Differential association of insulin resistance with cognitive and somatic symptoms of depression

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Differential association of insulin resistance with cognitive and somatic symptoms of depression

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Abstract

Aim To examine the associations of depressive symptoms with insulin resistance, evaluating somatic and cognitive depressive symptoms separately.

Methods A total of 328 individuals (mean age 60 years) referred for exercise stress testing, taking part in the Mechanisms and Outcomes of Silent Myocardial Ischemia study, completed the Beck Depression Inventory II. A fasting venous blood sample was collected for assessments of insulin and glucose level; the HOMA-IR (homeostatic model assessment of insulin resistance) was calculated. In principal component analysis, Beck Depression Inventory II items were forced to load onto two components (somatic and cognitive depressive symptoms). Adjusting for age, sex, BMI, medication use, smoking, physical activity, diabetes and cardiovascular disease, general linear model analyses were conducted to examine the associations between the components and log HOMA-IR.

Results Principal component analysis showed that nine items loaded onto a cognitive depressive symptoms component and 10 items loaded onto a somatic depressive symptoms component. When examined separately, both components were significantly associated with log HOMA-IR however, when including both components simultaneously in the model, only somatic depressive symptoms remained significantly associated with log HOMA-IR. Back-transformed, a one-unit change in somatic depressive symptoms was associated with a 1.07 (95% CI 1.002, 1.14) change in HOMA-IR and a one-unit change in cognitive depressive symptoms was associated with a 1.03 (95% CI 0.97, 1.14) change in HOMA-IR.

Conclusion Somatic depressive symptoms seem to be more strongly associated with insulin resistance than do cognitive depressive symptoms. Monitoring somatic depressive symptoms may be more appropriate than monitoring cognitive depressive symptoms among depressed individuals with high insulin resistance.

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Introduction

The bidirectional relationship between depressive symptoms and Type 2 diabetes is well established [1–4]. This is important, given that comorbid depression increases the health and economic costs of diabetes. For example, a US study showed that total healthcare expenditure on people with depression and diabetes was nearly five times (US $247 m) that of people with diabetes without depression (US $53 m) [5]. The prevention, detection and management of depressive symptoms may reduce the costs and morbidity associated with Type 2 diabetes.

Impaired fasting glucose and impaired glucose tolerance are abnormalities of glucose handling that generally precede the development of overt Type 2 diabetes. These conditions are characterized by high levels of resistance to the action of insulin that may progress to Type 2 diabetes. It remains unclear whether an association exists between insulin resistance and depressive symptoms. As shown in a recent review...
by Silva et al. [6], six cross-sectional studies reported a positive relationship, two a negative relationship and two no relationship between insulin resistance and depressive symptoms. Additionally, in the Relationship between Insulin Sensitivity and Cardiovascular Disease study, designed to ascertain whether insulin resistance predicts a worsening of cardiovascular disease risk factors, diabetes, obesity, atherosclerosis and cardiovascular disease, no relationship between insulin resistance and depressive symptoms was observed at 3-year follow-up [7]. The reasons for inconsistencies in the literature are unclear but they may be related to the use of inappropriate covariate adjustment (both under- and over-adjustment), heterogeneous populations, and different measures of insulin resistance. Notably, no previous study that assessed depression using questionnaires examined whether specific components of depression were associated with insulin resistance.

Although symptom dimensions of depression have not been examined in relation to diabetes or insulin resistance, they have been explored in association with cardiovascular disease. In general, studies in people with cardiovascular disease have reported two factors of depression: cognitive (for example, self-criticalness and self-dislike) and somatic (for example, fatigue and loss of appetite). Compared with cognitive symptoms, somatic symptoms of depression are more prevalent in patients with cardiovascular disease [8] and are more strongly associated with cardiovascular prognosis [8–11]. This pattern seems to be evident in patients with acute myocardial infarction [8–11] and stable cardiovascular disease [12]. Potentially, different depression profiles may be more strongly related to biological processes related to heart disease. Insulin resistance plays a crucial role in the development of atherosclerosis [13] and appears to predict future cardiovascular disease [14,15], so differing depressive profiles could help explain the equivocal findings between insulin resistance and depression.

The aim of the present study was to investigate the nature of the relationship between depression (and its components) and insulin resistance among outpatients referred for cardiac stress testing. In our sample, we expected the Beck Depression Inventory II to be composed of two factors—somatic and cognitive. Given the cardiovascular disease literature noted above, we also hypothesized that the somatic symptoms of the Beck Depression Inventory II would have a stronger association with insulin resistance compared with the cognitive symptoms of the Beck Depression Inventory II.

**Methods**

**Participants**

The present study is a secondary analysis of the Mechanisms and Outcomes of Silent Myocardial Ischemia study, a longitudinal study designed to investigate factors influencing silent myocardial ischaemia and the risk silent ischaemia confers on cardiovascular outcomes. In the Department of Nuclear Medicine of the Montreal Heart Institute between May 2005 and December 2006, we invited individuals to participate if they were referred for assessment of possible coronary ischemia using exercise single-photon emission computed tomography. The specific exclusion criteria were: 1) known or suspected pregnancy or breast-feeding; 2) currently having a pain disorder other than angina; 3) the use of prescription or non-prescription analgesic on the day of testing; 4) having smoked within 6 h of the test; 5) the use of non-steroidal anti-inflammatory agents, coxibs or anti-neo plastic agents within 7 days of the test; 6) severe or comorbid conditions such that the participant was not expected to survive 12 months; 7) a history of drug or alcohol abuse; 8) inability to understand the nature, scope and possible consequences of the study; and 9) inability to understand French or English. A total of 907 patients were recruited; however, because of the restricted assessment time (single-photon emission computed tomography camera availability) only a subset of 328 participants had completed assessments of fasting insulin and glucose levels for the calculation of insulin resistance. No significant differences for age, sex or cardiovascular disease status were observed between the subsample and those who did not have a completed blood evaluation. Before participation, written consent was obtained from all participants. The study was approved by the Human Ethics Committee of the Montreal Heart Institute.

**Procedure**

Participants completed a single-photon emission computed tomography rest–stress test protocol, after which they were administered the Primary Care Evaluation of Mental Disorders [16], a structured, psychiatric diagnostic interview that contains components for the evaluation of mood and anxiety disorders. Finally, participants completed a sociodemographic and medical history questionnaire that included the Beck Depression Inventory II.
Assessments

Mood disorders
The Primary Care Evaluation of Mental Disorders [16] is a brief (5–15 min) structured psychiatric interview that yields diagnoses for the most common Diagnostic and Statistical Manual of Mental Disorders (mood and anxiety disorders) seen in primary care settings. The mood disorders module has similar sensitivity (83%) and specificity (88%) to longer interviews, for example, the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders [16].

Depressive symptoms
Depressive symptoms were assessed with the widely used Beck Depression Inventory II, which contains 21 items scored from 0 to 3, with higher scores indicating greater symptom severity [17]. The Beck Depression Inventory II has good internal consistency ($\alpha = 0.84$, $P = 0.007$) and acceptable test–retest reliability ($\alpha = 0.69$, $P = 0.009$) [18]. Previous psychometric evaluations of the Beck Depression Inventory II suggest that items load onto two factors: cognitive and somatic symptoms, and that two subscales can be used, although it should be noted that the specific structure of the two factors is not consistent across populations and no study has established specific sub-scales in the type of population we assessed. In the present sample, internal consistency for the total scale was very good ($\alpha = 0.91$).

Insulin resistance
Fasting insulin was measured using an immunoassay sandwich technique (Roche Diagnostics, Laval, QC, Canada). Plasma glucose concentration was measured using a glucose oxidase assay (Siemens Diagnostics, Burlington, ON, Canada). Insulin resistance was measured using the formula for HOMA-IR: HOMA-IR = [fasting glucose (mmol/l) x fasting insulin (μU/ml)]/22.5 [19,20]. Widely used in epidemiologic studies, HOMA-IR is a valid estimate of insulin resistance. It has high concurrent validity with the hyperinsulinaemic-euglycaemic clamp technique, which is considered the ‘gold standard’ for assessing insulin sensitivity [21]. Insulin resistance measured using HOMA-IR has a large, negative correlation with the hyperinsulinaemic-euglycaemic clamp technique ($r = -0.82$, $P < 0.001$) [21].

Statistical analyses

Symptom dimensions of depression
Based on previous research [22], we anticipated a distinction between two depressive symptom factors: somatic and cognitive. Responses to the 21-item Beck Depression Inventory II were subjected to principal component analysis using oblique rotation (promax). Promax rotation was used because the two factors were expected to correlate [22]. The Kaiser–Meyer–Olkin measure verified the sampling adequacy for the analysis, Kaiser–Meyer–Olkin = 0.91, and all Kaiser–Meyer–Olkin values for individual items were $>0.87$, well above the acceptable limit of 0.5 [23]. Although five components had eigenvalues $>Kaiser’s criterion of 1, only the first two components were retained based on the Scree test. Combined, these two components accounted for 42% of the total variance, similar to other reports [24]. In interpreting the rotated factor pattern, an item was said to load on a given component if the factor loading was $\geq 0.40$ for that component and $<0.40$ for the other.

Primary analyses
Missing data were handled using missing-at-random assumptions following Rubin’s rules [25]. The PROC MI method of multivariate imputation in SAS v. 9.3 (SAS Institute, Cary, NC, USA) was used to generate five copies of the dataset. These were analysed independently, each with missing values imputed. PROC MIANALYZE was used to average estimates of the variables to give a single mean estimate and adjusted standard error according to Harrell’s guidelines [26]. All analyses included 328 participants.

The Kolmogorov–Smirnov test was used to test for normality. HOMA-IR did not follow a normal distribution. Thus, a logarithmic transformation was performed and analyses were conducted using log HOMA-IR. General linear models were conducted, examining the effect of total Beck Depression Inventory II score, somatic symptom score and cognitive symptom score on log HOMA-IR. Model 1 examined each symptom score separately while model 2 included both somatic and cognitive symptom scores simultaneously. All analyses included age, sex, smoking, physical activity, BMI, the presence of an anxiety disorder, antidepressant use, anxiolytic use, the presence of diabetes, diabetes medication use and the presence of cardiovascular disease (defined as having had a previous myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, or cerebrovascular event or being diagnosed with coronary heart failure) as covariates, chosen a priori. All analyses were performed using SAS version 9.3. P values $<0.05$ were considered to indicate statistical significance. For ease of interpretation, the resulting measures of association were back-transformed and presented as geometric means and 95% CIs.

Results

Participant characteristics
Participants had a mean (sd) age of 59.7 (9.5) years and 26.5% were women. Just over half of the participants had a history of cardiovascular disease or had cardiovascular disease risk factors. Other participant characteristics are shown in Table 1. Total Beck Depression Inventory II scores ranged from 0 (no depressive symptoms) to 48 (severe depressive symptoms), with 19.5% of participants scoring $\geq 14$, which is considered to be the threshold for mild depression.
Symptom dimensions of depression

Based on the principal component analysis, nine items loaded on the first component, subsequently labelled the cognitive component (Table 2) and 10 items loaded on the second component, labelled the somatic component. Participants’ mean score on the items from each of the two factors was calculated and multiplied by the number of items, creating their cognitive and somatic symptom sum scores. Finally, two items (pessimism, agitation) loaded onto neither of the two factors and were therefore excluded from subsequent analyses. The correlation between the cognitive and somatic components was 0.67 ($P < 0.0001$). Cognitive symptom scores ranged from 0 to 22 out of a possible 27, while somatic symptom scores ranged from 0 to 23 out of a possible 30.

Total Beck Depression Inventory II score, mood disorders and insulin resistance

The values for HOMA-IR ranged from 0.06 to 45.25. Adjusting for covariates, total Beck Depression Inventory II score was significantly associated with log HOMA-IR [geometric $\beta$ (95% CI) 1.05 (1.03, 1.13), partial $\eta^2 = 0.03$, $P = 0.003$]. A one-unit change in Beck Depression Inventory II was associated with a 1.05 change in HOMA-IR. For the purposes of illustration, Table 3 shows HOMA-IR values for each adjusted Beck Depression Inventory II quartile. Additionally, the presence of any mood disorder was significantly associated with greater HOMA-IR [geometric $\beta$ (95% CI) = 1.99 (1.72, 6.80), partial $\eta^2 = 0.046$, $P = 0.013$].

Symptom dimensions of depression and insulin resistance

When examined in separate general linear model analyses, both the somatic component [geometric $\beta$ (95% CI) = 1.08 (1.03, 1.14), partial $\eta^2 = 0.04$, $P = 0.002$] and the cognitive component [geometric $\beta$ (95% CI) = 1.08 (1.01, 1.15), partial $\eta^2 = 0.01$, $P = 0.022$] were significantly associated with HOMA-IR, adjusting for covariates. As with total Beck Depression Inventory score, Table 3 shows the relationships between adjusted cognitive and somatic quartiles and HOMA-IR.

When including both components simultaneously in the model, the somatic component remained significantly associated with HOMA-IR [geometric $\beta$ (95% CI) = 1.07 (1.002,
1.14), partial $\eta^2 = 0.04, P = 0.045$] but the cognitive component did not [geometric $\beta (95\% \text{ CI}) = 1.03(0.95, 1.11)$, partial $\eta^2 = 0.01, P = 0.536$]. That is, a one-unit change in somatic depressive symptoms was associated with a 1.07 change in HOMA-IR and a one-unit change in cognitive depressive symptoms with a 1.03 change in HOMA-IR, respectively, when both components were in the model. For all models, when sensitivity analyses were conducted excluding patients with diabetes or those taking diabetic medications, no differences in statistical significance or effect size were observed.

**Discussion**

In the present study, overall depressive symptoms as measured using the Beck Depression Inventory II were positively associated with insulin resistance. In our principal component analysis, the Beck Depression Inventory II separated into two factors, labelled somatic and cognitive depressive symptoms. When examined in separate models, both symptoms were associated with HOMA-IR but when both were included in the model, only the somatic factor remained significantly associated with HOMA-IR. Our results may help explain previous equivocal reports examining the relationship between overall depression and insulin resistance. The association between depression and insulin resistance may be biased towards those who have relatively more somatic symptoms. There may be something unique about insulin resistance, such that it is accompanied by somatic symptoms of depression, or somatic depressive symptoms could simply be consequences of greater somatic comorbidity and the signs of insulin resistance could be misinterpreted as depressive symptoms. Similar arguments have been made regarding the somatic factors common to both depression and cardiovascular disease [9,27]; however, in the present study, the association between somatic symptoms and insulin resistance was unaffected by covariate adjustment for the presence of heart disease or diabetes.

Several mechanisms may explain why depression, and the somatic component in particular, is associated with insulin resistance. Depression can dysregulate the hypothalamic-pituitary-adrenal axis, leading to elevated cortisol secretion, and visceral fat deposition [28]. Visceral adiposity, in turn, is associated with excessive lipid deposits in the liver, resulting in impaired insulin signalling [29,30]. Moreover, visceral adipose tissue probably leads to inflammatory cytokine production, further contributing to impaired insulin signalling [30]; however, we did not assess cortisol and inflammatory cytokines, so we were unable to examine this pathway. Depression may also influence glucose metabolism and insulin resistance through behavioural processes. For example, depressed individuals generally tend to report poor health behaviours (for example, poor compliance and adherence to medical treatments, smoking, physical inactivity) [31,32]. Moreover, patients with depression often have a diminished appetite but with relative excess consumption of fat [33,34]. In turn, dietary fat intake is associated with diminished insulin sensitivity independent of body mass, and thus may lead to elevated insulin resistance [35,36]. In the present study, BMI did not account for the association between depression and insulin resistance, but BMI does not paint the whole picture in terms of nutrition. We did not assess diet in this study, so we cannot exclude the possibility that dietary changes accompanying depression (a somatic symptom) contributed to elevated insulin resistance.

Although cognitive symptoms were not associated with insulin resistance when adjusting for the somatic symptoms, there was an association when looking at the cognitive symptoms alone. It might be that the blood–brain barrier inhibits the influence of insulin resistance on cognitive symptoms. That is, a threshold level of insulin resistance may need to be reached in order to overcome the blood–brain barrier to produce cognitive symptoms [37]. Further research is needed to explore the mechanisms linking insulin resistance and depression.

<table>
<thead>
<tr>
<th>Total Beck Depression Inventory II score</th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric mean of HOMA-IR</td>
<td>7.38</td>
<td>9.99</td>
<td>10.41</td>
<td>17.85</td>
</tr>
<tr>
<td>Somatic subscale of Beck Depression Inventory II</td>
<td>6.47</td>
<td>11.33</td>
<td>10.57</td>
<td>14.96</td>
</tr>
<tr>
<td>Cognitive subscale of Beck Depression Inventory-II</td>
<td>10.12</td>
<td>12.07</td>
<td>10.55</td>
<td>17.62</td>
</tr>
</tbody>
</table>

HOMA-IR, homeostatic model assessment of insulin resistance.

**Table 3** Adjusted geometric means of homeostatic model assessment of insulin resistance by quartile for total Beck Depression Inventory II score and somatic and cognitive subscales
The results of the present study should be interpreted in the light of some limitations. First, the cross-sectional nature of the study precludes determination of the temporality of the association between depression and insulin resistance. Causality cannot be determined and remains to be further investigated. Second, one could question whether our HOMA-IR measurement produced a valid assessment of insulin resistance. The hyperinsulinaemic-euglycaemic glucose clamp technique is the gold standard for measuring insulin resistance, but is difficult to implement in large epidemiological studies. Nevertheless, insulin resistance scores measured using HOMA-IR correlate well with insulin sensitivity estimates obtained from the euglycaemic clamp in men and women, older and younger individuals, obese and non-obese individuals, and in participants with and without diabetes. In addition, HOMA-IR explains 65% of the variance in insulin resistance as measured by euglycaemic clamp [21]. Third, although the results of our principal component analysis were generally consistent with previous studies, a few items in our sample loaded on different factors compared with samples of outpatients with clinical depression [22] and primary care outpatients [38]. Specifically, pessimism loaded on neither factor in the present study but loaded on the cognitive factor in Steer et al. [22] and Arnau et al. [38]. Indecisiveness loaded on the cognitive factor in the present study but loaded on the somatic factor in both previous studies. Additionally, changes in sleep loaded on the somatic factor in the present study but loaded significantly on neither factor in Steer et al. [22], although our finding was consistent with that of Arnau et al. [38]. Moreover, in the study by Arnau et al., self-criticalness did not load on either factor. The samples used in previous analyses, however, may not be comparable with the sample in our analysis, which is consistent with the hypothesis that symptoms lie in different dimensions conditional on the background and diagnostic make-up of the sample [39]. A final possible limitation is that the majority of study participants were not clinically depressed, although the range of Beck Depression Inventory II scores was quite wide (0–48) and this wide range suggests that the results are generalizable to both sub-clinical and clinical levels of depression. Additionally, 19.5% of the sample had a Beck Depression Inventory II score of ≥14, indicative of mild depression on the Beck Depression Inventory II, and this is consistent with studies involving similar populations. Finally, the finding that a continuous relationship exists between Beck Depression Inventory II scores and insulin resistance is consistent with previous reports showing a continuous relationship between depressive symptoms and cardiovascular risk [40].

Despite the aforementioned limitations, the present study has notable strengths. To our knowledge, it is the first study to examine the structure of depression in patients referred for cardiac stress testing. In addition, it is the first study to examine the association between insulin resistance and components of depression, which may help to explain why previous studies show conflicting findings. We provide further insight into the complex relationship between depression and insulin resistance.

In conclusion, depression was associated with insulin resistance in our sample of individuals referred for exercise stress testing, and the somatic symptoms of depression appeared to be more strongly linked to insulin resistance than did the cognitive symptoms. These results may help explain why some previous studies did not find an association between depression and insulin resistance. In addition, our results suggest that it may be more important to monitor the somatic symptoms of depression when treating depressed individuals with high insulin resistance than it is to monitor the cognitive symptoms, although outcome and treatment trials are needed to confirm this supposition.

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Competing interests

None declared.

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