Impaired Glucose Homeostasis in First-Episode Schizophrenia: A Systematic Review and Meta-analysis

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IMPORTANCE Schizophrenia is associated with an increased risk of type 2 diabetes. However, it is not clear whether schizophrenia confers an inherent risk for glucose dysregulation in the absence of the effects of chronic illness and long-term treatment.

OBJECTIVE To conduct a meta-analysis examining whether individuals with first-episode schizophrenia already exhibit alterations in glucose homeostasis compared with controls.

DATA SOURCES The EMBASE, MEDLINE, and PsycINFO databases were systematically searched for studies examining measures of glucose homeostasis in antipsychotic-naive individuals with first-episode schizophrenia compared with individuals serving as controls.

STUDY SELECTION Case-control studies reporting on fasting plasma glucose levels, plasma glucose levels after an oral glucose tolerance test, fasting plasma insulin levels, insulin resistance, and hemoglobin A1c (HbA1c) levels in first-episode antipsychotic-naive individuals with first-episode schizophrenia compared with healthy individuals serving as controls. Two independent investigators selected the studies.

DATA EXTRACTION Two independent investigators extracted study-level data for a random-effects meta-analysis. Standardized mean differences in fasting plasma glucose levels, plasma glucose levels after an oral glucose tolerance test, fasting plasma insulin levels, insulin resistance, and HbA1c levels were calculated. Sensitivity analyses examining the effect of body mass index, diet and exercise, race/ethnicity, and minimal (≤2 weeks) antipsychotic exposure were performed.

DATA SYNTHESIS Of 3660 citations retrieved, 16 case-control studies comprising 15 samples met inclusion criteria. The overall sample included 731 patients and 614 controls. Fasting plasma glucose levels (Hedges g = 0.20; 95% CI, 0.02 to 0.38; P = .03), plasma glucose levels after an oral glucose tolerance test (Hedges g = 0.61; 95% CI, 0.16 to 1.05; P = .007), fasting plasma insulin levels (Hedges g = 0.41; 95% CI, 0.09 to 0.72; P = .01), and insulin resistance (homeostatic model assessment of insulin resistance) (Hedges g = 0.35; 95% CI, 0.14 to 0.55; P = .001) were all significantly elevated in patients compared with controls. However, HbA1c levels (Hedges g = −0.08; CI, −0.34 to 0.18; P = .55) were not altered in patients compared with controls.

CONCLUSIONS AND RELEVANCE These findings show that glucose homeostasis is altered from illness onset in schizophrenia, indicating that patients are at increased risk of diabetes as a result. This finding has implications for the monitoring and treatment choice for patients with schizophrenia.
large-scale epidemiologic studies have established that people with schizophrenia die 15 to 30 years earlier than the general population and that 60% or more of this premature mortality is due to causes not related to the central nervous system, predominantly cardiovascular. Rates of type 2 diabetes are estimated to be 2 to 3 times higher in schizophrenia than in the general population, with a prevalence of 10% to 15%. Although antipsychotic use may contribute to this association, a link between schizophrenia and diabetes was already observed in the 19th century, long before the introduction of antipsychotics and in an era when diets did not have such a propensity to induce metabolic derangements. For over a decade, there has been a drive to identify whether schizophrenia confers an inherent risk for the development of type 2 diabetes by investigating patients at illness onset before the potentially confounding effects of chronic illness and long-term antipsychotic treatment. Several studies have focused on the presence or absence of type 2 diabetes in patient cohorts compared with controls. The results from meta-analyses of these studies examining the prevalence of type 2 diabetes in individuals with first-episode psychosis and controls have found no significant differences between the 2 groups. However, there are 2 limitations with restricting analyses to an established diagnosis of type 2 diabetes. The first limitation is that patients may be less likely to seek medical attention, so there is the risk of underreporting. The second is that the development of type 2 diabetes takes time, with peak onset in middle age, and so may not have had time to develop in patients with first-episode schizophrenia. Type 2 diabetes shows a progression through a period of insulin resistance, elevated insulin levels, and impaired glucose tolerance (prediabetes) before the development of symptoms and a patient eventually receiving a diagnosis of type 2 diabetes. If a study’s outcome is whether criteria are met for a diagnosis of type 2 diabetes, significant alterations in glucose homeostasis between patient and control groups may be missed. In view of these limitations, we performed a meta-analysis of studies that focused on measures of glucose control in individuals either at risk for psychosis or in their first episode of psychosis. The aim of our meta-analysis was to test the hypothesis that individuals with first-episode schizophrenia exhibit alterations in glucose homeostasis compared with matched controls.

Methods

Selection Procedures
A systematic review was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (eTables 1 and 2 in the Supplement). Two of us (T.P. and K.B.) independently searched MEDLINE (from 1946 to week 2 of April 2016), EMBASE (from 1947 to April 25, 2016), and PsycINFO (from 1806 to week 2 of April 2016). The following key words were used: (schizophrenia or schizophrenia or schizophrenia or psychosis or psychotic) and (early onset or first episode or at risk or ultra high risk or prodrome) and (medication or drug or antipsychotic)

(glucose or diabetes or type 2 or prediabetes or intolerance or oral glucose tolerance test or OGTT) or fasting or random or insulin or insulin resistance or hemoglobin [Hb] A1c or homeostatic or homeostatic model assessment of insulin resistance (HOMA-IR).

Studies in any language were considered, although all the included articles were published in English. The search was complemented by hand-searching of meta-analyses and review articles. Abstracts were screened and the full texts of relevant studies were retrieved. If full texts or abstracts were not available, authors were contacted and articles requested. Two of us (T.P. and K.B.) selected the final studies for review and meta-analysis.

Selection Criteria
Inclusion criteria were (1) a DSM or International Statistical Classification of Diseases and Related Health Problems diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, schizophrenia spectrum or psychotic disorder not otherwise specified, or an at-risk mental state for psychosis according to research criteria; (2) first episode of illness (defined either as first treatment contact [inpatient or outpatient] or duration of illness up to 5 years following illness onset); (3) antipsychotic naïve or minimal exposure (≤2 weeks of antipsychotic treatment); (4) a healthy control group; (5) glucose homeostasis assessment including 1 or more fasting plasma glucose concentration, random plasma glucose concentration, oral glucose tolerance test (OGTT), percentage of hemoglobin A1c that is glycated (HbA1c), or insulin resistance as measured using the homeostatic model assessment (HOMA). The OGTT was required to meet the American Diabetes Association (ADA) and World Health Organization (WHO) criteria, namely, serum glucose concentration measured 2 hours after a 75-g oral glucose load following an overnight fast. Fasting serum glucose and insulin concentrations were defined as concentrations of either measure taken after an overnight fast in accordance with the ADA and WHO criteria. HOMA measurements of insulin resistance were required to follow either the original HOMA-IR formula (fasting plasma insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5) or the updated HOMA2 formula via the University of Oxford Diabetic Trials Unit HOMA2 calculator, version 2.2 (http://www.dtu.ox.ac.uk).

Key Points

Question Do individuals with first-episode schizophrenia already demonstrate evidence of glucose dysregulation?

Findings In this meta-analysis of 14 case-control studies comprising 1345 participants, individuals with first-episode schizophrenia had elevated fasting plasma glucose levels, elevated plasma glucose levels after an oral glucose tolerance test, and elevated fasting plasma insulin levels, as well as greater insulin resistance compared with healthy individuals serving as controls.

Meanings Glucose homeostasis is altered from illness onset in schizophrenia, indicating that patients are at increased risk for type 2 diabetes as a result; this finding has implications for the monitoring and treatment of patients with schizophrenia.
Exclusion criteria were (1) studies only assessing diagnosis of type 1 or type 2 diabetes, (2) patients with multiple episodes of schizophrenia, (3) chronic antipsychotic treatment (>2 weeks’ lifetime exposure), (4) substance- or medication-induced psychotic disorder, (5) physical comorbidity that may affect glucose homeostasis (eg, prior diagnoses of type 1 or type 2 diabetes, other endocrine disorders [eg, Cushing syndrome or acromegaly], pancreatitis, congenital disorders known to increase risk of type 2 diabetes [eg, Klinefelter or Turner syndrome], and other systemic illnesses that may affect pancreatic function [eg, cystic fibrosis, hemochromatosis, or any chronic systemic inflammatory illness]), and (6) absence of measures in a healthy control group.

A small proportion of articles included patients with a limited duration of antipsychotic use (2 weeks maximum). In these cases, authors were contacted to obtain access to data concerning patients who were drug naive. If these data were not available, sensitivity analyses were performed examining only studies of patients who had no antipsychotic exposure.

WHO identifies obesity as the strongest risk factor for type 2 diabetes from evidence based on studies across 188 countries. In view of this observation, sensitivity analyses were performed examining studies in which patients and controls were matched on body mass index (BMI) to determine whether failure to match BMI influenced results. The matching was confirmed by either review of study methods or by confirmation of no significant difference between mean BMI levels of the patient and control groups (a 2-tailed P value <.05 was deemed significant). WHO recognizes several other risk factors for type 2 diabetes relating to BMI, including unhealthy diet and physical inactivity. Individuals with schizophrenia engage in significantly less physical exercise than controls, with even lower levels of physical activity observed in early stages of the illness. In addition, the prodrome is associated with decreased physical activity and poor eating habits. To address whether differences in diet and exercise between patient and control groups influenced the results, sensitivity analyses examining groups matched for diet and exercise were performed. Diet and exercise matching was confirmed either by review of study methods or by confirmation of no significant difference between mean diet and exercise parameters of the patient and control groups (a 2-tailed P value <.05 was deemed significant). Nonmodifiable risk factors for type 2 diabetes, such as ethnicity, are also recognized, and in this context, sensitivity analyses were also performed examining studies in which participants were matched for ethnic background.

Recorded Variables
For every study, data were extracted according to the following model: author, year of publication, country, design (ie, prospective, cross-sectional, case-control, and retrospective), matching criteria for patients and controls (confirmed by review of study methods or by confirmation of nonsignificance between mean parameter levels of patient and control groups; a 2-tailed P value <.05 was deemed significant), whether or not patient groups were antipsychotic naive (and if not, duration of treatment), and mean (SD) measure of glucose homeostasis in patient and control groups. If there were multiple publications for the same data set, data were extracted from the study with the largest data set. The Table demonstrates this data extraction with the exception of raw glucose homeostasis measurements (mean and SDs), which are documented in eTables 3-7 in the Supplement. The parameters of glucose homeostasis available in the studies described in the Table but not included in meta-analysis, along with the rationale behind exclusion, are documented in the eAppendix in the Supplement.

Statistical Analysis
A 2-tailed P < .05 was deemed significant. A random-effects model was used in all analyses owing to an expectation of heterogeneity of data across studies. Standardized mean differences in glucose homeostasis measurements between patient and control cohorts were used as the effect size, determined using Hedges adjusted g. The 95% CI of the effect size was also calculated. The direction of the effect size was positive if individuals with schizophrenia demonstrated higher values of glucose homeostatic measurements compared with controls. Heterogeneity across studies was assessed using the Cochran Q statistic. Inconsistency across studies was assessed with the I² statistic, with an I² value of less than 25% deemed to have low heterogeneity; 25% to 75%, medium heterogeneity; and greater than 75%, high heterogeneity. Publication bias and selective reporting were assessed using the Egger test of the intercept (although this factor was not calculated when <10 studies were analyzed as recommended by the Cochrane Collaboration) and represented diagrammatically with funnel plots, again as recommended by the Cochrane Collaboration (eFigures 1-5 in the Supplement).

Results

Retrieved Studies
After exclusion of studies reporting on overlapping data sets, 16 case-control studies comprising 15 samples met inclusion criteria and were analyzed. The search process is demonstrated in Figure 1, and the final studies selected are summarized in the Table. The overall sample included 731 patients and 614 controls.

Fasting Plasma Glucose Concentration
Fasting plasma glucose concentration in patients and controls was analyzed using data from 14 studies comprising 718 patients and 599 controls. Fasting plasma glucose concentration was significantly elevated in patients compared with controls (Hedges g = 0.20; 95% CI, 0.02 to 0.38; P = .03) (Figure 2). There was significant between-sample heterogeneity, with an I² value of 58.29% (Cochran Q = 31.17; P = .003). Findings of the Egger test (P = .07) suggested that publication bias was not significant. Restricting the analyses to antipsychotic-naive patients by excluding the 3 studies that included patients with up to 2 weeks of antipsychotic treatment demonstrated that fasting plasma glucose conc-
Plasma glucose concentration was significantly elevated in patients compared with controls (Hedges $g = 0.61$; 95% CI, 0.16-1.05; $P = .007$) (Figure 2). Between-sample heterogeneity was significant, with an $I^2$ value of 82.40% (Cochran $Q = 17.05$; $P = .001$). A sensitivity analysis examining studies in which patients and controls were matched for ethnicity demonstrated that fasting plasma glucose concentration after OGTT remained significantly elevated in patients compared with controls (Hedges $g = 0.78$; 95% CI, 0.40-1.17; $P < .001$). In the context of low study numbers, sensitivity analyses to assess the impact of BMI, antipsychotics, or diet and exercise were not performed.

### Fasting Plasma Insulin Concentration

Fasting plasma insulin concentration in patients and controls was analyzed using data from 11 studies comprising 512 patients and 448 controls. Fasting plasma insulin concentration was significantly raised in patients compared with controls (Hedges $g = 0.41$; 95% CI, 0.09-0.72; $P = .01$) (Figure 3). Between-sample heterogeneity was significant, with an $I^2$ value of 80.80% (Cochran $Q = 52.09$; $P < .001$). Find-
ings of the Egger test \(P = .12\) suggested that publication bias was not significant. Excluding the 3 studies that included patients with up to 2 weeks of antipsychotic treatment \(^{27-29}\) to restrict the analyses to antipsychotic-naive patients demonstrated that fasting plasma insulin concentration remained significantly elevated in patients compared with controls (Hedges \(g = 0.47; 95\% CI, 0.03-0.91; P = .04\)). Exclusion of 1 study that examined non-BMI-matched patients and controls \(^{34}\) demonstrated that fasting plasma insulin concentration remained significantly elevated in patients compared with controls (Hedges \(g = 0.38; 95\% CI, 0.04-0.72; P = .03\)). A sensitivity analysis examining studies in which patients and controls were matched for ethnicity \(^{26,31,34,37,46}\) demonstrated that fasting insulin concentration remained significantly elevated in patients compared with controls (Hedges \(g = 0.49; 95\% CI, 0.30-0.68; P < .001\)). In the context of low study numbers, a sensitivity analysis to assess the impact of diet and exercise was not performed.

**Insulin Resistance**

Insulin resistance as measured using the HOMA-IR tool in patients and controls was analyzed using data from 10 studies \(^{26,28-32,34,38,39}\) comprising 485 patients and 400 controls. HOMA-IR was significantly raised in patients compared with controls (Hedges \(g = 0.35; 95\% CI, 0.14-0.55; P = .001\)) (Figure 3). Between-sample heterogeneity was moderate but significant, with an \(I^2\) value of 55.40\% (Cochran \(Q = 20.18\); \(P = .02\)). Findings of the Egger test \(P = .10\) suggested that publication bias was not significant. Excluding the 2 studies that included patients with up to 2 weeks of antipsychotic treatment \(^{38,31}\) to restrict the analyses to antipsychotic-naive patients demonstrated that HOMA-IR remained significantly elevated in patients compared with controls (Hedges \(g = 0.44; 95\% CI, 0.23-0.65; P < .001\)). Exclusion of 1 study that examined non-BMI-matched patients and controls \(^{34}\) demonstrated that HOMA-IR remained significantly elevated in patients compared with controls (Hedges \(g = 0.31; 95\% CI, 0.09-0.53; P = .005\)). A sensitivity analysis examining studies in which patients and controls were matched for ethnicity \(^{26,31,34,39}\) demonstrated that HOMA-IR remained significantly elevated in patients compared with controls (Hedges \(g = 0.66; 95\% CI, 0.43-0.88; P < .001\)). In the context of low study numbers, a sensitivity analysis to assess the impact of diet and exercise was not performed.

**HbA\(_1c\) Analysis**

The HbA\(_1c\) levels were analyzed using data from 4 studies \(^{27,34,38,41}\) comprising 166 patients and 164 controls. The HbA\(_1c\) levels were not altered in patients compared with controls (Hedges \(g = -0.08; 95\% CI, -0.34 to 0.18; P = .55\)) (eFigure 7 in the Supplement). Between-sample heterogeneity was moderate as indicated by an \(I^2\) value of 31.50\%, but a Cochrane \(Q\) value of 4.38 \(P = .22\) suggested nonsignificant heterogeneity. Of these 4 studies, 2 studies examined patients with up to 2 weeks of antipsychotic use \(^{38,41}\) and 1 study examined non-BMI-matched patients and controls. \(^{34}\) In the context of low study numbers, sensitivity analyses were not performed.

**Discussion**

Our main findings are that patients with schizophrenia show raised fasting plasma glucose levels, reduced glucose tolerance, raised fasting plasma insulin levels, and increased insulin resistance at illness onset. With the exception of fasting glucose levels, these alterations were also seen when analyses were restricted to antipsychotic-naive and BMI-matched samples. When analysis was restricted to diet and exercise-matched samples, significance was maintained for raised fasting glucose levels in patients. All results remained significant when analyses were restricted to samples matched for race/ethnicity. No significant differences were demonstrated in HbA\(_1c\) levels, although this result should be interpreted with caution owing to the small sample size used in this analysis. The results of our meta-analysis extend recent studies showing high rates of diabetes in patients with chronic schizophrenia by demonstrating that altered glucose homeostasis is present from illness onset.

**Strengths and Limitations**

By focusing our analysis on patients with first-episode schizophrenia, an attempt was made to limit the duration of secondary illness-related factors known to affect glucose homeostasis. However, individuals in the prodromal state and those with
Figure 2. Fasting Glucose Concentrations and Glucose After an Oral Glucose Tolerance Test (OGTT) in Patients With First-Episode Schizophrenia and Controls

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size, No.</th>
<th>Fasting glucose</th>
<th>Elevated in Patients</th>
<th>Elevated in Controls</th>
<th>Relative Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient</td>
<td>Control</td>
<td>Hedges g</td>
<td>95% CI</td>
<td></td>
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<tr>
<td><strong>Fasting glucose</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Zhang et al, 2015</td>
<td>120</td>
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<td>40</td>
<td>70</td>
<td>-0.11</td>
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<tr>
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<td>Arranz et al, 2004</td>
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<td>50</td>
<td>0.23</td>
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</tr>
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<tr>
<td>Saddichha et al, 2008</td>
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<tr>
<td>Garcia-Rizo et al, 2016</td>
<td>84</td>
<td>98</td>
<td>-0.21</td>
<td>-0.50 to 0.08</td>
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<td>Chen et al, 2013</td>
<td>49</td>
<td>30</td>
<td>-0.19</td>
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<td>Sengupta et al, 2008</td>
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<td></td>
<td>718</td>
<td>599</td>
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<td>0.02 to 0.38</td>
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<td><strong>OGTT</strong></td>
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<td>271</td>
<td>237</td>
<td>0.61</td>
<td>0.16 to 1.05</td>
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Significant elevation in fasting glucose concentration (Hedges g = 0.20, 95% CI, 0.02-0.38; P = .03) and glucose concentration after OGTT (Hedges g = 0.61; 95% CI, 0.16-1.05; P = .007) in patients. Each square shows the effect size for a single study, with the horizontal line running through each square illustrating the width of the 95% CI. The size of the squares reflects the weight attributed to each study. Diamonds illustrate the summary effect sizes, the middle of each diamond represents the summary effect size, and the width of the diamond depicts the width of the overall 95% CI.

First-episode schizophrenia already have poorer dietary habits, decreased physical activity, and an increased likelihood of smoking compared with age-matched controls.23-25,47 Our search did not find any studies that examined glucose homeostasis in individuals at risk for developing psychosis that matched our inclusion criteria, and the duration of untreated psychosis was documented in only 5 of the 16 studies analyzed.27,28,32,36,38 Since our definition of first-episode psychosis was documented in only 5 of the 16 studies used in this meta-analysis analyzed patients with schizophrenia as well as individuals with schizotypal disorder, brief psychotic disorder, and psychosis not otherwise specified,27,37,38,41 which may contribute to heterogeneity in the sample. There was also variability in matching criteria for patients and controls, which might be significant given the effect of demographic variables on risk for type 2 diabetes.22 Nevertheless, 8 studies documented that participants were matched for race/ethnicity,26,31,34,36,39,41 and our sensitivity analyses suggest that differences in ethnicities between groups were not responsible for the overarching findings of the meta-analysis. Two studies failed to match for sex,26,33 1 study failed to match for age,30 and only 8 studies documented that participants were matched for smoking status.26-28,31,33,34,39,41 (Table and eTable 8 in the Supplement). Other limitations of our analyses include between-sample heterogeneity in glucose homeostasis parameters.
Figure 3. Fasting Insulin Concentrations and Insulin Resistance (Homeostatic Model Assessment—Insulin Resistance [HOMA-IR]) in Patients With First-Episode Schizophrenia and Controls

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size, No.</th>
<th>Fasting insulin</th>
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<td>0.95</td>
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Significant elevation in fasting insulin concentration (Hedges $g = 0.41$; 95% CI, 0.09-0.72; $P = .01$) and HOMA-IR ($HOMA-IR = 0.35$; 95% CI, 0.14-0.55; $P = .001$) in patients. Each square shows the effect size for a single study, with the horizontal line running through each square illustrating the width of the 95% CI. The size of the squares reflects the weight attributed to each study. Diamonds illustrate the summary effect sizes, the middle of each diamond represents the summary effect size, and the width of the diamond depicts the width of the overall 95% CI.

Tested, including the use of either the original HOMA-IR equation $^{20}$ or the HOMA2 equation $^{21}$ Nevertheless, the random-effects model that we used is robust to heterogeneity, and the fact that findings were consistent across different methods suggests that they are robust to technical variation.

In view of the findings of our meta-analysis, prospective studies investigating the effect of lifestyle factors on the glucose dysregulation seen in patients with first-episode schizophrenia would help to determine the degree to which alterations in intrinsic to schizophrenia or the consequences of emerging symptoms. Longitudinal studies examining the efficacy of early interventions targeting a reduction in diabetic risk (both lifestyle based and pharmacologic) in individuals with schizophrenia who exhibit subtle early aberrances in glucose homeostasis would be useful.

Although the findings of this meta-analysis may in part reflect poorer lifestyle habits in patients compared with controls, other mechanisms may also contribute to the link between schizophrenia and altered glucose regulation. Both schizophrenia and type 2 diabetes are associated with early developmental risk factors, such as low birth weight, preterm birth, gestational diabetes, and maternal malnutrition or obesity. The increased risk of impaired glucose homeostasis and schizophrenia in the context of early developmental insults is demonstrated by studies examining survivors from the 1944-1945 Dutch famine and the 1959-1961 Chinese famine. These studies demonstrate a relative risk of approximately 2 for developing schizophrenia in individuals conceived or in early gestation during a period of famine, $^{46}-^{55}$ as well as an increased risk of impaired glucose tolerance later in life. $^{51}$ Stress and hypercortisolemia may also contribute to this association between the 2 conditions, with antipsychotic-naive individuals with first-episode psychosis exhibiting higher baseline cortisol levels and blunted cortisol awakening response compared with controls. $^{52}$ There is also evidence for a shared genetic vulnerability. Relatives of individuals with schizophrenia experience higher rates of type 2 diabetes, $^{53}-^{55}$ and genome-wide association studies have revealed shared susceptibility genes between schizophrenia and type 2 diabetes. $^{56,57}$ Evidence to support the existence of pleiotropy between these genes has been demonstrated by a network analysis examining common signaling pathways involved in both schizophrenia and type 2 diabetes, with identification of proteins that play a role in calcium signaling, adipoctykin signaling, Akt signaling, and γ-secretase-mediated ErbB4 signaling. $^{57}$ Thus, dysfunction in common signaling pathways may drive central neurologic dysfunction as well as peripheral metabolic dysfunction.
Conclusions

Regardless of the mechanism, this meta-analysis has demonstrated an association between schizophrenia and early derangements in glucose homeostasis. The OGTT is a more sensitive measure of abnormalities in glucose metabolism than fasting plasma glucose level\(^{58,59}\) and is recognized by WHO as the only means of identifying individuals with impaired glucose tolerance. The use of fasting plasma glucose measurement alone as a screen for type 2 diabetes results in approximately 30% of type 2 diabetes cases being missed.\(^{62}\) Indeed, the OGTT has been recommended for screening and monitoring of patients with schizophrenia spectrum disorders owing to its increased sensitivity.\(^{61}\) This sensitivity lends further significance to the large effect size for raised glucose concentrations after OGTT seen in patients with schizophrenia compared with controls. Although predominantly used in research, HOMA-IR is well validated as a surrogate marker of insulin resistance, with its results correlating well with standard tests of insulin resistance, such as the hyperinsulinemic-euglycemic clamp.\(^{62}\) Therefore, the results from this analysis have major clinical implications. They indicate that individuals with schizophrenia present at the onset of illness with an already vulnerable phenotype for the development of type 2 diabetes. Given that several antipsychotic drugs may worsen glucose regulation,\(^{63,64}\) there is thus a responsibility placed on the treating clinician to select an appropriate antipsychotic at an appropriate dose so as to limit the metabolic impact of treatment. Furthermore, the association between schizophrenia and glucose dysregulation suggests that patients should be educated regarding diet and physical exercise, as well as diabetic screening, and offered early lifestyle and pharmacologic interventions to combat the risk of progression to type 2 diabetes.

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ARTICLE INFORMATION

Accepted for Publication: November 11, 2016.
Published Online: January 11, 2017.
doi:10.1001/jamapsychiatry.2016.3803

Author Contributions: Dr Pillinger had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest Disclosures: Dr Howes has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organized by AstraZeneca, Autifony, BMS, Eli Lilly, Heptares, Janssen, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand, and Roche. No other disclosures were reported.

Funding/Support: This study was funded by grants MC-A656-5QD30 from the Medical Research Council-UK, 666 from the Maudsley Charity Trust and King’s College London, Research Biomedical Research Centre at South London and Maudsley National Health Service Foundation Trust and King’s College London.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Tony Cohn, MBChB, MSc, FRCPC (Psychiatry and Nutritional Sciences, University of Toronto), provided data. There was no financial compensation.


