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The Effect of Bariatric Surgery on Long-Term Depression Treatment in Obese Patients

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Abstract

Objective: In a large multi-site cohort of Veterans who underwent Roux-en-Y gastric bypass (RYGB) or laparoscopic sleeve gastrectomy (LSG), initiation of (i.e., incident) and persistence of (i.e., continuation of pre-operative) depression treatment are compared with matched non-surgical controls.

Background Summary Data: Bariatric surgery has been associated with short-term improvements in depression but less is known about longer-term outcomes.

Methods: In a retrospective cohort study, we matched 1,713 Veterans with depression treatment who underwent bariatric surgery in Veterans Administration (VA) bariatric centers from FY 2001–2016 to 15,056 non-surgical controls using sequential stratification and examined persistence of depression treatment via generalized estimating equations. Incidence of depression treatment

was compared using Cox regression models between 2,227 surgical patients and 20,939 matched non-surgical controls without depression treatment at baseline.

Results: In surgical patients with depression treatment at baseline, the use of postsurgical depression treatment declined over time for both surgical procedures, but post-surgical patients had greater use of depression treatment at 5 years (RYGB: odds ratio (OR)=1.24, 95% confidence interval (CI): 1.04–1.49; LSG: OR=1.27, 95% CI: 1.04–1.56) compared with controls. Among those without depression treatment at baseline, bariatric surgery was associated with a higher incidence of depression treatment compared with matched controls (RYGB: hazard ratio (HR)=1.34, 95% CI: 1.17–1.53; LSG: HR at 1–5 years=1.27, 95% CI: 1.10–1.47).

Conclusions: Bariatric surgery was associated with a greater risk of post-operative incident depression treatment and greater persistence of post-operative depression treatment. Depression may worsen for some patients after bariatric surgery, so clinicians should carefully monitor their patients for depression post-operatively.

Mini Abstract

Bariatric surgery has been associated with short-term improvements in depression but less is known about long-term initiation (i.e., incident) and persistence of (i.e., continuation of pre-operative) depression treatment. Compared with matched non-surgical patients with severe obesity in a large multi-site retrospective cohort, bariatric surgery patients without depression treatment at baseline had a greater risk of incident post-operative depression treatment; those who were receiving depression treatment before surgery had greater persistence of post-operative depression treatment. Depression worsens for some patients after bariatric surgery, so clinicians should carefully monitor their patients for depression post-operatively.

Keywords

depression; treatment; obesity; surgery; bariatric; gastric bypass; sleeve gastrectomy; Veterans; matching

Introduction

Depression is common in patients with obesity, especially in those with severe obesity who will undergo bariatric surgery.¹ Many obese patients take antidepressants, and these can be associated with weight gain.^{2,3}

Bariatric surgery has been shown to reduce self-reported depressive symptoms.^{4,5} Some of this improvement may be attributable to concurrent depression treatment via medications or counseling.^{5–8} A recent systematic review identified 8 studies evaluating changes in depressive symptoms at least 24 months following bariatric surgery.³ Most of these studies reported improvements in depressive symptoms; however, self-reported depression⁷ and depression treatment⁶ at 7 years appeared to return close to baseline levels. None of these studies included a matched non-surgical control group. More recently, a 5-year report of changes in quality of life from the single-site STAMPEDE randomized trial comparing surgical and intensive medical treatment of severe obesity and diabetes reported that psychological and social functioning was unaffected by surgically-induced weight loss.⁹

These prior studies have several limitations. Most prior studies were uncontrolled pre-post studies of surgical patients,^{3,5,7} or were studies of surgical and non-surgical cohorts having few patients⁹, examined non-US cohorts,^{6,10} or the patients studied underwent bariatric procedures that are no longer performed.¹⁰ Few prior studies examined post-surgical trends in depression treatment among patients who received baseline depression treatment separately from patients who did not have baseline depression treatment. It is important to examine these post-surgical trends separately as antidepressants are often continued after surgery^{11,12} without reassessment of depression in patients who are receiving baseline depression treatment. Finally, the sleeve gastrectomy procedure (LSG) is now the most widely performed bariatric procedure worldwide, but few prior studies have examined post-surgical depression treatment in patients undergoing LSG.

To address these limitations of the prior literature, we conducted a nationwide, retrospective cohort study among US Veterans to examine post-surgical trends in depression treatment among those with and without depression treatment at baseline and stratified by surgical procedure. We hypothesized that post-surgical patients would have lower rates of depression treatment than matched non-surgical patients, regardless of their baseline treatment status.

Methods

Study Design and Study Population

We conducted a retrospective cohort study of Veterans Administration (VA) patients who underwent bariatric surgery that were matched to a cohort of severely obese Veterans who did not undergo bariatric surgery. This study was approved by the Institutional Review Boards of the Durham VAMC and Kaiser Permanente Washington Health Research Institute. We identified 10,653 Veterans with procedure codes for any of four bariatric surgical procedures (open or laparoscopic RYGB, laparoscopic SG (LSG), and adjustable gastric band (AGB)) in a VA bariatric center between 10/1/2000 and 9/30/2016. We ultimately excluded AGB procedures from our analyses because they were rarely performed in the cohort and their use has declined rapidly worldwide. After applying additional standard exclusions (Supplemental Figure 1) that we have applied in prior analyses,^{13,14} the final surgical cohort included 3,940 patients who underwent RYGB or LSG.

Due to the time-varying nature of surgical eligibility (e.g., BMI and other clinical criteria that changed over time), a sequential stratification matching approach was used to identify all potential non-surgical control patients for each bariatric surgery patient using VA electronic health record (EHR) data.¹⁵⁻¹⁷ For each surgical patient, we identified a set of eligible potential matches who were similar to the surgical patient for a variety of characteristics that influence long-term outcomes and the likelihood of receiving bariatric surgery but who had not yet had bariatric surgery. Potential matches were required to exactly match the values of the surgical patient on the following: sex, race (white/non-white), diabetes status, VA regional network, and a history of chronic prescription opioid use, depression treatment, or unhealthy alcohol use in the prior two years. Additionally, surgical patients and potential matches had to be within 5 years of age of each other and have a similar BMI measurement. Up to 10 matches with the closest BMI measurements to that of

the surgical case were then selected among potential matches. Any surgical case without a representative match was excluded from the study (Supplemental Figure 1).

Control patients could match to more than one surgical patient at any time during the study period if they had an eligible BMI measurement. The matching process was not contingent upon future information, so 681 control patients (representing 800 matches) who received bariatric surgery after they matched to a surgical patient contributed person-time to the control group in models until they received bariatric surgery. Follow-up time for matched controls was censored at their date of surgery. The final control cohort included 32,015 individual patients representing 35,995 matches.

This final analytic cohort was then stratified based on the presence or absence of depression treatment at baseline. Patients in the surgical and non-surgical groups were identified as having baseline depression treatment if they had at least 30 days of antidepressant prescriptions filled and a concurrent diagnosis of depression and/or at least two outpatient psychotherapy visits for depression within the 12 months prior to and including the index date (day of surgery). We required at least 30 days of antidepressants to allow an inclusive definition of depression treatment. Veterans not meeting these criteria were designated as not having baseline depression treatment. We matched 2,227 surgical patients without depression treatment at baseline to 20,939 non-surgical matches and 1,713 surgical patients with baseline depression treatment to 15,056 non-surgical matches.

Depression Treatment Outcomes

Incident Depression Treatment: Among Veterans who were not receiving depression treatment at baseline, incident depression treatment was considered to begin on the date of the first prescription fill for antidepressants (Supplemental Table 1) that was associated with at least 60 days of total treatment or on the date of the second outpatient psychotherapy visit for depression. In both circumstances, the treatment had to be associated with a depression diagnosis 90 days prior to 15 days following the treatment and all must have occurred within a rolling 12-month window.¹⁸ Depression treatment was censored at the earliest date among death, 5 years post-surgery, the end of the study period (6/30/2019), and (for matches only) when a bariatric procedure was initiated, if applicable.

Persistent Depression Treatment: A separate analysis with a person-year unit of analysis investigated the persistence of depression treatment for up to 5 years after surgery (1–365 days after, 366–730 days after, etc.) among patients with depression treatment at baseline. Persistence was indicated in each year after surgery if a patient had at least 60 days of antidepressant fills or at least two psychotherapy visits; a concurrent depression diagnosis was not required.

Statistical Analysis

Covariate balance between the surgical patients and non-surgical matches was evaluated using standardized differences.¹⁹ The association between each bariatric surgery procedure and depression treatment incidence among Veterans who did not have baseline depression treatment was examined descriptively in the matched cohorts using Kaplan-Meier estimators

separately for the two procedure types (RYGB, LSG). Depression treatment incidence by procedure type was then compared between surgical and matched control patients who did not have baseline depression treatment using a Cox model analysis with a robust sandwich variance estimator²⁰ to account for the fact that the same individual could have been matched to multiple surgical patients. Inspection of log(-log[survival]) curves and Schoenfeld residuals found that the proportional hazards assumption was satisfied for RYGB procedures at all times, and for LSG when time was differentiated into the first year following surgery and the remainder of the follow-up period.²¹

Depression treatment persistence up to five years after surgery was then compared between surgical patients and matched non-surgical controls who had baseline depression treatment using a logistic regression fit via generalized estimating equations (GEEs), separately for the two procedure types. Based on minimizing quasi-likelihood under the Independence Model Criterion (QIC), quadratic time trends best fit the data and interactions with an indicator of receipt of surgery were included. An exchangeable working correlation was utilized and empirical sandwich standard errors, clustered on each individual, accounted for potential over-dispersion and correlation among repeated measurements. The *a priori* level of statistical significance was 0.05 for all analyses and all were conducted using SAS 9.4.

Results

Depression Treatment Persistence: Matched Cohorts who had Baseline Depression Treatment

Mean follow-up was 9.7 years (median=9.6) in patients undergoing RYGB (n=941) and 8.8 years (median=8.5) for their matched non-surgical controls (n=8,114; Supplementary Table 2). Mean BMI was higher in RYGB patients (46.2 kg/m² vs. 44.3 kg/m², standardized mean difference (SMD)=0.29) than matched controls. RYGB patients were more likely to be married (50.4% vs. 41.1%, SMD=0.30) and had more outpatient visits than matched controls (23.6 vs. 20.3, SMD =0.20).

Mean follow-up was 5.4 years (median=5.0) in patients undergoing LSG (n=772) and 5.1 years (median=4.8) for their matched non-surgical controls (n=6,942). The cohorts were well matched, though LSG patients were more likely to be married (49.4% vs. 40.5%, SMD=0.33) and had slightly more VA outpatient visits in the year prior to baseline (23.8 vs. 20.2, SMD=0.22) compared with matched controls. Over one-third of LSG patients and their matched controls had post-traumatic stress disorder (35.8% vs 36.6%, SMD=0.02).

In cohorts with depression treatment at baseline, trends in model-estimated post-surgical depression treatment decreased with generally similar trends between surgical patients and non-surgical controls (Supplemental Figure 2). Model-estimated depression treatment persistence decreased from 85–88% of patients in the two surgical cohorts at 1 year to 81–82% of patients at 5 years (Supplemental Table 3). The proportion receiving depression treatment in the non-surgical matched cohorts decreased slightly more, from 86–88% at 1 year to 77–78% of patients at 5 years.

Regression analyses found that persistence of depression treatment was significantly higher for RYGB patients 5 years after surgery (Figure 1; odds ratio (OR)=1.24, 95% confidence interval (CI): 1.04–1.49). Similarly, persistence of depression treatment in the LSG cohort was also significantly higher for LSG patients compared with matched controls five years after surgery (OR=1.27, 95% CI: 1.04–1.56).

Depression Treatment Incidence: Matched Cohorts who did not have Depression Treatment at Baseline

Patients undergoing RYGB who did not have baseline depression treatment (n=1,275) and matched controls (n=11,895) were similar in nearly all observed characteristics (Supplementary Table 4). Surgical patients were more likely to be married (54.1% vs. 45.2%, SMD=0.32) and had more VA outpatient visits in the year prior to baseline (18.3 vs. 13.8, SMD=0.32). Mean follow-up was 10.0 years (median=10.3) for surgical patients and 9.3 years (median=9.3) for their matched controls. LSG patients (n=952) and matched controls (n=9,044) without depression at baseline were well-matched on nearly all characteristics, except more LSG patients were married (50.5% vs. 45.4%, SMD=0.19) and LSG patients had more outpatient visits (18.2 vs. 12.7, SMD=0.42). Mean follow-up was 5.6 years (median=5.2) for LSG patients and 5.2 years (median=4.9) for their matched controls.

The unadjusted Kaplan-Meier estimated 5-year depression treatment initiation rates were 34.7% for RYGB patients and 27.9% for matched controls, and the unadjusted depression treatment initiation rates were 31.5% for LSG patients and 26.2% for matched controls at 5 years (Figure 2).

In adjusted Cox regression (Figure 3), RYGB was associated with a 34% higher depression treatment incidence compared with matched controls (hazard ratio (HR)=1.34, 95% CI: 1.17–1.53). The model for LSG showed non-proportional hazards, so the model was stratified by time at 1 year. LSG was associated with a 27% higher depression treatment incidence at 1–5 years after surgery (HR=1.27, 95% CI: 1.10–1.47), but there was no significant difference in depression incidence (HR=0.87, 95% CI: 0.71–1.07) in the first year after surgery.

Discussion

In this nationwide, retrospective cohort study of Veterans undergoing bariatric surgery from FY 2001–2016 and matched to non-surgical patients with severe obesity, there was an increased incidence of depression treatment at 5 years among bariatric patients who did not have depression treatment at baseline. There was also a greater persistence of depression treatment at 5 years among patients who were receiving depression treatment at baseline. These observations were present for both RYGB and LSG patients. This increased risk in depression treatment for surgical patients was counter to our original hypothesis, and it suggests that more research is needed to examine the longer-term mental health outcomes of bariatric patients.

We did not have access to data on long-term changes in depression symptoms, so it is not possible to determine whether the greater risk of depression treatment in surgical

patients was due to greater severity of depression symptoms or to more active screening and management of mental health conditions in surgical patients that facilitated more appropriate treatment for underlying depression. Conceivably, there may have been better quality of depression screening and care for post-bariatric patients with severe obesity than patients who did not undergo bariatric surgery. Alternatively, it is possible that unmeasured baseline differences may have accounted for these differences. Several prior studies have suggested that depression symptoms decrease in the short- and mid-term (periods longer than 24 months) following bariatric surgery (Gill 2019; Dawes). Most of these prior studies did not include non-surgical control patients, so their findings are not incongruent with ours – patients who undergo bariatric surgery can have improvements in their depression symptoms while still having a greater persistence of depression treatment than matched non-surgical patients with depression.

It is not currently clear why post-bariatric patients may have a greater long-term risk of depression treatment than matched controls, and more research on this is warranted. We believe there are several possible explanations that should be explored in additional research. First, it is possible that findings reflect increased treatment for depression, but not increased depression. The finding could be due to the identification of undiagnosed depression in post-bariatric patients. This could occur if bariatric surgery results in the unmasking of depression among patients who had other concerns or problems of greater magnitude at the time of surgery (e.g., chronic pain or body image concerns that masked depression), or this could occur if VA health systems are doing a better job of screening for depression in post-bariatric patients. In addition, it is possible that patients who are successful accessing bariatric surgery are also more successful accessing treatment for depression. Alternatively, findings could indicate that patients who undergo bariatric surgery have increased depression in the long-term. Depression could be a long-term consequence of bariatric surgery in several scenarios, including: the psychological impact of insufficient weight loss or weight regain causing depression; depression developing after the patient is no longer able to use eating/food as a coping strategy; an increased incidence of alcohol and opiate use (as we have previously described^{13,14}) after bariatric surgery could contribute to depression; and finally, micronutrient and vitamin deficiencies, such as B12, zinc, and selenium deficiencies, which are common after surgery, could cause depression.^{22,23}

The current study is unique because of the 5 years of follow-up in a nationwide, multicenter cohort that included non-surgical control patients with severe obesity. These patients were carefully matched based on characteristics that are related to the incidence and persistence of depression, including chronic prescription opioid use and unhealthy alcohol use. Furthermore, nearly all studies of bariatric surgery and depression have pooled patients with and without prior depression treatment at baseline, which precludes an examination of the incidence of new depression treatment occurring after bariatric surgery.

Our findings add further evidence to suggest that bariatric patients should have careful, long-term psychological follow-up. We have previously reported that bariatric surgery was associated with a greater probability of developing unhealthy alcohol use in the 3–8 years after bariatric procedures compared with matched controls.¹⁴ We also found that bariatric surgery was associated with greater incidence of chronic persistent opioid use but was not

associated with greater persistence of opioid use.¹³ Other observational cohort studies have found a greater incidence of suicide after bariatric surgery than in matched non-surgical populations.²⁴ A recent study found that there were no improvements in psychological or social measures of quality of life among patients 5 years after being randomized to bariatric surgery or intensive medical and lifestyle intervention.⁹ Although bariatric surgery has significant benefits in terms of reduced body weight, diabetes prevalence, and a risk of death, these findings suggest that mental health outcomes may not be improved and in some patients may be worsened relative to non-surgical group.

This study has several limitations that should be acknowledged. First, this is a study of Veterans and results may not generalize to non-Veterans undergoing bariatric surgery. Second, confounding in this retrospective cohort study was reduced via sequential stratification matching but residual unobserved confounding may persist after matching.²⁵ Given sample size and statistical constraints related to the number of variables that could be accommodated in the matching process, we could not match on every available characteristic and BMI imbalances in two cohorts were statistically but likely not clinically significant. The estimated effect estimates represent associations and not necessarily the causal effect of bariatric surgery on depression treatment outcomes. Second, antidepressant use and psychotherapy visit data were identified from VA EHR data only, so depression treatment obtained outside VA were not ascertained. Third, patients with at least 30 days of antidepressant fills but no corresponding depression diagnosis were considered to be without depression treatment, which could occur either if antidepressants were prescribed for non-depression use or if a depression diagnosis was not coded for actual depression treatment. We were unable to differentiate the two scenarios using administrative data, but could have under-counted depression treatment likely to a minor degree; because they were heavy outpatient users (20–23 total outpatient visits and 16 mental health visits at baseline), they had ample opportunity to be diagnosed. Finally, as mentioned previously, we did not have access to data on self-reported depression symptoms, so we cannot ascertain differences in depression symptom severity across groups.

Conclusion

Compared with matched non-surgical patients with severe obesity, bariatric surgery was associated with a greater risk of incident depression treatment after surgery in those without depression treatment at baseline and greater persistence of post-operative depression treatment among those who were receiving depression treatment before surgery. More research is needed to understand whether this finding reflects worsened depression after surgery or that more rigorous psychological follow-up of bariatric patients after surgery resulted in improved case identification. Depression worsens for some patients after bariatric surgery, so clinicians should carefully monitor their patients for depression post-operatively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest Disclosures:

Dr. Maciejewski reports research grants for National Institutes of Health (NIH), Veterans Affairs Health Services Research and Development Service (VA HSR&D) and National Committee for Quality Assurance (NCQA) and ownership of Amgen stock due to his spouse's employment. Dr. Arterburn reports research grants from NIH and PCORI outside of the submitted work. Dr. Bradley reports research grants from NIH, Agency for Healthcare Research and Quality (AHRQ) and work for NCQA outside of the submitted work. All other authors have no conflicts of interest to disclose.

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The National Institute on Drug Abuse had no role in the design, conduct, collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript. The opinions expressed are those of the authors and not necessarily those of the Department of Veterans Affairs, the United States Government, Duke University, the Kaiser Permanente Washington Health Research Institute, or the University of Washington.

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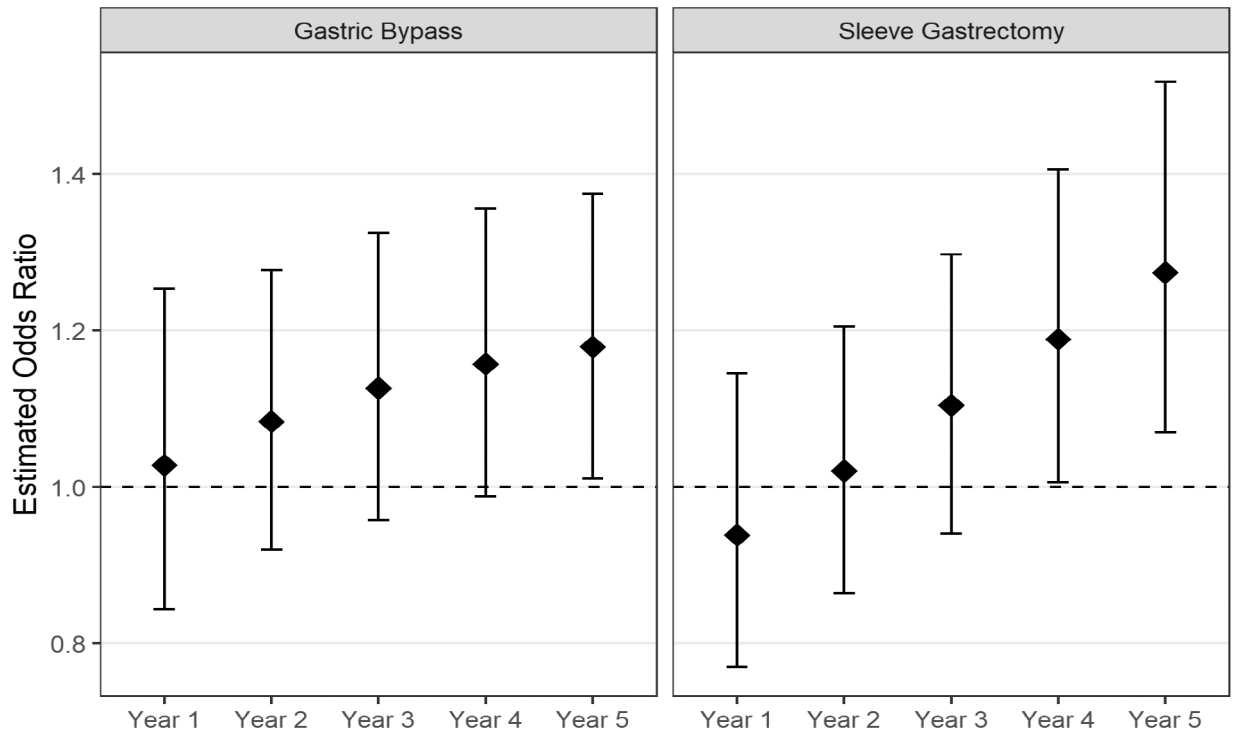


Figure 1. Odds Ratios and 95% Confidence Intervals Comparing the Odds of Persisting with Depression Treatment up to 5 Years in Bariatric Patients and Matched Non-Surgical Patients among those with Depression Treatment at Baseline, by Bariatric Procedure

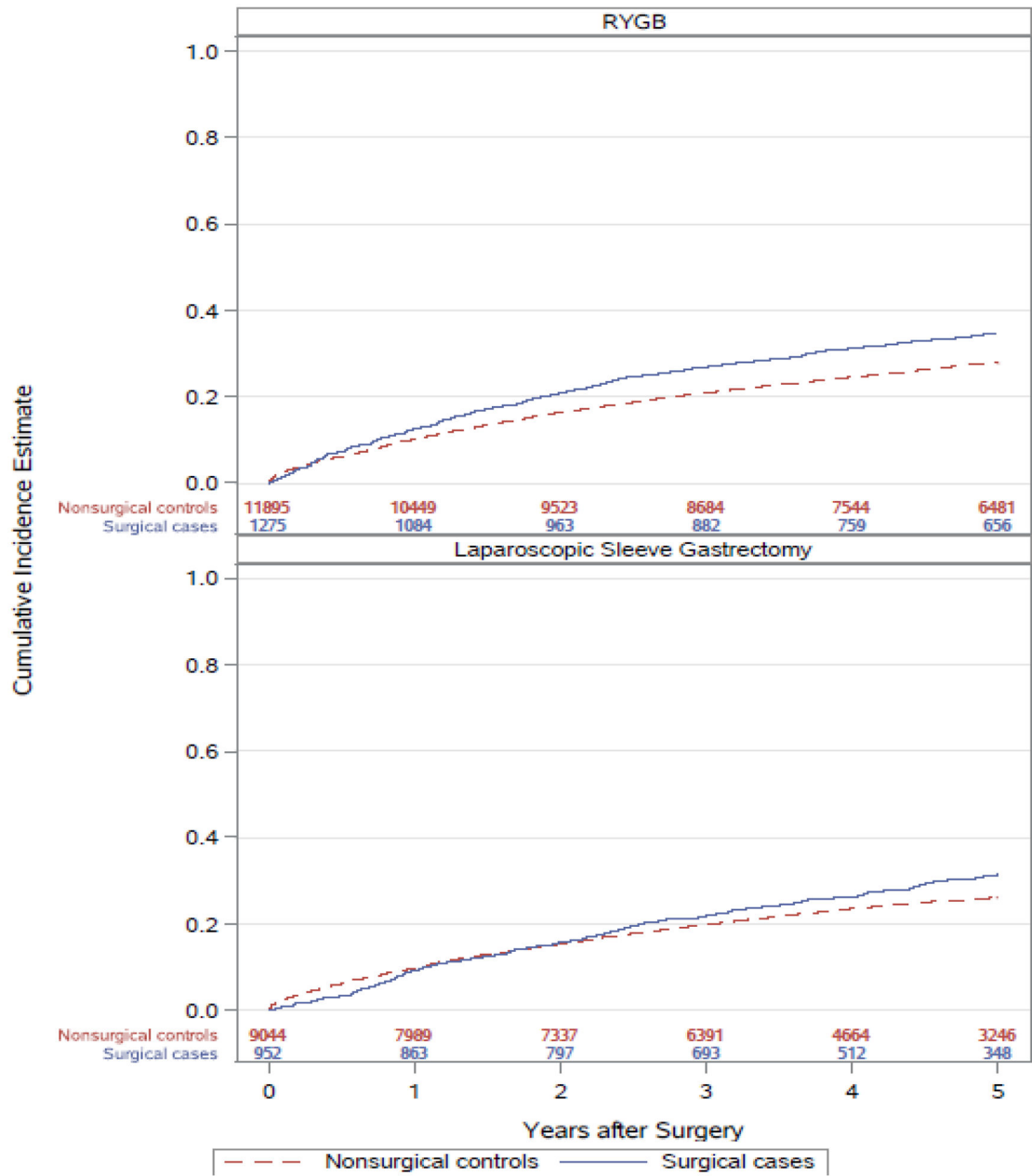


Figure 2. Unadjusted Depression Treatment Incidence: Kaplan-Meier Estimated Cumulative Incidence of Post-operative Depression Treatment up to 5 Years in Bariatric Surgical Patients and Matched Non-Surgical Patients without Baseline Depression Treatment, by Bariatric Procedure

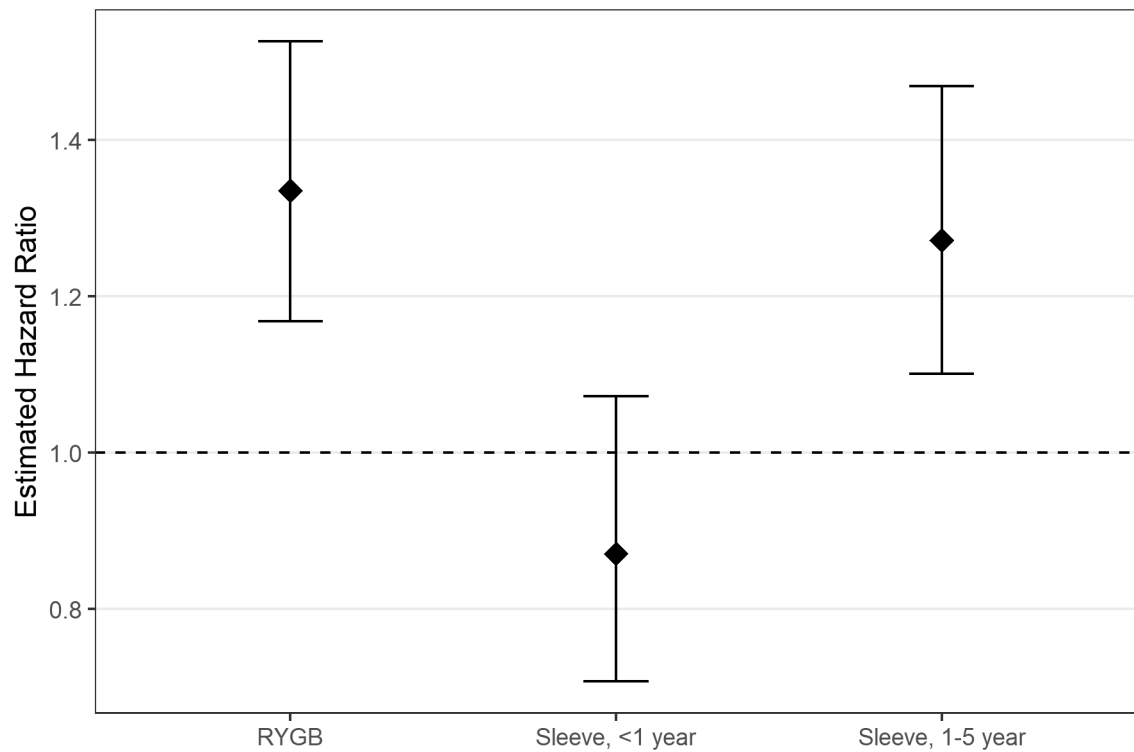


Figure 3. Adjusted Depression Treatment Incidence: Association and 95% Confidence Intervals of Bariatric Surgery and Depression Treatment Incidence up to 5 Years after Surgery in Patients without Baseline Depression Treatment

Note: The proportional hazards assumption was not met for patients receiving LSG, so hazard ratios were estimated separately for the first year of follow-up and the remaining years 1–5. Proportional hazards assumption was met for patients undergoing RYGB procedures, so hazard ratios were estimated for the entire 5-year period for these cohorts. Hazard ratios and 95% confidence intervals are from Cox models in matched surgical patients and non-surgical controls without depression treatment at baseline. HR=hazard ratio; RYGB=Roux-en-Y gastric bypass; Sleeve=laparoscopic sleeve gastrectomy.