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

Jessica G. Mills a,b,c,*, Theresa A. Larkin b,c, Chao Deng b,c, Susan J. Thomas b,c

a School of Psychology, Faculty of Arts, Social Sciences and Humanities, University of Wollongong, Wollongong, Australia
b Illawarra Health and Medical Research Institute, University of Wollongong, Australia
c School of Medicine, Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, Australia

A R T I C L E   I N F O

Keywords:
Major depressive disorder
Cortisol
Weight changes
Problematic eating behaviours
Food addiction

A B S T R A C T

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
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.
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 | Sex |
|-----------------|------------------------|-----|
| MDD             | MDD Decreased (M | SD) | MDD Unchanged (M | SD) | Control (M | SD) | Sig. * | Effect Size | M | SD | p |
| N               | 30 (7)                 | 43 (60) | 60 (40)          | 0.101 | 0.031 | 26 (5) | 0.137 | 0.790 | 0.001 |
| Biometrics      |                        |       |                  |       |       |       |       |       |       |
| Age             | 27 (9)                 | 25 (7) | 25 (7)           | 0.010 | 0.013 | 26 (5) | 0.137 | 0.790 | 0.001 |
| BMI             | 27.1 (3.4)             | 25.1 (5.3) | 0.001 | 0.009 | 25.7 (4.3) | 0.003 | 0.006 | 0.056 | 0.001 |
| Waist           | 19 (14)                | 16 (12) | 0.002 | 0.037 | 91 (12) | 0.157 | 0.007 | 0.017 | 0.008 |
| DASS Depression | 23.2 (8.2)             | 25.9 (9.6) | 0.001 | 0.039 | 25.2 (9.6) | 0.001 | 0.005 | 0.075 | 0.002 |
| DEBQ Emotional  | 2.2 (0.9)              | 3.6 (0.9) | 0.001 | 0.041 | 2.2 (1.0) | 0.001 | 0.038 | 0.104 | 0.010 |
| Restrained      | 2.7 (1.1)              | 2.6 (0.9) | 0.002 | 0.087 | 2.0 (0.9) | 0.001 | 0.008 | 0.051 | 0.003 |
| YFAS Severity   | 40.3 (29.4)            | 85.6 (46.4) | 0.001 | 0.030 | 41.1 | 0.056 | 0.019 | 0.017 | 0.008 |

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).

*p* indicates significance for MDD Decreased/Unchanged combined (n = 37) compared to MDD Increased (n = 43) and controls (n = 60).

*b* indicates significance for Welch’s ANOVA.

Indicates effect size 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 transformed and untransformed for 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 α < .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 and 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).

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. Aliquotted 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.

Means and standard deviations for participant characteristic data, by Appetite/Weight Change groups and Sex (total N = 140; MDD and control participants).
controls, after accounting for demographic variables and depressive problematic eating behaviours in individuals with MDD and healthy cortisol accounted for unique variance in indices of adiposity and collinearity and homoscedasticity were satisfied for all analyses. Ance values greater than 0.10 and variance inflation factor values below 3.3. Multiple linear regression analyses

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).

| Variable          | Cortisol | Log-Cortisol | Main Effect* | Effect Size | Interaction |
|-------------------|----------|--------------|--------------|-------------|-------------|
| Appetite/Weight   |          |              | p            |             |             |
| MDD Decreased     | 30       | 192.08 (108.04) | 5.12 (0.58) | .027        | partial η² | .139        |
| MDD Unchanged     | 7        | 208.62 (95.93) | 5.21 (0.64) | .053        |             |             |
| MDD Increased     | 43       | 146.01 (83.93) | 4.79 (0.67) | .354        |             |             |
| Control           | 60       | 138.21 (92.07) | 4.70 (0.71) | .567        |             |             |
| Sex               |          |              | p            |             |             |
| Male              | 60       | 175.40 (94.43) | 4.99 (0.65) | .058        | .027        |             |
| Female            | 80       | 140.88 (94.43) | 4.73 (0.68) |             |             |             |
| Covariate         |          |              | p            |             |             |
| Age               | –        | –            | .018         | .041        |             |             |

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, R² = 0.137), where Age was positively (β = .0286, p = .001), and cortisol inversely (β = -.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, R² = 0.239), with Age being positively (β = .372, p < .001), and cortisol inversely (β = -.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, R² = 0.313), with Sex (β = .299, p < .001) and depressive symptoms (β = .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, R² = 0.144), with Sex (β = .190, p = .021) and depressive symptoms (β = .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, R² = 0.327), with only depressive symptoms associated with greater Food Addiction severity (β = .555, p < .001). However, the model was not significant for External eating (F (4, 135) = 1.650, p = .165, R² = 0.047), and cortisol was not a predictor of any problematic eating behaviour (Emotional eating: β = −.045, p = .551; Restrained eating: β = −.044, p = .089; External eating: β = −.051, p = .567; Food Addiction severity: β = −.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 [24,25].

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 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...
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.

### Financial Support

This research received no specific grant from any funding agency,
commercial or not-for-profit sectors. Jessica Mills’ PhD candidature was supported by an Australian Government Research Training Program Scholarship.

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.cprne.2021.100067.

References
[1] C. Blanco, O. Vega-Lopez, J. Stewart, S. Liu, B. Grant, D. Hasin, 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, J. Clin. Psychiat. 73 (2) (2012) 224–232, https://doi.org/10.4088/JCP.11m06227.
[2] F. Luppino, L. de Wit, P. Bouvy, T. Stijnen, P. Cuijpers, B. Penninx, F. Zitman, Overweight, obesity and depression: a systematic review and meta-analysis of longitudinal studies, Arch. Gen. Psychiat. 67 (3) (2010) 220–229, https://doi.org/10.1001/archgenpsychiatry.2010.2.
[3] M. Mannan, A. Manum, S. Doi, A. Claravino, Is there a bi-directional relationship between depression and obesity among adult men and women? Systematic review and bias-adjusted meta-analysis, Asian Journal of Psychiatry 21 (2015) 51–66, https://doi.org/10.1016/j.ajp.2015.12.008.
[4] R. Rubin, M. Peyrot, S. Gaussoin, M. Espeland, D. Williamson, L. Faulconbridge, T. Wadden, L. Elwing, M. Safford, G. Evans-Hudnal, R. Wing, W. Knolwer, Four-year analysis of cardiovascular disease risk factors, depression symptoms and antidepressant medicine use in the Look AHEAD (Action for Health in Diabetes) Clinical Trial of weight loss in diabetes, Diabetes Care 36 (5) (2013) 1088–1094, https://doi.org/10.2337/dci12-1871.
[5] J. Mills, T. Larkin, C. Deng, S. Thomas, Weight gain in Major Depressive Disorder: linking appetite and disordered eating to leptin and ghrelin, Psychiatr. Res. 279 (2019) 244–251, https://doi.org/10.1016/j.psychres.2019.03.017.
[6] J. Mills, S. Thomas, T. Larkin, C. Deng, Overeating and food addiction in major depressive disorder: links to peripheral dopamine, Appetite 148 (2020), 104586, https://doi.org/10.1016/j.appet.2020.104586.
[7] J. Herbert, Cortisol and depression: three questions for psychiatry, Med. Clin. North Am. 94 (3) (2012) 449–469, https://doi.org/10.1016/j.mcl.2012.05.004.
[8] J. Kelder, G. Williams, J. Veldhuis, Pathophysiology of hypercortisolism in depression, Acta Psychiatr. Scand. 115 (suppl.433) (2007) 90–103, https://doi.org/10.1111/j.1600-0447.2007.00967.x.
[9] M. Juruena, M. Bocharova, B. Agustini, A. Young, Atypical depression and non-atypical depression: Is HP A axis function a biomarker? A systematic review, J. Affect. Disord. 233 (2017) 45–67, https://doi.org/10.1016/j.jad.2017.09.052.
[10] M. Bremmer, D. Deeg, A. Beekman, B. Penninx, L. Lips, W. Hoogendijk, Major depression in late life is associated with both hype and hypercortisolism, Biol. Psychiat. 62 (2007) 479–486, https://doi.org/10.1016/j.biopsych.2006.11.035.
[11] E. Suarez, J. Sundry, A. Erkani, Depressive vulnerability and gender-specific patterns of neuro-immune dysregulation, patterns of neuro-immune dysregulation: what the ratio of cortisol to C-reactive protein can tell us about loss of normal regulatory control, Brain Behav. Immun. 44 (2015) 137–147, https://doi.org/10.1016/j.bbi.2014.09.020.
[12] S. Laborde, F. Lautenbach, M. Allen, C. Herbert, S. Achtzehn, The role of trait emotional intelligence in emotion regulation and performance under pressure, Pers. Indiv. Differ. 57 (2014) 43–47, https://doi.org/10.1016/j.paid.2013.09.013.
[13] S. Vreeburg, W. Hoogendijk, J. van Pelt, B. Hoëndjik, J. Verheugen, R. van Vliet, J. Smith, F. Zitman, B. Penninx, Major depressive disorder and hypothalamic-pituitary-adrenal axis activity, Arch. Gen. Psychiat. 66 (6) (2009) 617–626, https://doi.org/10.1001/archgenpsychiatry.2009.56.
[14] B. Sanggaard, J. Otten, Patient specific modelling of the HPA axis related to clinical diagnosis of depression, Math. Biosci. 287 (2017) 24–35, https://doi.org/10.1016/j.mbs.2016.10.007.
[15] D. Brillon, B. Zheng, R. Campbell, D. Matthews, Effect of cortisol on energy expenditure and amino acid metabolism in humans, Am. J. Physiol. 268 (31) (1995) E501–E531.
[16] S. George, S. Khan, H. Briggs, J. Abelson, CRH-stimulated cortisol release and food intake in healthy, non-obese adults, Psychoneuroendocrinology 35 (4) (2010) 607–612, https://doi.org/10.1016/j.psyneuen.2009.09.017.
[17] D. Klein, L. Mayer, J. Schebendach, B. Walsh, Physical activity and cortisol in anorexia nervosa, Psychoneuroendocrinology 32 (2007) 539–547, https://doi.org/10.1016/j.psyneuen.2006.09.008.
[18] D. Lee, E. Kim, C. Choi, Technical and clinical aspects of cortisol as a biochemical marker of chronic stress, BMJ Reports 48 (4) (2015) 209–216, https://doi.org/10.5437/BMRRep.2015.48.2.275.
[19] A. Chao, A. Jastreboff, M. White, C. Grillo, R. Sinha, Stress, cortisol and other appetite hormones: prospective prediction of 6-month changes in food cravings and weight, Obesity 25 (4) (2017) 713–720, https://doi.org/10.1002/oby.21970.
[20] D. Delman, N. Pecoraro, S. Akana, S. L’Eau, F. Gomez, S. Manalo, Chronic stress and obesity: a new view of comfort food, Proc. Natl. Acad. Sci. U. S. A. 100 (20) (2003) 11696–11701, https://doi.org/10.1073/pnas.193466610.
[21] D. V. Sheehan, Mini International Neuropsychiatric Interview 7.0, 2015 (Medical Outcomes Systems).
[38] S. Lovibond, P. Lovibond, Manual for the Depression, Anxiety and Stress Scales, second ed., Psychology Foundation, 1995.

[39] T. van Strien, J. Frijters, G. Bergers, P. Defares, The Dutch Eating Behaviour Questionnaire (DEBQ) for assessment of restrained, emotional and external eating behaviour, Int. J. Eat. Disord. 5 (2) (1986) 295–315, https://doi.org/10.1002/1098-108x(198602)5:2<295::aid-eat22600502093.0co;2-t.

[40] L. Nandam, M. Brazel, M. Zhou, D. Jhaveri, Cortisol and Major Depressive Disorder – translating findings from humans to animal models and back, Front. Psychiatr. 10 (2020) 974, https://doi.org/10.3389/fpsyt.2019.00974.