The weight of subclinical vascular disease & neuroticism in late-life depression
Marijnissen, Radboud

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2014

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Citation for published version (APA):

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Download date: 03-07-2024
Association between metabolic syndrome and depressive symptom profiles; a role for adiponectin?

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Association between metabolic syndrome and depressive symptom profiles - Sex-specific?

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*Journal of Affective Disorders* 151 (2013) 1138-1142
Abstract

Background – The association between depression and metabolic syndrome is becoming more obvious. Waist circumference (WC) might be the most important metabolic syndrome (MetS) feature in relation to late-life depression, with a possible mediating role for adiponectin.

Methods – Cross-sectional population based survey, part of Nijmegen Biomedical Study; 1277 participants (50-70 years). We measured all components of MetS, plasma adiponectin levels and depressive symptoms using Beck Depression Inventory (BDI). Using two factors derived from BDI-items by principal component analysis, representing a cognitive-affective and a somatic-affective symptom cluster, were conducted multiple regression analyses for each component of metabolic syndrome. Separate models testing BDI sum score and both depressive symptom clusters as dependent variables, respectively, were used. We explored sex-differences as well as a hypothesised mediating effect of adiponectin.

Results – The presence of MetS as well as number of metabolic risk factors were significantly associated with BDI sum score. In men WC, triglycerides and HDL cholesterol explained variance in depressive symptoms, whereas in women this effect was confined to WC. Moreover, irrespective of sex, all associations were primarily driven by the somatic–affective symptom-cluster. Adiponectin neither mediated nor moderated any of the associations found.

Conclusions – Although pathophysiological mechanisms underlying the association between metabolic disturbances and depression remains to be elucidated, our study points to sex-differences as well as a specific phenotype of depression that is associated with metabolic disturbances.

Keywords
Depression, Metabolic Syndrome X, Aged, Adiponectin
The metabolic syndrome and depressive symptom profiles

Introduction

The metabolic syndrome, defined as a cluster of cardiovascular risk factors, predicts future vascular events. Several studies have also found associations between depression and the metabolic syndrome (Koponen et al, 2008; Akbaraly et al, 2011; Pan et al, 2012) as well as with its individual components like impaired glycemic control (Gale et al, 2010). Recently, the concept of ‘metabolic depression’ has been proposed based on findings of an increased incidence of late-life depression in persons with the metabolic syndrome as well as a protracted course of depression in depressed patients who also have metabolic syndrome characteristics (Vogelzangs et al, 2011). The chronic form of the atypical depression is associated with inflammatory and metabolic dysregulation while the chronic form of the melancholic depression is associated with hypothalamic-pituitary-adrenal (HPA)-axis hyperactivity (Lamers et al, 2012). Waist circumference seems the most important metabolic syndrome feature in relation to depression (Vogelzangs et al, 2011). Longitudinal studies have indeed confirmed a reciprocal relationship between depression and obesity (Vogelzangs et al, 2008; Luppino et al, 2010; Pan et al, 2012). Recently, the predictive value of obesity for the onset of depression appeared to be partly dependent on metabolic health (Hamer et al, 2012).

Some aspects of the association between the metabolic syndrome and depression, however, need further clarification, in particular the heterogeneity of depression and the metabolic activity of adipose tissue.

Firstly, depressive disorder is a heterogeneous syndrome. Accumulating evidence shows that the somatic-affective symptom cluster of depression is particularly related to vascular health (de Jonge et al, 2006; Roest et al, 2011). Similarly, somatic-affective in contrast to cognitive-affective symptoms, are associated specifically with waist circumference but not with body mass index (Marijnissen et al, 2011). Other components of the metabolic syndrome have not been examined in relation to depressive symptom profiles.

Secondly, visceral fat tissue is metabolically active by the secretion of cytokines, among which leptin, resistin and adiponectin, collectively called the adipokines. In older men, high leptin levels are associated with an increased onset of depressive symptoms especially in the presence of abdominal obesity (Milaneshi et al, 2012). In contrast to other adipokines, adiponectin expression is a protective cytokine for vascular health and lowered concentrations have been demonstrated in visceral obesity, insulin resistance, diabetes mellitus, metabolic syndrome and hypertension independent of body mass index (Mathieu et al, 2009; Zeugmann et al, 2010; Taylor et al, 2010; Yadav et al, 2012;
Baden et al, 2012; Matsuzamwa et al, 2011). Adiponectin has also been linked to mood regulation (Wilhelm et al, 2012), but results are contradictory.

The primary objective of the present study was to explore the association between depressive symptom clusters and the metabolic syndrome as well as its individual components in a community-based sample of middle-aged and older persons. We hypothesised that we would find an association between especially the somatic-affective symptom cluster of depression with the metabolic syndrome and/or its individual components. Our second objective was to explore the role of adiponectin within these associations, hypothesising mediating effects of adiponectin within the associations found.

**Methods**

**Sample**
The present sample was drawn from the Nijmegen Biomedical Study (NBS), a population-based survey conducted in the Eastern part of The Netherlands among people aged 20 through 90 years. For details we refer to a previous publication (Hoogendoorn et al, 2006). In 2004 and 2005 a questionnaire was sent to all participants (n=2807) in the age group 50 through 70 years. This questionnaire contained items on general health, use of medication and psychiatric symptoms (including the Beck Depression Inventory). A total of 2114 persons were invited to participate in a study on atherosclerosis, of which 1517 (72%) persons responded positively. These participants were invited to come to the hospital in order to participate in a detailed assessment of atherosclerotic disease, its risk factors and consequences (see Holewijn et al, 2010). This latter group was considered eligible for the present study. The Medical Ethics Committee of the Radboud University Medical Centre Nijmegen approved the study protocol (in accordance with the Declaration of Helsinki), and all participants provided written informed consent.

**Variables of interest**

**Depressive symptoms** - Depressive symptoms were measured with the Beck Depression Inventory (BDI-I). The BDI-I is a 21-item self-report questionnaire with excellent psychometric characteristics (Beck et al, 1987). Each item is rated on a 0 to 3 scale, with 0 representing ‘absence’ and 1-3 representing increasing levels of severity of the symptom. The BDI-I yields a total score ranging from 0 to 63. Based on previous research in this field, a sum score ≥10 is indicative of clinically significant depressive symptoms (Marijnissen et al, 2011).
Metabolic syndrome - The Metabolic syndrome (MS) was defined according to the International Diabetes Federation (IDF) (www.idf.org/webdata/docs/IDF-Meta_def_final.pdf, 2006). Taking into account the use of antihypertensives and anti-diabetics the following individual components of the MS were measured. Systolic blood pressure and diastolic blood pressure were measured using an oscillometricphgmanometer (Criticon model no. 1846, Criticon Inc., USA). Waist circumference was measured at the level of the umbilicus. Triglycerides, HDL cholesterol and glucose concentrations were determined using commercially available enzymatic reagents (AEROSET1 System, Abbott, USA).

Adiponectin - Plasma concentration of Adiponectin was determined using enzyme-linked immune sorbent assays (Elisadevelopment System, Duoset, R&D Systems, Minneapolis, MN, USA). All lipid-lowering medication, when used, was discontinued for 4 weeks prior to the measurements (Holewijn et al, 2010).

Covariates
In addition to age and sex, the following potential confounders were a priori considered in our analyses based on their relationship with depressive symptoms and obesity. The first set of confounders included lifestyle factors such as smoking, use of alcohol, physical activity and use of psychotropic drugs known to affect body weight (Simon et al, 2008). Smoking was based on self-reported information and classified as current, former or never. Use of alcohol was based on the number of standardized units per week. Excessive use (>21 drinks/week for men, >14 drinks/week for women) was assessed. Physical activity was based on the number of exercise sessions per week of more than 30 minutes of moderate to vigorous activity (Stampfer et al, 2000) and dichotomized as 0 or 1 session versus 2 or more sessions. The use of psychotropic drugs was based on self-report data regarding the previous month. People were instructed to collect medication containers before filling in this questionnaire. The use of antidepressants, lithium and antipsychotic drugs as psychotropic drugs were included as these drugs influence body weight (Schwartz et al, 2004). Somatic co-morbidity, other than cardiovascular disease or diabetes mellitus was lumped together and coded as present or absent.

Statistical Methods
Missing items on the BDI were imputed with the series mean in case 1 or 2 items were missing. As the BDI sum score had a skewed distribution in our sample, we applied a log-transformation in order to obtain a normal distribution. All further analyses were conducted using the log-transformed sum score. All other variables were normally distributed.
Principal components analysis (PCA) was conducted on the 21 individual BDI items to
obtain fewer factors/components while retaining the original item information (Marijnissen et al, 2011). PCA was selected as factor extraction method for two reasons: its ultimate goal is to reduce data into components useful for other purposes, and it has superior ability to remedy multicolinearity between factors should it exist (Costello et al, 2009). Varimax rotation was selected because it forces factors to be uncorrelated. Factor scores were calculated on the basis of unstandardized item factor loadings and transformed into standardized z scores (using the Anderson-Rubin method) to increase their interpretability. The scree plot of eigenvalues and the number of complex items revealed a two-factor solution as the optimal solution, comparable with the traditional two-factor structure of the BDI (cognitive-affective versus somatic-affective symptoms), as in a previous factor analysis of the BDI in a Dutch cardiac population (de Jonge et al, 2006). In our sample, the explained variance is 24.1% for factor 1 (cognitive-affective symptoms) and 7.6% for factor 2 (somatic-affective symptoms) (Kaiser-Meyer-Olkin measure of sampling adequacy = 0.898, Bartlett test of sphericity chi-square = 5.074, degrees of freedom (df) = 210, P< .001) (See Marijnissen et al, 2011). See chapter 3 in Statistical methods for description of the principal components analysis and chapter 3 Table 1 for the factor loadings of the depressive symptom dimensions. The metabolic syndrome (yes/no), the number of metabolic risk factors (range 0 – 5) and the individual components of the metabolic syndrome were regressed separately on the BDI sum score as well as the BDI symptom cluster indices (i.e. the standardized factor scores on the cognitive affective cluster and somatic affective clusters) by multiple linear regression models. All analyses were fully adjusted for the potential confounders described above. Subsequently, we examined the association between adiponectin and depression using multiple linear regression models with BDI sum score as well as the somatic-affective and cognitive-affective cluster indices as the dependent variables. These models were also fully adjusted for the confounders described above. In case of a significant association, we added adiponectin to the final model to examine a potentially mediating role of adiponectin. A change of 10% of B between the depression measure and metabolic component was considered a relevant degree of mediation. Furthermore, effect-modification was checked by subsequently including interaction terms between adiponectin and the MS as well as its individual components in the different models. Analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 17.0 (Inc. Chicago).
Results

Of the 1517 subjects who had consented to participate in the study of non-invasive measurements of atherosclerosis, 240 participants were excluded. Reasons for exclusion were not responding to the postal questionnaire containing the BDI (n=185); having 3 or more missing items on the BDI (n=37); missing data for any of the metabolic syndrome components (n=7), or violating the rules for a reliable measurement of atherosclerotic disease or its risk factors (i.e. having smoked before coming to the hospital, n=4; not obeying the fasting rule, n=2; and not stopping their lipid lowering medication, n=5). This left a final study sample of 1277 people of which all characteristics are described in Table 1.

Excluded subjects (240/1517, 15.8%) differed from included subjects (n=1277) with respect to age (62.1 (SD=5.9) versus 61.1 (SD=5.9) years; t=2.54, df=1515, p=.011), current smoking (26.5% versus 17.0%; \chi^2=12.0, df=1, p=.001), excessive alcohol usage (7.1% versus 11.7%; \chi^2=4.3, df=1, p=.037), somatic co-morbidity other than cardiovascular disease or diabetes mellitus (6.7% versus 14.4%, \chi^2=10.3, df=1, p=.001). No differences were found with respect to any of the metabolic parameters.

We found that the metabolic syndrome was associated with depressive symptoms in our whole sample (see Table 2). This association was stronger when we included the total number of risk factors as a independent variable than when simply using the presence or absence of the metabolic syndrome (B=0.030, \beta=.11, p<.001 and B=0.047, \beta=.06, p=.022, respectively). Examining the cognitive-affective symptom cluster and the somatic-affective symptom cluster, separately, we found that the metabolic syndrome was specifically associated with somatic-affective symptoms (B=0.196, \beta=.09, p=.001). Also waist circumference, triglycerides, HDL cholesterol and diabetes or increased glucose were specifically associated with the somatic-affective symptoms in separate regression analyses (B=0.011, \beta=.14, p<.001; B=0.086, \beta=.07, p=.010; B=0.252, \beta=.09, p=.002, B=0.077, \beta=.05, p=.051, respectively). In contrast, diastolic blood pressure was specifically associated with the cognitive-affective symptom cluster (B =-0.006, \beta=-.060, p=.038). Overall, associations were stronger in males compared to females.

With respect to sex differences, we found that waist circumference was associated with depressive symptoms in both sexes (males: B=0.003, \beta=.10, p=.013; for females: B=0.004, \beta=.13, p=.001), whereas triglycerides and HDL cholesterol were associated with depressive symptoms only in males (B=0.029, \beta=.08, p =.050 and B=-0.156, \beta=-.14 p<.001, respectively).
Irrespective of sex, all associations found between depression and metabolic syndrome or its components were mainly driven by the somatic-affective symptom cluster (see also Table 2).

Adiponectin showed neither a linear nor a U-shape association with depressive symptoms or symptom profiles in the whole sample as well as when stratified for sex.
Table 2  Association between metabolic syndrome (components) and depressive symptoms\textsuperscript{a}.

<table>
<thead>
<tr>
<th>Sample</th>
<th>BDI sum score</th>
<th></th>
<th>BDI symptom dimension\textsuperscript{b}</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cognitive-affective cluster</td>
<td>Somatic-affective cluster</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>β</td>
<td>P value</td>
<td>B</td>
</tr>
<tr>
<td>Whole sample (n=1277)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic Syndrome (yes/no)</td>
<td>0.047</td>
<td>0.63</td>
<td>0.22</td>
<td>-0.004</td>
</tr>
<tr>
<td>Metabolic Syndrome (no. of risk factors)</td>
<td>0.030</td>
<td>0.112</td>
<td>&lt;.001</td>
<td>0.008</td>
</tr>
<tr>
<td>• Waist circumference</td>
<td>0.003</td>
<td>0.120</td>
<td>&lt;.001</td>
<td>0.003</td>
</tr>
<tr>
<td>• Triglycerides (mmol/l)</td>
<td>0.028</td>
<td>0.066</td>
<td>0.16</td>
<td>0.005</td>
</tr>
<tr>
<td>• HDL cholesterol (mmol/l)</td>
<td>-0.087</td>
<td>-0.091</td>
<td>0.002</td>
<td>-0.113</td>
</tr>
<tr>
<td>• Systolic blood pressure</td>
<td>0.000</td>
<td>0.013</td>
<td>0.633</td>
<td>-0.003</td>
</tr>
<tr>
<td>• Diastolic blood pressure</td>
<td>-0.002</td>
<td>-0.046</td>
<td>0.102</td>
<td>-0.006</td>
</tr>
<tr>
<td>• Diabetes (or increased Glucose)</td>
<td>0.077</td>
<td>0.053</td>
<td>0.051</td>
<td>-0.020</td>
</tr>
<tr>
<td>Males (n=627)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic Syndrome (yes/no)</td>
<td>0.047</td>
<td>0.64</td>
<td>0.110</td>
<td>-0.026</td>
</tr>
<tr>
<td>Metabolic Syndrome (no. of risk factors)</td>
<td>0.032</td>
<td>0.119</td>
<td>0.003</td>
<td>0.002</td>
</tr>
<tr>
<td>• Waist circumference</td>
<td>0.003</td>
<td>0.099</td>
<td>0.013</td>
<td>0.001</td>
</tr>
<tr>
<td>• Triglycerides (mmol/l)</td>
<td>0.029</td>
<td>0.077</td>
<td>0.050</td>
<td>0.004</td>
</tr>
<tr>
<td>• HDL cholesterol (mmol/l)</td>
<td>-0.156</td>
<td>-0.139</td>
<td>&lt;.001</td>
<td>-0.152</td>
</tr>
<tr>
<td>• Systolic blood pressure</td>
<td>-0.001</td>
<td>-0.035</td>
<td>0.394</td>
<td>-0.005</td>
</tr>
<tr>
<td>• Diastolic blood pressure</td>
<td>-0.001</td>
<td>-0.030</td>
<td>0.448</td>
<td>-0.007</td>
</tr>
<tr>
<td>• Diabetes or increased glucose</td>
<td>0.094</td>
<td>0.071</td>
<td>0.074</td>
<td>-0.048</td>
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<tr>
<td>Females (n=650)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic Syndrome (yes/no)</td>
<td>0.046</td>
<td>0.63</td>
<td>0.107</td>
<td>0.010</td>
</tr>
<tr>
<td>Metabolic Syndrome (no. of risk factors)</td>
<td>0.028</td>
<td>0.107</td>
<td>0.006</td>
<td>0.016</td>
</tr>
<tr>
<td>• Waist circumference</td>
<td>0.004</td>
<td>0.127</td>
<td>0.001</td>
<td>0.005</td>
</tr>
<tr>
<td>• Triglycerides (mmol/l)</td>
<td>0.029</td>
<td>0.056</td>
<td>0.149</td>
<td>0.022</td>
</tr>
<tr>
<td>• HDL cholesterol (mmol/l)</td>
<td>-0.044</td>
<td>-0.051</td>
<td>0.197</td>
<td>-0.099</td>
</tr>
<tr>
<td>• Systolic blood pressure</td>
<td>0.000</td>
<td>0.005</td>
<td>0.895</td>
<td>-0.001</td>
</tr>
<tr>
<td>• Diastolic blood pressure</td>
<td>-0.002</td>
<td>-0.060</td>
<td>0.121</td>
<td>-0.005</td>
</tr>
<tr>
<td>• Diabetes or increase glucose</td>
<td>0.046</td>
<td>0.029</td>
<td>0.457</td>
<td>0.019</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Linear regression analyses adjusted for age, sex, smoking (yes/no), severe alcohol (yes/no), sports (0 -1 vs >=2), use of weight gaining psychotropic drugs (yes/no), chronic co-morbidity (yes/no)

\textsuperscript{b} Symptom profiles based on PCA with varimax rotation.
(all p-values >.16). (See Table 3). Adiponectin thus by definition could not mediate the association between depression and metabolic health indices. Subsequently, we explored whether adiponectin moderated the effect of metabolic health indices on the total BDI sum score, cognitive-affective symptom cluster and somatic affective symptom cluster in the whole sample or in a sex-specific way. None of the 72 interaction terms tested were significant at the 5% levels.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Association between adiponectin and depressive symptoms.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BDI sum score</td>
</tr>
<tr>
<td></td>
<td>Cognitive affective cluster</td>
</tr>
<tr>
<td>Association with adiponectin*</td>
<td>B</td>
</tr>
<tr>
<td>• Whole sample (n=1277)</td>
<td>0.001</td>
</tr>
<tr>
<td>• Males (n=627)</td>
<td>-0.004</td>
</tr>
<tr>
<td>• Females (n=650)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

* Linear regression analyses adjusted for age, sex, smoking (yes/no), severe alcohol (yes/no), sports (0 -1 vs >=2), use of weight gaining psychotropic drugs (yes/no), chronic co-morbidity (yes/no)

Discussion

Main findings
We show that the association between the metabolic syndrome and depressive symptoms is primarily driven by the somatic-affective symptom cluster of depression. In both sexes, the number of risk factors of the metabolic syndrome shows a stronger association with depressive symptoms than simply the presence of the metabolic syndrome. In women, however, the waist circumference is the sole factor driving the association, whereas in men the association is driven by waist circumference, HDL cholesterol and triglycerides. In contrast to our expectations, adiponectin neither mediated nor moderated these associations.

Relation between metabolic syndrome and depressive symptoms
The association between the metabolic syndrome and depression is in line with the hypothesis of ‘metabolic depression’, a subtype of depression with a chronic course.
Waist circumference seems the most important metabolic syndrome feature in relation to depression (Vogelzangs et al, 2011). Interestingly, the predictive value of obesity for the onset of depression may be dependent on metabolic health as only metabolically unhealthy obese compared to metabolically healthy obese persons had an elevated risk of developing depressive symptoms (Hamer et al, 2012). We extend these findings by pointing to sex-specificity of findings and depressive symptom profiles.

Firstly, the sex differences in our study are intriguing. Although the strength of the overall association between number of metabolic risk factors was similar in males ($\beta=0.12$) and females ($\beta=0.11$), in males several individual components were associated with depressive symptoms, whereas in females the association was confined to waist circumference only. Two explanations could be put forward. First, as results for the individual components are less pronounced in women, but all are in the same direction, it could also be explained by the fact that vascular disease in females develops at a later age (Roger et al, 2012; Van de Leeuw et al, 2013) as well as the relative importance of other pathways to depression in women, like neuroticism (Sutin et al, 2010). Secondly, it may point to pathophysiological differences between male and female depression. Parallel to our sex-specific findings for HDL-cholesterol levels, previous studies on the association between cholesterol levels and depression also demonstrated sex-specific effects (Tedders et al, 2011; Ancelin et al, 2010).

Secondly, the association between depressive symptoms and metabolic syndrome or its components relies primarily on the somatic-affective symptom cluster. Somatic-affective symptoms of depression largely overlap with features of sickness behaviour, including general weakness and fatigue, which are generally thought to be induced by inflammatory processes (Dantzer et al, 2008). Interestingly, a recent study found inflammation specifically associated with somatic-affective symptoms (Duijvis et al, 2013). This is in line with studies in which somatic-affective, but not cognitive-affective symptoms of depression predict cardiovascular morbidity and mortality (de Jonge et al, 2006; Linke et al, 2009). Together, these findings may point to a specific subtype of depression.

Relation between depressive symptoms and adiponectin, as a mediating factor
In contrast to our expectations, adiponectin neither mediated nor moderated the associations between depression and metabolic health. Our results are in contrast with recent finding that depressed inpatients with the metabolic syndrome (n=17) had a lower adiponectin level then patients without the metabolic syndrome (n=53) (Zeugmann et al, 2010) suggesting an additive affect of the metabolic syndrome and
major depression on adiponectin levels. Nonetheless, studies on adiponectin in depression have reported inconsistent results. Two studies have reported negative findings: one study did not find any association between depressive symptoms and adiponectin level (Pan et al, 2008), the other study did not find any difference in adiponectin levels in depressed individuals before and after treatment with antidepressive medication (Chen et al, 2010). In contrast, several other studies did find decreased plasma adiponectin level in patients with a major depression (Cizza et al, 2010; Lehto et al, 2010; Diniz et al, 2012), although one study also found an inverse effect of elevated adiponectin levels in elderly with subsyndromal depression (Jeong et al, 2012). These inconsistencies suggest a complex relation between depression and adiponectin. As adiponectin has been extensively linked to cardiovascular and inflammatory pathways (Lago et al, 2007; Mathieu et al, 2009; Taylor et al, 2010; Fernandez-Sanchez et al, 2011; Hui et al, 2012), we also examined interactions between the different metabolic health parameters and adiponectin on the association with depression. The results of these exploratory analyses, however, were rather negative.

**Methodological considerations**
Some limitations of this study have to be acknowledged for proper interpretation. First, the cross-sectional design limits causal interpretation of the findings. Second, being a population-based survey, some selection bias might have occurred toward the healthier part of the population. Finally, we did not measure depression according to formal diagnostic criteria. Although depressive symptoms are generally considered on a continuum with depressive disorder, it is not clear whether this assumption holds true. Especially lower levels of depressive symptoms in the population may be confounded by underlying somatic illnesses (Thoms et al, 2010). This limitation might also explain the negative findings with respect to adiponectin.

**Final conclusion and clinical implications**
Although the pathophysiological mechanisms underlying the association between metabolic disturbances and depression remains to be elucidated, our study point to sex-differences as well as a specific phenotype of depression that is associated with metabolic disturbances. Future studies on the concept of metabolic depression should therefore take different symptom dimensions of depression into account.
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The metabolic syndrome and depressive symptom profiles


