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Increased Risk for Major Depressive Disorder in Severely Obese Patients after
Bariatric Surgery — a 12-year Nationwide Cohort Study

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Conflict of interests

All of the authors **report that they have** no conflicts of interest **to disclose**, financial or otherwise.

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Abstract

Background Bariatric surgery is associated with a significant improvement in depressive mood in the initial postoperative years, but the maintenance of the improvement is under debate.

Aim To explore the association between bariatric surgery and major depressive disorder (MDD) in a 12-year nationwide cohort study.

Method Using the National Health Insurance Research Database of Taiwan, we identified 2302 patients who underwent bariatric surgery in 2001-2009. These patients were matched by propensity score to 6493 obese patients who did not receive bariatric surgery. We followed the surgical and control cohorts until death, any diagnosis of MDD or December 31, 2012. We used Cox proportional hazard regression models to calculate the relative risk of MDD in those who received bariatric surgery.

Results Overall, there was a 1.70-fold (95% CI: 1.27-2.27) higher risk of MDD in the surgical group. Subjects receiving malabsorptive procedures showed a higher risk of MDD (3.01, 95% CI: 1.78-5.09) than those receiving restrictive procedures (1.51, 95% CI: 1.10-2.07). Stratified by follow-up period, there was a higher risk of MDD in the surgical group (2.92, 95% CI: 1.75-4.88) than in the restrictive group four years after bariatric surgery.

Conclusions Bariatric surgery was significantly associated with an elevated risk of

MDD.

Key words: bariatric surgery, depression, obesity

KEY MESSAGES

1. Bariatric surgery is associated with a significant improvement in depressive mood in the initial **postoperative** years, but the improvement is not maintained. Less is known about the relationship between bariatric surgery and risk of major depressive disorder.
2. This first nationwide cohort study found that bariatric surgery was significantly associated with **an elevated** risk of MDD (aHR: 1.70; CI: 1.27-2.27), mainly with malabsorptive procedures (aHR: 3.01; CI: 1.78-5.09) and **at time points** more than four years after surgery (aHR: 2.92; CI: 1.75-4.88) compared with **the risk in** matched controls. These findings imply an association between long-term malabsorption and the **postoperative** incidence of MDD.
3. Long-term malabsorption might be related to the incidence of major depressive disorder after bariatric surgery. The **possible** causal relationship between nutritional deficiency after bariatric surgery and major depressive disorder warrants further investigation.

Introduction

Obesity is an important public health issue globally. The worldwide prevalence of overweight and obesity in adults was **approximate** 36.9% in men and 38.0% in women **as of** 2013[1]. The estimated prevalence of obesity among the middle-aged is 15% to 20% in Europe [2]. The most effective and sustained treatment for severe obesity is bariatric surgery, which has **increased** more than seven-fold worldwide in the last decade [3]. Moreover, bariatric surgery **is** associated with a long-term reduction in overall mortality and with decreased incidences of diabetes, myocardial infarction, and stroke [4, 5]; but an increase in risk of fracture [6]. Depression **has been** another **important** health issue in the last few decades. Approximately 20% of U.S. adults have at least one episode of major depressive disorder (MDD) in their lifetime [7]. **Additionally**, the World Health Organization has ranked depression as the fourth leading cause of disability worldwide [8]. Obesity and depression interact closely. **Unsurprisingly**, depression is the most common mental health condition among patients seeking and undergoing bariatric surgery [9]. Bariatric surgery is associated with a significant reduction in depressive mood over the initial **postoperative** years; but this **improvement** is not maintained [10-16]. One study examined depression before and after bariatric surgery using the Beck Depression Inventory (BDI) questionnaire and observed **dramatically lower** in the BDI scores

during the first year after bariatric surgery **than** 4 years later [11]. In an intervention study of obesity using 487 Swedish obese subjects **matched** 1:1 **with** conventionally treated controls, the surgical group had a greater improvement in quality of life than the conventional group. Although the improvement was maintained for 2 years after surgery, the peak value of quality of life in the surgical group was observed at 6-12 months [12]. Similar studies subsequently examined the effect of bariatric surgery on depression over a longer period [13-16]. In a 3-year follow-up study, depressive symptoms in **severely** obese subjects were persistently improved **in the** **postoperative** compared to **the preoperative** condition [15], whereas there was no difference in BDI scores **between** obese patients **who had undergone** gastric bypass and obese patients without gastric bypass in a 7-year follow-up study [14].

Several studies have aimed to **determine** why the positive impact on depressive mood after bariatric surgery disappears after a few years. **The most common cause of this decline is unclear, but candidates** include disappointment from expectations of weight loss, the occurrence of weight regain, and recurring comorbidities [9, 17]. However, the association between preoperative mental health conditions and **the degree of** postoperative weight loss remains unclear [9, 18]. In addition, poor nutrient absorption could lead to depression, as **noted** in updated clinical guidelines [19]. A decline in the serum level of antidepressants was also found in **patients after** bariatric

surgery, supporting the hypothesis of malabsorption [20].

The aim of this study was to compare the incidence of MDD **between** severely obese patients undergoing bariatric surgery and matched **severely obese** controls. We also examined the relationship between bariatric surgery and the risk of MDD **for** different surgical types and observation periods.

Materials and Methods

Data Source

We used the National Health Insurance Research Database (NHIRD) to conduct this study. The National Health Insurance program, which began in 1995, has enrolled up to 99% of Taiwan's 23 million people [21]. The **present** study was approved by the institutional review board of the National Health Research Institutes in Taiwan (EC1030701-E).

From the NHIRD, we selected those who had a diagnosis of morbid obesity (ICD-9-CM 278.01, n=21465) between 2001 and 2009. A detailed flowchart of **the** selection process and **the** matching **of controls** is shown in Fig 1. After excluding those who received bariatric surgery before the diagnosis of morbid obesity (n=287), we divided the candidate subjects into 2 groups based on whether they received bariatric surgery during the follow-up period. For the surgical group (n=2689), we

also excluded those who had a prior diagnosis of depression (ICD-9-CM 296.2 and 296.3, n=157) before surgery and those who had missing data (n=2). At the end, the remaining subjects who had morbid obesity but did not receive bariatric surgery served as the control pool for the **subsequent** matching procedures. The first date of bariatric surgery for each subject was defined as the index date for that subject in the surgical group. The propensity scores of all study subjects were calculated by using multivariable logistic regression adjusting for age, sex, Charlson Comorbidity Index (CCI) [22], diabetes, hypertension, hyperlipidemia, and the year **when morbid obesity was diagnosed**. To select **individuals** who did not receive bariatric surgery as **a comparable control group, we used** the 1:3 propensity score matching method [23] and the nearest neighbor algorithm with a perfect proportion of 0.995 to 1.0 [24]. We assigned the index date of each surgical subject to **the** corresponding matched controls. In the control group, we also excluded 312 subjects who had a prior diagnosis of depression and 15 subjects with missing data. After the matching procedures **were complete**, 2302 subjects **who received** bariatric surgery and 6493 controls who did not receive bariatric surgery **were included further analyses**. We followed the study subjects until death, any diagnosis of major depressive disorder, or December 31, 2012, whichever came first.

The clinical procedure codes **for** bariatric surgery used in this study were divided

into 2 subgroups: the malabsorptive procedures included ICD-9-CM 44.31 (high gastric bypass), 44.38 (laparoscopic gastroenterostomy), and 44.39 (other gastroenterostomy without gastrectomy), **while** the restrictive procedures included ICD-9-CM 43.82 (laparoscopic sleeve gastrectomy), 43.89 (open and other partial gastrectomy), 44.68 (laparoscopic gastroplasty), 44.69 (other repair of stomach), 44.95 (laparoscopic gastric restrictive procedure), and 44.99 (other operations on stomach).

Definition of Research Variables

The main outcome of this study was the occurrence of MDD defined as **an admission diagnosis of MDD or the use of antidepressant drugs** (ICD-9-CM code 296.2 or 296.3). The main comorbidities controlled in this study include diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM code 401), and hyperlipidemia (ICD-9-CM code 272). Study subjects were considered to have comorbidities if they had at least 2 ambulatory visits and 1 hospitalization with the **corresponding** diagnosis within 3 years before the first diagnosis of morbid obesity.

Statistical Analysis

The baseline data are presented by frequency, with percentages for categorical variables and the means with standard deviation for continuous variables. T tests and χ^2 tests are used to describe the differences between the surgical and control groups

for categorical variables and continuous variables, respectively. The incidence of MDD is defined as the number of events divided by the **number of** follow-up person-years, which **was** calculated from the index date to the diagnosis of MDD, death, or December 31, 2012, whichever occurred first. We used Cox proportional hazards regression to assess adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) of MDD for the surgical group compared to the controls. The Schoenfeld residuals test [25] and complementary log–log plots **showed that** **proportional hazards assumption was not violated**. In the multivariable analyses, we adjusted for all covariates shown in Table 1. To test the possibility of selection bias, we also followed up the excluded depressive subjects after **the** index date to compare the **differences in readmission** for MDD and **regular** use of antidepressant drugs between **the** bariatric surgery and control groups. To evaluate the effects of different surgical procedures, we divided the bariatric surgery group into those who received malabsorptive procedures and those **who received** restrictive procedures. And, to clarify the changes in depression risk during the follow-up, we also estimated the HRs of depression in the following time periods: <1, 1-1.99, 2-2.99, 3-3.99, and > 4 years after the index date. All p values were 2-sided, and **differences with p values** <0.05 were considered significant. All analyses were **conducted** using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

The surgical patients, 61.9% of whom were women, had a mean age of 32.2 years. The matched controls, 61.5% of whom were women, had a mean age of 32.8 years. The two groups were similar in most of the baseline characteristics **for** which they were matched (Table 1). Since we **applied** propensity score matching according to age group (treated as a categorical variable rather than a continuous variable), there was difference **in** mean age between **the** surgical and **the** control groups (P=0.0199). The difference would be further adjusted when applying Cox regression multivariate regression analyses.

By the end of the 12-year study period, there were a total of 72 incidences of MDD in the surgical group (mean follow-up 4.89 years, 6.40 cases per 1000 person years) and 123 incidence of MDD in the matched control group (mean follow-up 4.98 years, 3.81 cases per 1000 person years)(Table 2). Overall, there was a **significant** 1.70-fold **increase** (95% CI: 1.27-2.27) **in the** risk of MDD in the surgical group compared with the controls after adjusting for age, sex, CCI, diabetes, hypertension, hyperlipidemia, and the year morbid obesity was diagnosed. We also followed up the excluded depressive subjects after **the** index date and there was no significant difference **in readmission** for MDD or **regular use of antidepressant** drugs between **the** bariatric surgery (123.4 per 1000 person-years) and control (133.0 per 1000

person years) groups (data not shown). Therefore, the exclusion of prior depression did not increase selection bias. With regard to the type of surgery, 337 (14.6%) subjects underwent malabsorptive procedures and 1965 (85.4%) underwent restrictive procedures. The adjusted relative risk of MDD was 3.01 (95% CI: 1.78-5.09) in **patients who underwent** malabsorptive procedures and 1.51 (95% CI: 1.10-2.07) in **those who underwent** restrictive procedures **compared with controls**. Furthermore, we found that the malabsorptive group had **an elevated risk of** MDD (adjusted HR: 2.27, CI: 1.28-4.03) compared with the restrictive group.

In Kaplan-Meier analysis (Table 3 and Fig 2), the incidences of MDD were 4.90 per 1000 person-years during the first year, 5.10 per 1000 person-years during the second year, 4.89 per 1000 person-years during the third year, 6.51 per 1000 person-years during the fourth year, and 9.26 per 1000 person-years past the first 4 years for the surgical group, compared with 4.84, 3.73, 3.93, 3.26, and 3.33, respectively, for the matched controls. Our findings revealed **an elevated** risk of MDD in the surgical group (aHR: 2.92, 95% CI: 1.75-4.88) four years after bariatric surgery.

Discussion

To our knowledge, this is the first nationwide cohort study to compare the incidence of MDD **between** obese patients **who have undergone** bariatric surgery **and obese controls who have not**. We found a **significant** 1.50-fold **increase in the** risk of MDD in the surgical group compared with the control **group**. In addition, the risk of MDD increased 2.36-fold **with** the malabsorptive type of surgery and 1.38-fold **with** the restrictive type of surgery compared with controls, implying that malabsorption plays a more important role **than restricted food intake in** MDD development. It was also found that the incidence of MDD increased 4 years after surgery compared with the **incidence in** controls. These findings depict the trajectory of MDD development after bariatric surgery.

In previous studies, bariatric surgery was associated with a modest reduction in clinical depressive mood over the initial **postoperative** years, but this **reduction** was not sustained. Most studies prospectively compared **scores on a** depressive scale, using questionnaires prior to and after the surgery, and found **that** improvement **peaked** at 6-12 months [12, 26] or one year after surgery [15, 16]. Nevertheless, the improvement became attenuated and **non-significant** compared with **the** preoperative condition after a seven-year follow-up [14]. One British study, defining clinical depression as a medical diagnosis recorded in the British Clinical Practice Research

Datalink, found that **a sample of** 3045 patients had **an** increased prevalence of depression **compared with their preoperative status, although the difference was not statistically significant** [10]. Similarly, a Swedish obese intervention study **reported** that peak improvements **in** health-related quality of life (HRQL) in the surgical group were observed during the first year of weight loss [27]. Interestingly, a cohort study in Norway compared changes in comorbidities and mood status **a group receiving surgery and groups receiving specialized medical care** and found that although the surgical groups maintained greater reduction of hypertension and diabetes, **they also had a significantly higher incidence of new cases of MDD**[28]. A meta-analysis also found that the evidence regarding the association between mental health conditions and postoperative weight loss was conflicting [29]. We wonder what factors might have resulted in new **cases of** MDD after **weight reduction and the remission of obesity-related comorbidities.**

Strikingly, the risk of MDD increased 3.01-fold in the malabsorptive surgery **group** and 1.51-fold in the restrictive surgery **group** compared with controls, implying that malabsorption plays a more important role **than restricted food intake** in MDD development. “Malabsorptive” operations combine two methods: restriction and malabsorption. Taking gastric bypass (RYGB: Roux-en-Y gastric bypass) as an example, the superior part of the stomach is cut **down to a small pouch to restrict its**

food-storage capacity and the duodenum and jejunum **are bypassed to cause** malabsorption. “Restrictive” operations such as sleeve gastrectomy and gastric banding **essentially decrease the size of the stomach.** Therefore, malabsorptive procedures are more effective **than restrictive procedures** in weight reduction, but patients tend to have poorer digestion and absorption **with the former type** [30, 31].

Accordingly, clinical guidelines have urged caution against micronutrient deficiency after bariatric surgery [19, 32, 33]. To date, no study has examined the association between micronutrient deficiency and depression after bariatric surgery, despite their theoretical relation. One review examined the association between nutrition and depression, and found that deficiencies of micronutrients (folate and vitamin B₁₂) and trace minerals (iron, zinc, and selenium) tended to be more common among depressed than non-depressed persons [34]. Folate and vitamin B₁₂ are two of **the** most **commonly** deficient micronutrients after bariatric surgery [35, 36]. The prevalence of folate deficiency was similar among malabsorptive and restrictive operations, whereas vitamin B₁₂ deficiency was more prevalent with malabsorptive operations **than with restrictive operations** [36]. Iron, zinc, and selenium **are absorbed by** the duodenum and jejunum. Therefore, patients undergoing bariatric surgery, especially those receiving malabsorptive procedures, are recommended to receive postoperative nutritional supplementation [19, 31, 33]. Currently, dietetic counseling is mandatory

during the first year but optional later [19]. There is **not yet a** consensus on how long nutritional deficiencies should be monitored after surgery, **and patients' needs vary depending on** surgical type, categories of nutrients, and the year surgery was received [37]. In our study, the incidence of MDD increased 4 years after surgery compared with the controls, implying **that** the postoperative **nutrient** deficiency might progress slowly and is related to the late onset of MDD. Therefore, long-term monitoring for nutritional support after bariatric surgery is necessary.

The prevalence and incidence of MDD **vary** among different ages, periods, cohorts, and countries. In the elderly in Taiwan, for example, the prevalence of MDD was 5.9%, which was **the highest among the** different age **groups** [38]. In different periods, the cumulative prevalence of MDD increased from 1.67 to 17.24 per 1000 and the annual incidence of treated MDD increased from 1.89 to 2.58 per 1000 in 10 years [39]. Furthermore, the lifetime prevalence for MDD ranges from 1.5 cases per 100 adults in Taiwan to 19.0 cases per 100 adults in Beirut. **In addition,** the annual incidence of MDD **ranges** from 0.8 cases per 100 adults in Taiwan to 5.8 cases per 100 adults in New Zealand [40]. In our current study, the **overall** incidence of MDD (surgical: control= 6.40:3.81 per 1000 **person-years**) was higher than **the incidence** **in** the Taiwanese population (2.58 per 1000 year-person), but **lower than** in western countries.

This study has several limitations. First, although we performed propensity score matching and excluded preoperative depression history in both groups to minimize the impact of measured covariates, our findings cannot demonstrate unobserved confounding factors. As our study used a matched controlled cohort, the estimated HRs addressed only the **correlation**, not the causal **relationship**, between bariatric surgery and **the** incidence of MDD. To minimize probable confounders, we excluded subjects with history of depression prior to surgery in both groups, and we matched comorbidities in controls by propensity scoring. More convincingly, compared to previous studies which tended to employ questionnaires, our study sought to minimize self-reported bias by defining MDD using medical records plus antidepressant prescriptions. Second, data on **body mass index (BMI) before and after** surgery were not available. Using ICD-9-CM diagnostic codes, we included all subjects with severe obesity defined as either $BMI \geq 40 \text{ kg/m}^2$ or $BMI \geq 35 \text{ kg/m}^2$ plus at least one comorbidity; however, the NHIRD did not record the severity of obesity. Although there was no record of BMI in our database, the previous investigation and meta-analysis implying the relationship regarding the degree of weight reduction and remission of MDD was inconsistent [9, 18, 29]. Third, we were unable to assess the use of self-**administered** medications and nutritional supplements, which may have altered moods and nutrition status. Despite the limitations, the data is longitudinal and

nationally representative. There are very few studies that have looked at the association between bariatric surgery and new onset MDD postoperatively.

In conclusion, our study demonstrates that severely obese patients undergoing bariatric surgery had **a** higher risk of MDD than the matched controls, with the difference at a significant level 4 years after surgery. The **elevated** risk of MDD was more **severe** in patients receiving malabsorptive than restrictive procedures. The association between micronutrient deficiencies and depression after bariatric surgery warrants further investigation. Understanding the long-term outcomes of bariatric surgery **in terms of** MDD should be a priority for public health policy.

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Table 1. Baseline Characteristics of the Patients Receiving Bariatric Surgery and the

Matched Controls

	Matched Controls N=6493	Bariatric Surgery N=2302
<u>Years of follow-up</u> , mean(SD)	4.98 (2.06)	4.89 (2.17)
Age (years), mean (SD)	32.8 (10.7)	32.2 (9.8)
Age group, n (%)		
0-19	414 (6.4)	153 (6.7)
20-34	3846 (59.2)	1366 (59.3)
35-49	1825 (28.1)	643 (27.9)
50-64	400 (6.2)	137 (6.0)
≥65	8 (0.1)	3 (0.1)
Sex, n (%)		
Male	2498 (38.5)	877 (38.1)
Female	3995 (61.5)	1425 (61.9)
CCI, n (%)		
0	4935 (76.0)	1721 (74.8)
1-2	1191 (18.3)	440 (19.1)
≥3	367 (5.7)	141 (6.1)
Year of morbid obesity diagnosis, n (%)		
≤2005	1703 (26.2)	594 (25.8)
2006-2007	2046 (31.5)	724 (31.5)
2008-2009	2744 (42.3)	984 (42.7)
Diabetes, n (%)	699 (10.8)	261 (11.3)
Hypertension, n (%)	1280 (19.7)	430 (18.7)
Hyperlipidemia, n (%)	917 (14.1)	337 (14.6)

The propensity score matched controls were matched by age, sex, CCI, history of diabetes, hypertension, hyperlipidemia, and year of morbid obesity diagnosis.

Abbreviation: CCI, Charlson Comorbidity Index.

Table 2. Risk of Major Depressive Disorder in Patients Receiving Bariatric Surgery

Compared With Matched Controls, by Type of Surgical Procedure

	N	Event	Person-years	Incidence †	HR	Adjusted HR
Matched Controls	6493	123	32304.48	3.81	1.0	1.0
Bariatric surgery	2302	72	11247.87	6.40	1.69 (1.26-2.26)**	1.70 (1.27-2.27)**
Malabsorptive procedure	337	16	1534.69	10.43	2.76 (1.64-4.65)**	3.01 (1.78-5.09)**
Restrictive procedure	1965	56	9713.17	5.77	1.52 (1.10-2.08)*	1.51 (1.10-2.07)*

Adjusted HR was adjusted for age, sex, Charlson Comorbidity Index, history of diabetes, hypertension, hyperlipidemia, and year of morbid obesity diagnosis.

Malabsorptive procedures included ICD-9-CM 44.31 (high gastric bypass), 44.38 (laparoscopic gastroenterostomy), and 44.39 (other gastroenterostomy without gastrectomy).

Restrictive procedures included ICD-9-CM 43.82 (laparoscopic sleeve gastrectomy), 43.89 (open and other partial gastrectomy), 44.68 (laparoscopic gastroplasty), 44.69 (other repair of stomach), 44.95 (laparoscopic gastric restrictive procedure), and 44.99 (other operations on stomach).

†Incidence was represented per 1000 person-years.

*P < 0.05; **p<0.001.

Table 3. Risk of Major Depressive Disorder in Patients Receiving Bariatric Surgery
and Matched Controls by Follow-Up Period

Time since index date (years)	N	Event	Person-years	Incidence †	HR	Adjusted HR
<1						
Matched Controls	6493	31	6409.02	4.84	1.0	1.0
Bariatric surgery	2302	11	2245.07	4.90	1.02 (0.51-2.02)	1.01 (0.51-2.02)
1-1.99						
Matched Controls	6287	23	6170.81	3.73	1.0	1.0
Bariatric surgery	2187	11	2155.36	5.10	1.37 (0.67-2.81)	1.38 (0.67-2.83)
2-2.99						
Matched Controls	6018	23	5859.23	3.93	1.0	1.0
Bariatric surgery	2102	10	2046.67	4.89	1.25 (0.59-2.62)	1.25 (0.59-2.62)
3-3.99						
Matched Controls	5606	16	4903.98	3.26	1.0	1.0
Bariatric surgery	1934	11	1688.93	6.51	2.00 (0.93-4.30)	1.97 (0.92-4.25)
≥4						
Matched Controls	4221	30	9022.03	3.33	1.0	1.0
Bariatric surgery	1470	29	3132.90	9.26	2.81 (1.68-4.68)**	2.92 (1.75-4.88)**

Adjusted HR was adjusted for age, sex, Charlson Comorbidity Index, history of diabetes, hypertension, hyperlipidemia, and year of morbid obesity diagnosis.

†Incidence was represented per 1000 person-years.

*p<0.05; **p<0.001

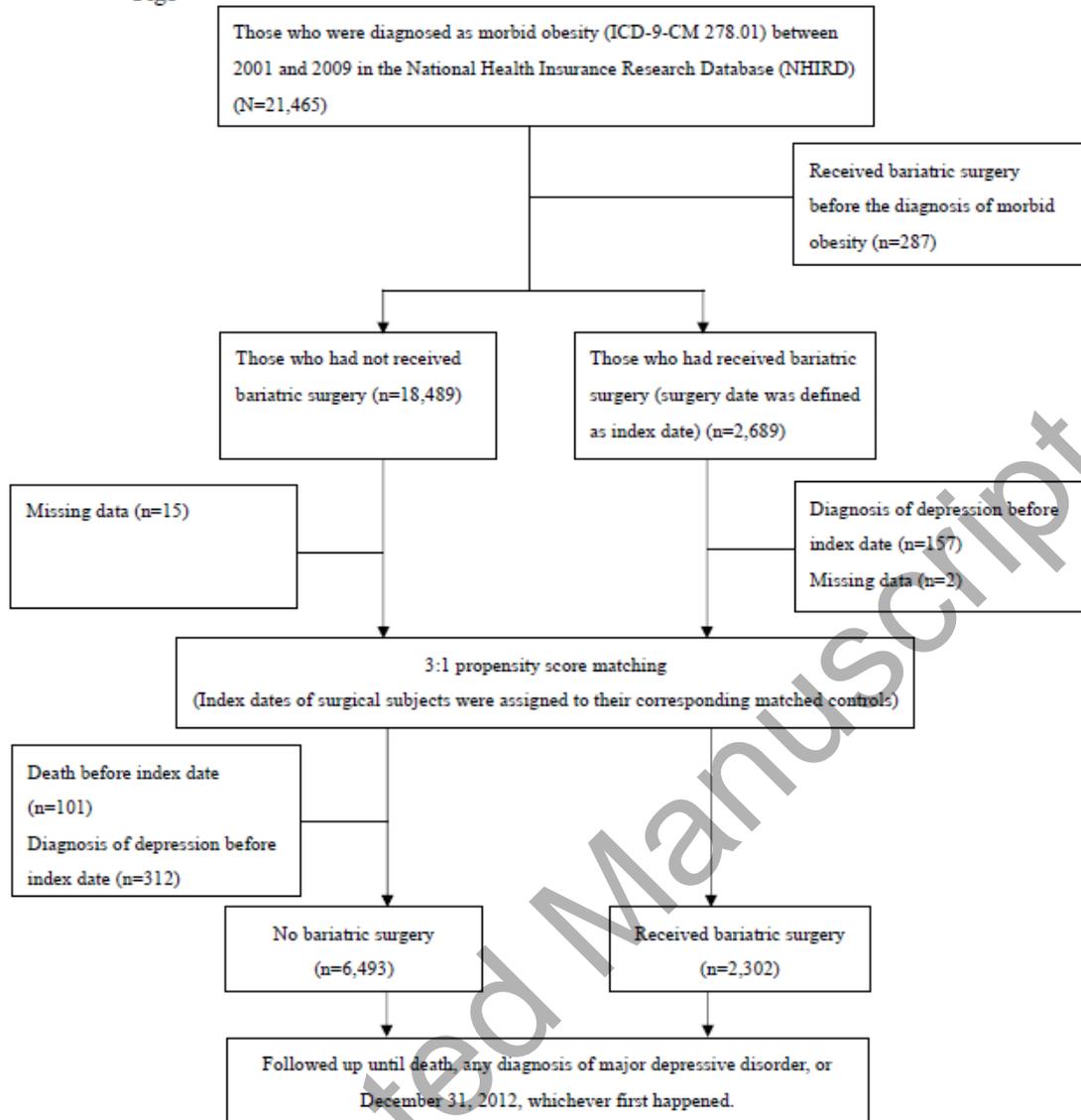
Figure Legend

Fig 1. Diagram showing the flow of subjects through the process of selection and matching.

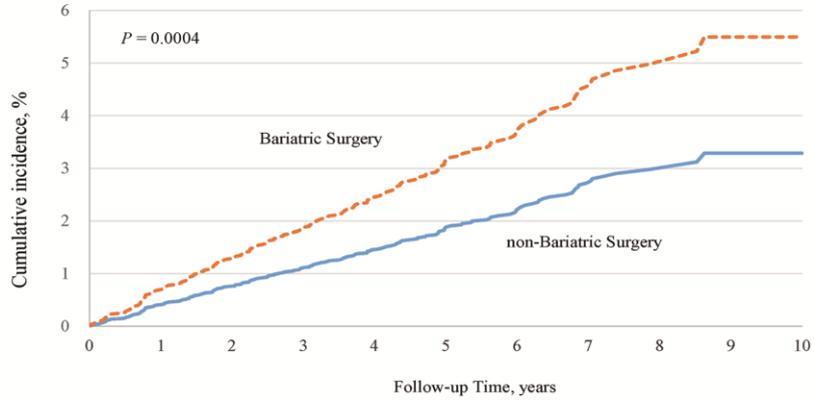
Fig 2. Cumulative incidence of major depressive disorder in patients receiving bariatric surgery and matched controls, using Cox proportional hazards regression analyses with adjustment for age, sex, Charlson Comorbidity Index, history of diabetes, hypertension, hyperlipidemia, and year of morbid obesity diagnosis.

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Fig1



Cox proportional hazards regression



		Follow-up Time, years											
Population at risk													
non-BS	6493	6287	6018	5606	4221	3009	2107	1285	512	67	16		
BS	2302	2187	2102	1934	1470	1013	664	434	240	64	0		
Event													
non-BS	0	31	54	77	93	106	113	121	122	123	123		
BS	0	11	22	32	43	53	60	67	71	72	72		

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