Original Article
EPIDEMIOLOGY/GENETICS

Obesity

Change in Use of Sleep Medications After Gastric Bypass Surgery or Intensive Lifestyle Treatment in Adults with Obesity

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Objective: To examine the change in use of hypnotics and/or sedatives after gastric bypass surgery or intensive lifestyle modification in adults with obesity.

Methods: Adults with obesity who underwent gastric bypass surgery or initiated intensive lifestyle modification between 2007 and 2012 were identified through the Scandinavian Obesity Surgery Registry and a Swedish commercial weight loss database. The two cohorts were matched on BMI, age, sex, education, history of hypnotics and/or sedatives use, and treatment year (surgery $n = 20{,}626$; lifestyle $n = 11{,}973$; 77% women, mean age 41 years, mean BMI 41 kg/m^2). The proportion of participants with filled hypnotics and/or sedatives prescriptions was compared yearly for 3 years.

Results: In the matched treatment cohorts, 4% had filled prescriptions for hypnotics and/or sedatives during the year before treatment. At 1 year follow-up, following an average weight loss of 37 kg and 18 kg in the surgery and intensive lifestyle cohorts, respectively, this proportion had increased to 7% in the surgery cohort but remained at 4% in the intensive lifestyle cohort (risk ratio 1.7; 95% CI: 1.4-2.1); at 2 years, the proportion had increased to 11% versus 5% (risk ratio 2.0; 95% CI: 1.7-2.4); and at 3 years, it had increased to 14% versus 6% (risk ratio 2.2; 95% CI: 1.9-2.6).

Conclusions: Gastric bypass surgery was associated with increased use of hypnotics and/or sedatives compared with intensive lifestyle modification.

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Introduction

Between 1980 and 2014, the worldwide prevalence of obesity increased rapidly to 10.8% in men and 14.9% in women and in Sweden to 21.4% in men and 18.6% in women (1). The corresponding prevalences for class III obesity (BMI $\geq$ 40 kg/m^2) were 0.6%, 1.6%, 0.9%, and 1.5%, respectively (1). This is concerning because obesity affects various aspects of health (2), including sleep (3).

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Disclosure: IN is the previous director of the Scandinavian Obesity Surgery Registry. JO is the current director. CM, MN, and JS report receiving consulting fees for participation in the scientific advisory committee of Itrim. Further, MN has received research grants from Pfizer, Cambridge Weight Plan, Novo Nordisk, and Astra Zeneca; royalty payments from Studentlitteratur for coauthoring chapters in a Swedish textbook on obesity; and lecture or consulting fees from Pfizer, Sanofi-Aventis, Roche, and Strategic Health Resources. AP and JES have participated in a Novo Nordisk advisory board. The other authors declared no conflict of interest.

Author contributions: WLN and MN drafted the manuscript and carried out the statistical analysis. All authors critically revised the manuscript for important intellectual content and contributed to and approved the final version. They are the guarantors. WLN, MN, GB, AP, and JES conceived and designed the study. MN acquired the data, provided administrative, technical, and material support, and supervised the study. MN and GB had full access to all of the data in the study. WLN and MN take full responsibility for the integrity of the data and the accuracy of the data analysis as well as the final decision to submit for publication.

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Obesity has been associated with sleep disorders such as obstructive sleep apnea, insomnia, and restless leg syndrome (3). Perhaps as a consequence, individuals with obesity have also been found to use more hypnotics and/or sedatives than individuals without obesity (4). Weight loss interventions have been shown to improve a range of sleep parameters, mostly those associated with obstructive sleep apnea (5,6), but their effect on use of hypnotics and sedatives is unclear. This is an important area to address, as use of hypnotics and sedatives has been associated with vehicle accidents (7), fall-related injuries (8), cognitive decline (9), and mortality (10).

Using Swedish nationwide and virtually complete registers, we aimed to assess the effect of weight loss through gastric bypass surgery versus intensive lifestyle modification on use of hypnotics and/or sedatives in adults with obesity. We hypothesized that the use of hypnotics and sedatives would decrease following weight loss due to improvements in obesity-related sleep disorders and to a greater degree after gastric bypass surgery than intensive lifestyle modification, due to the higher magnitude of weight loss after surgery.

Methods

This study included individuals from the Scandinavian Obesity Surgery Registry (SOReg), which is a nationwide prospective registry of bariatric surgery patients, and the Itrim Health Database, which is a registry of individuals who underwent weight loss through a low- or very-low-calorie diet (LCD/VLCD) with lifestyle modification (11-14). Individuals were linked to the nationwide Swedish Prescribed Drug Register, health registers at the National Board of Health and Welfare, and Statistics Sweden using the Swedish personal identity number, a unique identifier for each Swedish resident.

All analyses were conducted on deidentified data, and the study was approved by the regional ethics review board in Stockholm, Sweden. Participants were given the option to opt out of the registries.

Data sources

SOReg. SOReg is a nationwide registry for patients who undergo bariatric surgery in Sweden (13). It is currently estimated to cover approximately 99% of all bariatric surgeries, including both public and private provision. Data on various health factors, including BMI, are collected as part of clinical practice and recorded electronically.

The Itrim Health Database. The Itrim Health Database contains health information on participants of a commercially available intensive lifestyle modification program in Sweden. Baseline and quarterly follow-up data on various health factors, including BMI, were collected from 35 Itrim centers across Sweden, utilizing the same information technology platform.

The Prescribed Drug Register. The Prescribed Drug Register records all filled prescriptions in Sweden. It contains detailed individual-level information on the date, type, and amount of prescriptions filled. We accessed data on prescriptions registered between July 1, 2005, and September 30, 2015.

Other registers. Data on age, sex, education, and emigrations were collected for each individual from the Longitudinal Integration Database for Health Insurance and Labor Market Studies, the Education Register, and the Total Population Register (15) at Statistics Sweden. Data on hospital visits and deaths were available through linkage with the National Patient Register and the Causes of Death Register at the National Board of Health and Welfare.

Inclusion and exclusion criteria

We restricted the study population to individuals who were at least 18 years old, with a BMI between 30 and 50 kg/m^2 at the start of treatment. SOReg patients undertaking nongastric bypass surgery were excluded (2%). As we required each individual to have prescription data from 2 years prior to 3 years after initiation of treatment, we restricted the study population to those who initiated treatment between July 1, 2007, and September 30, 2012. Individuals who emigrated after treatment initiation were excluded from the study (SOReg: $n = 126$, Itrim: $n = 54$).

Matching

Individuals from SOReg and Itrim were matched on treatment year and the set of covariates identified through a directed acyclic graph (Supporting Information Figure S1) (16) built using DAGitty v.2.3 (DAGitty software, Utrecht, Netherlands) (17). The minimal sufficient adjustment set for producing an unbiased estimate of the total effect of bariatric surgery on sleep problems included age, sex, socioeconomic status, baseline BMI, and sleep problems prior to treatment. We used data on education levels as a proxy for socioeconomic status (18).

Coarsened exact matching techniques were used, which involves categorizing values of each matching factor into substantively meaningful groups (Supporting Information Table S1) upon which exact matching was then performed (19). To minimize loss of information, we allowed matching strata to include different numbers of surgery patients and intensive lifestyle modification participants.

Exposures

Patients in the surgery cohort (from SOReg) underwent gastric bypass. Participants in the intensive lifestyle treatment cohort (from Itrim) underwent a 3-month dietary weight loss phase facilitated by LCD or VLCD, followed by a 9-month weight maintenance phase (Supporting Information Methods S1) (11). The choice of LCD or VLCD was based on the participants' baseline BMI, personal preference, and contraindication status. Treatment with LCD/VLCD produces a greater degree of weight loss than other nonsurgical treatments (11,20) and was selected as the comparator cohort due to presence of obesity and intention to lose weight.

Outcome and follow-up

The main outcome was hypnotics and/or sedatives prescriptions filling, identified via the nationwide Prescribed Drug Register through the World Health Organization Anatomical Therapeutic Chemical (ATC) codes under N05C (Supporting Information Table S2). Medications were excluded if their primary indication included health conditions other than sleep problems, such as mental health disorders (clomethiazole [N05CM02] and Valerianae radix [N05CM09]). Midazolam (N05CD08) was excluded as it is indicated for preoperative sedation. Collectively, the excluded medications constituted

0.26% of all sleep medication prescriptions in the matched data set throughout the entire study period.

The categorical outcome was defined as the proportion of individuals with at least one filled prescription of the selected medications in a given year. The continuous outcome was defined as annual mean treatment dose of hypnotics and/or sedatives, calculated as follows:

$$\frac{(Number\ of\ pills\ filled\ in\ a\ year) \times (dose\ per\ pill\ filled)}{defined\ daily\ doses}$$

where defined daily doses (DDDs) refers to the daily dose of a particular medication recommended by the World Health Organization (21).

Individuals were followed from treatment initiation until death or end of follow-up, whichever came first. All individuals in the current data set had at least 3 years follow-up. We also created a second matched data set composed of the subgroup of individuals with 5 years follow-up.

Covariates

Baseline weight and height measurements were used to calculate BMI. Poor mental health was defined as a history of inpatient stays or outpatient visits for psychiatric disorders (ICD10: F00-F99) and/or prescribed medications for mental health disorders (ATC codes: N06, N05A, and N05B). In the surgery cohort, information on use of continuous positive airway pressure (CPAP) was obtained during clinical examination at baseline. History of inpatient stays and outpatient visits for any cause were identified through the National Patient Register, and prescription history was identified from the Prescribed Drug Register.

Statistical analysis

We compared the proportion of individuals with filled hypnotics and/or sedatives prescriptions post treatment in the surgery and intensive lifestyle cohorts using a generalized linear model with log link, assuming a binomial distribution (or Poisson in the event of nonconvergence). Analyses were also performed using linear regression to estimate the mean between-cohort difference in annual treatment dose in individuals with filled hypnotic and/or sedative prescriptions prior to treatment. All analyses were weighted to take into account the different sizes of matching strata.

Subgroup analysis. Subgroup analyses and treatment interaction tests were performed by baseline age, sex, education level, BMI, and mental health status.

Within-group analysis. To assess dose-response relationship between BMI change and outcomes, we repeated the analyses comparing outcomes by tertiles of 1-year %BMI change separately for the surgery and the intensive lifestyle cohorts. In the surgery cohort, we also investigated the outcome in patients with versus without CPAP at baseline (CPAP use data were not available in the intensive lifestyle cohort).

Sensitivity analysis. We repeated the main analysis in the matched data set, additionally adjusting for the original matching variables (continuous age, continuous BMI, cumulative DDDs within 2 years prior to treatment, and treatment year), indicators of poor mental health, and history of health care contacts from 1 year to 2 years prior to treatment (measured through history of inpatient stays, outpatient visits, and filled prescription for any medications). Health care contacts in the year immediately prior to treatment (from 0 to 1 year prior to treatment) were not considered because they may be unusually high during that year, especially in the surgery cohort.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina) and Stata version 14 (StataCorp, College Station, Texas). A statistically significant finding was defined as a two-sided P value of < 0.05.

Results

Study population

Before matching, there were 24,291 individuals in the surgery cohort and 13,095 individuals in the intensive lifestyle treatment cohort. After matching, the numbers were 20,626 (85% of the starting sample) and 11,973 (91% of the starting sample), respectively (Supporting Information Figure S2).

Baseline characteristics

Before matching, surgery patients were more likely to be younger, have lower education, have higher BMI, and have filled hypnotics and/or sedatives prescriptions than intensive lifestyle participants. After matching, discrepancies across treatment cohorts were no longer detected, except for BMI, which remained 0.5 kg/m^2 (95% CI: 0.4-0.6; $P < 0.001$) higher in the surgery than the intensive lifestyle cohort (Table 1). In the matched sample, surgery patients were also more likely to have poor mental health and to have had health care contacts prior to treatment compared with the intensive lifestyle participants.

Weight loss and hypnotics and/or sedatives use after surgery and intensive lifestyle modification

The mean 1-year weight loss was 37 kg in the surgery and 18 kg in the intensive lifestyle cohort (mean difference 19 kg, 95% CI: 18-20; $P < 0.001$). The three most commonly prescribed hypnotics and sedatives were zopiclone, zolpidem, and propiomazine, accounting for 96% of all prescriptions in both treatment cohorts throughout the study period (Supporting Information Table S2 and Supporting Information Figure S3).

During follow-up, the risk of having filled hypnotics and/or sedatives prescriptions was higher in the surgery than the intensive lifestyle cohort, and the risk ratio increased with longer follow-up, peaking at 3 years (risk ratio 2.2, 95% CI: 1.9-2.6; $P < 0.001$; Figure 1). In the second matched data set, the proportion continued to increase for up to 5 years of follow-up (Figure 1).

Among those with filled hypnotics and/or sedatives prescriptions prior to treatment, mean treatment dose increased more in the surgery than the intensive lifestyle cohort, with a mean difference at 3 years of 57 DDDs (95% CI: 39-75; $P < 0.001$; Figure 2). In the second matched data set, the mean difference continued to increase for up to 5 years of follow-up (Figure 2).

TABLE 1 Baseline characteristics

Matching factor	Before matching			After matching		
	Surgery (n = 24,291)	Intensive lifestyle (n = 13,095)	Mean difference or risk ratio (95% CI)	Surgery (n = 20,626)	Intensive lifestyle (n = 11,973)	Mean difference or risk ratio (95% CI)
Mean age (y)	41.3 (10.9)	46.0 (12.0)	−4.7 (−5.0 to 4.5)	41.2 (10.7)	41.3 (11.1)	−0.1 (−0.3 to 0.0)
Men, *n* (%)	5,715 (23.5)	3,071 (23.5)	1.0 (1.0 to 1.0)	4,791 (23.2)	2,781 (23.2)	*Exactly matched*
University education, *n* (%)	5,173 (21.4)	6,203 (47.6)	0.4 (0.4 to 0.5)	4,514 (21.9)	2,620 (21.9)	*Exactly matched*
Mean BMI at screening (kg/m^2)	41.5 (4.0)	34.5 (3.8)	7.0 (6.9 to 7.1)	41.4 (4.0)	40.9 (4.2)	0.5 (0.4 to 0.6)
Filled hypnotics/sedatives prescriptions at 0-1 y pretreatment, *n* (%)	3,543 (14.6)	1,185 (9.1)	1.6 (1.5 to 1.7)	826 (4.0)	479 (4.0)	*Exactly matched*
Mean treatment dose (DDD)	317 (452)	188 (313)	129 (101 to 156)	70 (91)	67 (90)	3 (−1 to 7)
Filled hypnotics and/or sedatives prescriptions between 1-2 y pretreatment, *n* (%)	3,529 (14.6)	1,174 (9.0)	1.6 (1.5 to 1.7)	883 (4.3)	513 (4.3)	*Exactly matched*
Mean treatment dose (DDD)	288 (429)	190 (352)	97 (70 to 124)	65 (83)	66 (84)	0 (-5 to 4)
Other covariates						
Use of continuous positive airway pressure, *n* (%)	2,223 (9.2)	NA	NR	1,831 (8.9)	NA	NR
Indicators of poor mental health, *n* (%)	7,187 (29.6)	2,293 (17.5)	1.7 (1.6 to 1.8)	4,797 (23.3)	1,806 (15.1)	1.5 (1.4 to 1.7)
Health care contacts 1-2 y pretreatment						
Outpatient visits, *n* (%)	14,289 (58.8)	5,136 (39.2)	1.5 (1.5 to 1.5)	11,609 (56.3)	4,737 (39.6)	1.4 (1.3 to 1.5)
Inpatient stays, *n* (%)	3,483 (14.3)	1,274 (9.7)	1.5 (1.4 to 1.6)	2,688 (13.0)	1,238 (10.3)	1.3 (1.1 to 1.4)
Filled prescription for any medications, *n* (%)	21,778 (89.7)	10,577 (80.8)	1.1 (1.1 to 1.1)	18,241 (88.4)	9,751 (81.4)	1.1 (1.1 to 1.1)

All mean values are presented with standard deviations.
Mean difference is for continuous variables, and risk ratio is for categorical values.
All data were weighted to take into account different sizes of matching strata.
Indicators of poor mental health: inpatient stay or outpatient visit listing a mental health diagnosis, or filled prescriptions for mental health indications.
Proportions of individuals with filled hypnotics and/or sedatives prescriptions stratified by levels of matching factors in the unmatched data set are shown in Supporting Information Figure S6.
Abbreviations: DDDs, defined daily doses; NA, not available; NR, not relevant.

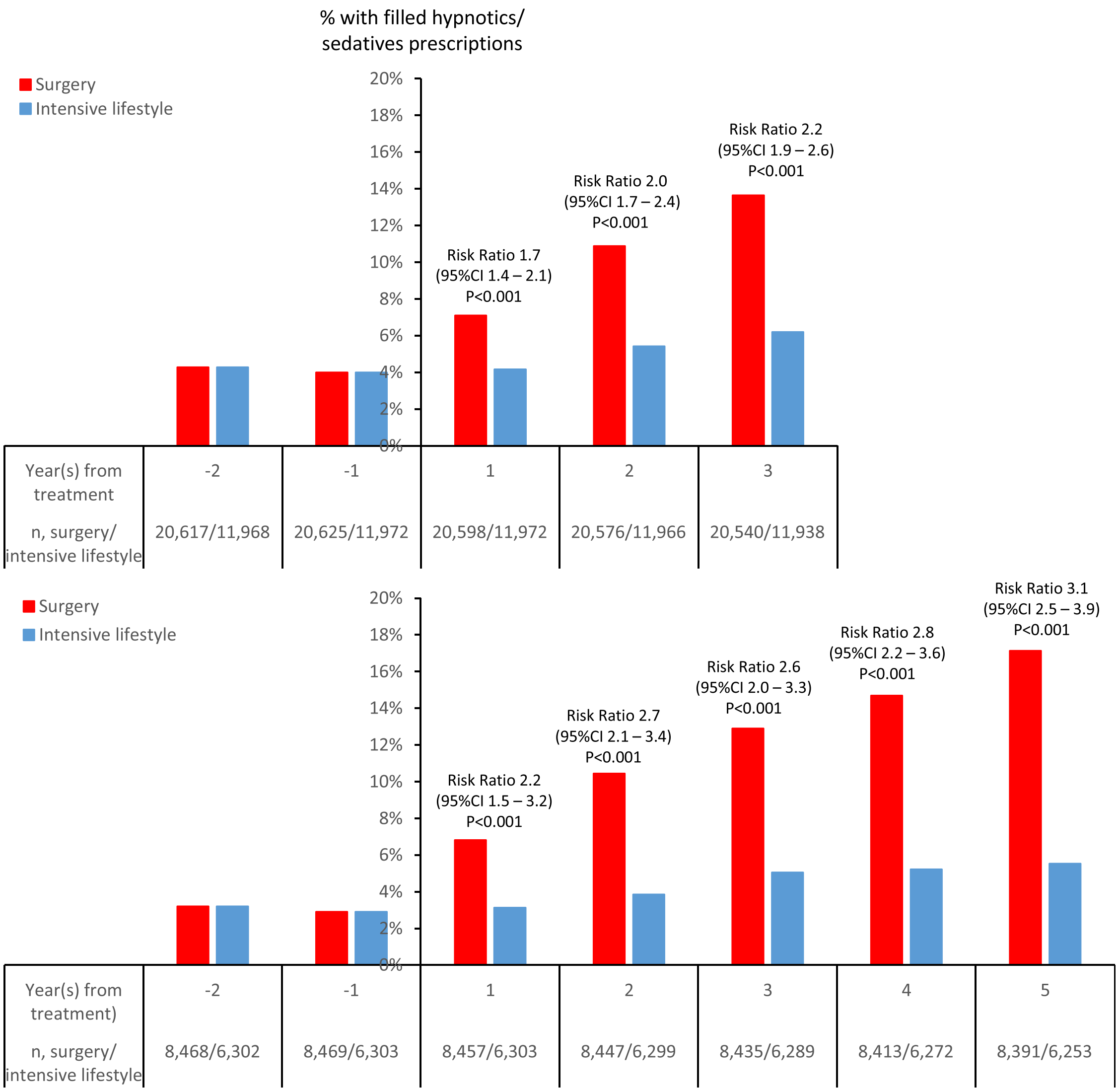


Figure 1 Proportion of patients with filled hypnotics and/or sedatives prescriptions in the matched study population with 3 years of follow-up (upper panel) and in the subgroup with 5 years of follow-up (lower panel). Risk ratios (95% CI) apply to the between-cohort differences at each follow-up time point. Baseline characteristics of subgroups with 5 years of follow-up are shown in Supporting Information Table S3. The proportion of patients with filled hypnotics and/or sedatives prescriptions in the unmatched study population is shown in Supporting Information Figure S4. [Color figure can be viewed at wileyonlinelibrary.com]

Adjustment for the original matching variables prior to categorization (Supporting Information Table S1) and/or indicators of poor mental health and/or history of health care contacts before treatment resulted in ≤ 0.2 change for risk ratios and ≤ 2 DDD change for mean differences, which remained statistically significant at all time points.

Subgroup analyses

In 12 out of 14 subgroups investigated, surgery patients were at greater risk of having filled hypnotics and/or sedatives prescriptions than intensive lifestyle participants during follow-up (Figure 3). Within each level of educational attainment, the risk was increased in the surgery compared to the intensive lifestyle cohort. We found a statistically significant interaction by baseline BMI, but there was no clear dose-response relationship.

In individuals with filled hypnotics and/or sedatives prescriptions prior to baseline, we did not find any treatment-subgroup interactions regarding dose, potentially due to low power (Figure 3).

Within-group analyses

Percent BMI change. No dose-response relationship was found for 1-year %BMI change and the outcome in either the surgery or the intensive lifestyle cohort (Figure 4).

Baseline use of CPAP (surgery only). The risk of having filled hypnotics and/or sedatives prescriptions 3 years after treatment did not differ by baseline use of CPAP. Among those with filled hypnotics and/or sedatives prescriptions at baseline, mean treatment dose increased more in patients without than with CPAP at baseline (Figure 4).

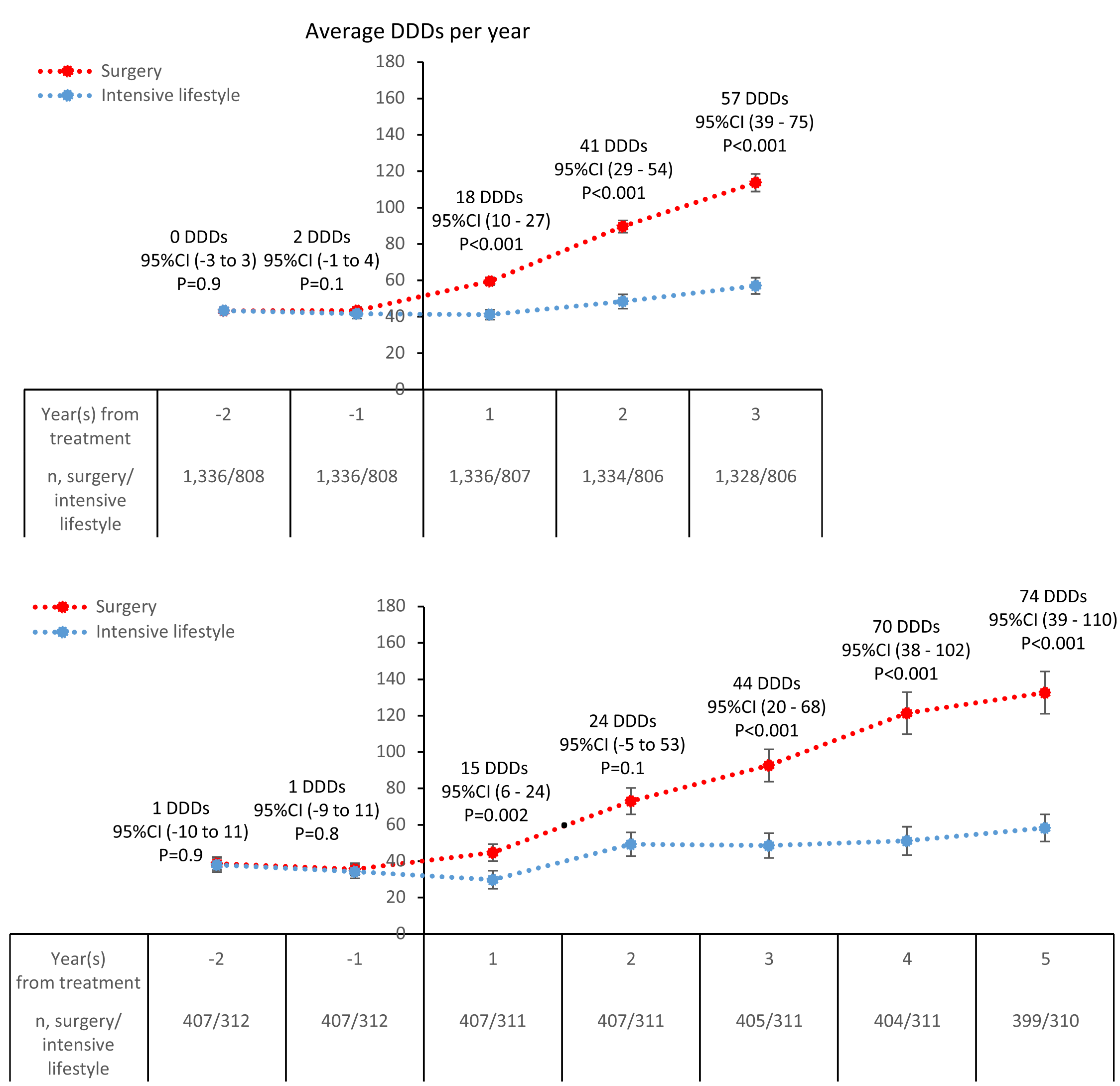


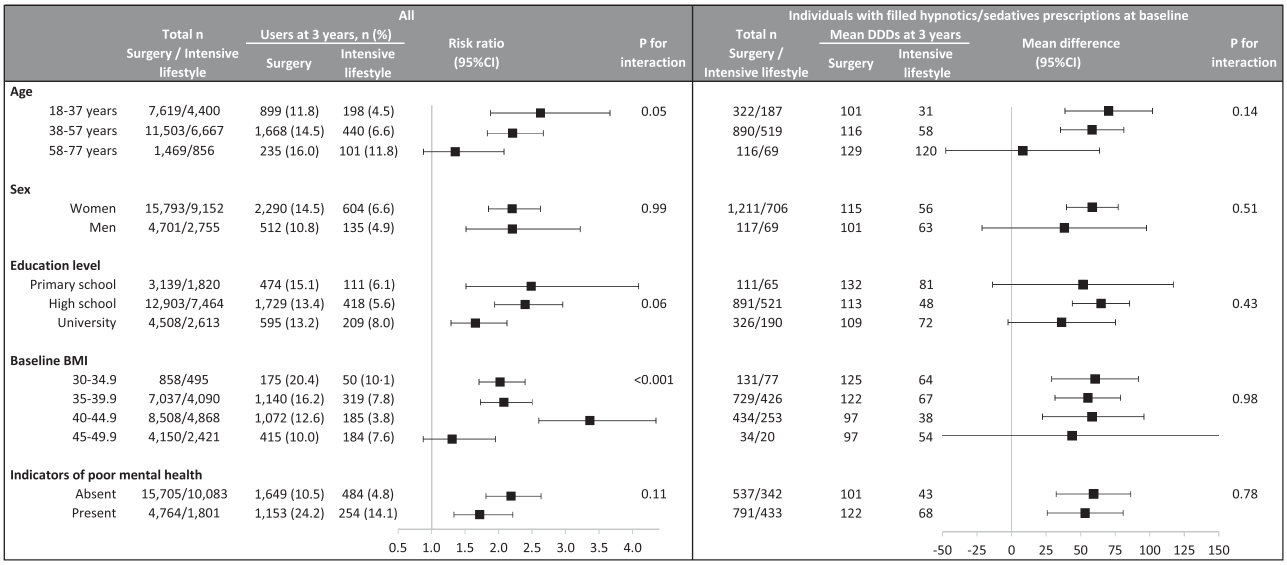
Figure 2 Mean treatment dose among those with filled hypnotics and/or sedatives prescriptions at 1 and/or 2 years prior to treatment, in the matched study population with 3 years of follow-up (upper panel) and in the subgroup with 5 years of follow-up (lower panel). Error bars are 95% CI. Mean differences (95% CI) apply to the between-cohort differences at each follow-up time point. Baseline characteristics of subgroups with 5 years of follow-up are shown in Supporting Information Table S3. Mean treatment dose among those with filled hypnotics and/or sedatives prescriptions in the unmatched study population are shown in Supporting Information Figure S5. Abbreviations: DDDs, defined daily doses. [Color figure can be viewed at wileyonlinelibrary.com]

Discussion

We found higher use of hypnotics and/or sedatives following gastric bypass compared with intensive lifestyle modification at 3- and 5-year follow-ups, and this difference was present in 12 out of 14 subgroups investigated. There was no evidence in either treatment cohort for a dose-response relationship between %BMI change at 1 year and change in use of hypnotics and/or sedatives at 3 years.

Our finding of an increased use of hypnotics and/or sedatives after gastric bypass is consistent with that from an uncontrolled 2-year follow-up study of 165 Norwegian patients (22) and from a Swedish study comparing 3,139 gastric bypass patients with 31,390 general population controls over 4 years of follow-up (23). Note that the Swedish study did not match for baseline BMI.

Because we did not find evidence for a dose-response relationship between %BMI change and change in use of hypnotics and/or sedatives, nor any change after substantial nonsurgically induced weight loss, it is likely that the increased use was driven by the undertaking of gastric bypass surgery and not by weight loss per se. While we cannot identify the cause of this phenomenon through our study, a number of plausible explanations can be identified in the literature. One possibility is “addiction transfer,” whereby patients stop overeating for anxiety relief but acquire other compulsive disorders such as alcoholism or substance abuse after bariatric surgery (24). The mechanism is unclear, and whether compulsive eating behavior prior to surgery can be considered as addiction remains debatable (25), but this phenomenon is continually being reported in bariatric surgery patients (24). One way to test this hypothesis is through a subgroup analysis by baseline mental health status. In this study, there



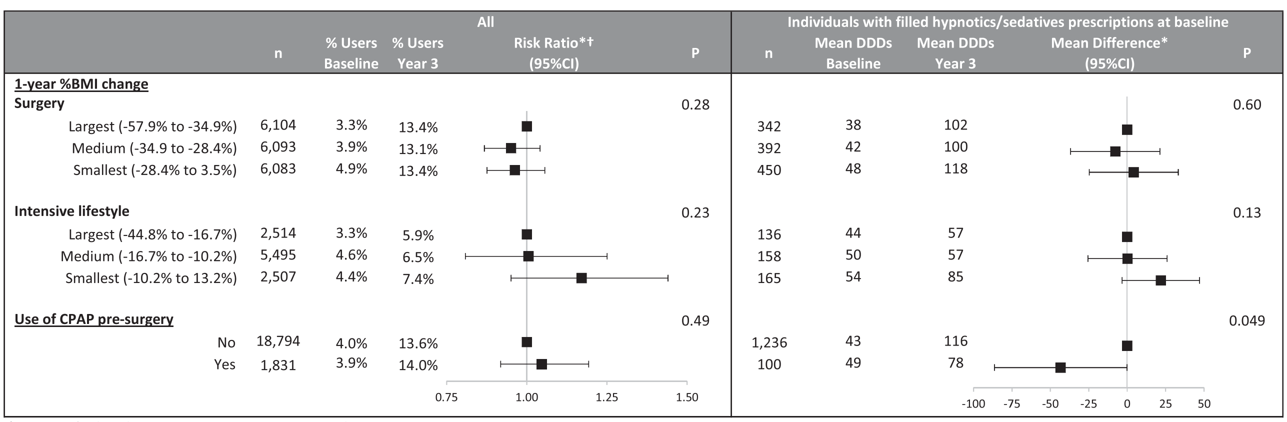
	Total n Surgery / Intensive lifestyle	Users at 3 years, n (%) Surgery	Users at 3 years, n (%) Intensive lifestyle	P for interaction
Age				
18-37 years	7,619/4,400	899 (11.8)	198 (4.5)	0.05
38-57 years	11,503/6,667	1,668 (14.5)	440 (6.6)	
58-77 years	1,469/856	235 (16.0)	101 (11.8)	
Sex				
Women	15,793/9,152	2,290 (14.5)	604 (6.6)	0.99
Men	4,701/2,755	512 (10.8)	135 (4.9)	
Education level				
Primary school	3,139/1,820	474 (15.1)	111 (6.1)	
High school	12,903/7,464	1,729 (13.4)	418 (5.6)	0.06
University	4,508/2,613	595 (13.2)	209 (8.0)	
Baseline BMI				
30-34.9	858/495	175 (20.4)	50 (10·1)	<0.001
35-39.9	7,037/4,090	1,140 (16.2)	319 (7.8)	
40-44.9	8,508/4,868	1,072 (12.6)	185 (3.8)	
45-49.9	4,150/2,421	415 (10.0)	184 (7.6)	
Indicators of poor mental health				
Absent	15,705/10,083	1,649 (10.5)	484 (4.8)	0.11
Present	4,764/1,801	1,153 (24.2)	254 (14.1)	

Individuals with filled hypnotics/sedatives prescriptions at baseline	Total n Surgery / Intensive lifestyle	Mean DDDs at 3 years Surgery	Mean DDDs at 3 years Intensive lifestyle	P for interaction
Age				
18-37 years	322/187	101	31	0.14
38-57 years	890/519	116	58	
58-77 years	116/69	129	120	
Sex				
Women	1,211/706	115	56	0.51
Men	117/69	101	63	
Education level				
Primary school	111/65	132	81	
High school	891/521	113	48	0.43
University	326/190	109	72	
Baseline BMI				
30-34.9	131/77	125	64	
35-39.9	729/426	122	67	0.98
40-44.9	434/253	97	38	
45-49.9	34/20	97	54	
Indicators of poor mental health				
Absent	537/342	101	43	0.78
Present	791/433	122	68	

Figure 3 Use of hypnotics and/or sedatives in the two treatment cohorts at 3-year follow-up, stratified by baseline characteristics, categorically in the overall matched study population (left) and continuously among those with filled hypnotics and/or sedatives prescriptions at 1 and/or 2 years prior to treatment (right). Abbreviation: DDDs, defined daily doses.

was no interaction between treatment cohort and baseline mental health status; i.e., use of sleep medication during follow-up was higher in the surgery cohort compared with the intensive lifestyle cohort, regardless of the baseline mental health status. Perhaps a more specific marker of poor mental health or addictive behavior is needed.

Another plausible explanation is that gastric bypass increases the risk of alcoholism and substance abuse (26-29), which in turn leads to poor sleep (30,31). Malabsorption after gastric bypass may explain the increased mean treatment dose among baseline users, but not the uptake of new users after surgery (32). One could also argue that hypnotics and/or sedatives use could increase after surgery due to patients having more frequent contact with clinicians at follow-up than intensive lifestyle participants. However, this is unlikely to be the full explanation, given the continuous uptake of new users even at 3 to 5 years follow-up, when health care contacts for postoperative care have presumably decreased. In addition, we observed greater dose increases in individuals in the surgery than the lifestyle cohort, among those using hypnotics and/or sedatives at baseline, and these individuals already have an established contact with a physician.



	All: n	% Users Baseline	% Users Year 3	P	Individuals with filled hypnotics/sedatives prescriptions at baseline: n	Mean DDDs Baseline	Mean DDDs Year 3	P
1-year %BMI change								
Surgery				0.28				0.60
Largest (-57.9% to -34.9%)	6,104	3.3%	13.4%		342	38	102	
Medium (-34.9 to -28.4%)	6,093	3.9%	13.1%		392	42	100	
Smallest (-28.4% to 3.5%)	6,083	4.9%	13.4%		450	48	118	
Intensive lifestyle				0.23				0.13
Largest (-44.8% to -16.7%)	2,514	3.3%	5.9%		136	44	57	
Medium (-16.7% to -10.2%)	5,495	4.6%	6.5%		158	50	57	
Smallest (-10.2% to 13.2%)	2,507	4.4%	7.4%		165	54	85	
Use of CPAP pre-surgery				0.49				0.049
No	18,794	4.0%	13.6%		1,236	43	116	
Yes	1,831	3.9%	14.0%		100	49	78	

*adjusted for baseline age, sex, education and cumulative DDDs prior to treatment

†Poisson distribution assumed

Figure 4 Within-treatment cohort analysis of the relationship of BMI change and of presurgical use of CPAP on the categorical outcome (with filled hypnotics and/or sedative prescriptions, Yes/No) in the overall matched study population (left) and for the continuous outcome (mean treatment dose, DDDs) among those with filled hypnotics and/or sedatives prescriptions at 1 and/or 2 years prior to treatment (right). *Adjusted for baseline age, sex, education, and cumulative DDDs prior to treatment. †Poisson distribution assumed. Abbreviations: CPAP, continuous positive airway pressure; DDDs, defined daily doses.

In the presence of obstructive sleep apnea, most hypnotics and/or sedatives are to be used with caution (33,34). It is possible that clinicians start to prescribe more hypnotics and/or sedatives to treat residual sleep problems following substantial improvement in severity of obstructive sleep apnea post bariatric surgery (recently shown in another study using SOReg data (35)), as use of hypnotics and/or sedatives is no longer contraindicated. If this was the case, we should observe a greater increase in hypnotics and sedatives prescription fillings among baseline CPAP users than in those without CPAP. Instead, we found a lower mean treatment dose at 3 years after surgery among CPAP users than in those without CPAP at baseline, although both cohorts increased their use compared to baseline. Also, at baseline, the use of hypnotics and/or sedatives did not differ between those with and without CPAP. It seems that despite published warnings, hypnotics and sedatives are still often used in patients with CPAP, potentially to aid with sleep and improve compliance (36-39).

Our study utilized nationwide registry data, which implies minimum loss to follow-up for the outcome (0.5% due to emigrations), large sample size, and high generalizability within the Swedish population, which is predominantly Caucasian. Use of hypnotics and/or sedatives was assessed through filled prescriptions recorded in the Prescribed Drug Register, providing better accuracy than self-reported data. We included participants in an intensive lifestyle modification program as our comparator cohort, which addressed previous concerns over lack of studies on bariatric surgery with comparator interventions producing sufficient weight loss (40). The average magnitude of 1-year weight loss from the intensive lifestyle cohort in this study (18 kg) is substantially larger than other conventional treatment comparators in previous bariatric surgery studies (max 8 kg) (20).

There are several limitations to this study. Even though we minimized the overlap between sleep and mental health problems by excluding medications with shared indications for mental health problems, we cannot control the off-label use of the remaining medications, and there is often more than one reason to prescribe a certain medication. Nevertheless, even if use of hypnotics or sedatives is not a perfect marker for sleep problems, our finding of increased hypnotics and sedatives after bariatric surgery remains a clinically important observation. Also, our estimates were robust to adjustments for baseline mental health.

This study was not a randomized controlled trial and is therefore prone to confounding. We attempted to minimize confounding by matching on covariates identified through a directed acyclic graph, but we cannot prove if our diagram is true and complete. There may be other inherent (personality) differences between the surgery and intensive lifestyle treatment cohorts that we do not capture, which may contribute to the observed differences. For instance, before matching, intensive lifestyle participants had higher levels of education, likely representing a more health-conscious population who may be more resistant to pharmacological aid such as hypnotics or sedatives. In our analysis, we aimed to capture this difference in health-seeking behavior between the treatment cohorts by adjusting for history of health care contacts. The estimates changed by ≤ 0.2 for risk ratios and ≤ 2 DDDs for mean differences, but this may not be sufficient. However, surgery increased the risk of having filled hypnotics and/or sedatives prescriptions compared with intensive lifestyle in all education level subgroups.

The surgery cohort in our current study only included gastric bypass. Our results may not be generalizable to other procedure types.

Conclusion

We found that the use of hypnotics and/or sedatives increased following gastric bypass, and the increase continued for up to 5 years. We saw no change in use of hypnotics and/or sedatives in the intensive lifestyle treatment group. Future studies are needed to identify the underlying mechanisms and assess whether these results may be observed after other bariatric or even nonbariatric surgeries. Our findings indicate the need for sleep medication monitoring and management following gastric bypass to prevent uptake of new users and continuous increase in the mean treatment dose of hypnotics and sedatives after gastric bypass. O

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