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ORIGINAL ARTICLE

Epidemiology/Genetics

Non-alcohol substance use disorder after bariatric surgery in the prospective, controlled Swedish Obese Subjects study

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Abstract

Objective: The goal of this study was to investigate whether bariatric surgery is associated with substance use disorder (SUD) with substances other than alcohol.

Methods: The prospective, controlled Swedish Obese Subjects study enrolled 2010 patients with obesity who underwent bariatric surgery (gastric bypass $n = 265$; vertical banded gastroplasty $n = 1369$; gastric banding $n = 376$) and 2037 matched control individuals receiving usual obesity care. Participants with SUD other than alcohol use disorder were identified using *International Statistical Classification of Diseases* (ICD) codes from the Swedish National Patient Register (covering treatment in hospital but not primary care). Those with a history of non-alcohol SUD were excluded. Median follow-up was 23.8 years.

Results: During follow-up, non-alcohol SUD incidence rates per 1000 person-years with 95% CI were 1.6 (0.8–3.1), 0.8 (0.5–1.2), 1.1 (0.5–2.2), and 0.6 (0.4–0.8) for gastric bypass, vertical banded gastroplasty, gastric banding, and control individuals, respectively. Only gastric bypass was associated with increased incidence of non-alcohol SUD (adjusted hazard ratio 2.54 [95% CI: 1.14-5.65], $p = 0.022$) compared with control participants.

Conclusions: Gastric bypass surgery was associated with increased risk of non-alcohol SUD, and this should be considered in long-term postoperative care.

INTRODUCTION

In carefully selected patients with obesity, bariatric surgery is a safe and effective treatment, resulting in long-term weight loss, reduced risk of obesity comorbidities, such as diabetes and

See Commentary, pg. 1979.

cardiovascular disease [1–4], and longer life expectancy [5, 6]. In addition, most studies also have reported improvements in quality of life after bariatric surgery [7]. However, bariatric surgery is not without risks and both short- and long-term side effects of this treatment have been described [1].

One previously acknowledged side effect of bariatric surgery is an increased intoxication level after alcohol consumption. Risk of rapid and heightened peak of alcohol concentrations in the blood has been clearly described for gastric bypass surgery [8–10], but sleeve gastrectomy may also result in increased risk of alcohol intoxication [11]. It has subsequently been reported that gastric bypass surgery is associated with an increased incidence of alcohol abuse [12–14]. In 2016, the American Society for Metabolic and Bariatric Surgery published a position statement concluding that gastric bypass surgery is associated with increased risk of developing alcohol use disorder [15]. In recent years, studies have indicated that substances other than alcohol may also be overconsumed after bariatric surgery. As an example, an increased risk of hospitalization for substance use disorder (SUD) with substances other than alcohol has been observed for patients undergoing gastric bypass surgery compared with the general population [16]. It has also been shown that self-reported illicit drug use was higher after gastric bypass surgery compared with gastric banding [17]. Furthermore, increased use of prescribed medications such as opioids and hypnotics and/or sedatives [16, 18] has also been reported following gastric bypass surgery compared with the general population or individuals with obesity. This suggests that a possible link between bariatric surgery and SUD with substances other than alcohol warrants further investigation. To this end, we examined the association between bariatric surgery and the incidence of SUD (excluding alcohol use disorder) in the prospective, controlled Swedish Obese Subjects (SOS) study.

Study Importance

What is already known?

- Alcohol use disorder is a well-described side effect for some bariatric procedures, but less is known about abuse of other substances.

What does this study add?

- The incidence of non-alcohol substance use disorder was increased after gastric bypass surgery compared with control individuals receiving usual obesity care.

How might these results change the direction of research or the focus of clinical practice?

- The risk of non-alcohol substance use disorder should be considered in the care of patients treated with gastric bypass surgery.

METHODS

Seven ethics review boards in Sweden (Gothenburg, Karolinska Institute, Linköping, Lund, Umeå, Uppsala, Örebro) approved the study protocol. All patients provided written or oral informed consent. The study has been registered at ClinicalTrials.gov (NCT01479452).

Study participants and interventions

The SOS study is a nonrandomized, matched, prospective study comparing bariatric surgery with usual obesity care. The study involved 25 public surgical departments and 480 primary health care centers throughout Sweden. Inclusion criteria were age between 37 and 60 years and body mass index (BMI) of at least 34 kg/m^2 for men and 38 kg/m^2 for women. The exclusion criteria were the following: earlier operation for gastric or duodenal ulcer, earlier bariatric surgery, gastric ulcer during the past 6 months, myocardial infarction during the past 6 months, ongoing malignancy or active malignancy during the past 5 years, bulimic eating pattern, psychiatric or cooperative problems contraindicating bariatric surgery, drug or alcohol (>0.75 L 40% liquor per week or corresponding ethanol amount) abuse, other contraindicating conditions (e.g., antiphlogistic treatment, continuous glucocorticoid).

In total, 4047 patients were included between September 1, 1987, and January 31, 2001. The surgery group ($n = 2010$) consisted of patients electing bariatric surgery, and the type of bariatric surgery (nonadjustable or adjustable gastric banding $n = 376$, vertical banded gastroplasty [VBG] $n = 1369$, or gastric bypass $n = 265$) was determined by the surgeon. A contemporaneously matched control group of 2037 individuals was created using 18 matching variables [19]. Patients in the control group were given the usual obesity care provided by their primary health care centers. This treatment was not prespecified by the study protocol and it varied between centers. Details on weight loss attempts in the control group during the first 10 years of the study have been reported [20].

In the current study, the per-protocol principle was applied in all analyses. In addition, patients with previous SUD ($n = 27$) were excluded from the analyses.

Data collection, outcomes, and covariates

The primary end point of the SOS study was overall mortality [21], although the original SOS study protocol from 1987 also specified that negative effects of the included treatments should be reported. Power calculations were based on the primary end point.

Data on SUD diagnoses during follow-up were obtained using *International Statistical Classification of Diseases* (ICD) codes from the Swedish National Patient Register (NPR). The NPR contains data on all diagnoses during hospital stays (from 1964) or hospital-based outpatient care (from 2001). ICD-8, ICD-9, and ICD-10 codes used to define a SUD diagnosis are presented in Table 1. These ICD

TABLE 1 ICD codes used for identification of SUD events in the National Patient Register and number of events for each code

ICD code	Description	Events in control group, $n = 2030$	Events in gastric banding group, $n = 373$	Events in VBG group, $n = 1353$	Events in gastric bypass group, $n = 264$
Person-years of follow-up		42,770	6582	27,084	5542
ICD-10					
F11[a]	Opioid related disorders	5[b]	2	9	3
F12[a]	Cannabis related disorders	0	0	0	0
F13[a]	Sedative, hypnotic, or anxiolytic related disorders	10[b]	2	10	3
F14[a]	Cocaine related disorders	0	0	2	0
F15[a]	Other stimulant related disorders	0	0	0	0
F16[a]	Hallucinogen related disorders	0	1	0	0
F18[a]	Inhalant related disorders	0	0	0	0
F19[a]	Other psychoactive substance related disorders	6	4	14	3
Z715[a]	Drug abuse counseling and surveillance	0	0	0	0
Z722[a]	Problems related to lifestyle, Drug use	0	0	0	0
ICD-9					
292[a]	Drug psychoses	0	0	0	0
304[a]	Drug dependence	2	1	1	0
305X[a]	Drug use disorder	2		1	0

Abbreviations: ICD, *International Statistical Classification of Diseases*; SUD, substance use disorder; VBG, vertical banded gastroplasty.
[a]Indicates a wild card search identifying all underlying codes.
[b]One patient in the control group had simultaneous F11 and F13 codes and is listed twice. In addition to the codes in the table, ICD-8 codes (294.3[a], 304[a], 970.00, and 971[a]) were used to identify patients with non-alcohol SUD prior to inclusion in the study.

codes do not include codes for alcohol or tobacco use disorders. The cutoff date for the current report was December 31, 2020, and the median follow-up time was 23.8 years (interquartile range: 19.6–27.0 years).

BMI was calculated based on measured height and weight. Education level, alcohol consumption, and smoking were self-reported in questionnaires. Psychiatric care or psychiatric drug use was defined as previously described [22] based on ICD codes in NPR or self-reported use of psychiatric drugs.

Statistical analysis

Patients were censored at the date of emigration or death. Two patients in the surgery group withdrew consent and one obtained an unlisted identity number, making linkage impossible, and they were therefore censored immediately after inclusion in the study. Control patients who underwent bariatric surgery ($n = 288$ out of 2030) and patients in the surgery group who underwent surgical reinstatement during follow-up ($n = 100$ out of 1990), for example band removal, were censored at the time of this surgery [23]. In addition, patients undergoing a conversion to other bariatric procedures [23] were also censored at the date of this surgery. Three patients included in the surgery group never received the intervention and were, in the current analysis, included in the control group.

Mean values and standard deviations (SD) were used to describe baseline characteristics of the participants. Differences between group means were analyzed with one-way ANOVA (continuous variables) or Fisher exact tests (dichotomous variables). Time-to-first SUD event was analyzed using Kaplan–Meier estimates of cumulative incidence. Differences in rates of SUD events between groups were compared with log-rank tests. Cox proportional hazard models were used to estimate the differences between surgery and control groups or between the groups defined by different surgical techniques. Unadjusted analyses as well as analyses adjusted for preselected baseline risk factors for SUD (age, sex, BMI, current smoking, alcohol consumption, educational level, psychiatric care or psychiatric drug use, and year of inclusion in the study) were performed. Differences between groups were expressed as hazard ratios (HR) or adjusted HR with 95% confidence intervals (CI). Statistical analyses were carried out using Stata, version 14 (StataCorp LP), and p values below 0.05 were considered to be statistically significant.

RESULTS

Baseline characteristics and weight changes during follow-up

Baseline characteristics of the SOS study participants included in the current analysis are shown in Table 2. After exclusion of patients with non-alcohol SUD prior to inclusion, the study population consisted of 2030 patients in the control group and 373, 1353, and 264 patients in the gastric banding, VBG, and gastric bypass groups, respectively.

TABLE 2 Baseline characteristics of the participants

Variable	Control group, *n* = 2030	Banding group, *n* = 373	VBG group, *n* = 1353	GBP group, *n* = 264
Age (y)	48.7 (6.3)	47.6 (6.0)	47.1 (5.9)	47.0 (6.0)
BMI (kg/m^2)	40.1 (4.7)	41.7 (4.3)	42.3 (4.4)	43.8 (5.2)
Sex (% male)	29.2	31.1	29.0	28.4
Alcohol intake (g/d)	5.3 (8.1)	5.9 (7.8)	4.9 (7.1)	5.5 (7.2)
Current smoking	20.6	27.7	25.5	23.1
Ever smoking	57.7	68.0	68.1	64.8
University education	21.1	9.9	13.2	14.8
Psychiatric care or psychiatric drug use	15.5	19.6	16.1	17.8
Year of inclusion	1994.3 (3.5)	1993.1 (3.3)	1993.9 (3.1)	1996.6 (3.6)

Note: Data are presented as % or as means (SD).
Abbreviations: Banding, gastric banding; GBP, gastric bypass; VBG, vertical banded gastroplasty.

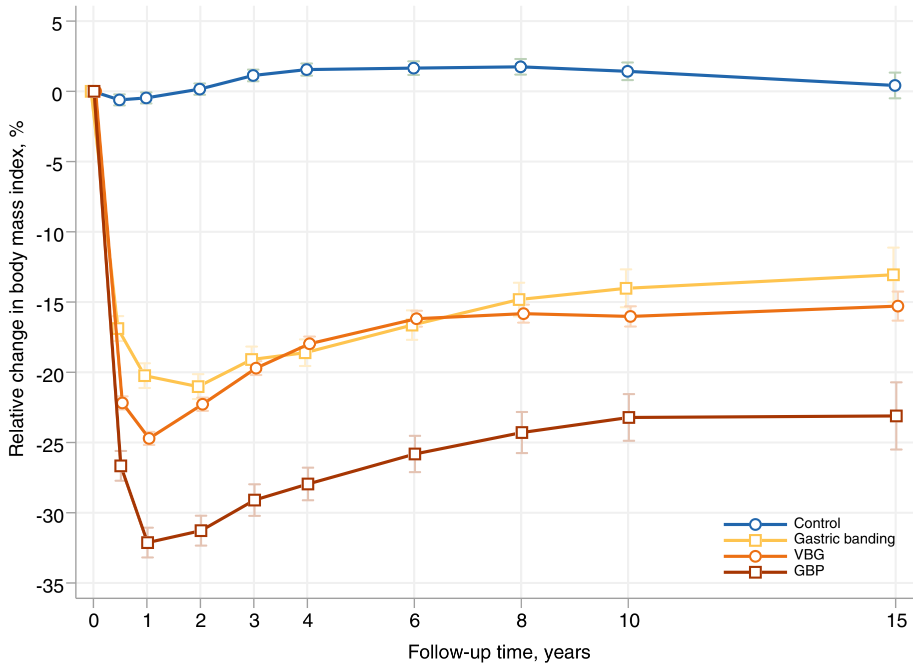

FIGURE 1 BMI change in the SOS study. GBP, gastric bypass; SOS, Swedish Obese Subjects; VBG, vertical banded gastroplasty

Patients in the three surgical groups were younger, had higher BMI, were more often current or former smokers, and were less likely to have a university level education as compared with patients in the control group (Table 2).

Patients in the three surgery groups experienced a rapid reduction of BMI during the first year after surgery, and this was followed by a weight regain, whereafter BMI stabilized after approximately 8 to 10 years of follow-up (Figure 1). BMI changes in the control group during follow-up were, on average, small (Figure 1).

Incidence of SUD

During follow-up, non-alcohol SUD was diagnosed in 24 patients in the control group (incidence rate/1000 person-years [IR/1000 p-y], 0.6 [95% CI: 0.4–0.8]). Nine patients in the gastric bypass group (IR/1000 p-y: 1.6, 95% CI: 0.8–3.1), twenty-one patients in the VBG group (IR/1000 p-y: 0.8, 95% CI: 0.5–1.2), and seven patients in the gastric banding group (IR/1000 p-y: 1.1, 95% CI: 0.5–2.2) were diagnosed with non-alcohol SUD during follow-up (log-rank test $p = 0.035$). The numbers of events for specific SUD diagnoses are shown in Table 1. The most common diagnoses were other psychoactive substance related disorders (ICD-10 code, F19), sedative, hypnotic, or anxiolytic related disorders (F13), and opioid related disorders (F11). The cumulative incidence of non-alcohol SUD over 30 years of follow-up in the control and three surgery groups is shown in Figure 2 and the between-group Cox proportional hazard model comparisons are shown in Table 3. The incidence of non-alcohol SUD was higher in the gastric bypass group compared with the control group (HR = 2.88 [95% CI: 1.34–6.18], $p = 0.007$;

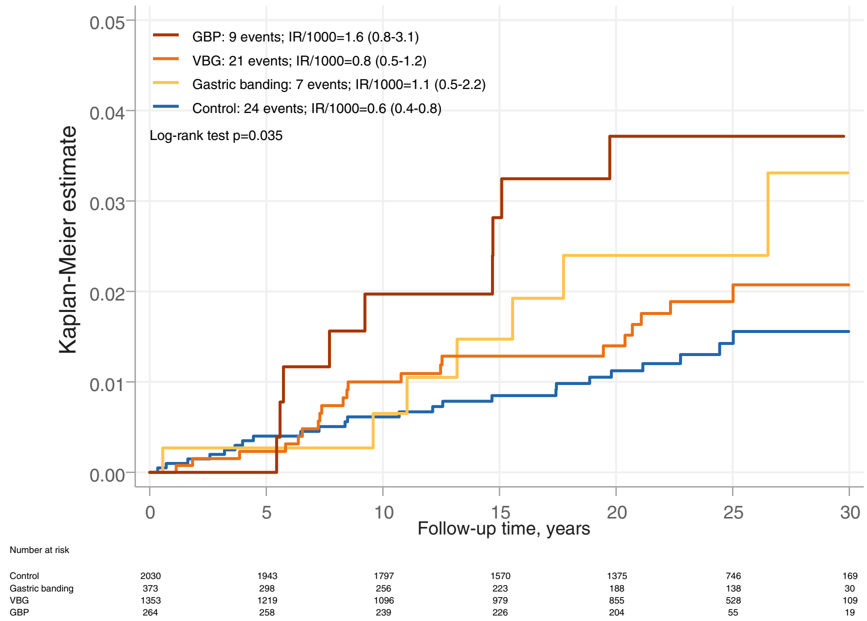

FIGURE 2 Cumulative incidence of non-alcohol SUD in the SOS study. SUD events were identified in the National Patient Register using ICD codes. The x-axis is truncated at 30 years but all observations were included in the analyses. GBP, gastric bypass; IR/1000, incidence rate/1000 person-years; SOS, Swedish Obese Subjects; SUD, substance use disorder; VBG, vertical banded gastroplasty

TABLE 3 Cox proportional hazard ratios for SUD with the surgery group stratified by surgical procedure

Comparison	Unadjusted HR (95% CI)	*p* value	Adjusted[a] HR (95% CI)	*p* value
GBP vs. control	2.88 (1.34–6.18)	0.007	2.54 (1.14–5.65)	0.022
VBG vs. control	1.38 (0.77–2.49)	0.279	1.41 (0.78–2.56)	0.260
Banding vs. control	1.92 (0.83–4.44)	0.130	1.68 (0.72–3.90)	0.228
GBP vs. banding	1.50 (0.56–4.01)	0.416	1.51 (0.53–4.30)	0.437
GBP vs. VBG	2.08 (0.96–4.53)	0.064	1.80 (0.78–4.19)	0.171
VBG vs. banding	0.72 (0.31–1.69)	0.453	0.84 (0.35–2.00)	0.692

Abbreviations: Banding, gastric banding; GBP, gastric bypass; HR, hazard ratio; VBG, vertical banded gastroplasty.
[a]Adjusted for baseline age, sex, BMI, current smoking, alcohol consumption, education level, psychiatric care or psychiatric drug use, and inclusion year.

adjusted HR = 2.54 [95% CI: 1.14–5.65], $p = 0.022$). In contrast, no difference in non-alcohol SUD incidence was observed between patients who had undergone VBG or gastric banding compared with control patients (Table 3). In addition, when the groups that had undergone different surgical procedures were compared with each other, no statistical difference in incidence of non-alcohol SUD was detected (Table 3).

DISCUSSION

In this study we examined the incidence of non-alcohol SUD after bariatric surgery or usual obesity care in the SOS study using register data. The results show that gastric bypass surgery was associated with an increased incidence of non-alcohol SUD. We have previously reported an association between alcohol abuse and gastric bypass surgery in the same cohort, and together, these results suggest that patients who have undergone gastric bypass surgery are at increased risk of addictive diseases.

The number of patients with SUD in the SOS cohort is low, and this may to some extent be explained by the exclusion of alcohol-related disorders in the current study. In addition, some individuals at high risk of SUD may have been prevented from participation in the SOS study because the exclusion criteria included drug or alcohol abuse or psychiatric or cooperative problems contraindicating bariatric surgery. Furthermore, there is always uncertainty when calculating the incidence or prevalence of substance use in a population, no matter which method is used. In the current study, SUD diagnoses were identified in the Swedish NPR. SUD diagnoses are most likely underreported, and, in addition, the register does not contain SUD events from primary care, meaning that less severe cases not requiring hospital stays and hospital-based outpatient care were not captured. Selfreports may also underestimate SUD, especially if individuals perceive negative outcomes of admitting substance use. Despite this, self-reported substance use data usually have a relatively high concordance with biochemically verified substance use [24, 25]. Hence, even though most methodological approaches to estimate substance abuse underestimate the absolute incidence and prevalence, the results are most likely robust as long as the same method of estimation is used for all groups compared. In doing so, as in this study, underreporting affects all groups similarly.

When investigating the effects of bariatric surgery, the study design is a key issue. Previous studies of the association between bariatric surgery and substance abuse have used different types of comparator groups. Some studies have included individuals with obesity [18, 26, 27] or the general population [16] as comparator groups. Other studies have used different types of bariatric procedures [17, 28, 29] as the comparator group whereas some have not included a comparator group at all [30, 31]. Such variability in experimental designs may influence the results. In addition, the previously mentioned studies [16–18, 26–31] have analyzed different outcomes, such as use of specific classes of drugs [18, 26, 27] or diagnosis-based criteria [16, 29], to address the association between bariatric surgery and substance abuse. These differences in study design make direct comparisons between our results and previous studies challenging; however, a synthesis of the current literature indicates that an association between gastric bypass surgery and non-alcohol SUD exists. Our observation that the incidence of non-alcohol SUD after gastric bypass surgery is higher compared with carefully matched control patients with obesity supports this.

There is currently no clear mechanistic explanation for the association between bariatric surgery and substance abuse. For the association between alcohol abuse and gastric bypass surgery, altered pharmacokinetics of alcohol after the operation [8–10] is the most plausible mechanistic explanation. Altered pharmacokinetics of orally administered substances, including morphine, after gastric bypass has been described [32], but the literature on this topic is very limited. An increased risk of non-alcohol SUD after gastric bypass surgery could also be related to the analgesia used during the bariatric procedure itself or reoperation. However, the relatively late separation of the SUD incidence curves (after 6–8 years of follow-up) indicates that analgesia after the primary bariatric procedure is probably not a major contributor to the increased incidence of SUD seen in this study. Other theories on why patients undergoing gastric bypass surgery develop SUD include the concept of “addiction transfer/behavioral substitution” [33, 34] or that gastric bypass surgery may change brain reward processing [35]. Additional studies designed to identify mechanisms are needed to explain the association between gastric bypass and SUD.

Our analyses of SUD in the SOS study have some limitations. The SOS study was not randomized owing to ethical considerations related to the high risks associated with bariatric surgery in the 1980s. Furthermore, because the SOS study is a long-term study started in the 1980s, the majority of patients have undergone older surgical procedures that are very rarely used today. Our study therefore includes a limited number of participants treated by gastric bypass and none treated by sleeve gastrectomy. Furthermore, the NPR does not include visits to primary health care centers and therefore a number of SUD events may have been missed and the incidence rates are subjected to underestimation. However, this underestimation of SUD events will most likely affect the surgery and the control groups in a similar way. Limitations in generalizability may also exist, for instance, the relevance for younger age groups or patients in countries with different availability of addictive substances. Major strengths of the current study include the long-term follow-up, the prospective design, the relatively large number of participants, and the well-matched control group.

CONCLUSION

We conclude that patients treated with gastric bypass have an elevated risk of non-alcohol SUD. Pre- and postoperative care of these patients should include assessment of the risk of substance abuse that extends beyond alcohol abuse. In addition, further studies specifically designed to address this risk, which include all currently used surgical procedures, are warranted.O

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov identifier NCT01479452.

DATA AVAILABILTY STATEMENT

The data are subject to legal restrictions according to national legislation. Confidentiality regarding personal information in studies is regulated in the Public Access to Information and Secrecy Act (SFS 2009:400), OSL. There is a possibility to apply to get access to public documents that an authority holds. In this case, the University of Gothenburg is the specific authority that holds the documents. A request to get access to public documents can be rejected or granted with reservations. If the authority refuses to disclose the documents the applicant is entitled to get a written decision that can be appealed to the administrative court of appeal.

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