

## Original Article

**Cite this article:** McLaughlin AP *et al* (2024). Peripheral inflammation associated with depression and reduced weight loss: a longitudinal study of bariatric patients. *Psychological Medicine* **54**, 601–610. <https://doi.org/10.1017/S0033291723002283>

Received: 26 January 2023

Revised: 26 June 2023

Accepted: 17 July 2023

First published online: 31 August 2023

**Keywords:**


Bariatric surgery; CRP; cytokines; depression; inflammation; obesity

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# Peripheral inflammation associated with depression and reduced weight loss: a longitudinal study of bariatric patients

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**Abstract**

**Background.** Research implicates inflammation in the vicious cycle between depression and obesity, yet few longitudinal studies exist. The rapid weight loss induced by bariatric surgery is known to improve depressive symptoms dramatically, but preoperative depression diagnosis may also increase the risk for poor weight loss. Therefore, we investigated longitudinal associations between depression and inflammatory markers and their effect on weight loss and clinical outcomes in bariatric patients.

**Methods.** This longitudinal observational study of 85 patients with obesity undergoing bariatric surgery included 41 cases with depression and 44 controls. Before and 6 months after surgery, we assessed depression by clinical interview and measured serum high-sensitivity C-reactive protein (hsCRP) and inflammatory cytokines, including interleukin (IL)-6 and IL-10.

**Results.** Before surgery, depression diagnosis was associated with significantly higher serum hsCRP, IL-6, and IL-6/10 ratio levels after controlling for confounders. Six months after surgery, patients with pre-existing depression still had significantly higher inflammation despite demonstrating similar weight loss to controls. Hierarchical regression showed higher baseline hsCRP levels predicted poorer weight loss ( $\beta = -0.28$ ,  $p = 0.01$ ) but had no effect on depression severity at follow-up ( $\beta = -0.02$ ,  $p = 0.9$ ). Instead, more severe baseline depressive symptoms and childhood emotional abuse predicted greater depression severity after surgery ( $\beta = 0.81$ ,  $p < 0.001$ ; and  $\beta = 0.31$ ,  $p = 0.001$ , respectively).

**Conclusions.** Depression was significantly associated with higher inflammation beyond the effect of obesity and other confounders. Higher inflammation at baseline predicted poorer weight loss 6 months after surgery, regardless of depression diagnosis. Increased inflammation, rather than depression, may drive poor weight loss outcomes among bariatric patients.

**Introduction**

Depression and obesity are highly comorbid disorders, rapidly increasing in prevalence globally (Finkelstein, Ruhm, & Kosa, 2005; Otte *et al.*, 2016). The co-occurrence of depression and obesity are leading causes of disability and mortality (DiMatteo, Lepper, & Croghan, 2000; Milaneschi, Lamers, Berk, & Penninx, 2020; Strawbridge *et al.*, 2015; Upadhyay, Farr, Perakakis, Ghaly, & Mantzoros, 2018), which presents a significant healthcare concern. The association between depression and obesity appears stronger in longitudinal studies than in cross-sectional studies (Luppino *et al.*, 2010; Milaneschi *et al.*, 2017), suggesting that a common pathophysiological mechanism is driving this high comorbidity. Further highlighting the bidirectional relationship between depression and obesity, weight loss interventions are associated with improvements in depressive symptoms (Capuron *et al.*, 2011; Perez-Cornago *et al.*, 2014).

The only effective, long-term weight loss intervention for obesity is bariatric surgery, where patients can lose up to 60% to 70% of their excess weight (Schroeder, Garrison, & Johnson, 2011). Although the rapid weight loss induced by bariatric surgery is typically associated with a dramatic improvement in depressive symptoms (Fu, Zhang, Yu, Mao, & Su, 2021; Gill *et al.*, 2019; Spirou, Raman, & Smith, 2020), some studies have observed that a preoperative depression diagnosis is associated with reduced weight loss and worse depression

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prognosis following bariatric surgery (Galioto & Crowther, 2013; Martens *et al.*, 2021; Pedro *et al.*, 2020; van Hout, Verschure, & van Heck, 2005). However, the inconsistent findings may also be due to these studies using self-report questionnaires instead of clinical interviews to assess depressive symptoms (Spirou *et al.*, 2020). Given that depression rates are very high in bariatric surgery candidates, with approximately 45% of bariatric surgery having a presurgical diagnosis of depression (Alabi *et al.*, 2018), there is an urgent medical need to identify whether depression is a risk factor for poor clinical outcomes after bariatric surgery (Van den Eynde *et al.*, 2021).

Chronic inflammation is a hallmark of obesity, as adipose tissue accumulation stimulates the production of proinflammatory cytokines, resulting in elevated C-reactive protein (CRP) levels (Thompson *et al.*, 2016). Peripheral inflammation, driven by proinflammatory cytokine activity, has also been suggested to play a role in the pathophysiology of depression (Capuron & Miller, 2011; Dantzer & Walker, 2014; Raison *et al.*, 2010). Cytokine abnormalities in the periphery are closely associated with cytokine abnormalities in the central nervous system (CNS) (Enache, Pariante, & Mondelli, 2019), which can lead to neuroinflammation in brain regions such as the anterior cingulate cortex, hypothalamus, amygdala, and hippocampus (Borsini *et al.*, 2018; Duan *et al.*, 2018; Goldsmith, Bekhbat, Mehta, & Felger, 2022; Meier *et al.*, 2016; Zunszain *et al.*, 2012). Abnormalities within these brain regions and neurotransmitter systems are found in depression and obesity (Capuron, Lasselien, & Castanon, 2017). Therefore, increased inflammation, primarily mediated by cytokines in the periphery and CNS, demonstrates a biological pathway that may underlie the high comorbidity between depression and obesity (Chan, Cathomas, & Russo, 2019).

Given the putative role of inflammation in the vicious cycle between depression and obesity, inflammation may influence weight loss and depression outcomes following bariatric surgery. Indeed, bariatric patients who exhibit more considerable reductions in inflammatory markers during the early post-surgical period demonstrate greater weight loss and improved metabolic health (Illán Gómez *et al.*, 2016; O'Rourke *et al.*, 2019). Other studies have shown that reductions in BMI following surgery were associated with improved depressive symptoms and lower CRP levels (Capuron *et al.*, 2011; Perez-Cornago *et al.*, 2014). More recently, transcriptomic analyses of bariatric patients observed upregulated cytokine signaling pathways associated with depression severity at baseline and remission after surgery (Moisan *et al.*, 2021). Disentangling the temporal relationships between changes in depressive symptoms and weight loss during the postoperative period is crucial, as longitudinal studies of bariatric patients suggest that changes in depressive symptoms and weight loss in the first postoperative year significantly influence long-term outcomes (Geerts *et al.*, 2021; Smith *et al.*, 2020). Together, these findings suggest that changes in inflammatory markers associated with depression may contribute to the high heterogeneity in weight loss and mental health outcomes among bariatric patients.

Here, to our knowledge, we conducted the first study to investigate differences in serum and adipose cytokines between obese patients with and without depression undergoing bariatric surgery. We aimed to identify risk factors for poor clinical outcomes after surgery by measuring inflammatory biomarkers and depression assessed by clinical interviews before surgery and 6 months after. We also assessed potential confounders, including socio-demographic variables, diabetic status, antidepressant use,

childhood trauma, and physical activity. We hypothesized that: (1) bariatric patients with depression will demonstrate higher inflammation relative to control bariatric patients; (2) higher inflammation at baseline will predict reduced weight loss and higher severity of depressive symptoms after surgery.

## Methods and materials

### Study design

This longitudinal observational case-control study recruited patients undergoing bariatric surgery at King's College Hospital as part of the ongoing Bariatric Surgery & Depression (BARIDEP) study. We recruited 85 bariatric candidates before their bariatric surgery procedure and followed them up 6 months after, between March 2018 and November 2021. Patients provided written informed consent, underwent eligibility screening, and were compensated with vouchers for participation. We provided the vouchers after each study visit to reimburse patients for their time, but the voucher amounts were minimal to prevent the risk of financial incentives influencing their decision to participate in the study. The Ethics Committee of the National Research Ethics Service East of England approved the study (18/LO/350). We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for case-control studies and collected biological samples in accordance with the 2004 Human Tissue Act.

### Participants

We collected socio-demographic, medical history, and neuropsychiatric data to assess patients for eligibility through structured clinical interviews with a trained researcher. Self-reported responses from patients were cross-validated with their medical records.

Participants were eligible if they were (1) obese, classified as BMI  $\geq 35$ ; (2) undergoing either Roux-en-Y Gastric Bypass (RYGB) or Sleeve Gastrectomy (SVG) bariatric surgery at King's College Hospital; (3) aged between 18 and 70 years old; (4) able to read and write English fluently. Participants were excluded if they (1) were pregnant or breastfeeding; (2) had a past or current primary diagnosis of psychotic disorder; (3) were taking high doses of anti-inflammatory medication likely to compromise the interpretation of immunological data (including, but not limited to, non-steroidal anti-inflammatory drugs for chronic pain, antibiotics, oral steroids, immunosuppressive drugs, or monoclonal antibodies that block inflammatory cytokines; see medication exceptions in page one of the Supplement); (4) met criteria for alcohol abuse, drug abuse or dependence in the last 6 months; (5) participated in a clinical trial of an investigational drug within the last year; (6) had a lifetime history of any severe medical disorder or recent infection or illness likely to compromise the interpretation of immunological data.

Patients with depression (cases) were eligible if they met the criteria for current major depressive disorder (MDD), as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), using the Mini International Neuropsychiatric Interview (MINI) (Sheehan *et al.*, 1998). Patients with depression were excluded if they had a lifetime history of bipolar disorder or non-affective psychosis. Control patients were eligible if they had no personal history of MDD or treatment with any antidepressant for depressive symptoms and no current or lifetime history of severe mental illness,

including affective and psychotic disorders, as defined by the DSM-5, using the MINI.

### Assessment of clinical measures related to depression and obesity

Depressive symptoms were measured using the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS), which included the 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), and the National Institute of Mental Health addition of eight atypical depression symptoms (Singh & Williams, 2006).

We also assessed other clinical variables associated with MDD and obesity in bariatric populations to control for potential confounders, including (1) the Childhood Trauma Questionnaire measured the severity of different types of childhood trauma, encompassing five clinical subscales: Emotional Abuse, Physical Abuse, Sexual Abuse, Emotional Neglect, Physical Neglect (Bernstein et al., 1994); (2) the short-form International Physical Activity Questionnaire (IPAQ) assessed the physical activity levels of participants (Craig et al., 2003).

### Body composition and weight loss

BMI and weight were measured on a Tanita MC-780MA professional body composition analyzer. Outcome weight loss was calculated as weight loss percentage (WLP), which is considered the most sensitive measure of postoperative weight loss (Hatoum & Kaplan, 2013). We also reported excess weight loss percentage to allow for comparison with other studies (see online Supplementary Table S1 for equations).

### Serum inflammatory markers

Markers of peripheral inflammation, measured in serum, included high-sensitivity CRP (hsCRP), proinflammatory cytokines IL-6, IL-2, TNF- $\alpha$ , IL-8, IL-1 $\beta$ , IL-12p70, IL-13, and anti-inflammatory cytokines IL-4 and IL-10. hsCRP is considered a reliable biomarker of low-grade chronic inflammation present in individuals with MDD, as hsCRP tests can detect slight elevations in CRP levels (between 0.5 to 10 mg/L) that would go unnoticed with standard CRP testing (that only detect acute inflammation above 10 mg/L). Blood samples were collected from participants at baseline and follow-up in the phlebotomy clinic at King's College Hospital; serum hsCRP samples were analyzed by Viapath laboratory. We measured serum cytokine levels using Meso Scale Discovery (MSD) V-PLEX sandwich immunoassays, MSD Pro-inflammatory Panel 1 human kit (Dabitaio, Margolick, Lopez, & Bream, 2011; King et al., 2019a), and plates were read on an MSD QuickPlex SQ 120 (Hepgul et al., 2012; Russell et al., 2019). All inter and intra-assay coefficients of variations were <10%. The lowest detectable values of cytokine assays are reported in online Supplementary Table S2. Clinically elevated hsCRP levels were defined as hsCRP  $\geq$  3 mg/L (Miller & Raison, 2016; Pearson et al., 2003).

### Adipose inflammatory markers

Adipose tissue samples were collected during participants' bariatric surgery operations at King's College Hospital. Cytokines, measured in visceral adipose tissue, included proinflammatory IL-6, IL-2, TNF- $\alpha$ , IL-8, IL-1 $\beta$ , IL-12p70, IL-13, and anti-

inflammatory IL-4 and IL-10. We measured cytokine levels using MSD V-PLEX sandwich immunoassays, MSD Proinflammatory Panel 1 human kit (Dabitaio et al., 2011; King et al., 2019a), and plates were read on an MSD QuickPlex SQ 120 (du Plessis et al., 2016; Gletsu et al., 2006). All inter and intra-assay coefficients of variations were <10%. Protein content in tissue homogenates was measured spectrophotometrically by protein OD A280 (NanoDrop, Thermo Fisher Scientific). Cytokine concentrations were normalized and expressed per milligram of protein present in adipose tissue to account for inter-individual fat cell size variability (DiGirolamo & Fine, 2001).

### Statistical analysis

We conducted a power size calculation in G Power to determine a sample size requirement of >70 bariatric patients to have an 80% power of detecting an effect size of  $d = 0.68$ , alpha level = 0.05,  $p < 0.05$  two-tailed, according to a meta-analysis finding higher IL-6 levels in depressed patients compared with healthy controls with an effect size of  $d = 0.68$  [7].

Primary outcomes were evaluated in cases *v.* controls using analysis of covariance (ANCOVA). Inflammatory markers were logarithmic or square-root transformed. Covariates at baseline and time of surgery included age, BMI, gender, ethnicity, diabetic status, antidepressant use, and smoking status. Across the total sample, participants self-identified as African (5.9%), Asian (1.2%), Black British (8.2%), Caribbean (7.1%), Gypsy (1.2%), Hispanic (1.2%), Latin American (1.2%), multiracial (Black and White) (4.7%), other multiracial (2.4%), White British (63.6%), and White other (3.5%). Due to the large proportion of participants of white ethnicity and the small cell sizes of participants from other ethnic backgrounds, data on ethnicity were collapsed into a dichotomized variable where participants were classified as either being of white ethnicity or non-white ethnicity.

Sensitivity analyses showed no significant effect on gender, ethnicity, diabetic status, and time to follow-up on inflammatory markers at follow-up. Therefore, covariates for inflammatory markers at follow-up included participant group, age, BMI at follow-up, surgery type, smoking status since surgery, and antidepressant use after surgery. Further analysis of inflammatory markers showing significant group differences was carried out with sample-wide correlations between serum and adipose inflammatory markers, and between inflammatory markers with depression scores at baseline or follow-up.

Predictors of secondary outcomes (WLP and HAM-D scores at follow-up) were evaluated in the total sample using hierarchical regression modeling. Firstly, baseline covariates for models were evaluated in scatter plots and selected if they showed significant bivariate correlations with outcome measures. Hierarchical regression was carried out in steps: (1) strength and significance of socio-demographic and clinical confounders were assessed; (2) strength and significance of baseline predictors were assessed, controlling for confounders; (3) backward elimination removed weak predictors until the models with the highest performance metrics were identified for each outcome measure.

A two-tailed  $p$  value <0.05 was considered statistically significant. Statistical analyses were conducted by A.P.M. using R software, version 4.1.1.

### Results

The sample included 85 bariatric surgery candidates with a mean (s.d.) age of 46.5 (11.6) years, and 51 (60%) participants were

**Table 1.** Sample characteristics, weight and psychopathology at baseline and 6-month follow-up after bariatric surgery

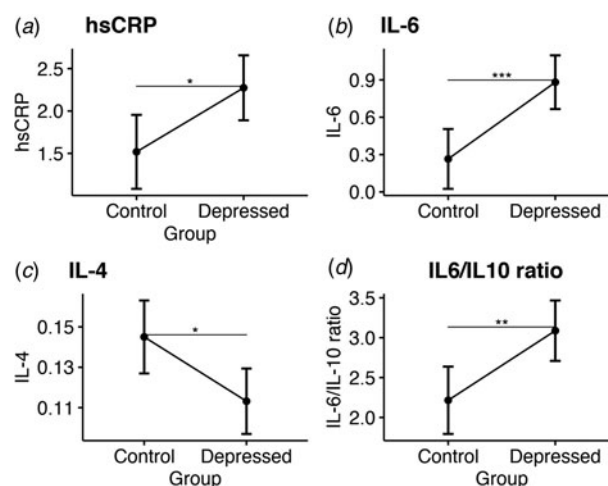
Variable	Baseline			Follow-up		
	Depressed (N = 41)	Controls (N = 44)	p value	Depressed (N = 29)	Controls (N = 37)	p value
Descriptive characteristics						
Age in years, mean (s.d.)	49 (12.1)	44.1 (10.8)	0.05	48 (12.3)	44.4 (10.3)	0.20
Gender, female (%)	26 (63)	25 (57)	0.69	19 (66)	22 (60)	0.80
Ethnicity, white (%)	32 (78)	24 (55)	0.04	23 (79)	18.0 (49)	0.02
Diabetic status (%)	22 (54)	23 (52)	>0.99	NA	NA	
Current smoker (%)	9 (22)	9 (21)	>0.99	4 (14)	4 (11)	0.41
RYGB v. VSG surgery (%)	NA	NA		15 (48)	19 (49)	>0.99
Weight measures						
Weight in kg, median (range)	143.5 (86.6–172.2)	124.3 (105.2–255.4)	0.79	107.1 (77–154.7)	96 (74.2–200.3)	0.20
BMI, median (range)	47.7 (36.7–63.9)	47.8 (36–85.1)	0.85	37.2 (27.3–59.3)	36 (24.8–67.9)	0.48
Weight loss percentage, mean (s.d.)	NA	NA		20.4 (1.48)	21 (1.43)	0.71
Excess weight loss percentage, mean (s.d.)	NA	NA		37 (3.19)	39.4 (3.08)	0.48
Clinical measures						
HAM-D score, median (range)	16 (9–29)	1 (0–6)	<0.001	6 (0–35)	0 (0–35)	<0.001
Atypical symptom score, median (range)	8 (2–20)	0 (0–10)	<0.001	2 (2–11)	0 (0–8)	0.003
Antidepressant use (%)	31 (75.6)	0 (0)	<0.001	14 (53.8)	0 (0)	<0.001
IPAQ total active days, median (range)	2 (0–14)	6 (0–21)	0.002	3 (0–21)	7 (3–21)	0.001

s.d., standard deviation; NA, not applicable; RYGB, Roux-en-Y gastric bypass; VSG, vertical sleeve gastrectomy surgery; BMI, body mass index; HAM-D, Hamilton Depression Rating Scale 17 for depressive symptoms; IPAQ, International Physical Activity Questionnaire.

female. Before bariatric surgery, 41 patients with depression and 44 control patients completed a baseline assessment; 29 patients with depression and 37 control patients completed a follow-up assessment 6 months after bariatric surgery. Of the 29 patients who met the criteria for depression at baseline, 19 (65.5%) no longer met the clinical criteria for depression at their follow-up assessment. There were no significant differences in weight loss between groups at follow-up after adjustment for confounders. Socio-demographic, weight loss and clinical data are reported in Table 1. Childhood trauma scores are reported in online Supplementary Table S3.

### Inflammatory markers

Before surgery, ANCOVA showed that bariatric patients with depression had significantly higher inflammation compared with controls based on their higher hsCRP levels (adjusted mean: 2.27 [CI 1.89–2.66] v. 1.52 [CI 1.08–1.95];  $p = 0.02$ ); higher IL-6 levels (adjusted mean: 0.88 [CI 0.67–1.1] v. 0.27 [CI 0.03–0.51];  $p = 0.001$ ); higher IL-6/IL-10 ratio (adjusted mean: 3.09 mg/L [CI 2.71–3.47] v. 2.22 [CI 1.79–2.64];  $p = 0.006$ ) and lower IL-4 levels (adjusted mean: 1.11 [CI 0.09–1.13] v. 0.15 [CI 0.13–1.63],  $p = 0.018$ ; see Fig. 1). No significant group differences were observed for all other cytokines (see Table 2). Sensitivity analyses confirmed sample-wide correlations between higher IL-6 and IL-6/IL-10 ratio levels with more severe baseline depressive symptoms ( $R = 0.3$  and  $p = 0.005$ ;  $R = 0.29$  and  $p = 0.007$ , respectively), while IL-4 levels were negatively correlated with baseline depressive symptoms at trend-level ( $R = -0.2$  and  $p = 0.06$ ; see online Supplementary Table S4 for all correlations).



**Figure 1.** Group comparisons of mean serum inflammatory markers at baseline. Estimated marginal means and confidence intervals for: (a) High sensitivity C-reactive protein. (b) Interleukin 6. (c) Interleukin 4. (d) The ratio of interleukin 6 to interleukin 10.

At the time of surgery, ANCOVA showed that bariatric patients with depression had significantly higher adipose INF- $\gamma$  levels compared with controls (adjusted mean:  $-2.94$  [CI  $-3.54$  to  $-2.34$ ] v.  $-3.97$  [CI  $-4.7$  to  $-3.24$ ];  $p = 0.04$ ). All other adipose cytokines showed no significant group differences (see Table 2), and no significant correlations were observed between adipose cytokines and serum cytokines (see online Supplementary

**Table 2.** Serum inflammatory markers at baseline, adipose tissue inflammatory markers at time of surgery, and serum inflammatory markers at 6-month follow-up after bariatric surgery

Inflammatory markers	Serum at baseline			Adipose tissue at time of surgery			Serum at 6-month follow-up		
	Depressed (N=41)	Controls (N=44)	p value	Depressed (N=17)	Controls (N=18)	p value	Depressed (N=19)	Controls (N=33)	p value
Raw values mg/L, mean (s.d.)									
hsCRP	11.59 (10.17)	9.24 (10.62)	0.02	NA	NA	NA	9.19 (13.43)	3.69 (5.82)	0.06
IL-6	2.47 (1.28)	1.85 (1.22)	0.007	0.63 (1.35)	1.63 (4.98)	0.47	2.44 (2.33)	1.35 (0.65)	0.008
IL-2	0.16 (0.13)	0.16 (0.12)	0.09	0.01 (0.01)	0.01 (0.00)	0.84	0.26 (0.20)	0.28 (0.23)	0.62
IL-4	0.018 (0.01)	0.021 (0.01)	0.02	0.00 (0.00)	0.00 (0.01)	0.42	0.02 (0.01)	0.02 (0.01)	0.23
TNF- $\alpha$	4.16 (1.06)	3.84 (1.25)	0.54	0.02 (0.01)	0.02 (0.02)	0.58	4.10 (1.47)	3.43 (1.04)	0.31
IL-10	0.56 (1.57)	0.33 (0.21)	0.29	0.00 (0.00)	0.00 (0.00)	0.36	0.30 (0.12)	0.71 (1.80)	0.24
IL-8	11.61 (10.14)	10.71 (4.06)	0.46	0.43 (0.31)	0.63 (0.95)	0.11	17.18 (20.64)	12.42 (4.74)	0.36
IL-1 $\beta$	0.04 (0.04)	0.04 (0.03)	0.32	0.04 (0.03)	0.07 (0.13)	0.73	0.17 (0.06)	0.13 (0.07)	0.11
IL-12p70	0.12 (0.13)	0.15 (0.29)	0.29	0.01 (0.00)	0.01 (0.00)	0.40	0.13 (0.09)	0.12 (0.07)	0.85
IL-13	0.34 (0.20)	0.44 (1.04)	0.63	0.04 (0.01)	0.04 (0.01)	0.62	0.20 (0.16)	0.26 (0.19)	0.32
INF- $\gamma$	4.35 (3.00)	5.80 (9.65)	0.43	0.08 (0.12)	0.04 (0.02)	0.04	8.81 (15.47)	5.11 (8.10)	0.1
IL-6/IL-10 ratio	9.38 (6.88)	5.88 (3.48)	0.006	0.28 (0.14)	0.32 (0.13)	0.88	8.74 (8.21)	4.28 (2.89)	0.005

s.d., standard deviation; hsCRP, high sensitivity C-reactive protein; IL, interleukin; TNF, tumor necrosis factor; INF, interferon.

Table S5), or between adipose cytokines and depressive symptoms (see online Supplementary Table S4).

At follow-up, ANCOVA showed that bariatric patients with depression still had significantly higher IL-6 levels (adjusted mean: 0.56 [CI 0.27–0.86] v. 0.09 [CI –0.26 to 0.43],  $p=0.008$ ) and higher IL-6/IL-10 ratio (adjusted mean: 1.77 [CI 1.31–2.23] v. 0.99 [CI 0.46–1.53],  $p=0.005$ ), a trend for higher hsCRP levels (adjusted mean: 1.26 [CI 0.67 to –1.86] v. 0.6 [CI –0.1 to 1.3];  $p=0.06$ ), but no difference in IL-4 levels (see Fig. 2). No significant group differences were observed for all other serum cytokines at follow-up (see Table 2). Sensitivity analyses confirmed sample-wide correlations between higher serum IL-6 and IL-6/IL-10 ratio levels with more severe depressive symptoms follow-up ( $R=0.45$  and  $p<0.001$ ;  $R=0.49$  and  $p<0.001$ , respectively), but IL-4 levels were not correlated with depressive symptoms at follow-up ( $R=0.13$  and  $p=0.4$ ; see online Supplementary Table S4 for all correlations).

### Predicting patient outcomes after surgery

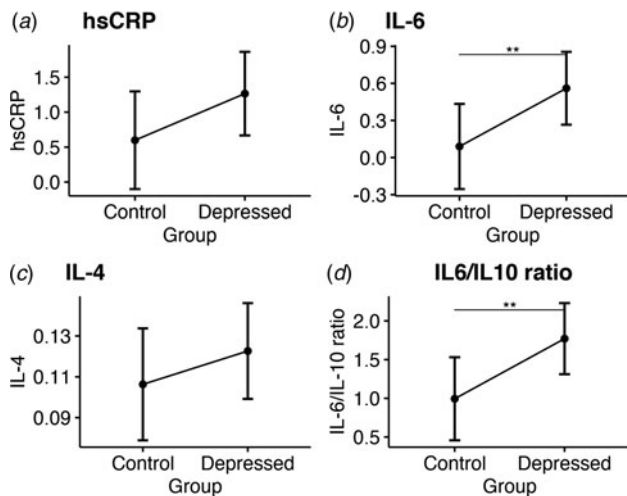
We selected baseline inflammatory markers and clinical measures as covariates for hierarchical regression based on significant correlations with weight loss and depression severity at 6-month follow-up after surgery (see online Supplementary Table S6). Baseline predictors were adjusted against socio-demographic and clinical confounders in separate hierarchical regression models for weight loss (see online Supplementary Table S7) and depression severity (see online Supplementary Table S8).

The final multivariable regression model predicting weight loss after bariatric surgery showed that higher baseline hsCRP levels predicted reduced weight loss at 6-month follow-up ( $\beta=-0.28$  [CI –0.34 to –0.04],  $p=0.01$ ), along with socio-demographic and clinical confounders including VSG surgery (as opposed to RYGB), higher age (at trend-level), female gender, diabetic status, and current smoking status (see Fig. 3a).

The final multivariable regression model predicting depression severity after bariatric surgery showed no effect of baseline hsCRP on HAM-D depressive symptoms at 6-month follow-up ( $\beta=-0.02$  [CI –0.38 to 0.34],  $p=0.9$ ; see online Supplementary Table S7). Instead, higher baseline HAM-D scores and higher childhood emotional abuse scores predicted higher depression severity after surgery ( $\beta=0.81$  [CI 0.55–1.09],  $p<0.001$ ; and  $\beta=0.31$  [CI 0.22–0.85],  $p=0.001$ , respectively). In contrast, higher baseline atypical scores predicted lower depression severity after surgery ( $\beta=-0.36$  [CI –1.04 to –0.16],  $p=0.008$ ; see Fig. 3b). Of the socio-demographic or clinical variables, only non-diabetic status was associated with lower depression severity at trend-level.

### Discussion

Our study is the first to show that depression diagnosis is uniquely associated with significant hsCRP, IL-6, and IL-6/10 ratio levels in patients with obesity undergoing bariatric surgery. Six months after surgery, IL-6 and IL-6/10 ratio levels were still significantly higher in patients with pre-existing depression, despite no differences in postoperative weight loss between depressed and control groups. Multivariable regression confirmed these findings, showing higher baseline inflammation predicted reduced weight loss after surgery rather than baseline depressive symptoms. In contrast with our predictions, baseline inflammation was not associated with depression outcomes after surgery. Instead, baseline depression severity and childhood emotional

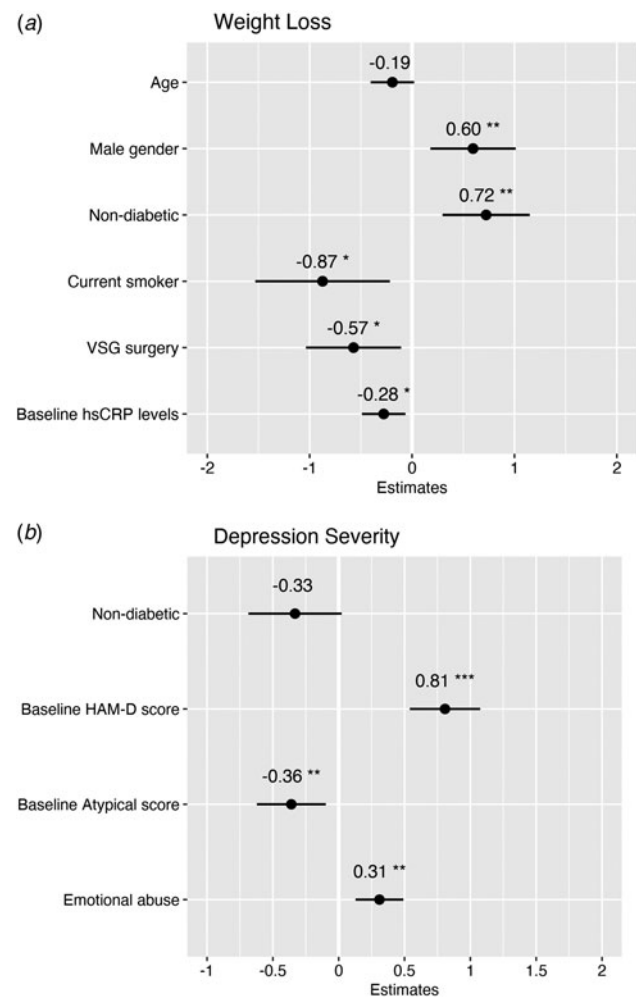


**Figure 2.** Group comparisons of mean serum inflammatory markers at 6-month follow-up. Estimated marginal means and confidence intervals for: (a) High sensitivity C-reactive protein. (b) Interleukin 6. (c) Interleukin 4. (d) The ratio of interleukin 6 to interleukin 10.

abuse were significant risk factors for higher depression severity after surgery. Overall, bariatric surgery led to remarkable weight loss in all patients within 6 months, and the majority of patients with pre-operative depression also experienced significant remission of their depressive symptoms, assessed by clinical interview.

Our findings of increased inflammation in the depressed group are consistent with the growing body of literature finding elevated hsCRP or IL-6 associated with depression in non-obese populations (Osimo et al., 2020) and our previous work showing elevated hsCRP associated with comorbid depression and overweight (McLaughlin et al., 2022). Obesity is known to increase peripheral inflammatory markers significantly. However, our results showed that depression diagnosis was uniquely associated with increased hsCRP, IL-6, and IL-6/10 ratio and decreased IL-4 levels after controlling for BMI and socio-demographic confounders. Similar to other studies of depressed patients (Dixon, Dixon, & O'Brien, 2003; Jha et al., 2020; Lamers et al., 2019; Moriarity, Slavich, Alloy, & Olino, 2023; Roohi, Jaafari, & Hashemian, 2021), we observed significant correlations between serum inflammatory markers hsCRP, IL-6, IL-6/10 ratio, and IL-4 with higher depressive symptom severity. More recently, transcriptomic analyses of bariatric patients revealed upregulation of cytokine networks IL-6 and IL-4 associated with depression (Moisan et al., 2021). Given the lack of associations between adipose cytokines with depressive symptoms, it is likely that serum cytokines were responsible for driving the higher inflammation we observed in patients with depression. These convergent findings reveal a molecular signaling pathway through which inflammatory cytokine activity in the periphery increases the risk for inflammation-induced depressive symptoms via increased IL-6, IL-6/10 ratio, and decreased IL-4.

Despite the high number of studies investigating depression and weight loss in bariatric patients, our study is the first to control for the effect of inflammation on depression and weight loss outcomes. Our findings showed that high baseline inflammation could be an underlying confounder driving the association between preoperative depression and poor weight loss in bariatric patients. While recent meta-analyses suggest preoperative



**Figure 3.** Multivariable regression models showing baseline predictors of weight loss and depression severity 6 months after bariatric surgery. (a) The weight loss model predicted 36% adjusted variance in weight loss at 6 months after surgery with an average prediction error rate of 5.6%. (b) The depression severity model predicted 54% adjusted variance in depressive symptoms 6 months after surgery with an average prediction error rate of 6.1%.

depression is not associated with reduced weight loss in the short to mid-term period after bariatric surgery (Dixon et al., 2003; Dymek, Le Grange, Neven, & Alverdy, 2002; Fu et al., 2021; Gill et al., 2019; Kops et al., 2020; Scholtz et al., 2007; White et al., 2015), other studies with extended follow-up periods found that a subset of patients with preoperative depression demonstrated reduced weight loss (da Cruz et al., 2018; Lai et al., 2020; Morgan, Ho, & Platell, 2020). Given that our results showed patients with depression were more likely to be inflamed and higher inflammation negatively influenced weight loss, it seems plausible that patients with depression would be more vulnerable to weight regain in the long term. Therefore, the poor weight loss outcomes in bariatric patients with depression could be a consequence of higher pre-operative inflammation, rather than pre-operative depression *per se*.

If the high inflammation in patients with depression persists and negatively affects weight loss, it may also contribute to a higher risk of severe or recurring depressive symptoms in the long term. Indeed, patients who fail to lose weight postoperatively have a higher risk for depression (Lim, Zhang, & Ho, 2018; van

Hout et al., 2005; White, Courcoulas, & King, 2022). Although baseline inflammation was not associated with depression severity at the 6-month follow-up in our sample, the literature suggests that patients with pre-operative depression may become more vulnerable to weight regain or returning depressive symptoms 2–3 years after bariatric surgery (Gill et al., 2019; Morgan et al., 2020; Spirou et al., 2020). Therefore, patients with inflammation-induced depression may be at higher risk for poor weight loss outcomes and subsequent depression relapse, but such temporal relationships may only become evident in the long term. Additionally, differences in cytokine responses may fluctuate over time in response to surgical stress and subsequent weight loss. Yet, meta-analyses have observed significant heterogeneity among changes in cytokine levels post-surgery, irrespective of the duration of follow-up or changes in BMI (Askarpour, Khani, Sheikhi, Ghaedi, & Alizadeh, 2019; Khosravi-Largani et al., 2019). While our study revealed persistent heightened immune dysregulation in serum IL-6 and IL-6/10 ratio of the depressed group at 6 months post-surgery, these increases seemed unrelated to adipose tissue markers and post-operative changes in body weight, suggesting other factors, such as peripheral immune cell markers, may need to be explored further.

Finally, our results finding higher baseline depression severity and a history of childhood emotional abuse were risk factors for postoperative depression severity are consistent with other research highlighting the need for patients with severe depression and childhood trauma to receive additional psychiatric support post-surgery (King et al., 2019b; Spirou et al., 2020). Meta-analytic evidence has consistently identified childhood emotional abuse as a pervasive risk factor for depression risk and severity (Humphreys et al., 2020; Mandelli, Petrelli, & Serretti, 2015). Moreover, in bariatric patients, higher levels of childhood emotional abuse have been shown to predict less improvement or even worsening of depressive symptoms in a dose-response manner for up to 7 years post-surgery (King et al., 2019b). As childhood emotional abuse can cause individuals to develop enduring negative cognitive beliefs, this may result in deeply internalized cognitive patterns and persistent depressive symptoms that are resistant to improvement (Jopling, Tracy, & LeMoult, 2020), despite achieving successful weight loss through bariatric surgery. In contrast, higher baseline atypical symptoms predicted significantly lower classical depressive symptom severity after surgery. Atypical depressive symptoms are predominantly metabolic in nature (Łojko & Rybakowski, 2017; Milaneschi et al., 2020), and we observed a remarkable improvement in atypical symptoms following bariatric surgery. Therefore, patients with more atypical depressive symptoms may experience a greater psychological benefit from bariatric surgery than patients with a classical presentation of depression. Identifying which subgroups of patients would benefit most from psychological treatment could improve the allocation of clinical resources in the post-surgery period (Di Lorenzo et al., 2020).

Our study was limited by the relatively short 6-month follow-up period. However, the first postoperative year seems crucial in determining long-term mental health and successful weight loss (Geerts et al., 2021; Smith et al., 2020). Additionally, a recent clinical trial found that the optimal time to initiate psychological treatment for bariatric patients was shortly after surgery and before significant weight loss occurred (Paul et al., 2021). Therefore, data collected from early post-surgical periods may help predict which subgroups of patients are most vulnerable to experiencing poor clinical outcomes after surgery. Additionally,

our study may have been limited by the significant time commitment required from participants to allow for comprehensive data collection during the study visits. Although we provided vouchers to compensate participants for their time and scheduled study visits to coincide with their hospital appointments, the financial incentive of the vouchers was minimal, which may have deterred some participants from taking part.

Our findings identifying potential risk factors for poor outcomes after bariatric surgery have clinical and research implications. Firstly, bariatric candidates with high inflammation may represent an ideal subgroup of patients for stratification in clinical trials to investigate whether anti-inflammatory medications improve postoperative weight loss or depression symptoms. Significant postoperative reductions in CRP have been associated with improved weight loss and metabolic health in bariatric patients (Illán Gómez et al., 2016; O'Rourke et al., 2019), while anti-inflammatory treatments improve antidepressant response in patients with high inflammation (Nettis et al., 2021; Raison et al., 2013). It remains to be seen whether bariatric patients with depression represent a distinct inflammatory immunophenotype of patients with depression or whether distinct inflammatory profiles also exist within this population (Felger & Miller, 2020). Future studies will need to consider other peripheral blood biomarkers associated with inflammatory cytokine activity (Cavaleri et al., 2023), to further clarify the immune pathways involved in depressive symptom dimensions.

In this longitudinal observational study of 85 patients with obesity undergoing bariatric surgery, depression diagnosis was associated with significantly higher serum inflammation before and 6 months after surgery. Our findings suggest that increased inflammation, rather than depression diagnosis, may be responsible for the high variability in weight loss and depression outcomes among bariatric patients. Future research should combine inflammatory biomarkers and clinical data in longitudinal prediction models to accurately identify risk factors for poor outcomes after bariatric surgery. Understanding the inflammatory pathways underlying the vicious cycle between depression and obesity, and how interventions such as bariatric surgery may break this cycle, may inform future strategies addressing the rising prevalence of these conditions.

**Supplementary material.** The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291723002283>.

**Acknowledgements and Disclosures.** The study received funding support from 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. Professor 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). Ms Milton received funding through the Neuro-Immune Interactions in Health & Disease Wellcome Trust PhD Training Programme (218452/Z/19/Z) at King's College London. Ms Patsalos received salary support from the National Institute of Health and Care Research (NIHR) Maudsley Biomedical Research Centre (BRC) at South London and Maudsley NHS Foundation Trust (SLaM) and King's College London (KCL). We thank the staff at King's College Hospital, the study participants, and their families for their contribution to this research. Part of this work was presented as a poster at the 2021 British Association of Psychopharmacology conference in London, UK. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. Professor Mondelli received research

funding from Johnson & Johnson as part of a research program on depression and inflammation, but this is unrelated to the work presented in this study. No other disclosures were reported.

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