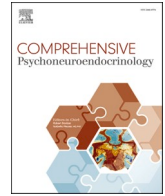


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Cortisol in relation to problematic eating behaviours, adiposity and symptom profiles in Major Depressive Disorder

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ABSTRACT

Aims: Major Depressive Disorder (MDD) is associated with an increased risk of chronic disease related to weight gain, problematic eating behaviours and neuroendocrine changes. MDD is frequently associated with altered hypothalamic-pituitary-adrenal axis activity and cortisol secretion, where cortisol has been implicated in regulating energy balance, food intake and depressogenic weight changes. However, little research has examined the relationships between cortisol, adiposity and depressogenic problematic eating behaviours.

Method: Plasma cortisol concentrations were compared between 37 participants with MDD reporting appetite/weight loss, 43 participants with MDD reporting appetite/weight gain, and 60 healthy controls, by sex. Associations between cortisol, indices of adiposity and problematic eating behaviours were then assessed after accounting for demographic variables and depressive symptoms. Depressive symptoms were assessed using the Depression subscale of the Depression, Anxiety and Stress Scale, and eating behaviours with the Dutch Eating Behaviours Questionnaire and Yale Food Addiction Scale.

Results: Participants with MDD reporting appetite/weight loss had higher cortisol compared to controls, and marginally higher cortisol than those with MDD reporting appetite/weight gain. Cortisol negatively and significantly accounted for unique variance in body mass index and waist circumference after accounting for variance associated with age, sex and depressive symptoms, however it was not a significant predictor of problematic eating behaviours, such as emotional eating or food addiction. Cortisol concentrations did not differ between sexes.

Conclusion: The results indicate that cortisol is related to lower indices of adiposity and depressogenic symptoms of appetite/weight loss but is not related to problematic eating behaviours and appetite increases in MDD. These findings provide further evidence that the melancholic and atypical subtypes of MDD are associated with differential neuroendocrine and anthropometric indices, as well as behavioural and symptom profiles. Further research investigating the temporal nature of the identified relationships may assist in facilitating the development of improved interventions for individuals affected by weight changes in MDD.

1. Introduction

It is well established that individuals with Major Depressive Disorder (MDD) are at an increased risk of chronic health conditions, particularly cardiometabolic abnormalities such as obesity, metabolic syndrome and cardiovascular disease [1–4]. A proposed link between MDD and chronic disease is weight gain linked to problematic eating behaviours and changes in neuroendocrine pathways [5,6]. The most frequently reported neuroendocrine change in MDD is dysregulated

hypothalamic-pituitary-adrenal (HPA) axis activity and cortisol secretion [7,8]. However, little research has examined the relationships between cortisol, adiposity, depressogenic problematic eating behaviours and symptom profiles.

There is substantial heterogeneity in MDD symptom profiles [9,10], however latent class analyses suggest that appetite and weight change patterns and sex differences in depressive symptom presentation are the most consistent means of differentiating MDD subtypes [11–13]. Melancholic MDD is characterised by appetite and weight loss, in

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addition to non-reactive mood, anhedonia and insomnia, and is more prevalent in males [14,15]. In contrast, atypical MDD is associated with hyperphagia and weight gain, as well as greater mood reactivity, interpersonal sensitivity, hypersomnia and leaden paralysis, and is more prevalent in females [14,16]. Related to hyperphagia and weight gain, atypical MDD also features a high prevalence of problematic eating behaviours [5,6]. Such eating behaviours include *Emotional* eating, or greater food intake in response to negative emotions or stress; *Restrained* eating, or intentionally restricting food intake to promote weight loss or maintain a certain body weight; and *External* eating, or greater food intake in response to sensory food cues [17,18]. A fourth dysregulated eating behaviour is *Food Addiction*, which is the excessive intake of highly palatable foods associated with the development of addiction-like behaviours, such as cravings for high sugar and fat foods, and withdrawal symptoms when such foods are not consumed [19].

There is some evidence that melancholic and atypical MDD are also associated with different neural responses to food and metabolic signalling pathways. Neuroimaging studies indicate that depressed individuals with appetite and weight gain exhibit greater and more sustained activation in dopamine-mediated reward circuitry in response to, and greater attentional biases towards, highly palatable foods compared to those reporting appetite and weight loss [14,20]. With respect to endocrine factors, atypical MDD is associated with elevated leptin, insulin, triglycerides and inflammatory cytokines, and lower ghrelin, compared to melancholic MDD [14,21]. We previously identified that problematic eating behaviours in MDD were more common in those with an atypical MDD symptom profile and associated with plasma leptin, ghrelin and dopamine, BMI and waist circumference [5,6,22]. These findings suggest that eating behaviours in MDD are linked to physiological factors, and that depressed individuals who experience weight gain as part of atypical MDD may be at a greater risk of chronic health conditions than those with melancholic MDD [5,6,14].

Cortisol may also be relevant to depressogenic appetite and weight changes. Dysregulation of the HPA axis is a common neurobiological feature of MDD [8,23] that varies by depressogenic subtype. Melancholic MDD is associated with HPA axis hyperactivity and elevated cortisol concentrations, typically related to an acute stage of the stress response. In contrast, atypical MDD is linked to prolonged HPA axis activation following early life stressors, resulting in chronically low cortisol levels [24,25]. Males often demonstrate higher cortisol concentrations than females irrespective of depression diagnoses [26,27]. Across diagnostic groups and sexes, higher cortisol is associated with greater psychopathology [23], emotionality [28] and stress [29]. Cortisol release is stimulated by increased metabolic demand or expenditure such as stress or hunger [30–32], with catabolic effects to increase energy mobilisation [33,34]. To more effectively regulate sustained increased energy demands, it has been suggested that cortisol may also stimulate food intake, particularly of highly palatable foods, which may contribute to weight gain [25,35]. As such, cortisol may be relevant to the appetite and weight symptom profiles that differentiate melancholic and atypical MDD.

Given the high prevalence of overeating in MDD, particularly food addiction [6], and the relationships between overeating, stress, biological factors and weight [5,36], evaluating the relationships between cortisol, adiposity, depressogenic problematic eating behaviours and symptom profiles may lead to a greater understanding of the pathways between MDD and chronic disease. Despite the links between cortisol, appetite and weight, to our knowledge the specific relationships between cortisol and problematic eating behaviours are yet to be examined. Such an understanding may inform more effective intervention approaches, as cortisol may be a modifiable risk factor for appetite and weight changes in MDD. The aim of the current study was to therefore determine any associations between cortisol, problematic eating behaviours and weight presentations in participants with MDD and healthy controls. It was predicted that:

1. Plasma cortisol levels will be significantly higher in those with MDD presenting with decreased appetite/weight compared to those with MDD reporting increased appetite/weight and controls, with effects stronger in males than females.
2. Plasma cortisol levels will be associated with problematic eating behaviours and adiposity as measured by BMI and waist circumference, after accounting for age, sex and levels of depressive symptoms.

2. Methods

2.1. Participants

The current study is part of a broader investigation into MDD, and we previously reported on peripheral dopamine levels in the same cohort of participants [6]. One hundred and forty (140) adults (60 male) were recruited via media and university advertisements and were included in the study. Eighty (80) individuals reporting depressive symptoms were included in the MDD group and were carefully pre-screened to confirm a current major depressive episode based on DSM-5 criteria using the Mini International Neuropsychiatric Interview, version 7.0.2 (MINI; [37]). Depressed participants were required to not be receiving any current or recent pharmacological, somatic or psychological treatment for MDD. Sixty (60) individuals with no currently diagnosed psychiatric diagnoses or significant mental health history comprised the control group. Corticosteroid use, neurological illness and substance use disorders were general exclusion criteria. All participants were asked to provide information regarding current medical conditions and medications. No participant in the MDD or control group was taking medication for depression or any other psychological condition. Ethics approval was received from the local ethics committee.

2.2. Psychometric assessments

Participants completed the 21-item Depression, Anxiety and Stress Scale (DASS-21; [38]). For the current study, the *Depression* subscale was used as a measure of depression-related symptomology. Problematic eating behaviours, consisting of emotional, restrained and external eating behaviours, were evaluated using the 33-item Dutch Eating Behaviours Questionnaire (DEBQ; [39]). Food addiction-related symptomology, such as cravings for highly palatable foods and food withdrawal-related symptoms, were assessed using the 35-item Yale Food Addiction Scale (YFAS, version 2; [19]). A composite score of all YFAS subscales was calculated to index food addiction severity.

2.3. Procedure

Participants attended one appointment at the local Clinical Research and Trials Unit between 9:00 and 11:00am. Written informed consent was obtained from all participants. Participants in the MDD group were interviewed using the MINI [37] to confirm a current depressive episode at the time of their visit. MDD participants were asked to indicate any changes to their appetite or weight by endorsing either daily increases or decreases to their appetite over the preceding two-week period and/or a 5% (or 3 kg) decrease/no change or increase to their weight in the previous month in order to determine their appetite and weight symptom presentation [9,37]. For all participants, waist circumference, weight and height were measured, and body mass index (BMI) values were calculated. A phlebotomist then obtained a 10 ml blood sample from the antecubital vein into EDTA-coated tubes, which were placed on ice immediately after collection. All blood samples were collected between 9:00–11:00am to control for diurnal variations in cortisol. Participants were not required to fast, however food intake details in the 12 h preceding blood samples were recorded. The questionnaires were then completed.

2.4. Data and statistical analysis

Ten (10) µl per millilitre of aprotinin inhibitor was added to each blood sample to prevent blood coagulation immediately following collection. Blood samples were then centrifuged at 4 °C, at 3000 rpm for 10 min. Aliquoted plasma was stored at -80 °C until analysis. Plasma cortisol levels were determined using a standard enzyme linked immunosorbent assay testing method with detection at 450 nm and sensitivity of 2.45 ng/ml (Abcam, Cambridge, United Kingdom). Standards and samples were analysed in duplicate. The inter- and intra-assay coefficients for the cortisol ELISAs were <10% and <9% respectively.

Statistical analyses were performed using ‘Statistical Package for the Social Sciences’ (SPSS, Version 26). The dependent variables for this study were plasma cortisol levels, demographics and biometrics (age, sex, BMI, waist circumference) and the psychometric questionnaire scores (DASS-Depression, DEBQ, YFAS). Plasma cortisol levels were natural-log transformed to better approximate a normal distribution prior to statistical analyses. Questionnaire scores were also natural-log transformed, however effects and interactions were equivalent for transformed and untransformed psychometric data. Consequently, results based on untransformed questionnaire data only are reported.

A two-way factorial analysis of variance (ANOVA) was used to investigate differences in cortisol concentrations with the between-subjects factors of Appetite and Weight Change (MDD decreased/unchanged, MDD increased, control as determined by their endorsement of DSM criteria during the MINI interview) and Sex (male, female), and age as a covariate. Welch’s ANOVAs were performed where between-group violations in homogeneity of variance were detected and are reported where appropriate. Multiple linear regressions were then conducted to investigate whether cortisol accounted for unique variance in indices of adiposity (BMI, waist circumference) and problematic eating behaviours (*Emotional, Restrained, External eating, Food Addiction*). An $\alpha < .05$ was considered statistically significant for all analyses. To achieve statistical power of 80%, with significance at $p < .05$, for a factorial ANCOVA with three groups with a medium effect size (0.3) a total of 111 participants are required. Further, for a multivariate regression with four predictors, with a medium effect size (0.15), a total of 85 participants are required. These calculations demonstrate that the current study is adequately powered (G*Power, version 3.1.9.6).

3. Results

3.1. Participant characteristics

General participant characteristics, including demographic, biometric and psychometric information, are summarised in Table 1 and were previously reported in relation to plasma dopamine levels [6]. Participants were aged between 18 and 63 years. When participants were sub-classified by appetite/weight symptom profile based on their responses to the clinical interview, no control participants reported any changes to their appetite or weight. In contrast, all 80 MDD self-reported either decreased ($n = 30$) or increased ($n = 43$) appetite/weight, with only $n = 7$ unchanged. Due to the small cell sizes, the similar profiles between the Decreased and Unchanged groups as indicated in Table 1, and the focus on weight gain and overeating in MDD, the unchanged ($n = 7$) and decreased ($n = 30$) subgroups were combined for the purposes of statistical analyses. By Appetite and Weight Change, there were 19 males and 18 females in the MDD decreased/unchanged group, 15 males and 28 females in the MDD increased group, and 26 males and 34 females in the control group. The sex distribution between Appetite and Weight Change groups was not significant ($p = .331$). Blood collection times and times since previous meals also did not differ significantly between groups ($p = .716$ and $p = .310$ respectively). However, BMI, waist circumference, *Emotional eating, External eating, and Food Addiction* severity were significantly higher in those with MDD reporting increased appetite/weight compared to those with MDD reporting decreased appetite/weight and controls. Depressive symptoms and *Restrained eating* were higher across both MDD groups compared to controls. Females reported more *Emotional and Restrained eating* than males, with no further effects identified (Table 1).

3.2. Cortisol

Means and standard deviations for the raw and log-transformed cortisol data (ng/ml) are presented in Table 2. Log-cortisol differed significantly by Appetite/Weight Change group, with Least Significant Difference-corrected post-hoc analyses indicating that MDD participants with decreased/unchanged appetite/weight had significantly higher log-cortisol levels compared to controls ($p = .008$), and marginally higher levels compared to MDD participants with increased appetite/weight ($p = .053$). However, log-cortisol levels did not differ significantly between MDD participants with increased appetite/weight and controls ($p = .584$). Age was a significant covariate, and no sex or interaction effect was identified.

Table 1
Means and standard deviations for participant characteristic data, by Appetite/Weight Change groups and Sex (total $N = 140$; MDD and control participants).

Variables	Appetite/Weight Change					Sig. ^a	Effect Size η_p^2/ω^2	Sex		Sig.	Effect Size η_p^2/ω^2
	MDD Decreased M (SD) N	MDD Unchanged M (SD) N	MDD Increased M (SD) N	Control M (SD) N	Male M (SD) N			Female M (SD) N			
Biometrics	Age	24 (4)	27 (7)	27 (9)	25 (7)	.410	.013	26 (5)	25 (8)	.790	.001
	BMI	23.5 (5.1)	27.1 (3.4)	28.8 (5.9)*	25.1 (5.3)	.001 ^a	.090 ^b	25.7 (4.3)	26.2 (6.7)	.556 ^a	.001 ^b
	Waist	85 (14)	93 (8)	96 (16)*	86 (12)	.002 ^a	.073 ^b	91 (12)	88 (13)	.157 ^a	.007 ^b
DASS	Depression	25.2 (8.2)*	17.1 (9.6)	25.9 (9.6)*	2.8 (9.6)	<.001 ^a	.729 ^b	15.5 (12.9)	15.4 (13.5)	.956 ^a	.001 ^b
DEBQ	Emotional	2.2 (0.9)	2.2 (0.9)	3.6 (0.9)*	2.0 (0.7)	<.001	.419	2.2 (1.0)	2.8 (1.1)*	<.001	.104
	Restrained	2.4 (1.1)*	2.7 (1.1)	2.6 (0.9)*	1.9 (0.8)	.002	.087	2.0 (0.9)	2.5 (1.0)*	.008	.051
	External	3.0 (0.7)	3.1 (0.4)	3.4 (0.6)*	3.0 (0.7)	.006	.074	3.1 (0.7)	3.1 (0.7)	.556	.003
YFAS	Severity	40.3 (29.4)	51.2 (28.6)	85.6 (46.4)*	25.8 (23.0)	<.001 ^a	.300 ^b	41.1 (34.2)	54.2 (46.3)	.056 ^a	.019 ^b

Note: MDD = Major Depressive Disorder; BMI = Body Mass Index; DASS = Depression, Anxiety and Stress Scale; DEBQ = Dutch Eating Behaviours Questionnaire; YFAS = Yale Food Addiction Scale. *Indicates a significant difference compared to the other condition(s).

^a Indicates significance for MDD Decreased/Unchanged combined ($n = 37$) compared to MDD Increased ($n = 43$) and controls ($n = 60$).

^a Indicates significance for Welch’s ANOVA.

^b Indicates ω^2 values.

Table 2

Means and standard deviations for cortisol data (ng/ml), by Appetite/Weight Change groups and Sex (total N = 140; MDD and control participants).

Variable			Cortisol	Log-Cortisol	Main Effect [#]	Effect Size	Interaction
		n	M (SD)	M (SD)	p	partial η^2	p
Appetite/Weight	MDD Decreased	30	192.08 (108.04)	5.12 (0.58)	.027	.053	.139
	MDD Unchanged	7	208.62 (95.93)	5.21 (0.64)			
	MDD Increased	43	146.01 (83.93)	4.79 (0.67)			
	Control	60	138.21 (92.07)	4.70 (0.71)			
Sex	Male	60	175.40 (94.43)	4.99 (0.65)	.058	.027	
	Female	80	140.88 (94.43)	4.73 (0.68)			
Covariate	Age	–	–	–	.018	.041	–

Note: MDD = Major Depressive Disorder. Significance noted for log-transformed data only. # Indicates significance for MDD Decreased/Unchanged combined (n = 37) compared to MDD Increased (n = 43) and controls (n = 60).

3.3. Multiple linear regression analyses

Six multiple regression models were employed to assess whether cortisol accounted for unique variance in indices of adiposity and problematic eating behaviours in individuals with MDD and healthy controls, after accounting for demographic variables and depressive symptoms (Table 3). For all analyses, Age, Sex, depressive symptoms (DASS-Depression) and cortisol concentrations were entered as independent variables. The dependent variables of interest for indices of adiposity included BMI and waist circumference values, and for problematic eating behaviours consisted of *Emotional*, *Restrained*, *External* eating, *Food Addiction* severity scores. Visual inspection of plots, tolerance values greater than 0.10 and variance inflation factor values below 2 indicated that the assumptions of normality, linearity, multicollinearity and homoscedasticity were satisfied for all analyses.

The predictors (Age, Sex, depressive symptoms (DASS-Depression) and cortisol concentrations) together significantly accounted for 13.7% of variance in BMI ($F(4, 135) = 5.354, p < .001, R^2 = 0.137$), where Age was positively ($\beta = 0.286, p = .001$), and cortisol inversely ($\beta = -0.168, p = .048$), associated with BMI values. The same predictors also accounted for a significant 23.9% of variance in waist circumference ($F(4, 135) = 10.610, p < .001, R^2 = 0.239$), with Age being positively ($\beta = 0.372, p < .001$), and cortisol inversely ($\beta = -0.171, p = .033$), associated with waist circumference.

For problematic eating behaviours, the predictors collectively explained a significant 31.3% of variance in *Emotional* eating ($F(4, 135) = 15.405, p < .001, R^2 = 0.313$), with Sex ($\beta = 0.299, p < .001$) and depressive symptoms ($\beta = 0.471, p < .001$) associated with greater *Emotional* eating. The predictors also explained 14.4% of variance in *Restrained* eating ($F(4, 135) = 5.694, p < .001, R^2 = 0.144$), with Sex ($\beta = 0.190, p = .021$) and depressive symptoms ($\beta = 0.303, p < .001$) associated with greater *Restrained* eating. In addition, the four predictors collectively accounted for a significant 32.7% of variance in *Food Addiction* severity ($F(4, 135) = 16.399, p < .001, R^2 = 0.327$), with only depressive symptoms associated with greater *Food Addiction* severity ($\beta = 0.555, p < .001$). However, the model was not significant for *External* eating ($F(4, 135) = 1.650, p = .165, R^2 = 0.047$), and cortisol was not a predictor of any problematic eating behaviour (*Emotional* eating: $\beta = -0.045, p = .551$; *Restrained* eating: $\beta = -0.144, p = .089$; *External* eating: $\beta = -0.051, p = .567$; *Food Addiction* severity: $\beta = -0.122, p = .105$).

4. Discussion

There is a paucity of research examining depressogenic problematic eating behaviours in relation to cortisol concentrations. The current study identified that plasma cortisol was significantly higher among depressed individuals reporting decreased/unchanged appetite and weight compared to healthy controls and marginally higher compared to depressed individuals reporting increased appetite and weight. After accounting for demographic variables and depressive symptoms, cortisol was a negative predictor of adiposity measures including BMI

and waist circumference. However, cortisol was not significantly associated with problematic eating behaviours. These findings suggest that cortisol is more closely associated with melancholic, but not atypical, presentations of MDD, providing further evidence of differential neuroendocrine, behavioural and symptom profiles between depressogenic subtypes.

Plasma cortisol concentrations were significantly higher in depressed participants with decreased/unchanged appetite/weight compared to healthy controls and were marginally higher in depressed participants with increased appetite/weight. However, cortisol did not differ significantly between depressed participants with increased appetite/weight and healthy controls. Elevated cortisol in depressed individuals with decreased/unchanged appetite/weight is consistent with a melancholic MDD symptom profile [14,15] and aligns with previous studies suggesting that higher cortisol concentrations have greater catabolic effects, including reductions in appetite, decreases in body mass and increased energy expenditure [33,34]. Due to its roles in the stress response and catabolism, elevated plasma cortisol in depressed individuals with appetite and weight loss may reflect short-term energy mobilisation [25,34,35]. This is supported in the current study since cortisol negatively predicted measures of adiposity, with higher levels associated with smaller BMI and waist circumference measures. In contrast, the marginally lower cortisol in MDD individuals with appetite/weight gain may be indicative of an atypical MDD symptom profile [14,16], whereby lower cortisol levels may be consistent with a chronic stress response in individuals with appetite and weight gain and may relate to highly palatable food intake to assist with sustained metabolic functioning [34,35].

However, the current results suggest that cortisol may not be significantly associated with an atypical MDD symptom presentation. Cortisol concentrations were similar between depressed individuals reporting appetite/weight gain and healthy controls, indicating that cortisol dysregulation in the subgroup reporting increased appetite/weight may be minimal or similar to standard HPA axis fluctuations [21, 40]. Relatedly, after accounting for age, sex and depressive symptoms cortisol was not a significant predictor of problematic eating behaviours including emotional eating or food addiction, which are characteristic of an atypical MDD symptom profile. To our knowledge, this is the first study to examine these relationships. Despite the observed associations between cortisol and adiposity, the absence of significant relationships between cortisol and problematic eating behaviours may be a broader reflection of the catabolic effects of cortisol, where increased cortisol is associated with greater metabolism, energy mobilisation and propensity for weight loss [33,34]. Alternatively, it may be related to a floor effect of eating scores in males, who tend to report significantly lower rates of problematic eating behaviours than females [6]. Otherwise, the lack of relationships between cortisol and problematic eating behaviours may be due to the greater regulation of the latter by other neuropeptides, such as leptin, ghrelin or peripheral dopamine [5,6]. Our previous research indicates that these hormones, particularly leptin, were closely related to problematic eating behaviours and weight changes in atypical MDD and in females; however, these hormones were not linked to

Table 3
Overall models, standardised and unstandardised regression coefficients for the hierarchical regressions (total N = 140).

Model	BMI			Waist			DEBQ Emotional			DEBQ Restrained			DEBQ External			YFAS Food Addiction		
	B	β	p	B	β	p	B	β	p	B	β	p	B	β	p	B	β	p
	$F(4, 135) = 1.137$			$F(4, 135) = 10.610, p < .001, R^2 = .239$			$F(4, 135) = 15.405, p < .001, R^2 = .313$			$F(4, 135) = 5.694, p < .001, R^2 = .144$			$F(4, 135) = 1.650, p = .165, R^2 = .047$			$F(4, 135) = 16.399, p < .001, R^2 = .327$		
Age	.228	.286	.001*	.757	.372	<.001*	.007	.045	.534	-.010	-.069	.396	-.007	.068	.432	.164	.028	.698
Sex	.271	.024	.774	-4.003	-.137	.077	.665	.299	<.001*	.377	.190	.021*	.060	.043	.616	11.442	.136	.062
DASS Depression	.047	.110	.180	.227	.206	.008*	.039	.471	<.001*	.023	.303	.001*	-.010	.196	.024	1.760	.555	<.001*
Cortisol	-1.407	-.168	.048*	-3.639	-.171	.033*	-.073	-.045	.551	-.207	-.144	.089	-.052	-.051	.567	-7.451	-.122	.105

Note: BMI = Body Mass Index; DASS = Depression, Anxiety and Stress Scale; DEBQ = Dutch Eating Behaviours Questionnaire, YFAS = Yale Food Addiction Scale. *Indicates a significant predictor.

weight loss. Collectively, these findings suggest that cortisol may be of greater importance to the pathophysiology and symptom presentation of melancholic MDD, particularly to appetite/weight loss related symptoms, and not implicated to the same extent in atypical MDD. These results add to a growing body of research indicating broader neuroendocrine involvement in MDD than previously understood, with hormones associating with specific symptom types [5,6,14].

The marginally higher cortisol concentrations occurring in males compared to females is partially consistent with previous research indicating a possible sexual dimorphism in HPA axis activity [26,27]. The elevated cortisol in MDD, particularly in those reporting appetite and weight loss, in combination with cortisol being associated with lower BMI and waist circumference values suggests that males with higher cortisol levels may be more prone to weight loss as part of melancholic MDD, whereas females with lower cortisol levels may be more prone to weight gain as part of atypical MDD. It is possible that the higher cortisol in males may be indicative of an acute stress response, whereas lower cortisol in females may reflect chronic HPA axis activation linked to early-life stressors [25]. These dimorphisms warrant further research, as cortisol levels may relate to sex differences in melancholic and atypical MDD, in terms of appetite presentations and energy levels.

Overall, the current study adds to a growing body of literature supporting the role of neuroendocrine factors in depressogenic appetite and weight symptom presentations [5,6; Simmons et al., 2018]. The observed pattern of results highlight that cortisol appears to be more specifically linked to depressogenic appetite and weight loss [33,34], as opposed to problematic eating behaviours and weight gain. These findings also suggest that hormonal differences are related to symptom presentations in MDD, in that cortisol appears to be related to the potential pathophysiology of appetite and weight loss and HPA axis hyperactivity in melancholic MDD compared to an atypical MDD symptom presentation of overeating and weight gain. Through subtyping this heterogeneous condition, it may be possible to progress treatments for MDD and associated chronic health conditions.

Some limitations of the current study should be acknowledged. The study design was cross-sectional in nature, and as such causation cannot be inferred. Longitudinal studies are needed in order to better understand the role of cortisol and the HPA axis in depressogenic eating and weight changes. Cortisol was measured in plasma as a static measure of cortisol concentrations, however given its natural diurnal fluctuations it is possible that the observed results may vary if other indices of cortisol were used. As such, alternate dynamic measures of cortisol, such as diurnal slope or morning awakening curve, in relation to eating behaviours and weight should be investigated in future studies. Subjective hunger levels were also not accounted for in the current study. While measures of increased and decreased appetite were included in this study, hunger analogue scales may be useful in future studies to provide a quantitative index of appetite. Other potential covariates, such as the age of onset of MDD and detailed dietary intake, should also be accounted for in future studies.

In conclusion, this study indicates that cortisol is significantly higher in MDD presentations characterised by reductions in appetite/weight and is negatively related to adiposity, but is not associated with depressogenic problematic eating behaviours and weight gain. These findings provide further evidence that melancholic and atypical subtypes of MDD are associated with different neuroendocrine, anthropometric, behavioural and symptom profiles, which supports the heterogeneous nature of MDD and the need to analyse by symptom subtypes. Further research into the role of cortisol in the onset of appetite/weight loss in MDD may provide an opportunity for improved or tailored interventions for those affected by weight changes in MDD.

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Contributors

JM was involved in study design, data collection, data and statistical analysis and manuscript preparation. TL and ST were involved in study design, data and statistical analysis and review of the manuscript for important content. CD was involved in study design and review of the manuscript for important content.

Ethical standards

All procedures contributing to this work comply with the Australian National Statement on Ethical Conduct in Human Research (2007), as revised in 2018.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cpnec.2021.100067>.

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