# Plasma levels of leptin and adiponectin and depressive symptoms in young adults

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ABSTRACT

Circulating levels of adipokines are known to be associated with depression. This study aimed to investigate a possible association between leptin, adiponectin and dimensional measures of depressive symptoms in young adults with and without psychiatric illness. Total plasma adiponectin and leptin levels were measured in 194 young adults seeking psychiatric ambulatory care and 57 healthy controls. Depressive symptoms were assessed using the Montgomery-Åsberg Depression Self-Rating Scale (MADRS-S). Analysis was performed on men and women separately. P-leptin levels were significantly elevated in patients compared with controls and correlated with total MADRS-S scores in the women. Women with P-leptin in the highest quartile reached a significantly higher MADRS-S score than women in the lowest quartile, but this difference disappeared after adjusting for body mass index (BMI) and antidepressant use. MADRS-S score was associated with P-leptin in female patients without antidepressant use, independently of BMI. There was no association between P-leptin levels and current major depression. P-adiponectin levels were not associated with depressive symptoms or current major depression. The findings indicate that P-leptin levels are associated with depressive symptom severity in young women; however, the association is linked to other factors, which challenges its usefulness as a biomarker for depression in clinical psychiatry.

## 1. Introduction

Emerging data indicate a pathophysiological link between inflammation, alterations in the hypothalamic-pituitary-adrenal (HPA) axis and depression, making immunologically active proteins important biomarker candidates (Dowlati et al., 2010; Miller et al., 2009; Miller and Raison, 2016).

Leptin is an adipocyte-derived hormone with pro-inflammatory and anorexigenic properties that is involved in the regulation of the HPA axis (Ahima and Osei, 2004; Bonnavion et al., 2015; Fantuzzi and Faggioni, 2000; Licinio et al., 2004). Leptin crosses the blood-brain barrier (BBB) through receptor-mediated transport (Banks et al., 1996; Caro et al., 1996; Schwartz et al., 1996) and leptin receptors are widely expressed in the human brain, including the hypothalamus and amygdala (Burguera et al., 2000). Cumulative evidence suggests an antidepressant effect by leptin in animal models (Hryhorczuk et al., 2013).

Adiponectin is an adipocyte-derived hormone with mostly anti-inflammatory properties (Matsuzawa et al., 2004; Ouchi and Walsh, 2007; Scherer et al., 1995; Yokota et al., 2000). This hormone is present in cerebrospinal fluid (CSF) and its receptors are expressed in the human pituitary, hypothalamus and hippocampus (Ebinuma et al., 2007; Kos et al., 2007; Kusminski et al., 2007; Neumeier et al., 2007; Psilopanagioti et al., 2009; Zhang et al., 2011). Adiponectin crosses the BBB in mice and rats and there is evidence indicating that it also transverses the BBB in humans (Kos et al., 2007). Intracerebroventricular injection of adiponectin decreases depressive-like behaviour in mice. Additionally, intracerebroventricular injection of an adiponectin neutralising antibody stimulates stress-induced depressive-like behaviour (Liu et al., 2012; Yau et al., 2014).

Studies showing an association between leptin and major depressive disorder (MDD) or depression severity are inconsistent (Carvalho et al., 2014; Hryhorczuk et al., 2013). Two studies describe a specific association between elevated leptin levels and MDD with atypical features (Gecici et al., 2005; Milaneschi et al., 2017). One study indicates that elevated leptin levels at delivery are a protective factor for the development of depressive symptoms postpartum (Skalkidou et al., 2009),
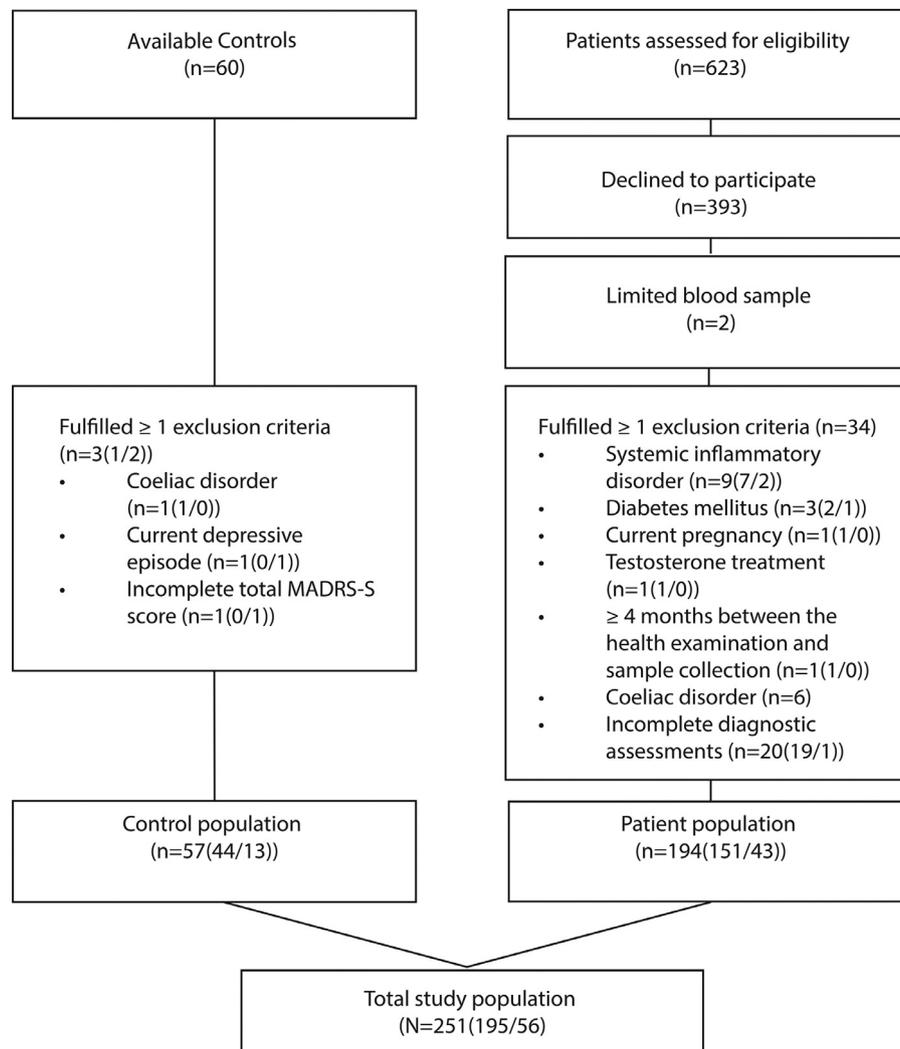
Fig. 1. Flowchart of exclusion criteria. Total (women/men).

whereas another suggests elevated leptin levels 24–48 h after delivery are a risk factor (Chen et al., 2016).

Most studies observe lower levels of adiponectin in serum (Diniz et al., 2012; Lehto et al., 2010; Shelton et al., 2015) and plasma (Cizza et al., 2010; Leo et al., 2006) in patients with MDD compared with controls but report conflicting results on the possible association between adiponectin levels and depression severity. One recent study reports elevated serum adiponectin in women with depressive symptoms 10 days postpartum (Yildiz et al., 2017).

To our knowledge no study has addressed the issue of dimensionality in depressive symptoms in relation to circulating levels of adiponectin and leptin in a general psychiatric population of young adults. Young adults are of interest in research on psychiatric illness given that most mental disorders have relatively early ages of onset (i.e. by the age of 24 years) with later onsets being mostly comorbid conditions (Kessler et al., 2005). Young adulthood is also a time of transition and mental disorders may be particularly detrimental for employment and education in this age group (Suvisaari et al., 2009). Early diagnostics and treatment of MDD is crucial in decreasing the risk of complications later in life (e.g., early cardiovascular disease) (Goldstein et al., 2015).

To assess the usefulness of leptin and adiponectin as biomarkers for depression in young adults we investigated to what extent circulating levels of leptin and adiponectin are associated with dimensional measures of depressive symptoms in young adults with and without current mental disorder.

## 2. Methods

### 2.1. "Uppsala Psychiatric Patient Samples" (UPP)

Data and samples used in this study were obtained from the patient cohort "Uppsala Psychiatric Patient Samples" (UPP). The UPP is an infrastructure for the collection of biological material from patients with psychiatric symptoms at the Department of General Psychiatry at Uppsala University Hospital, Sweden (Cunningham et al., 2017; Sundberg et al., 2016; Syk et al., 2017). The infrastructure was established in October 2012 and all consecutive new patients aged 18 to 25 years who received ambulatory care at the "Young Adults" section were asked to participate in the UPP. The patient data and samples in this study were gathered between 2012 and 2014.

Since 2013, individuals without previous or current contact as patients within psychiatry were recruited to the UPP from a pool of university students and personnel and included in a control cohort. The control data and samples comprising this study were collected between 2013 and 2015.

Participants in the UPP (both patients and controls) first underwent an initial clinical health examination at the time of inclusion. Blood pressure was measured while seated, weight was measured with a digital scale in kg and waist and hip circumferences were measured with the patient standing in light clothing. Body mass index (BMI) was calculated as weight in kgs divided by height in squared meters. The

participants returned for a second visit in which questionnaires on socio-demographics, medical history, heredity and current medication were answered in conjunction with blood sample collection.

Psychiatric diagnoses were assessed using the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria (Association, 2000). Patients were interviewed at the clinic, either by trained medical doctors or psychologists. The assessment was based on two meetings: at the first meeting, a clinical interview was performed and at the second a diagnostic interview, either the M.I.N.I.-International Neuropsychiatric Interview (M.I.N.I. 6.0) (Sheehan et al., 1998) or the Swedish version of the Structural Clinical Interview for DSM IV axis I disorders (SCID-I) (First et al., 1996). Diagnostic interviews were conducted to evaluate the criteria; however, the validity of the assessment was increased through the interviewers' previous clinical evaluations. After study initiation, an extra step was added to the study protocol, wherein the controls were interviewed with the diagnostic interview M.I.N.I. 6.0. Depressive symptoms were assessed in all participants with the Montgomery-Åsberg Depression Self-Rating Scale (MADRS-S) in parallel with blood sample collection (Mattila-Evenden et al., 1996). It is a self-rating 9-item scale assessing nine domains: mood, feelings of unease, sleep, appetite, ability to concentrate, initiative, emotional involvement, pessimism and zest for life. The items are rated on a Likert scale from 0 to 6 points and the total score ranges from 0 to 54 points, with higher scores indicating greater severity (Cunningham et al., 2011).

### 2.2. Study design and participants

The study was designed as a cross-sectional observational study. During the study period, 623 patients were invited to participate in the UPP and 230 agreed to participate, of whom 194 (84%) were included in this study. Of 60 available controls, 57 (95%) participated (see Fig 1 for details).

Exclusion criteria were cancer, systemic inflammatory disease, coeliac disorder, diabetes mellitus, treatment with testosterone, pregnancy or incomplete data or insufficient diagnostic assessments, or if ≥4 months had passed between the health examination and the blood sample collection. Controls were excluded if they had a current depressive episode. History of depression or insufficient diagnostic assessment with a structured interview did not serve as exclusion criteria for the controls. In total, 194 patients (151 females, 43 males) and 57 controls (44 females, 13 males) were included in the study. Thirty-six of the female controls and 12 of the male controls were interviewed with M.I.N.I. 6.0.

### 2.3. Blood sample collection and analysis

Whole blood was collected from non-fasting participants during office hours. Plasma was isolated and stored frozen at −80 °C at Uppsala Biobank. Total adiponectin and leptin were measured in duplicate with a solid phase two-site sandwich enzyme-linked immunsorbent assay (ELISA) (Mercodia AB, Uppsala, Sweden) in plasma according to the manufacturer's instructions, with a deviation of use of lower sample volume (10 µl for adiponectin and 10 µl and 25 µl for leptin) for sample dilution. Assay sensitivity was 1.25 ng/mL for adiponectin and 0.05 ng/mL for leptin. Analysis was performed on two occasions ($t_1$ and $t_2$). At $t_1$, blood samples collected from patients were analysed; at $t_2$, blood samples collected from controls were analysed. The ELISA sensitivity analysis for P-leptin had a cut-off value at 1.05 ng/L at $t_1$ and 0.09 at $t_2$. Values below the cut-off levels were analysed as null. P-leptin was below the cut-off value for three patients at $t_1$ and five controls at $t_2$. The total assay mean coefficient of variation was 5.6% for adiponectin and 5.0% for leptin. For two individuals, a limited sample prevented analyses at $t_1$.

### 2.4. Ethics

Ethics approval was obtained from the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2012/081, 2012/081/1, 2012/081/2 and 2013/219). Fully informed and written consent were obtained from each participant. Patients were given both written and verbal information about the study and seemed to understand the information and appreciate the reasonably foreseeable consequences of a decision to participate or not to participate. We have also monitored the patients' response to participation in research, which was overwhelmingly positive (Cunningham et al., 2017).

### 2.5. Statistics

Data were analysed using IBM SPSS Statistics version 21 software. Statistical significance was defined as $p < 0.05$. Data were regarded as normally distributed if the following conditions were met: skewness divided by the standard error of skewness between ± 2 and visually estimated normal distribution (histogram, box-plot). The total MADRS-S scores were normally distributed. The waist-to-hip ratio was normally distributed for the women but not for the men. BMI, P-leptin and P-adiponectin were not normally distributed. Categorical comparisons were calculated using Chi-square tests or Fisher's exact test when applicable. Spearman's correlation was used to analyse the relationship between continuous variables and the Mann-Whitney test was performed to compare differences between two groups when the dependent variable was continous or ordinal. A Kruskal Wallis test was conducted to evaluate differences when more than two groups were compared.

A generalized linear model for quartiles of P-leptin in relation to total MADRS-S scores was carried out first without and then with the inclusion of potential confounding factors (BMI and antidepressants). As a subanalysis, BMI was replaced as a predictor by the waist-to-hip ratio. BMI was chosen for the primary analysis because BMI was available for a larger sample than the waist-to-hip ratio. Smoking was not included in the analysis because of missing data and other variables (e.g., age, thyroid disorder, hormonal contraceptives, mood stabilisers/anti-psychotics and alcohol addiction) were considered as potential confounders but not included in the analysis because of the absence of significant correlations with total MADRS-S scores or P-leptin in a Spearman's bivariate analysis.

## 3. Results

### 3.1. Participant characteristics

Participant characteristics are described in Table 1. There was an overrepresentation of women ($n = 195$) compared with men ($n = 56$) in the population. Women and men did not differ in total MADRS-S scores or BMI. No difference was noted in BMI between patients and controls but the waist-to-hip ratio was higher in patients. The patients were younger and female patients had a higher prevalence of smoking than female controls. There was no difference in P-leptin or P-adiponectin between female smokers and female non-smokers where data was available ($n = 176$), but the smokers had higher MADRS-S scores ($p < 0.01$).

### 3.2. Elevated P-leptin and P-adiponectin in women compared with men

P-leptin and P-adiponectin were elevated in women when compared with men ($p < 0.01$). Therefore, subsequent analyses were performed on women and men separately. P-leptin levels were elevated in patients compared with controls in both women ($p = 0.02$) and men ($p = 0.03$). No significant difference was observed in P-adiponectin between patients and controls (Table 1).

**Table 1**
Basic participant characteristics and clinical data.

| | Women Controls ($n = 44$) | Patients ($n = 151$) | *P*-value | Men Controls ($n = 13$) | Patients ($n = 43$) | *P*-value |
|---|---|---|---|---|---|---|
| **Basic characteristics** | | | | | | |
| Age (years) (Md (Q1, Q3)) | 22 (20; 24) | 21 (19; 23) | ** | 24 (22; 26) | 21 (19; 23) | ** |
| Current smoker (*n* (%)) [a] | 1 (2) | 49 (32) | ** | 1 (8) | 3 (7) | – |
| **Psychiatric characteristics (*n* (%))** | | | | | | |
| Antidepressants [b] | 3 (7) | 70 (46) | ** | 0 (0) | 22 (51) | ** |
| Mood stabilisers and/or anti-psychotics [c] | 0 (0) | 44 (29) | ns | 0 (0) | 13 (30) | ns |
| Any anxiety disorder [d] | 1 (2) | 97 (64) | ** | 0 (0) | 27 (63) | ** |
| Current MDD | 0 (0) | 66 (44) | ** | 0 (0) | 19 (44) | ** |
| Life-time history of depressive episode | 3 (7) | 136 (90) | ** | 2 (15) | 32 (74) | ** |
| Bipolar Disorder (I, II,UNS) | 0 (0) | 26 (17) | ** | 0 (0) | 5 (12) | ns |
| Alcohol and/or substance addiction [e] | 1 (2) | 15 (10) | ns | 0 (0) | 4 (9) | ns |
| Bulimia nervosa [f] | 0 (0) | 15 (10) | * | 0 (0) | 1 (2) | ns |
| Anorexia nervosa [f] | 0 (0) | 3 (2) | ns | 0 (0) | 0 (0) | – |
| Other diagnosis | 1[g](2) | 5 (3) | ns | 0 (0) | 2 (5) | ns |
| MADRS-S total score (Md (Q1, Q3)) | 5 (2; 7) | 24 (17; 30) | ** | 6 (3; 11) | 22 (11; 29) | ** |
| **Metabolic status (Md (Q1, Q3))** | | | | | | |
| BMI (kg/m$^2$) [h] | 22.4 (20.2; 23.7) | 22.6 (20.3; 26.2) | ns | 22.5 (21.8; 24.8) | 22.5 (20.4; 25.5) | ns |
| Waist-to-hip ratio [i] | 0.71 (0.68; 0.75) | 0.74 (0.72; 0.79) | ** | 0.80 (078; 082) | 0.83 (0.80; 0.87) | * |
| P-leptin (ng/ml) | 13.08 (9.20; 20.80) | 18.41 (10.15; 32.43) | * | 1.78 (0.63; 4.26) | 3.88 (2.17; 8.27) | * |
| P-adiponectin (µg/ml) | 10.40 (8.87; 12.46) | 10.48 (8.41; 12.72) | ns | 7.86 (5.65; 8.94) | 8.28 (6.18; 9.32) | ns |

*Significant at the <0.05 level; **Significant at the <0.01 level; ns = Nonsignificant; Q1 = 25th percentile; Q3 = 75th percentile; Md = Median;
[a] Missing data = 15 female patients, 4 female controls, 39 male patients and 8 male controls;
[b] SSRI, SNRI, mirtazapine, tricyclic antidepressants and/or bupropion;
[c] lamotrigine, lithium, quetiapine, haloperidol and/or olanzapine;
[d] Missing data = 7 female patients;
[e] Missing data = 7 female patients and 1 male patient;
[f] Missing data = 8 female patients and 1 male patient;
[g] Anxiety UNS;
[h] Missing data = 7 female patients;
[i] Missing data = 14 female patients, 2 female controls and 4 male patients.

### 3.3. P-leptin levels correlate with BMI and the waist-to-hip ratio

BMI correlated with P-leptin in both women ($r = 0.66$) and men ($r = 0.49$), $ps < 0.01$ and inversely correlated with P-adiponectin in women but not in men ($r = -0.28$, $p < 0.01$ vs. $-0.19$, $p = 0.15$). There was no association between total MADRS-S scores and BMI. The waist-to-hip ratio correlated with P-leptin in both women ($r = 0.31$) and men ($r = 0.39$), $ps < 0.01$ and inversely correlated with P-adiponectin in women but not in men ($r = -0.23$, $p < 0.01$ vs. $-0.041$, $p = 0.77$).

### 3.4. Positive association between P-leptin levels and MADRS-S scores in women

P-leptin levels were positively correlated with total MADRS-S scores in women ($r = 0.18$, $p = 0.01$) but not in men. To gain a better visualisation of the skewed P-leptin values P-leptin levels were divided into quartiles in the female study population. Fig 2 illustrates elevated MADRS-S scores in the quartile with the highest P-leptin levels ($\geq 28.87$ ng/ml).

Table 2 presents a generalized linear model showing that women (patients and controls) with P-leptin in the highest quartile reported approximately a six-point higher MADRS-S score than women in the lowest quartile (P-leptin $\leq 9.99$ ng/ml, $p < 0.01$). However, in a second model the difference between the groups was no longer significant after controlling for BMI and the use of antidepressants. The model remained statistically significant when BMI and the use of antidepressants were controlled for separately. Replacing BMI with the waist-to-hip ratio did not affect the statistical significance of these results. When a generalized linear model was performed on the female patient population without controls ($n = 151$), the same pattern appeared, with the women in the highest quartile (P-leptin $\geq 32.44$ ng/ml) reporting significantly higher total MADRS-S scores than those in the lowest quartile
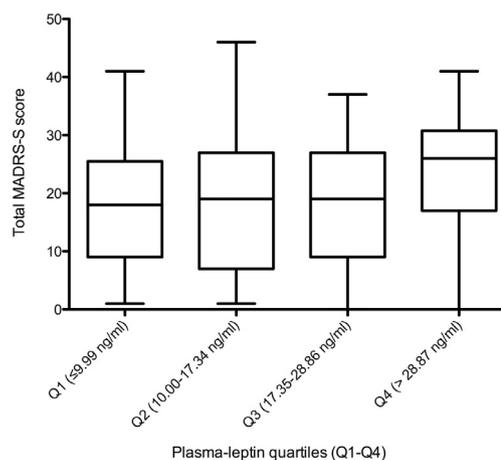


**Fig. 2.** Boxplots illustrating differences in total MADRS-S scores between the quartiles of P-leptin in the total female study population.

(P-leptin $\leq 10.15$ ng/ml, $p < 0.05$). Again, the difference was not significant in a second model ($n = 144$) that controlled for BMI and the use of antidepressants. The model was still statistically significant when only the use of antidepressants was controlled for but was no longer statistically significant when BMI was included in the model. Subgroup analysis of women with BMI < 25 ($n = 142$) did not change the results (data not shown).

To further explore the association between MADRS-S and P-leptin a subgroup analysis was performed on female patients without antidepressant use using a generalized linear model with the MADRS-S score as the dependent variable. In this subgroup a correlation was found between total MADRS-S scores and P-leptin levels when controlling for BMI ($n = 79$, $B = 0.17$, $p < 0.02$). Using a generalized linear model, we observed no association between MADRS-S scores and

**Table 2**
**Generalized linear model for the total MADRS-S score and P-leptin levels in the female study population (Model 1, $N$ = 195).** The association between high P-leptin and high MADRS-S scores was not significant after inclusion of BMI and antidepressants in the analysis (Model 2, $n$ = 188).

| | MADRS-S score | | | |
| | Model 1 B (95% CI) | *P*-value | Model 2 B (95% CI) | *P*-value |
|---|---|---|---|---|
| **P-leptin: 1st quartile** compared with 4th quartile | −6.12** (−10.22- −2.02) | <0.01 | −5.06 (−10.13 to 0.024) | 0.05 |
| **P-leptin: 2nd quartile** compared with 4th quartile | −5.26* (−9.36- −1.16) | 0.01 | −3.46 (−8.21 to 1.29) | 0.15 |
| **P-leptin: 3rd quartile** compared with 4th quartile | −5.24* (−9.34- −1.16) | 0.01 | −3.99 (−8.57 to 0.58) | 0.09 |
| **BMI** | | | 0.113 (−0.26 to 0.48) | 0.55 |
| **Antidepressants**[a] | | | 4.25** (1.14 to 7.36) | <0.01 |

* $p < 0.05$;
** $p < 0.01$; P-leptin levels: 1st quartile: ≤9.99 ng/ml; 2nd quartile: 10.00–17.34 ng/ml; 3rd quartile: 17.35–28.86 ng/ml; 4th quartile: ≥28.87 ng/ml;
[a] SSRI, SNRI, mirtazapine, tricyclic antidepressants and/or bupropion.

P-leptin when controlling for BMI in female patients currently using antidepressants ($n$ = 65).

### 3.5. Post-hoc analysis of P-leptin levels in relation to DSM-IV diagnostic groups

A post-hoc analysis of P-leptin levels in relation to DSM-IV diagnostic groups revealed that female patients with bipolar depression had elevated P-leptin values when compared with controls ($p$ = 0.01). This difference did not remain significant after controlling for BMI in a generalized linear model with a gamma distribution. P-leptin levels did not differ between controls and patients with current MDD. Treatment with mood stabilisers or anti-psychotics (lamotrigine, olanzapine, haloperidol, quetiapine or lithium) was not associated with P-leptin levels.

### 3.6. No association between P-adiponectin and depressive symptom severity

P-adiponectin was not correlated with total MADRS-S scores in women or men and there was no difference in total MADRS-S scores between quartiles of P-adiponectin in the female study population. P-adiponectin levels did not differ between controls and patients with current MDD.

## 4. Discussion

Analysis of plasma levels of leptin in young adults as regards dimensional measures of depressive symptoms revealed a positive association between P-leptin levels and self-reported depressive symptoms in women. Additionally, no relationship was found between plasma levels of adiponectin and degree of depressive symptoms. Importantly, these findings reflect a clinically relevant population in the sense that a high proportion of new patients have been prescribed antidepressant treatment before referral to specialist psychiatric care.

Results of previous studies are conflicting, with some describing a negative association and others a positive association between leptin and depression (Carvalho et al., 2014; Chen et al., 2016; Hryhorczuk et al., 2013; Morris et al., 2012; Skalkidou et al., 2009). A recent meta-analysis suggests that this discrepancy might partly be caused by the

effects of BMI and differences in BMI between controls and patients with MDD (Carvalho et al., 2014). Age or inclusion of patients with different subtypes of MDD might also contribute to diverse results between studies (Gecici et al., 2005; Hryhorczuk et al., 2013; Milaneschi et al., 2017). In our study the positive association between P-leptin and the severity of depressive symptoms in a population with mostly mild to moderate depressive symptom severity is in line with the results from the meta-analysis by Carvalho et al. describing higher peripheral leptin levels in participants with mild to moderate MDD compared with controls but no significant difference between controls and individuals with severe depression (Carvalho et al., 2014).

Our results are also consistent with Esel et al.'s study that reported a positive correlation between MADRS scores and P-leptin levels only in female patients with MDD, but not in male patients (Esel et al., 2005). Given that many studies mix male and female study participants, a sex difference in the association between P-leptin and depression might partly explain the contradictory results in the literature (Esel et al., 2005; Hafner et al., 2012; Rubin et al., 2002). Peripheral leptin values have been shown to correlate with C-reactive protein (CRP) in women (Samara et al., 2010) and, hypothetically, may be related to inflammation-induced changes in mood and behaviour more frequently seen in women (Moieni et al., 2015). However, considering the limited size of the male study population and that P-leptin levels were elevated in male patients compared with controls, the lack of association between P-leptin and depressive symptoms in males should be interpreted with caution.

The association between MADRS-S scores and P-leptin did not remain significant when BMI and antidepressants were controlled for in the analysis. However, there was a significant association, independent of BMI, between MADRS-S and P-leptin in the female patients without use of antidepressants. This finding is consistent with the Esel et al. study as it describes a positive association in drug-free women with MDD before and after controlling for BMI as a covariate (Esel et al., 2005). Our results suggest that the positive association might be clinically relevant only for patients who have yet to begin treatment with antidepressants. One possible explanation for these findings would be that some antidepressants increase P-leptin levels, which has previously been described in a few longitudinal studies (Esel et al., 2005; Schilling et al., 2013).

Previous studies suggest that the association between leptin and depressive symptoms is modulated by abdominal adiposity (Milaneschi et al., 2014; Morris et al., 2012) Although this was not directly adressed in the study, a close link was observed between leptin levels, depressive symptoms and BMI.

In animal models leptin has an antidepressant effect (Hryhorczuk et al., 2013). That we still see a positive association between severity of depressive symptoms and leptin levels might be explained by variations in leptin sensitivity related to adiposity. This speculation is in line with studies suggesting that low leptin biological signalling is associated with increased risk of depressive symptoms (Hryhorczuk et al., 2013; Milaneschi et al., 2014). That leptin resistance might be a possible treatment target in obese patients with depression is supported by a recent study indicating that fluoxetine induces leptin sensitivity via brain-derived neurotrophic factor (BDNF) in mice (Scabia et al., 2018).

Previous work on adiponectin and depression can be divided into two camps: one with no differences found between depressed patients and controls and the other with lower levels in patients with MDD. Carvalho et al.'s meta-analysis revealed that peripheral adiponectin levels were significantly lower in MDD patients than in controls when assayed with radioimmunoassay (RIA), but not with ELISA (Carvalho et al., 2014). This finding could possibly explain the results of our study in that adiponectin was measured with ELISA. Another possible explanation of our results is that adiponectin levels might be dependent on disease progress (Jeong et al., 2012). Regrettably, because of lack of data on disease duration, P-adiponectin levels could not be

compared between patients with new onset MDD and chronic MDD.

The passage of adiponectin across the BBB has not yet been proven in humans, but the reports of some studies indicate that adiponectin does traverse the BBB (Ebinuma et al., 2007; Kos et al., 2007; Kusminski et al., 2007; Neumeier et al., 2007; Psilopanagioti et al., 2009; Yau et al., 2014; Zhang et al., 2011). However, even if adiponectin crosses the BBB, total adiponectin concentration in plasma might not be a good representation of the concentration of different adiponectin isoforms in plasma or CSF. Adiponectin circulates in human plasma in multiple isoforms: high, medium and low molecular weight forms (Kadowaki and Yamauchi, 2005). High molecular weight adiponectin does not seem to cross the BBB and low molecular weight and medium molecular weight adiponectin concentrations remain mostly stable in CSF in obese mice even when total peripheral adiponectin is decreased (Kadowaki et al., 2008). If there is an association between depression and just one of the adiponectin isoforms in plasma or CSF, it might not have been detected in this study given that only total plasma adiponectin was measured.

This study differs from earlier work in some important ways. First, our analysis is conducted on a comparatively large general psychiatric population of young adults in ambulatory care without selection based on DSM-IV diagnosis criteria. An argument for this method can be that a subanalysis of patients based on DSM-IV diagnoses revealed no significant differences between diagnosis groups after controlling for BMI. In addition, most patients have a lifetime experience of depression and comorbidity is common. That there was no significant difference in P-leptin between controls and patients with MDD could indicate that a potential association between P-leptin and depressive symptoms might not be specific to MDD or to the typical subtype of MDD. Second, data analysis based on depressive symptoms combined both controls and patients and thereby allowed for a much larger dimensional range.

A limitation of this study is that it was conducted on non-fasting blood samples collected during office hours. However, although peripheral adiponectin and leptin levels have diurnal variation, one study with repeated measures indicates that they are relatively stable during the day (Cizza et al., 2010). Still, leptin levels are influenced by sleep patterns and eating behaviour, which were not controlled in this study (Farr et al., 2015). There was no association between P-leptin levels and mood stabilising treatment or antipsychotics in our study population, but it is possible that this lack of association is due to the pooling together of medications with different pharmacological mechanisms. In fact, previous studies have described an association between leptin concentration and antipsychotics (Potvin et al., 2015).The MADRS-S is limited in that it does not measure increased need of sleep and increased appetite. Therefore, atypical features of depression were not evaluated. The range of MADRS-S scores satisfactorily covers the bottom and middle range of values. However, only patients receiving outpatient care were included, making it difficult to generalise the results to an inpatient care population. Because of the cross-sectional study design, no conclusions can be drawn about the causality of the association between P-leptin and depressive symptoms. Because of missing data, smoking status was not included in the multivariate analyses. This exclusion might be a limitation as some studies have reported decreased adiponectin levels in current smokers (Kotani et al., 2012). The small size of the male study population influences generalisation of conclusion, i.e. the size was too small to perform subgroup analyses for the men. One possible reason for the small number of male controls is selection bias. However, for the male patients, a more likely reason is the patient configuration of the young adult psychiatric outpatients in Uppsala, Sweden. Twenty-two per cent of the patients and 23% of the controls in this study were men, which correspond well with the expected percentage of young men seeking ambulatory psychiatric care in Uppsala (20%) (Ramirez et al., 2009).

Our findings indicate that P-leptin is associated with the severity of depressive symptoms in young women, but the effects of BMI and the use of antidepressants might limit its usefulness as a clinical biomarker for depression. Moreover, we report that total P-adiponectin was not associated with the severity of depressive symptoms or current MDD in young adults.

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