DOI:
10.1016/j.psyneuen.2023.106387

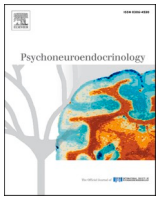
Document Version
Publisher's PDF, also known as Version of record

Psychoneuroendocrinology 158 (2023) 106387

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



Disentangling the effects of depression and perceived stress on cortisol levels in individuals with obesity: Preliminary results from a cross-sectional study

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ARTICLE INFO

Keywords:
Depression
Obesity
Cortisol levels
Perceived stress

ABSTRACT

Background: Hypothalamic-pituitary-adrenal (HPA) axis dysregulation has been suggested to play a role in the association between depression and obesity. The study aimed to investigate differences in cortisol levels in individuals with obesity with and without depression and the role of perceived stress on these differences.
Methods: Saliva samples were collected at awakening, 15-, 30- and 60-minutes post-awakening from 66 individuals with obesity (30 with major depressive disorder and 36 without major depressive disorder). Salivary cortisol was analysed using ELISA technique. Linear Mixed Models were used for group differences in cortisol awakening response (CAR) with adjustment for socio-demographic confounders and binge eating.
Results: Individuals with obesity and depression had lower CAR compared with individuals with obesity without depression ($\beta = -0.44$; $p = 0.036$). When controlling for perceived stress, CAR was no longer influenced by depression ($\beta = -0.09$; $p = 0.75$), but individuals with moderate/high stress had lower CAR compared with those with low stress ($\beta = -0.63$; $p = 0.036$).
Conclusions: Our results suggest that differences in CAR between individuals with obesity with and without depression could be due to higher levels of perceived stress in the depressed subjects.

1. Introduction

Obesity and depression are two highly prevalent and comorbid disorders and important contributors to global disability (WHOfact-sheets, obesity). Although the evidence of comorbidity between obesity and depression is now well-established (Luppino et al., 2010), the mechanisms underlying this relationship are poorly understood. A better understanding of the drivers of the high comorbidity between these two disorders is urgently needed to identify more effective treatments for individuals suffering with both obesity and depression.

Hypothalamic-pituitary-adrenal (HPA) axis dysregulation has been suggested as a likely candidate. Previous literature has consistently reported that patients suffering from depression show hyperactivation of the HPA axis, leading to increased cortisol production and elevated immune biomarkers (Perrin et al., 2019; Haapakoski et al., 2015; Howren et al., 2009; Zunszain et al., 2011). It has been proposed that the dysfunction of the glucocorticoid receptor (GR) could be the cause of these abnormalities, leading to a reduced ability of cortisol to mediate the negative feedback of the HPA axis and thus, to regulate its own production, and to activate an anti-inflammatory response. Cortisol hypersecretion is followed by different endocrine consequences, such as inhibition of the growth hormone axis, thyroid axis, and gonadal axis, causing reduced muscle and bone mass and accumulated visceral fat (Nicolaides et al., 2015). The consequent visceral obesity and loss of muscle mass have been associated with clinical symptoms of metabolic syndromes, such as dyslipidemia, hypertension and type 2 diabetes mellitus (Fardet and Fève, 2014). In fact, studies in both human and animal models have reported that cortisol promotes the accumulation of central white adipose tissue and weight gain (Björntorp and Rosmond, 2000). Taken together, this evidence supports the HPA axis as a

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https://doi.org/10.1016/j.psyneuen.2023.106387
Received 23 March 2023; Received in revised form 23 August 2023; Accepted 10 September 2023
Available online 22 September 2023

potential biological system involved in the aetiology of obesity.

HPA axis abnormalities have been found in individuals with obesity and metabolic syndrome (Anagnostis et al., 2009; Pasquali et al., 1993; Weaver et al., 1993); however, the results in obesity are largely inconsistent (Incollingo Rodriguez et al., 2015). Different clinical observational studies have shown positive and negative correlations with BMI and waist circumference with cortisol levels, though, the most consistent result is a negative association between BMI and morning serum or salivary cortisol levels (Champaneri et al., 2013; Kumari et al., 2010). A blunted cortisol awakening response (CAR) has been generally associated with greater adiposity; however, in the same review, the authors also reported evidence of an association between obesity and HPA axis hyperactivity (Incollingo Rodriguez et al., 2015). It has been suggested that these inconsistencies could be related to variability in levels of chronic and perceived stress among individuals. A previous study has shown that women with high levels of self-perceived stress had a higher abdominal obesity and greater emotional eating compared with women reporting low levels of self-perceived stress (Tomiyama et al., 2011). The women with high stress also demonstrated lower diurnal cortisol and a blunted cortisol response to a stressor, where cortisol correlated negatively with abdominal diameter. Therefore, it is possible that chronic or high perceived stress could account for attenuated HPA response in individuals with obesity.

Childhood trauma (including childhood physical, sexual, and emotional abuse and/or neglect) is among the most pertinent risk factors for the development of both depression and obesity in adulthood (Chapman et al., 2004; Gunstad et al., 2006). Additionally, HPA axis abnormalities have been linked to exposure to traumatic events in childhood (Heim et al., 2008) and early exposure to life stress has been linked to an increased cortisol reactivity in adulthood (Harkness et al., 2011). However, it remains unclear whether and how HPA axis abnormalities in individuals with obesity are influenced by comorbidity of depression, exposure to stress or childhood trauma. Understanding and disentangling the role of the HPA axis in the comorbidity between obesity and depression is an important step towards breaking the vicious cycle between these two disorders.

Our study aims to investigate the influence of depression, perceived stress, and childhood trauma on the HPA axis activity in patients with obesity. In particular, we aim to: 1. investigate whether HPA axis activity differs between individuals with obesity with and without depression; 2. examine the effect of recent perceived stress on cortisol in individuals with obesity with and without depression; and 3. investigate the possible effects of childhood trauma on HPA axis activity in individuals with obesity. We hypothesise that: 1. individuals with obesity suffering from depression will have reduced cortisol awakening response when compared with individuals with obesity without depression; 2. high perceived stress will be associated with reduced cortisol awakening response in individuals with obesity; and 3. individuals who have been exposed to childhood trauma will have increased activation of the HPA axis.

2. Materials and methods

2.1. Subjects

This cross-sectional, observational study included patients with obesity undergoing bariatric surgery, who were recruited from the bariatric clinic at a King's College Hospital (KCH) as part of the longitudinal BARIDEP (Bariatric surgery and depression) study (Anna McLaughlin et al., 2023). The total sample (n = 66) constituted of two groups: one group of patients with a diagnosis of current major depressive disorder and a control group without any history of depression (we will refer to the group with obesity and without depression as the comparison group). In particular, 30 patients had a current Diagnostic and Statistical Manual Version 5 (DSM-5) diagnosis of major depressive disorder, confirmed by Mini International Neuropsychiatric Interview (MINI) (63% female; mean age: 48; mean BMI: 50 kg/m^2) and 36 patients had no past or present DSM-5 diagnosis of severe mental illness, including affective disorders and psychotic disorders as confirmed by MINI (61% female; mean age: 45; mean BMI: 48 kg/m^2). Participants were considered eligible for the study if they 1) suffered with obesity (classified as BMI $\geq$35); 2) aged between 18 and 70 years old; and 3) were able to read and write English fluently. Participants were excluded if they 1) were pregnant or breastfeeding; 2) had a past or present primary diagnosis of psychotic disorder; 3) were taking high doses of anti-inflammatory medication (antibiotics, steroids, NSAIDs, etc); 4) met criteria for alcohol abuse, drug abuse or dependence in the last 6 months. The study was approved by the London Bridge Research Ethics Committee, United Kingdom (reference: (Gunstad et al., 2006)/LO/0350). All participants provided written consent before performing any study-related activity.

2.2. Clinical measures

At baseline, patients underwent a short clinical interview using the MINI to diagnose or rule out the presence of psychiatric disorders according to DSM-5 (Association, 2013). Patients were also assessed with the Hamilton Depression Rating Scale (HAM-D) to assess the severity of depressive symptoms (Hamilton, 1960). Medical history, concomitant medication, and demographic characteristics of the participants were documented.

The participant's perception of stress and to what degree they found the events in their lives to be unpredictable, uncontrollable and challenging was evaluated using the Perceived Stress Scale (PSS) (Linn, 1986). Participants were divided into two groups according to their PSS scores; 22 participants had a low perceived stress score (score between 0 and 13), and 44 had a moderate to high perceived stress score (score between 14 and 40) were combined to create a moderate/high-stress group (Perceived stress scale.).

The Childhood Trauma Questionnaire (CTQ) was used to assess the presence and severity of different types of childhood trauma: Emotional Abuse (EA), Emotional Neglect (EN), Physical Abuse (PA), Physical Neglect (PN) and Sexual Abuse (SA) (Bernstein et al., 1994). The total CTQ score was obtained by adding together the values of the different subscales. The CTQ is extensively used in clinical and population samples and has good psychometric properties (Scher et al., 2004). The values of the subscales of the CTQ were dichotomized into none, mild, moderate and severe in accordance with the manual (Bernstein et al., 2003). Exposure to recent stressful life events (which happened in the 6 months before assessment) was assessed using the Brief Life Events Questionnaire (Brugha and Cragg, 1990). The presence of binge eating was assessed using the Binge Eating Scale (Gearhardt et al., 2009).

2.3. Salivary cortisol

Saliva samples were collected by the participant at home at six time-points during the day (at awakening, 15-, 30- and 60-minutes post-awakening, at noon and at 8 pm) (Mondelli et al., 2010; Nikkheslat et al., 2015), using salivette sampling devices (Sarstedt, Leicester, UK). During the collection of the samples, participants used a self-reported questionnaire, and they were excluded from the analyses if the required intervals between time-points were not respected. A high-sensitivity salivary cortisol enzyme immunoassay kit (Salimetrics) available in commerce was used to analyse the salivary cortisol levels (nmol·min/L). Cortisol values were calculated using the SoftMax Pro 4.8 software, with a 4-parameter fit. The analytical sensitivity was set to 0.19 nmol/l and the Inter and intra-assay coefficient of variations ranged 8–10% and 6–10%, respectively. In order to assess the activity and responsiveness of the HPA axis, we conducted a comparison of the mean values at the different time points, and we calculated Cortisol Awakening Response (CAR) with the use of the 4 time points of 0-, 15-, 30-, and 60-minutes post-awakening and the diurnal cortisol using the 3

main points over the whole day (awakening, noon and 8 pm). The trapezoidal formula introduced by Pruessner et al (Pruessner et al., 2003). was used for the calculation.

2.4. Statistical analysis

Statistical analysis to assess group differences in demographic variables was performed using SPSS software, version 26. Data was evaluated for normality and logarithmically transformed if required and Chi-squared, or Independent-Samples T-Test, Mann-Whitney U Test or Kruskal-Wallis test were used, as appropriate. Using R Studio software, Linear Mixed Models (LMM) were applied to assess group differences in cortisol awakening response. LMM allows for random parameter estimates, non-independent observations (repeated measures) and accommodates missing values. Variables included in the model to determine effects on cortisol levels included the changes over the four time-points (awakening, 15 min after awakening, 30 min after awakening and 60 min after awakening), potential confounders (age, BMI, male gender vs. female gender, white ethnicity vs. non-white ethnicity (including Caribbean, black British, Hispanic, Asian, African) and current smokers vs. non-smokers), participant group (depressed vs. comparison and PSS moderate-high stress vs. PSS low stress) and binge eating scale score. Participant ID was included as a random intercept to allow for individual variability in cortisol levels. Homogeneity of variance plots were used to determine if residuals were normally distributed. Models required square root transformation of cortisol levels to ensure homogeneity of variance and therefore standardised coefficients and standardised confidence intervals are shown (Gelman, 2008). For each model, the conditional R-squared was reported as it takes both the fixed and random effects into account (Nakagawa et al., 2017).

To investigate the differences in cortisol levels between the comparison group and the depressed group divided by low and moderate/high PSS, the above analyses were repeated with participants stratified into three separate groups: not depressed with low stress, not depressed with moderate-high stress and depressed patients with moderate-high stress. Structural equation model (SEM), or path analysis, using Amos SPSS was used to assess the influence of depression and PSS on cortisol levels.

Finally, non-parametric Spearman's correlation was used to investigate the associations between childhood trauma and brief life events with cortisol levels. The threshold for statistical significance of all tests was defined as two-tailed $p \leq 0.05$.

3. Results

3.1. Sample characteristics

The sociodemographic and clinical characteristics of the sample are reported in Table 1.

Between the two groups (depression group and comparison group) there was a significant difference in binge eating ($p = 0.005$) and PSS ($p < 0.001$), a trend in ethnicity ($p = 0.073$), while age, BMI, gender, diabetic status and smoking status were similar between individuals with and without depression.

3.2. Effects of depression on cortisol levels

Results from the repeated measures linear mixed model evaluating group differences in CAR cortisol levels are presented in Table 2 and Fig. 1. There was a significant effect of the participant group on CAR, as patients with depression had lower CAR compared with the comparison group ($p = 0.036$). However, there was no difference in diurnal cortisol levels throughout the day between the two groups.

The conditional R^2 value was 0.697, meaning the model explained 69.7% of the variance in cortisol levels.

Table 1
Comparison of the sociodemographic and clinical characteristics between the depression group and the comparison group. BMI: Body Mass Index; HAM-D: Hamilton Depression Rating Scale; PSS: Perceived Stress Scale.

Variable	Comparison Group, N = 36	Depression group, N = 30	p-value[1]
Age			0.247
Mean ± se	45 ± 2	48 ± 2	
Median (Range)	44 (25, 67)	49 (19, 66)	
BMI			0.743
Mean ± se	50 ± 2	48 ± 1	
Median (Range)	47 (37, 85)	48 (36, 64)	
Gender, n (%)			0.853
Female	22 (61%)	19 (63%)	
Male	14 (39%)	11 (37%)	
Ethnicity, n (%)			0.073
Non-white	16 (45%)	7 (23%)	
White	20 (55%)	23 (77%)	
Diabetic status, n (%)			0.589
Diabetic	18 (50%)	13 (43%)	
Non-diabetic	18 (50%)	17 (57%)	
Current smoker, n (%)	8 (22%)	6 (20%)	0.826
HAM-D			**< 0.001**
Mean ± se	2 ± 0	18 ± 1	
Median (Range)	1 (0, 6)	16 (9, 29)	
Binge eating scale total			**0.005**
Mean ± se	10 ± 1	15 ± 1	
Median (Range)	9 (0, 29)	17 (3, 34)	
PSS			**< 0.001**
Mean ± se	11 ± 1	24 ± 1	
Median (Range)	10 (0, 20)	22 (17, 36)	

[1] Pearson's Chi-squared test; Independent-Samples T-Test; Independent-Samples Mann-Whitney U Test

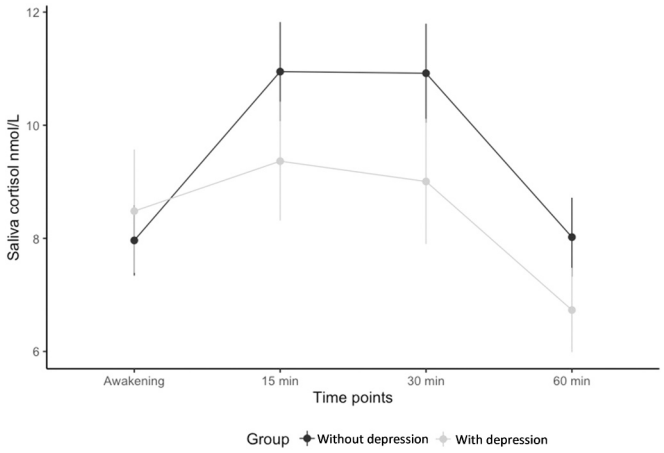

Fig. 1. Salivary cortisol levels for the cortisol awakening response (CAR) at the different time points for each group of patients with obesity with and without depression.

3.3. Effects of perceived stress scale and childhood trauma on cortisol levels

We then analysed the effects of PSS on cortisol levels by dividing the subjects according to PSS score: comparison group with low PSS, comparison group with moderate/high PSS and depression group with moderate/high PSS (in the depression group, we did not have any subject with low PSS scores). The sociodemographic and clinical characteristics of the sample divided by PSS are reported in Table 3. Among the three groups, there was a significant difference in age ($p = 0.033$) and binge eating (<0.001), while gender, BMI, ethnicity, diabetic status and smoking status were similar across the three groups.

Results from the repeated measures linear mixed model evaluating differences in CAR cortisol levels in groups divided by PSS, controlling

Table 2
Repeated measures linear mixed model evaluating group differences in CAR cortisol levels.

	Depression group model		
Variables	std. Beta	std. CI	p-value
(Intercept)	-0.1	-0.57 – 0.38	**0.006**
Awakening to 15 min	0.37	0.18 – 0.56	**< 0.001**
Awakening to 30 min	0.34	0.15 – 0.53	**< 0.001**
Awakening to 60 min	-0.13	-0.33 – 0.06	0.176
Age	0.14	-0.08 – 0.36	0.218
BMI	0.01	-0.20 – 0.23	0.904
Gender (Male)	-0.48	-0.92 – −0.04	**0.033**
Background (White)	0.62	0.17 – 1.08	**0.008**
Diabetic status (non-diabetic)	-0.18	-0.60 – 0.24	0.384
Smoking (Yes)	0.04	-0.45 – 0.54	0.861
Depression diagnosis (vs. not depression)	-0.44	-0.85 – −0.03	**0.036**
Marginal R^2 / Conditional R^2	0.163 / 0.697		

Table 3
Comparison of sociodemographic and clinical characteristics between comparison group with low PSS, comparison group with moderate/high PSS and depression group with moderate/high PSS. BMI: Body Mass Index; HAM-D: Hamilton Depression Rating Scale; PSS: Perceived Stress Scale.

Variable	Comparison group, low PSS, N = 22	Comparison group, mod/high PSS, N = 14	Depression group, mod/high PSS, N = 30	p-value[1]
Age				**0.033**
Mean ± se	48 ± 2	39 ± 2	48 ± 2	
Median (Range)	50 (25, 67)	38 (28, 54)	48 (19, 66)	
BMI				0.800
Mean ± se	50 ± 2	50 ± 3	48 ± 1	
Median (Range)	46 (37, 85)	48 (37, 72)	48 (36, 64)	
Gender, n (%)				0.936
Female	13 (56%)	5 (56%)	19 (62%)	
Male	19 (44%)	9 (44%)	11 (38%)	
Ethnicity, n (%)				0.11
Non-white	9 (41%)	7 (50%)	7 (23%)	
White	13 (59%)	7 (50%)	23 (77%)	
Diabetic status, n (%)				0.683
Diabetic	10 (45%)	8 (57%)	17 (57%)	
Non-diabetic	12 (55%)	6 (43%)	13 (43%)	
Current smoker, n (%)	5 (22%)	3 (21%)	6 (20%)	0.972
HAM-D				**< 0.001**
Mean ± se	1 ± 0	3 ± 0	18 ± 1	
Median (Range)	1 (0, 5)	2 (0, 6)	16 (9, 29)	
Binge eating scale total				**0.001**
Mean ± se	8 ± 1	15 ± 2	16 ± 1	
Median (Range)	5 (0, 21)	15 (3, 29)	17 (3, 34)	

[1] Pearson's Chi-squared test; ANOVA; Kruskal-Wallis test

for the effect of confounders, are presented in Fig. 2 and Table 4. There was a significant effect of PSS on CAR, as highly stressed patients demonstrated lower CAR compared with low-stressed patients (p = 0.036). However, there was no more difference between subjects with and without depression when the effect of PSS was considered. The conditional R2 value was 0.702, meaning the model explained 70.2% of the variance in cortisol levels.

These results were confirmed by structural equation model (SEM). This model revealed significant relation between PSS and CAR (β = -0.314, p = 0.027), but not between depression and CAR (Fig. 3). Moreover, there was a significant covariance between depression and PSS (β = 0.598, p = 0.001).

There was no difference in diurnal cortisol levels among the groups.

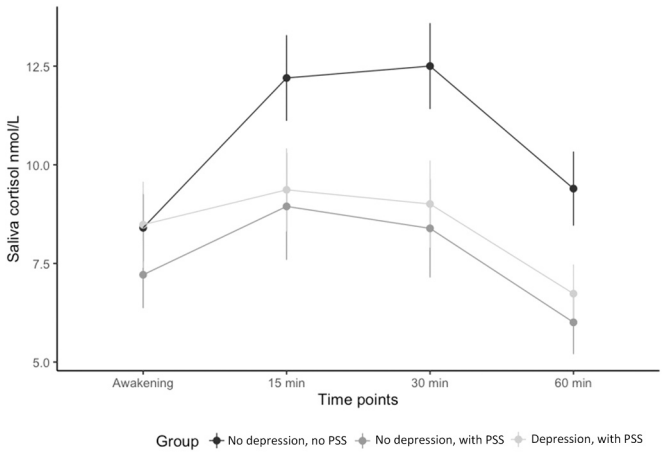

Fig. 2. Salivary cortisol levels for the cortisol awakening response (CAR) at the different time points for each group: patients with obesity with and without depression with moderate-high perceived stress scale (PSS) score and patients with obesity without depression and with a low score of PSS.

Table 4
Repeated measures linear mixed model evaluating group differences in CAR cortisol levels, controlling for the effect of confounders.

	Depression & PSS groups model		
Variables	std. Beta	std. CI	p-value
(Intercept)	0.19	-0.35 – 0.73	**0.001**
Awakening to 15 min	0.37	0.18 – 0.56	**< 0.001**
Awakening to 30 min	0.34	0.15 – 0.53	**< 0.001**
Awakening to 60 min	-0.13	-0.32 – 0.06	0.18
Age	0.06	-0.17 – 0.29	0.596
BMI	-0.03	-0.25 – 0.18	0.755
Gender factor (Male)	-0.44	-0.87 – −0.01	**0.047**
Background factor (White)	0.55	-0.17 – −1.08	**0.008**
Diabetic status (non-diabetic)	-0.28	-0.70 – 0.14	0.186
Smoking (Yes)	0.04	-0.45 – 0.52	0.880
Binge eating scale total	0.08	-0.14 – 0.30	0.459
Depression diagnosis (vs. without depression)	-0.09	-0.63 – 0.46	0.754
PSS moderate-high stress (vs. low stress)	-0.63	-1.21 – −0.04	**0.036**
Marginal R^2 / Conditional R^2	0.207 / 0.710	0.207 / 0.713	

3.4. Childhood trauma (CTQ) and brief life events (LEQ)

There was not a significant correlation between CTQ or LEQ and CAR

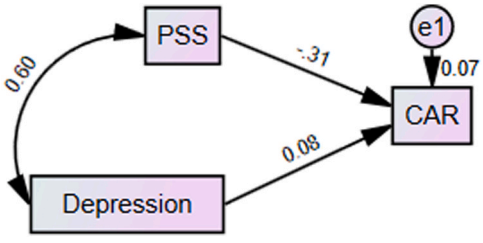

Fig. 3. Structure model showing the relationship between depression and PSS towards CAR.

in the whole sample.

4. Discussion

Our results show a difference in the levels of CAR between subjects with obesity with depression and subjects with obesity without depression, with depressed individuals presenting lower CAR compared with the comparison group, while there was no difference in the levels of cortisol throughout the day between the two groups. Perceived stress had a significant effect on CAR, as highly stressed patients demonstrated lower CAR compared with low-stressed patients. The difference in CAR between subjects with and without depression was no longer present when the effect of perceived stress was considered, suggesting that this difference was due to the higher levels of perceived stress in the subjects with depression. We found that levels of childhood trauma were similar between the group with and without depression and, in contrast with our hypothesis, we did not find any correlation between childhood trauma and cortisol levels.

Our result of low CAR in patients with both obesity and depression is in accordance with the study of Huber and colleagues who also showed a blunted response to awakening in subjects suffering with depression (Huber et al., 2006). This is also in line with findings in individuals with atypical depression which is more frequent in subjects with obesity (Pistis et al., 2021) and is characterized by metabolic and circadian disruption (weight gain, increased appetite, fatigue, and hyper-insomnia). Meta-analyses have suggested that patients with atypical depression present HPA axis hypoactivity (lower diurnal cortisol levels) (Juruena et al., 2018; Lamers et al., 2013). Longitudinal studies have also supported these findings, showing that, in children, lower cortisol levels are associated with higher BMI at age 18 (Ruttle et al., 2014). Therefore, HPA axis hypoactivity may be indicative of a pathophysiological process, capable of influencing mood and weight gain, which is unique to depressed patients with metabolic disturbances.

Interestingly, perceived stress was negatively correlated with CAR levels across the whole sample. These results suggest that the awakening cortisol levels are significantly influenced by the level of subjective stress. Indeed, the group with a higher perceived stress score demonstrated a flattened cortisol awakening response compared with the group with a lower perceived stress score. This could be due to the fact that with chronic exposure to stress or chronically high perceived stress, the body is no longer able to support the HPA axis stimulation, reaching a condition of exhaustion and thus, the HPA axis becomes hypoactive. Indeed, previous studies have shown a link between chronic stress and reduced CAR in healthy subjects (Duan et al., 2013). This phenomenon has been also detected in subjects with different stress-related disorders, including chronic fatigue syndrome, fibromyalgia, lower back pain, post-traumatic stress disorder, and burnout (Griep et al., 1998; Pruessner et al., 1999; Penninx et al., 2007). This may be particularly relevant for individuals with obesity, as different studies have indicated that subjects with elevated stress levels are more likely to develop obesity (Harding et al., 2014; Torres and Nowson, 2007). In particular, psychosocial stress has been suggested to be linked to the development of obesity via biological and behavioural pathways. For example, increased accumulation of fat and promoted visceral adiposity are widely acknowledged consequences of the biological response to stress (Björntorp, 2001; Wardle et al., 2011). Hence, targeting subjective stress could be beneficial in the treatment or the prevention of obesity as well as of comorbidity of depression and obesity (Xenaki et al., 2018).

The similar levels of childhood trauma between individuals with obesity with and without depression in our sample could be potentially due to the high prevalence of childhood trauma in the population with obesity (Williamson et al., 2002). Indeed, childhood trauma has been suggested as an important risk factor for the development of obesity (Danese and Tan, 2014). We did not find a direct association between exposure to childhood trauma and cortisol in our sample; this may be due to a more complex relationship between childhood trauma and HPA axis activity involving the severity or frequency of trauma, which could not be captured in our study. It is also possible that the effect of childhood trauma on the HPA axis may happen indirectly through increased levels of perceived stress, but we could not test this hypothesis in our study.

Our study has few limitations. First, our sample did not include a group of depressed patients with low PSS; however, very few patients with obesity with depression may experience low levels of stress (Tomiyama et al., 2011), so the results are still generalisable to this population. Second, our study included a relative small sample size for subsample analyses and all the participants were recruited from bariatric surgery clinic; although this made the sample less heterogenous, the results are more likely to reflect abnormalities in the bariatric population rather than a wider population with obesity. Another limitation could be represented by the cross-sectional design of the study which could not allow us to make any conclusion on which abnormality appears first, highlighting the need for longitudinal studies. Lastly, we did not collect specific data on socioeconomic status and therefore could not include this as possible covariate in our model.

In conclusion, our findings suggest that high levels of perceived stress may contribute to HPA axis abnormalities, such as a blunted cortisol awakening response, in individuals with comorbid depression and obesity. Future studies should investigate whether personalised treatments aimed at reducing perceived stress and regulating HPA axis activity (such as anti-glucocorticoid treatments) can help improve depressive symptoms or support weight loss in individuals with obesity and depression. Longitudinal research studies will also be needed to identify whether depression, obesity, or HPA axis dysregulation appears first in order to better identify the appropriate first target for intervention.

Funding

This project was supported by the National Institute for Health and Care Research (NIHR) Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. Prof Mondelli is also funded by MQ: Transforming Mental Health (Grant: MQBF/1 and MQBF/4) and the Medical Research Foundation (Grant: MRF-160-0005-ELP-MONDE).

Declaration of Competing Interest

The author declares no conflicts of interest.

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