Disentangling the relationship between depression, obesity and cardiometabolic disease

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The Association Between Overall and Abdominal Adiposity and Depressive Mood: A Cross-Sectional Analysis in 6459 Participants

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ABSTRACT

Objective
We aimed to evaluate the association between measures of adiposity with depressive mood and specific depressive symptoms.

Methods
This study was performed in the Netherlands Epidemiology of Obesity (NEO) study, a population-based study that consists of 6671 middle-aged individuals. We examined the association between measures of overall adiposity (BMI and total body fat), and abdominal adiposity (waist circumference and visceral adipose tissue), with depressive mood severity subgroups and 30 depressive symptoms. Multinomial logistic regression was performed adjusting for potential confounding.

Results
Measures of adiposity were associated with depressive mood in a graded fashion. Total body fat showed the strongest association with mild (Odds Ratio (OR): 1.59 per standard deviation, 95% Confidence Interval (95% CI): 1.41-1.80) and moderate to very severe (OR: 1.97, 95% CI: 1.59-2.44) depressive mood. Regarding individual symptoms of depressive mood, total body fat was associated with most depressive symptoms (strongest associations for hyperphagia and fatigability).

Conclusions
In the general population, overall and abdominal adiposity measures were associated with depressive mood. This association encompasses most of the depressive symptoms and appeared to be the strongest with specific “atypical” neurovegetative symptoms, which may be an indication of an alteration in the energy homeostasis.

INTRODUCTION

Obesity and depression are serious health conditions that both constitute major economic and social burdens worldwide [1]. Although there is an abundance of research that examined the complex association between both conditions, the conclusions are inconsistent [2]. Where the larger body of evidence is leaning toward the presence of a link between obesity and major depressive disorder (MDD) [3], there are studies that reported that both conditions are unrelated [4] or only reported the presence of an association in sub-groups, for example in women [5].

A recent review [3] summarized the epidemiological evidence of the interconnection between obesity and MDD from large meta-analyses: overall, evidence suggests that obesity and depression are bidirectionally associated, with the presence of one increasing the risk of developing the other. Nevertheless, several important aspects of the relationship between obesity and depression need to be clarified. First of all, the majority of previous work in this field define obesity according to body mass index (BMI=body weight in kg/(height in m^2)) [6]. However, BMI is an approximation of total body fat and does not distinguish between high muscle or fat mass [7]. Furthermore, BMI value does not inform us about the distribution of the fat in the body [7, 8]. This could be of importance, because it is known that especially abdominal adiposity is associated with inflammation, insulin resistance and metabolic syndrome [9].

Depression is also a heterogeneous condition: patients with a diagnosis of the same depressive disorder may endorse very different symptoms. This heterogeneity may have contributed to the inconsistency and variability observed in the reported association between adiposity and depression. This association appears to be stronger in certain subgroups of patients. Emerging evidence suggests that the MDD link with obesity measures, and related metabolic and inflammatory dysregulations (i.e. high lipid and glucose levels, low HDL-cholesterol and high inflammation markers), is stronger for patients with a symptom profile often labeled as “atypical”, including neurovegetative symptoms related to energy metabolism such as hyperphagia, hypersomnia, fatigability and physical exhaustion [10]. Results from the Netherlands Study of Depression and Anxiety (NESDA) cohort showed for instance that among patients with Major Depressive Disorder (MDD) appetite upregulation and ’leaden paralysis’ (described as the feeling of being physically weighted down) during an active depressive episode were the symptoms most strongly associated with BMI and obesity-related inflammatory (high C-reactive protein (CRP) and tumor necrosis-α (TN-α)) [11] and endocrine (high leptin) alterations [12]. Whether this link between obesity

correlates and specific depressive symptoms exists also in the general population is unknown.

We set out to coherently interrogate the relationship between overall and abdominal adiposity and depressive mood and its individual symptoms in 6459 participants from a population-based cohort (Netherlands Epidemiology of Obesity (NEO) study). Several measures of adiposity were examined, including overall (BMI and total body fat) and abdominal or central (waist circumference and visceral adipose tissue) adiposity. Among these measures, total body fat and visceral adipose tissue are accurate measures for overall and abdominal adiposity, respectively. Furthermore, we examined the specific associations between the measures of adiposity with 30 depression-related symptoms (assessed by Inventory of Depressive Symptomatology-Self Report 30 questionnaire (IDS-SR30)).

METHODS

Study design and population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based cohort study including 6671 men and women aged 45 to 65 years [13]. All inhabitants with a self-reported body mass index (BMI) of 27 kg/m^2 or higher and living in the greater area of Leiden, the Netherlands were eligible to participate in the NEO study. In addition, all inhabitants aged between 45 and 65 years from one adjacent municipality (Leiderdorp, the Netherlands) were invited to participate irrespective of their BMI, allowing for a reference distribution of BMI. Prior to the study visit, participants completed questionnaires at home with respect to demographic, lifestyle, and clinical information. Participants visited the NEO study center after an overnight fast for an extensive physical examination including anthropometry. In a random subgroup of participants without contraindications (i.e., body circumference ≥ 170 cm, implanted metallic devices, or claustrophobia) magnetic resonance imaging (MRI) of abdominal fat was performed. The present analysis is a cross-sectional analysis of the baseline measurements of the NEO study. The NEO study was approved by the medical ethics committee of Leiden University Medical Center (LUMC) and all participants gave written informed consent. We selected 6459 participants with complete measures of body mass index (BMI), depressive symptoms via IDS-SR30 and relevant covariates. Among these participants, 6428 were available for analyses based on total body fat, 6420 for waist circumference and 2475 for visceral adipose tissue.

Measures of adiposity

For this analysis, we assessed four adiposity measures: body mass index (BMI), total body fat, waist circumference and visceral adipose tissue. We used BMI

and the percent of total body fat as measures of overall adiposity; and waist circumference and visceral adipose tissue as measures of abdominal adiposity. Body height was measured with a vertically fixed, calibrated tape measure. Body weight and total body fat were measured by Tanita bioelectrical impedance balance (TBF-310, Tanita International Division, UK). BMI was calculated by dividing the weight by the height squared (kg/m^2). For abdominal fat, waist circumference was measured with a measuring tape placed midway horizontally between the lower costal margin and the iliac crest. For visceral adipose tissue, analyses were performed in a random subgroup of participants without contraindications. Visceral adipose tissue was assessed by a turbo spin echo imaging protocol using MRI. Imaging was performed on a 1.5 Tesla MR system (Philips Medical Systems, Best, The Netherlands). At the level of the fifth lumbar vertebra, three transverse images each with a slice thickness of 10 mm were obtained during a breath hold. The fat depots were converted from the number of pixels to squared centimeters for all three slides, using in-house-developed software (MASS, Medis, the Netherlands). In the analysis, the average of the three slices was used [14].

Assessment of depressive mood

We asked all participants to complete the Dutch translation of the IDS-SR30 questionnaire, which assesses specific depressive symptoms during the last week and their severity. The IDS-SR30 rates (via a 4-level response system) the presence of a wide array of depressive symptoms, including core symptoms of major depressive episodes, melancholic (e.g., anhedonia, nonreactive mood, psychomotor retardation/agitation, appetite or weight decrease, early morning awakening, and self-outlook) and atypical (e.g., mood reactivity, leaden paralysis (physical exhaustion), weight gain or increased appetite, hypersomnia, and interpersonal sensitivity) features, and commonly associated symptoms (e.g., irritability, anxiety, somatic complaints). The total score ranges from 0 to 84, with higher scores indicating higher severity.

We regarded the participants as having clinically relevant depressive mood when their IDS-SR30 total score was ≥ 14. Furthermore, we grouped the participant according to the clinically predefined severity cut-offs as follow: score ≤ 13 as "no depressive mood" status (n=4540, reference), 14-25 as "mild depressive mood" (n=1397), 26-38 as "moderate depressive mood" (n=428), 39-48 is "severe depressive mood" (n=68) and 49-84 is "very severe depressive mood" (n=26) [15]. For analysis purposes and due to the relatively small sample size in moderate, severe and very severe sub-categories, they have been merged into "moderate to very severe".

Covariates

By a self-reported questionnaire, participants were asked to report their date of birth, ethnicity, educational level (as a proxy for the socioeconomic status), tobacco smoking status and alcohol consumption. Participants reported the frequency, duration and intensity of their physical activity during leisure time, which was expressed in metabolic equivalents of tasks in hours per week [16]. Caloric intake (KJ/day) was estimated by a food frequency questionnaire [17]. For the antidepressants N06AA and N06A, participants were asked to bring all the medications that they have been using for the last month to the NEO study centre. Then, all prescribed and self-medication were recorded by research nurses based on Anatomical Therapeutic Chemical Classification System (ATC).

Statistical analysis

In the NEO study, individuals with a BMI of 27 kg/m^2 or higher were oversampled. To correctly represent associations in the general population adjustments for the oversampling of individuals with high BMI were made [18]. This was done by weighting individuals towards the BMI distribution of participants from the Leiderdorp municipality [19], whose BMI distribution was similar to the BMI distribution of the general Dutch population. All results are based on weighted analyses. Consequently, the results apply to a population-based study without oversampling of individuals with a BMI ≥ 27 kg/m^2. Characteristics of the study population were expressed as a mean with standard deviation (SD), a median (25th and 75th) or as percentages (%). We standardized all measures of adiposity to a mean of zero and a standard deviation of one to allow comparison across different measures.

First, we examined the association between each measure of adiposity with the IDS-SR30 clinical groups using multinomial logistic regression models; the "no depressive mood" groups was set as the reference group. The first model was adjusted for age and sex; the second model was adjusted for age, sex, education level, tobacco smoking, alcohol consumption, physical activity, caloric intake, and ethnicity. Additionally, since abdominal adiposity is strongly related to overall adiposity (Table S 1), all abdominal adiposity analyses were adjusted for total body fat [20]. Subsequently, we repeated these analyses after excluding participants who were using N06AA and N06A antidepressants. Finally, we stratified our main analysis (i.e., the multinomial logistic regression between adiposity measures and depressive mood) by sex.

Second, we used logistic regression to examine the relationship between the overall and abdominal adiposity measurements and the 30 individual items from the IDS-SR30. For each item, the four-level answer system was dichotomized to code for low (reference: levels 0) versus medium-high (levels 1,2,3) symptoms.

Likewise, this analyses were adjusted for age and sex in the first model, and the confounding factors in model 2. Additionally, in order to account for the average depressive symptoms severity, adjustment for the IDS-SR30 total score was done (model 3 and 4). Analyses that included abdominal adiposity were additionally adjusted for total body fat. All statistical analysis were performed with STATA statistical software (StataCorp, College Stations, Texas, USA), version 14.0).

RESULTS

Baseline characteristics for all 6459 participants included in this analysis of NEO cohort are shown in Table 1. The mean age in the NEO population was 55.7 years (standard deviation (SD)): 6.0 years), 56.4% of participants were women and 95.0% were of Caucasian ethnicity. There are large differences in the total body fat and visceral adipose tissue between men and women. Out of the total NEO population 24.3% participants had depressive mood problems. Finally, in the IDS-SR30 questionnaire women reported more depressive symptoms than men (9 points (25^{th}-75^{th} percentiles): 6-15)) versus (6 points (25^{th}-75^{th} percentiles): 3-11)).

Measures of adiposity and depressive mood

The percentage of participants with depressive mood in each quartile of adiposity measures are illustrated in Figure 1. For all adiposity measures the proportion of individuals with mild and moderate to very severe depressive mood is largest in the highest adiposity measure quartile. Odds ratios (OR) and 95% confidence intervals from adjusted multinomial logistic regression for the association between overall and abdominal adiposity measures and the severity of the depressive mood are shown in Table 2. Overall and abdominal adiposity measures were positively associated with mild and moderate to very severe depressive mood in a graded fashion, with higher ORs for the moderate to very severe depressive mood than mild depressive mood. In general, ORs of total body fat were relatively higher than those obtained from other adiposity measures. For example, increased total body fat was associated with mild and moderate to very severe depressive mood (OR: 1.59 (95% CI: 1.41-1.80)), (OR: 1.97 (95% CI: 1.59-2.44)) respectively. In covariate-adjusted models, measures of abdominal adiposity were also associated with depressed mood (waist circumference: mild depressed mood (OR: 1.45 (95% CI: 1.33 -1.59)) and moderate to very severe depressive mood (OR: 1.82 (95% CI: 1.59-2.08)); visceral adipose tissue, mild depressed mood (OR: 1.36 (95% CI: 1.19-1.54)) and moderate to very severe depressive mood (OR: 1.57 (95% CI: 1.25-1.97)). Nevertheless, further adjustment for total body fat substantially reduced the magnitude of these estimates (Table 2), suggesting that the association between abdominal adiposity and depression may largely explained by total body fat (i.e., the association between visceral adipose tissue and mild and moderate to very severe depressive mood was (OR: 1.08 (95% CI: 0.90-1.29)), (OR: 1.23 (95% CI: 0.87-1.73)) respectively).

Table 1. Baseline characteristics for 6459 men and women aged 45 to 65 years included in the analysis from Netherlands Epidemiology of Obesity study.

Characteristics	Total population	Men (43.6%)	Women (56.4%)
Age (years)	55.7 (6.0)	56.1 (6.1)	55.5 (6.0)
Educational level (% high)	45.9	48.0	44.3
Tobacco smoking (%)			
Never	38.5	34.4	41.7
Former	45.4	47.0	44.1
Current	16.1	18.6	14.2
Alcohol consumption (g/day)	14.7 (16.3)	20.5 (19.2)	10.3 (11.9)
Physical activity (metabolic equivalent of task (MET)-hours per week)	120.1 (59.5)	118.3 (62.4)	121.5 (57.1)
Ethnicity (% Caucasian)	94.9	95.1	94.8
Depressive mood characterization			
Current depressive mood (%)	24.3	16.6	30.2
IDS-SR30 total score	8 (4, 13)	6 (3, 11)	9 (6, 15)
None (%)	75.7	83.4	69.7
Mild (%)	18.5	12.4	23.3
Moderate to very severe (%)	5.8	4.2	7.0
Use of antidepressants (%)	6.6	4.5	8.2
Measures of adiposity			
Overall adiposity			
BMI (Kg/m^2)	26.3 (4.5)	26.9 (3.7)	25.9 (4.9)
Total body fat (%)	31.6 (24.8, 38.3)	24.5 (21.2, 28.1)	37.0 (32.3, 41.4)
Abdominal adiposity			
Waist circumference (cm)	92.2 (13.4)	98.5 (10.9)	87.3 (13.1)
Visceral adipose tissue (cm^2)	89.8 (56.1)	115.8 (57.7)	66.7 (42.9)

Normally distributed data shown as mean and standard deviation (SD), skewed distributed data shown as median (25th ,75th percentiles) and categorical data are shown as percentage. High education level: university or college education, while other education level: none, primary school or lower vocational education. IDS-SR30: Inventory of Depressive Symptomatology (self-report). BMI: body mass index. Number of individual with available data for each adiposity measures (BMI=6459, total body fat n=6428, waist circumference=6420, visceral adipose tissue n=2475).

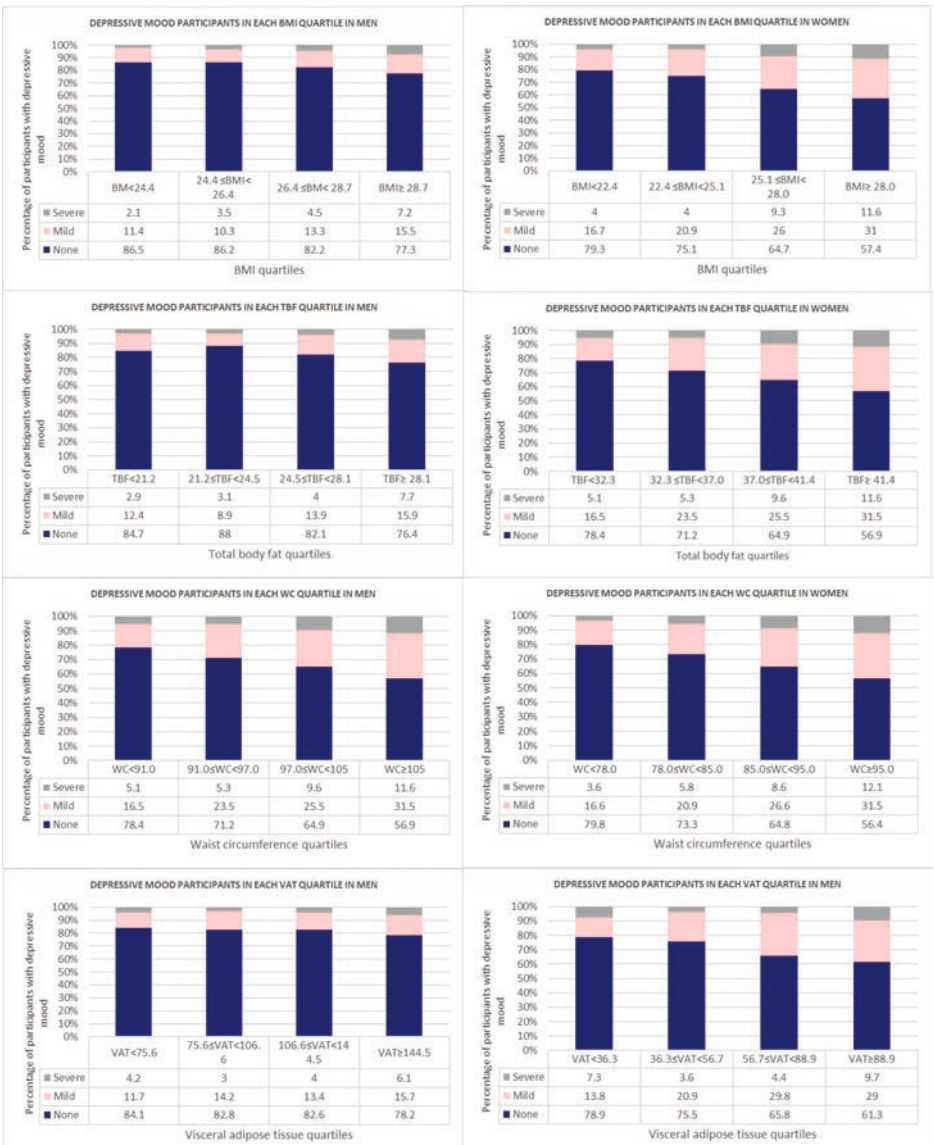

Figure 1. The percentage of participants with depressive in each quartile of adiposity measures

When we repeated the analyses of multinomial logistic regression between overall and abdominal adiposity and depressive mood categories after exclusion of participants who were using antidepressants (6.6%) for any reason, results did not materially change (Table S 2). We also excluded individuals with type 2 diabetes, cardiovascular disease and hypertension and the effect estimates again did not

materially change (Table S 3). The sex-stratified analyses are shown in Table S 4. Overall, direction and strength of effect sizes were similar between sexes.

Table 2. Results of the multinomial logistic regression analysis of the association between overall and abdominal adiposity measures and the severity of depressive mood.

	1 SD	OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Overall adiposity						
		None (75.7%)	Mild (18.5%)		Moderate to very severe (5.8%)	
BMI (kg/m^2)	4.5	Reference	1.36 (1.27-1.47)	1.35 (1.25-1.46)	1.63 (1.48-1.81)	1.58 (1.42-1.75)
Total body fat (%)	8.7	Reference	1.61 (1.43-1.81)	1.59 (1.41-1.80)	2.06 (1.66-2.56)	1.97 (1.59-2.44)
Abdominal adiposity						
Waist circumference (cm)	13.4	Reference	1.28 (1.08-1.52)	1.25 (1.05-1.49)	1.90 (1.44-2.51)	1.82 (1.37-2.43)
Visceral adipose tissue (cm^2)	56.1	Reference	1.09 (0.92-1.30)	1.08 (0.90-1.29)	1.27 (0.89-1.81)	1.23 (0.87-1.73)

OR: odds ratio per standard deviation. IDS-SR30: Inventory of depressive symptomatology (self-report). None: score (0-13). Mild: score (14-25). Moderate to very severe: (26-84). BMI: body mass index. For analysis purposes moderate, severe and very severe IDS-SR30 groups have been merged into (moderate to very severe). Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, educational level, smoking, alcohol consumption, physical activity, caloric intake and ethnicity. Models for waist circumference and visceral adipose tissue were additionally adjusted for total body fat. Number of individual with available data for each adiposity measures (BMI=6459, total body fat n=6428, waist circumference=6420, visceral adipose tissue n=2475).

Body fat measurements and depressive mood symptoms

The logistic regression analysis results of overall and abdominal adiposity measures and the individual 30 items of IDS-SR30 are shown in Figure 2 and fully reported Table S 5. We found that overall and abdominal adiposity measurements were significantly associated with 27 (BMI), 26 (total body fat), 14 (waist circumference), and 2 (visceral adipose tissue) of the 30 depressive mood symptoms. We ranked the ORs of the fully adjusted model (i.e., model2) of logistic regression of overall and abdominal measures and the individual items of IDS-SR30 from high to low (Table S 6). "Atypical" neurovegetative symptoms, such as hyperphagia, low energy level and physical exhaustion were consistently among top ranked symptoms across different measures of adiposity. Symptoms of problems falling asleep and early morning awakening showed no association with adiposity measures.

Figure 2. Results of logistics regression between adiposity measures and individual items of IDS-SR30 questionnaire (model 2)

DISCUSSION

This study examined the nature of the association between accurate measures of adiposity (i.e., total body fat and visceral adipose tissue) and depressive mood in a population-based study that consisted of 6459 middle-aged individuals. We found that especially total body fat, and to a lesser extent other measures of overall and abdominal adiposity, was positively associated with the depressive mood in a graded fashion; as the severity of obesity increases, the severity of depressive mood increases.

In this study, we were able to replicate the previously reported positive association between BMI and depressive mood [2, 3, 21]. However, the question remained whether this positive association is due to high body fat or high muscle mass. To answer this question, we investigated the association between total body fat as estimated by bio-impedance analysis and depressive mood. Previous studies that investigated the association between total body fat and depression were small. The presence of a positive association between total body fat and depression was observed only in women in a previous work that aimed to determine the sex-specific relationship between obesity and depression (n=67) [22]. In the current study, we were able to detect a positive association between total body fat and depressive mood both in men and women, which may imply that total body fat specifically plays a crucial role in relation to depression.

We also set out to examine whether abdominal adiposity contributes to the previously reported association between adiposity and depressive mood. Compiled evidence has indicated that waist circumference, which has been used as a proxy for visceral adiposity, is positively associated with depression [23]. Nonetheless, waist circumference does not discriminate between visceral adipose tissue and abdominal subcutaneous fat [23, 24]. A population-based study of well-functioning older participants [25] showed that depressive mood at baseline predicted an elevation of the visceral adipose tissue measured by the computed tomographic (CT) scanning after five years follow-up. In our analysis, we found a positive association between the measures of abdominal adiposity (both waist circumference and visceral adipose tissue) and depressive mood. Nonetheless, since abdominal adiposity can be an indicator for overall adiposity we adjusted the analysis for total body fat to estimate the specific association of abdominal fat. As it has been reported previously [24], we found that the association between visceral adipose tissue and depressive mood attenuated after taking into account the total body fat adjustment, which may indicate that total body fat is a large contributor to the association between adiposity and depression. Interestingly, we found that the pattern of the main results were similar when stratifying the analyses by sex. This suggests that, despite the established differences in adiposity and depression

prevalence across sex, the association between adiposity and depressive mood is consistent in men and women.

Depressive mood is a heterogeneous condition [26]. It has previously been suggested [10, 27] that adiposity related immune-metabolic dysregulations such as abnormal glucose, triglyceride, C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis-α (TN-α) concentrations are mainly associated with "atypical" neurovegetative symptoms of depression [28]. Using data from the NESDA cohort [12], it has been shown that among patients with a current diagnosis of MDD, higher leptin concentration in the blood (which directly associated with the adiposity level in the body) is associated with symptoms related to energy metabolism like hyperphagia, fatigability and physical exhaustion, independently from BMI. More recent evidence confirmed that the association between this phenotypic constellation, and adiposity and immuno-metabolic dysregulation markers (i.e., C-reactive protein (CRP) and leptin) extended down to the genetic level. Large collaborative genetic studies [29, 30] reported that subjects with a MDD diagnosis reporting hyperphagia or weight gain during the most severe depressive episode in their lifetime, carried a higher number of risk variants for immuno-metabolic traits such as obesity, C-reactive protein (CRP), leptin, and triglycerides dysregulation. In the present study, we demonstrated that both overall and abdominal adiposity were most strongly associated with the same cluster of depressive mood symptoms that relate to energy metabolism (i.e. hyperphagia, low energy level, and increased physical exhaustion) in addition to the more typical symptoms of depressive mood.

Biologically, depression is associated with imbalances in either the hypothalamic-pituitary-adrenal (HPA) axis, the immune system (inflammation), or the regulation of the metabolic pathways. Since these physiological systems are also highly interconnected, it is a challenging process to look at each one of them individually [3, 31]. Accumulation of adipose tissue above the normal levels is associated with low-grade inflammation, insulin resistance [32], leptin resistance [33], and imbalanced activity of the hypothalamic-pituitary-adrenal (HPA) axis [34] which are known to be directly or indirectly associated with depressive mood [35]. Previous studies suggested that the neuroendocrine signaling processes that regulate both mood and energy metabolism are strongly interconnected [36]. Leptin hormone stimulates the proopiomelanocortin (POMC) neuron in the nucleus of the hypothalamus that activates the transcription of the melanocortin peptides (i.e. α, β, and γ MSH, and Mc3r and Mc4r) [37]. These peptides have been suggested to be responsible for regulating energy intake and energy expenditure [38]. Common forms of obesity are thought to be associated with leptin resistance in the brain, blunting its anorexigenic effect and consequently disinhibiting feeding and energy storage despite increasing circulating leptin [39]. An impact of leptin on depression has been suggested by research on animal models [40,

41] indicating antidepressant-like effects of leptin, although exact underlying mechanisms remain unknown. It has been proposed [42] that alterations of the leptin–melanocortin pathway may impair not only its anorexigenic effect, leading to obesity, but also its effect on mood regulation, potentially leading to the development of depression. Furthermore, genome-wide association studies for both obesity and depression show an intersectional association between genes that show strong hits in both conditions, such as neural growth regulator 1 (*NEGR1*) and olfactomedin 4 (*OLFM4*). Noteworthy, these genes play a role in energy regulating mechanism by modulating the synaptic plasticity in brain areas essential for regulating both mood and appetite [3]. We could hypothesize that the impairment of energy homeostasis systems may represent the link that mechanistically connect adiposity with depressive mood. This mechanism may act in two, non-mutually exclusive, ways: as common underlying factor influencing the liability to both depression and obesity, or as mediating mechanisms in causal relationships between the two conditions.

Several additional mechanisms may explain the association between adiposity and depressive mood, including social and behavioral factors such as social rejection, exclusion and/or stigma [43]. An agent-based approach to study the effect of social rejection on depression found that individuals with obesity are more vulnerable to develop depression when obesity is less common in their social networks [44]. It is also possible that behavioral factors that define depressive mood such as low motivation, low energy level, physical inactivity and overconsumption of energy-dense food disturb the body homeostasis and lead to an accumulation of adiposity [36].

Some methodological aspects should be considered. The NEO study is a population-based study in which adiposity measures and depressive mood along with potential confounding factors where thoroughly phenotyped. However, the cross-sectional design of this study does not allow us to draw a conclusion about the directionality of associations. Second, although we adjusted for a large number of covariates in the models, based on the nature of observational studies, residual confounding may still be present. Third, the question of whether total body fat or abdominal fat is more important cannot be answered from this data. Fourth, the depressive mood was assessed only via the self-report IDS-SR30 that may introduce a misclassification of the participants with depressive mood. Nevertheless, this instruments has been extensively validated and used in previous research and the proportion of identified patients with depressive mood in the present study (~30%) is similar to the previous report in populations with obesity [45].

In conclusion, in this study we showed that in the general population overall and abdominal adiposity measures were positively associated with the depressive

mood. This association encompasses almost all depressive symptoms but was strongest for a specific cluster of ''atypical'' neurovegetative depressive symptoms that indicate a deformity in the energy metabolism and homeostasis pathways. Our results suggests that the energy homeostasis dysfunction could connect the mechanisms responsible for developing both adiposity and depressive mood, either as a common cause or in a mediating role. Future longitudinal and experimental studies that exploit the available '-omics' technologies, such as metabolomics and proteomics, are needed to fully elucidate the pathophysiological links that may connect adiposity and depression.

REFERENCES

1. Mathers, C.D. and D. Loncar, *Projections of global mortality and burden of disease from 2002 to 2030.* PLoS Med, 2006. **3**(11): p. e442.
2. de Wit, L., et al., *Depression and obesity: a meta-analysis of community-based studies.* Psychiatry Res, 2010. **178**(2): p. 230-5.
3. Milaneschi, Y., et al., *Depression and obesity: evidence of shared biological mechanisms.* Mol Psychiatry, 2018.
4. Delahanty, L.M., et al., *Psychological and behavioral correlates of baseline BMI in the diabetes prevention program (DPP).* Diabetes Care, 2002. **25**(11): p. 1992-8.
5. Heo, M., et al., *Depressive mood and obesity in US adults: comparison and moderation by sex, age, and race.* Int J Obes (Lond), 2006. **30**(3): p. 513-9.
6. Ohayon, M.M., *Epidemiology of depression and its treatment in the general population.* J Psychiatr Res, 2007. **41**(3-4): p. 207-13.
7. *Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee.* World Health Organ Tech Rep Ser, 1995. **854**: p. 1-452.
8. Camhi, S.M., et al., *The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: sex and race differences.* Obesity (Silver Spring), 2011. **19**(2): p. 402-8.
9. Despres, J.P., et al., *Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk.* Arterioscler Thromb Vasc Biol, 2008. **28**(6): p. 1039-49.
10. Lamers, F., et al., *Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression.* Mol Psychiatry, 2013. **18**(6): p. 692-9.
11. Lamers, F., et al., *Metabolic and inflammatory markers: associations with individual depressive symptoms.* Psychol Med, 2018. **48**(7): p. 1102-1110.
12. Milaneschi, Y., et al., *Leptin Dysregulation Is Specifically Associated With Major Depression With Atypical Features: Evidence for a Mechanism Connecting Obesity and Depression.* Biol Psychiatry, 2017. **81**(9): p. 807-814.
13. de Mutsert, R., et al., *The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection.* Eur J Epidemiol, 2013. **28**(6): p. 513-23.
14. van der Meer, R.W., et al., *Pioglitazone improves cardiac function and alters myocardial substrate metabolism without affecting cardiac triglyceride accumulation and high-energy phosphate metabolism in patients with well-controlled type 2 diabetes mellitus.* Circulation, 2009. **119**(15): p. 2069-77.
15. Rush, A.J., et al., *The Inventory of Depressive Symptomatology (IDS): psychometric properties.* Psychol Med, 1996. **26**(3): p. 477-86.
16. Wendel-Vos, G.C., et al., *Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity.* J Clin Epidemiol, 2003. **56**(12): p. 1163-9.

17. Siebelink, E., A. Geelen, and J.H. de Vries, *Self-reported energy intake by FFQ compared with actual energy intake to maintain body weight in 516 adults.* Br J Nutr, 2011. **106**(2): p. 274-81.

18. Korn, E.L. and B.I. Graubard, *Epidemiologic studies utilizing surveys: accounting for the sampling design.* Am J Public Health, 1991. **81**(9): p. 1166-73.

19. Lumley, T., *Analysis of Complex Survey Samples.* Journal of Statistical Software, 2004. **9**(8): p. 1-19.

20. Seidell, J.C. and C. Bouchard, *Visceral fat in relation to health: is it a major culprit or simply an innocent bystander?* Int J Obes Relat Metab Disord, 1997. **21**(8): p. 626-31.

21. Luppino, F.S., et al., *Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies.* Arch Gen Psychiatry, 2010. **67**(3): p. 220-9.

22. Li, L., et al., *Gender-Specific Relationship between Obesity and Major Depression.* Front Endocrinol (Lausanne), 2017. **8**: p. 292.

23. Hach, I., et al., *Associations between waist circumference and depressive disorders.* J Affect Disord, 2006. **92**(2-3): p. 305-8.

24. Everson-Rose, S.A., et al., *Depressive symptoms and increased visceral fat in middle-aged women.* Psychosom Med, 2009. **71**(4): p. 410-6.

25. Vogelzangs, N., et al., *Depressive symptoms and change in abdominal obesity in older persons.* Arch Gen Psychiatry, 2008. **65**(12): p. 1386-93.

26. Benazzi, F., *Various forms of depression.* Dialogues Clin Neurosci, 2006. **8**(2): p. 151-61.

27. Howren, M.B., D.M. Lamkin, and J. Suls, *Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis.* Psychosom Med, 2009. **71**(2): p. 171-86.

28. Novick, J.S., et al., *Clinical and demographic features of atypical depression in outpatients with major depressive disorder: preliminary findings from STAR*D.* J Clin Psychiatry, 2005. **66**(8): p. 1002-11.

29. Milaneschi, Y., et al., *Polygenic dissection of major depression clinical heterogeneity.* Mol Psychiatry, 2016. **21**(4): p. 516-22.

30. Milaneschi, Y., et al., *Genetic Association of Major Depression With Atypical Features and Obesity-Related Immunometabolic Dysregulations.* JAMA Psychiatry, 2017. **74**(12): p. 1214-1225.

31. Stetler, C. and G.E. Miller, *Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research.* Psychosom Med, 2011. **73**(2): p. 114-26.

32. Kahn, S.E., R.L. Hull, and K.M. Utzschneider, *Mechanisms linking obesity to insulin resistance and type 2 diabetes.* Nature, 2006. **444**(7121): p. 840-6.

33. Patel, S.B., et al., *Leptin: linking obesity, the metabolic syndrome, and cardiovascular disease.* Curr Hypertens Rep, 2008. **10**(2): p. 131-7.

34. Vicennati, V., et al., *Cross-talk between adipose tissue and the HPA axis in obesity and overt hypercortisolemic states.* Horm Mol Biol Clin Investig, 2014. **17**(2): p. 63-77.

35. Kaestner, F., et al., *Different activation patterns of proinflammatory cytokines in melancholic and non-melancholic major depression are associated with HPA axis activity.* J Affect Disord, 2005. **87**(2-3): p. 305-11.

36. Yu, Y.H., *Making sense of metabolic obesity and hedonic obesity.* J Diabetes, 2017. **9**(7): p. 656-666.

37. Millington, G.W., *The role of proopiomelanocortin (POMC) neurones in feeding behaviour.* Nutr Metab (Lond), 2007. **4**: p. 18.

38. van der Klaauw, A.A. and I.S. Farooqi, *The hunger genes: pathways to obesity.* Cell, 2015. **161**(1): p. 119-132.

39. Jequier, E., *Leptin signaling, adiposity, and energy balance.* Ann N Y Acad Sci, 2002. **967**: p. 379-88.

40. Garza, J.C., et al., *Leptin restores adult hippocampal neurogenesis in a chronic unpredictable stress model of depression and reverses glucocorticoid-induced inhibition of GSK-3beta/beta-catenin signaling.* Mol Psychiatry, 2012. **17**(8): p. 790-808.

41. Yamada, N., et al., *Impaired CNS leptin action is implicated in depression associated with obesity.* Endocrinology, 2011. **152**(7): p. 2634-43.

42. Lu, X.Y., *The leptin hypothesis of depression: a potential link between mood disorders and obesity?* Curr Opin Pharmacol, 2007. **7**(6): p. 648-52.

43. Slavich, G.M. and M.R. Irwin, *From stress to inflammation and major depressive disorder: a social signal transduction theory of depression.* Psychol Bull, 2014. **140**(3): p. 774-815.

44. Mooney, S.J. and A.M. El-Sayed, *Stigma and the etiology of depression among the obese: An agent-based exploration.* Soc Sci Med, 2016. **148**: p. 1-7.

45. Lin, H.Y., et al., *Psychiatric disorders of patients seeking obesity treatment.* BMC Psychiatry, 2013. **13**: p. 1.

SUPPLEMENTARY MATERIAL

Full version of supplementary materials can be found through the following link: https://ars.els-cdn.com/content/image/1-s2.0-S0306453019304147-mmc1.docx

Table S 5. Results of logistic regression between the adiposity measures and the individual items from the IDS-SR30 ranked based on their ORs from high to low. (Model 2)

	BMI	Total body fat	Waist circumference	Visceral adipose tissue
1	12. Increase in appetite (Hyperphagia)	12. Increase in appetite (Hyperphagia)	18. Thought of death or suicide	20. Low energy level (Fatigability)
2	20. Low energy level (Fatigability)	30. Physical exhaustion	23. Psychomotor retardation (Feeling slowed down)	30. Physical exhaustion
3	30. Physical exhaustion	20. Low energy level (Fatigability)	20. Low energy level (Fatigability)	18. Thought of death or suicide
4	14. Increased weight (Within the last two weeks)	14. Increased weight (Within the last two weeks)	12. Increase in appetite (Hyperphagia)	10. Diminished quality of mood
5	25. Having Aches and pains	25. Having Aches and pains	10. Diminished quality of mood	16. Self-criticism or blame
6	13. Decreased weight (Within the last two weeks)	13. Decreased weight (Within the last two weeks)	30. Physical exhaustion	23. Psychomotor retardation (Feeling slowed down)
7	21.Diminished capacity of pleasure or enjoyment	21.Diminished capacity of pleasure or enjoyment	08. Diminished reactivity of mood	15. Concentration / decision-making problems
8	19. Diminished interest in people and activity	19. Diminished interest in people and activity	16. Self-criticism or blame	17.Future pessimism
9	26. Having other bodily symptoms	26. Having other bodily symptoms	05. Feeling sad	12. Increase in appetite (Hyperphagia)
10	10. Diminished quality of mood	10. Diminished quality of mood	19. Diminished interest in people and activity	19. Diminished interest in people and activity