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Weight gain in Major Depressive Disorder: Linking appetite and disordered eating to leptin and ghrelin

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Abstract
Major Depressive Disorder (MDD) involves changes in appetite and weight, with a subset of individuals at an increased risk of weight gain. Pathways to weight gain may include appetite disturbances, excess eating, and dysregulation of appetite hormones. However, little research has simultaneously examined relationships between hormones, eating behaviours and MDD symptoms. Plasma ghrelin and leptin, biometrics, eating behaviours and psychopathology were compared between depressed (n = 60) and control (n = 60) participants. Depressed participants were subcategorised into those with increased or decreased appetite/weight for comparison by subtype. The Dutch Eating Behaviours Questionnaire and Yale Food Addiction Scale measured eating behaviours. Disordered eating was higher in MDD than controls, in females than males, and in depressed individuals with increased, compared to decreased, appetite/weight. Leptin levels were higher in females only. Leptin levels correlated positively, and ghrelin negatively, with disordered eating. The results provide further evidence for high levels of disordered eating in MDD, particularly in females. The correlations suggest that excessive eating in MDD is significantly linked to appetite hormones, indicating that it involves physiological, rather than purely psychological, factors. Further, longitudinal, research is needed to better understand whether hormonal factors play a causal role in excessive eating in MDD.

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Weight gain in Major Depressive Disorder: Linking appetite and disordered eating to leptin and ghrelin.

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ii. Contributors

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iv. 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:

Major Depressive Disorder (MDD) involves changes in appetite and weight, with a subset of individuals at an increased risk of weight gain. Pathways to weight gain may include appetite disturbances, excess eating, and dysregulation of appetite hormones. However, little research has simultaneously examined relationships between hormones, eating behaviours and MDD symptoms. Plasma ghrelin and leptin, biometrics, eating behaviours and psychopathology were compared between depressed (n = 60) and control (n = 60) participants. Depressed participants were subcategorised into those with increased or decreased appetite/weight for comparison by subtype. The Dutch Eating Behaviours Questionnaire and Yale Food Addiction Scale measured eating behaviours. Disordered eating was higher in MDD than controls, in females than males, and in depressed individuals with increased, compared to decreased, appetite/weight. Leptin levels were higher in females only. Leptin levels correlated positively, and ghrelin negatively, with disordered eating. The results provide further evidence for high levels of disordered eating in MDD, particularly in females. The correlations suggest that excessive eating in MDD is significantly linked to appetite hormones, indicating that it involves physiological, rather than purely psychological, factors. Further, longitudinal, research is needed to better understand whether hormonal factors play a causal role in excessive eating in MDD.

Keywords: leptin, ghrelin, depression, obesity, emotional eating, food addiction

1. Introduction:

Research indicates that obesity increases the risk of Major Depressive Disorder (MDD) by approximately 18-55%, and in turn, MDD increases the risk of obesity by approximately 37-58% (Luppino et al., 2010; Heiskanen et al., 2013; Mannan, Mamum, Doi & Clavarino, 2015). The prevalence rates of both MDD and obesity are increasing annually, with these rises attributed to physiological and psychological stress, obesogenic environments and changes in modern lifestyles (Hidaka, 2012). Consequently, individuals with MDD are at increased risk of developing additional health complications, including cardiovascular disease and metabolic syndrome (Cassano & Fava, 2002; Penninx et al., 2013). Identifying potential mechanisms for weight gain in MDD may help improve interventions aimed at reducing the likelihood of chronic disease in these at-risk individuals.

Changes in appetite and weight are diagnostic criteria for MDD (American Psychiatric Association, 2013), with the direction of appetite/weight changes differing by MDD subtype. Melancholic MDD is characterised by decreased appetite and weight loss. In contrast, atypical MDD features hyperphagia, weight gain (American Psychiatric Association, 2013), higher BMI values, increased endocrine dysregulation and more frequent instances of cardiovascular disease and metabolic syndrome (e.g. Gecici et al., 2005; Lamers et al., 2016; Milaneschi et al., 2017). Epidemiological studies have indicated that atypical MDD is now 40% more prevalent than melancholic MDD; indicating that ‘atypical’ symptoms, including weight gain, are increasingly becoming more ‘typical’ (Blanco et al., 2012; Privitera et al., 2013). Despite clearly established risks for chronic disease (Cassano & Fava, 2002; Penninx et al., 2013), there is a lack of both specific treatment guidelines for the treatment or prevention of depressogenic weight gain, and integrated approaches that address both biological and physiological factors. The long-term success of weight loss programs in general is also limited (MacLean et al., 2015). Understanding the mechanisms underlying the

pathways to weight gain in MDD may allow for better preventative strategies in individuals at risk due to MDD.

Pathways to weight gain in MDD may include appetite disturbances linked to neuroendocrine changes and associated disordered eating. Disordered eating may act as a coping mechanism for psychological distress, as foods, particularly those high in carbohydrates, can dampen physiological stress responses produced by the hypothalamic-pituitary-adrenal (HPA) axis (e.g. Dallman et al., 2003). Disordered eating includes emotional eating, increasing food intake in response to emotional distress; restrained eating, deliberately restricting food intake to prevent weight gain or encourage weight loss; and external eating, increasing food intake in response to sensory food cues (van Strien et al., 2016). Depressed mood and MDD symptom severity are associated with emotional eating (e.g. van Strien et al., 2016; Paans et al., 2018), increased consumption of food in response to external cues, and with restricting food intake (e.g. Sevincer et al., 2017).

Food addiction characterises a subset of disordered eating behaviours, defined by a preference for highly palatable foods and addiction-like behaviours such as a loss of control and withdrawal (Piccini et al., 2015). Dopaminergic reward pathways can be activated by highly palatable foods, particularly those high in carbohydrates or fat, which can result in addiction-like behaviours similar to substance use disorders (e.g. Gearhardt, Corbin & Brownell, 2009; Piccini et al., 2015). Food addiction can be measured using the Yale Food Addiction Scale (YFAS; Gearhardt et al., 2009), with a prevalence of 5-10% in the general population, and 15-25% in obese individuals (Meule & Gearhardt, 2014; Hauck et al., 2017). In a recent pilot, we found that 25% of a sample with MDD met Yale criteria for food addiction, considerably higher than general community samples (Mills et al., 2018).

The concept of food addiction is still controversial, since food is necessary for survival whereas psychoactive substances that form the basis of other addictions are not (e.g.

Ziauddeen & Fletcher, 2013: Onaolapo & Onaolapo, 2018). The composition of modern foods has been altered to increase their palatability and hedonistic qualities compared to naturally occurring foods (Leigh & Morris, 2018), to the extent that they could be argued to act similarly to addictive substances. There is increasing evidence of an overlap between activation of neural reward circuitry in response to food and drugs of addiction (e.g. Gearhardt et al., 2011; Volkow et al., 2012). Several studies have linked the concept of food addiction to MDD (e.g. Gearhardt et al., 2012; Eichen et al., 2013; Mills et al., 2018). As such, it is possible that obesogenic environments promoting the availability of highly palatable foods may be related to the increased prevalence of atypical MDD characterised by weight gain, however further research is needed.

While previous studies indicate that MDD is associated with disordered eating (e.g. Bailly et al., 2012; van Strien et al., 2016), food addiction (e.g. Eichen et al., 2013; Mills et al., 2018) and weight gain (e.g. Blanco et al., 2012), the mechanisms underlying the relationships between these factors are unclear. The hunger and satiety hormones ghrelin and leptin are related to HPA axis activity and suppression of stress responses, and therefore may be associated with MDD and associated symptomatic appetite/weight changes (Roubos et al., 2012; Spencer et al., 2014). However, little research has examined direct relationships between these hormones, disordered eating behaviours and appetite/weight changes in MDD.

Leptin is secreted by adipocyte cells in proportion to adipose tissue mass, with critical roles in regulating adipose tissue and body weight (Maffei et al., 1995). Leptin has important anorexigenic effects, acting as an appetite suppressant during times of energy excess (Elmqist et al., 1998; Trayhurn et al.,, 1999; Lu, 2007). Leptin resistance, or having high leptin levels but decreased leptin sensitivity (e.g. Pan et al.,, 2014) has been implicated in the pathogenesis of obesity (Zigman & Elmquist, 2003; Ozsoy et al., 2014). Since leptin is secreted relative to adipose tissue mass, higher levels signal the increased availability of fat and in turn lead to a

reduction in food intake such that stored fat can be utilised for energy. However, in leptin resistance individuals become desensitised to endogenous satiety signals, resulting in elevated leptin levels without the usual satiety, and subsequently increased food intake and weight gain or obesity (e.g. Maffei et al., 1995).

Human research investigating leptin levels in MDD has identified inconsistent results, with either lower (e.g. Kraus et al., 2001; Atmaca et al., 2003; Westling, et al., 2004) or elevated (e.g. Antonijevic et al., 1998; Jimenez et al., 2009; Morris et al., 2012) leptin levels in MDD versus control populations. In contrast, several studies, including large-scale meta-analyses, have indicated no difference between diagnostic groups (e.g. Hafner et al., 2012; Ozsoy et al., 2014; Carvalho et al., 2014). Individuals with atypical MDD have higher leptin levels compared to controls, and individuals with melancholic MDD (e.g. Gecici et al., 2005; Lamers et al., 2016a; Milaneschi et al., 2017), suggesting that leptin may be involved in a subset of individuals with increased appetite/weight.

Ghrelin is secreted from the stomach and gastrointestinal tract (Kojima et al., 1999), with important orexigenic roles in promoting increased food intake (e.g. Wren et al., 2000) and increased adiposity (e.g. Tschop et al.,, 2001; Thompson et al., 2004). Significantly lower total ghrelin concentrations have been observed in obese humans, indicating possible downregulation of ghrelin levels associated with excessive eating (e.g. Atalayer et al., 2013).

Studies of ghrelin in MDD are also inconsistent, with elevated (e.g. Kurt et al., 2008; Atescelik et al., 2017; Ozsoy et al., 2014) lowered (e.g. Barim et al., 2009) or no difference between MDD and control participants observed (e.g. Kluge et al., 2009; Lawson et al., 2011; Matsuo et al., 2012). Whether ghrelin levels differ by melancholic/atypical subtype is currently unclear, however due to its role in stimulating appetite levels (e.g. Wren et al., 2000) ghrelin levels may possibly be higher in those experiencing appetite/weight gain, or possibly lowered due to the downregulation observed in obesity (Atalayer et al., 2013).

The inconsistent results for leptin and ghrelin levels may be accounted for by the heterogeneity in appetite/weight change symptom profiles in MDD. Previous studies have either combined symptom subtypes (e.g. Antonijevic et al., 1998; Ozsoy et al., 2014) or have classified symptoms based on broader atypical MDD criteria, differing also in the classification methods used (e.g. Gecici et al., 2005; Lamers et al., 2016; Milaneschi et al., 2017). These inconsistent classification methods may act as potential confounds in these studies. In addition, leptin levels are more strongly correlated with appetite and weight gain and not other atypical symptoms (e.g. Milaneschi et al., 2017), suggesting that comparison by appetite/weight symptom profile may provide a clearer understanding of relationships between appetite hormones and weight gain than atypical criteria more generally.

Leptin and ghrelin are noted to vary between sexes, with higher leptin and ghrelin levels reported in females than males (e.g. Antonijevic et al., 1998; Soriano-Guillen et al., 2016); which may be explained by females having different body fat compositions than males for reproductive purposes (Blaak, 2001). However, sex differences in leptin and ghrelin levels are not always observed (e.g. Kluge et al., 2009; Tschop et al., 2001). In humans, leptin and ghrelin levels have also previously been correlated with body mass index (BMI) and waist circumference (e.g. Mills et al., 2018; Akamizu et al., 2004), suggesting potential roles for both hormones as risk factors for chronic diseases. However, no studies have simultaneously examined associations between appetite hormones, disordered eating and BMI in MDD.

Our previous pilot study (Mills et al., 2018) found that a high proportion of participants with MDD reported disordered eating, including emotional and restrained eating as measured by the Dutch Eating Behaviours Questionnaire (van Strien et al., 1986), and food addiction behaviours as measured by the Yale Food Addiction Scale (Gearhardt et al., 2009). Disordered eating was higher in females with MDD than males with MDD. Further,

disordered eating correlated positively with leptin levels, suggesting that leptin resistance may be involved in disordered eating in MDD. The current study expands on our previous work by investigating eating behaviours in relation to neurobiological measures in a new cohort. Leptin and ghrelin levels, biometrics and psychometric indices of mood and problematic eating behaviours were compared between individuals with MDD and healthy controls. Given the heterogeneous nature of MDD, participants with MDD were further subcategorised by appetite/weight symptom presentation to compare subtypes. It was predicted that:

1. Participants with MDD would report greater levels of disordered eating compared to controls. By symptom profile, MDD participants with increased appetite/weight would demonstrate higher instances of these behaviours than MDD participants without increased appetite/weight; with effects being greater in females.
2. Psychometric indices of problematic eating behaviours, food addiction and depression severity will correlate with leptin and ghrelin levels.
3. Leptin and ghrelin levels would not differ significantly between depressed and non-depressed participants overall. However, at the subgroup level in MDD, these values will be higher in those with increased appetite/weight compared to those with reduced or unchanged appetite/weight; with effects being greater in females.

2. Methods:

2.1 Participants

One hundred and twenty (120) adults aged between 18 and 54 years (M = 25.05, SD = 6.61 years; 68 female) participated. Participants were recruited by media and university advertisements. Depressed participants were pre-screened to confirm that they currently met DSM-5 criteria prior to inclusion in the MDD group (N = 60). Control participants (N = 60)

were age and gender matched to the MDD group. Depressed participants were not receiving any current or recent psychological, pharmacological or somatic treatment for MDD. All control participants had no history of diagnosed mental disorders. Use of corticosteroids, neurological illness and substance use were general exclusion criteria. Participants were asked to provide information about any medical conditions and medications being taken. The study received approval from the local ethics committee.

2.2 Measures

Depressive symptom severity was assessed using the Beck Depression Inventory (BDI-II), a 21 item self-report questionnaire (Beck et al., 1996). Disordered eating, including *Emotional, Restrained and External* eating, were measured using the Dutch Eating Behaviours Questionnaire (DEBQ; van Strien et al., 1986). Food addiction and related behaviours, including *Withdrawal* symptoms, *Cravings* and *Tolerance* to increased food intake, were assessed using the Yale Food Addiction Scale (YFAS; Gearhardt et al., 2009).

2.3 Procedure

Participants attended one visit at the university clinical trials research unit. All participants provided informed written consent. Depressed participants were interviewed to confirm that they met criteria for MDD using the Mini Neuropsychiatric Interview, version 7.0.2 for DSM-5 (MINI; Sheehan, 2015). Depressed participants were asked to indicate whether they had experienced any recent changes to their appetite or weight. To meet the criteria for increased or decreased/unchanged appetite/weight, MDD participants were required to endorse a 5% (or 3 kilogram) increase or decrease to their weight that was not the result of deliberate weight changes, such as intentional weight loss, in the previous month (Sheehan, 2015).

Participants' height, weight, waist circumference, blood pressure and heart rate were measured, then a 10ml blood sample was obtained by a phlebotomist. All blood samples were taken between 9:00-11:00am. Participants were not required to fast, however details of food consumption in the previous 12h were recorded. Participants then completed the psychometric questionnaires.

2.4 Data and Statistical Analysis

Blood samples were centrifuged at 4°C, at 2800rpm for 10 min immediately following blood collection. Plasma was stored in a -80°C freezer until analysis. Plasma leptin and total ghrelin levels were measured using standard ELISA testing kits (Abcam, Cambridge, United Kingdom and Thermofisher Scientific, Carlsbad, United States of America respectively). The intra- and inter-assay coefficients of the leptin ELISA were <10% and <12% respectively, and <6% and <8.5% for the total ghrelin ELISA.

Statistical analysis was conducted using 'Statistical Package for the Social Sciences' (SPSS, Version 23). The dependent variables of interest were the psychometric measurements (BDI, DEBQ and YFAS scores), plasma leptin and total ghrelin levels. Due to the relationship between leptin and adipogenesis (e.g. Maffei et al., 1995), to control for potential confounding effects of visceral fat, plasma leptin was normalised to waist circumference (in metres) prior to statistical analysis.

Two-way factorial analyses of variance (ANOVA) were used to test for differences in the dependent variables with the between-subjects factors of Diagnosis (MDD, control) and Sex (male, female), with Age and BMI used as covariates. Further two-way factorial ANOVAs were used to test for subgroup differences in the variables as a function of appetite and weight changes in MDD participants only, with the between-subjects factors of Appetite and Weight Categories (increased, decreased/no change) and Sex (male, female), with Age and BMI also as covariates. Pearson's correlation coefficients and Spearman's rank

correlations were used to determine relationships between the variables. For all statistical tests, $\alpha < .05$ was considered statistically significant. Post-hoc analyses were conducted using Bonferroni corrections.

3. Results:

3.1 Analyses of MDD (combined subtypes) compared to controls:

3.1.1 Demographic and Biometric Data

Participant characteristics are shown in Table 1. There were 34 females and 26 males in both MDD ($N = 60$) and control ($N = 60$) groups. No participants had a diagnosed eating disorder, and none were current smokers. Of the 120 participants, 30 (18 MDD) had not consumed any food or drink other than water for approximately 12h.

The groups did not differ significantly in age. Males weighed more than females ($F(1, 116) = 18.159$, $p < .001$). No further differences for Diagnosis, Sex or interaction effects were significant for biometric data (Table 1).

Table 1:
Means and standard deviations for biometric data, by Diagnosis and Sex (total *N* = 120; MDD and control participants).

		Diagnosis				Sex			
Variable		Control M (SD)	MDD M (SD)	Effect *p*	Effect Size partial η^2	Male M (SD)	Female M (SD)	Effect *p*	Effect Size partial η^2
	Sample size (*n*)	60	60	-	-	52	68	-	-
Biometrics	Age (years)	25.40 (7.17)	24.70 (6.03)	0.422	0.006	25.31 (5.38)	24.85 (7.44)	0.709	0.001
	Weight (kg)	73.29 (16.67)	74.65 (16.13)	0.721	0.001	80.79 (13.98)*	68.76 (16.18)	< 0.001	0.135
	BMI (kg/m^2)	25.10 (5.35)	25.80 (5.41)	0.580	0.003	25.51 (4.35)	25.40 (6.06)	0.910	0.000
	Waist Circumference (m)	0.89 (0.14)	0.85 (14.30)	0.150	0.018	0.90 (0.12)	0.82 (0.13)	0.071	0.028

Note: MDD = Major Depressive Disorder; BMI = Body Mass Index. * Indicates a significant difference compared to the other diagnostic group or sex being compared.

3.1.2 Psychometric Data

Participants with MDD had significantly higher Total BDI scores compared to controls ($F(1, 116) = 354.013$, $p < .001$). Females had higher Total BDI scores than males ($F(1, 116) = 4.860$, $p = .029$). The interaction between Diagnosis and Sex was not significant.

Depressed participants scored significantly higher on the *Emotional* ($F(1, 116) = 20.194$, $p < .001$) and *Restrained* ($F(1, 116) = 9.576$, $p = .002$) subscales of the DEBQ compared to controls. Females also scored significantly higher on the *Emotional* ($F(1, 116) = 10.392$, $p = .002$) and *Restrained* ($F(1, 116) = 6.268$, $p = .014$) subscales compared to males. *External* eating did not differ between diagnostic groups or sexes. No interaction effect between Diagnosis and Sex was observed for any DEBQ subscales.

Endorsement rates for each YFAS symptom are presented in Table 3. Seventeen (28%; 13 female) MDD participants met the YFAS criteria for food addiction compared to two (3%; both female) of controls. Overall, participants with MDD had significantly more food addiction symptoms than controls ($F(1, 116) = 22.139$, $p < .001$), and scored significantly higher than controls on each YFAS subscale, with the exception of *Continued Use Despite Problems*. *Withdrawal* scores were significantly higher in females compared to males ($F(1, 116) = 4.208$, $p = .042$), with no further differences by Sex, and no interaction effects identified **(**Table 2).

Table 2:
Means and standard deviations for psychometric data, by Diagnosis and Sex (total *N* = 120; MDD and control participants).

		Diagnosis				Sex			
Psychometrics		Control M (SD)	MDD M (SD)	Effect *p*	Effect Size partial η^2	Male M (SD)	Female M (SD)	Effect *p*	Effect Size partial η^2
	Sample size (*n*)	60	60	-	-	52	68	-	-
BDI	Total Score	4.80 (4.75)	30.72 (9.59)*	< 0.001	0.753	16.06 (13.82)	19.06 (15.88)*	0.029	0.040
DEBQ	Emotional Eating	1.99 (0.72)	2.75 (1.11)*	< 0.001	0.148	2.07 (0.95)	2.60 (.99)*	0.002	0.082
	Restrained Eating	1.94 (0.83)	2.49 (1.07)*	0.002	0.076	1.97 (0.93)	2.40 (1.01)*	0.014	0.051
	External Eating	2.98 (0.71)	3.20 (0.67)	0.117	0.021	3.08 (0.72)	3.10 (0.69)	0.923	0.000
YFAS	Increased Intake	0.13 (0.34)	0.33 (0.48)*	0.012	0.053	0.27 (0.45)	0.21 (0.41)	0.410	0.006
	Failure to Quit	0.10 (0.30)	0.37 (0.49)*	0.001	0.093	0.15 (0.36)	0.29 (0.46)	0.059	0.030
	Time Taken to Obtain	0.10 (0.30)	0.37 (0.49)*	0.001	0.096	0.27 (0.45)	0.21 (0.41)	0.400	0.006
	Activities Given Up	0.02 (0.13)	0.28 (0.45)*	< 0.001	0.138	0.13 (0.35)	0.16 (0.37)	0.662	0.002
	Adverse Consequences	0.07 (0.25)	0.30 (0.46)*	0.001	0.090	0.15 (0.36)	0.21 (0.41)	0.452	0.005
	Tolerance	0.03 (0.18)	0.28 (0.45)*	< 0.001	0.111	0.17 (0.38)	0.15 (0.36)	0.685	0.001
	Withdrawal	0.10 (0.30)	0.42 (0.50)*	< 0.001	0.121	0.17 (0.38)	0.32 (0.47)*	0.042	0.035
	Use Despite Problems	0.08 (0.28)	0.22 (0.41)	0.061	0.030	0.10 (0.30)	0.19 (0.40)	0.144	0.018
	Failed Role Obligations	0.02 (0.13)	0.17 (0.38)*	0.006	0.063	0.10 (0.30)	0.09 (0.29)	0.880	0.000
	Physically Hazardous Use	0.08 (0.28)	0.30 (0.46)*	0.002	0.079	0.21 (0.41)	0.18 (0.38)	0.621	0.002
	Cravings	0.07 (0.25)	0.23 (0.43)*	0.012	0.053	0.12 (0.32)	0.18 (0.38)	0.348	0.008
	Symptom Count	0.80 (3.35)	3.27 (3.45)*	< 0.001	0.160	1.85 (2.89)	2.18 (3.12)	0.519	0.004

Note: MDD = Major Depressive Disorder; BDI = Beck's Depression Inventory; DEBQ = Dutch Eating Behaviours Questionnaire; YFAS = Yale Food Addiction Scale. YFAS subscales are scored dichotomously and occur between 0.00 and 1.00. * Indicates a significant difference compared to the other diagnostic group or sex being compared.

Table 3:
Endorsement rates for Yale Food Addiction Scale (YFAS) data, by Diagnosis and Sex (total *N* = 120; MDD and control participants).

		Sex		Diagnosis	
		Male %	Female %	Control %	MDD %
	Sample size (*n*)	52	68	60	60
YFAS	Increased Intake	26.92	20.59	13.33	33.33
	Inability to Quit	15.38	29.41	10	36.67
	Time Taken to Obtain	26.92	20.59	10	36.67
	Activities Given Up	13.46	16.18	1.67	28.33
	Adverse Consequences	15.38	20.59	6.67	30
	Tolerance	17.30	14.71	3.33	28.33
	Withdrawal	17.30	32.35	10	41.67
	Use Despite Problems	9.61	19.12	8.33	21.67
	Failed Role Obligations	9.61	8.82	1.67	16.67
	Physically Hazardous Use	21.15	17.65	8.33	30
	Cravings	11.54	17.65	6.67	23.33

Note: MDD = Major Depressive Disorder; YFAS = Yale Food Addiction Scale.

3.1.3 Leptin and Ghrelin

Initial inspection of the distribution of the waist-circumference normalised leptin data across all participants indicated a positively skewed distribution (skewness = 6.448, *SE* = .231). The normalised leptin data were subsequently natural-log transformed (e.g. Milaneschi et al., 2012; Mills et al., 2018). Following log-transformation, three univariate outliers were detected, two of which were MDD participants with leptin levels below the limit of detection. Eleven participants (8 MDD, 3 control; 10 female) had reported insulin dysregulation issues (three had diabetes, two had insulin resistance and six had polycystic ovarian syndrome). In order to eliminate potential confounding effects, the univariate outliers and leptin data from all participants with insulin dysregulation disorders were excluded from subsequent leptin analyses (e.g. Mills et al., 2018). Means and standard deviations for the log-transformed

leptin values are displayed in Table 4. Log-normalised leptin values did not differ between participants who elected to fast and those who did not ($F(1, 102) = .103$, $p = .749$).

Accounting for age and BMI, log-normalised leptin values were not significantly different between MDD and control participants. Females had significantly higher log-normalised leptin values than males ($F(1, 100) = 110.391$, $p < .001$). BMI was a significant covariate ($F(1, 100) = 77.460$, $p < .001$), however Age as a covariate, and the interaction between Diagnosis and Sex, were non-significant.

Means and standard deviations for the ghrelin data are also displayed in Table 4. Inspection of the ghrelin data indicated a normal distribution (skewness = .135, $SE = .231$), and no outliers in boxplot diagrams were detected. Participants reporting insulin dysregulation issues ($n = 11$) were also excluded from ghrelin analyses. Ghrelin values did not differ between fasting and non-fasting participants ($F(1, 105) = .164$, $p = .686$).

Ghrelin values did not differ significantly between MDD and control participants, or by Sex, after accounting for age and BMI as potential covariates. BMI was identified as a significant covariate ($F(1, 103) = 8.007$, $p = .006$), however Age as a covariate and the interaction between Diagnosis and Sex were non-significant.

Table 4:
Means and standard deviations for raw and log-transformed leptin (*N* = 106) and ghrelin (*N* = 109) (ng/ml), by Diagnosis and Sex (MDD and control participants).

Variable			Leptin	Log-Leptin	Main Effect	Effect Size	D x S Interaction		Ghrelin	Main Effect	Effect Size	D x S Interaction
		n	M (SD)	M (SD)	*p*	partial η^2	*p*	*n*	M (SD)	*p*	partial η^2	*p*
Diagnosis	Control	56	8.51 (13.44)	1.11 (1.58)	0.173	0.018	0.814	57	2.77 (1.22)	0.994	0.000	0.668
	MDD	55	16.94 (38.80)	1.42 (1.90)				52	2.70 (1.25)			
Sex	Male	48	3.10 (5.17)	0.13 (1.49)	<0.001	0.525		51	2.54 (1.10)	0.150	0.020	
	Female	58	20.26 (36.66)	2.19 (1.32)				58	2.90 (1.31)			
Covariates	Age	-	-	-	0.104	0.026	-	-	-	0.241	0.013	-
	BMI	-	-	-	<0.001	0.436	-	-	-	0.006	0.072	-

Note: MDD = Major Depressive Disorder; BMI = Body Mass Index. Leptin values normalised to waist circumference. Significance noted for log-transformed data.

3.2 Analysis by Appetite/Weight Change Sub-Groups in MDD

All 60 MDD participants were categorised based on self-reported increases (n = 28), decreases (n = 25) or no changes (n = 7) to their appetite/weight from the clinical interview. Data from participants with increased appetite/weight were compared to those with decreased or unchanged appetite/weight (n = 32) combined. Further analyses were performed removing the seven participants with unchanged appetite/weight due to potential differences from participants experiencing appetite/weight dysregulation, however the results were equivalent in terms of significant effects and interactions. Hence, the results from the total sample are reported. There were 17 females and 11 males in the increased group, and 17 females and 15 males in the decreased/unchanged group. The Appetite/Weight Categories did not differ in sex distributions (χ^2 (1, N = 60) = .350, p = .554) or age.

Weight (F(1, 56) = 4.041, p = .049) and BMI (F(1, 56) = 7.480, p = .008) was significantly higher in participants reporting increased appetite/weight than those with decreased/unchanged appetite/weight. Participants with increased appetite/weight also scored significantly higher on the *Emotional* eating subscale of the DEBQ (F(1, 56) = 37.388, p < .001) and reported a greater number of YFAS food addiction symptoms (F(1, 56) = 13.650, p = .001) They also scored significantly higher on each of the YFAS subscales (data not shown). Sex differences for the biometric and psychometric data were as reported previously in sections 3.1.1 and 3.1.2.

Following the exclusion of 10 MDD participants for insulin dysregulation issues as previously described (section 3.3), log-normalised leptin and ghrelin values did not differ between participants who elected to fast and those who did not, and they were not significantly different between those with increased or decreased/unchanged appetite/weight. BMI was a significant covariate in both analyses. Sex effects reflected those reported previously for the larger comparison (section 3.1.3). No further differences or interaction

effects based on Appetite/Weight Categories or Sex were identified. Means and standard deviations for the biometric, psychometric and endocrine data are displayed in Table 5.

Table 5:
Means and standard deviations for biometric, psychometric (*N* = 60), leptin (*N* = 50; ng/ml) and ghrelin (*N* = 52; ng/ml) by Appetite/Weight Categories (increased compared to decreased/unchanged) and Sex (MDD participants only).

		Appetite/Weight Categories				Sex			
Variables		Increased M (SD)	Decreased/Unchanged M (SD)	Effect *p*	Size partial η^2	Male M (SD)	Female M (SD)	Effect *p*	Size partial η^2
	Sample Size (*n*)	28	32	-	-	26	34	-	-
Biometrics	Weight (kg)	78.37 (16.6)	71.4 (15.23)	0.49*	0.67	79.98 (16.48)	70.58 (14.82)	0.14*	0.104
	BMI (kg/m^2)	27.81 (4.99)	24.04 (5.20)	0.008*	0.118	25.21 (4.77)	26.25 (5.87)	0.580	0.006
	Waist Circumference (m)	0.93 (0.14)	0.86 (0.14)	0.072	0.056	0.90 (0.13)	0.90 (0.15)	0.839	0.001
BDI	Total Score	31.96 (10.21)*	29.62 (9.02)	0.444	0.011	27.73 (9.44)	33.00 (9.18)	0.041*	0.072
DEBQ	Emotional Eating	3.49 (0.98)*	2.10 (0.75)	<0.001*	0.400	2.41 (1.12)	3.01 (1.03)	0.024*	0.087
	Restrained Eating	2.52 (0.97)	2.47 (1.17)	0.964	0.000	2.17 (1.01)	2.73 (1.07)	0.051	0.066
	External Eating	3.35 (0.63)	3.08 (0.69)	0.087	0.051	3.10 (0.73)	3.30 (0.63)	0.447	0.010
YFAS	Symptom Count	4.96 (3.74)	1.78 (2.37)	0.001*	1.96	2.81 (3.31)	3.62 (3.57)	0.415	0.012
Hormones	Leptin (ng/ml)[3]	1.88 (2.00)	1.03 (1.74)	0.536	0.009	0.24 (1.66)	2.51 (1.40)	<0.001*	0.506
	Ghrelin (ng/ml)[33]	2.68 (1.39)	2.71 (1.14)	0.594	0.006	2.48 (1.16)	2.92 (1.31)	0.260	0.027

Note: MDD = Major Depressive Disorder; BMI = Body Mass Index; BDI = Beck's Depression Inventory; DEBQ = Dutch Eating Behaviours Questionnaire; YFAS = Yale Food Addiction Scale. [#] N = 50; normalised to waist circumference. [33] N = 52. * Indicates a significant difference compared to the other appetite/weight group or sex being compared.

3.3 Correlation Analyses

BMI correlated positively with *Restrained* ($r(120) = .200$, $p = .028$) and *Emotional* ($r(120) = .274$, $p = .002$) eating. Waist circumference also correlated positively with *Emotional* eating ($r(120) = .248$, $p = .006$). YFAS Symptom Count scores correlated positively with participant weight ($r(120) = .217$, $p = .017$), BMI ($r(120) = .285$, $p = .002$) and waist circumference ($r(120) = .310$, $p = .001$). Total BDI scores positively correlated with the *Restrained* ($r(120) = .335$, $p < .001$) and *Emotional* ($r(120) = .462$, $p < .001$) subscales of the DEBQ, and with the YFAS Symptom Count score ($r(120) = .501$, $p < .001$). YFAS Symptom Count scores further correlated with *Restrained* ($r(120) = .216$, $p = .018$), *Emotional* ($r(120) = .548$, $p < .001$) and *External* ($r(120) = .211$, $p = .020$) eating.

Log-normalised leptin values correlated positively with weight ($r(106) = .203$, $p = .037$), BMI ($r(106) = .490$, $p < .001$) and waist circumference ($r(106) = .378$, $p = < .001$). Log-normalised leptin values correlated positively with *Emotional* ($r(106) = .334$, $p < .001$) and *Restrained* ($r(106) = .366$, $p = < .001$) eating, and the *Failure to Quit* ($r(106) = .289$, $p = .003$), *Adverse Consequences* ($r(106) = .198$, $p = .042$) and *Continued Use Despite Problems* ($r(106) = .218$, $p = .025$) subscales of the YFAS. Ghrelin values correlated negatively with weight ($r(109) = -.239$, $p = .012$), BMI ($r(109) = -.247$, $p = .010$) and waist circumference ($r(109) = -.253$, $p = .008$) and *Restrained* eating ($r(120) = -.190$, $p = .048$).

4. Discussion:

The current study examined relationships between disordered eating, the hunger/satiety hormones ghrelin and leptin and symptomatic weight changes in MDD. It was found that disordered eating was higher in MDD than controls, in females than males, and in a subset of depressed individuals with appetite/weight gain compared to decreased/unchanged appetite/weight. Leptin levels correlated positively, and ghrelin negatively, with disordered eating.

Emotional and restrained eating behaviours were higher in MDD than controls. Food addiction symptoms were also higher in MDD, with 28% of MDD participants compared to 3% of control participants meeting the Yale criteria for food addiction; double that reported in general community samples (Meule & Gearhardt, 2014) and replicating our earlier findings (Mills et al., 2018). These findings align with previous studies indicating that MDD is associated with increased emotional (e.g. van Strien et al., 2016; Paans et al., 2018), restrained (e.g. Sevincer et al., 2017) and food addiction eating behaviours (e.g. Eichen et al., 2013; Gearhardt et al., 2012). Consistent with our previous study, emotional eating and food addiction were also higher in females compared to males (e.g. Mills et al., 2018). In addition, they were higher in participants in the MDD subgroup who had increased compared to reduced or unchanged appetite/weight, consistent with previous research identifying a higher prevalence of these behaviours in overweight and obese populations compared to normal weight controls (e.g. Bailly et al., 2012). These findings provide evidence in support of dysregulated appetite and food intake patterns in MDD, particularly in females. Increased intake of highly palatable foods and related behaviours may be used to minimise psychological distress or dampen physiological stress responses produced by the HPA axis (e.g. Dallman et al., 2003; Leow et al., 2018), therefore acting as a potential coping mechanism for stress or low mood. This is supported by the positive associations between MDD symptom severity, emotional eating and food addiction. Given that increased food intake and emotional eating have been linked to weight fluctuations (e.g. Keller & Siegrist, 2015), these findings provide support for such behaviours acting as potential risk factors for weight gain in those with increased appetite/weight in MDD, particularly females.

Leptin levels were positively correlated with emotional and restrained eating, and food addiction symptoms including loss of control in food consumption and continuing to eat despite negative consequences. Leptin was also positively associated with BMI and weight.

The associations between problematic eating behaviours and leptin are consistent with our previous study (Mills et al., 2018), which identified that disordered eating was correlated with leptin levels. Higher leptin levels correlating positively with measures of emotional eating and food addiction relating to increased food intake lead to the suggestion of possible leptin resistance, because higher leptin levels would normally be expected to be associated with satiety rather than behaviours related to increased food intake. In the current study we provide new information about the relationships between ghrelin and some eating behaviours, with ghrelin levels negatively correlating with restrained eating. This suggests that individuals with higher ghrelin levels may be more likely to experience hunger and increased food intake, with a lower degree of control over these behaviours. Comfort eating in MDD is often viewed as having psychological underpinnings (e.g. Leow et al., 2018), however the associations between leptin, ghrelin and disordered eating in MDD suggest that excessive eating behaviours are also related to physiological pathways, which is relevant to intervention approaches. Further research is required to assess the temporal nature and causal relationships between these variables.

Leptin and ghrelin levels did not differ significantly by diagnosis, consistent with some previous studies investigating leptin (e.g. Carvalho et al., 2014; Mills et al., 2018) and ghrelin (e.g. Kluge et al., 2009; Matsuo et al., 2012) levels in MDD, but are in contrast to other studies reporting either elevated or lowered levels (e.g. Antonijevic et al., 1998; Ozsoy et al., 2014). The inconsistencies in findings may be due to the heterogeneous nature of symptom profiles in MDD, which has not been a notable factor in previous research. However, in the current study, neither leptin or ghrelin levels differed significantly by appetite/weight symptom profile. These findings, in combination with the aforementioned correlations, suggest that leptin and ghrelin may be specifically linked to disordered eating

behaviours in MDD as opposed to the disorder more generally, and differences may not be clearly discernable in between-groups analyses.

Clear sex differences were observed in relation to leptin levels, with females having higher waist-normalised leptin levels than males. These results are consistent with previous findings (e.g. Antonijevic et al., 1998; Mills et al., 2018). Because females store more body fat for reproductive purposes (Blaak, 2001), and leptin secretion is proportional to adipose tissue mass (Maffei et al., 1995), females may have naturally higher leptin levels. No sex difference was observed in ghrelin levels, consistent with some previous studies (e.g. Tschop et al., 2001) but in contrast to others (e.g. Soriano-Guillen et al., 2016), indicating that further research is required to examine ghrelin levels in relation to depressogenic weight gain in females also.

These findings help to better understand potential biological, psychological and behavioural pathways associated with depressogenic weight gain, which have previously not been studied in unison. While we did not find an influence of MDD or depression subtypes in leptin levels, their significant correlation with problematic eating behaviours warrants further investigation. Collectively, the identified variables represent promising targets for research into potentially modifiable risk factors for disordered eating behaviours, which may act as risk factors for weight gain in MDD. If increased leptin occurs in the absence of satiety behaviours, but rather in association with depressogenic increased eating corresponding to leptin resistance, this may be a potential therapeutic target to address problematic eating and weight gain risk in a large subset of individuals with MDD, particularly females. The potential of leptin as a therapeutic target for other symptoms in MDD is currently being considered (Ge et al., 2018), however its potential role in weight gain associated with MDD has received little consideration to date.

There are some limitations of the study which need to be considered. Participants were not required to fast prior to blood sampling; previous leptin and ghrelin studies have used both fasting and non-fasting protocols (e.g. Milaneschi et al., 2017; Mills et al., 2018). Previous research has found that non-fasting leptin levels are not significantly different from fasting leptin levels (e.g. Hancox & Landhuis, 2011). Additionally, ghrelin levels maintain characteristic meal-related changes at meal times even when fasting (e.g. Natalucci et al., 2005). We did compare subgroups of participants who had not consumed food or drink for 12h with those who had and did not find significant hormonal differences, however use of differing protocols should be considered when interpreting hormone results. Potential confounding variables, such as participants' dietary nutrient intake, physical activity levels and menstrual phase in female participants were also not controlled for. Much previous leptin research does not include information on physical activity or menstrual phase (e.g. Ozsoy et al., 2014; Milaneschi et al., 2017), however these factors should be considered in future studies. This study is also limited by its cross-sectional design. Longitudinal research is necessary to examine temporal relationships, if any, between disordered eating, appetite hormones and weight gain in MDD.

In conclusion, the current study provides new information regarding problematic eating behaviours in MDD and their relationships to hormones and other symptoms. While comfort eating in MDD is often viewed as an emotional issue, the results suggest that self-reported excessive eating in MDD correlates with appetite hormones, implying that these behaviours may have a greater physiological basis than previously understood, related to appetite and core depressive symptoms. The results also suggest that leptin dysregulation may be important to depressogenic excessive eating and weight gain, representing a potential treatment target for weight gain and associated chronic disease in individuals affected by MDD, particularly females. Future longitudinal research is warranted into these factors.

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