipsychotic exposure does not alter striatal dopamine levels and dopamine synthesis capacity in first-episode patients with schizophrenia (115). While highly speculative, this high dopaminergic reserve in the first-episode may help potentially explain why metabolic side effects have not been related to cognitive deficits in first-episode patients.

ii. Gut microbiome mediated interactions: In addition to the mechanisms of direct receptor action, the role of the gut microbiome (GMB) represents another pathway that may mediate the relationship between cognitive and metabolic dysfunction in schizophrenia (116). The GMB is the collective term for the community of microorganisms residing in the digestive tract. High throughput sequencing is beginning to provide insight into the differences in GMB composition among those with and without schizophrenia. An increased alpha diversity in the GMB has been reported in patients with schizophrenia and has been found to be a significant predictor of schizophrenia status (117). Within the GMB of patients with schizophrenia, most microbial taxa are derived from bacteria and arachae (117). At the phylum level, individuals with schizophrenia appear to have higher proportions of Firmicutes and lower proportions of Bacteroidetes and Actinobacteria in comparison to healthy controls (118). Overall, individuals with schizophrenia have been found to have greater species diversity than those without (119). The severity of different symptom domains of schizophrenia has been found to be significantly correlated

with increases in *Lactobacillus* (120). When looking solely at the interplay between the GMB and schizophrenia, it appears that abnormalities in the GMB contribute to the production of key molecules (such as Brain-derived neurotrophic factor) and/or the promotion of an intestinal immune response (120). Both human and mice studies have confirmed that an altered composition of the GMB influences adverse cognitive and metabolic changes seen in schizophrenia (121–123). The relationship between the GMB and schizophrenia pathogenesis becomes even more complicated when antipsychotics are introduced. There are several overlapping sites of action among the GMB and APs (124), and some APs have been shown to modulate the composition of the GMB, which incidentally has been shown to cause weight gain (125). The interactions between schizophrenia, APs, and the GMB have gained increasing attention over the past few years, however to date only one study has investigated the use of antipsychotic and their effect on the GMB in humans (125). This lack of knowledge represents an opportunity to better understand the pathophysiology of schizophrenia concurrently to metabolic comorbidity associated with the GMB and may lead to new therapeutic interventions to target both psychopathological and metabolic indices.

iii. Central insulin resistance: While receptor action and gut microbiome mediated interactions may underlie these relationships, central insulin resistance might be the final common pathway by which metabolic and cognitive outcomes interact. Central insulin has been well-established to regulate cognition in humans. Intranasal insulin, which delivers insulin directly to the CNS, is demonstrated to enhance declarative and working memory (126). Thus, dysregulation or resistance to central insulin action could result in impaired cognition, and indeed, recent work suggests that insulin is the common link between metabolic disorders and disorders of cognition (127). Central insulin resistance has been found to be a central piece of the pathology in cognitive dysfunction in the context obesity and type 2 diabetes, as well as, in aging and dementia. Insulin resistance has been shown to be associated with impaired hippocampal synaptic plasticity and memory (128), as well as, neurogenesis (129). It is possible that this involves the palmitic acid pathway (128). Furthermore, addressing this pathology via administration of insulin intranasally is emerging as a possible treatment strategy in Alzheimer's dementia (130). Interestingly, work from our lab demonstrates that short term use of APs can induce central insulin resistance resulting in glucose dysregulation and changes in feeding independently of weight gain and other longer term metabolic dysfunction (131). The propensity of APs to cause insulin resistance both in the short term, and in the long term via changes in weight and adiposity, might explain, at least in part, worsening of cognition seen in schizophrenia patients with long standing illness who accumulate metabolic dysfunction over time.

iv. Microangiopathy: Another mechanism by which APs, metabolic abnormalities and cognition might interact is microangiopathy or microvascular abnormalities. Microangiopathy is a well-known consequence of metabolic abnormalities including diabetes and metabolic syndrome (132, 133), and is closely related with the development of insulin resistance (134). While classical targets include the eye, the kidney, and the peripheral nervous system, more recent work shows that the effect is more widespread and includes the brain and adipose tissue as well (132). Microangiopathic changes in the brain have been implicated in cognitive decline (135). Furthermore, there is preliminary evidence that APs may affect the neurovascular unit and small vessels in frontal cortex in a post-mortem study (136). Thus, it is possible that microangiopathy could be a potential mechanism by which APs, metabolic abnormalities and cognition interact. The gradual development of microangiopathy would also, in part, explain why the relationship between metabolic abnormalities and cognitive decline is seen later on in the illness course.

Thus, the effects of APs on cognition and metabolic outcomes likely result from a complex relationship between differential receptor binding, changes in glucose metabolism, insulin sensitivity, the gut microbiome, blood vessel related changes, along with other yet to be described mechanisms to manifest in the clinical outcomes seen. This complex interaction, combined with underlying pathophysiological and lifestyle factors, is likely responsible for the heterogeneity in results when addressing the relationship between APs, cognition, and metabolic disturbances.

Concluding Thoughts

There is still a great deal of uncertainty regarding the relationship between cognition, APs, MetS and schizophrenia. First, there are varying results regarding whether APs actually improve cognition, which aspects of cognition are improved, and the degree of improvement. APs are shown to cause metabolic dysregulation that has been shown to negatively impact cognition. It is tempting to simplify the scenario and assume that as APs induce metabolic dysfunction, cognition should therefore be impaired. However, this does not seem to consistently be the case, given that in some cases, though metabolic side effects were observed, this was not associated with impairments in cognition. As a case in point, young, AP-naïve individuals are most vulnerable to obesogenic effects of AP medications, yet, as reviewed here, the association between MetS and cognitive deficits appears to be most prominent in individuals in the chronic stage of illness. Moreover, it might be expected that individual AP agents that are associated with the greatest metabolic risk (i.e., olanzapine and clozapine), should be associated with worse cognitive functioning. Again, this does not appear to be the case. At first glance these observations would appear to argue against a direct association between AP-induced metabolic adverse effects and detrimental cognitive effects. However, several other points warrant consideration. Firstly, early weight gain, glucose, and lipid abnormalities induced by AP medications may not, in themselves, be sufficient to immediately translate to cognitive impairments. It is possible then that adverse metabolic side-effects of APs act as a catalyst for later development of microvascular insults to the brain that may take place several years following onset of individual metabolic

comorbidities. It is perhaps also not surprising that a "between agent," "according to metabolic liability" effect on cognition is not observed. As discussed in earlier sections, the between agent difference in metabolic liability appears to diminish overtime. Thus, it can be argued that individual differences between agents may be relatively less important than the acceleration in metabolic risk that occurs overtime.

To summarize, the relationship between metabolic comorbidity and worse cognitive function appears to be generalizable to patients with schizophrenia. The current literature, however, does not allow assessment and establishment of a causal connection between the well-recognized metabolic adverse effects of APs and cognitive deficits. A proposed threshold effect in the relationship between metabolic dysfunction and cognition could suggest that earlier on in treatment, metabolic adverse effects related to treatment may have a minimal impact on cognition. However, once an individual passes a certain threshold of metabolic dysregulation, they likely become susceptible to cognitive impairment. Thus, the impact of metabolic side effects may begin to override any positive or neutral effects on cognition observed in individual taking APs once this threshold (which may be dependent on many factors) is reached. Brains of schizophrenia patients show evidence of accelerated aging even early on in the illness (123). Thus, metabolic aberrations may interact with and add to the existing deficits, and thereby contribute to cognitive impairment, with brain aging perhaps playing a role. Like many psychiatric disorders, schizophrenia has been hypothesized to be a syndrome of accelerated aging (137, 138). Support for this stems from the shared syndromes and risk factors between schizophrenia and age related cognitive and metabolic chronic diseases, such as Alzheimer's Disease and Type II diabetes, respectively. Patients with schizophrenia have an increased risk of diabetes and experience an earlier onset of this illness (139). While the focus has been on AP-related metabolic dysregulation, we are reminded that lifestyle factors (smoking, dietary habits, activity levels) also play a critical role in accumulation of metabolic risk in severe mental illness, and both the primary disorder, as well as, accumulation of metabolic risk has been shown to accelerate aging related changes (140, 141).

Going forward, there are important therapeutic implications to keep in mind in regards metabolic disturbances and cognition. Lifestyle interventions, such as diet and exercise, to prevent and/or correct metabolic abnormalities (whether due to APs, lifestyle or illness pathophysiology) can have gains above and beyond physical health. In particular, the available literature suggests that improvement of metabolic status may improve or prevent further impairment of cognition in patients with schizophrenia. For example, a recent review by Firth et al. (142) found that aerobic exercise improved cognitive functioning in patients in schizophrenia (104). In addition, reduction/prevention of AP-induced metabolic side effects is particularly important in the AP-naive and youth population, as APs appear to have the greatest potential to improve cognition at the beginning of treatment, yet AP-naive population are at greatest risk of AP-induced metabolic side effects. This review highlights that assessment of metabolic factors should be considered when studying cognition in schizophrenia, as these metabolic disturbances may be influencing cognitive outcomes. Future studies investigating the mechanism behind the impact of metabolic disturbances upon cognition are suggested to allow for more specific treatments. Overall, more research is required to identify the complex interactions between APs, metabolic status, and cognition, in schizophrenia to enable patients to receive the maximum therapies for cognitive improvements.

AUTHOR CONTRIBUTIONS

NM, CK, SA, and MH contributed to the conception and design of the review. NM, CK, SA, and MH wrote the first draft of the manuscript. KC-D, FC, PG, GR, VT, DM, AG-G, and AC wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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MINI REVIEW
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Increased Risk of Metabolic Syndrome in Antidepressants Users: A Mini Review

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Mounting evidence has shown that the risk of metabolic syndrome (MetS) is substantially overlapping in the diagnostic subgroups of psychiatric disorders. While it is widely acknowledged that patients receiving antipsychotic medications are at higher risk of MetS than antipsychotic-naive ones, the association between antidepressants and MetS is still debated. The goal of our mini review was to analyse the relationship among depressive symptoms, antidepressant use and the occurrence of MetS. Adhering to PRISMA guidelines, we searched MEDLINE, reference lists and journals, using the following search string: ((("Mental Disorders"[Mesh]) AND "Metabolic Syndrome"[Mesh]) AND "Antidepressive Agents"[Mesh]), and retrieved 36 records. Two reviewers independently assessed records and the mini review eventually included the data extracted from 8 studies. The Newcastle-Ottawa Scale was used to assess the quality of the selected studies. Overall, the results of the mini review seem to support the association among depressive symptoms, antidepressants therapy and MetS. Except for H1-R high-affinity ones, the relationship between antidepressants and MetS still needs to be clarified. Considering the widespread prescription of antidepressants, both on behalf of psychiatrists and primary care physicians, further research on this topic is recommended.

Keywords: metabolic syndrome, depression, antidepressants, cardiometabolic disease, review, preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement

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INTRODUCTION

Metabolic syndrome (MetS) is a cluster of obesity, insulin resistance, hypertension, impaired glucose tolerance or diabetes, hyperinsulinemia, elevated triglycerides and low high-density lipoprotein (HDL) concentrations (1, 2). A syndrome can be regarded as "a clustering of factors that occur together more often than by chance alone and for which the cause is often uncertain" (3). According to the International Diabetes Federation (IDF) definition, MetS is characterized by central adiposity plus two or more of the following four factors (4): (1) raised concentration of triglycerides: ≥150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality; (2) reduced concentration of HDL cholesterol: 40 mg/dl (1.03 mmol/l) in men and 50 mg/dl (1.29 mmol/l) in women, or specific treatment for this lipid abnormality; (3) raised blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or treatment of previously diagnosed hypertension; and (4) raised fasting plasma glucose concentration ≥100 mg/dl (5.6 mmol/l) or

previously diagnosed type 2 diabetes. Furthermore, the IDF lists ethnic group–specific thresholds for waist circumference to define central adiposity (5).

National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria require three out of five factors to establish the diagnosis of MetS, i.e., abdominal obesity (waist circumference >88 cm for women or > 102 cm for men), increased triglycerides (≥150 mg/dL), reduced HDL cholesterol (<50 mg/dL for women or <40 mg/dl for men), high blood pressure (≥130/85) (6) and high fasting glucose (≥100 mg/dL) (7).

A vast body of literature (8–16) has pointed to a major role of mental illness (especially bipolar disorder, depression, anxiety, and suicidal ideation) in the future development of MetS and associated diseases. A variety of factors may be responsible for MetS in patients suffering from mental illnesses, such as lifestyle, diet, tendency to insulin resistance, and medication side-effects, especially those of antipsychotics (17). Antipsychotics, mostly second generation ones (SGAs) such as clozapine, olanzapine, and risperidone, seem to be involved in the development of MetS (18, 19). Albeit the pathophysiology of SGAs-induced metabolic alterations is not yet fully elucidated, increased food intake, weight gain, hyperglycemia, lipid accumulation in adipose cells and liver are hallmarks of this problem (19).

Several studies (20–23) have shown a high comorbidity between major depressive disorder (MDD) and MetS (24, 25). Depression can cause a 2-fold increase in the risk of MetS in the general population, probably due to poor health-related behaviors (26). Furthermore, independent of the psychiatric disorder diagnosis, antidepressants may have a direct impact on MetS (27), and overall negative consequences for cardiometabolic health (28–31).

While prescription of antidepressant medication is increasing (30) and there is evidence of weight gain induced by antidepressants (31), the association between Mets and antidepressants still remains only partially understood. The introduction of tricyclic antidepressants (TCAs) in the late 1960s, followed by that of selective serotonin re-uptake inhibitors (SSRIs) in the 1980s, together with the increase of long-term prescriptions (in the 1990s and 2000s) and to the more recent use of higher doses of antidepressants, have contributed to a tendency toward over prescribing of antidepressants (32). Although there is much evidence supporting the association between MetS dysregulations and the use of TCAs, particularly abdominal obesity (33, 34), the effects of SSRIs on MetS are far less clear (35, 36).

Considering the possible role of mental illness in the future development of MetS and the need to clarify the impact of antidepressant treatment on MetS, the aim of this mini-review was to address the relationship among depressive symptoms, antidepressant use and the occurrence of MetS.

METHODS

Adhering to PRISMA guidelines, a literature search was conducted in MEDLINE on 13 February 2018, using the following search string: (((“Mental Disorders”[Mesh]) AND “Metabolic Syndrome”[Mesh]) AND “Antidepressive Agents”[Mesh]). The search was restricted to the English language. To be included in the mini review, papers had to be cross-sectional or cohort studies designed with the purpose of analyzing the association between MetS, depressive symptoms or antidepressants therapy. Two reviewers (CG and EG) independently triaged the titles and then the abstracts to exclude those that were clearly inappropriate. Possible disagreement between reviewers was resolved by joint discussion with a third review author (PZ). Reasons for the exclusion of papers from the review were reported in the PRISMA flow diagram.

After selection of the relevant studies, reviewers extracted and tabulated data using a standard form (**Table 1**). Extracted data included country of origin, research objectives, databases and period assessed, study design, participants’ features. Some data were tabulated, while other, including those about educational and occupational level, socio-demographic data collection methods, lifestyle data collection methods, anthropometric measurements (including waist circumference and Body Mass Index [BMI]), were reported in the text description in the Results section.

Outcome data were presented as count data. Narrative data extracted from the papers included in this mini review are reported in **Table 1**. Where necessary, text descriptions were used to highlight information that was not captured in the Table.

Finally, the Newcastle-Ottawa Scale (NOS) (44) was used to assess the quality of the selected cohort studies. The quality of cross sectional studies was evaluated through an adapted version of the NOS (45).

The need for an Ethics Committee approval was waived, since we just collected and synthesized data from previous clinical trials in which informed consent had already been obtained.

RESULTS

Selection

The PubMed literature search identified 36 articles. After title, abstract, and eventually full-text screening, 8 papers (1, 37–43) met inclusion criteria for this mini-review (see **Figure 1** for more details) (46).

Study Design and Features

Of the 8 studies included in our mini-review, 2 used a prospective cohort design (37, 41), and 6 a cross-sectional design (1, 38–40, 42, 43). In 3 studies the number of participants was ≤99 (38, 40, 43), 2 studies had a sample ranging from 100 to 240 individuals (37, 41), 3 studies included more than 250 patients (1, 39, 42). The average number of participants was of 277 ± 296 (SD) (min 60, max 970 participants). Only one study (39) was multicentric, involving 5 centers, while the other 7 ones were monocentric. Six studies were performed in Europe (38–43), 1 in the United States of America (1), and 1 in Asia (37). Only five studies reported data on the recruitment setting: specifically, two studies included inpatients from a psychiatric ward (40, 41); two studies recruited outpatients (1, 37), while the sample was mixed (both inpatients and outpatients) in 1 study (39). Three studies

TABLE 1 | Narrative synthesis of the studies included in the mini-review.

Authors	Country and study period	Design and number of participants	Participants' features (mean age, gender, % M)	Assessment of depression	Antidepressant class	Other medications	Comorbidities	MetS criteria and %	Main results	Nos
Crichton et al. (1)	USA, 1975–2011	Cross-Sectional *N* = 970	n/a, M/F, 41%	Performed by an examiner	n/a	n/a	n/a	IDF, 44	High risk of MetS and low HDL in patients with depressive symptoms; high risk of MetS, low HDL, carbohydrate metabolism disorders (diabetes) and hypertension in patients on antidepressant therapy.	9
Hung et al. (37)	Taiwan, 2008–2009	Cross Sectional *N* = 229	44 year, M/F, 63%	n/a	SSRI—SNRI—Others	yes	n/a	IDF, 22	BMI related to MetS. Pharmacotherapy seem to be related to high BMI.	5
Kopf et al. (38)	Germany, n/a	Prospective Cohort *N* = 78	53 year, M/F, 31%	Performed by an examiner and self-administered questionnaire	SSRI—TCA	yes	no	IDF, n/a	Treatment of depression exerts a mainly beneficial effect on lipid regulation.	6
Luppino et al. (39)	Holland, 2004–2009	Cross Sectional *N* = 827	43 year, M/F, 38%	Performed by an examiner	SSRI—TCA—Others	n/a	yes	NCE-ATP III, 26	Depression severity weakly associated with glucose levels. There seem to be a mediating role for TCA and NSRI antidepressant use in increasing triglycerides levels, with limited clinical differences.	5
Margari et al. (40)	Italy, 2013–2013	Cross Sectional *N* = 160	50 y, M/F, n/a	Performed by an examiner	n/a	yes	yes	NCE-ATP III, 29	Positive association between antidepressant treatment and triglycerides and triglycerides/HDL ratio levels.	6
Sagud et al. (41)	Croatia, n/a	Cross Sectional *N* = 203	53 year, n/a, n/a	Performed by an examiner	SSRI—NRI—SNRI—Others	yes	yes	NCE-ATP III, n/a	MetS was observed in 33.5 % of patients (no significant differences between TRD and non-TRD), without correlation with cardiovascular risk factors.	5
Salvi et al. (42)	Italy, 2008–2012	Cross Sectional *N* = 289	50 year, M/F, 63%	Performed by an examiner	SSRI—TCA—SNRI—Others	yes	no	NCE-ATP III, 25	Greater frequency of MetS in patients treated with H1 high affinity antagonists.	7
Stanojević et al. (43)	Serbia, 2013–2013	Prospective Cohort *N* = 60	48 year, M/F, 52%	Performed by an examiner	SSRI	n/a	n/a	NCE-ATP III, 38	In depressed patients, elevated CRP levels associated with increased frequency of MetS.	3

N, Number; M, Male; F, Female; y, Years; MetS, Metabolic Syndrome; n/a, not applicable; SSRI, Selective serotonin reuptake inhibitors; TCA, Tricyclic antidepressant; SNRI, Serotonin–norepinephrine reuptake inhibitors; BMI, Body Mass Index; HDL, High Density Lipoprotein; NOS, Newcastle Ottawa Scale.

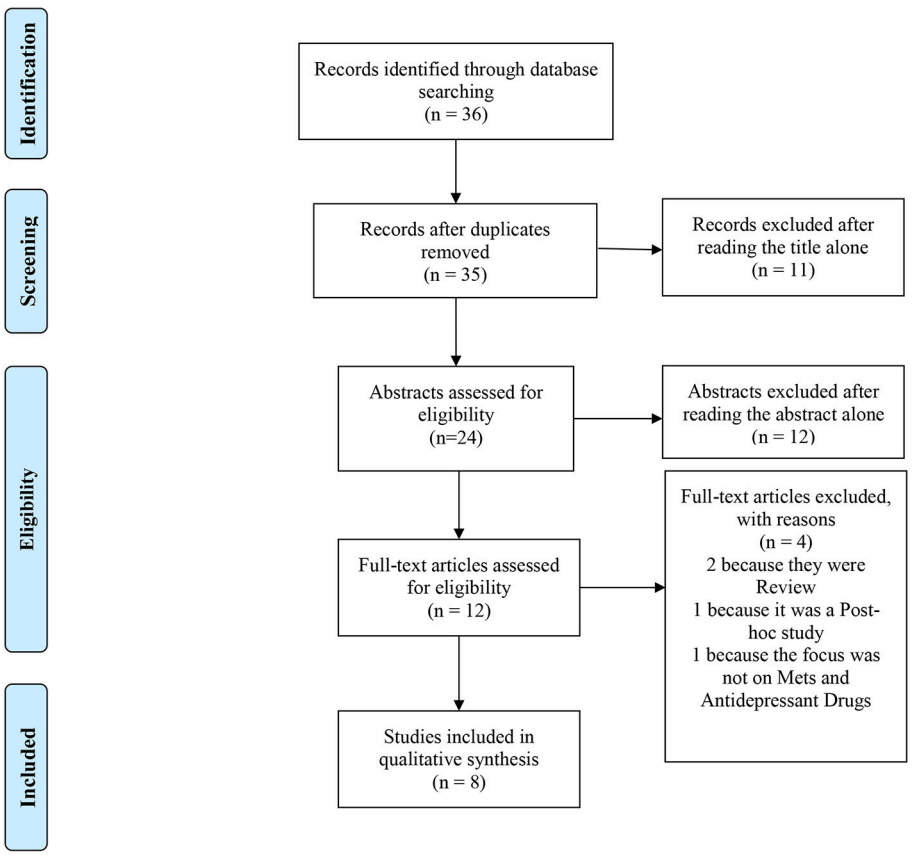

FIGURE 1 | PRISMA 2009 flow diagram. Adapted from Moher et al. (47).

did not report information about recruitment setting (38, 42, 43). Only 2 studies (38, 41) reported data about the staff involved in the research, composed by doctors and nurses.

The average duration of the studies was 113 ± 180 (SD) months, ranging from a minimum of 10 to a maximum of 432 months. All the studies included in the mini review had obtained ethic committee approval.

Socio-Demographic and Lifestyle Features

Participants' age ranged from 18 to 98, with a mean of 47.73 ± 3.51 (SD) years. All the included studies involved participants of both genders. All studies reported sociodemographic data, which were retrieved from medical records in 6 studies (1, 38, 40–43); only one study (37) specified details about participants' occupational status. Six studies provided lifestyle data, obtained by medical records in 2 studies (38, 41), by the anamnesis in 2 other studies (40, 42), and via a specific questionnaire in the last 2 studies (1, 43)

Seven studies (1, 37, 39–43) analyzed participants' smoking habits; this information was retrieved from a direct question in 3 studies (40, 42, 43), from a self-report measure (the Nutrition and Health Questionnaire) in one study (1), and from previous-year medical records consultation in another one study (41). The source of this information was not specified in 2 studies (37, 39).

Alcohol consumption was described by all included studies. Anyway, only 1 study reported data on participants' eating habits (1), as assessed by the Nutrition and Health Information Questionnaire (32).

Two studies reported information about physical activity: 1 study (48) used the Nurses' Health Study Activity Questionnaire (49) and MET-hours per week (a metabolic equivalent is a unit that describes the energy expenditure of a specific activity) for each activity (50); 1 study reported data on structured physical activity or 30 min of walking per day (42).

Metabolic Parameters

NCE-ATP III and IDF criteria for MetS were adopted, respectively, by 5 (39–43) and 3 of the selected studies (1, 37, 38). Seven studies collected blood examinations (1, 37–43); 7 studies recorded blood pressure (1, 37, 39–43); last, 7 studies reported information about anthropometric measures (1, 37, 39–43). All the studies included in this mini-review collected data about hypertriglyceridemia (>150 mg/dl), arterial hypertension (>130/85 mmHg) and fasting hyperglycemia (>110 mg/dl); furthermore, 7 studies assessed HDL cholesterol as well (men <40 mg/dl, women <50 mg/dl) (37–43). Waist circumference was measured in 6 studies; in 4 of them, abdominal obesity was diagnosed for values above the following cutoffs: >102 cm

for men and >88 cm for women (39, 41–43); 2 studies adopted different cutoff values: >94 cm (1), and >90 cm for men and >80 cm for women (37), respectively. Seven studies reported data on BMI (1, 37–43).

Antidepressant Medication and Depressive Symptoms

Six studies reported data on type of antidepressant agents (37–39, 41–43).

Six studies reported data on SSRI (37–43); only one on norepinephrine reuptake inhibitors (NRIs) (41); 4 studies on Serotonin and norepinephrine reuptake inhibitors (SNRI) (37, 39, 41, 42); 3 studies reported data on Tricyclic and tetracyclic antidepressants (TCA) (38, 39, 42); 3 studies reported data also on other drugs (37, 39, 41).

With more detail, Stanojević et al. (43) compared 35 SSRI medication-treated patients; Kopf et al. (38) analyzed 78 depressed patients in treatment with amitriptyline or paroxetine; Salvi et al. (42) involved 294 antidepressant-treated patients with bipolar disorder, treated with the use of antidepressants (SSRI, TCA, SNRI, and other medications); Hung et al. (37) analyzed different antidepressants, including paroxetine, trazodone, escitalopram, fluoxetine and venlafaxine; Luppino et al. (39) compared 302 primary care outpatients, 445 secondary care outpatients and 80 inpatients, with major depressive disorder (MDD), treated with TCA or Serotonin and norepinephrine reuptake inhibitors (SNRIs) and mirtazapine; Sagud et al. (41) analyzed patients data in therapy with SSRIs, SNRIs, tianeptine, mirtazapine, bupropion, reboxetine, and maprotiline.

Only 1 study reported information about the specific phase of MDD (41), while 4 studies included details about the severity of depressive symptoms (38–42). All studies adopted specific questionnaires for the assessment of depression (1, 38–43). In 7 studies the questionnaire was a clinician-administered interview (1, 37–39, 41–43), while in 1 study both a clinician-administered interview and a self-administered questionnaire were used (40). More specifically, 4 studies (37, 38, 41, 43) used the Hamilton Depression (HAM-D) Rating Scale (44), one (1) the CES-D scale (44), one (1) the Zung self-rating depression scale (44), another one (42) the Clinical Global Impressions Scale (CGI-BD) (51) and the Structured Clinical Interview (SCID) (52), and a last one (40) used the Brief Psychiatric Rating Scale (BPRS) (53), the HAM-D Rating Scale (44), the Spielberger State-Trait Anxiety Inventory (STAI) (53, 54) and the Personality Diagnostic Questionnaire (PDQ-4+) (53).

Psychiatric and Medical Comorbidity

Four studies included participants who were treated with other psychiatric medications beyond antidepressants (37, 38, 40, 43). One study evaluated cognitive function (1). Five studies analyzed other psychiatric variables (37, 38, 40–42). Three studies reported information about medical comorbidities (39, 41), and 2 studies about treatment for medical conditions beyond depression (40, 41).

Outcomes and Assessment of the Quality of Studies

Stroke was reported in 1 study (1), Cardiovascular Disease (CVD) in 3 studies (37, 39, 41). The NOS scores ranged from 3 to 9, with a mean score of 5.75 ± 1.75 (SD).

Cross-Sectional Studies

Sagud et al. (41) assessed 203 inpatients with MDD, including both treatment resistant (TRD) and non-treatment resistant (non-TRD) individuals. They did not find any relationship between MetS and treatment resistance.

Crichton et al. (1) suggested that cardiovascular risk factors attenuated the relation between depression and MetS; moreover they shown that, while depression appeared to increase the risk of CVD (1), CVD could promote the onset of depression.

The cross-sectional study by Salvi et al. (42) involved 294 antidepressant-treated patients with bipolar disorder. No association was found between the use of antidepressants (SSRI, TCA, SNRI, and others) and MetS. However, subjects on H1-R high-affinity antidepressants treatment ($N = 15$) showed a higher prevalence of MetS, likely due to the anti-histaminic effect of this type of antidepressants, which counteracts histamine central anorexigenic effects (6) and increases adipose tissue deposition (8).

Luppino et al. (39) compared 302 primary care outpatients, 445 secondary care outpatients and 80 inpatients with MDD. No significant difference among patients recruited in the three treatment settings was found either in the prevalence of MetS (26% primary, 24% secondary care, and 28% inpatients) or in clinical and laboratory measures including waist circumference (WC), BMI, LDL cholesterol, glucose and diastolic blood pressure (DBP). However, inpatients reported higher waist-hip ratio, total cholesterol and triglyceride levels and lower HDL cholesterol levels and systolic blood pressure than outpatients. Results showed significant associations for TCA use with higher DBP ($\beta = 0.10$, $P = 0.003$) and LDL-cholesterol ($\beta = 0.07$, $P = 0.04$), while the use of other antidepressants (Serotonin and norepinephrine reuptake inhibitors-SNRIs and mirtazapine) was associated with higher triglyceride levels ($\beta = 0.10$, $P = 0.004$).

Hung et al. (37) studied 229 outpatients, 85 males and 144 females, recruited by systematic sampling of 1,147 outpatients affected by anxiety and mood disorders. The authors analyzed the impact of pharmacotherapy and psychiatric diagnoses on MetS and found that 51 (22.3%) subjects of 229 outpatients matched MetS criteria, likely due to treatment with antipsychotics and mood stabilizers. The study also shown that antidepressant-treated (paroxetine, trazodone, duloxetine, escitalopram, fluoxetine, and venlafaxine) patients and patients treated with other medication than-antidepressants (antipsychotics and mood stabilizers) did not significantly differ as far as MetS risk is concerned.

Margari et al. (40) evaluated the differences in anthropometric measures, biochemical variables, MetS and cardiovascular risk in a sample of 83 psychiatric inpatients under pharmacological treatment and 77 internal medicine patients. Female psychiatric patients showed higher levels of triglycerides (mg) and of

homeostatic model assessment (HOMA) index than males. Patients with unipolar depression reported highest triglycerides and triglycerides/HDL ratio levels with a strong relation with antidepressant treatment.

Cohort Studies

Stanojević et al. (43) compared 35 SSRI medication-treated patients with recurrent depressive disorder and 25 healthy controls. Elevated C-reactive protein (CRP) levels were found to be associated with an increased frequency of MetS in depressed patients. While no statistically significant difference was found between depressed patients and controls regarding either the prevalence of MetS or CRP levels, waist circumference and total cholesterol levels were significantly higher in the first than in the latter.

Kopf et al. (38) analyzed lipoprotein composition, insulin sensitivity and salivary cortisol in 78 depressed patients in treatment with amitriptyline or paroxetine at baseline (t0) and after 35 days of treatment. No change in quantitative insulin sensitivity check index (QUICKI) was found after 35 days of treatment. Moreover, only patients on amitriptyline treatment showed increased levels of triglycerides ($P < 0.05$). Parameters of cholesterol metabolism improved slightly without differences between treatment groups. The authors concluded that both the antidepressant treatments assessed might exert a mainly beneficial effect on lipid regulation.

Narrative Analysis

A summary of extracted data is reported in **Table 1**.

DISCUSSION

Previous studies suggested a higher risk of unhealthy behaviors (i.e., excessive alcohol consumption, smoking, obesity, lack of physical activity) (55, 56) in depressed patients, both with a current depressive episode or with a lifetime diagnosis of depression (57), which may contribute to their increased risk of MetS. Moreover, severity of depression seems to correlate with smoking, obesity and physical inactivity following a dose–response mechanism (58–60). Actually, Pan and coworkers' systematic review (18) described an association between depression and MetS in adults and supported early detection and management of depression among patients with MetS and vice versa.

The current mini review included two cohort (37, 41) and six cross-sectional studies (1, 38–40, 42, 43). Most of them were performed in Europe and involved a single center. Patients were recruited from different settings, including psychiatric wards, outpatient services or both. Six studies reported data on the type of antidepressant assessed (37–39, 41–43), and 6 studies included patients treated with other psychiatric medications beyond antidepressants (37, 38, 40–43).

As regards correlation between MetS and antidepressants use, only one study (42) showed that the risk of Mets was greater for patients treated with antidepressants with high affinity binding to histamine H1-receptors. There seems to be an association between the use of antidepressant medication and alterations of lipid profile. In particular, Luppino et al. (39) suggested a mediating role of TCA and NSRI antidepressant use on the increase of triglycerides level (40), while Crichton et al. (1) suggested a correlation with carbohydrate metabolism disorders (diabetes) and hypertension in patients on antidepressant therapy. Hung et al. (37) postulated that pharmacotherapy may lead to over-weight problems.

The studies included in this mini review, consistent with a previous report on this topic (61), support the hypothesis that, beyond the use of antidepressant medications, MetS may be associated with depressive symptoms, especially when associated with neurovegetative features, and that the inflammatory response may play a key role in this phenomenon. Indeed, the study by Stanojević et al. (43) found that elevated CRP levels in depressed patients were associated with an increased frequency of MetS.

Two studies included in the mini review (1, 39) support the idea that the increased rate of Mets in depressed patients might depend on the involvement of both depressive symptoms and antidepressants use. In particular, one study (1) showed that, among patients with depressive symptoms and lower HDL rates, there seems to be a higher risk of MetS Sagud et al. (41) did not find any significant difference between TRD and non-TRD in the occurrence of MetS or cardiovascular risk factors.

Only the cross sectional study by Kopf et al. (38), observed an inverse correlation between cortisol and cholesterol in the obese subgroup of amitriptyline or paroxetine-treated patients, consistent with the widely acknowledged association of depression and low cholesterol levels (9, 10), and supporting the hypothesis that antidepressants may exert a mainly beneficial effect on lipid regulation.

Moreover, studies using IDF criteria reported stronger correlations among depression and Mets than those using NCEP ATP-III ones (40–42) with the exception of the study by Kopf et al. (38).

Strengths

Our mini review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (46). Quality of included studies was assessed with the NOS (NOS scores ranged from 3 to 9). Accuracy of MEDLINE search was guaranteed by using MeSH terms and text words related to research studies on association between MetS, depression and antidepressants.

LIMITS

The mini review was limited to publications in English language available in the MEDLINE database. The choice of a simple single search query might have caused the inclusion of a limited number of articles in the mini review. Therefore, it is possible that the literature search we performed was not comprehensive, and that excluding other electronic databases and languages other than English may have caused the exclusion of potentially interesting articles. Nonetheless, recently it has been suggested that there is no significant effect on the outcome of a review including only one database rather than more than one (62, 63).

CONCLUSIONS

The results of this mini review seem to slightly support the association among depressive symptoms, antidepressants therapy and MetS. Nonetheless, due to the absence of reliable and detailed trial data reported in the studies included in the review, it could be difficult to tease out effects of depression from those of the medications used.

Overall, antidepressants do not seem clearly associated with MetS, except for H1-R high-affinity ones. Notwithstanding the limitations described above and the heterogeneity of the selected studies (i.e., study design, sample size, analysis, participants' and setting features, classification criteria of depression and MetS, different antidepressant drugs), implications seem to emerge especially for antidepressant-treated patients with depressive symptoms, receiving also antipsychotics or mood stabilizers, who should be carefully monitored for MetS and the correlated potentially life-threatening clinical conditions (such as diabetes/CVD).

Prevention strategies, early diagnosis, integrated and collaborative health care systems should be available for patients with MetS and depression; treatment and lifestyle changes should be considered in high-risk patients.

AUTHOR CONTRIBUTIONS

CG and PZ contributed to the conception and design of the work, with decision about search string used on Pubmed database. EG and CG developed and implemented the methods of the manuscript. EG and CG independently triaged the titles and abstracts identified by the search to remove those that were clearly inappropriate. The remaining papers, to be included, had to satisfy all the predetermined eligibility criteria. Possible disagreements regarding study inclusion were resolved by discussion with PZ. After selection of the relevant studies, PC and MC-S independently extracted and tabulated data on study design and outcome data using a standard form. GB, LL, and EG prepared the manuscript. EG performed statistical analysis. CG, EG, and PZ revised it critically for important intellectual content.

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Does the Time of Drug Administration Alter the Metabolic Risk of Aripiprazole?

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Antipsychotic drugs cause metabolic abnormalities through a mechanism that involves antagonism of D_2 dopamine receptors (D_2R). Under healthy conditions, insulin release follows a circadian rhythm and is low at night, and in pancreatic beta-cells, D_2Rs negatively regulate insulin release. Since they are sedating, many antipsychotics are dosed at night. However, the resulting reduction in overnight D_2R activity may disrupt 24 h rhythms in insulin release, potentially exacerbating metabolic dysfunction. We examined retrospective clinical data from patients treated over approximately 1 year with the antipsychotic drug aripiprazole (ARPZ), a D2R partial agonist. To identify effects of timing on metabolic risk, we found cases treated with ARPZ either in the morning ($n = 90$) or at bedtime ($n = 53$), and compared hemoglobin A1c, and six secondary metabolic parameters across the two groups. After controlling for demographic and clinical factors, patients treated with ARPZ at night had a significant decrease in HDL cholesterol, while in patients who took ARPZ in the morning had no change. There was a non-significant trend toward higher serum triglycerides in the patients treated with ARPZ at night vs. morning. There were no group differences in hemoglobin A1c, BMI, total cholesterol, LDL cholesterol, or blood pressure. Patients taking APPZ at night developed a worse lipid profile, with lower HDL cholesterol and a trend toward higher triglycerides. These changes may pose additional metabolic risk factors compared to those who take ARPZ in the morning. Interventions based on drug timing may reduce some of the adverse metabolic consequences of antipsychotic drugs.

Keywords: antipsychotic, diabetes mellitus, metabolism, circadian rhythm, weight gain, cholesterol, dopamine

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INTRODUCTION

Serious mental illnesses (SMI) including Bipolar Disorder, Major Depression, and Schizophrenia are commonly treated with antipsychotic medications. While these drugs differ in their pharmacological mechanisms and clinical profiles, all are associated with weight gain, metabolic changes in glucose and lipid homeostasis, hypertension and increased risk for non-insulin dependent (type 2) diabetes mellitus (T2D)(1). SMI is associated with early mortality, in large part due to metabolic disease (2–4). The mechanisms underlying this elevated risk are multifactorial. Considerable evidence reveals that the presence of SMI may be an independent risk factor for the development of insulin resistance and metabolic disease (5, 6). When examined in healthy controls

in laboratory settings, antipsychotic drugs have direct effects on glucose metabolism in Burghardt et al. (7). Even drugs considered "metabolically neutral" like aripiprazole (ARPZ) may promote glucose intolerance (8). Therefore, the metabolic consequences of antipsychotic drugs may further exacerbate metabolic risk in the SMI population that is already vulnerable by its predisposition to metabolic diseases. Accordingly, induced weight gain is a major limitation of antipsychotic drug treatment, and a common reason for premature discontinuation (9). There is an important need to reduce the metabolic burden on SMI patients treated with antipsychotics.

Circadian mechanisms may contribute to antipsychotic-induced metabolic disturbances. Circadian clocks in the brain, liver, adipocytes, and endocrine organs serve important roles in regulating feeding behaviors, activity, glucose homeostasis, and lipid metabolism (10–14). Insulin release is regulated by the circadian clock, with levels that peak during the day, anticipating the food intake and higher levels of blood sugar that typically occur during wakefulness. At night, insulin levels are low, facilitating the breakdown of lipid and glycogen stores to maintain glucose homeostasis during the fasting period associated with sleep (15). In mutant mice with pancreatic beta cell-specific knockout of the circadian clock, animals gain weight and develop insulin resistance, phenotypes that resemble non-insulin dependent T2D in humans (11). Similarly, humans with T2D show disrupted circadian rhythms in insulin release (16).

Among its many functions, the circadian clock also regulates dopamine, including its biosynthesis (17), the release of striatal dopamine in the CNS (18), and the expression of dopamine receptors (19). Interestingly, dopamine is also important in the pancreas to negatively regulate the release of insulin by beta islet cells (20). By blocking the D_2/D_3 dopamine receptors, antipsychotic drugs have potent effects on glucose stimulated insulin release, leading to disinhibition of insulin signaling, greater overall release in response to a glucose challenge, and decreasing insulin-stimulated glucose uptake (21, 22).

Due to their observed effects on beta cells and increasing insulin release, we hypothesized that an antipsychotic drug taken when insulin levels are high in the morning would show a more favorable metabolic profile (especially glucose levels) compared to the same drug taken in the evening when insulin levels are low (14). To test this hypothesis, we used a naturalistic, retrospectively ascertained cohort to compare patients who took aripiprazole (ARPZ), an antipsychotic drug that selectively targets the D_2 dopamine receptor (D_2R) in the morning against those who took ARPZ at night. Hemoglobin A1c (HbA1c) was used as the primary endpoint to estimate changes in glucose sensitivity. Lipid profile, body mass index (BMI) and blood pressure were examined as secondary measures of metabolic health.

MATERIALS AND METHODS

Study Design

Using pharmacy records at the VA San Diego Healthcare System (VASDHS), we conducted a retrospective chart review to compare long term metabolic outcomes in veterans taking ARPZ in the morning vs. those taking ARPZ at night. Data from 14 years (January 1, 2002 to December 31, 2016) were included in the analysis. The research was reviewed and approved by the VASDHS IRB to ensure compliance with all pertinent regulations regarding human subjects research.

Drug Selection and Dosing

ARPZ was previously considered metabolically neutral, but recently has been associated with weight gain and metabolic disturbances (23–25). Therefore, ARPZ was expected to be informative, with a wide range of metabolic outcomes, and perhaps sensitive to differences in dosing schedule. Moreover, while many antipsychotic drugs target a variety of receptors, the mechanism of ARPZ is relatively selective as a partial agonist at D_2R. Finally, large numbers of patients take ARPZ at different times across the day, while other drugs we considered (e.g., olanzapine, risperidone, perphenazine, haloperidol) were strongly biased toward night or day, and/or prescribed in insufficient numbers to yield a suitable cohort after applying exclusion criteria. For each subject, pharmacy prescription orders were analyzed. Subjects were considered to have taken the drug in the morning if the instructions indicated morning, daily, qDAY or qAM. Subjects were considered to have taken the drug at night when the instructions indicated qHS or bedtime. Only oral ARPZ was considered. Daily doses ranging from 2 to 30 mg were included. In secondary analyses of dose, subjects taking 2 and 5 mg were consolidated into a single group, as were subjects taking 15 and 20 mg to account for the small number of subjects taking 2 and 15 mg doses. Those taking injectable ARPZ or any other antipsychotic drugs (oral or injectable) were excluded. Compliance with ARPZ was estimated by the frequency of on time refills requested by the patient. Medication compliance was defined as a proportion of days covered > 0.8.

Subjects

All subjects were veterans receiving standard clinical care for SMI at the VASDHS. The study included adult patients (age 18–75 years) taking ARPZ for a range of SMI indications including psychotic disorders [schizophrenia (SCHZ), schizoaffective disorder (SAD), or unspecified psychosis], bipolar disorders (BD), including bipolar I, bipolar II, unspecified bipolar disorder, and depressive disorders [major depressive disorder (MDD), MDD with psychotic features, post-traumatic depression and any unspecified depression]. Comorbid PTSD was pervasive in our cohort, but not considered a primary indication for ARPZ. Subjects with a diagnosis of Alzheimer's disease, Parkinson's disease, dementia or other neurocognitive disorder were excluded from consideration. Subjects with existing metabolic disorders including T2D, essential hypertension, and hypercholesterolemia were included.

Selection of Study Cohort

Study subjects were selected based on their use of long-term ARPZ with confirmed compliance. We sought subjects taking the medication for approximately 1 year. The index date was defined as the first day that ARPZ was released to the patient and the target end date was defined as the index date plus 365 days.

Subjects were included in the study if two HbA1c reading were present, one within 3 months of the start of ARPZ, and one 9–15 months later (i.e., target end date ± 3 months). Further inclusion criteria were compliance with clinical and laboratory screening for metabolic changes, both at baseline and at the end of the 1-year study period, covering HbA1c, serum glucose, fasting lipid panel, blood pressure, weight and BMI.

Data Collection

As outcome measures, we selected one primary variable, change in HbA1c, and six related secondary variables: weight gain, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, blood pressure. Height was recorded to allow calculation of BMI, but was not considered as an outcome variable, as it was not expected to change as a result of drug treatment. Demographic variables (age, sex, and race) and clinical data (dose of ARPZ, hypertension, use of metformin, use of a statin drug) were considered as potential modifiers. Also considered as modifiers were medications commonly used in SMI that significantly affect weight (valproic acid, mirtazapine, and topiramate). Smoking, alcohol and substance use history were not reliably recorded in the pharmacy database and were not included. Only data sets including complete baseline and follow-up HbA1c, lipid panel, and blood pressure measures were used. Missing data for BMI was allowed (applied to 34 subjects).

Statistical Analyses

A one-way analysis of covariance (ANCOVA) comparing morning versus nighttime APRZ groups for change in individual metabolic parameters, using age, dose, sex, and race as covariates. For univariate analyses of categorical measures, we used a chi squares test. Additional *post-hoc* tests were performed using ANOVA or *t*-tests. Statistical significance for each variable was considered as $p < 0.05$. Analyses were conducted using SPSS version 20 (IBM, Armonk NY).

TABLE 1 | Demographic characteristics of study sample.

Characteristic	Morning *N* = 90	Bedtime *N* = 53	*P*-value
AGE			
Age range (Years)	30–73	24–67	
Age (mean ± SEM)	53.46 ± 1.1	53.26 ± 1.2	NS
Male sex, n (%)	79 (87.7)	49 (92.4)	NS
FOLLOW-UP PERIOD			
Range (days)	249–554	295–552	
Observation days (Mean ± SEM)	385 ± 6.1	400 ± 9.4	NS
DIAGNOSIS			
Psychotic disorder (%)	11 (21)	22 (24)	NS
Depressive disoder (%)	28 (53)	42 (47)	
Bipolar disorder (%)	14 (26)	26 (29)	
RACE			
Caucasian, n (%)	56 (62)	31 (58)	NS
African American, n (%)	17 (19)	9 (17)	
Asian American, n (%)	6 (7)	6 (11)	
Other/Unknown, n (%)	11 (12)	6 (11)	
DOSE ARIPIPRAZOLE, *N* (%)			
Average Dose (Mean ± SEM)	15.2 ± 0.9	12.1 ± 1.3	0.05*
2–5 mg, *n* (%)	14 (16)	27 (51)	
10 mg, *n* (%)	32 (36)	9 (17)	
15–20 mg, *n* (%)	24 (27)	8 (15)	
30 mg, *n* (%)	16 (18)	9 (17)	
OTHER MEDICAL FACTORS			
Diagnosis hypertension, *n* (%)	51 (57)	36 (68)	NS
Mirtazapine use, n (%)	7 (8)	4 (8)	NS
Metformin use, n (%)	2 (2)	0 (0)	NS
Statin use, n (%)	7 (8)	1 (2)	NS

RESULTS

After applying inclusion and exclusion criteria, our initial screen identified 1,009 subjects treated for 1 year with ARPZ that had at least one HbA1c reading during the treatment period. However, only 143 subjects had complete data that were suitable for analysis (i.e., data for each metabolic measure at the start and end of the study period). Of these, a majority ($n = 90$) were treated with oral ARPZ in the morning and the remainder ($n = 53$) were treated with ARPZ at night. The mean time of follow-up was similar for both groups (slightly longer than 1 year, **Table 1**). The majority of subjects in both groups were male, but there was no significant difference between groups in gender distribution. Age, racial background, treatment for diabetes, treatment for hypercholesterolemia, and the use of weight altering medications was similar between groups (**Table 1**). The average dose (mean ±SEM) of ARPZ used in each group was 15.1 ± 0.9 mg for the morning group, and 12.1 ± 1.3 mg for the night group, reflecting the fact that the morning group was more likely to get ARPZ doses of 10-20 mg, while the nighttime group was more like to get doses of 2–5 mg. These differences were statistically significant (**Table 1**).

Baseline HbA1c levels were 6.69 ± 0.15% for the morning group and 6.25 ± 0.22% for the night group (mean ± SEM), values that exceed the upper healthy limit (5.7%). In the morning group 36% (33/90) had HbA1c ≥6.5% (cutoff value for probable D2M). In the night group, the number was similar 33% (18/53), indicating both groups showed evidence of poor glycemic control, and were at high risk for D2M and other metabolic disorders (**Table 2**). Over the course of treatment, there was a statistically insignificant reduction in mean HbA1c levels in both groups, and significant effect of ARPZ dose, with higher doses significantly associated with greater HbA1c reduction (**Figure 1**). However, regarding time of dosing and change in HbA1c, our primary outcome variable, there were no significant differences between daytime and nighttime schedules either nominally or after adjusting for age, dose, sex, and race.

Among the secondary measures, serum HDL showed a significant reduction in the night dosing group compared to the morning group (**Table 2**). The effects remained significant after

TABLE 2 | Metabolic parameters before/after treatment with oral aripiprazole.

Outcome	Morning (AM)	Bedtime (PM)	*P*-value unadjusted	*P*-value adjusted
FOLLOW-UP PERIOD				
Range (days)	249–554	295–552		
Observation days (Mean ± SEM)	385 ± 6.1	400 ± 9.4	NS	NS
BLOOD GLUCOSE				
Baseline HbA1c (% glycosylated)	6.7 ± 0.2	6.4 ± 0.2	NS	NS
Change HbA1c (% glycosylated)	−0.2 ± 0.1	−0.2 ± 0.2	NS	NS
HbA1c ≥ 5.7% at baseline, number (%)	33 (37%)	18 (34%)	NS	NS
BODY WEIGHT				
Baseline BMI (kg/m^2)	33.4 ± 6.9	32.9 ± 6.6	NS	NS
Change BMI (kg/m^2)	0.85 ± 2.3	0.6 ± 1.9	NS	NS
SERUM CHOLESTEROL (MG/DL)				
Baseline total cholesterol	184.4 ± 5.8	183.7 ± 6.2	NS	NS
Change total cholesterol	−5.3 ± 5.1	−2.5 ± 6.2	NS	NS
Baseline LDL cholesterol	102.4 ± 4.2	103.3 ± 5.4	NS	NS
Change LDL cholesterol	−5.9 ± 43.4	−2.8 ± 36.6	NS	NS
Baseline HDL cholesterol	43.2 ± 1.3	46.9 ± 2	NS	NS
Change HDL cholesterol	0.2 ± 0.9	−3.8 ± 1.3	0.009	0.04*
Baseline triglycerides	221 ± 1	166 ± 7	NS	NS
Change triglycerides	22124.6 ± 13.2	31.6 ± 12.0	0.06	0.11
BLOOD PRESSURE (mmHg)				
Baseline systolic	130 ± 18.6	129 ± 16.6	NS	NS
Change systolic	−2.57 ± 20.8	−1.4 ± 20	NS	NS
Baseline diastolic	78 ± 14.3	80 ± 11.4	NS	NS
Change diastolic	−2.4 ± 16.8	−2.6 ± 15.9	NS	NS

** statistically significant after adjusting for age, sex, dose, race.*

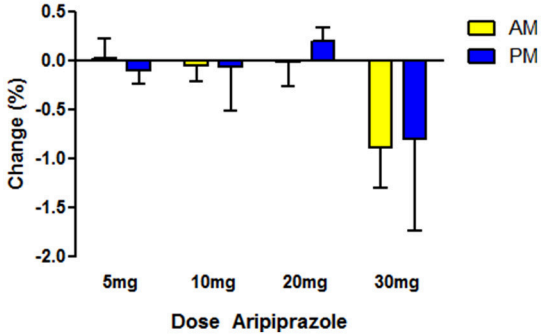

FIGURE 1 | Effects on glucose homeostasis as measured by hemoglobin A1c (HbA1c) glycosylation after treatment for ~1 year with aripiprazole. The highest dose (30 mg) was associated with reductions in HbA1c in both the morning (AM) and night time (PM) group (Two-Way ANOVA, dose $p < 0.05$, Time NS, interaction NS). Time of administration made no difference in HbA1c. For morning group, $N = 90$ with $N = 14$–36 in each dose category. For night time, $N = 53$, with $N = 8$–27 in each dose category. Data indicate mean values of post minus pre HbA1c readings. Error bars reflect standard error of the mean (SEM).

adjusting for age, dose, sex, and race. In *post-hoc* tests we found that the effects of timing on HDL cholesterol were nominally present across the entire dose range (5–30 mg), but reached statistical significance only at the 20 mg dose (**Figure 2**). Serum triglycerides showed a non-significant trend toward increase in the nighttime group compared to the daytime group (**Table 2**). There were no differences between nighttime and daytime ARPZ dosing in the other outcome measures: total cholesterol, BMI, LDL, diastolic, and systolic blood pressure (**Table 2**).

DISCUSSION

Food intake, sleep and metabolism are tightly coordinated and interrelated physiological processes connected by two common features: the circadian clock and dopamine signaling (14). The circadian clock strongly influences the 24 h. sleep-wake cycle, and through this effect on activity on requisite caloric expenditure, dictates the energy needs of the body. Accordingly, glycogenolysis, lipolysis, adipogenesis, and numerous other bioenergetic processes also follow circadian rhythms (15). Disruption of rhythms in experimental animals causes hyperglycemia, hyperlipidemia, and other metabolic consequences (10–13), and in humans, T2D is associated with altered rhythms in insulin release (16). Dopamine is one of the signaling systems that link brain activity to peripheral metabolism (26). The mesolimbic/mesocortical dopamine systems are involved in goal directed activity and arousal. These forebrain dopamine systems stimulate wakefulness and feeding behaviors in response to stimuli such as orexins, serotonin, and neuropeptides. In the periphery, dopamine negatively regulates insulin release from pancreatic beta cells and leptin from adipocytes (27, 28). Dopaminergic agonists such as bromocriptine suppress insulin and leptin release by reducing peak amplitude of their rhythmic release, and have been associated with improved metabolic function in obese subjects with metabolic syndrome, and subjects suffering from T2D (29, 30).

For the reasons above, we hypothesized that antagonism of the D_2R by ARPZ would have differential effects on metabolism depending on the circadian cycle, and the time of drug administration. We expected this effect to emerge independently of master clock in the suprachiasmatic nucleus which is largely depleted in D_2R (14). Instead, we expected the effect to emerge from the peripheral action of ARPZ on D_2R and D_3R in islet beta cells, thereby increasing overnight insulin release, with subsequent flattening of the insulin rhythm (i.e., amplitude reduction). Given the retrospective nature of the

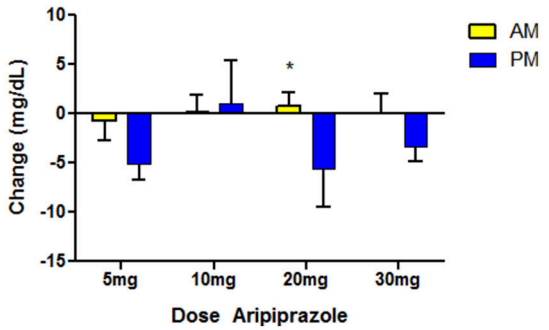

FIGURE 2 | Effects on HDL cholesterol after ∼1-year treatment with aripiprazole. Time of administration made a significant difference in HDL levels at ∼1-year follow-up, with reductions seen only in the night time (PM), and not in the morning (AM) group. The difference was nominally present at most doses, but only the 20 mg dose showed a significant difference in a *post-hoc* *T*-test (* indicates $p < 0.05$ indicates). For morning group N=90, with N=14-36 in each dose category. For night time group, $N = 53$ PM, with $N = 8$–27 in each dose category. Data indicate mean values of post minus pre-HDL readings. Error bars reflect standard error of the mean (SEM).

study, we were not able to assess insulin directly, and relied upon HbA1c as a proxy. Perhaps because of the nature of HbA1c, which averages blood glucose levels over weeks, we failed to detect a time of day dependent difference in HbA1c, our primary endpoint. However, we did find differences in HDL cholesterol associated with the time of ARPZ administration. Low HDL cholesterol is a risk factor for cardiovascular disease (31). The decrease in serum HDL observed exclusively in the ARPZ night treated group indicates this risk factor was exacerbated over the course of treatment selectively in the night group while remaining constant in the morning group. This finding could indicate that the metabolic consequences of ARPZ, and perhaps other antipsychotic drugs could be mitigated or worsened by the administration schedule. As metabolic side effects are a major limitation to the use of antipsychotics in SMI, the ability to reduce this risk would mark an important advance.

Based on previous literature, we hypothesize that nightly dosing with ARPZ could interfere with typical rhythms of insulin or leptin release that typically reach nadir overnight in human subjects. Elevated insulin/leptin at night may lead to reduced lipolysis or similar catabolic adaptations to provide the body glucose during overnight fasting. Insulin stimulates triglyceride accumulation, a key mechanism involved in reducing HDL in T2D (32). While not statistically significant, we did observe a nominal difference toward elevated triglycerides in patients treated at night with ARPZ. Cholesterol levels, including HDL cholesterol has been show to oscillate over the day in a circadian manner, with higher amplitude oscillations in total cholesterol associated with greater longevity (33). T2D subjects with a strong predisposition toward night time activity (evening chronotypes) show lower levels of HDL cholesterol, and elevated triglycerides (34), a factor that may contribute to the excess mortality observed in evening chronotypes in the general population (35). Therefore, we propose that one explanation for the observed elevations in triglyceride, and reductions in HDL could be due to ARPZ disrupting rhythms in insulin.

We conducted our study in a population of veterans with SMI who were chronically treated with ARPZ for approximately 1 year. The long-term follow-up data for our subjects including laboratory monitoring and verified compliance are important strengths of our work. However, this study population was distinctive in several key respects and may not generalize to other groups. ARPZ is not available as a first line medication at the VASDHS and requires prior authorization from the pharmacy. Therefore, the vast majority of subjects in our study were older, male, and already receiving one or more antipsychotic medications prior to receiving ARPZ. Indeed, they may have been preferentially selected for treatment with ARPZ because they experienced metabolic side effects as a result of prior treatments with another antipsychotic drug. The high incidence in our study of hyperglycemia at baseline, and the trend toward metabolic improvement in some domains supports this interpretation. Notably, the ARPZ morning group received higher average doses of medication compared to the nighttime group, despite the fact that high dose ARPZ is more likely to be sedating (36). This could speak to possible group differences in activity or sleep that were not assessed using our approach. Future prospective studies conducted in drug naïve subjects would be informative.

ARPZ has a long half-life of approximately 75 h. and active metabolites (e.g., dehydro-ARPZ) with even longer half-lives (>94 h). Therefore, steady state drug levels are unlikely to explain our findings. However, the major metabolic pathways affecting metabolism of ARPZ in the liver, CYP2D6 and CYP3A4 have been shown to oscillate under the regulation of the circadian clock and it remains possible that one or more ARPZ metabolites may fluctuate over the circadian time course (37, 38). Perhaps more importantly, peak ARPZ levels and pharmacological effects occur rapidly after oral administration, and in the mouse, mesolimbic dopamine release and the expression of both D2 and D3 dopamine receptors are rhythmic (18, 19). Therefore, the primary drug targets of ARPZ may oscillate independently of drug levels, and despite the long half-life of ARPZ, there may be important pharmacodynamic consequences of drug administration, particularly as it relates to time-sensitive processes like insulin rhythms.

Our data must be interpreted with a number of considerations and caveats in mind. ARPZ has an unusual mechanism of action, working primarily as a partial agonist at D_2R and D_3R, but also has affinity for serotonin receptors including 5-HT1A, 5-HT2A, 5-HT2B, and 5-HT7, effects that can modulate dopamine indirectly (39). As the drug is neither fully inhibitory nor excitatory at dopamine receptors, conclusions about the metabolic effects of dopamine antagonism across the circadian cycle must be made cautiously. We interpret our data in the context of a substantial body of work that suggests D_2R blockade is the common mechanism across all antipsychotic drugs, all of which cause weight gain to some extent, and accordingly that blockade of dopamine receptors is likely an important mechanism underlying metabolic dysfunction. However, future studies addressing this hypothesis should use drugs with a simpler mechanism to more clearly delineate this relationship.

Our study design had a number of important limitations. First, the study was retrospective without random assignment. The stringency of our inclusion criteria reduced the sample size, making the sample insufficiently powered to address some key issues such as gender differences and the role of smoking, alcohol and other key clinical variables. Next, we relied on pharmacy records to determine dosing schedules, and were unable to verify that our subjects took the medication at the stated time. Finally, there was significant heterogeneity in our sample in psychiatric diagnoses, duration of illness, prior medication history, and medical comorbidity. Nonetheless, we contend that this work marks an important preliminary step in identifying circadian mechanisms underlying antipsychotic induced metabolic dysfunction. Future studies with uniform inclusion/exclusion criteria, random assignment, prospective assessment and detailed laboratory analyses of diurnal insulin levels, glucose tolerance, and lipid profiles are warranted. If empirically supported, manipulations to the dosing schedule of antipsychotic drugs could point the way to relatively simple, and cost-effective methods to reduce the medical comorbidity associated with antipsychotic drugs in the treatment of SMI.

Previous Presentation

Oral presentation at the 2017 VA VISN 22 Conference for Pharmacy Residents and Preceptors in San Diego, CA. Poster at the 2017 Annual Meeting of the Society for Neuropsychopharmaocology, Palm Desert CA.

AUTHOR CONTRIBUTIONS

DC, SL, ZF, and MM designed the study, DC and CE extracted the data, DC and MM performed the analyses. DC, MM, and ZF wrote the manuscript.

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