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 six 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 (β=-0.28, P=.01) but had no effect on depression severity at follow-up (β=-0.02, P=0.9). Instead, more severe baseline depressive symptoms and childhood emotional abuse predicted greater depression severity after surgery (β=0.81, P< .001; and β=0.31, P=.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 six 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 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; C. L. 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, Lasselin, & 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). Morerecently, 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., 2020; 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 interview before surgery and six 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 & 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 six 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 ≥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 six 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 (CTQ) 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 weight loss excess weight loss (EWL) to allow for comparison with other studies (see 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-α, IL-8, IL-1β, 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 (Dabitao, Margolick, Lopez, & Bream, 2011; E. King et al., 2019), 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 Table S2. Clinically elevated hsCRP levels were defined as hsCRP≥3mg/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-α, IL-8, IL-1β, 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 (Dabitao et al., 2011; E. King et al., 2019), 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 *vs.* 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 were 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 <.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 (SD) age of 46.5 (11.6) years, and 51 (60%) participants were 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 six 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 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 to 2.66] *vs.* 1.52 [CI: 1.08 to 1.95]; P=.02); higher IL-6 levels (adjusted mean: 0.88 [CI: 0.67 to 1.1] *vs.* 0.27 [CI: 0.03 to 0.51]; P=.001); higher IL-6/IL-10 ratio (adjusted mean: 3.09 mg/L [CI: 2.71 to 3.47] *vs.* 2.22 [CI: 1.79 to 2.64]; P=.006) and lower IL-4 levels (adjusted mean: 1.11 [CI: .09 to 1.13] *vs.* 0.15 [CI: 0.13 to 1.63], P=.018; see Figure 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=.005; R=0.29 and P=.007, respectively), while IL-4 levels were negatively correlated with baseline depressive symptoms at trend-level (R=-0.2 and P=.06; see Table S4 for all correlations).

At the time of surgery, ANCOVA showed that bariatric patients with depression had significantly higher adipose INF-γ levels compared with controls (adjusted mean: -2.94 [CI: -3.54 to -2.34] *vs.* -3.97 [CI: -4.7 to -3.24]; P=.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 Table S5), or between adipose cytokines and depressive symptoms (see 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 to 0.86] *vs.* 0.09 [CI: -0.26 to 0.43], P=.008) and higher IL-6/IL-10 ratio (adjusted mean: 1.77 [CI: 1.31 to 2.23] *vs.* 0.99 [CI: 0.46 to 1.53], P=.005), a trend for higher hsCRP levels (adjusted mean: 1.26 [CI: 0.67-1.86] *vs.* 0.6 [CI: -0.1 to 1.3]; P=.06), but no difference in IL-4 levels (see Figure 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<.001; R= 0.49 and P< .001, respectively), but IL-4 levels were not correlated with depressive symptoms at follow-up (R=0.13 and P=.4; see 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 six-month follow-up after surgery (see Table S6). Baseline predictors were adjusted against socio-demographic and clinical confounders in separate hierarchical regression models for weight loss (see Table S7) and depression severity (see Table S8).

The final multivariable regression model predicting weight loss after bariatric surgery showed that higher baseline hsCRP levels predicted reduced weight loss at six-month follow-up (β=-0.28 [CI: ﻿-0.34 to -0.04], P=.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 Figure 3A).

The final multivariable regression model predicting depression severity after bariatric surgery showed no effect of baseline hsCRP on HAM-D depressive symptoms at six-month follow-up (β=-0.02 [CI: ﻿-0.38 to 0.34], P =.9; see Table S7). Instead, higher baseline HAM-D scores and higher childhood emotional abuse scores predicted higher depression severity after surgery (β=0.81 [CI: ﻿0.55 to 1.09], P < .001; and β=0.31 [CI: ﻿0.22 to 0.85], P =.001, respectively). In contrast, higher baseline atypical scores predicted lower depression severity after surgery (β=-0.36 [CI: ﻿-1.04 to -0.16], P=.008; see Figure 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 significantly 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 abuse were significant risk factors for higher depression severity after surgery. Overall, bariatric surgery led to remarkable weight loss in all patients within six 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., 2021). 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, 2022; 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 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; M. A. 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; G. E. White, Courcoulas, & King, 2020). Although baseline inflammation was not associated with depression severity at the six-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 six 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 (W. C. King et al., 2019; 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 seven years post-surgery (W. C. King et al., 2019). As childhood emotional abuse can cause individuals to develop enduring negative cognitive beliefs, this may result in deeply internalised 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 six-month follow-up period. However, the first postoperative year seems crucial in determining long-term mental health and successful weight loss (Geerts et al., 2020; 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; Charles L. 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 six 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.

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**References**

Alabi, F., Guilbert, L., Villalobos, G., Mendoza, K., Hinojosa, R., Melgarejo, J. C., . . . Zerrweck, C. (2018). Depression Before and After Bariatric Surgery in Low-Income Patients: the Utility of the Beck Depression Inventory. *Obesity Surgery, 28*(11), 3492-3498. doi:10.1007/s11695-018-3371-0

Askarpour, M., Khani, D., Sheikhi, A., Ghaedi, E., & Alizadeh, S. (2019). Effect of Bariatric Surgery on Serum Inflammatory Factors of Obese Patients: a Systematic Review and Meta-Analysis. *Obesity Surgery, 29*(8), 2631-2647. doi:10.1007/s11695-019-03926-0

Bernstein, D. P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., . . . Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *American Journal of Psychiatry, 151*(8), 1132-1136. doi:10.1176/ajp.151.8.1132

Borsini, A., Cattaneo, A., Malpighi, C., Thuret, S., Harrison, N. A., Consortium, M. R. C. I., . . . Pariante, C. M. (2018). Interferon-Alpha Reduces Human Hippocampal Neurogenesis and Increases Apoptosis via Activation of Distinct STAT1-Dependent Mechanisms. *Int J Neuropsychopharmacology, 21*(2), 187-200. doi:10.1093/ijnp/pyx083

Capuron, L., Lasselin, J., & Castanon, N. (2017). Role of Adiposity-Driven Inflammation in Depressive Morbidity. *Neuropsychopharmacology, 42*(1), 115-128. doi:10.1038/npp.2016.123

Capuron, L., & Miller, A. H. (2011). Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacology & Therapeutics, 130*(2), 226-238. doi:10.1016/j.pharmthera.2011.01.014

Capuron, L., Poitou, C., Machaux-Tholliez, D., Frochot, V., Bouillot, J. L., Basdevant, A., . . . Clement, K. (2011). Relationship between adiposity, emotional status and eating behaviour in obese women: role of inflammation. *Psychological Medicine, 41*(7), 1517-1528. doi:10.1017/S0033291710001984

Cavaleri, D., Bartoli, F., Capogrosso, C. A., Guzzi, P., Moretti, F., Riboldi, I., . . . Carrà, G. (2023). Blood concentrations of neopterin and biopterin in subjects with depression: A systematic review and meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 120*, 110633. doi:10.1016/j.pnpbp.2022.110633

Chan, K. L., Cathomas, F., & Russo, S. J. (2019). Central and Peripheral Inflammation Link Metabolic Syndrome and Major Depressive Disorder. *Physiology (Bethesda), 34*(2), 123-133. doi:10.1152/physiol.00047.2018

Craig, C. L., Marshall, A. L., SjÖStrÖM, M., Bauman, A. E., Booth, M. L., Ainsworth, B. E., . . . Oja, P. (2003). International Physical Activity Questionnaire: 12-Country Reliability and Validity. *Medicine & Science in Sports & Exercise, 35*(8), 1381-1395. Retrieved from https://journals.lww.com/acsm-msse/Fulltext/2003/08000/International\_Physical\_Activity\_Questionnaire\_.20.aspx

da Cruz, M. R. R., Branco-Filho, A. J., Zaparolli, M. R., Wagner, N. F., de Paula Pinto, J. S., Campos, A. C. L., & Taconeli, C. A. (2018). Predictors of Success in Bariatric Surgery: the Role of BMI and Pre-operative Comorbidities. *Obesity Surgery, 28*(5), 1335-1341. doi:10.1007/s11695-017-3011-0

Dabitao, D., Margolick, J. B., Lopez, J., & Bream, J. H. (2011). Multiplex measurement of proinflammatory cytokines in human serum: comparison of the Meso Scale Discovery electrochemiluminescence assay and the Cytometric Bead Array. *Journal of Immunological Methods, 372*(1-2), 71-77. doi:10.1016/j.jim.2011.06.033

Dantzer, R., & Walker, A. K. (2014). Is there a role for glutamate-mediated excitotoxicity in inflammation-induced depression? *Journal of Neural Transmission, 121*(8), 925-932. doi:10.1007/s00702-014-1187-1

Di Lorenzo, N., Antoniou, S. A., Batterham, R. L., Busetto, L., Godoroja, D., Iossa, A., . . . Silecchia, G. (2020). Clinical practice guidelines of the European Association for Endoscopic Surgery (EAES) on bariatric surgery: update 2020 endorsed by IFSO-EC, EASO and ESPCOP. *Surgical Endoscopy, 34*(6), 2332-2358. doi:10.1007/s00464-020-07555-y

DiGirolamo, M., & Fine, J. B. (2001). Cellularity Measurements. In G. Ailhaud (Ed.), *Adipose Tissue Protocols* (pp. 65-75). Springer New York.

DiMatteo, M. R., Lepper, H. S., & Croghan, T. W. (2000). Depression Is a Risk Factor for Noncompliance With Medical Treatment: Meta-analysis of the Effects of Anxiety and Depression on Patient Adherence. *Archives of Internal Medicine, 160*(14), 2101-2107. doi:10.1001/archinte.160.14.2101

Dixon, J. B., Dixon, M. E., & O'Brien, P. E. (2003). Depression in association with severe obesity: changes with weight loss. *Archives of Internal Medicine, 163*(17), 2058-2065. doi:10.1001/archinte.163.17.2058

du Plessis, J., Korf, H., van Pelt, J., Windmolders, P., Vander Elst, I., Verrijken, A., . . . van der Merwe, S. (2016). Pro-Inflammatory Cytokines but Not Endotoxin-Related Parameters Associate with Disease Severity in Patients with NAFLD. *PloS one, 11*(12), e0166048-e0166048. doi:10.1371/journal.pone.0166048

Duan, Y., Zeng, L., Zheng, C., Song, B., Li, F., Kong, X., & Xu, K. (2018). Inflammatory Links Between High Fat Diets and Diseases. *Frontiers in Immunology, 9*. doi:10.3389/fimmu.2018.02649

Dymek, M. P., Le Grange, D., Neven, K., & Alverdy, J. (2002). Quality of Life after Gastric Bypass Surgery: A Cross-Sectional Study. *Obesity Research, 10*(11), 1135-1142. doi:10.1038/oby.2002.154

Enache, D., Pariante, C. M., & Mondelli, V. (2019). Markers of central inflammation in major depressive disorder: A systematic review and meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and post-mortem brain tissue. *Brain, Behavior, and Immunity, 81*, 24-40. doi:10.1016/j.bbi.2019.06.015

Felger, J. C., & Miller, A. H. (2020). Identifying Immunophenotypes of Inflammation in Depression: Dismantling the Monolith. *Biological Psychiatry, 88*(2), 136-138. doi:10.1016/j.biopsych.2020.04.024

Finkelstein, E. A., Ruhm, C. J., & Kosa, K. M. (2005). ECONOMIC CAUSES AND CONSEQUENCES OF OBESITY. *Annual Review of Public Health, 26*(1), 239-257. doi:10.1146/annurev.publhealth.26.021304.144628

Fu, R., Zhang, Y., Yu, K., Mao, D., & Su, H. (2021). Bariatric surgery alleviates depression in obese patients: A systematic review and meta-analysis. *Obesity Research Clinical Practice, 16*(1),10-16. doi:10.1016/j.orcp.2021.11.002

Galioto, R., & Crowther, J. H. (2013). The effects of exposure to slender and muscular images on male body dissatisfaction. *Body Image, 10*(4), 566-573. doi:10.1016/j.bodyim.2013.07.009

Geerts, M. M., Van Den Berg, E. M., Van Riel, L., Peen, J., Goudriaan, A. E., & Dekker, J. J. M. (2020). Behavioral and psychological factors associated with suboptimal weight loss in post-bariatric surgery patients. *Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity*. doi:10.1007/s40519-020-00930-7

Gill, H., Kang, S., Lee, Y., Rosenblat, J. D., Brietzke, E., Zuckerman, H., & McIntyre, R. S. (2019). The long-term effect of bariatric surgery on depression and anxiety. *Journal of Affective Disorders, 246*, 886-894. doi:10.1016/j.jad.2018.12.113

Gletsu, N., Lin, E., Zhu, J. L., Khaitan, L., Ramshaw, B. J., Farmer, P. K., . . . Smith, C. D. (2006). Increased plasma interleukin 6 concentrations and exaggerated adipose tissue interleukin 6 content in severely obese patients after operative trauma. *Surgery, 140*(1), 50-57. doi:10.1016/j.surg.2006.01.018

Goldsmith, D., Bekhbat, M., Mehta, N. D., & Felger, J. C. (2022). Inflammation-related functional and structural dysconnectivity as a pathway to psychopathology. *Biological Psychiatry, 93*(5),405-418. doi:10.1016/j.biopsych.2022.11.003

Hamilton, M. (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry, 23*(1), 56-62. doi:10.1136/jnnp.23.1.56

Hatoum, I. J., & Kaplan, L. M. (2013). Advantages of percent weight loss as a method of reporting weight loss after Roux-en-Y gastric bypass. *Obesity, 21*(8), 1519-1525. doi:10.1002/oby.20186

Hepgul, N., Pariante, C. M., Dipasquale, S., DiForti, M., Taylor, H., Marques, T. R., . . . Mondelli, V. (2012). Childhood maltreatment is associated with increased body mass index and increased C-reactive protein levels in first-episode psychosis patients. *Psychological Medicine, 42*(9), 1893-1901. doi:10.1017/s0033291711002947

Humphreys, K. L., LeMoult, J., Wear, J. G., Piersiak, H. A., Lee, A., & Gotlib, I. H. (2020). Child maltreatment and depression: A meta-analysis of studies using the Childhood Trauma Questionnaire. *Child Abuse and Neglect, 102*, 104361. doi:10.1016/j.chiabu.2020.104361

Illán Gómez, F., Gonzálvez Ortega, M., Aragón Alonso, A., Orea Soler, S., Alcaraz Tafalla, M., Pérez Paredes, M., & Lozano Almela, M. (2016). Obesity, endothelial function and inflammation: the effects of weight loss after bariatric surgery. *Nutricion Hospitalaria, 33*(6), 1340-1346. doi:10.20960/nh.793

Jha, M. K., Cai, L., Minhajuddin, A., Fatt, C. C., Furman, J. L., Gadad, B. S., . . . Trivedi, M. H. (2020). Dysfunctional adaptive immune response in adolescents and young adults with suicide behavior. *Psychoneuroendocrinology, 111*, 104487. doi:10.1016/j.psyneuen.2019.104487

Jopling, E., Tracy, A., & LeMoult, J. (2020). Childhood Maltreatment, Negative Self-Referential Processing, and Depressive Symptoms During Stress. *Psychology Research and Behavior Management, 13*, 79-87. doi:10.2147/prbm.S231505

Khosravi-Largani, M., Nojomi, M., Aghili, R., Otaghvar, H. A., Tanha, K., Seyedi, S. H. S., & Mottaghi, A. (2019). Evaluation of all Types of Metabolic Bariatric Surgery and its Consequences: a Systematic Review and Meta-Analysis. *Obesity Surgery, 29*(2), 651-690. doi:10.1007/s11695-018-3550-z

King, E., O'Brien, J., Donaghy, P., Williams-Gray, C. H., Lawson, R. A., Morris, C. M., . . . Thomas, A. (2019). Inflammation in mild cognitive impairment due to Parkinson's disease, Lewy body disease, and Alzheimer's disease. *International Journal of Geriatric Psychiatry, 34*(8), 1244-1250. doi:10.1002/gps.5124

King, W. C., Hinerman, A., Kalarchian, M. A., Devlin, M. J., Marcus, M. D., & Mitchell, J. E. (2019). The impact of childhood trauma on change in depressive symptoms, eating pathology, and weight after Roux-en-Y gastric bypass. *Surgery for Obesity and Related Diseases, 15*(7), 1080-1088. doi:10.1016/j.soard.2019.04.012

Kops, N. L., Vivan, M. A., de Castro, M. L. D., Horvath, J. D. C., Costa, F. S., & Friedman, R. (2020). Binge eating scores pre-bariatric surgery and subsequent weight loss: A prospective, 5 years follow-up study. *Clinical Nutrition ESPEN, 38*, 146-152. doi:10.1016/j.clnesp.2020.05.013

Lai, C., Aceto, P., Santucci, F. R., Pierro, L., Petrucci, I., Cacioppo, M., . . . Raffaelli, M. (2020). Preoperative psychological characteristics affecting mid-term outcome after bariatric surgery: a follow-up study. *Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity, 26,* 585–590. doi:10.1007/s40519-020-00892-w

Lamers, F., Milaneschi, Y., Smit, J. H., Schoevers, R. A., Wittenberg, G., & Penninx, B. (2019). Longitudinal Association Between Depression and Inflammatory Markers: Results From the Netherlands Study of Depression and Anxiety. *Biological Psychiatry, 85*(10), 829-837. doi:10.1016/j.biopsych.2018.12.020

Lim, R. B. C., Zhang, M. W. B., & Ho, R. C. M. (2018). Prevalence of All-Cause Mortality and Suicide among Bariatric Surgery Cohorts: A Meta-Analysis. *International Journal of Environmental Research and Public Health, 15*(7), 1519. doi:10.3390/ijerph15071519

Łojko, D., & Rybakowski, J. (2017). Atypical depression: current perspectives. *Neuropsychiatric Disease and Treatment, 13*, 2447-2456. doi:10.2147/ndt.s147317

Luppino, F. S., de Wit, L. M., Bouvy, P. F., Stijnen, T., Cuijpers, P., Penninx, B. W., & Zitman, F. G. (2010). Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Archives of General Psychiatry, 67*(3), 220-229. doi:10.1001/archgenpsychiatry.2010.2

Mandelli, L., Petrelli, C., & Serretti, A. (2015). The role of specific early trauma in adult depression: A meta-analysis of published literature. Childhood trauma and adult depression. *European Psychiatry, 30*(6), 665-680. doi:10.1016/j.eurpsy.2015.04.007

Martens, K., Hamann, A., Miller-Matero, L. R., Miller, C., Bonham, A. J., Ghaferi, A. A., & Carlin, A. M. (2021). Relationship between depression, weight, and patient satisfaction 2 years after bariatric surgery. *Surgery for Obesity and Related Diseases, 17*(2), 366-371. doi:10.1016/j.soard.2020.09.024

McLaughlin, A. P., Nikkheslat, N., Hastings, C., Nettis, M. A., Kose, M., Worrell, C., . . . Mondelli, V. (2021). The influence of comorbid depression and overweight status on peripheral inflammation and cortisol levels. *Psychological Medicine*, 1-8. doi:10.1017/s0033291721000088

Meier, T. B., Drevets, W. C., Wurfel, B. E., Ford, B. N., Morris, H. M., Victor, T. A., . . . Savitz, J. (2016). Relationship between neurotoxic kynurenine metabolites and reductions in right medial prefrontal cortical thickness in major depressive disorder. *Brain, Behavior, and Immunity, 53*, 39-48. doi:10.1016/j.bbi.2015.11.003

Milaneschi, Y., Lamers, F., Berk, M., & Penninx, B. (2020). Depression Heterogeneity and Its Biological Underpinnings: Toward Immunometabolic Depression. *Biological Psychiatry*. doi:10.1016/j.biopsych.2020.01.014

Milaneschi, Y., Lamers, F., Peyrot, W. J., Baune, B. T., Breen, G., Dehghan, A., . . . the Major Depressive Disorder Working Group of the Psychiatric Genomics, C. (2017). Genetic Association of Major Depression With Atypical Features and Obesity-Related Immunometabolic Dysregulations. *JAMA Psychiatry, 74*(12), 1214-1225. doi:10.1001/jamapsychiatry.2017.3016

Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nature Reviews Immunology, 16*(1), 22-34. doi:10.1038/nri.2015.5

Moisan, M. P., Foury, A., Dexpert, S., Cole, S. W., Beau, C., Forestier, D., . . . Capuron, L. (2021). Transcriptomic signaling pathways involved in a naturalistic model of inflammation-related depression and its remission. *Translational Psychiatry, 11*(1), 203. doi:10.1038/s41398-021-01323-9

Morgan, D. J. R., Ho, K. M., & Platell, C. (2020). Incidence and Determinants of Mental Health Service Use After Bariatric Surgery. *JAMA Psychiatry, 77*(1), 60-67. doi:10.1001/jamapsychiatry.2019.2741

Moriarity, D. P., Slavich, G. M., Alloy, L. B., & Olino, T. M. (2022). Hierarchical Inflammatory Phenotypes of Depression: A Novel Approach Across Five Independent Samples and 27,730 Adults. *Biological Psychiatry*. doi:10.1016/j.biopsych.2022.08.017

Nettis, M. A., Lombardo, G., Hastings, C., Zajkowska, Z., Mariani, N., Nikkheslat, N., . . . Mondelli, V. (2021). Augmentation therapy with minocycline in treatment-resistant depression patients with low-grade peripheral inflammation: results from a double-blind randomised clinical trial. *Neuropsychopharmacology*. doi:10.1038/s41386-020-00948-6

O'Rourke, R. W., Johnson, G. S., Purnell, J. Q., Courcoulas, A. P., Dakin, G. F., Garcia, L., . . . Wolfe, B. M. (2019). Serum biomarkers of inflammation and adiposity in the LABS cohort: associations with metabolic disease and surgical outcomes. *International Journal of Obesity, 43*(2), 285-296. doi:10.1038/s41366-018-0088-z

Osimo, E. F., Pillinger, T., Rodriguez, I. M., Khandaker, G. M., Pariante, C. M., & Howes, O. D. (2020). Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. *Brain, Behavior, and Immunity, 87*, 901-909. doi:10.1016/j.bbi.2020.02.010

Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M., . . . Schatzberg, A. F. (2016). Major depressive disorder. *Nature Reviews Disease Primers, 2*, 16065. doi:10.1038/nrdp.2016.65

Paul, L., van der Heiden, C., van Hoeken, D., Deen, M., Vlijm, A., Klaassen, R. A., . . . Hoek, H. W. (2021). Cognitive Behavioral Therapy Versus Usual Care Before Bariatric Surgery: One-Year Follow-Up Results of a Randomized Controlled Trial. *Obesity Surgery, 31*(3), 970-979. doi:10.1007/s11695-020-05081-3

Pearson, T. A., Mensah, G. A., Alexander, R. W., Anderson, J. L., Cannon, R. O., Criqui, M., . . . Vinicor, F. (2003). Markers of Inflammation and Cardiovascular Disease. *Circulation, 107*(3), 499-511. doi:10.1161/01.cir.0000052939.59093.45

Pedro, J., Neves, J. S., Ferreira, M. J., Guerreiro, V., Salazar, D., Viana, S., . . . Carvalho, D. (2020). Impact of Depression on Weight Variation after Bariatric Surgery: A Three-Year Observational Study. *Obesity Facts, 13*(2), 213-220. doi:10.1159/000506404

Perez-Cornago, A., de la Iglesia, R., Lopez-Legarrea, P., Abete, I., Navas-Carretero, S., Lacunza, C. I., . . . Zulet, M. A. (2014). A decline in inflammation is associated with less depressive symptoms after a dietary intervention in metabolic syndrome patients: a longitudinal study. *Nutrition Journal, 13*, 36. doi:10.1186/1475-2891-13-36

Raison, C. L., Dantzer, R., Kelley, K. W., Lawson, M. A., Woolwine, B. J., Vogt, G., . . . Miller, A. H. (2010). CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-alpha: relationship to CNS immune responses and depression. *Molecular Psychiatry, 15*(4), 393-403. doi:10.1038/mp.2009.116

Raison, C. L., Rutherford, R. E., Woolwine, B. J., Shuo, C., Schettler, P., Drake, D. F., . . . Miller, A. H. (2013). A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA psychiatry, 70*(1), 31-41. doi:10.1001/2013.jamapsychiatry.4

Roohi, E., Jaafari, N., & Hashemian, F. (2021). On inflammatory hypothesis of depression: what is the role of IL-6 in the middle of the chaos? *Journal of Neuroinflammation, 18*(1), 45. doi:10.1186/s12974-021-02100-7

Russell, A., Hepgul, N., Nikkheslat, N., Borsini, A., Zajkowska, Z., Moll, N., . . . Pariante, C. M. (2019). Persistent fatigue induced by interferon-alpha: a novel, inflammation-based, proxy model of chronic fatigue syndrome. *Psychoneuroendocrinology, 100*, 276-285. doi:10.1016/j.psyneuen.2018.11.032

Scholtz, S., Bidlake, L., Morgan, J., Fiennes, A., El-Etar, A., Lacey, J. H., & McCluskey, S. (2007). Long-term outcomes following laparoscopic adjustable gastric banding: postoperative psychological sequelae predict outcome at 5-year follow-up. *Obesity Surgery, 17*(9), 1220-1225. doi:10.1007/s11695-007-9212-1

Schroeder, R., Garrison, J. M., Jr., & Johnson, M. S. (2011). Treatment of adult obesity with bariatric surgery. *American Family Physician, 84*(7), 805-814.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59 Suppl 20*, 22-33;quiz 34-57.

Singh, T., & Williams, K. (2006). Atypical depression. *Psychiatry (Edgmont), 3*(4), 33-39.

Smith, K. E., Mason, T. B., Cao, L., Crosby, R. D., Steffen, K. J., Garcia, L., . . . Mitchell, J. E. (2020). Trajectories of depressive symptoms and relationships with weight loss in the seven years after bariatric surgery. *Obesity Research & Clinical Practice, 14*(5), 456-461. doi:10.1016/j.orcp.2020.08.007

Spirou, D., Raman, J., & Smith, E. (2020). Psychological outcomes following surgical and endoscopic bariatric procedures: A systematic review. *Obesity Reviews, 21*(6), e12998. doi:10.1111/obr.12998

Strawbridge, R., Arnone, D., Danese, A., Papadopoulos, A., Herane Vives, A., & Cleare, A. J. (2015). Inflammation and clinical response to treatment in depression: A meta-analysis. *European Neuropsychopharmacology, 25*(10), 1532-1543. doi:10.1016/j.euroneuro.2015.06.007

Thompson, A. L., Koehler, E., Herring, A. H., Paynter, L., Du, S., Zhang, B., . . . Gordon‐Larsen, P. (2016). Weight Gain Trajectories Associated With Elevated C‐Reactive Protein Levels in Chinese Adults. *Journal of the American Heart Association, 5*(9), e003262. doi:10.1161/jaha.116.003262

Upadhyay, J., Farr, O., Perakakis, N., Ghaly, W., & Mantzoros, C. (2018). Obesity as a Disease. *Medical Clinics of North America, 102*(1), 13-33. doi:10.1016/j.mcna.2017.08.004

Van den Eynde, A., Mertens, A., Vangoitsenhoven, R., Meulemans, A., Matthys, C., Deleus, E., . . . Van der Schueren, B. (2021). Psychosocial Consequences of Bariatric Surgery: Two Sides of a Coin: a Scoping Review. *Obesity Surgery, 31*(12), 5409-5417. doi:10.1007/s11695-021-05674-6

van Hout, G. C., Verschure, S. K., & van Heck, G. L. (2005). Psychosocial predictors of success following bariatric surgery. *Obesity Surgery, 15*(4), 552-560. doi:10.1381/0960892053723484

White, G. E., Courcoulas, A. P., & King, W. C. (2020). Long-term Satisfaction with Roux-en-Y Gastric Bypass Surgery: Results from a Multicenter Prospective Cohort Study. *Annals of Surgery*. doi:10.1097/sla.0000000000004625

White, M. A., Kalarchian, M. A., Levine, M. D., Masheb, R. M., Marcus, M. D., & Grilo, C. M. (2015). Prognostic Significance of Depressive Symptoms on Weight Loss and Psychosocial Outcomes Following Gastric Bypass Surgery: A Prospective 24-Month Follow-Up Study. *Obesity Surgery, 25*(10), 1909-1916. doi:10.1007/s11695-015-1631-9

Zunszain, P. A., Anacker, C., Cattaneo, A., Choudhury, S., Musaelyan, K., Myint, A. M., . . . Pariante, C. M. (2012). Interleukin-1beta: a new regulator of the kynurenine pathway affecting human hippocampal neurogenesis. *Neuropsychopharmacology, 37*(4), 939-949. doi:10.1038/npp.2011.277

**Figure Titles & Legends**

**Figure 1 Title:** Group Comparisons of Mean Serum Inflammatory Markers at Baseline.

**Figure 1 Legend:** 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.

**Figure 2 Title:** Group Comparisons of Mean Serum Inflammatory Markers at Six-Month Follow-Up.

**Figure 2 Legend:** 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.

**Figure 3 Title:** Multivariable Regression Models ShowingBaselinePredictors of Weight Loss and Depression Severity Six Months After Bariatric Surgery.

**Figure 3 Legend**: (A) The weight loss model predicted 36% adjusted variance in weight loss at six months after surgery with an average prediction error rate of 5.6%. (B) The depression severity model predicted 54% adjusted variance in depressive symptoms six months after surgery with an average prediction error rate of 6.1%.