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1 **The influence of comorbid depression and overweight status on peripheral**
2 **inflammation and cortisol levels**

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7

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1 **Abstract**

2

3 **Background:** Depression and overweight are each associated with abnormal immune system
4 activation. We sought to disentangle the extent to which depressive symptoms and overweight
5 status contributed to increased inflammation and abnormal cortisol levels.

6 **Methods:** Participants were recruited through the Wellcome Trust NIMA Consortium. The
7 sample of 216 participants consisted of 69 overweight patients with depression; 35 overweight
8 controls; 55 normal-weight patients with depression and 57 normal-weight controls. Peripheral
9 inflammation was measured as high-sensitivity C-Reactive Protein (hsCRP) in serum. Salivary
10 cortisol was collected at multiple points throughout the day to measure cortisol awakening
11 response and diurnal cortisol levels.

12 **Results:** Overweight patients with depression had significantly higher hsCRP compared with
13 overweight controls ($p=0.042$), normal-weight depressed patients ($p<0.001$) and normal-
14 weight controls ($p<0.001$), after controlling for age and gender. Multivariable logistic
15 regression showed that comorbid depression and overweight significantly increased the risk of
16 clinically elevated hsCRP levels $\geq 3\text{mg/L}$ (OR: 2.44, 1.28-3.94). In a separate multivariable
17 logistic regression model, overweight status contributed most to the risk of having hsCRP
18 levels $\geq 3\text{mg/L}$ (OR: 1.52, 0.7-2.41), while depression also contributed a significant risk (OR:
19 1.09, 0.27-2). There were no significant differences between groups in cortisol awakening
20 response and diurnal cortisol levels.

21 **Conclusion:** Comorbid depression and overweight status is associated with increased hsCRP,
22 and the coexistence of these conditions amplified the risk of clinically elevated hsCRP levels.
23 Overweight status contributed most to the risk of clinically elevated hsCRP levels, but
24 depression also contributed to a significant risk. We observed no differences in cortisol levels
25 between groups.

1 **Introduction**

2 Rates of depression and obesity have risen dramatically in recent years, with each
3 disorder separately posing a major health concern and economic cost to society (Abdelaal, le
4 Roux, & Docherty, 2017; James et al., 2018; Malhi & Mann, 2018). Depression and obesity
5 are highly comorbid disorders, and the coexistence of these conditions significantly increases
6 the risk for developing subsequent disorders, likely due to the chronic inflammatory state that
7 they induce (Ouakinin, Barreira, & Gois, 2018). High levels of inflammatory markers have
8 been widely described in depression (Baumeister, Russell, Pariante, & Mondelli, 2014; Enache,
9 Pariante, & Mondelli, 2019; Haapakoski, Mathieu, Ebmeier, Alenius, & Kivimäki, 2015;
10 Howren, Lamkin, & Suls, 2009; Valkanova, Ebmeier, & Allan, 2013), with a recent meta-
11 analysis finding that approximately 25% of patients with depression presented with elevated
12 peripheral inflammation (Osimo, Baxter, Lewis, Jones, & Khandaker, 2019). However, weight
13 gain also increases peripheral inflammation, and studies of patients with depression have found
14 that 20% of patients to be obese and 50% to be overweight (Papakostas et al., 2005). Therefore,
15 it is unclear whether the increased inflammation observed in patients with depression is
16 predominantly due to the high rates of overweight and obesity in this group. As inflammation
17 may be both a causal mechanism and potential treatment target for depressive symptoms, it is
18 crucial to understand to what extent depression and weight gain each contribute to the increased
19 inflammation observed in patients with depression (Ambrosio et al., 2018).

20
21 Inflammation likely plays a key role in modifying the bidirectional relationship
22 between depression and obesity, but not all patients with depression demonstrate increased
23 inflammation. Patients with depression who have both increased inflammation and metabolic
24 disturbances may have a distinct ‘immuno-metabolic’ form of depression (Milaneschi, Lamers,
25 Berk, & Penninx, 2020). This type of depression is a significant risk factor for weight gain and

1 subsequent obesity (Hasler, 2004) and was specifically associated with increased peripheral
2 levels of inflammatory markers, such as C-reactive protein (CRP) (Lamers et al., 2013).
3 Increased CRP levels have clinical relevance for depression (Andrew H. Miller & Charles L.
4 Raison, 2016), as CRP ≥ 3 mg/L was associated with an increased risk of developing depression
5 later in life (Au, Smith, Garipey, & Schmitz, 2015), and a lack of response to antidepressant
6 medication (Chamberlain et al., 2019; Zhang et al., 2019). Conversely, reductions in body
7 mass index (BMI) following weight loss interventions are associated with an improvement in
8 depressive symptoms and lower CRP levels (Capuron et al., 2011; Perez-Cornago et al., 2014).
9 These data demonstrate the crucial role of inflammation, as measured by CRP, in the interface
10 between depression and weight gain (Ambrosio et al., 2018).

11

12 Depression with metabolic disturbances has also been associated with dysregulated
13 hypothalamic-pituitary-adrenal (HPA) axis activity (Gold, 2015). The HPA axis produces the
14 anti-inflammatory stress hormone cortisol, which is involved in regulating mood, metabolism,
15 and circadian rhythms. Meta-analyses have suggested that patients with this subtype of
16 depression have lower diurnal cortisol levels, meaning HPA axis hypoactivity (Lamers,
17 Vogelzangs et al. 2013, Juruena, Bocharova et al. 2018). In contrast, patients who exhibit the
18 more classic symptoms of depression, such as reduced appetite and insomnia, tend to
19 demonstrate HPA axis hyperactivity (Juruena, Bocharova, Agustini, & Young, 2018; Lamers
20 et al., 2013). This association was mechanistically supported by longitudinal studies finding
21 that lower cortisol levels in children are associated with higher BMI at age 18 (Ruttle et al.,
22 2014), and that blunted cortisol responses lead to further weight gain and increased
23 inflammation (Champaneri et al., 2013). HPA axis hypoactivity may therefore be indicative of
24 a pathophysiological process, capable of influencing mood and weight gain, which is unique
25 to depressed patients with metabolic disturbances.

1 Research investigating inflammatory markers and their association with depressive
2 symptoms in individuals with obesity is typically complicated by a high incidence of other
3 inflammatory disorders, such as atherosclerosis, diabetes, cardiovascular disease, and
4 hypertension (Upadhyay, Farr, Perakakis, Ghaly, & Mantzoros, 2018). Once patients have
5 developed comorbid depression and obesity, they become more vulnerable to developing
6 subsequent inflammatory conditions. These conditions are associated with an increased risk of
7 recurrent depressive episodes (Nigatu, Bultmann, & Reijneveld, 2015), demonstrating the
8 vicious cycle to which these patients may be liable. Therefore, it is vital to confirm the
9 association between depressive symptoms and inflammation in a sample free of comorbid
10 disorders, as the presence of other disorders may confound this relationship. It is also important
11 to identify which subgroup of patients with depression are most vulnerable so that they can be
12 prioritised for clinical interventions targeted at reducing their risk of developing further
13 comorbidities.

14
15 Therefore, we investigated inflammatory mechanisms, in the form of pro-inflammatory
16 hsCRP and anti-inflammatory cortisol, to determine how these biomarkers are associated with
17 depression and overweight status. We also investigated whether the presence of comorbid
18 depression and overweight increased inflammation to a clinically relevant level. Crucially, our
19 study used a sample of patients with depression who were free of other comorbid disorders,
20 with a comparison group of overweight controls, who were otherwise healthy.

21
22 This is the first study to explore differences in hsCRP levels and HPA axis activity in
23 overweight individuals with and without depression, as well as normal-weight individuals with
24 and without depression. Our cross-sectional study aimed to investigate: 1) whether overweight
25 patients with depression had increased inflammation relative to all other groups; 2) what extent

1 overweight status and depression status contributed to clinically elevated hsCRP levels
2 $\geq 3\text{mg/L}$; 3) whether overweight patients with depression had lower diurnal cortisol levels
3 relative to all other groups.

4

5 **Methods**

6 Clinical data, blood samples, and saliva samples were collected in a cross-sectional,
7 observational design, as part of a multi-centre study investigating immune Biomarkers in
8 Depression (BIODEP), through the Wellcome Trust Consortium for Neuroimmunology of
9 Mood Disorders and Alzheimer's disease (NIMA). The study was approved by the Research
10 Ethics Committee (National Research Ethics Service East of England, Cambridge Central, UK;
11 approval number: 15/EE/0092). All procedures contributing to this work comply with the
12 ethical standards of the relevant national and institutional committees on human
13 experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants
14 provided written informed consent and underwent eligibility screening prior to taking part in
15 any study procedures.

16

17 **Participants**

18 Participants were aged 25-50 years inclusive and recruited at five clinical research study
19 centres (King's College London, Oxford, Cambridge, Brighton and Glasgow) from primary
20 and secondary NHS health services and the general population. Participants were excluded if
21 they 1) were pregnant or breastfeeding; 2) were underweight (defined as BMI < 18); 3) were
22 taking medication likely to compromise the interpretation of immunological data (including,
23 but not limited to, statins, corticosteroids, antihistamines and anti-inflammatory medications);
24 4) met criteria for alcohol abuse, drug abuse or dependence in the last six months; 5) had
25 participated in a clinical trial of an investigational drug within the last 12 months; 6) had

1 lifetime history of any serious medical disorder likely to compromise the interpretation of
2 immunological data; 7) had a recent infection or illness likely to compromise the interpretation
3 of immunological data. Patients with depression were considered eligible if they met the
4 criteria for Major Depressive Disorder (MDD). Patients with depression were excluded if they
5 had a lifetime history of bipolar disorder or non-affective psychosis. Healthy controls were
6 considered eligible if they had no personal history of MDD or treatment with a monoaminergic
7 antidepressant for depressive symptoms or any other indication, as well as no current or
8 lifetime history of any major psychiatric disorder as defined by Diagnostic and Statistical
9 Manual Version 5 (DSM-5).

10

11 **Sample groups**

12 The current sample was selected from a larger sample of participants taking part in the
13 BIODIEP study, where participants were recruited based on their clinical response to
14 antidepressants as described by our group previously (Chamberlain et al., 2019; Nikkheslat et
15 al., 2019). For the purpose of the current study, participants from the BIODIEP pool were
16 grouped according to their BMI status (overweight participants with BMI ≥ 25) and then
17 categorised these participants according to the presence of depression (MDD patients versus
18 healthy controls).

19

20 **Demographic and clinical measures**

21 Age, gender, smoking status, and medical history were documented by semi-structured
22 clinical interviews. Height and weight were measured for calculation of BMI (kg/m^2) and
23 overweight status was defined as BMI ≥ 25 . History and diagnosis of MDD and other
24 psychiatric disorders were assessed with the Structured Clinical Interview for DSM-5 (Kübler,

1 2013). The severity of depressive symptoms was assessed using 17-item Hamilton Rating Scale
2 for Depression (HAM-D) (Hamilton, 1960).

3

4 **High sensitivity C-Reactive Protein (hsCRP)**

5 Peripheral inflammation was measured as serum levels of high-sensitivity CRP
6 (hsCRP), which has been demonstrated as a reliable biomarker of inflammation associated with
7 MDD. Participants fasted for 8 hours and abstained from strenuous exercise for 72 hours prior
8 to their blood draw, which was carried out between 8:00 and 10:00. Blood samples were
9 collected in clotting tubes, allowed to coagulate at room temperature for 30-60 minutes, then
10 centrifuged at 1600 Relative Centrifugal Force for 15 minutes. The serum samples were
11 separated and transported to a central laboratory (Q2 solutions) where they were analysed on
12 the day of collection. Samples were exposed to anti-CRP-antibodies on latex particles, and the
13 increase in light absorption due to complex formation was used to quantify hsCRP levels, using
14 Turbidimetry on Beckman Coulter AU analysers. Inter and intra-assay coefficient of variations
15 were <10%. The measure of hsCRP was calculated from one blood draw taken at the time of
16 clinical assessment, for each participant. In line with previous studies, clinically elevated
17 hsCRP levels were defined as $hsCRP \geq 3mg/L$ (A. H. Miller & C. L. Raison, 2016; Pearson et
18 al., 2003).

19

20 **Salivary cortisol**

21 Participants were issued with the materials and instructions for collecting the saliva
22 samples at the time of their clinical interview. Our previously published literature describes the
23 collection procedure for saliva samples in more detail (Nikkheslat et al., 2019). Using salivette
24 sampling devices (Sarstedt, Leicester, UK), samples were self-collected by participants at
25 home at six time points throughout the day; at awakening, 15, 30 and 60 minutes after

1 awakening, 12:00 and at 20:00. Individuals who described problems during sample collection
2 in the self-recorded questionnaire, or who did not respect the time-intervals required, were
3 removed from the analysis. The current study included only participants who completed saliva
4 sample collections accurately and who provided an adequate amount of saliva for cortisol
5 measurement. Salivary cortisol levels were measured using a commercially available high-
6 sensitivity salivary cortisol enzyme immunoassay kit from Salimetrics. SoftMax Pro 4.8
7 software was used to calculate the cortisol values, following a 4-parameter fit. The analytical
8 sensitivity was set to 0.19 nmol/l. Inter and intra-assay coefficient of variations ranged from 8-
9 10% and 6-10%, respectively. To investigate the activity and responsiveness of the HPA axis,
10 we first compared the mean values at the various time points of salivary cortisol collection;
11 and secondly, we calculated the area under the curve with respect to the increase (AUC_i) for
12 the cortisol awakening response using the four time points of 0, 15, 30, and 60 minutes after
13 awakening; and the area under the curve with respect to the ground (AUC_g) for the diurnal
14 cortisol using the three points: awakening, noon and 20:00. AUC_g indicated the total amount
15 of cortisol produced and overall HPA axis activity during the day. AUC_i indicated the variation
16 (either positive or negative) in cortisol concentration and thus signified the HPA axis reactivity
17 and response to the stress of awakening. The formulas for the calculations of the AUC were
18 derived from the trapezoidal formula introduced by Pruessner et al. (Pruessner, Kirschbaum,
19 Meinschmid, & Hellhammer, 2003).

20

21 **Statistical analysis**

22 All statistical analyses were performed using R software, version 4.0.0. Data were
23 evaluated for normality and logarithmic transformed if required. To assess group differences
24 in demographic variables, Chi-squared or Kruskal-Wallis tests were used, as appropriate. To
25 address the first hypothesis, group differences in logarithmic-transformed hsCRP levels were

1 assessed using two-way analysis of covariance (ANCOVA), with group and gender as factors
2 and age as a covariate. Pairwise comparisons were carried out using the False Discovery Rate
3 (FDR) correction, with the alpha set at 0.05 (5%). Effect size differences in hsCRP groups
4 relative to the normal-weight controls were calculated using Cohen's *d*. To address the second
5 hypothesis, two models of multivariable logistic regression were used. The first assessed how
6 much risk comorbid depression and overweight contributed to the hsCRP levels $\geq 3\text{mg/L}$
7 relative to other participant groups, with age and gender as covariates. The second assessed
8 how much risk depression and overweight status ($\text{BMI} \geq 25$) separately contributed to hsCRP
9 levels $\geq 3\text{mg/L}$, with age and gender as covariates. To address the third hypothesis, group
10 differences in cortisol awakening response (AUC_i) and logarithmic-transformed diurnal
11 cortisol (AUC_g) were assessed using two-way analysis of covariance (ANCOVA), with
12 adjustment for age and gender. The threshold for statistical significance of all tests was defined
13 as two-tailed $p \leq 0.05$.

14

15 **Results**

16 **Sample demographics**

17 The demographic and clinical characteristics of the sample are presented in Table 1.
18 Age and gender were significantly different between groups, while ethnicity and smoking
19 status were similar across groups, in both samples. Although the proportion of smokers were
20 not significantly different between groups, we repeated all analyses excluding smokers to
21 determine if smoking status significantly influenced hsCRP and cortisol levels. As the direction
22 of the results did not change for any of the relevant tests after excluding smokers, we have
23 reported results for the full sample, with the data for non-smokers presented in the supplement.
24 A similar number of overweight patients with depression and normal-weight patients with
25 depression were currently taking antidepressant medication (47 patients vs. 39 patients,

1 $x^2=0.019, p=0.889$) and a two-way ANCOVA showed that both groups had a similar age of
2 onset of depressive symptoms ($F(1, 109)=1.617, p=0.206$, with adjustment for age and gender.

4 **High sensitivity C-Reactive Protein (hsCRP)**

5 A two-way ANCOVA showed a significant effect of group on hsCRP, with adjustment
6 for age and gender $F(3, 211)=16.43, p<0.001$. As there was no significant interaction between
7 group and gender on hsCRP, $F(3, 211)=1.4, p=0.245$, pairwise comparisons with the FDR
8 correction were carried out, comparing the main effects of group, but not gender. Overweight
9 patients with depression had significantly higher hsCRP compared with overweight controls
10 ($p=0.042$), normal weight depressed patients ($p<0.001$) and normal weight controls ($p<0.001$;
11 see Figure 1). Within the group of overweight patients with depression there were six
12 individuals with extreme BMI values ≥ 40 indicating morbid obesity. When excluding these
13 individuals from analysis, a two-way ANCOVA showed a significant effect of group on
14 hsCRP, with adjustment for age and gender $F(3, 201)=15.11, p<0.001$. As there was no
15 significant interaction between group and gender on hsCRP, $F(3, 207)=1.36, p=0.257$, pairwise
16 comparisons with the FDR correction were carried out, comparing the main effects of group,
17 but not gender. Overweight patients with depression had higher hsCRP compared with
18 overweight controls at trend-level ($p=0.068$), and significantly higher hsCRP compared with
19 normal weight depressed patients ($p<0.001$) and normal weight controls ($p<0.001$).

21 Multivariable logistic regression analysis was performed to investigate whether group
22 status contributed to the risk of having hsCRP $\geq 3\text{mg/L}$, after controlling for age and gender.
23 Overweight patients with depression were at a significantly increased risk of having hsCRP
24 $\geq 3\text{mg/L}$ (OR: 2.44, 95% confidence interval (CI)=1.28-3.94, $p<0.001$), overweight controls
25 did not have a significantly increased risk of hsCRP $\geq 3\text{mg/L}$ (OR: 1.51, 95% CI=-0.33-2.87,

1 $p=0.13$), normal-weight patients with depression did not have a significantly increased risk of
2 $\text{hsCRP} \geq 3\text{mg/L}$ (OR: 1.08, 95% CI=-0.6-2.4, $p=0.28$), while normal-weight controls were at a
3 significantly decreased risk of $\text{hsCRP} \geq 3\text{mg/L}$ (OR: -4.39, 95% CI=-7.04 to -1.97, $p<0.001$).
4 Age and gender were not significantly associated with $\text{hsCRP} \geq 3\text{mg/L}$ (OR:0.01, 95%
5 confidence interval (CI) = -0.04-0.06, $p=0.621$, OR:0.61, 95% CI=-0.19-1.47, $p=0.145$,
6 respectively).

7

8 Multivariable logistic regression analysis was also performed to investigate the
9 association between depression and overweight status on $\text{hsCRP} \geq 3\text{mg/L}$, after controlling for
10 age and gender. Depression status was significantly associated with $\text{hsCRP} \geq 3\text{mg/L}$ (OR: 1.09,
11 95% CI=0.27-2.01, $p=0.013$) and overweight status was significantly associated with hsCRP
12 $\geq 3\text{mg/L}$ (OR: 1.52, 95% CI=0.7-2.41, $p<0.001$). Age and gender were not significantly
13 associated with $\text{hsCRP} \geq 3\text{mg/L}$ (OR:0.62, 95% confidence interval (CI)=-0.04-0.06, $p=0.647$,
14 OR:0.01, 95% confidence interval (CI)=-0.19-1.47, $p=0.137$ respectively).

15

16 **Cortisol**

17 A two-way ANCOVA showed no significant differences between groups in CARi , after
18 adjustment for age and gender, $F(3, 162)=0.473$, $p=0.701$. Similarly, a two-way ANCOVA
19 showed no significant differences between groups in logarithmic-transformed AUCg , after
20 adjustment for age and gender, $F(3, 167)=0.719$, $p=0.542$.

21 **Discussion**

22 To our knowledge, this is the first study to observe significantly higher hsCRP levels
23 in overweight patients with depression relative to overweight controls, as well as depressed
24 and non-depressed normal-weight participants. Of clinical relevance, overweight patients with
25 depression had the highest risk for hsCRP levels $\geq 3\text{mg/L}$, indicating clinically elevated

1 peripheral inflammation. Our results demonstrate that coexisting depression and overweight
2 may exacerbate peripheral inflammation and highlights the urgent need to optimise treatment
3 strategies for these patients. We observed no differences in HPA axis activity between groups.
4

5 Our findings regarding elevated hsCRP levels in overweight patients with depression
6 are consistent with previous studies in normal-weight patients with depression and obese
7 patients with depression (Haapakoski et al., 2015; Rethorst, Bernstein, & Trivedi, 2014). Of
8 note, our study design separating overweight and normal-weight participants, from those with
9 and without depression, was able to demonstrate the separate and comorbid association
10 between these disorders and hsCRP levels $\geq 3\text{mg/L}$. Peripheral inflammation is believed to
11 initiate and perpetuate a range of sickness-related behaviour, such as fatigue, weakness,
12 malaise, sleep, and disturbed appetite (Dantzer, 2006), which may further maintain the vicious
13 cycle between weight gain and depressive symptoms. The increased risk for overweight
14 patients with depression to have clinically elevated hsCRP $\geq 3\text{mg/L}$ is concerning, as CRP is a
15 predictor of all-cause mortality (Li et al., 2017). Increased mortality and risk of developing
16 subsequent comorbid disorders in patients with depression places a substantial burden on
17 healthcare infrastructure and the economy (Tremmel, Gerdtham, Nilsson, & Saha, 2017), in
18 addition to reduced quality of life for these individuals (Nigatu, Reijneveld, de Jonge, van
19 Rossum, & Bultmann, 2016). Answering the question of whether depression or weight gain
20 contributed more to inflammation was identified as a key objective by a recent meta-analysis
21 (Ambrosio et al., 2018), so that research for this field can progress into therapeutic
22 interventions designed to break the cyclic pattern between these disorders.
23

24 Testing CRP levels in overweight patients with depression could be useful for
25 recommending adjunct anti-inflammatory treatments or predicting their likelihood of

1 developing additional comorbidities in the future. Indeed, several clinical trials have observed
2 that higher BMI at baseline predicted a poorer response to antidepressant treatments (Jha et al.,
3 2018; Uher et al., 2009), while we have previously shown that immune-metabolic status was
4 associated with a poorer response to antipsychotic medication in individuals with psychosis
5 (Nettis et al., 2019). Anti-inflammatory drugs improve the therapeutic action of antidepressants
6 (Bai et al., 2020; Haroon, Raison, & Miller, 2012), which could be particularly useful in the
7 context of chronically inflamed overweight patients with depression. Overweight patients with
8 hsCRP ≥ 3 mg/L may prove ideal criterion to test this, as stratifying patients to specific
9 treatments according to inflammatory markers seems to improve treatment response (Cuthbert
10 & Insel, 2013; Kohler, Krogh, Mors, & Benros, 2016).

11

12 The lack of significant differences between groups in HPA axis activity was surprising,
13 as HPA axis dysregulation has been implicated in both obesity and depression (Incollingo
14 Rodriguez et al., 2015), however, the nature of the dysregulation is not always consistent. A
15 systematic review comparing atypical depression with the melancholic (typical) presentation,
16 found that atypical patients demonstrated lower cortisol relative to melancholic patients, but
17 not so low that they were significantly different from controls (Juruena et al., 2018). In contrast,
18 our study observed no differences in cortisol levels, despite hsCRP levels varying dramatically
19 between groups. Dysregulation of the HPA axis may change over illness course, with
20 hypotheses suggesting that at first cortisol levels are highly responsive to peripheral
21 inflammation, but over time this responsivity declines (Gold, 2015; Perrin, Horowitz, Roelofs,
22 Zunszain, & Pariante, 2019). Another explanation is that specific symptoms are responsible for
23 changes in HPA axis activity (Iob, Kirschbaum, & Steptoe, 2020), and that antidepressant use
24 additionally modifies HPA axis activity, as our group recently observed (Nikkheslat et al.,

1 2019). Ultimately, our sample of patients may have been too heterogeneous in terms of
2 depressive symptoms, antidepressant use and illness course to identify group differences.

3
4 Our study design was substantially strengthened by our strict exclusion criteria, encompassing
5 recent illnesses and comorbid disorders, such as atherosclerosis, diabetes and cardiovascular
6 disease, which often confounds research in patients with obesity. We also excluded patients
7 taking medications that could influence immunological data, such as statins, corticosteroids,
8 antihistamines, anti-inflammatory medications. Additionally, the direction of our results was
9 maintained after we removed smokers and individuals with extreme BMI values ≥ 40 ,
10 suggesting that our findings are robust. Our study was limited by a lack of additional body
11 composition and clinical measures, as these would have enabled us to define an immune-
12 metabolic subgroup of patients within our sample. However, using overweight status as defined
13 by BMI has high translational value for clinical settings. Our sample consisted of
14 predominantly white participants, which limits the generalisability of the results. Our study
15 could have been improved by the measurement of lifestyle factors, particularly physical
16 activity, sleep and diet, as these factors may confound the relationship between depression and
17 weight gain (Schmidt et al., 2015). Future studies should be designed to include more diverse
18 participant samples and adjust for lifestyle factors as covariates as they may explain some of
19 the heterogeneity in the association between depressive symptoms and inflammation.

20

21 Chronic inflammation is likely a key modifier in the vicious cycle between depressive
22 symptoms and weight gain. If the cycle can be reversed, meaning that a reduction in depressive
23 symptoms is accompanied by healthy behaviour such as exercise and healthy eating, which
24 indirectly reduces inflammation and leads to excess weight loss, this would result in a better
25 quality of life for patients and a vast reduction in global healthcare burdens and economic cost

1 (Jantaratnotai, Mosikanon, Lee, & McIntyre, 2017; Nigatu et al., 2016; Tremmel et al., 2017).
2 Ultimately, our data suggest that depression and overweight are separately associated with
3 increased inflammation, but this association is amplified when these conditions coexist.
4 Patients with depression with BMI ≥ 25 would likely benefit from further research to determine
5 if a higher level of clinical support or anti-inflammatory treatment approaches could potentially
6 improve depressive symptoms and reduce the risk of developing further comorbidities in this
7 subgroup of patients.

8

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6

7 **Conflicts of interest**

8 SRC consults for Cambridge Cognition and Shire; and his input in this project was
9 funded by a Wellcome Trust Clinical Fellowship (110049/Z/15/Z). ETB was employed half-
10 time by GlaxoSmithKline, and held stock in GSK, until May 2019; he has since worked full
11 time for University of Cambridge; he was holding stock (not currently) in GSK. ETB is an
12 NIHR Senior Investigator. NAH consults for GSK. PdB, DJ and WCD are employees of
13 Janssen Research & Development, LLC., of Johnson & Johnson, and hold stock in Johnson &
14 Johnson. The other authors report no financial disclosures or potential conflicts of interest.

15

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3

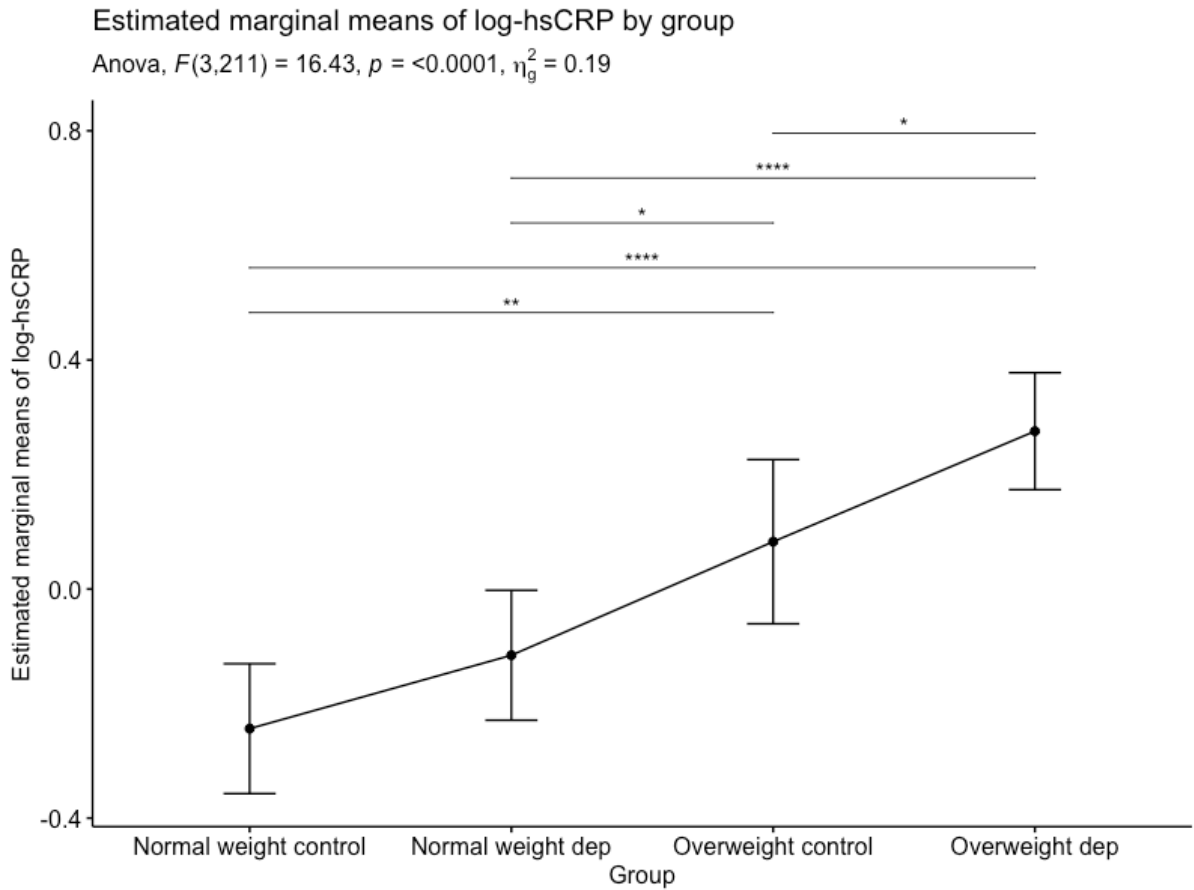
1 **Table 1: Comparison of sample groups**

Variables	Groups				Group tests	
	Overweight & depressed N= 69	Overweight control N= 35	Normal weight & depressed N= 55	Normal weight control N= 57	Statistic	P
Demographics						
Median age in years (range)	38 (25 – 50)	38 (25 – 48)	32 (25 – 50)	30 (24 – 50)	K = 18.368	<0.001
Gender, female (%)	43 (62.3%)	17 (48.6%)	40 (72.7%)	44 (77.2%)	$\chi^2 =$ 9.495	0.023
BMI (range)	28.8 (25.3 – 47.8)	28.4 (25 – 35.6)	22.1 (18.1 – 24.9)	22.4 (18.4 – 24.9)	K = 161.87	<0.001
Ethnicity, white (%)	63 (91.3%)	29 (82.9%)	45 (81.8%)	45 (78.9%)	$\chi^2 =$ 4.102	0.251
Smoking status, smoker (%)	11 (15.9%)	3 (8.6%)	11 (20%)	6 (10.5%)	$\chi^2 =$ 3.199	0.362
Clinical						
Median HAM-D total score (range)	19 (14 – 31)	0 (0 – 5)	18 (14 – 26)	0 (0 – 7)	K = 162.83	<0.001
Currently on antidepressants (%)	47 (68.1%)	NA	39 (70.9%)	NA	$\chi^2 =$ 0.019	0.889
Mean age of depression onset \pm SD	24.6 \pm 9.8	NA	25.2 \pm 9.4	NA	F = 1.617	0.206
hsCRP						
Median hsCRP (range)	2.2 (0.2 – 15.3)	1.3 (0.2 – 11.8)	0.7 (0.2 – 8.8)	0.5 (0.2 – 5.2)	K = 43.725	<0.001
Mean log hsCRP mg/L \pm SD Cohen's <i>d</i> effect size vs controls	0.28 \pm 0.48 1.25	0.09 \pm 0.43 0.89	-0.12 \pm 0.42 0.35	-0.25 \pm 0.35	F = 16.43	<0.001
hsCRP \geq 3mg/L (%)	26 (37.7%)	5 (14.3%)	6 (10.9%)	3 (5.3%)	$\chi^2 =$ 25.96	<0.001
Salivary cortisol						
Mean CAR AUCi (nmol min/L) \pm SD	100.53 \pm 248.99	75.79 \pm 240.98	41.62 \pm 240.43	86.46 \pm 299.78	F = 0.473	0.701
Mean log AUCg (nmol hour/L) \pm SD	1.65 \pm 0.18	1.66 \pm 0.23	1.72 \pm 0.2	1.7 \pm 0.26	F = 1.25	0.293

2

3 BMI= body mass index, HAM-D= Hamilton Depression Rating Scale 17 for depressive symptoms, hsCRP=
4 high sensitivity C-reactive protein, SD = standard deviation, CAR= cortisol awakening response, AUCi= area
5 under the curve with respect to increase, AUCg= area under the curve with respect to ground.

1 **Figure 1 caption:** Estimated marginal means of logarithmic transformed hsCRP levels for
 2 each group. A two-way ANCOVA showed a significant effect of group on log hsCRP, with
 3 adjustment for age and gender $F(3, 211)=16.43, p<0.001$. Significance of pairwise
 4 comparisons, with the False Discovery Rate correction set at 5%, are shown within the figure.



1 **Supplementary material**

2

3 **Table 1: Comparison of sample groups with non-smoking participants only**

Variables	Groups				Group tests	
	Overweight & depressed N= 58	Overweight control N= 32	Normal weight & depressed N= 44	Normal weight control N= 51	Statistic	P
Demographics						
Median age in years (range)	38.5 (25 – 50)	37 (25 – 48)	30 (25 – 50)	30 (24 – 50)	K = 15.16	0.002
Gender, female (%)	36 (62.1%)	15 (46.9%)	33 (75%)	39 (76.5%)	$\chi^2 = 9.744$	0.021
BMI (range)	29.6 (25.3 – 47.8)	28.5 (25 – 35.6)	22 (18.1 – 24.9)	22.4 (18.8 – 24.9)	K = 138.57	<0.001
Ethnicity, white (%)	52 (89.7%)	26 (81.2%)	36 (81.8%)	40 (78.4%)	$\chi^2 = 2.711$	0.438
Clinical						
Median HAM-D total score (range)	19 (14 – 31)	0 (0 – 5)	18 (14 – 26)	0 (0 – 7)	K = 141.16	<0.001
Currently on antidepressants (%)	37 (63.8%)	NA	31 (70.5%)	NA	$\chi^2 = 0.245$	0.621
Mean age of depression onset \pm SD	25 \pm 9.8	NA	25.4 \pm 9.2	NA	F = 1.623	0.206
hsCRP						
Median hsCRP (range)	2.25 (0.2 – 15.3)	1.4 (0.2 – 11.8)	0.7 (0.2 – 8.8)	0.5 (0.2 – 5.2)	K = 30.514	<0.001
Mean log hsCRP mg/L \pm SD	0.27 \pm 0.51	0.09 \pm 0.48	-0.11 \pm 0.43	-0.23 \pm 0.36	F = 12.07	<0.001
Cohen's <i>d</i> effect size vs controls	1.11	0.81	0.29			
hsCRP \geq 3mg/L (%)	23 (39.7%)	4 (12.5%)	5 (11.4%)	3 (5.9%)	$\chi^2 = 24.405$	<0.001
Salivary cortisol						
Mean CAR AUCi (nmol min/L) \pm SD	99.8 \pm 262	87.7 \pm 238	6.79 \pm 228	89 \pm 311	F = 0.889	0.448
Mean log AUCg (nmol hour/L) \pm SD	1.66 \pm 0.18	1.67 \pm 0.23	1.7 \pm 0.18	1.72 \pm 0.23	F = 0.082	0.495

4 BMI= body mass index, HAM-D= Hamilton Depression Rating Scale 17 for depressive symptoms, hsCRP=
5 high sensitivity C-reactive protein, SD = standard deviation, CAR= cortisol awakening response, AUCi= area
6 under the curve with respect to increase, AUCg= area under the curve with respect to ground.

7

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