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Metabolic and inflammatory markers: associations with individual depressive symptoms

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Abstract

Background. Literature has shown that obesity, metabolic syndrome and inflammation are associated with depression, however, evidence suggests that these associations are specific to atypical depression. Which of the atypical symptoms are driving associations with obesity-related outcomes and inflammation is unknown. We evaluated associations between individual symptoms of depression (both atypical and non-atypical) and body mass index (BMI), metabolic syndrome components and inflammatory markers.

Methods. We included 808 persons with a current diagnosis of depression participating in the Netherlands Study of Depression and Anxiety (67% female, mean age 41.6 years). Depressive symptoms were derived from the Composite International Diagnostic Interview and the Inventory of Depressive Symptomatology. Univariable and multivariable regression analyses adjusting for sex, age, educational level, depression severity, current smoking, physical activity, anti-inflammatory medication use, and statin use were performed.

Results. Increased appetite was positively associated with BMI, number of metabolic syndrome components, waist circumference, C-reactive protein and tumor necrosis factor-α. Decreased appetite was negatively associated with BMI and waist circumference. Psychomotor retardation was positively associated with BMI, high-density lipoprotein cholesterol and triglycerides, and insomnia with number of metabolic syndrome components.

Conclusion. Increased appetite – in the context of a depressive episode – was the only symptom that was associated with both metabolic as well as inflammatory markers, and could be a key feature of an immuno-metabolic form of depression. This immuno-metabolic depression should be considered in clinical trials evaluating effectiveness of compounds targeting metabolic and inflammatory pathways or lifestyle interventions.

Introduction

Obesity, metabolic syndrome and inflammation have been consistently found to be associated with major depressive disorder (MDD). Both obesity and metabolic syndrome were found to increase the risk of MDD and vice versa in meta-analyses (Luppino *et al.* 2010; Pan *et al.* 2012), while a recent Mendelian randomization study finding no proof of a causal association between obesity and depression suggested possible reverse causality between obesity and depression (Hung *et al.* 2014). An association between inflammatory markers and depression has also been reported by several meta-analyses (Howren *et al.* 2009; Dowlati *et al.* 2010; Hiles *et al.* 2012) and gene-expression studies (Mostafavi *et al.* 2014; Jansen *et al.* 2016), supporting the idea that cytokines play a role in the pathogenesis of depression (Raison *et al.* 2006). Obesity and inflammation go hand in hand, as the production of cytokines in adipose tissue [such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6)] gives rise to a pro-inflammatory state in obesity.

The associations between obesity and inflammation with depression thus seem robust, however, there is some evidence to suggest that this may be in particular true for atypical depression. Atypical depression according to DSM involves the presence of mood reactivity plus at least two of the following symptoms: increased appetite or weight gain, hypersomnia, leaden paralysis and interpersonal rejection sensitivity. However, this definition has been questioned, and variations of the DSM definition have been used in different studies (Angst *et al.* 2006).

Evidence that associations with obesity and metabolic syndrome may be specific to atypical depression comes from both cross-sectional and longitudinal work. Higher rates of obesity and metabolic syndrome have been found in atypical depression *v.* non-atypical subtypes by our group (Lamers *et al.* 2013) and others (Sullivan *et al.* 2002; Kaestner *et al.* 2005; Seppala *et al.* 2012; Yoon *et al.* 2012; Rudolf *et al.* 2014). Atypical depression significantly predicted

weight gain in the Zurich Cohort Study (Hasler *et al.* 2004), and was associated with obesity in the NESARC study (Levitan *et al.* 2012). Women with atypical – but not melancholic depression – were more likely to have a higher fat mass than controls (Cizza *et al.* 2012), and in elderly with depression those with atypical forms had most metabolic dysregulation (Vogelzangs *et al.* 2014). More recently, the PsyColaus study also provided evidence for a longitudinal link between atypical depression on the one hand and obesity, and metabolic syndrome on the other hand (Lasserre *et al.* 2014, 2017). Furthermore, independent associations of an atypical depressive subtype with the rs9939609 SNP of the FTO gene (i.e. fat mass and obesity related gene) (Milaneschi *et al.* 2014) and with genomic profile risk scores for BMI and triglycerides (Milaneschi *et al.* 2016) provide evidence for the theory that atypical depression may be a metabolic disorder on a more fundamental level. Also, we found increased low-grade inflammation in atypical but not in non-atypical depressive subtypes (Lamers *et al.* 2013; 2016), which has been found in other (Kaestner *et al.* 2005; Yoon *et al.* 2012; Hickman *et al.* 2014; Rudolf *et al.* 2014), but not all studies (Anisman *et al.* 1999; Karlovic *et al.* 2012; Glaus *et al.* 2014). For the metabolic syndrome, the association with atypical depression seems driven by the obesity/endocrine components (i.e. higher waist circumference, lower high-density lipoprotein (HDL) cholesterol and higher triglycerides) (Lamers *et al.* 2013). Overall, this evidence suggests that obesity, obesity-related/endocrine components of the metabolic syndrome and inflammation may thus be more common in – or even specific to – an atypical depressive subtype.

However, which symptoms exactly drive the association between atypical depression and these measures is difficult to tell, because of the use of different definitions of atypical depression across studies. While some use strict DSM criteria (Rudolf *et al.* 2014), other studies have used a 2-out-of-3 or 2-out-of-2 symptom approach (fatigue, overeating, oversleeping) (Angst *et al.* 2006; Yoon *et al.* 2012), or used atypical depressive subtypes derived from data-driven analysis (Sullivan *et al.* 2002; Lamers *et al.* 2013). A helpful approach therefore would be to evaluate which of the individual symptoms of depression are associated with obesity, metabolic syndrome and inflammation. Knowing which specific atypical depressive symptom contributes most to the previously found metabolic and inflammatory abnormalities may provide insight into the pathophysiological mechanisms of the atypical depressive subtype, and can contribute to development of a more empirically-based definition of what may be an immuno-metabolic form of depression.

The aim of the current study was therefore to evaluate which of the individual atypical depressive symptoms are associated with BMI, the metabolic syndrome components waist circumference, HDL-cholesterol, and triglycerides, and inflammatory markers in a cohort of depressed individuals. For completeness, we also included all core symptoms of depression not included in the atypical depression definition, to evaluate whether non-atypical symptoms indeed play a (lesser) role in associations with these outcomes.

Sample

Baseline data from the Netherlands Study of Depression and Anxiety (NESDA) were used. NESDA is an ongoing longitudinal naturalistic cohort study of 2981 persons, aged 18–65 years at baseline, with lifetime and/or current depressive and/or anxiety disorders ($n = 2329$; 78%) and healthy controls ($n = 652$; 22%). Participants were recruited from the community ($n = 564$; 19%), primary care ($n = 1610$; 54%) and specialized mental health care ($n = 807$; 27%) from September 2004 through February 2007 at three study sites (Amsterdam, Groningen, Leiden). Exclusion criteria used were having a primary clinical diagnosis of psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder, and not being fluent in Dutch. Ethical review boards of all participating centers approved the study, and all participants signed informed consent. A detailed description of the NESDA study design can be found elsewhere (Penninx *et al.* 2008). Participants were interviewed to collect information on psychopathology, demographics and physical and psychosocial functioning. Also, a medical assessment, and self-administered questionnaires were completed. Fasting blood samples were collected as well. Psychiatric diagnoses were obtained with the Composite International Diagnostic Interview (CIDI) interview, version 2.1 (World Health Organization, 1997), according to DSM-IV criteria. The CIDI interviews were conducted by specially trained clinical research staff. For the current study, we included 808 persons with a current (1-month recency) diagnosis of MDD ($n = 734$) or minor depression ($n = 74$) at baseline, who had complete depression symptom data.

Measures

Depressive symptoms

Depressive symptoms were derived from the CIDI diagnostic interview. Additional atypical symptoms not included in the CIDI (i.e. leaden paralysis, interpersonal rejection sensitivity and mood reactivity) were based on dichotomized items of the Inventory of Depressive Symptomatology (IDS) (score 0–1 = absent, score 2–3 = present) as used before (Lamers *et al.* 2010). For the DSM criterion weight/appetite changes, we only considered changes in appetite, since weight change may too closely resemble outcomes such as waist circumference and BMI. Separate variables were made for increased appetite and for decreased appetite. For sleep, two separate variables were made to indicate insomnia and hypersomnia. Similarly, psychomotor changes were reflected in a variable for retardation and another variable for agitation. All symptoms were coded dichotomous (absent/present).

Metabolic and inflammatory outcomes

BMI was calculated by dividing weight (kg) by squared height (m^2). Metabolic syndrome components were evaluated in two ways. First, a count of the five metabolic syndrome components using adjusted ATP-III criteria (Grundy *et al.* 2005) was made as an index of severity of metabolic syndrome. ATP-III criteria are as follows: (1) waist circumference >102 cm in men or >88 cm in women, (2) triglycerides ⩾1.7 mmol/l (150 mg/dl) or medication for hypertriglyceridemia, (3) HDL-cholesterol <1.03 mmol/l (40 mg/dl) in men or <1.30 mmol/l (50 mg/dl) in women or medication for reduced HDL-cholesterol, (4) blood pressure ⩾130/85 mmHg or medication for hypertension and (5) fasting plasma glucose ⩾5.6 mmol/l (100 mg/dl) or medication for elevated glucose. Second, continuous measures of waist circumference, HDL-cholesterol and triglycerides – the three components that previously seemed to differentiate between an atypical depressive and melancholic subtype (Lamers *et al.*

2013) – were used. Continuous measures for HDL-cholesterol and triglycerides were adjusted for medication. For HDL-cholesterol 0.10 mmol/l was subtracted for use of fibrates (C10AB) and 0.15 mmol/l was subtracted for use of nicotinic acid (C10AD, C10BA01); for triglycerides 0.67 mmol/l was added for use of fibrates and 0.19 mmol/l was added for use of nicotinic acid use, as described previous (Licht *et al.* 2010).

Inflammatory markers C-reactive protein (CRP), IL-6 and TNF-α were determined from fasting morning blood plasma. Plasma levels of CRP were measured in duplicate by an in-house high-sensitivity enzyme-linked immunosorbent assay (ELISA) based on purified protein and polyclonal anti-CRP antibodies (Dako, Glostrup, Denmark). The lower detection limit of CRP is 0.1 mg/l and the sensitivity is 0.05 mg/l. Intra- and inter-assay coefficients of variation were 5% and 10%, respectively. Plasma IL-6 levels were measured in duplicate by a high-sensitivity ELISA (PeliKine CompactTM ELISA, Sanquin, Amsterdam, the Netherlands). The lower detection limit of IL-6 is 0.35 pg/ml and the sensitivity is 0.10 pg/ml. Intra- and inter-assay coefficients of variation were 8% and 12%, respectively. Plasma TNF-α levels were assayed in duplicate using a high-sensitivity solid phase ELISA (Quantikine HS Human TNF-α Immunoassay, R&D systems, Minneapolis, MN, USA). The lower detection limit of TNF-α is 0.10 pg/ml and the sensitivity is 0.11 pg/ml. Intra- and interassay coefficients of variation were 10% and 15%, respectively.

Covariates

Sociodemographic variables included sex, age and educational level (in years). We also adjusted for depression severity to make sure that potential associations were an effect of the specific symptom rather than overall symptom severity. Severity of depressive symptoms was assessed with the Quick Inventory of Depressive Symptomatology (QIDS) (Rush *et al.* 2003). We chose to use the QIDS rather than the full IDS because the full IDS score contains the atypical items leaden paralysis and interpersonal rejection sensitivity – which are used as independent variables in this study. The QIDS is a shortened version of the full IDS containing only the DSM core symptoms of depression. Physical activity was measured with the International Physical Activity Questionnaire (Craig *et al.* 2003). Current smoking (yes/no) was considered as a potential confounder due to its association with inflammatory and metabolic markers as well as with depressive subtypes. Medication use was based on inspection of medication containers. Antidepressant use included selective serotonin reuptake inhibitors (SSRIs; ATC code N06AB), tricyclic antidepressants (TCAs; ATC codes N06AA) and other antidepressants (ATC codes N06AF, N06AG, N06AX). We also assessed statin use (ATC codes C10AA) and anti-inflammatory medication use (ATC codes M01A, M01B, A07EB, A07EC).

Statistical analysis

Analysis of variance (ANOVA) was used for continuous outcomes, logistic regression analysis for dichotomous outcomes, and a Poisson regression for count outcomes. Univariable models to evaluate the association between individual symptoms and metabolic and inflammatory outcomes were performed. These were followed by multivariable models containing all symptoms with $p < 0.10$ in univariable models (Model 1). For appetite, sleep and psychomotor symptoms the opposite pairs (increase and decrease) were both selected in multivariable analysis if one of these had a $p < 0.10$ in univariable analysis. Potential covariates were added to the model (Model 2 -QIDS severity score, sex, age, educational level, physical activity, smoking). Because triglycerides and inflammatory markers had a non-normal distribution they were transformed using the natural logarithm (LN).

Results

Sample characteristics, symptom frequencies and mean or median levels of outcome measures in the entire sample are reported in Table 1. Seventy-six percent of the sample was female with an average age of 41.6 years (s.d. 12.1).

Univariable models

Overall, results from univariable models show an important role for increased appetite – being associated with five out of eight outcomes. Increased appetite and insomnia were positively associated with BMI, number of metabolic syndrome criteria and waist circumference, while decreased appetite was inversely associated with these outcomes (Table 2). In contrast, decreased appetite showed inverse associations with BMI, number of metabolic syndrome criteria and waist circumference. Psychomotor retardation was positively associated with BMI and triglycerides, and inversely associated with HDL. Psychomotor agitation was positively associated with the number of metabolic syndrome criteria and negatively associated with HDL. Fatigue/energy loss was positively associated with BMI and waist circumference while presence of mood reactivity was inversely associated with triglycerides and positively associated with HDL. Feelings of guilt and worthlessness were associated with lower waist circumference.

Increased appetite and leaden paralysis were associated with higher levels of CRP, while decreased appetite was associated with lower CRP levels. Increased appetite was also positively associated with TNF-α. No individual symptoms were associated with IL-6.

Multivariable models

In multivariable models (Table 3) that were adjusted for several covariates including overall symptom severity, anti-inflammatory medication and statin use, the associations with the atypical symptom increased appetite largely persisted. Increased appetite was positively associated with five out of eight outcomes, namely BMI ($B = 2.71$, $p < 0.0001$), number of metabolic syndrome components ($B = 0.20$, $p = 0.006$), waist circumference ($B = 5.80$ $p < 0.0001$), CRP ($B = 0.33$, $p = 0.004$) and TNF-α ($B = 0.16$, $p = 0.006$). Decreased appetite was negatively associated with BMI ($B = -1.37$, $p = 0.001$) and waist circumference ($B = -2.36$, $p = 0.02$). Psychomotor retardation was associated with higher BMI ($B = 0.73$, $p = 0.049$) and higher triglycerides ($B = 0.09$, $p = 0.02$) and lower HDL ($B = -0.07$, $p = 0.04$). Having insomnia was associated with a higher number of metabolic syndrome components ($B = 0.17$, $p = 0.03$). Depression severity as measured with the QIDS was only significantly associated with waist circumference ($B = 1.29$, $p = 0.01$). Additional correction for antidepressant use yielded similar results (data not shown).

Table 1. Sample characteristics and symptom prevalence

	Sample (*N* = 808)
Female, *N* (%)	541 (67.0)
Age, mean (s.d.)	41.6 (12.1)
Education (years), mean (s.d.)	11.4 (3.2)
Current smokers, *N* (%)	357 (44.2)
Physical activity (1000 MET minutes/wk), median (IQR)	2.42 (1.06–4.51)
QIDS depression score, mean (s.d.)	13.6 (4.5)
Diagnostic status	
MDD, *N* (%)	734 (90.8)
Minor depression, *N* (%)	74 (9.2)
Medication use, *N* (%)	
SSRI	231 (28.7)
TCA	27 (3.3)
Other antidepressants	87 (10.8)
Anti-inflammatory medication	41 (5.1)
Statins	63 (7.8)
Symptom prevalence, *N* (%)	
Atypical symptoms	
Mood reactivity	579 (71.7)
Increased appetite	208 (25.7)
Hypersomnia	358 (44.3)
Leaden paralysis	526 (65.1)
Interpersonal sensitivity	327 (40.5)
(Non-atypical) MDD core symptoms	
Depressed mood	754 (93.3)
Loss of interest	768 (95.0)
Decreased appetite	285 (35.3)
Insomnia	635 (78.6)
Psychomotor retardation	264 (32.7)
Psychomotor agitation	294 (36.4)
Fatigue/energy loss	758 (93.8)
Guilt/worthless	680 (84.2)
Concentration/ indecisiveness	788 (97.5)
Suicidal thoughts	520 (64.4)
Metabolic and Inflammatory markers	
BMI. mean (s.d.)	26.0 (5.3)
Obesity (BMI ⩾ 30), *N* (%)	166 (20.5)
Metabolic syndrome, *N*, (%)	179 (22.7)
No. of Metabolic Syndrome components, median (IQR)	1 (1–2)
Waist circumference (cm), mean (s.d.)	90.0 (14.5)
Triglycerides (mmol/l), median (IQR)	1.15 (0.80–1.62)
HDL (mmol/l), mean (s.d.)	1.60 (0.44)
CRP (mg/l), median (IQR)	1.33 (0.53–3.45)
IL-6 (pg/ml), median (IQR)	0.83 (0.51–1.34)
TNF-α (pg/ml), median (IQR)	0.80 (0.60–1.10)

Discussion

The results of this study clearly show that of all depressive symptoms, increased appetite is the most important symptom driving associations of depression with BMI, metabolic syndrome and inflammation. While there was already some evidence to suggests that associations with metabolic and inflammatory markers were specific to atypical depression, these results suggest that increased appetit (in the context of a depressive episode) is core to the atypical subtype, being associated with more than half of the outcomes. These effects were independent of depression severity. Mood reactivity – the cardinal symptom of atypical depression-, interpersonal rejection sensitivity and hypersomnia were not associated with any of the outcome measures, while leaden paralysis was only marginally associated with the increased CRP level.

Psychomotor retardation and insomnia were also associated with some of the outcomes. The finding of insomnia being associated with a higher number of metabolic syndrome components fits with research showing associations between short sleep duration and obesity-related measures, high blood pressure, diabetes and cardiovascular disease (Dashti *et al.* 2015). Another explanation is that this association is driven by sleep apnea, a prevalent disorder in persons with depression (Stubbs *et al.* 2016) as well as in persons with obesity (Punjabi, 2008). Psychomotor retardation may be linked to BMI through lower physical activity levels. We found no potential clues on mechanisms from the literature for the associations between psychomotor retardation and lower HDL and higher triglycerides.

We previously showed that inflammation, BMI and metabolic syndrome components were associated with an atypical depressive subtype compared with controls. In contrast, those with a more typical/melancholic subtype did not differ from controls on these outcome measures and even had a lower BMI compared with controls (Lamers *et al.* 2013). The current analyses in which we further explored the responsible individual symptoms, show that when evaluating individual symptoms among persons with MDD, the associations with BMI, metabolic syndrome components and inflammation to a large extent seem to be attributable to the atypical symptom of increased appetite. A recent study found an association between appetite change and increased CRP, but did not distinguish increased from decreased appetite (Jokela *et al.* 2016). It could very well be that this finding is driven by increased appetite. Indeed, Lasserre and colleagues found that increased appetite during an episode significantly predicted increase in waist circumference during 5-year follow-up (Lasserre *et al.* 2017).

The finding that both decreased as well as increased appetite are important in the associations with BMI and waist circumference is not surprising as changes in appetite and subsequent weight change directly impact these measures. It should however be noted that the increased appetite evaluated in this study represent increases *in the context of a depressive episode*, rather than general overeating. The finding fits with the found association between atypical depression – but not melancholic depression – and the rs9939609 SNP of the FTO gene (Milaneschi *et al.* 2014) (a fat mass and obesity related gene involved in appetite regulation) and with higher genome-wide genomic profile risk scores (GPRS) for BMI and triglycerides in atypical depression (Milaneschi *et al.* 2016). The latter results for the GPRS-BMI and GPRS-triglycerides persisted when repeating analyses using increased appetite/weight as an alternative phenotype (Milaneschi *et al.* 2016) indicating that this symptom may be

Table 2. Univariable associations of individual depressive symptoms in depressed persons with metabolic and inflammatory outcomes (N = 808)

	BMI (*n* = 807)		Number of MetSyn criteria (*N* = 790)		Waist circumference (*N* = 806)		Triglycerides[a] (*n* = 791)		HDL-cholesterol (*n* = 792)		CRP[a] (*n* = 797)		IL-6[a] (*n* = 797)		TNFa[a] (*n* = 791)	
	B (S.E.)	*p* Value	*B* (S.E.)	*p* Value	*B* (S.E.)	*p* Value	*B* (S.E.)	*p* Value	*B* (S.E.)	*p* Value	*B* (S.E.)	*p* Value	*B* (S.E.)	*p* Value	*B* (S.E.)	*p* Value
Atypical symptoms																
Mood reactivity	−0.59 (0.41)	0.16	−0.10 (0.06)	0.09	−1.87 (1.13)	0.098	−0.09 (0.04)	0.02	0.08 (0.04)	0.02	0.07 (0.10)	0.47	−0.11 (0.08)	0.14	−0.07 (0.05)	0.17
Increased appetite	3.50 (0.41)	<0.0001	0.19 (0.06)	0.002	6.36 (1.14)	<0.0001	0.06 (0.04)	0.19	−0.01 (0.04)	0.85	0.36 (0.10)	<0.0001	−0.02 (0.08)	0.77	0.18 (0.05)	0.001
Hypersomnia	−0.41 (0.38)	0.28	−0.07 (0.06)	0.23	−0.16 (1.03)	0.87	0.05 (0.04)	0.20	−0.04 (0.03)	0.22	0.03 (0.09)	0.77	0.07 (0.07)	0.29	−0.01 (0.05)	0.86
Leaden paralysis	0.71 (0.39)	0.07	0.10 (0.06)	0.09	1.69 (1.07)	0.11	0.07 (0.04)	0.08	−0.05 (0.03)	0.13	0.21 (0.09)	0.02	0.06 (0.07)	0.42	0.06 (0.05)	0.19
Interpersonal sensitivity	0.62 (0.38)	0.10	0.02 (0.06)	0.80	0.65 (1.04)	0.53	−0.03 (0.04)	0.43	−0.05 (0.03)	0.16	0.09 (0.09)	0.35	0.03 (0.07)	0.67	0.04 (0.05)	0.43
(Non-atypical) MDD core symptoms																
Depressed mood	0.77 (0.75)	0.31	0.05 (0.12)	0.65	−0.15 (2.04)	0.94	−0.02 (0.07)	0.78	−0.04 (0.06)	0.50	−0.08 (0.18)	0.67	0.10 (0.14)	0.49	−0.03 (0.09)	0.75
Loss of interest	0.19 (0.86)	0.82	−0.05 (0.13)	0.69	1.51 (2.35)	0.52	0.02 (0.08)	0.84	−0.07 (0.07)	0.31	0.03 (0.21)	0.90	0.03 (0.16)	0.85	0.05 (0.10)	0.65
Decreased appetite	−2.38 (0.38)	<0.0001	−0.14 (0.06)	0.03	−4.59 (1.05)	<0.0001	−0.03 (0.04)	0.48	0.03 (0.03)	0.41	−0.19 (0.09)	0.04	−0.03 (0.07)	0.65	−0.08 (0.05)	0.07
Insomnia	1.12 (0.45)	0.01	0.25 (0.07)	0.001	2.48 (1.24)	<0.05	0.07 (0.04)	0.10	−0.04 (0.04)	0.31	0.18 (0.11)	0.10	0.05 (0.08)	0.52	0.02 (0.05)	0.77
Psychomotor retardation	1.00 (0.40)	0.01	0.08 (0.06)	0.17	1.88 (1.08)	0.08	0.10 (0.04)	0.007	−0.10 (0.03)	0.004	0.07 (0.10)	0.46	0.002 (0.07)	0.98	0.08 (0.05)	0.08
Psychomotor agitation	0.70 (0.39)	0.07	0.11 (0.06)	0.05	2.01 (1.06)	0.06	0.10 (0.04)	0.79	−0.09 (0.03)	0.008	0.14 (0.09)	0.13	−0.09 (0.07)	0.23	0.02 (0.05)	0.68
Fatigue/energy loss	2.06 (0.78)	0.008	0.11 (0.12)	0.36	4.53 (2.13)	0.03	0.07 (0.08)	0.36	−0.10 (0.07)	0.11	0.21 (0.19)	0.26	0.08 (0.14)	0.58	0.04 (0.09)	0.65
Guilt/worthless	−0.46 (0.51)	0.37	−0.01 (0.08)	0.87	−2.92 (1.39)	0.04	0.04 (0.05)	0.46	−0.05 (0.04)	0.26	−0.04 (0.12)	0.77	−0.01 (0.09)	0.90	0.02 (0.06)	0.76
Concentration/ indecisiveness	1.89 (1.20)	0.12	0.09 (0.19)	0.62	2.45 (3.27)	0.46	0.04 (0.12)	0.76	−0.03 (0.10)	0.77	−0.30 (0.29)	0.30	0.04 (0.22)	0.85	−0.12 (0.14)	0.39
Suicidal thoughts	−0.25 (0.39)	0.52	0.05 (0.06)	0.39	−0.08 (1.06)	0.94	0.05 (0.04)	0.20	−0.04 (0.03)	0.25	−0.01 (0.09)	0.94	0.01 (0.07)	0.89	0.05 (0.05)	0.31

[a]LN transformed

All B (SE) are derived from ANOVAs, except for number of metabolic syndrome components: these were drawn from Poisson GEE model

Table 3. Multivariable[a] associations of individual symptoms with metabolic and inflammatory markers

	BMI		No. Metabolic Syndrome components		Waist circumference		Triglycerides[b]		HDL		CRP[b]		TNF-a[b]	
	B (S.E.)	*p* Value	*B* (S.E.)	*p* Value	*B* (S.E.)	*p* Value	*B* (S.E.)	*p* Value	*B* (S.E.)	*p* Value	*B* (S.E.)	*p* Value	*B* (S.E.)	*p* Value
Atypical symptoms														
Mood reactivity			0.01 (0.07)	0.89	0.68 (1.07)	0.53	0.01 (0.04)	0.77	0.03 (0.04)	0.39				
Increased appetite	**2.71 (0.43)**	**<0.0001**	**0.20 (0.07)**	**0.006**	**5.80 (1.12)**	**<0.0001**					**0.33 (0.11)**	**0.004**	**0.16 (0.06)**	**0.006**
Hypersomnia	−0.41 (0.35)	0.25	−0.01 (0.06)	0.85	−0.04 (0.91)	0.97								
Leaden Paralysis	−0.18 (0.41)	0.66	0.03 (0.07)	0.71			0.01 (0.04)	0.83			0.18 (0.10)	0.09		
(Non-atypical) MDD core symptoms														
Decreased appetite	**−1.37 (0.40)**	**0.001**	−0.08 (0.07)	0.26	**−2.36 (1.02)**	**0.02**					−0.10 (0.10)	0.32	−0.04 (0.05)	0.49
Insomnia	0.74 (0.43)	0.08	**0.17 (0.08)**	**0.03**	1.58 (1.10)	0.15								
Psychomotor retardation	**0.73 (0.37)**	**0.049**	0.05 (0.06)	0.41	1.10 (0.95)	0.25	**0.09 (0.04)**	**0.02**	**−0.07 (0.03)**	**0.04**			0.07 (0.05)	0.14
Psychomotor agitation	0.17 (0.36)	0.64	0.03 (0.06)	0.64	0.39 (0.93)	0.67	−0.03 (0.04)	0.34	−0.04 (0.03)	0.18			0.00 (0.05)	0.92
Fatigue/energy loss	1.31 (0.73)	0.07			3.35 (1.85)	0.07								
Guilt/worthlessness					−2.33 (1.22)	0.06								
Depression severity[c]	0.35 (0.20)	0.08	0.03 (0.04)	0.42	1.29 (0.52)	**0.01**	0.04 (0.02)	0.08	−0.01 (0.02)	0.44	−0.01 (0.05)	0.80	0.02 (0.02)	0.38

[a]Models included all symptoms with $p < 0.10$ in univariable models and were additionally corrected for sex, age, educational level, depression severity, current smoking, physical activity, anti-inflammatory medication use, statin use. Empty cells indicate that symptom was not selected for multivariable models ($p > 0.10$). Significant *p*-values (<0.05) are printed in bold.
[b]LN transformed.
[c]Standardized QIDS score.

driving these associations. The association of increased appetite with CRP and TNF-α may be driven by increased fat mass resulting in a larger cytokine production in adipocytes, which stimulates the liver to produce CRP. While this study cannot answer questions regarding the temporal ordering of events, it can be hypothesized that increased BMI and atypical depression have a shared genetic vulnerability (Milaneschi *et al.* 2014; Samaan *et al.* 2015), with increased appetite being an important factor in both the increased weight and increased levels of cytokines that in turn can induce sickness behavior, which ultimately could induce an atypical depressive episode. In a more integrative model, social and psychological factors interacting with the environment should also be taken into account. Overall, one can speculate that increased appetite is core to a depressive subtype that is current DSM atypical depressive subtype, and in which immune and metabolic dysregulation – including increased BMI – are part of the phenotype. On the other hand, while genetic research suggests a pleiotropic genetic effect (Milaneschi *et al.* 2014, 2016), we nevertheless cannot rule out that other mechanisms are at play and that the association between increased appetite and obesity is not specific to atypical forms of depression.

As pointed out by the NIMH RDoC initiative, DSM diagnostic categories may not underlie etiological mechanisms (Insel *et al.* 2010), which hampers research. DSM criteria for MDD do not differentiate increased from decreased appetite/weight, but perhaps we should, now that accumulating evidence suggests different underlying biosignatures in depression with increased appetite. This 'immuno-metabolic depression' as we could call it (to discern it from DSM atypical depression in which mood reactivity is a core feature) seems a promising phenotype for future genetic and biological research. This term has been suggested before for groups of patients with metabolic abnormalities (McIntyre *et al.* 2007; Vogelzangs *et al.* 2011).

The question remains what is triggering increased appetite. Associations between mood and food intake are highly complex (Singh, 2014). Food is a natural reward which intake leads to the release of dopamine. One thought is that increased appetite in atypical depression could be the result of a disturbance on reward perceived from food that is regulated by the mesolimbic reward centers (Korte *et al.* 2015). Indeed, Simmons and colleagues found depression-related increased appetite to be associated with hyperactivation of putative mesocorticolimbic reward circuitry, while decreased appetite was associated with hypoactivation of insular regions that support monitoring the body's physiological state (Simmons *et al.* 2016). Research has shown that eating palatable foods (high in sugar and fat) trigger neuroadaptive responses (via dopamine D2 receptors) in the same brain regions of reward and pleasure that are active in drug addiction (Singh, 2014; Korte *et al.* 2015). Increased food intake as response to a stressful event (emotional or comfort eating) can be thought of as a form of self-medication. A recent study finding showed diet quality to be significantly lower in those with atypical depression than those with melancholic depression (Rahe *et al.* 2015) indicating that not only food quantity but also food quality (or preference) is altered in atypical depression. Another actor in appetite regulation relevant to atypical depression is leptin, an appetite-decreasing hormone with antidepressant-like effects excreted by white fat cells. Leptin was found to be increased in atypical depression (Gecici *et al.* 2005; Milaneschi *et al.* 2016) and increased appetite despite high leptin levels is thought to be the result of leptin resistance. To date, pharmacological approaches targeting leptin resistance have shown limited success (Santoro *et al.* 2015).

Other treatment options relevant for metabolic depression include anti-inflammatory agents, statins and lifestyle interventions. A small meta-analysis of four trials adding an NSAID to an antidepressant regimen in depressed persons concluded that this could be a promising strategy (Na *et al.* 2014). Another meta-analysis and a systematic review including more studies have however recommended that further study is need, in particular to evaluate which subgroups would benefit most from such add-on treatments (Kohler *et al.* 2014; Eyre *et al.* 2015). Metabolic depression could be such a subgroup, since one study showed that infliximab add-on treatment was only effective in those with high baseline levels of CRP (Raison *et al.* 2013). Statins lower LDL cholesterol, but can also increase HDL-cholesterol and lower triglycerides. Two studies evaluating augmenting antidepressant treatment with statin found beneficial effects (Ghanizadeh & Hedayati, 2013; Haghighi *et al.* 2014). Non-pharmacological interventions, such as dietary interventions and weight loss programs could contribute to better metabolic outcomes and better mood in metabolic depression.

When interpreting these findings, some limitations need to be taken into account. Mood reactivity, leaden paralysis and interpersonal rejection sensitivity were not assessed in the CIDI but using the self-report IDS, which assesses symptoms within the past 7 days. Further, because this is a cross-sectional study we cannot make causal inferences. Also, the sample did not include inpatients and results may therefore not be generalizable to the more severe, inpatient population. Strengths of the study include the use of diagnostic interviews for assessment of most MDD symptoms, the relatively large sample and comprehensive set of metabolic and inflammatory markers.

The results have implications for research on associations between depression and somatic outcomes and biological variables. It is important to explore possible effect modification by depression subtype when associations between depression and biological variables are found. Only then can we begin to understand the complex etiological mechanisms that underlie depression. Especially studies on metabolic or inflammatory markers in depression should evaluate whether associations are limited to those with atypical features – in particular increased appetite and/or weight – and stratify analyses if necessary. For this, however, it is necessary that studies collect enough information to discern subtypes; rather than appetite change, the direction of the effect (increase *v.* decrease) is important to collect.

To conclude, we found increased appetite–in the context of a depressive episode- to be the most important symptom driving the associations between depression and metabolic and inflammatory markers. Appetite regulation could be an important factor in the onset of an immuno-metabolic form of depression. Both studies on the biology of depression and clinical trials evaluating effectiveness of compounds targeting metabolic and inflammatory pathways or lifestyle interventions in depression should take specificity to immuno-metabolic depression into consideration.

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Declaration of Interest. None.

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