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Abstract

**Aims**—To understand the metabolic and temporal links in the relationship between diabetes and depression, we determined the association between depressive symptoms and unrecognized glucose intolerance.

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Competing interests
Nothing to declare.
Methods—In a cross-sectional study, 1047 subjects without known diabetes were screened for diabetes or pre-diabetes using the oral glucose tolerance test and for depressive symptoms using the Patient Health Questionnaire (PHQ).

Results—Mean age was 48 years, body mass index 30 kg/m$^2$; 63% were female, 54% black, 11% previously treated for depression and 10% currently treated; 5% had diabetes and 34% pre-diabetes. Median PHQ score was 2 (interquartile range 0–5). Depressive symptoms did not increase with worsening glucose tolerance, after adjusting for age, sex, ethnicity, body mass index, family history, exercise, education and depression treatment.

Conclusions—There is no association between depressive symptoms and unrecognized glucose intolerance. However, it remains possible that diagnosed diabetes, with its attendant health concerns, management issues, and/or biological changes, may be a risk for subsequent development of depression. Thus, patients with newly diagnosed diabetes should be counselled appropriately and monitored for the development of depression.

Keywords
diabetes; impaired glucose tolerance; psychosocial

Introduction
The morbidity of diabetes is compounded by concomitant depression in 11–32% of patients with diagnosed diabetes, a twofold higher prevalence than that in unaffected populations [1]. Patients with co-morbid depression are more likely to have poor glycaemic control [2] and more marked diabetic complications [3]. Moreover, as depression confers a higher risk for coronary heart disease [4], the risk for coronary heart disease may be additive when both diseases are present [5].

Although evidence of the relationship between depression and diabetes is strong, the mechanism of the association remains unclear: depression may lead to diabetes or diabetes may lead to depression. To determine whether depression is linked to the metabolic abnormality per se, we determined the prevalence of depressive symptoms along the continuum of glucose tolerance in individuals without previously known diabetes.

Patients and methods

Subjects
Subjects in the Screening for Impaired Glucose Tolerance (SIGT) Study [6], approved by the Emory University Institutional Review Board, were recruited from January 2004 to February 2007 at Emory University (Atlanta, GA, USA). Eligibility included no known history of diabetes, not using steroids, not pregnant and relatively good health. All participants gave written consent.

Assessments
Glucose tolerance was classified by American Diabetes Association (ADA) criteria with a 75-g oral glucose tolerance test (OGTT) [7]. Pre-diabetes was defined as impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). Plasma glucose was measured in the Grady Memorial Hospital Clinical Laboratory (Beckman LX-20: Beckman, Brea, CA, USA).

Depressive symptoms were measured using the Patient Health Questionnaire-9 (PHQ-9) [8], a nine-item, self-administered, validated screening tool for depression, with scaled responses (0–3 per item, maximum total 27) [8]. Higher scores indicate more depressive symptoms.
Compared with a psychiatric interview, a score $\geq 9$ provided 95% sensitivity and 84% specificity for Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV depressive disorder [9]. Symptoms are rated minimal for a score 0–4, mild 5–9, moderate 10–14, moderately severe 15–19 and severe 20–27 [9]. Because of the low prevalence of depressive symptoms in our population, additional analyses of symptom severity were performed by grouping moderate, moderately severe and severe symptoms. The PHQ-9 appears to be valid in our population as score and symptom severity rose with depression treatment (both $P < 0.0001$ for trend from never treated to past treatment to current treatment).

Exercise levels were determined from selected items of the self-administered Cross-Cultural Activity Participation (CAPS) Typical Week Physical Activity survey [10]. The cross-sectional study design precluded use of exercise diaries.

Family history of diabetes (first-degree relative), current smoker, diet history by Diet History Questionnaire (version 1.0; National Cancer Institute, National Institutes of Health, Bethesda, MD, USA) [11], depression history and education level were collected by self-report.

Statistical analysis

Glucose tolerance was coded as normal glucose tolerance (NGT) = 0, pre-diabetes = 1 or diabetes = 2. Linear regression was performed to test for trend for selected variables as glucose tolerance worsened. To adjust for potential confounders [age, sex, ethnicity, body mass index (BMI), education, family history, exercise, past or current depression treatment], multivariable ordinal logistic regression was performed, as well as subanalyses comparing depressed and non-depressed subjects matched for age, sex, ethnicity and BMI. Multivariable linear regression was performed to analyse the relationship between depressive symptoms and glucose levels [fasting plasma glucose (FPG), 2-h post-challenge glucose (2hPG)]. PHQ scores were analysed as categorical and continuous variables in separate analyses. Two-way interactions of all covariates with PHQ score were initially included in the models. Statistical analyses were conducted using SPSS 15.0 (SPSS Inc., Chicago, IL. USA) and Stata 10 (StataCorp LP, College Station, TX, USA).

Results

Of the 1047 subjects (Table 1), 11% reported past depression treatment and 10% current treatment; 61% had NGT, 17% isolated IFG, 9% isolated IGT, 9% IFG and IGT (IFG + IGT) and 5% diabetes.

The median PHQ score was 2 (IQR 0–5). Subjects with higher PHQ scores or greater severity of depressive symptoms were younger, less educated and more likely to smoke and had higher BMI and daily intake of saturated fat (all $P < 0.05$). Older age, higher BMI, male sex, family history of diabetes and less education were associated with a greater likelihood of glucose intolerance (all $P < 0.02$). However, no association was observed between glucose tolerance and depressive symptoms or history of depression treatment (all $P > 0.10$ for trend).

In multivariable analysis, only older age, higher BMI, male sex and family history were independently associated with worsening glucose tolerance, but depressive symptoms (by PHQ score or symptom severity) and past or current depression treatment were not (Table 2). None of the covariate interactions with depressive symptoms were significant and there was no difference in glucose intolerance in depressed compared with non-depressed subjects, matched for age, sex, ethnicity and BMI (all $P > 0.3$, data not shown). Similarly, no association was found between any measure of depression and either FPG or 2hPG levels (data not shown).
Discussion

To understand the relationship between diabetes and depression, we asked whether unrecognized glucose intolerance was associated with depressive symptoms in individuals without known diagnosis of diabetes. No association was observed between depressive symptoms and glucose intolerance, indicating that depression is unlikely to be as a result of early glucose intolerance itself.

The association between diabetes and depression is well established [1,3], but the mechanisms are unclear. Depression is reported to be a risk factor for the development of diabetes [12], but prospective studies of incident diabetes in non-diabetic cohorts [13–22] have been limited by use of depression surveys rather than diagnostic interviews, suboptimal diabetes diagnostic criteria and lack of adjustment for confounders. The only study [13] that assessed depression by diagnostic interview found no association with incident diabetes. As depression surveys may indicate disease burden more than the presence of major depression [23,24], there is some risk of misclassification bias. An OGTT was used in only four studies Short report [16,18,20,22], but as nearly half of new diabetes diagnoses are made by 2hPG levels alone [25], prior studies which omitted the OGTT are subject to misclassification bias. Adjustment for age, sex, ethnicity, obesity and family history of diabetes was not carried out in most studies, except one of a cohort of Japanese men, which may not be generalizable to women or other ethnic groups [20]. A secondary analysis of the Diabetes Prevention Program (DPP) [22] adjusted for all of these variables except family history and found no association between diabetes and depressive symptoms, using the Beck Depression Inventory. However, an association was observed between ‘continuous depression treatment’ and incident diabetes in placebo and lifestyle treatment groups, but not the metformin group. The lack of association between depressive symptoms and diabetes is consistent with our findings, which included individuals across the glucose tolerance continuum, while the DPP was limited to those with IGT and/or IFG.

Conversely, diagnosed diabetes has been reported as a risk factor for subsequent development of depression [16,24]. It is possible that, as pre-diabetes progresses to diabetes over several years, depression could develop even in the early stages of diagnosed diabetes, as a result of emotional, physical and financial costs of diabetes care (e.g. poor quality of life, illness intrusiveness, challenges to coping skills, disability) [26], combined with underlying neuroendocrine, inflammatory and oxidative stress abnormalities [27,28].

To our knowledge, our findings are the first assessment of the prevalence of depressive symptoms across the continuum of unrecognized glucose intolerance, adjusting for established risk factors, diet, exercise and socio-economic status. However, our study has limitations. As all subjects were recruited on a volunteer basis, there may have been a selection bias towards higher family history of diabetes, healthier lifestyles and/or lower depression rates. In addition, as depression questionnaires provide only a measure of depressive symptoms and cannot establish a diagnosis of depression without a psychiatric interview, our study is at risk of misclassification bias—although the PHQ accurately identified our patients treated for depression. Misclassification biases may have also been introduced through self-reported diet, exercise and history of diabetes and depression. However, history of depression was internally corroborated by reported use of antidepressant medication(s). With regard to diabetes history, patients who were unaware of their diagnosis would not have suffered the possible depressive consequences of diabetes as a chronic disease and potential misclassification would not confound the relationship between depression and diabetes in our study. Self-reported physical activity was inversely correlated with BMI and depressive symptoms in our population (both $P > 0.0001$), confirming previous associations [14,15] and suggesting reasonable accuracy. Additionally, the cross-sectional design of our study precluded determination of the effect of depression duration and severity on incident prediabetes and diabetes over time, although we...
were able to adjust for past and current depression treatment. Finally, our findings regarding the relationship between depression and diabetes must be interpreted in light of the low prevalence of depressive symptoms in our study compared with the general population [9]. In particular, the low prevalence of the more severe categories of depression in our population limits the power to detect an association with glucose intolerance. Therefore, our findings must be viewed in light of these limitations.

The mechanisms which underlie the association between diabetes and depression are likely to be multifactorial. Our results are consistent with the hypothesis that depression is an epiphenomenon of diagnosed diabetes, but not of undiagnosed or newly diagnosed diabetes or pre-diabetes. Additional investigation is needed to determine whether patients with newly diagnosed diabetes would benefit from screening for the development of depression and vice versa.

**Abbreviations**

2hPG, 2-h post-challenge glucose; BMI, body mass index; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IFG + IGT, combined IFG and IGT; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PHQ, Patient Health Questionnaire.

**Acknowledgements**

We thank the other members of the SIGT research group: Jack Kaufman, Aisha Bobcombe, Eileen Osinki, Amy Barerra and Circe Tsui. We also appreciate the support of the Emory GCRC and its staff. This work was supported in part by DK070715 and RR017643 (MKR), the Dana Foundation and Forest Pharmaceuticals (DM), HS07922 and DK066204 (LSP, WSW, PK and VV), K24HL077506, K24HL077506, R01HL68630 and R01AG026255 (VV) and RR00039.

Portions of this work were presented at the Scientific Sessions of the American Diabetes Association on June 9, 2006 in Washington, DC.

**References**

## Table 1

### Patient characteristics

<table>
<thead>
<tr>
<th>Variable*</th>
<th>All</th>
<th>NGT</th>
<th>All pre-DM</th>
<th>Isolated IFG</th>
<th>Isolated IGT</th>
<th>IFG + IGT</th>
<th>DM</th>
<th>Coefficient for trend</th>
<th>P-value for trend&lt;sup&gt;‡&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects (%)</td>
<td>1047 (100)</td>
<td>642 (61)</td>
<td>352 (34)</td>
<td>178 (17)</td>
<td>84 (9)</td>
<td>90 (9)</td>
<td>53 (5)</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48 (12)</td>
<td>46 (12)</td>
<td>52 (10)</td>
<td>51 (10)</td>
<td>52 (10)</td>
<td>54 (10)</td>
<td>55 (10)</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>37</td>
<td>29</td>
<td>51</td>
<td>60</td>
<td>51</td>
<td>45</td>
<td>45</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Black ethnicity (%)</td>
<td>54</td>
<td>55</td>
<td>51</td>
<td>43</td>
<td>57</td>
<td>59</td>
<td>62</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Body mass index (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>30.3 (6.7)</td>
<td>29.2 (6.8)</td>
<td>31.6 (6.3)</td>
<td>31.0 (6.4)</td>
<td>31.0 (6.3)</td>
<td>33.4 (5.6)</td>
<td>33.9 (6.6)</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Family history of DM (%)</td>
<td>50</td>
<td>46</td>
<td>53</td>
<td>49</td>
<td>57</td>
<td>57</td>
<td>73</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>12</td>
<td>11</td>
<td>14</td>
<td>16</td>
<td>10</td>
<td>12</td>
<td>11</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>% saturated fat/day</td>
<td>10.1 (2.9)</td>
<td>10.0 (2.9)</td>
<td>10.4 (3.0)</td>
<td>10.5 (3.1)</td>
<td>10.2 (3.1)</td>
<td>10.4 (2.6)</td>
<td>10.6 (2.1)</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PHQ score</td>
<td>2.0 (0–5.0)</td>
<td>2.0 (0–5.0)</td>
<td>2.0 (0–5.0)</td>
<td>2.0 (0–5.0)</td>
<td>2.0 (0–4.0)</td>
<td>2.0 (0–4.0)</td>
<td>2.0 (0–4.0)</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Depression severity (%)</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Minimal</td>
<td>74</td>
<td>75</td>
<td>72</td>
<td>71</td>
<td>77</td>
<td>70</td>
<td>77</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mild</td>
<td>19</td>
<td>19</td>
<td>20</td>
<td>21</td>
<td>14</td>
<td>23</td>
<td>11</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Moderate</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>9</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Moderate–severe</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Depression treatment (%)</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>13</td>
<td>14</td>
<td>6</td>
<td>4</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Exercise (MET h/week)</td>
<td>12.0 (0–32.0)</td>
<td>14.3 (15–34.3)</td>
<td>9.0 (0–28.0)</td>
<td>13.5 (0–34.5)</td>
<td>7.8 (0–33.8)</td>
<td>5.3 (0–20.0)</td>
<td>9.0 (0–26.8)</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Education (%)</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Some high school</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>High school</td>
<td>23</td>
<td>21</td>
<td>26</td>
<td>25</td>
<td>25</td>
<td>28</td>
<td>25</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2 years college or technical school</td>
<td>17</td>
<td>16</td>
<td>17</td>
<td>17</td>
<td>11</td>
<td>20</td>
<td>21</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>4 years college or more</td>
<td>59</td>
<td>62</td>
<td>56</td>
<td>55</td>
<td>63</td>
<td>51</td>
<td>49</td>
<td>0.014</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
Family history of DM, family history of diabetes (first-degree relatives only); % saturated fat/day, per cent of saturated fat intake per day; PHQ score, total raw score from the Patient Health Questionnaire; depressive symptom severity categories, minimal (PHQ score, 0–4), mild (score 5–9), moderate (score 10–14), moderate–severe (score 15–19), severe (score 20–27); exercise, metabolic equivalent (MET) h/week calculated as MET × h/week, where walking = 3 METs, resistance training = 3.5 METs, moderate conditioning = 4 METs, sports = 5 METs and vigorous conditioning = 8 METs [29].

There were missing data for the following variables: family history of DM (n = 8), current smoker (n = 9), % saturated fat/day (n = 99), depression treatment (past, n = 10; current, n = 3), exercise (n = 5) and education (n = 2).

† Glucose status: NGT, normal glucose tolerance; isolated IFG, impaired fasting glucose only; isolated IGT, impaired glucose tolerance only; IFG + IGT, impaired fasting glucose combined with impaired glucose tolerance; DM, diabetes mellitus.

§ SD, standard deviation; IQR, interquartile range.

§ P-value for trend for mean or per cent of variable from NGT to pre-diabetes (IFG, IGT, IFG + IGT) to diabetes.

¶ Given the low prevalence in the more severe categories of depressive symptoms, an analysis combining moderate, moderately severe and severe symptom groups into one group was performed. The P-value for trend remained non-significant (P = 0.622).
### Table 2
Multivariable ordinal logistic regression—effect on glucose status *

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.052</td>
<td>1.039–1.066</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.075</td>
<td>1.053–1.098</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Black ethnicity</td>
<td>0.948</td>
<td>0.703–1.280</td>
<td>0.729</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.581</td>
<td>1.943–3.428</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>1.540</td>
<td>1.175–2.019</td>
<td>0.002</td>
</tr>
<tr>
<td>Education level†</td>
<td>0.927</td>
<td>0.789–1.088</td>
<td>0.354</td>
</tr>
<tr>
<td>Depressive symptom severity‡</td>
<td>1.015</td>
<td>0.836–1.231</td>
<td>0.883</td>
</tr>
<tr>
<td>Past depression treatment</td>
<td>1.102</td>
<td>0.725–1.675</td>
<td>0.650</td>
</tr>
<tr>
<td>Current depression treatment</td>
<td>0.749</td>
<td>0.429–1.308</td>
<td>0.310</td>
</tr>
<tr>
<td>Exercise (MET h/week)</td>
<td>0.999</td>
<td>0.996–1.002</td>
<td>0.689</td>
</tr>
</tbody>
</table>

* Dependent variable: glucose tolerance status (ordinal variable from normal glucose tolerance to pre-diabetes (IFG, IGT, IFG + IGT) to diabetes); n = 1023 with complete data.

† Education level (ordinal variable): some high school, high school degree, 2-year college or technical school degree or 4-year college degree or higher.

‡ Depressive symptom severity determined by PHQ-9 and defined as an ordinal variable from minimal to severe symptoms: PHQ score of 0–4 = minimal symptoms; 5–9 = mild symptoms; 10–14 = moderate symptoms; 15–19 = moderately severe symptoms; and 20–27 = severe symptoms. Given the low prevalence in the more severe categories of depressive symptoms, an analysis combining moderate, moderately severe and severe symptom groups into one group was also performed. The odds ratio and P-value for trend remained non-significant (OR = 1.062, P = 0.602) and those of the other covariates were essentially unchanged.

BMI, body mass index; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MET, metabolic equivalent; PHQ, Patient Health Questionnaire.