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Impaired insulin signaling in unaffected siblings and patients with first episode psychosis

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Abstract

Patients with psychotic disorders are at high risk for type 2 diabetes mellitus, and there is increasing evidence that patients display glucose metabolism abnormalities before significant antipsychotic medication exposure. In the present study, we examined insulin action by quantifying insulin sensitivity in first episode psychosis (FEP) patients and unaffected siblings, compared to healthy individuals, using a physiological-based model and comprehensive assessment battery. Twenty-two unaffected siblings, 18 FEP patients and 15 healthy unrelated controls were evaluated using a 2-hour oral glucose tolerance test (OGTT), with 7 samples of plasma glucose and serum insulin concentration measurements. Insulin sensitivity was quantified using the oral minimal model method. Lipid, leptin, free fatty acids and inflammatory marker levels were also measured. Anthropometric, nutrient and activity assessments were conducted; total body composition and fat distribution were determined using whole-body dual energy x-ray

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Conflict of Interest

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absorptiometry. Insulin sensitivity significantly differed among groups (F=6.01, P=0.004), with patients and siblings showing lower insulin sensitivity, compared to controls (P=0.006, and P=0.002, respectively). Body mass index, visceral adipose tissue area (cm^2), lipids, leptin, free fatty acids, inflammatory markers and activity ratings were not significantly different among groups. There was a significant difference in nutrient intake with lower total kilocalories/kilogram body weight in patients, compared to siblings and controls. Overall, the findings suggest that familial abnormal glucose metabolism or a primary insulin signaling pathway abnormality is related to risk for psychosis, independent of disease expression and treatment effects. Future studies should examine underlying biological mechanisms of insulin signaling abnormalities in psychotic disorders.

1. Introduction

Patients with psychotic disorders have up to 20% shorter life expectancy compared to the general population, with increased mortality from cardiovascular disease and type 2 diabetes mellitus (T2DM)[1–3]. The disproportionately high rate of T2DM in patients with psychotic disorders is two to three-fold that found in the general population[4, 5], with studies indicating a prevalence of 10–15% in schizophrenia and bipolar disorder. Increasing evidence suggests that glucose metabolism abnormalities are present at psychotic illness onset and in drug-naïve patients[6–8]. A recent large population-based cohort study showed a high risk for diabetes in antipsychotic-naïve patients with schizophrenia[9].

There is likely a complex interplay of factors underlying risk for T2DM in patients with psychotic disorders[10]. Antipsychotic medications, the mainstay of treatment, induce weight gain, insulin resistance and T2DM[11–13]. Patients with psychotic disorders have high rates of conventional risk factors for T2DM, including obesity, sedentary lifestyle, poor diet, smoking and alcohol abuse, often accompanied by inadequate access to health services[14–16]. Several lines of evidence also suggest that patients with psychotic disorders have an endogenous risk for developing T2DM. Prevalence of diabetes is elevated in unaffected family members[17, 18], and genetic association and pathway analysis studies point to shared genetic risk factors between psychotic disorders and T2DM[19, 20], including the association of well-established T2DM gene variants with schizophrenia[21]. In this convergence of genetic and environmental risk factors for T2DM, the underlying physiology of impaired glucose metabolism in patients with psychosis remains to be elucidated.

Insulin action and secretion maintain glucose homeostasis, and insulin resistance may precede the development of T2DM by one to two decades[22]. Insulin resistance occurs when the effects of insulin do not effectively induce glucose disposal in skeletal muscle, inhibit glucose production in the liver nor suppress the release of lipids in adipose tissue, leading to loss of metabolic fuel homeostasis. Several measures of insulin resistance have been developed[23, 24], including the homeostatic model assessment of insulin resistance (HOMA-IR), minimal model assessments and clamp tests. HOMA-IR[25] is easy to perform and based on basal fasting measures of insulin and glucose concentrations. However, HOMA-IR does not measure postprandial glucose metabolism, and basal concentrations of insulin and glucose only represent one point in the complex glucose-insulin dose-response curve[24].

While euglycemic clamp[26] or intravenous glucose tolerance tests measure insulin action, these techniques are labor intensive and invasive. The oral minimal model method uses physiological-based models[24, 27], is less invasive, and quantifies insulin action during an oral, physiological perturbation, such as an oral glucose tolerance test (OGTT). This method specifically measures insulin sensitivity, quantifying effects of insulin in tissues to activate insulin signaling and phosphorylation pathways[28].

Recent meta-analyses[6, 7] showed that HOMA-IR is elevated in patients with first episode schizophrenia who are drug-naïve or have received less than two weeks of antipsychotic medication, compared to controls. A study by Spelman et al.[29] in adult relatives of patients with psychosis and first-episode drug-naïve patients suggests that an increase in HOMA-IR is also found in at-risk individuals, compared to controls. However, in another study of unaffected relatives and drug-naïve schizophrenia patients[30], relatives did not show differences in HOMA-IR compared to controls. These study results using HOMA-IR have limited interpretability for studying insulin action[23]. While HOMA-IR may be useful for large epidemiological studies[23], it is unclear exactly what it measures and it provides limited information on insulin signaling. There is a lack of studies specifically studying insulin action in individuals at risk for developing psychosis and patients early in psychotic illness.

As psychotic disorders are highly heritable[31], studies in unaffected relatives provide valuable information regarding heritable determinants of disease risk[32], and contribute to understanding pathophysiologic factors in psychosis. Particularly relevant to studying glucose metabolism, unaffected relatives may share predisposing traits for developing psychotic illness, without confounds of illness progression and treatment. In the present study, we examined insulin sensitivity measured by the oral minimal model in unaffected siblings and patients with first episode psychosis (FEP), compared to healthy controls, in a well-characterized sample with comprehensive anthropometric and nutrition measures. We hypothesized that both unaffected siblings and FEP patients would show a reduction in insulin sensitivity compared to controls, but that the reduction observed in siblings would be of lesser magnitude than that observed in patients.

2. Methods

2.1. Participants

We assessed 22 unaffected siblings, 18 FEP patients, and 15 healthy controls. Siblings were recruited through patients in McLean OnTrack, an outpatient FEP program at McLean Hospital[33], a support group for family members in McLean OnTrack and flyers posted at McLean Hospital. Proband diagnoses for siblings were ascertained by diagnostic interview and review of medical records, and included 4 with schizophrenia, 5 schizoaffective disorder, 11 bipolar disorder with psychotic features, and 2 psychosis not otherwise specified (NOS). Unaffected siblings had no history of psychotic or bipolar disorders, and were not taking psychotropic medications. Patients were recruited from McLean OnTrack, and enrolled in the study within one year of psychosis onset. Of the 18 patients, 2 were diagnosed with schizophrenia, 1 schizoaffective disorder, 11 bipolar disorder with psychotic features, 1 major depressive disorder with psychotic features, and 3 psychosis NOS. Patients were excluded if they had a diagnosis of current substance use disorder, or symptoms could

be attributed to general medical condition or substance use. Five unaffected sibling-patient pairs were related, whereas other siblings and patients were unrelated. Healthy controls were recruited with flyers on local college campuses, and had no psychiatric diagnoses nor history of same in first-degree relatives. Exclusion criteria for all participants included history of significant medical or neurologic illness, including diabetes, head trauma, or pregnancy. Participants were excluded if they were taking non-psychotropic medications known to influence glucose metabolism (including steroids, antidiabetics, weight loss agents). This study was conducted as part of an effort to collect multimodal data in FEP, including MRI, thus MR scan contraindication was an exclusion criterion. There was 1 patient-sibling pair with a first-degree relative with type 1 diabetes, 1 patient-sibling pair with first-degree relative with diabetes (type unknown), and 1 sibling with first-degree relative with T2DM. The study was approved by McLean Hospital Institutional Review Board, and participants provided written informed consent.

The Structured Clinical Interview for DSM-IV-TR (SCID)[34] was used for ascertaining diagnosis in participants. The following rating scales and cognitive assessments were administered as appropriate: MATRICS Consensus Cognitive Battery[35], Wisconsin Schizotypy Scales-short form[36], Symptom Checklist-90-Revised (SCL-90-R)[37], Positive and Negative Syndrome Scale (PANSS)[38], Beck Depression Inventory-II (BDI-II) [39], and State-Trait Anxiety Inventory (STAI)[40]. Hollingshead Four-Factor Index of Social Status was used to evaluate parental socioeconomic status. SCID Post-Traumatic Stress Disorder module and medical records were used to assess for history of trauma. Chlorpromazine equivalents were calculated based on daily dose of antipsychotic medication prescribed at the time of study[41–43].

2.2. Oral glucose tolerance test and oral minimal model

Participants were instructed to follow a three-day diet plan with minimum of 250g carbohydrate/day and fast for 12 hours prior to the OGTT. Participants were admitted to the Massachusetts General Hospital Clinical Research Center for study procedures. One intravenous catheter was placed in an antecubital vein. Baseline blood samples were obtained 10 minutes prior to administration of 75g of glucose at time 0: plasma glucose and serum insulin, basic chemistry profiles, lipid profile, complete blood count, serum leptin, c-reactive protein, interleukin-6, tumor necrosis factor-alpha and free fatty acids levels. Blood samples were drawn at times 0, 10, 20, 30, 60, 90, and 120 minutes for measurement of plasma glucose and serum insulin concentrations. Plasma glucose and serum insulin samples were collected in a gray-top (sodium fluoride) and gold-top tube, respectively. Laboratory Corporation of America performed laboratory assays. HOMA-IR was calculated using baseline glucose and insulin concentrations: serum insulin × plasma glucose/22.5[25].

The oral minimal model has been previously described[24, 27], and validated by tracer and euglycemic/hyperinsulinemic clamp studies[44, 45]. Based on plasma glucose and serum insulin concentrations measured during OGTT, the oral minimal model estimates insulin sensitivity by modeling glucose and insulin subsystems. An assumption of the model is that insulin action on glucose production and disposal takes place remotely from plasma, in the interstitium. Since the model uses OGTT data, the rate of glucose absorption is a variable,

which is necessarily modeled. We used a reduced sample minimal model with 2-hour protocol and 7-sample schedule[46]. Analyses of insulin sensitivity were conducted blinded to group status.

2.3. Nutritional Assessments

Weight(kg) and height(cm) were measured, and body mass index (BMI) was calculated(kg/m^2). Ideal body weight was obtained from Metropolitan Life Insurance Tables[47]. Iliac waist and broadest hip circumferences(cm) were measured and used to calculate waist-hip ratio. Bicep, tricep, suprailiac and subscapular skinfold measurements were performed using a Lange skinfold caliper (Beta-Technology, Santa Cruz, CA). Nutrient intake was collected using a four-day food diary, reviewed by a research dietician by direct interview. Nutrient analysis was calculated using Nutrition Data Systems for Research (version 2014, Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN)[48]. Resting energy expenditure (REE) was assessed by indirect calorimetry using a dilution canopy placed over the participant's head to measure oxygen consumption and carbon dioxide production in a resting state (Vmax Encore 29; CareFusion, Yorba Linda, CA)[49]. Body composition and abdominal visceral adipose tissue area were determined by whole-body dual energy x-ray absorptiometry (DXA) (Hologic QDR Discovery A; Hologic Inc, Waltham, MA). The International Physical Activity Questionnaire (IPAQ)[50] was administered to obtain estimates of physical activity.

2.4. Statistical analyses

We performed statistical analyses using SPSS (PASW) version 23 and STATA version 14. Our primary outcome measure was insulin sensitivity, and we used ANOVA analyses with contrasts to examine insulin sensitivity with diagnosis as a between-subjects factor. We used chi-square tests and ANOVAs as appropriate to compare demographic and clinical characteristics, glucose metabolism, lipid, and inflammatory measures, and anthropometric and nutrition measures among patient, sibling and control groups. For all analyses, we checked modeling assumptions, including normality of the measures, non-constant variance, and influential points. Insulin sensitivity values were log–transformed to approximate normal distribution. Our primary a priori analysis was to compare insulin sensitivity between patient, sibling and control groups. Other factors related to insulin signaling and metabolism were examined in exploratory analyses. For such other analyses, we did not correct for multiple comparisons because they were exploratory in nature. For primary insulin sensitivity analyses, we had 83% power to detect the reported effects. All hypothesis tests were two-sided and conducted with a confidence level of alpha=0.05.

As BMI and body mass composition are associated with insulin sensitivity[51], we conducted an exploratory mediation analysis to examine the role of BMI in the pathway between patient/siblings/control status and insulin sensitivity. Using methods previously described by Valeri and VanderWeele[52, 53], we implemented a mediation analysis to decompose the relationship between group status and insulin sensitivity and provide insight into the role of BMI as mediator as well as moderator of this relationship. As waist circumference was found to be different across groups, we also examined waist circumference's role as a mediator/moderator in a separate mediation analysis. We used a counterfactual approach to

examine direct and indirect effects of group status on insulin sensitivity through BMI (and waist circumference). This approach allowed us to take into account interactions between group status (exposure) and body composition (mediator). Age, sex and race were included in mediation models, given their well-known associations to glucose metabolism[54, 55]. Further details on mediation analyses are provided in Supplementary material.

3. Results

3.1. Demographic and Clinical Characteristics

Demographic and clinical characteristics of participants are shown in Table 1. Hollingshead scores (mean±SD) did not differ among patients (53.3±8.2), siblings (49.8±10.2) and controls (53.5±9.2) (F=0.91, P=0.41). There were 5 patients (27.8%) who were taking both antipsychotic and mood stabilizer medications, and 4 patients (22.2%) who were not taking psychotropic medications. Among 5 patients who smoked, a mean 3 cigarettes/day were used. SCL-90-R positive symptom distress index was increased in siblings, compared to controls (t=2.2, P=0.03). There were no other significant differences between siblings and controls on measures of psychological distress or psychosis-proneness, including SCL-90-R global severity index, Wisconsin schizotypy positive and negative factor scores, BDI-II or STAI total scores. There were no significant differences among groups for presence of history of traumatic events (χ^2=0.22, P=0.90).

3.2. Glucose Metabolism, Inflammatory and Lipid Measurements

Insulin sensitivity index differed significantly among groups (F=6.01, P=0.004), with patients and siblings showing lower insulin sensitivity, compared to controls (P=0.006, and P=0.002, respectively), while there was no significant difference between patients and siblings (Table 2, Figure 1). Baseline plasma glucose and serum insulin concentrations and HOMA-IR did not differ among groups. There were also no significant differences among groups on measures of lipids, leptin, nor inflammatory markers (Table 2).

3.3. Anthropometric, DXA, Physical Activity and Nutrient Intake Measurements

BMI did not significantly differ (F=2.61, P=0.08) between patients, siblings, and controls (Table 3). Waist-hip ratio and waist circumference significantly differed between groups (F=5.80, P=0.005), with patients showing greater waist circumference compared to siblings (P=0.04) and controls (P=0.002) and higher waist-hip ratio compared to siblings (P=0.03) and controls (P=0.001). Suprailiac skinfold was also greater in patients (F=4.05, P=0.02), compared to siblings (P=0.02) and controls (P=0.02). Other anthropometric measures, IPAQ high activity rating, REE, and DXA visceral adipose tissue area did not differ among groups.

There was a significant difference in total kilocalories per kilogram of body weight among groups (F=3.55, P=0.04), with patients showing lower intake compared to siblings (P=0.03) and controls (P=0.02), while there were no differences between siblings and controls (Supplementary Table 1).

3.4. Mediation analyses with BMI and waist circumference

There was evidence of significant direct effects of patient or sibling status on insulin sensitivity, independent of BMI, with effects of −0.60 (*confidence interval (CI)*= −1.09, −0.08) in patients and −0.72 (−1.24,0.21) in siblings. In the analysis for waist circumference, direct effects of patient or sibling status on insulin sensitivity were −0.50 (−0.99, −0.0001) in patients and −0.64 (−1.17, −0.11) in siblings. In patients, there was evidence of a significant effect of BMI on insulin sensitivity (*beta* = −0.10, *P* = 0.02) and an exposure-mediator (patient group-BMI) interaction (*beta* = 0.12, *P* = 0.04). In siblings, there was no evidence of exposure-mediator (sibling group-BMI) interaction (*beta* = −0.05, *P* = 0.43). Similarly, in patients, there was evidence of a significant effect of waist circumference on insulin sensitivity (*beta* = −0.06, *P* = 0.003) and an exposure-mediator (patient group-waist circumference) interaction (*beta* = 0.06, *P* = 0.02). In siblings, there was no evidence of exposure-mediator (sibling group-waist circumference) interaction (*beta* = −0.01, *P* = 0.77). Results of the mediation and interaction analyses for BMI explaining the effect of patient status on insulin sensitivity are shown in Table 4. Results were similar for waist circumference (Supplementary Table 2). Both BMI and waist circumference analyses yielded suggestive evidence of interactive mechanisms in patients.

3.5. Additional analyses

To examine effects of atypical antipsychotic medication on insulin sensitivity, we conducted a posteriori analysis of insulin sensitivity among groups, excluding patients taking atypical antipsychotics (n=8/18). Differences in insulin sensitivity among groups remained (*F*=5.56, *P*=0.007), with patients showing reduced insulin sensitivity (*P*=0.013) compared to controls, while there was no significant difference between patients and siblings. Among patients, there was no significant correlation between chlorpromazine equivalents and insulin sensitivity.

Mean (SD) insulin sensitivity was not significantly different (*P*=0.62) between 6 patients with non-affective psychosis (19.83(11.59)) and 12 patients with affective psychosis (18.66(12.29)). In addition, insulin sensitivity was not significantly different (*P*=0.25) between 9 siblings with non-affective psychosis proband (26.20(18.84)) and 11 patients with affective psychosis proband (20.12(22.55)).

4. Discussion

Our findings suggest that abnormalities in glucose metabolism and insulin signaling are related both to risk and expression of psychotic disorders and not solely to treatment effects or lifestyle factors in these conditions. Using a novel approach in psychosis to quantify insulin action with the oral minimal model, we found decreased insulin sensitivity in normoglycemic non-obese individuals at familial high risk for psychosis and stable FEP patients, compared to controls. Previous studies have not provided clear evidence for a primary insulin signaling abnormality in individuals at high risk for psychosis. Here, we provide such evidence for a decrease in insulin's biological effects in both early psychosis and risk. As performed in this study, using an oral perturbation of the system takes advantage of a physiological model to measure the effects of insulin in the presence of

glucose, amino acids, incretin hormone and neural signaling. Our findings strongly suggest a role for insulin signaling in the pathophysiology of psychotic disorders. With a decrease in insulin sensitivity, insulin pathways with important effects on metabolism and cell growth and differentiation may not be effectively activated[28]. It is notable that insulin in brain may play an important role in activating pathways that regulate neuronal growth and remodeling[56].

There may be genetic, environment, or gene-environment risk factors shared between psychotic disorders and T2DM, with shared underlying biological mechanisms. Dysfunctional energy metabolism and oxidative stress are key pathophysiologic mechanisms in T2DM[51], and we now also have converging evidence in psychotic disorders for energy metabolism impairment in the brain[57–59. 31]P magnetic resonance spectroscopy studies have revealed specific bioenergetic abnormalities and redox imbalance in FEP patients and unaffected siblings[60, 61]. In psychotic and bipolar disorders, recent evidence suggests that obesity and abnormal glucose metabolism are associated with severity of illness, greater number of hospitalizations, suicide attempts, and neurochemical-structural abnormalities[62–65]. In addition, activation of inflammatory pathways has been found in early and chronic stages of schizophrenia[66] and is intricately related to energy metabolism in T2DM[67]. With growing interest in the field of immunometabolism[68], the immune system may be a target for study and treatment of metabolic abnormalities in psychosis. Leveraging advances in treatment for metabolic disorders may prove beneficial in psychosis.

Insulin resistance is often associated with obesity, hypertension and dyslipidemia[51], but these factors may not necessarily be present in the development of insulin resistance. Of known potentiating or additive factors related to insulin sensitivity, most were not significantly different among groups in our sample, including BMI, DXA visceral adipose tissue area, activity, blood pressure, lipids, leptin, and inflammatory markers. Although waist circumference was higher in patients, compared to siblings and controls, it is an indirect measure of body mass composition compared to DXA, which measures the distribution of adipose tissue among fat depots. There were few significant differences in nutrient intake between groups, and total kcal/kg body weight, which was lower in patients, compared to siblings and controls, would not appear to explain the observed differences in insulin sensitivity. Furthermore, patients were in an early stage of psychotic illness with minimal antipsychotic exposure (50% of patients), and low chlorpromazine equivalents. Interestingly, exploratory mediation analyses revealed a strong direct effect, independent of BMI, of patient and sibling status on insulin sensitivity. However, in patients, results showed the presence of exposure-mediation interactions for both BMI and waist circumference in the relationship between patients and insulin sensitivity, while this was not the case in siblings. As expected, taking into account this exposure-mediation interaction in patients, the effect of BMI and waist circumference on insulin sensitivity was significant, suggesting that body composition factors may have had a different role in mediating and moderating this relationship in patients and siblings.

It is important to consider that patients and siblings may share environmental risk factors for T2DM. In our sample, patients and siblings did not differ in terms of socioeconomic status compared to controls. Early life stress and adverse childhood experiences may affect

activation of the hypothalamic–pituitary–adrenal(HPA) axis leading to dysregulation of metabolism, possibly lasting into adulthood[71]. While we did not find differences on presence of history of traumatic events between groups, future work could further explore the role of adverse childhood experiences on glucose metabolism in psychosis; effects which may vary based on individual exposure/vulnerability.

Of note, we used a dimensional approach to psychosis, including non-affective and affective psychotic disorders. We have found a high switch rate of psychotic diagnoses in McLean OnTrack[33], consistent with findings in a large longitudinal study of first-admission patients with psychotic disorders[72]. In support of our sample, studies have observed abnormalities of glucose metabolism across psychotic disorders[10], and these abnormalities may be shared determinants, with other factors influencing specific syndromic outcome. Also of note, unaffected siblings in our sample were at high genetic risk for psychosis, however, not necessarily at high clinical risk. Siblings showed high global functioning, and were similar to controls on psychosis-proneness, psychological distress, global cognitive functioning, and depression and anxiety measures.

This study has limitations to consider. First, our sample size was modest and larger studies are needed to further characterize the contribution of insulin signaling to risk and expression of psychosis. Second, as we did not include chronic patients, we cannot specifically compare how insulin sensitivity may evolve in chronic illness with greater antipsychotic exposure and lifestyle changes. Third, our cross-sectional data do not allow us to make inferences about causality, and future studies should use longitudinal designs to follow both at-risk individuals and FEP patients over time. Fourth, among patients, we did not have adequate-sized groups of patients to examine the potential effects of different antipsychotics on insulin sensitivity.

Overall, our study provides new findings of impaired insulin action in individuals at high genetic risk for psychosis and FEP patients. Our results highlight the need for intervention in early psychotic illness to improve body-wide metabolic status. Future studies should examine shared underlying biological mechanisms between psychosis and T2DM, and investigate the relationship between insulin signaling and brain energy metabolism dysfunction in both early psychosis and at-risk states.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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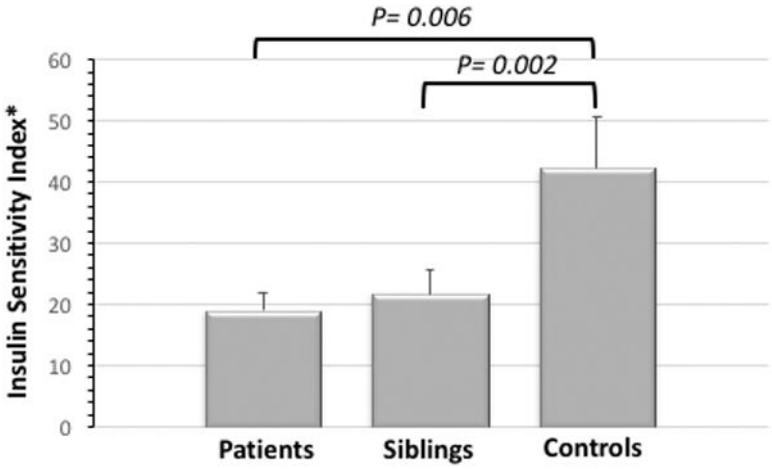

Figure 1.

Mean insulin sensitivity index in first episode psychosis patients, unaffected siblings and healthy controls. Error bars represent standard error of the mean. Significant differences between groups are noted.

*10-4 dl/kg/min per uU/ml.

Table 1

Demographic and Clinical Characteristics of Participants

Characteristic	Patients (n=18)	Siblings (n=22)	Controls (n=15)
Age, mean (SD)	23.6 (13.4)	24.2 (5.6)	22.5 (3.5)
Male gender, No.(%)	13 (72.2)	8 (36.4)	7 (41.2)
Race and Ethnicity, No. (%)			
Caucasian	15 (83.3)	19 (86.4)	10 (58.8)
African American	0	0	0
Hispanic	1 (5.6)	1 (4.5)	3 (17.6)
Asian	2 (11.1)	2 (9.1)	4 (23.5)
Left-handed, No.(%)	2 (11.1)	3 (13.6)	1 (5.9)
Education, mean (SD) [1]	5.0 (1.5)	5.4 (1.6)	5.4 (1.3)
Current smoking, No.(%) [*]	5 (27.8)	0 (0.0)	0 (0.0)
Lifetime Hospitalizations, No.(%)	1.8 (2.0)		
Prior suicide attempt, No.(%)	2 (11.1)		
PANSS total score, mean (SD)	43.1 (10.5)		
GAF score, mean (SD) [*]	63.5 (16.9)	87.2 (6.9)	
MCCB composite total score, mean (SD)[2]	43.4 (13.2)	47.6 (12.3)	52.6 (12.4)
Medications, No.(%)			
Atypical antipsychotic	8 (44.4)		
Clozapine	1 (5.6)		
Typical antipsychotic	1 (5.6)		
Lithium	7 (38.9)		
Mood stabilizer	10 (55.6)		
CPZ equivalent, mean (SD), mg/d	77 (104.92)		
Systolic blood pressure, mean (SD)	117.9 (12.9)	114.6 (11.7)	109.8 (9.0)
Diastolic blood pressure, mean (SD)	71.9 (6.8)	70.6 (7.9)	69.1 (11.4)

Abbreviations: MCCB, MATRICS Consenus Cognitive Battery; CPZ, Chlorpromazine; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning.

[1] Education range: 3= high school, 4= some college, 5=2-year college, 6= 4-year college graduate, 7= some graduate or professional school, and 8= completed graduate or professional school.

[2] MCCB data available for subset of patients (16), siblings (11) and controls (8).

[*] P<0.001

Table 2

Glucose Metabolism, Lipid and Inflammatory Measurements of Participants

	Patients (n=18)	Siblings (n=22)	Controls (n=15)	P
Fasting plasma glucose, mg/dL	82.1 (6.3)	82.4 (8.3)	81.3 (5.5)	0.89
Fasting serum insulin, μIU/L	6.75 (3.77)	7.9 (4.2)	6.5 (3.2)	0.50
Insulin sensitivity index[1]	19.1 (11.7)	21.6 (20.1)	43.5 (30.6)	0.004*
HOMA-IR	1.4 (0.8)	1.6 (0.9)	1.3 (0.7)	0.54
Total cholesterol, mg/dL	168.8 (21.1)	167.5 (31.6)	153.3 (20.1)	0.17
HDL cholesterol, mg/dL	52.1 (15.2)	56.3 (15.8)	53.5 (8.8)	0.62
LDL cholesterol, mg/dL	96.3 (25.1)	91.0 (26.3)	83.9 (21.8)	0.37
Triglycerides, mg/dL	102.6 (41.4)	101.3 (48.9)	82.5 (25.1)	0.31
Leptin, ng/mL	6.0 (4.1)	8.3 (5.7)	9.9 (14.6)	0.42
Free fatty acids, mEq/L	0.5 (0.2)	0.8 (1.4)	0.5 (0.3)	0.47
CRP, mg/L	1.7 (2.5)	1.7 (1.6)	0.7 (0.6)	0.22
IL-6, pg/mL	1.3 (0.8)	1.7 (2.7)	1.1 (0.8)	0.47
TNF-a, pg/mL	1.9 (2.6)	1.2 (0.6)	1.03 (0.3)	0.24
Prolactin, ng/ml	14.6 (13.4)	10.9 (4.2)	9.8 (2.3)	0.20

Abbreviations: HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HDL, high-density lipoprotein; LDL, low density lipoprotein; CRP, c-reactive protein; IL-6, interleukin-6, TNF-a, tumor necrosis factor-alpha.

Values are expressed as mean (SD).

[1] 10-4 dl/kg/min per uU/ml

* Statistically significant results.

Table 3

Anthropometric Measurements of Participants

	Patients (n=18)	Siblings (n=22)	Controls (n=15)	P
Body mass index, kg/m^2	26.5 (4.1)	24.6 (3.4)	23.5 (4.3)	0.08
Bicep skinfold, mm	8.9 (4.2)	8.9 (4.0)	8.7 (6.2)	0.98
Triceps skinfold, mm	17.7 (5.4)	18.1 (6.1)	16.8 (6.7)	0.83
Subscapular skinfold, mm	17.2 (5.6)	14.1 (4.9)	15.9 (7.0)	0.24
Suprailiac skinfold, mm	24.1 (5.6)	19.5 (5.4)	19.6 (7.2)	0.02
Waist-hip ratio	0.9 (0.1)	0.8 (0.1)	0.8 (0.1)	0.005
Waist circumference (iliac crest), cm	90.6 (9.9)	84.1 (9.1)	79.8 (9.7)	0.007
Widest hip circumference, cm	104.0 (7.2)	101.2 (7.7)	99.1 (9.2)	0.22
Ideal body weight, %	117.9 (16.6)	114.1 (16.5)	107.7 (21.0)	0.26
IPAQ High Activity, No. (%)	12 (66.7)	14 (66.7)	13 (76.5)	0.76
Resting energy expenditure, kcal/d	1533.8 (204.5)	1460.7 (363.1)	1315.13 (189.5)	0.08
VAT area (DXA), cm^2	77.2 (29.8)	61.8 (34.8)	56.2 (29.0)	0.14

Abbreviations: IPAQ, International Physical Activity Questionnaire; VAT, visceral adipose tissue area; DXA, dual-energy x-ray absorptiometry.

Values are expressed as mean (SD), except as indicated.

Table 4

Mediation analyses of insulin sensitivity with body mass index as mediator/moderator in patients with first episode psychosis.

	Coeff	S.E.	95% CI	P-value
Reference Interaction (INTref)	−0.17	0.15	−0.45, 0.11	0.25
Mediated Interaction (INTmed)	0.31	0.22	−0.13,0.75	0.17
Controlled Direct Effect (CDE)	−0.58	0.26	−1.09, −0.08	0.02
Pure Indirect Effect (PIE)	−0.27	0.19	−0.64,0.09	0.14
Total Effect (TE)	−0.72	0.27	−1.24, −0.20	0.01

Exposure-mediator interactions between group status and BMI were present in patients with first episode psychosis, and the effect of patient status on insulin sensitivity was analyzed into: 1) the effect neither due to mediation nor interaction (controlled direct effect (CDE)), 2) the effect only due to interaction between patient status and BMI (reference interaction (INTref)), 3) the effect only due to mediation through BMI (pure indirect effect (PIE)), and 4) the effect due both to mediation and interaction (mediated interaction (INTmed)).