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Brian J. Miller, Augusta University
David Goldsmith, Emory University
Nina Paletta, Augusta University
Joyce Wong, Augusta University
Prianka Kandhal, Augusta University
Carmen Black, Augusta University
Mark Rapaport, Emory University
Peter F. Buckley, Augusta University

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Parental Type 2 Diabetes in Patients with Non-affective Psychosis

Brian J. Miller, MD, PhD, MPH1, David R. Goldsmith, MD2, Nina Paletta, BS3, Joyce Wong, BS3, Prianka Kandhal, BS3, Carmen Black, MD3, Mark Hyman Rapaport, MD2, and Peter F. Buckley, MD3

1Department of Psychiatry and Health Behavior, Augusta University, Augusta, Georgia, US
2Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, Georgia, US
Medical College of Georgia, Augusta University, Augusta, Georgia, US

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Dear Editors

Studies antedating the advent of antipsychotics found an increased prevalence of abnormal glucose metabolism in patients with schizophrenia, although there were methodological limitations (Kohen, 2004). Abnormal glucose tolerance has been observed in antipsychotic-naïve patients with first-episode psychosis (Fernandez-Egea et al., 2009), as well as in the relatives of schizophrenia probands (Fernandez-Egea et al., 2008; Spelman et al., 2007). The concept of fetal origins of adult disease posits that events at key time points during gestation impact development and subsequent risk of adult disease (Schlotz et al., 2009), and several risk factors (e.g., birth and maternal factors, and immune genes) are common to schizophrenia and type 2 diabetes (DM2) (Kandhal and Miller, 2013). These findings suggest an increased risk of diabetes in schizophrenia, involving host-agent-environment interactions, that may be independent of antipsychotics. However, this intriguing hypothesis has been largely overshadowed by known metabolic side effects of second-generation antipsychotics (SGAs), which clearly increase the risk of DM2.

Several studies have reported an increased prevalence of a family history of DM2 in schizophrenia probands (Fernandez-Egea et al., 2008b; Mukherjee et al., 1989). The present study investigates associations between parental DM2 and non-affective psychoses. We hypothesized that in probands with non-affective psychosis, there is an increased prevalence of parental DM2, which is also a predictor of comorbid diabetes.
Two-hundred seventeen inpatients and outpatients aged 18–70 diagnosed with schizophrenia (n=119), schizoaffective (n=88), psychosis NOS (n=9), or brief psychotic disorder (n=1), and 67 controls were recruited in Augusta, Georgia, between July 2010 and November 2015. Exclusion criteria have been reported elsewhere (Miller et al., 2015). Medications were not standardized, although the majority (83%) were treated with SGA monotherapy. After written informed consent, subjects underwent a laboratory (blood draw between 8 and 9 AM after a ten-hour fast), physical and psychiatric diagnostic evaluation. Parental DM2 and psychiatric illness was obtained by self-report. Subjects were diagnosed with DM2 by either self-reported history or a fasting blood glucose ≥ 26 mg/dL. The study was approved by the IRB’s of Augusta University and the Georgia Department of Community Health.

Demographic and clinical characteristics were analyzed using either a Chi-square test or Student’s t-test (2-sided). Binary logistic regression models were used to evaluate subject group as a predictor of a parental DM2, controlling for age, sex, race, BMI, smoking, SES, and parental non-affective psychosis or bipolar disorder. Binary logistic regression models were also used to evaluate parental DM2 as a predictor of DM2 in non-affective psychosis, controlling for the same potential confounding factors. Results were considered statistically significant at the $\alpha=0.05$ level (two-sided). The data were analyzed using SPSS, version 22.

The Table provides demographic information and regression analyses for the study sample. Data on parental DM2 were missing (unknown/not reported) for n=35 (16.1%) patients and n=6 (9.0%) controls. There was a significant increased prevalence of parental DM2 in non-affective psychosis. Results were similar when restricting to subjects with schizophrenia, and subjects without a parental psychiatric history. After controlling for potential confounding factors, we found non-affective psychosis was associated with DM2 in the father (OR=3.7) or either parent (OR=2.8), consistent with previous studies (Fernandez-Egea et al., 2008b; Mukherjee et al., 1989). There was also a significant increased prevalence of parental DM2 in subjects with non-affective psychosis and comorbid DM2. In regression, parental diabetes was a significant predictor of comorbid DM2 (OR=3.7) in non-affective psychosis, also consistent with previous studies (Kusumi et al., 2011; Voruganti et al., 2007). This association underscores that screening parental DM2 status is germane to the clinical care of patients with non-affective psychoses, as it may inform on risk of incident diabetes with antipsychotic treatment.

It is intriguing that in this convenience sample, we found significant associations between non-affective psychosis and parental DM2. We explored parent-of-origin effects, controlled for multiple potential confounding factors, and confirmed DM2 status by both medical history and laboratory testing. An important limitation was that parental DM2 was obtained by self-report only, inducing a potential selective recall bias. It might be expected that patients would be less likely than controls to remember parental history because of greater cognitive impairment; however, our subjects psychosis were more likely to report such a history. In controls, the prevalence of parental DM2 was similar to estimates in this region of Georgia (8.8–11.1%; Georgia Department of Public Health, 2012). Our data do not allow us to determine whether the increased prevalence of parental DM2 is due to shared environmental or genetic factors, or gene-environment interactions. However, our results
support the hypothesis that the development of DM2 in non-affective psychosis is multifactorial and not merely a result of SGA use.

References


### Table
Demographic Characteristics of the Study Sample

<table>
<thead>
<tr>
<th></th>
<th>Non-Affective Psychosis (N=217)</th>
<th>Controls (N=67)</th>
<th><strong>p-value</strong></th>
<th>OR</th>
<th>95% CI</th>
<th><strong>p-value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (± SD)</td>
<td>42.2 ± 12.2</td>
<td>36.5 ± 14.4</td>
<td><strong>0.004</strong></td>
<td></td>
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<tr>
<td>BMI</td>
<td>30.9 ± 8.2</td>
<td>28.6 ± 6.2</td>
<td><strong>0.032</strong></td>
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<tr>
<td>Smoking (cigarettes/day)</td>
<td>7.8 ± 10.5</td>
<td>1.3 ± 3.9</td>
<td><strong>&lt;0.001</strong></td>
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<tr>
<td>SES</td>
<td>32.1 ± 10.7</td>
<td>62.0 ± 18.5</td>
<td><strong>&lt;0.001</strong></td>
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<tr>
<td>Mean paternal age at birth</td>
<td>30.1 ± 9.3</td>
<td>29.1 ± 6.4</td>
<td>0.533</td>
<td></td>
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<tr>
<td>Mean maternal age at birth</td>
<td>25.8 ± 6.9</td>
<td>25.3 ± 5.2</td>
<td>0.537</td>
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<td></td>
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<tr>
<td>Sex (% Male)</td>
<td>59.0</td>
<td>41.8</td>
<td><strong>0.017</strong></td>
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<td>Race (%)</td>
<td></td>
<td></td>
<td><strong>&lt;0.001</strong></td>
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<tr>
<td>Caucasian</td>
<td>29.0</td>
<td>46.3</td>
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<td>African descent</td>
<td>68.2</td>
<td>40.3</td>
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<tr>
<td>East/Southeast Asian</td>
<td>0.0</td>
<td>1.5</td>
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<tr>
<td>Western Asian</td>
<td>0.0</td>
<td>4.5</td>
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<tr>
<td>Hispanic</td>
<td>1.4</td>
<td>6.0</td>
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<tr>
<td>South Asian</td>
<td>0.9</td>
<td>1.5</td>
<td></td>
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<tr>
<td>Parental DM2 (% Yes)</td>
<td></td>
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<tr>
<td>Either parent (Mother, Father, or Both)</td>
<td>44.5</td>
<td>24.6</td>
<td><strong>0.006</strong></td>
<td>2.80</td>
<td>1.08–7.23</td>
<td><strong>0.034</strong></td>
</tr>
<tr>
<td>Father</td>
<td>23.3</td>
<td>12.9</td>
<td>0.099</td>
<td>4.21</td>
<td>1.16–15.33</td>
<td><strong>0.029</strong></td>
</tr>
<tr>
<td>Mother</td>
<td>30.0</td>
<td>13.8</td>
<td><strong>0.013</strong></td>
<td>2.53</td>
<td>0.84–7.57</td>
<td>0.097</td>
</tr>
</tbody>
</table>

*Sex and Race were analyzed using the Chi-square test; Student’s t-test, two-sided, was used for the other comparisons.*