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Problematic eating behaviours, changes in appetite, and weight gain in Major Depressive Disorder: The role of leptin

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Abstract

Background: Appetite and weight changes are core symptoms of Major Depressive Disorder (MDD), and those with MDD are at increased risk of obesity, cardiovascular disease and metabolic disorders. Leptin promotes satiety, with leptin dysregulation and resistance noted in obesity. However, the role of leptin in weight changes in MDD is not established. This study investigates leptin levels in relation to appetite and weight changes and problematic eating behaviours in MDD. Methods: Plasma leptin levels, psychopathology and biometrics were compared between participants meeting DSM-5 diagnostic criteria for MDD (n = 63) and healthy controls (n = 60). Depressed participants were also subcategorised according to increased, decreased or unchanged appetite and weight. The Dutch Eating Behaviour Questionnaire and Yale Food Addiction Scale were examined in a subset of participants with MDD. Results: Females with increased appetite/weight had higher leptin levels than those with stable or reduced appetite/weight, however males showed the opposite effect. Leptin levels were positively correlated with problematic eating behaviours. One quarter of the depressed subset, all females, met the Yale criteria for food addiction, approximately double the rates reported in general community samples. Limitations: The study is limited by a cross sectional design and a small sample size in the subset analysis of eating behaviours. Conclusions: The results provide new information about associations between leptin, sex-specific weight and appetite changes and problematic eating behaviours, which may be risk factors for cardiovascular and metabolic diseases in MDD, particularly in females. Future longitudinal research investigating leptin as a risk factor for weight gain in MDD is warranted, and may lead to early interventions aimed at preventing weight gain in at-risk individuals.

Keywords

eating, major, leptin, role, problematic, gain, weight, disorder:, appetite, depressive, changes, behaviours

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Problematic eating behaviours, changes in appetite, and weight gain in Major Depressive Disorder: The role of leptin.

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iii. Contributors

JM was involved in data collection, data and statistical analysis and manuscript preparation. ST and TL were involved in study design, data collection, data analysis and manuscript editing. NP and CD were involved in study design as well as editing of the final manuscript.

iv. Conflict of Interest

The authors declare no potential conflicts of interest.

v. Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Abstract:

Background: Appetite and weight changes are core symptoms of Major Depressive Disorder (MDD), and those with MDD are at increased risk of obesity, cardiovascular disease and metabolic disorders. Leptin promotes satiety, with leptin dysregulation and resistance noted in obesity. However, the role of leptin in weight changes in MDD is not established. This study investigates leptin levels in relation to appetite and weight changes and problematic eating behaviours in MDD.

Methods: Plasma leptin levels, psychopathology and biometrics were compared between participants meeting DSM-5 diagnostic criteria for MDD ($n = 63$) and healthy controls ($n = 60$). Depressed participants were also sub-categorised according to increased, decreased or unchanged appetite and weight. The Dutch Eating Behaviour Questionnaire and Yale Food Addiction Scale were examined in a subset of participants with MDD.

Results: Females with increased appetite/weight had higher leptin levels than those with stable or reduced appetite/weight, however males showed the opposite effect. Leptin levels were positively correlated with problematic eating behaviours. One quarter of the depressed subset, all females, met the Yale criteria for food addiction, approximately double the rates reported in general community samples.

Limitations: The study is limited by a cross sectional design and a small sample size in the subset analysis of eating behaviours.

Conclusions: The results provide new information about associations between leptin, sex-specific weight and appetite changes and problematic eating behaviours, which may be risk factors for cardiovascular and metabolic diseases in MDD, particularly in females. Future longitudinal research investigating leptin as a risk factor for weight gain in MDD is warranted, and may lead to early interventions aimed at preventing weight gain in at-risk individuals.

Keywords: leptin, Major Depressive Disorder, appetite, weight gain, obesity, food addiction

1. Introduction:

The global prevalence of Major Depressive Disorder (MDD) is rising annually, with this rise currently being attributed to increasing stress, endocrine dysfunction, modern lifestyle characteristics and dietary patterns (Hidaka, 2012). Altered eating behaviours, and appetite and weight dysregulation, are central diagnostic criteria of MDD (American Psychiatric Association, 2013). MDD is a risk factor for obesity, cardiovascular disease and metabolic syndrome (Cassano & Fava, 2002; Penninx et al., 2013), with a key risk factor being increased appetite; which can occur in MDD (American Psychiatric Association, 2013). Identifying biological and behavioural pathways between MDD and changes in appetite and weight could improve interventions. The hormone leptin is relevant due to its relationship with adiposity and role in satiety, however its relationship to MDD-related weight changes is not properly understood.

There are bidirectional influences between MDD, appetite and weight dysregulation, as MDD increases the risk of becoming obese, and obese individuals are at an increased risk of developing MDD (Kloiber et al., 2007; Luppino et al., 2010). However, depressed individuals may experience either increases or decreases in their appetite and/or weight (e.g. Li et al., 2014; Paans et al., 2017); therefore, it is important to consider individual depressive symptom profiles in research relating to health risks. Increased appetite and weight gain are features of atypical MDD, a sub-type of MDD further characterised by hypersomnia, psychomotor slowing, increased mood reactivity and sensitivity to interpersonal rejection (American Psychiatric Association, 2013). Atypical MDD is further associated with higher body mass index (BMI; Lassere et al., 2014), higher instances of metabolic syndrome (Lamers, Beekman, van Hemert, Schoevers & Penninx, 2016b) and increased endocrine dysregulation (e.g. Gecici et al., 2005; Lamers et al., 2016a; Milaneschi et al., 2017). There are also indications that weight gain and increased appetite, while previously referred to as ‘atypical’, are increasingly being identified as a ‘typical’ symptom of MDD (Privitera,

Misenheimer & Doraiswamy, 2013). Additionally, a large epidemiological survey indicated that the prevalence of MDD with atypical features was almost 40% higher than that of MDD without atypical features (Blanco et al., 2012). This apparent rise in MDD with weight gain may be associated with the increase of comfort foods in the environment (those high in fat and sugar), which people in emotional distress may seek out (Privitera et al., 2013).

Problematic eating behaviours have also been noted in MDD, which are commonly measured using the Dutch Eating Behaviours Questionnaire (DEBQ; van Strien et al., 1986). These include *Emotional eating*, or increasing food intake in response to negative emotions as a form of coping mechanism; *External eating*, or increased food intake in response to external food cues, including the sight and smell of food; and *Restrained eating*, or deliberately restricting food intake to lose weight or prevent weight gain (van Strien et al., 2016). More severe depressive symptoms are associated with higher emotional eating (van Strien et al., 2016), increased carbohydrate cravings (Christensen & Pettijohn, 2001), increased consumption of energy-dense foods in response to emotional distress (Konttinen et al., 2010) and increased food intake in response to internal and external food cues (Sevincer et al., 2017). Restrictive eating behaviours, and reduced food intake, have also been linked to depressive symptoms in previous studies (Polivy et al., 1978; Sevincer et al., 2017).

Another approach to understanding overeating is the concept of food addiction, which can be measured using the Yale Food Addiction Scale (YFAS; Gearhardt et al., 2009). It has been proposed that food addiction forms part of a continuum consisting of varying degrees of overeating behaviours that range from normal eating patterns to obesity (Piccinni et al., 2015). Food addiction is also associated with depressed mood, with one study reporting that obese individuals who met the YFAS criteria for food addiction displayed more severe depressive symptoms (Gearhardt et al., 2012). The prevalence of food addiction ranges from 5-10% in the general population, and 15-25% in obese individuals (Meule & Gearhardt, 2014). The preference for palatable foods, including those high in sugar, fat or carbohydrates

during periods of emotional distress (Lutter & Nestler, 2009; Hoch et al., 2015) has been attributed to their ability to reduce the psychological and physiological impact of stress (e.g. Dallman et al., 2003; Ulrich-Lai, 2016) and activate dopamine-based neural reward pathways (Gearhardt et al., 2011; Volkow et al., 2012), which can result in addiction-like behaviours; similar to alcohol or other psychoactive substances (e.g. Gearhardt et al., 2009; Piccinni et al., 2015). Food addiction is not yet recognised as a formal diagnosable disorder, and is currently defined as a substance-use disorder in the DSM-5 (American Psychiatric Association, 2013); however little is known about the relationships between addictive eating behaviours, leptin and MDD.

Leptin is a peptide hormone encoded by the *ob* gene secreted by adipocyte cells, with a critical role in regulating adipose tissue mass and energy balance as part of homeostasis (Lu, 2007). It has a fundamental role as an appetite suppressant during times of excess food consumption (Elmquist et al., 1998; Trayhurn et al., 1999), and is involved in weight regulation, where plasma leptin levels are released in proportion to adipose tissue mass (Maffei et al., 1995). However, although subcutaneous injection of leptin in lean and obese individuals may lead to decreased food intake and moderate weight loss (Heymsfield et al., 1999), the use of leptin as a long-term weight loss strategy has been unsuccessful (Halaas et al., 1997; Widdowson et al., 1997; Heymsfield et al., 1999; Levin & Dunn-Meynell, 2002). A possible explanation for this is leptin resistance, which is characterised by high leptin levels but decreased leptin sensitivity (e.g. Pan et al., 2014). Leptin resistance has been proposed as a mechanism in the pathogenesis of obesity (Zigman & Elmquist, 2003; Ozsoy et al., 2014), with obese animals and humans being noted to have naturally elevated levels of leptin in the absence of food intake (e.g. Maffei et al., 1995).

Leptin also moderates stress responses induced by the hypothalamic-pituitary-adrenal (HPA) axis. Leptin secretion has been demonstrated to inhibit corticosteroid production, and thereby suppressing stress adaptation responses (Bornstein et al., 1997; Roubos et al., 2012).

Failure of the HPA axis to execute appropriate stress responses may lead to the development of mental disorders such as MDD and anxiety (e.g. Blackburn-Munro & Blackburn-Munro, 2001). In animal studies, chronic stress decreases plasma leptin levels (Lu et al., 2006) and insufficient circulating leptin is associated with MDD-like behaviours (e.g. Ge et al., 2013; Liu et al., 2017). Administration of leptin to rats after laboratory stressors reversed MDD-like behaviour; suggesting that leptin may also have antidepressant like efficacy (Kim et al., 2006; Hirano, Miyata & Kamei, 2007). The relationship between leptin and stress, including symptom severity, remains relatively unexplored, particularly in the context of MDD where increased stress is a key feature of the condition (American Psychiatric Association, 2013).

Human studies comparing leptin levels in MDD have found inconsistent results, with either lower (e.g. Kraus et al., 2001; Westling et al., 2004; Atmaca et al., 2003) or elevated (e.g. Antonijevic et al., 1998; Jiménez et al., 2009; Morris et al., 2012) leptin levels overall between depressed and non-depressed individuals. In contrast, several studies (e.g. Häfner et al., 2012; Ozsoy et al., 2014) have identified no difference in leptin levels between depressed and non-depressed individuals; in some cases, even in the presence of appetite loss (Deuschle et al., 1996). No overall difference in leptin levels in individuals with MDD compared to controls was further supported by a recent large scale meta-analysis by Carvalho et al. (2014), however there were inconsistent results across the studies included. Studies comparing leptin levels across subtypes of MDD have also demonstrated inconsistent results. Individuals with typical/melancholic MDD often demonstrate lower leptin levels compared to controls and individuals with atypical MDD, with the latter demonstrating consistently higher leptin levels overall (e.g. Gecici et al., 2005; Lamers et al., 2016a, Milaneschi et al. 2017). The variability of these results may be due to heterogeneity in appetite and weight change symptoms in MDD, and subsequent alterations in leptin levels. Further, differences in leptin levels between subtypes of MDD with increased or decreased appetite/weight may have been

masked in previous research, as symptom subtypes are frequently combined in previous studies.

Further, the methods of classifying atypical MDD symptoms have differed between studies. Some studies have used solely DSM based criteria (e.g. Gecici et al., 2005; Lassere et al., 2014), and others have used latent class analysis based on a combination of questionnaire and diagnostic interview responses. The questionnaires and interviews used to measure depressive symptoms for latent class analysis vary, with measures such as the Inventory of Depressive Symptoms (IDS-SR; Rush et al., 1996), Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) and the Composite International Diagnostic Interview (CIDI; World Health Organisation, 1997) being used (e.g. Lamers et al., 2016a, 2016b; Milaneschi et al., 2017). However, it has been noted that latent class analysis classifications of MDD symptoms do not align completely with DSM-based criteria (Lamers et al., 2016a; 2016b). Therefore, the inconsistent methods may be a potential confounding factor in these studies. Further, not all atypical symptoms have been found to correlate with leptin levels; of the atypical symptoms, changes in weight gain and appetite are most strongly correlated with leptin levels (Lamers et al., 2016a; Milaneschi et al., 2017). This suggests that changes in appetite/weight may provide a clearer means of subtype classification for the purposes of examining connections between leptin, MDD, appetite and weight gain than the broader criteria of atypical MDD.

Some studies have indicated a sexual dimorphism in leptin levels, with females having higher leptin levels than males (Antonijevic et al., 1998; Rubin et al., 2002). However, other studies have indicated no difference in leptin levels between sexes (e.g. Hillemaier et al., 2006; Atmaca et al., 2003). However, there may be interactions between sex and depression status in terms of leptin (Milaneschi et al., 2012; Haleem et al., 2017). Depressed women are more prone to weight gain and obesity than males (e.g. Sutin & Zonderman, 2012; Grundy et al., 2014). It is therefore pertinent to investigate leptin levels by

sex and MDD status. Further, examining appetite and weight symptom presentations by sex is also important in order to elucidate specific relationships between leptin and MDD symptom profiles.

Due to its role in adiposity, leptin has consistently been correlated with body mass index (BMI) and waist circumference (e.g. Jow et al., 2006; Morris et al., 2012; Chen et al., 2016). Leptin has also been related to risk factors for cardiovascular disease, with elevated leptin levels associated with higher systolic and diastolic blood pressure (e.g. Beltowski, 2006; Ma et al., 2009) and heart rate (Brydon, 2011). This is particularly relevant to MDD because of its associations with obesity, cardiovascular disease and metabolic syndrome (Cassano & Fava, 2002; Penninx et al., 2013).

In summary, further research is needed to better understand relationships between leptin levels, eating behaviours and changes in appetite and weight in MDD, and whether these differ by sex. Previous leptin studies have also not measured stress severity, which is relevant considering the role of leptin in moderating activity of the HPA axis. While relationships between leptin, BMI and waist circumference have been previously noted, relationships between leptin and cardiovascular disease risk factors such as blood pressure and heart rate have not yet been sufficiently explored in MDD. Further, while leptin has been linked to depressed mood (Westling et al., 2004; Ozsoy et al., 2014), and depressed mood has been linked to problematic eating behaviours (e.g. van Strien et al., 2016; Sevincer et al., 2017), there is no direct research examining the relationships between food addiction and problematic eating behaviours in MDD, particularly in relation to leptin levels. An understanding of these unexplored relationships may elucidate relationships between MDD and other chronic health conditions.

In the current study, plasma leptin levels, biometrics, and psychometric measures of depression, anxiety and stress were compared between individuals with MDD and healthy controls. Depressed participants were sub-categorised to compare those with increased,

reduced or unchanged appetite and weight, by sex. Further, relationships between leptin, problematic eating behaviours and food addiction were examined in a subset of depressed participants. In line with previous literature, it was predicted that:

1. Leptin levels would not differ significantly between depressed and non-depressed participants overall.
2. Depressed participants with increased appetite/weight would demonstrate higher leptin levels than depressed participants with decreased or unchanged appetite/weight, with effects being greater in females;
3. Psychometric indices of depression severity, anxiety and stress would positively correlate with leptin levels;
4. Biometric indices of obesity and cardiovascular disease risk factors (including BMI and blood pressure), would positively correlate with plasma leptin levels, and;
5. Indices of problematic eating and food addiction would positively correlate with leptin levels.

2. Methods:

2.1 Participants

One hundred and twenty-three (123) adults aged between 18 and 69 years ($M = 31.87 \pm 12.88$ years; 70 female, 53 male) participated in the study. 63 participants met the diagnostic criteria for MDD, as confirmed by the Mini International Neuropsychiatric Interview; a valid semi-structured interview based on the DSM-5 designed to assess for psychiatric conditions (MINI; Sheehan et al., 1998; Lecrubier et al., 1997). Participants were recruited by media advertisements, notices and newsletters at the university.

Depressed participants were required to not be receiving any current or recent psychological or medication-based treatment for MDD. The 60 control participants had no history of diagnosed psychiatric disorders. Exclusion criteria across both groups were use of

corticosteroids, neurological illness and substance use disorders. Participants were asked to provide details of all medical conditions, medications and substance use. Eight participants reported a diagnosis of an insulin dysregulation disorder, including diabetes and polycystic ovarian syndrome. No participants had diagnosed eating disorders. No participants were current smokers. The study was approved by the local ethics committee, and all participants provided written informed consent.

2.2 Procedure

Data collection occurred at the University Clinical Research Trials Unit. All appointments were scheduled between 9:00am and 11:00am to control for diurnal variations in hormones. On arrival at the clinical trials unit, depressed participants were interviewed using the Mini Neuropsychiatric Interview, version 7.0.2 for DSM 5 (Sheehan, 2015) to confirm MDD diagnoses and symptoms, including weight and appetite changes. Control participants were also asked whether they had experienced recent changes in weight or appetite.

After provision of informed consent, height, weight, blood pressure and heart rate were taken. Waist circumference was measured in the depressed participants only. Following the provision of a non-fasting 10ml blood sample obtained by an experienced phlebotomist, participants then completed the Depression, Anxiety and Stress Scale; a 21 item self-report questionnaire assessing depression, anxiety and stress severity (DASS-21; Lovibond & Lovibond, 1995). The DASS-21 total score has high internal consistency (Cronbach's $\alpha = .94$; Gloster et al., 2008) The three subscales of the DASS-21 have demonstrated high internal consistency also (Cronbach's $\alpha = .96$ for depression, $.89$ for anxiety, $.93$ for stress; Brown, Chorpita, Korotitsch & Barlow, 1997).

During the study, when asked about appetite and weight changes, depressed participants frequently volunteered that they experienced loss of control around food cues

and increased emotional eating. Therefore, we obtained ethical approval to administer additional questionnaire measures to the remaining participants, to investigate eating behaviours in more detail, as an exploratory study. The Dutch Eating Behaviours Questionnaire (DEBQ; van Strien et al., 1986) and the Yale Food Addiction Scale (YFAS; Gearhardt et al., 2009) were administered to a subset of 33 depressed participants (20 female, 13 male) in order to investigate eating behaviours in the context of appetite and weight dysregulation in MDD. The DEBQ measures problematic eating styles, including restrained, emotional and external eating behaviours; with each of the three subscales demonstrating high internal consistency (Cronbach's $\alpha = .93$ for restrained, $.93$ for emotional, $.80$ for external eating; van Strien et al., 1986). The YFAS measures food addiction related behaviours, including withdrawal symptoms and loss of control around food cues; with the total YFAS score also demonstrating high internal consistency (Cronbach's $\alpha = .86$; Gearhardt et al., 2009).

2.3 Data and Statistical Analysis

Immediately following blood collection, blood samples were spun in a centrifuge at 4°C, at 2800rpm for 10 minutes. Plasma was immediately stored in a -80°C freezer until analysis. Plasma leptin levels were measured using a standard ELISA (Abcam, Cambridge, United Kingdom) testing kit. The intra- and inter-assay coefficients of the ELISA were <10% and <12% respectively.

Statistical analysis was conducted using 'Statistical Package for the Social Sciences' (SPSS, Version 23). A two-way factorial analysis of variance (ANOVA) was used to test for differences in the leptin levels, with the between subjects factors being Diagnosis (control, depressed) and Sex (male, female), and Age and BMI as covariates. A second two-way factorial ANOVA was used to test for differences in leptin levels as a function of appetite and weight changes, with the between subjects factors being Appetite and Weight Categories

(increased, decreased, no change) and Sex (male, female), with Age and BMI as covariates. Pearson's correlation coefficients and Spearman's rank correlations were used to determine relationships between the variables as appropriate. Post-hoc analyses were conducted using Bonferroni tests. For all statistical tests, $\alpha < .05$ was considered statistically significant.

3. Results:

3.1 Biometric and Psychometric Data

Biometric and psychometric data are displayed in Table 1. Diagnostic groups did not differ significantly in age. In terms of sex distributions, there were 35 females in both the MDD and control groups, 25 males in the control group and 28 males in the MDD group. The sex distributions between groups were not significant ($\chi^2(2, N = 123) = .097, p = .076$).

Systolic blood pressure was higher in males ($M = 135.38, SD = 12.92$) than females ($M = 117.04, SD = 11.64; F(1, 119) = 68.69, p < .001, \text{partial } \eta^2 = .366$). Diastolic blood pressure was also higher in males ($M = 80.11, SD = 11.43$) than females ($M = 75.63, SD = 9.24; F(1, 119) = 5.52, p = .020, \text{partial } \eta^2 = .044$). No significant effects for Diagnosis or interaction effects were identified for other biometric data.

Depressed participants scored significantly higher on each of the *Depression, Anxiety and Stress* subscales of the DASS compared to controls (Depression: $M = 23.21, SD = 9.38$ versus $M = 6.17, SD = 7.43, F(1, 119) = 117.59, p < .001, \text{partial } \eta^2 = .497$; Anxiety: $M = 13.59, SD = 10.65$ versus $M = 4.60, SD = 5.56, F(1, 119) = 30.70, p < .001, \text{partial } \eta^2 = .205$; Stress: $M = 21.90, SD = 9.60$ versus $M = 10.30, SD = 7.97; F(1, 119) = 49.99, p < .001, \text{partial } \eta^2 = .296$). No significant effects for Sex or interaction effects were identified for DASS scores.

Table 1:Means and standard deviations for biometric and psychometric data, by Diagnosis and Sex (total $n = 123$; MDD and control participants).

Variable	Sex			Effect p	Diagnosis		Effect p
	Male M (SD)	Female M (SD)			Control M (SD)	Depressed M (SD)	
	Sample Size (n)	53	70	-	60	63	-
Biometrics	Age (years)	33.94 (14.23)	30.30 (11.61)	.134	31.83 (10.98)	31.90 (14.55)	.764
	Weight (kg)	84.18 (14.60)	70.15 (17.32)	< .001**	74.53 (16.95)	77.78 (18.16)	.476
	BMI (kg/m ²)	26.52 (4.56)	25.57 (5.85)	.323	25.13 (4.49)	26.77 (5.95)	.147
	Systolic Blood Pressure (mmHg)	135.38 (12.92)	117.04 (11.64)	< .001**	126.40 (14.27)	123.56 (16.01)	.153
	Diastolic Blood Pressure (mmHg)	80.11 (11.43)	75.63 (9.24)	.020*	76.83 (9.86)	78.25 (10.99)	.422
	Heart Rate (bpm)	72.68 (13.68)	73.59 (10.40)	.693	73.29 (12.31)	73.13 (11.53)	.946
Psychometrics	DASS Depression	14.98 (11.55)	14.83 (12.45)	.856	6.17 (7.43)	23.21 (9.38)	< .001**
	DASS Anxiety	8.79 (8.50)	9.51 (10.47)	.580	4.60 (5.56)	13.59 (10.65)	< .001**
	DASS Stress	15.77 (9.81)	16.60 (11.14)	.495	10.30 (7.97)	21.90 (9.60)	< .001**

Note: DASS = Depression, Anxiety and Stress Scale.

* $\alpha < .05$, ** $\alpha < .01$.

3.2 Leptin Results

Four participants (2 MDD, 2 controls) did not provide a blood sample, so data from a total of 119 participants were included in the leptin analysis. There were eight univariate outliers in the leptin data detected using boxplot diagrams, with their plasma leptin concentration being greater than two standard deviations above the mean ($M = 142.97$, $SD = 204.48$). All outlier values belonged to depressed participants who reported insulin dysregulation disorders. Preliminary statistical analyses were conducted with and without the outliers. These initial results were similar, however when the outliers were removed a higher effect of leptin in MDD overall compared to healthy controls was no longer present. In order to eliminate the possibility of a potential confounding effect of insulin dysregulation on the leptin data, these outliers were excluded from subsequent analyses and only results without outliers are henceforth only reported.

Preliminary inspection of the distribution of the raw leptin data from the remaining 111 participants indicated a positively skewed distribution (skewness = 3.19, SE = .22). In line with previous human studies (e.g. Häfner et al., 2012; Milaneschi et al., 2012) the raw leptin data were natural-log transformed. Means and standard deviations for raw leptin and log-leptin values are displayed in Table 2 according to Diagnosis and Sex.

After accounting for age and BMI as potential covariates, log-leptin values did not differ significantly overall between participants with MDD compared to controls ($F(1, 111) = 1.99$, $p = .161$, partial $\eta^2 = .019$). Females ($M = 4.70$, $SD = 1.16$) had significantly higher log leptin values than males ($M = 3.15$, $SD = 1.54$, $F(1, 111) = 81.47$, $p < .001$, partial $\eta^2 = .438$). Age was identified as a significant covariate ($F(1, 111) = 4.43$, $p = .038$, partial $\eta^2 = .040$), as was BMI ($F(1, 111) = 73.86$, $p < .001$, partial $\eta^2 = .413$).

The interaction between Diagnosis and Sex was significant ($F(1, 111) = 4.99$, $p = .028$, partial $\eta^2 = .045$), with depressed males ($M = 3.43$, $SD = 1.40$) having higher log-leptin

levels than control males ($M = 2.82$, $SD = 1.66$). Leptin levels did not differ significantly between depressed ($M = 4.86$, $SD = 1.21$) and control females ($M = 4.56$, $SD = 1.12$) overall.

Table 2:

Means and standard deviations for raw and log-transformed leptin data, by Diagnosis and Sex (total $n = 111$; MDD and control participants).

Variable		Sample Size	Raw Leptin	Log-Leptin	Main Effect	Diagnosis x Sex Interaction
		n	M (SD)	M (SD)	p	p
Diagnosis	Control	58	106.31 (104.96)	3.85 (1.61)	.161	.028*
	Depressed	53	149.42 (226.30)	4.14 (1.48)		
Sex	Males	51	54.36 (63.95)	3.15 (1.54)	< .001**	
	Females	60	188.54 (211.59)	4.70 (1.16)		
Covariates	Age (years)	-	-	-	.038*	-
	BMI (kg/m ²)	-	-	-	< .001**	-

Note: significance noted for log-transformed data only.

* $\alpha < .05$, ** $\alpha < .001$.

3.3 Analysis by Appetite and Weight Change Groups

The 111 participants were classified according to whether they reported increased ($n = 19$, all depressed), reduced ($n = 20$, all depressed) or unchanged appetite/weight ($n = 72$, 12 depressed, 60 controls) from the clinical interview. No controls reported significant changes in their appetite/weight, whereas participants with MDD reported either increased, decreased or unchanged appetite/weight. One way ANOVAs indicated no significant differences in biometric variables between appetite/weight presentations (Table 3).

Table 3:

Means and standard deviations for biometric data, by appetite/weight categories. (total $n = 111$; MDD and control participants).

		Increases	Decreases	Unchanged	<i>p</i>
		Mean (SD)	Mean (SD)	Mean (SD)	
	Sample Size (<i>n</i>)	19	20	72	-
Biometrics	Age	34.95 (17.21)	29.60 (11.53)	32.15 (11.91)	.425
	Weight	79.01 (19.67)	76.00 (15.82)	74.91 (15.88)	.618
	BMI	27.52 (5.75)	25.56 (4.64)	25.30 (4.41)	.174
	Systole	121.95 (15.01)	122.00 (15.41)	126.53 (13.88)	.303
	Diastole	78.35 (9.04)	76.60 (13.69)	77.28 (9.50)	.861
	Heart Rate	73.65 (11.84)	70.15 (9.33)	73.21 (12.19)	.544

^a Indicates significant differences compared to the ‘Increased’ group.

* $\alpha < .05$, ** $\alpha < .01$.

The two-way ANOVA with Appetite/Weight categories (increased, decreased, no change) and Sex (male, female) as between group factors, with Age and BMI as covariates (Table 4), indicated that leptin values did not differ significantly across appetite/weight presentations ($F(2, 111) = .11, p = .900$). However, the interaction between Appetite/Weight categories and Sex was significant ($F(2, 111) = 3.53, p = .033$, partial $\eta^2 = .064$). Females with increased ($M = 5.20, SD = .87$) or unchanged ($M = 4.64, SD = 1.12$) appetite/weight had higher log-leptin values compared to females with decreased appetite/weight ($M = 4.16, SD = 1.53$). This pattern was the opposite in males, as those with decreased appetite/weight ($M = 3.65, SD = 1.69$) had higher log-leptin values than males with increased ($M = 3.31, SD = 0.99$) or unchanged ($M = 2.94, SD = 1.56$) appetite/weight.

Leptin values were again significantly higher for females ($M = 4.70, SD = 1.16$) compared to males ($M = 3.15, SD = 1.54, F(1, 111) = 36.90, p < .001$, partial $\eta^2 = .264$). BMI was a significant covariate ($F(1, 111) = 69.55, p < .001$, partial $\eta^2 = .578$), however age as a covariate was non-significant.

Table 4:

Means and standard deviations for raw and log-transformed leptin data, by Appetite/Weight Categories and Sex (total $n = 111$; MDD and control participants).

Variable		Sample Size	Raw Leptin	Log-Leptin	Main Effect	AW x S Interaction
		n	M (SD)	M (SD)	p	p
Appetite Weight Categories	Increases	19	192.72 (240.58)	4.60 (1.26)	.900	.033*
	Decreases	20	106.31 (156.71)	3.85 (1.60)		
	Unchanged	72	113.16 (156.30)	3.86 (1.58)		
Sex	Males	51	54.36 (63.95)	3.15 (1.54)	< .001**	
	Females	60	188.54 (211.59)	4.70 (1.16)		
Covariates	Age (years)	-	-	-	.133	-
	BMI (kg/m ²)	-	-	-	< .001**	-

Note: significance noted for log-transformed data only.

* $\alpha < .05$, ** $\alpha < .001$.

Weight correlated positively with systolic ($r(111) = .461, p < .001$) and diastolic ($r(111) = .383, p < .001$) blood pressure. BMI also correlated positively with systolic ($r(111) = .257, p = .006$) and diastolic ($r(111) = .390, p < .001$) blood pressure. Further, BMI was positively correlated with weight ($r(111) = .877, p < .001$). Log-leptin values correlated positively with BMI ($r(111) = .449, p < .001$), but were negatively correlated with systolic blood pressure, ($r(111) = -.240, p = .011$). No significant correlations were identified between log-leptin values, the remaining biometric measurements and DASS subscales.

3.4 Subset Analysis of Eating Addiction and Eating Behaviours in MDD

As a further exploratory analysis, waist circumference was measured, and the Dutch Eating Behaviours Questionnaire (DEBQ) and the Yale Food Addiction Scale (YFAS) were administered to 33 participants recruited to the MDD group ($n = 33$). Of these 33 participants, 15 reported increased, 11 decreased and 7 unchanged appetite/weight. Between-groups analyses based on appetite/weight presentations were not performed due to small cell sizes.

Independent samples *t* tests were performed to investigate Sex differences for the additional measures (Table 3). Waist circumference did not differ significantly between sexes ($t(31) = -.64, p = .528, \text{partial } \eta^2 = .013$). Females reported more *Restrained eating* behaviours ($M = 2.83, SD = 1.03$) than males on the DEBQ ($M = 1.72, SD = .64; t(31) = 3.45, p = .002, \text{partial } \eta^2 = .278$). Females also reported more frequent instances of *Emotional eating* ($M = 2.93, SD = 1.11$) than males ($M = 2.02, SD = .93; t(31) = 2.43, p = .021, \text{partial } \eta^2 = .160$). However, *Sensitivity to external food cues* was similar between sexes.

Eight (24%; all female) of the 33 depressed participants in the sub-analysis met the YFAS criteria for food addiction. The *Loss of control* subscale was higher in females ($M = .25, SD = .444$) than males ($M = .00, SD = .000; t(31) = 2.52, p = .021, \text{partial } \eta^2 = .116$). The *Large amounts of time spent acquiring food* subscale was also higher in females ($M = .40, SD = .50$) than males ($M = .08, SD = .28; t(31) = 2.37, p = .024, \text{partial } \eta^2 = .126$). Females reported higher scores than males for *Giving up important activities* for the sake of acquiring food ($M = .45, SD = .51, \text{versus } M = .08, SD = .28; t(31) = 2.71, p = .011, \text{partial } \eta^2 = .157$) and *Withdrawal symptoms* ($M = .45, SD = .51 \text{ versus } M = .08, SD = .28; t(31) = 2.71, p = .011, \text{partial } \eta^2 = .157$). Females had a higher total number of symptoms on the *Food addiction symptom count* ($M = 3.50, SD = 1.82$) than males ($M = 1.92, SD = 1.26; t(31) = 2.94, p = .006, \text{partial } \eta^2 = .193$). No further differences for the YFAS subscales between sexes were significant.

Table 5:

Means, standard deviations and symptom endorsement rates for the eating measures and biometrics in a subset of depressed participants, by Sex (total $n = 33$; MDD only).

Scale		Male	Female	p	Endorsement
		Mean (SD)	Mean (SD)		%
	Sample Size (n)	13	20	-	-
Biometrics	Waist Circumference (cm)	92.54 (13.70)	88.36 (18.89)	.528	-
DEBQ	Restrained	1.72 (.64)	2.83 (1.03)	.002*	-
	Emotional	2.02 (.93)	2.93 (1.11)	.021*	-
	External Cues	3.03 (.82)	3.34 (.72)	.257	-
YFAS	Loss of Control	.00 (.00)	.25 (.44)	.021*	15.2%
	Inability to Cut Down	1.00 (.00)	.85 (.37)	.083	91%
	Large amounts of Time	.08 (.28)	.40 (.50)	.024*	27.3%
	Giving up Activities	.08 (.28)	.45 (.51)	.011*	30.3%
	Continued Use Despite Issues	.38 (.51)	.50 (.51)	.530	45.5%
	Tolerance to Increased Food	.31 (.48)	.60 (.50)	.107	48.5%
	Withdrawal Symptoms	.08 (.28)	.45 (.51)	.011*	30.3%
	Symptom Count	1.92 (1.26)	3.50 (1.82)	.006*	-

Note: DEBQ = Dutch Eating Behaviours Questionnaire, YFAS = Yale Food Addiction Scale. YFAS subscales are scored dichotomously and occur between 0.00 and 1.00. * $\alpha < .05$.

Waist circumference was positively correlated with weight ($r(27) = .900, p < .001$), BMI ($r(27) = .874, p < .001$) and diastolic blood pressure ($r(27) = .413, p = .032$). Log-leptin values correlated positively with waist circumference ($r(25) = .510, p = .009$) and BMI ($r(25) = .549, p = .004$), and correlated negatively with heart rate ($r(25) = -.404, p < .001$). Log-leptin values were also positively correlated with DEBQ *Restrained eating* ($r(25) = .403, p = .046$), and *Emotional eating* ($r(25) = .438, p = .029$). No further results were significant.

4. Discussion:

This is one of the first studies to examine leptin in relation to increased weight and appetite in MDD. A significant interaction effect between appetite/weight categories and sex was observed with respect to plasma leptin levels. Females with increased or stable

appetite/weight had higher leptin levels than those with reduced appetite/weight; however the opposite effect occurred for males, whereby males with decreased appetite/weight had higher leptin than those with increased or stable appetite/weight. These effects were present with correction for age and BMI. Since leptin has a fundamental role as an appetite suppressant (e.g. Elmquist et al., 1998), the higher leptin levels in males with decreased appetite/weight is consistent with normal leptin regulation. However, higher leptin levels in females with increased appetite/weight may be consistent with an interpretation of leptin resistance, a condition which is characterised by chronically elevated leptin levels and decreased leptin sensitivity (Pan et al., 2014). It is possible that the female participants who reported appetite/weight increases have become desensitised to endogenous signals regarding stores of body fat. As such, they continue to experience high levels of hunger despite higher levels of circulating leptin. This may be coupled with continuing to eat as a coping strategy for any physiological and psychological stress they are experiencing, with certain foods dampening HPA activity (Dallman et al., 2003; Ulrich-Lai, 2016).

Leptin levels did not differ significantly between depressed and non-depressed participants in the current study. Further, no significant relationships between leptin levels and depression, anxiety or stress scores were present. Previous research has identified inconsistent results regarding leptin levels in MDD; some studies report increased leptin levels in depressed mood (Antonijevic et al., 1998; Morris et al., 2012), whereas others report lower or equivalent leptin levels in depressed participants versus controls (Carvalho et al., 2014; Westling et al., 2004; Atmaca et al., 2003; Häfner et al., 2012; Ozsoy et al., 2014). Symptom profiles present heterogeneously in MDD, and previous studies did not specifically analyse leptin levels as a function of increased or decrease weight and appetite. Also, despite previous literature linking leptin to depressed mood (e.g. Westling et al., 2004; Morris et al., 2012), the current results, in combination with previous studies, indicate that leptin may be

linked to sex-specific symptoms and pathophysiology of MDD (Lu, 2007), as opposed to the disorder as a whole.

A clear overall sex difference in terms of plasma leptin levels was observed in all analyses, with female participants having higher plasma leptin levels than males, irrespective of MDD or appetite/weight change status. This is consistent with previous findings of a sexual dimorphism in leptin studies (e.g. Antonijevic et al., 1998; Rubin et al., 2002). Females tend to store more body fat for reproductive purposes (Blaak, 2001) and given a certain BMI, females are likely to have a higher percentage of body fat than males. As leptin secretion is proportional to adipose tissue mass (Maffei et al., 1995), females may have higher circulating leptin levels. Higher leptin levels and body fat percentages may act as a risk factor for weight gain in depressed females, and may perhaps explain why females are more prone to weight gain in MDD (Sutin & Zonderman, 2012; Grundy et al., 2014). Increased weight gain further represents a risk factor for other associated health risks in MDD, including cardiovascular disease and metabolic syndrome (Cassano & Fava, 2002; Penninx et al., 2013). As such, higher leptin levels may also represent a risk factor for these conditions, particularly in depressed females; however further longitudinal research is needed to explore the time course of these factors.

Exploratory analysis of problematic eating behaviours and food addiction in a subset of depressed participants provided promising evidence. To our knowledge, relationships between leptin, MDD, problematic eating behaviours and eating addiction have not been previously reported. In the current study, instances of these problematic eating behaviours, including emotional and restrained eating, were consistently higher in depressed females compared to depressed males. These results indicate that these behaviours may represent sex-specific coping mechanisms for depressed mood, which are also linked to hormone levels. Further, while depressed mood has previously been associated with increased emotional eating and food intake in response to food cues (van Strien et al., 2016; Sevincer et al., 2017),

the current study is the first to identify a direct link between MDD, leptin levels and problematic eating behaviours, including eating addiction. Despite the small sample size for the subset analysis, which limited the power to detect effects, plasma leptin was positively correlated with restrained and emotional eating. This may provide further evidence of leptin resistance in MDD, given that there were higher instances of food consumption and related behaviours despite the presence of equivalent leptin levels. In addition, approximately one quarter of depressed participants in the sub-analysis, all females, met the YFAS criteria for food addiction, double the prevalence rates reported in non-clinical samples, and equivalent to that reported in obese samples (Meule & Gearhardt, 2014). This effect relating to food addiction has not, to our knowledge, been previously examined in a depressed sample. This suggests that food addiction may be a more common problem in MDD than previously realised. However, further research is needed to determine whether the role of leptin is causal or is a result of other mechanisms.

Overall, the results of the current study suggest that leptin is related to sex-specific weight changes and problematic eating behaviours in MDD, even after controlling for BMI. Leptin levels were higher in female participants with increased appetite or weight gain, however this pattern was the opposite in males, who showed higher leptin with decreased appetite or weight loss. Leptin levels were positively correlated with measures of comfort eating and loss of control in food consumption. These results provide further support for leptin dysregulation in problematic eating behaviours in MDD that differs by sex. Leptin resistance may be a factor in appetite and weight dysregulation, particularly in females, and problematic eating behaviours in MDD. Further elucidation of the pathways between depression, health indicators and problematic eating behaviours could assist in the development of early interventions and preventative measures for individuals at risk of weight gain and associated chronic disease due to MDD. Research aimed at identifying

interventions to treat leptin resistance is emerging (Pan et al., 2014), which in future may be of value in assisting in reducing the risk of weight gain for depressed individuals.

There are several limitations to the current study. Participants were not required to fast prior to blood collection, and diets were not controlled for. Previous leptin studies have used fasting and non-fasting protocols, and this should be considered when interpreting the results. Additional potential confounding variables, such as physical activity, were not controlled for, and should be considered for future studies. Further, the sub-investigation of food addiction and eating behaviour in relation to leptin was exploratory and conducted for only 33 participants. While these results are promising and showed that problematic eating behaviours were linked to leptin levels, larger studies with control participants are needed to investigate the predictive value of leptin and other hormones in relation to appetite and weight dysregulation. This may further serve as potential modifiable risk factors or points for early intervention in depression or obesity treatment.

In conclusion, the current study provides new insights into the relationships between leptin, problematic eating behaviours, weight gain and MDD. In particular, the results suggest a possible role of leptin resistance in problematic eating behaviours in MDD, particularly in females. This highlights the need for further, longitudinal, research evaluating the temporal relationships between these variables and the role of leptin and leptin resistance as potential risk factors for weight gain and associated cardiovascular and metabolic health risks in subsets of individuals with MDD. This may lead to opportunities for early interventions aimed at preventing weight gain in at-risk individuals with MDD, and help to address this growing problem.

5. References:

- Antonijevic, I.A., Murck, H., Frieboes, R.M., Horn, R., Brabant, G. & Steiger, A. (1998). Elevated nocturnal profiles of serum leptin in patients with depression. *Journal of Psychiatric Research*, *32*, 403-410.
- American Psychiatric Association. (2013). *Diagnostics and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing.
- Atmaca, M., Kuloglu, M., Texcan, E. & Ustundag, B. (2003). Serum leptin and cholesterol values in violent and non-violent suicide attempters. *Psychiatry Research*, *158*, 87-91.
- Beltowski, J. (2006). Role of leptin in blood pressure regulation and arterial hypertension. *Journal of Hypertension*, *24*(5), 789-801. doi: 10.1097/01.hjh.0000222743.06584.66
- Blaak, E. (2001). Gender differences in fat metabolism. *Current Opinion in Clinical Nutrition and Metabolic Care*, *4*, 499-502.
- Blackburn-Munro, G. & Blackburn-Munro, R.E. (2001). Chronic pain, chronic stress and depression: coincidence or consequence? *Journal of Neuroendocrinology*, *13*, 1009-1023.
- Blanco, C., Vesga-Lopez, O., Stewart, J.W., Liu, S-M., Grant, B.F. & Hasin, D.S. (2012). Prevalence, correlates, comorbidity and treatment seeking among individuals with a lifetime major depressive episode with and without atypical features: Results from the National Epidemiological Survey on Alcohol and Related Conditions. *Journal of Clinical Psychiatry*, *73*(2), 224-232. doi: doi:10.4088/JCP.10m06227.
- Bornstein, S.R., Uhlmann, K., Haidan, A., Ehrart-Bornstein, M. & Scherbaum, W.A. (1997). Evidence for a novel peripheral action of leptin as a metabolic signal to the adrenal gland: Leptin inhibits cortisol release directly. *Diabetes*, *46*, 1235-1238.
- Brown, T.A., Chorpita, B.F., Korotitsch, W. & Barlow, D.H. (1997). Psychometric properties of the Depression Anxiety and Stress Scales (DASS) in Clinical Samples. *Behaviour*,

- Research and Therapy*, 35(1), 79-89.
- Brydon, L. (2011). Adiposity, leptin and stress reactivity in humans. *Biological Psychology*, 86, 114-120. doi: 10.1016/j.biopsycho.2010.02.010.
- Carvalho, A.F., Rocha, D.Q.C., McIntyre, R.S., Mesquita, L.M., Kohler, C.A., et al. (2014). Adipokines as emerging depression biomarkers: A systematic review and meta analysis. *Journal of Psychiatric Research*, 59, 28-37. doi: 10.1016/j.jpsychires.2014.08.002
- Cassano, P. & Fava, M. (2002). Depression and public health: an overview. *Journal of Psychosomatic Research*, 53, 849-857.
- Chen, C., Goa, J., Zhang, J., Jia, L., Yu, T. & Zheng, Y. (2016). Serum leptin level measured 48h after delivery is associated with development of postpartum depressive symptoms: a 3 month follow up study. *Archives of Women's Mental Health*, 19, 1001-1008. doi: 10.1007/s00737-016-0647-z.
- Christensen, L. & Pettijohn, L. (2001). Mood and carbohydrate cravings. *Appetite*, 36, 137- 145. doi: 10.1006/appe.2001.0390.
- Dallman, M.F., Pecoraro, N., Akana, S.F., La Fleur, S.E., Gomez, F., Houshyar, H., Bell, M.E., Bhatnagar, S., Laugero, K.D. & Manalo, S (2003). Chronic stress and obesity: A new view of comfort food. *PNAS*, 100(1), 11696-11701.
- Deuschle, M., Blum, W.F., Englaro, P., Schweiger, U., Weber, B., Pflaum, C.D. & Heuser, I. (1996). Plasma leptin in depressed patients and healthy controls. *Hormone and Metabolic Research*, 28(12), 714-717.
- Elmqvist, J.K., Maratos-Flier, E., Saper, C.B. & Flier, J.S. (1998). Unravelling the central nervous system pathways underlying responses to leptin. *Nature Neuroscience*, 1(6), 445-450.
- Ge, J.F., Qi, C.G. & Zhou, J.N. (2013). Imbalance of leptin pathway and hypothalamus synaptic plasticity markers are associated with stress induced depression in rats.

- Behavioural Brain Research*, 249, 38-43. doi: 10.1016/j.bbr.2013.04.020.
- Gearhardt, A.N., Corbin, W.R. & Brownell, K.D. (2009). Preliminary validation of the Yale Food Addiction Scale. *Appetite*, 52, 430-436.
- Gearhardt, A.N., Yokum, S., Orr, P.T., Stice, E., Corbin, W.R. & Brownell, K.D. (2011). Neural correlates of food addiction. *Archives of General Psychiatry*, 68(8), 808 – 816. doi: 10.1001/archgenpsychiatry.2011.32.
- Gearhardt, A.N., White, M.A., Masheb, R.M., Morgan, P.T., Crosby, R.D. & Grillo, C.M. (2012). An examination of the food addiction construct in obese patients with binge eating disorder. *International Journal of Eating Disorders*, 45, 657-663.
- Gecici, O., Kuloglu, M., Atmaca, M., Tezcan, A.E., Tunckol, H, Murat Emul, H. & Ustundag, B. (2005). High serum leptin levels in depressive disorders with atypical features. *Psychiatry and Clinical Neurosciences*, 59, 736-738.
- Gloster, A.T., Rhoades, H.M., Novy, D., Klotche, J., Senior, A., Kunik, M., Wilson, N. & Stanley, M.A. (2008). Psychometric properties of the Depression, Anxiety and Stress Scale-21 in older primary care patients. *Journal of Affective Disorders*, 110, 248-259.
- Grundy, A., Cotterchio, M., Kirsh, V.A. & Kreiger, N. (2014). Associations between anxiety, depression, antidepressant medication, obesity and weight gain among Canadian women. *PLoS ONE*, 9(6), e99780. doi:10.1371/journal.pone.0099780
- Häfner, S., Baumert, J., Emeny, R.T, Lacruz, M.E, Thorand, B., Herder, C. et al. (2012). Sleep disturbances and depressed mood: a harmful combination associated with increased leptin levels in women with normal weight. *Biological Psychology*, 89, 163-169. doi: 10.1016/j.biopsycho.2011.10.005.
- Halaas, J.L., Boozer, C., Blair-West, J., Fidahusein, N., Denton, D.A. & Friedman, J.M. (1997). Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. *Proceedings of the National Academy of Science of the United States of America*, 94(16), 8878-8883.

- Haleem, D., Sheikh, S., Fawad, A. & Haleem, M. (2017). Fasting leptin and glucose in normal weight, overweight and obese men and women diabetes patients with and without clinical depression. *Metabolic Brain Disease*, doi:10.1007/s1101101799649.
- Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, 23, 56-62.
- Heymsfield, S.B., Greenberg, A.S., Fujioka, K., Dixon, R.M., Kushner, R., Hunt, T., et al. (1999). Recombinant leptin for weight loss in obese and lean adults: A randomised, controlled, dose escalation trial. *Journal of the American Medical Association*, 282(16), 1568-1575.
- Hidaka, B.H. (2012). Depression as a disease of modernity: explanations for increasing prevalence. *Journal of Affective Disorders*, 140, 205-214.
- Hillemacher, T., Bleich, S., Frieling, H., Schanze, A., Wilhelm, J., Sperling, W., Kornhuber, J. & Kraus, T. (2006). Evidence of an association of serum leptin levels and craving in alcohol dependence. *Psychoneuroendocrinology*, 32, 87-90. doi: 10.1016/j.psyneuen.2006.09.013.
- Hirano, S., Miyata, S. & Kamei, J. (2007). Antidepressant like effect of leptin in streptozotocin-induced diabetic mice. *Pharmacology, Biochemistry and Behaviour*, 86, 27-31.
- Hoch, T., Kreitz, S., Gaffling, S., Pischetsrieder, M. & Hess, A. (2015). Fat/carbohydrate ratio but not energy density determines snack food intake and activates brain reward areas. *Scientific Reports*, 5, 1-9. doi: 10.1038/srep10041.
- Jiménez, I., Sobrino, T., Rodríguez-Yanez, M., Pouso, M., Cristobo, I., Sabucedo, M., et al. (2009). High serum levels of leptin are associated with post-stroke depression. *Psychological Medicine*, 39, 1201- 1209.
- Jow, G.M., Yang, T.T. & Chen, C.L. (2006). Leptin and cholesterol levels are low in major depressive disorder, but high in schizophrenia. *Journal of Affective Disorders*, 90,

21-27. doi:10.1016/j.jad.2005.09.015.

Kim, C.S., Huang, T.Y., Garza, J., Ramos, F., Frazer, A., Liu, F. & Lu, X.Y. (2006).

Leptin induces antidepressant-like behavioural effects and activates specific signal transduction pathways in the hippocampus and amygdala of mice.

Neuropsychopharmacology, 31, S237-S238.

Kloiber, S., Ising, M., Reppermund, S., Horstmann, S., Dose, T., Majer, M., et al.

(2007). Overweight and obesity affect treatment response in major depression.

Biological Psychiatry, 62, 321–326. doi: 10.1016/j.biopsych.2006.10.001

Kontinen, H., Mannisto, S., Sarlio-Lahteenkorva, S., Silventoinen, K. & Haukkala, A.

(2010). Emotional eating, depressive symptoms and self-reported food consumption:

A population based study. *Appetite*, 54, 473-479. doi: 10.1016/j.appet.2010.01.014.

Kraus, T., Haack, M., Schuld, A., Hinze-Selch, D. & Pollmacher, T. (2001). Low leptin

levels but normal body mass indices in patients with depression or schizophrenia.

Neuroendocrinology, 73(4), 243-247.

Lamers, F., Bot, M., Jansen, R., Chan, M.K., Cooper, J.D., Bahn, S. & Penninx, B.W.

(2016a). Serum proteomic profiles of depressive subtypes. *Translational Psychiatry*,

6, e851, doi: 10.1038/tp.2016.115

Lamers, F., Beekman, A.T., van Hemert, A.M., Schoevers, R.A. & Penninx, B.W. (2016b).

Six year longitudinal course and outcomes of subtypes of depression. *British Journal of Psychiatry*, 208(1), 62-68. doi: doi: 10.1192/bjp.bp.114.153098.

Lassere, A.M., Glaus, J., Vandeleur, C.L., Marques-Vidal, P., Vaucher, J., Bastardot, F., et al.

(2014). Depression with atypical features and increase in obesity, body mass index, waist circumference and fat mass: A prospective, population based study. *JAMA Psychiatry*, 71(8), 881-888.

Lecrubier, Y., Sheehan, D.V., Weiller, W., Amorim, P., Bonora, I., Harnett Sheehan, K.,

Janavs, J. & Dunbar, G.C. (1997). The Mini International Neuropsychiatric Interview:

- A short diagnostic structured interview; reliability and validity according to the CIDI. *European Psychiatry*, 12(1), 224-231.
- Levin, B.E. & Dunn-Meynell, A.A. (2002). Reduced central leptin sensitivity in rats with diet induced obesity. *American Journal of Physiology*, 283(4), 941-948.
- Li, Y., Aggen, S., Shi, S., Gao, J., Li, Y., Tao, M., et al. (2014). The structure of the symptoms of major depression: exploratory and confirmatory factor analysis in depressed Han Chinese women. *Psychological Medicine*, 44, 1391-1401. doi: 10.1017/S003329171300192X.
- Liu, W., Liu, J., Xia, J., Xue, X., Wang, H., Qi, Z. & Ji L. (2017). Leptin receptor knockout- induced depression like behaviours and attenuated antidepressant effects of exercise are associated with STAT3/SOCS3 signalling. *Brain, Behaviour and Immunity*, 61, 297-305. doi: 10.1016/j.bbi.2017.01.001.
- Lovibond, S.H. & Lovibond, P.F. (1995). *Manual for the Depression Anxiety Stress Scales*. 2nd ed. Sydney: Psychology Foundation.
- Lu, X.Y., Kim, C.S., Frazer, A. & Zhang W. (2006). Leptin: a potential novel antidepressant. *Proceedings of the National Academy of Science of the United States*, 103, 1593-1598.
- Lu, X.Y. (2007). The leptin hypothesis of depression: a potential link between mood disorders and obesity. *Current Opinion in Pharmacology*, 7, 648-652.
- Luppino, F.S., de Wit, L.M., Bouvy, P.F., Stijnen, T., Cuijpers, P., Pennix, B.W. & Zitman, F. (2010). Overweight, obesity and depression: A systematic review and meta-analysis of longitudinal studies. *Archives of General Psychiatry*, 67(3), 220-229.
- Lutter, M. & Nestler, E.J. (2009). Homeostatic and hedonic signals interact in the regulation of food intake. *The Journal of Nutrition*, 139, 629-632. doi: 10.3945/jn.108.097618.

- Ma, D., Feitosa, M.F., Wilk, J.B., Laramie, J.M., Yu, K., Leidecker-Foster, C., Myers, R.H., Province, M.A. & Borecki, I.B. (2009). Leptin is associated with blood pressure and hypertension in women from the National Heart, Lung and Blood Institute Family Heart Study. *Hypertension*, *53*, 473-479.
- Maffei, M., Halaas, J., Ravussin, E., Pratley, R.E., Lee, G.H., Zhang, Y., et al. (1995). Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Natural Medicine*, *1*, 1155–1161. doi: 10.1038/nm1195-1155.
- Meule, A. & Gearhardt, A. (2014). Five years of the Yale Food Addiction Scale: Taking stock and moving forward. *Current Addiction Reports*, doi: 10.1007/s40429-014-0021-z.
- Milaneschi, Y., Simonsick, E., Vogelzangs, N., Strotmeyer, E.S., Yaffe, K., Harris, T.B., et al. (2012). Leptin, abdominal obesity and onset of depression in older men and women. *Journal of Clinical Psychiatry*, *73*(9), 1205-1211. doi: 10.4088/JCP.11m07552
- Milaneschi, Y., Lamers, F., Bot, M., Drent, M.L. & Penninx, B.W.J.H. (2017). Leptin dysregulation is specifically associated with major depression with atypical features: Evidence for a mechanism connecting obesity and depression. *Biological Psychiatry*, *81*, 807-814.
- Morris, A.A., Ahmed, Y., Stoyanova, N., Hooper, W.C., de Saerke, C., Gibbons, G. et al. (2012). The association between depression and leptin is mediated by adiposity. *Psychosomatic Medicine*, *74*(5), 483-488.
- Ozsoy, S., Besirli, A., Abdulrezzak, U. & Basturk, M. (2014). Serum ghrelin and leptin levels in patients with depression and the effects of treatment. *Psychiatry Investigation*, *11*(2), 167-172.
- Paans, N.P., Bot, M., Gibson-Smith, D., Spinhoven, P., Brouwer, I.A., Visser, M., & Penninx,

- B.W. (2017). Which biopsychosocial variables contribute more to weight gain in depressed persons? *Psychiatry Research*, *254*, 96-103. doi: 10.1016/j.psychres.2017.04.044.
- Pan, H., Guo, J., & Su, Z. (2014). Advances in understanding the interrelations between leptin resistance and obesity. *Physiology & Behaviour*, *130*, 157-169. doi: 10.1016/j.physbeh.2014.04.003.
- Penninx, B.W., Milaneschi, Y., Lamers, F., & Vogelzangs, N. (2013). Understanding the somatic consequences of depression: biological mechanisms and the role of depressive symptom profiles. *BMC Medicine*, *11*(129), doi: 10.1186/1741-7015-11-129.
- Piccinni, A., Marazziti, D., Vanelli, F., Francheschini, C., Baroni, S., Costanzo, D., Baroni, S., Mirko Cremone, I., Veltri, A. & Dell'Osso, L. (2015). Food addiction spectrum: A theoretical model from normality to eating and overeating disorders. *Current Medicinal Chemistry*, *22*(13), 1631-1638.
- Polivy, J., Herman, C.P., & Warsh, P. (1978). Internal and external components of emotionality in restrained and unrestrained eaters. *Journal of Abnormal Psychology*, *87*(5), 497- 504. doi: 10.1037/0021-843X.87.5. 497
- Privitera, G.J., Misenheimer, M.L. & Doraiswamy, P.M. (2013). From weight loss to weight gain: appetite changes in major depressive disorder as a mirror into brain-environment interactions. *Frontiers in Psychology*, *4*, doi: 10.3389/fpsyg.2013.00873.
- Roubos, E.W., Dahmen, M., Kozicz, T. & Lu, X. (2012). Leptin and the hypothalamic-pituitary-adrenal stress axis. *General and Comparative Endocrinology*, *177*, 28-36. doi: 10.1016/j.ygcen.2012.01.009.
- Rubin, R.T., Rhodes, M.E. & Czambel, R.K. (2002). Sexual diergism of baseline plasma leptin and leptin suppression by arginine vasopressin in major depressives and major controls. *Psychiatry Research*, *113*, 255-268.

- Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH (1996): The Inventory of Depressive Symptomatology (IDS): Psychometric properties. *Psychol Med* 26:477–486.
- Sevincer, G.M., Konuk, N., Ipekcioglu, D., Crosby, R.D., Cao, L., Coskum, H. & Mitchell, J.E. (2017). Association between depression and eating behaviours among bariatric surgery candidates in a Turkish sample. *Eating and Weight Disorders*, 22, 117-123.
- Sheehan, D. V. (2015). *Mini International Neuropsychiatric Interview 7.0*. Jacksonville, FL: Medical Outcomes Systems.
- Sheehan, D., Lecrubier, Y., Sheehan, K., Amorim, P., Janavs, J., Weiller, E.... Dunbar, G. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, 59, 22-33.
- Sutin, A.R. & Zonderman, A.B. (2012). Depressive symptoms are associated with weight gain among women. *Psychological Medicine*, 42, 2351-2360. doi: 10.1017/S0033291712000566
- Trayhurn, P., Hoggard, N., Mercer, J.G. & Rayner, D.V. (1999). Leptin: fundamental aspects. *International Journal of Obesity and Related Metabolic Disorders*, 23(1), 22-28.
- Ulrich-Lai, Y.M. (2016). Self medication with sucrose. *Current Opinion in Behavioural Sciences*, 9, 78-83.
- van Strien, T., Frijters, J.E., Bergers, G.P. & Defares, P.B. (1986). The Dutch Eating Behaviour Questionnaire (DEBQ) for assessment of restrained, emotional and external eating behaviour. *International Journal of Eating Disorders*, 5(2), 295-315.

- van Strien, T., Konttinen, H., Homberg, J.R., Engels, R.C. & Winkens, L.H. (2016). Emotional eating as a mediator between depression and weight gain. *Appetite*, *100*, 216-224. doi: 10.1016/j.appet.2016.02.034.
- Volkow, N.D., Wang, G.J., Fowler, J.S., Tomasi, D. & Baler, R. (2012). Food and drug reward: overlapping circuits in human obesity and addiction. *Current Topics in Behavioural Neurosciences*, *11*, 1-24. doi: 10.1007/7854_2011_169.
- Westling, S., Ahren, B., Traskman-Bends, L. & Westrin, A. (2004). Low CSF leptin in female suicidal attempters with major depression. *Journal of Affective Disorders*, *81*, 41-48.
- Widdowson, P.S., Upton, R., Buckingham, R., Arch, J. & Williams, G. (1997). Inhibition of food response to intra-cerebro-ventricular injection of leptin is attenuated in rats with diet induced obesity. *Diabetes*, *46*(11), 1782-1785.
- World Health Organization (1997): The Composite Interview Diagnostic Instrument. Geneva: World Health Organization.
- Zigman, J.M. & Elmquist, J.K. (2003). Mini review: from anorexia to obesity – the yin and yang of body weight control. *Endocrinology*, *144*(9), 3749-3756.