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Pros and cons of gastric bypass surgery in obese individuals with type 2 diabetes: nationwide, matched, observational cohort study

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TITLE PAGE

Complete title: Pros and cons of gastric bypass surgery in obese individuals with type 2 diabetes: nationwide, matched, observational cohort study

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Objectives: Long-term effects of gastric bypass (GBP) surgery have been presented in observational and randomized studies, but there are only limited data for obese persons with type 2 diabetes (T2DM), regarding postoperative complications.

Design: This is a nationwide observational study based on two quality registers in Sweden: the National Diabetes Register (NDR) and the Scandinavian Obesity Surgery Register (SOReg), as well other national databases.

Setting: After merging the data, we matched individuals with T2DM who had undergone GBP with those not surgically treated for obesity on propensity score, based on sex, age, BMI and calendar time. The risks of postoperative outcomes (rehospitalizations) were assessed using Cox regression models.

Participants: We identified 5,321 patients with T2DM in the SOReg, as well as 5,321 matched controls in the NDR, aged 18-65 years, with BMI >27,5 kg/m² and followed for up to 9 years.

Primary and secondary outcome measures: We assessed risks for all-cause mortality and hospitalizations for cardiovascular disease, severe kidney disease, as well as for surgical and other medical conditions.

Results: We confirmed lower risks of all-cause mortality (49%) and cardiovascular disease (34%), found positive effects for severe kidney disease but demonstrated significantly increased risks (2 to 9-fold) of several short-term complications after GBP, such as abdominal pain and gastrointestinal conditions, frequently requiring surgical procedures, apart from reconstructive plastic surgery. Long-term, the risk of anemia was 92% higher, malnutrition developed approximately 3 times as often, psychiatric diagnoses were 33% more frequent and alcohol abuse was 3 times as great as in the control group.

Conclusions: This nationwide study confirms the benefits and describes the panorama of adverse events after bariatric surgery in obese persons with T2DM. Long-term postoperative monitoring and support, and possibly also better selection of patients by appropriate specialists in interdisciplinary settings, should be provided to optimize the outcomes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Major strength of our study is the unique and nationwide character of our population with type 2 diabetes that received gastric bypass operation.
- The high data reliability as well the external validity allow the generalizing of our results to similar developed countries using the same criteria and contraindications for bariatric surgery and quality of care.
- Our nonrandomized observational study may be limited by some minor differences between the matched groups on the propensity score.
- We tried to eliminate major confounders by careful matching between the two groups as well with an adjusted Cox regression model, however we cannot exclude underlying residual confounders.
- We studied effects and postoperative events after gastric bypass in in-patients (rehospitalizations) leaving unassessed a large proportion of out-patients visiting the primary care.

MAIN TEXT

Introduction

The most effective method for ensuring long-term weight reduction in obese individuals as well as beneficial effects on mortality, cardiovascular disease (CVD) and CV risk factors is bariatric surgery, Roux-en-Y gastric bypass (GBP) in particular (1-3). These effects of GBP have also been shown in patients with type 2 diabetes (T2DM) in both observational (4-6) and randomized control trials (7-9) under different follow-up periods. However, it has also been demonstrated in cohorts with a low proportion of individuals with diabetes that GBP is associated with postoperative complications and readmission rates from 0.6% to 11.3% (10-13), as well as long-term adverse outcomes such as hypoglycemia (7), anemia, nutritional deficiencies (14), gallstones (3), depression (15), suicide and non-fatal self-harm (16) and alcohol problems (17).

Only few reports have addressed the long-term incidence of complications in obese patients with T2DM who have undergone bariatric surgery. The Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) study reported adverse events of GBP and sleeve gastrectomy compared to conventional medical therapy, but only in 142 individuals with T2DM randomized at a single center with follow-up period up to 5 years (7). Similarly, the Diabetes Surgery Study recently reported clinical effects and adverse events after GBP or lifestyle–medical management in 120 individuals after 5 years (18). Larger prospective studies such as Swedish Obese Subjects (SOS) study (1) and large American observational studies with broad samples (11, 19) have addressed postoperative outcomes of GBP or sleeve gastrectomy, but with only a small proportion of patients who have T2DM.

We recently conducted a nationwide observational study of individuals with T2DM who underwent GBP compared with matched individuals and reported beneficial effects on overall mortality and cardiovascular events (4), but we did not address short-term or long-term adverse effects. The objective of this observational cohort study is therefore to identify clinical benefits as well as a wide spectrum of early postoperative, as well long-term, adverse effects of GBP for up to 9 years in individuals with T2DM compared to obese individuals who have not received surgical treatment.

Research Design and Methods

This study is based on two nationwide quality registers in Sweden: the National Diabetes Register (NDR) and the Scandinavian Obesity Surgery Register (SOReg), as well as linked data from the Swedish Inpatient Register, the Cause of Death Register and the Statistics Sweden. All these databases have previously been described and validated (20, 21). The NDR is a quality register tool that provides nearly full coverage (90% for T2DM and 95% for T1DM) of Swedes with diabetes since 1996. SOReg started in 2007 as a quality and research register. Since 2010, it has covered virtually all bariatric procedures in Sweden. All bariatric centers report to the register (surgical complications, postoperative reports and longitudinal effects).

Patient and Public Involvement

All individuals provided verbal informed consent before being included in the NDR and SOReg databases and that data could be used for research. They did not, however, provide consent for this specific study. Patients have the rights to deny being included in studies by the time of register. Furthermore, data and patients' personal identity numbers identified and replaced by serial numbers in the National Board of Health and Welfare, so patients had not direct

involvement to the design and results of the study. The regional ethical review board at the University of Gothenburg, Sweden, approved the study.

After merging the data of SOReg and NDR, we identified individuals with diabetes and obesity who had undergone GBP between January 1, 2007 and December 31, 2015. We subsequently matched them with control patients in the NDR who had not undergone bariatric surgery. Propensity score matching (1:1) was performed on the basis of sex, age (18-75 years), body mass index (BMI) (>27,5 kg/m²) and calendar time.

We based our definition of T2DM on classical epidemiological criteria, i.e., treatment with diet, oral antihyperglycemic agents, insulin or different combinations, as well patients who were ≥40 years of age at the time of diagnosis.

All clinical characteristics at baseline were obtained from the NDR and SOReg, socioeconomic status was taken from Statistics Sweden, and presurgical and postsurgical diagnoses were taken from the Swedish Inpatient Register (ICD-10) (Table S1, supplementary material), which are held by the National Board of Health and Welfare. The Inpatient Registry records all inpatient admissions since 1987. We studied admissions to the hospitals by including specific diagnoses for coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure and valvular heart disease, as well as acute and chronic diseases that were related to diabetes mellitus (hyperglycemia, hypoglycemia with coma, amputation, kidney, liver and pulmonary diseases, cancer, anemia, malnutrition, dementia, psychiatric disorders and alcohol abuse). We also report surgical history, such as hospitalization due to bleeding, gastrointestinal (GI) surgery and leakage, wound complications, GI ulcers and reflux disease, bowel obstruction, hernia, gall bladder disease and pancreatitis, as well previous plastic surgery.

Patients were followed up to 9 years or until the first admission to the hospital for specific diagnoses or group of diagnoses or death. Controls who were treated with GBP were censored on the date of such treatment.

Statistical analysis

One matched control was selected for each GBP patient using propensity scores for longitudinal exposure (22). The outcome of the propensity score matching was assessed only through descriptive statistics comparing the matched groups. Thus, controls were matched to GBP patients based on the estimated risk score from a Cox regression model with time-updated data, where exposure for GBP was the endpoint. The model contained covariates for sex, age and BMI. Controls were selected in chronological order.

Descriptive statistics are presented using means with standard deviation for age and BMI, median with quartiles for income and counts with percentages for all other variables. Incidence rates for each outcome were estimated using counts and person-years. Comparisons between GBP patients and controls used Cox regression, adjusted for sex, age, BMI and socioeconomic factors (income, marital status, education level and country of origin). No adjustments were made for multiple inferences. Thus, while p-values below 5% were considered statistically significant, the outcome of individual hypothesis tests should be interpreted with caution.

Results

We identified 5,321 patients in the SOReg who had T2DM and had undergone GBP, as well as 5,321 matched controls in the NDR (flowchart, supplementary material). Both groups were followed for up to 9 years (mean, 4.5 years). Table 1 shows the baseline characteristics of both groups. There were some minor differences between the groups (standardized differences of more

than 0·1): the GBP persons had a slightly higher mean age and BMI and were less likely to be single (marital status), with a greater mean income and higher educational level. The groups were well matched with respect to previous cardiovascular, gastrointestinal, psychiatric and surgical diseases (standardized differences less than 0.1).

Table 2 shows the number of events and incidence rates during the follow-up period. Event rates for all-cause mortality were 72.9 and 142.1 per 10.000 person-years in GBP and the control group respectively (HR 0.51, 95% CI 0.43-0.62; Figure 1A). Risks for cardiovascular or coronary heart disease, acute myocardial infarction and congestive heart failure (Figure 1B) were also lower after GBP.

Other benefits were observed after GBP. Hospitalization for hyperglycemia was less frequent, and the risks of kidney disease (Figure 1C), leg amputation and cancer were lower (Table 2). The risks of hospitalization due to psychiatric disorders or alcohol abuse (Figure 1E-F) increased after GBP (73.1 and 26.5 per 10.000 person-years in GBP and the control group respectively, HR 1.33, 95% CI 1.13-1.58 and HR 2.90, 95% CI 2.16-3.88).

A number of adverse conditions were observed more often in the GBP group: abdominal pain, gallstones, gallbladder disease, pancreatitis, gastrointestinal ulcers, reflux, hernia, bowel obstruction, gastrointestinal leakage, wound complications and bleeding (Figure 2B-E). Gastrointestinal or plastic surgery (Figure 2A and 2F) was required more frequently, while the risk for pulmonary complications, embolism, deep vein thrombosis or liver disease was slightly lower. GBP individuals were also at greater risk for anemia (HR 1.92, 95% CI 1.33-2.76) and malnutrition (HR 2.81, 95% CI 1.98-3.97) (Figure 1D).

We analyzed results of GBP treatment in men and women using a Cox regression model adjusted for sex, age, BMI and socioeconomic factors (Table S2, supplementary material). The significant interactions we noted were risks for fatal CVD, atrial fibrillation, congestive heart failure and gastrointestinal surgery (higher in men after GBP, $p<0.05$), while women were at a higher risk (1.51, 95%CI 1.23-1.85) of being hospitalized due to a psychiatric disorder after GBP.

Discussion

This observational study compares outcomes after GBP (rehospitalizations) in individuals with obesity and TDM2 with a matched group of those who have not been surgically treated. We confirm the previously shown beneficial effects on all-cause mortality and cardiovascular morbidity in individuals with or without T2DM (1, 4), as well as presenting a panorama of short-term and long-term complications after GBP on a nationwide scale. Common reasons for postoperative hospital admissions were gastrointestinal conditions such as abdominal pain, gallstone/gallbladder disease, pancreatitis, gastrointestinal ulcer, leakage, reflux, hernia, bowel obstruction, psychiatric disorders and alcohol abuse.

Additional gastrointestinal surgery was performed in 17.6% of the GBP group, more than three times as much as in the control group. Gastrointestinal leakage, bleeding, abdominal pain and bowel obstruction are likely causes for these surgical interventions, as well as gallstone disease and cholecystitis, which are frequently observed after GBP and rapid weight loss (3, 23-25). Wanjura et al. recently showed that the incidence of cholecystectomy was substantially elevated before GBP and increased 6-36 months after surgery compared with the general population (24). Previous GBP doubled the risk of complications after cholecystectomy and almost quadrupled the risk of reoperation. It has been suggested that defective gallbladder emptying in conjunction

with the production of crystallization-promoting compounds (mucin) can contribute to the development of cholesterol crystals and gallstones in obese subjects during weight reduction (25).

Some postoperative complications were common shortly after GBP (leakage, wound complications and ulcer/reflux), while others (hernia, bowel obstruction and gallstone) generally increased after 1-2 years. These findings were expected, although the incidence of ulcers and reflux disease soon after GBP may be exaggerated due to the endoscopies for dyspepsia and dysphoric symptoms. Hernias may well be undiagnosed preoperatively but detected during surgery and become symptomatic after weight loss when the associated fat disappears. The incidence of wound complications and gastrointestinal leakage shortly after GBP was comparable to other studies with short follow-up periods and a small percentage of patients with diabetes (26-28). There were no major differences between men and women in the risk for specific postoperative complications, apart from a slightly higher incidence of additional surgical procedures and cardiovascular risk (fatal CVD) in men, as previously suggested (12, 29).

There was a 42% lower relative risk of hospitalization due to severe kidney disease after GBP. A systematic review has previously suggested that weight loss is associated with reductions in proteinuria and microalbuminuria. A retrospective cohort study showed a higher mean estimated glomerular filtration rate (eGFR) in patients up to three years after bariatric surgery than those with moderately impaired renal function (CKD stages 3 and 4) who were referred for, but did not receive, surgery (30, 31). There has been no prospective study in patients with severe renal disease. Retrospective data are limited by study design and estimations of renal function. eGFR calculations depend on muscle mass and serum creatinine levels, both of which change after weight loss independent of kidney function. Although the selection of patients eligible for

bariatric surgery can contribute to the apparent beneficial effects on risk of severe kidney disease, these results should prompt new studies concerning the effects on renal function, as well as optimal patients for surgery to treat weight loss. Improved glycemic and blood pressure control after GBP could also contribute to the apparent effects (32, 33) including changes in dose of antihypertensives, which are known to affect serum creatinine. We did not evaluate glycemic control in this study, but pronounced effects after bariatric surgery have been demonstrated repeatedly (7, 34, 35).

The anatomical and physiological consequences of GBP result in a higher risk of long-term deficiencies of several vitamins and minerals (36). The present study had no access to data from primary care, where follow-up should start 2 years after GBP, but malnutrition and anemia were twice as common. Poor compliance with vitamin and mineral supplements, as well as irregular follow-up, may very likely explain these results. A recent meta-analysis pointed to this potential problem in individuals without diabetes, suggesting that diabetes is not a risk factor per se (14). Adequate supplementation is paramount (37), since deficiencies after GBP tend to increase over time (14, 38).

A history of psychiatric disorders requiring hospitalization was not uncommon in either group of individuals with obesity in this study, and was 33% higher after GBP. Previous studies have shown that depression, which may improve in the first year following bariatric surgery, tends to progress (39) along with suicide and self-harm, particularly if they are preexisting conditions (15, 16). Thus, greater awareness is needed in order to identify vulnerable patients with a history of self-harm or depression who may need psychiatric services after GBP. In agreement with previous studies (17, 40) we confirmed a higher event rate of alcohol-related problems that lead to hospitalization after GBP, which points to the importance of careful selection of patients who

are offered surgery, as well as better follow-up of those with a history of alcohol-related risk behavior. The mechanisms of this well-known phenomenon are still unknown.

A major strength of this study is its nationwide coverage of patients with obesity and type 2 diabetes, all of whom received recent Roux-en-Y gastric bypass surgery. The results are likely to be generalizable to similar developed countries using the same criteria and contraindications for bariatric surgery and quality of care. All linked databases are characterized by high participation rates and validation of medical data (21, 41).

Our study was nonrandomized and observational, but with carefully matched groups to maximize the size of the cohort as well as to reduce the influence of confounding factors. Minor differences in clinical characteristics may still influence our results. We did not exclude patients with multiple comorbidities before the intervention because we would have lost substantial data and they had all qualified for GBP. We also used Cox proportional hazards regression modelling, including baseline characteristics, to minimize the effects of confounding. Certainly, we cannot rule out residual confounding, unobserved factors that may be related to both exposure and outcome. However, the external validity is most likely high as our study includes virtually all GBP patients with type 2 diabetes in Sweden during the time period.

Another limitation is that we captured diagnoses during hospitalization, not outpatient care. Comorbidities and incidence of postoperative outcomes may be underestimates as a result, but the systemic flaw could not be avoided. Nevertheless, measurement errors may potentially arise because the patients who had received surgery were followed up more frequently than the control group. GBP was the only surgical procedure we studied, given that sleeve gastrectomy and duodenal switch were not performed very often and follow-up data were too limited during the study period.

Individuals with obesity and type 2 diabetes who have undergone GBP are generally at a reduced risk of all-cause mortality and cardiovascular morbidity, as well as severe kidney disease and cancer to a lesser extent. They also have, however, significantly higher risks of postoperative complications and adverse events both short-term and long-term, mostly abdominal pain and gastrointestinal conditions that frequently require additional surgical procedures, apart from reconstructive plastic surgery. Long-term consequences observed more often are anemia, malnutrition, psychiatric disorders and alcohol abuse. In order to maximize the benefit and minimize the risk of problems, long-term postoperative monitoring and support should be provided. Better selection of patients for such treatment, performed by appropriate specialists in interdisciplinary settings, could probably also optimize outcomes.

Author Contributions: All authors contributed to the conception and design of the study. SF, MM, AMS, JO and IN contributed to the acquisition of data and SF performed the statistical analyses. All authors contributed to the interpretation of data. VL and BE drafted the article, and all authors contributed to critical revision. BE is the guarantor of this work, had full access to the data and assumes responsibility for their integrity and analysis.

Competing of interest: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in

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Data sharing statement: This is a registry study and therefore the data generated is not suitable for sharing beyond that contained within the report. Further information can be obtained from the corresponding author.

Ethical Approval: Ethics Review Board of the University of Gothenburg approved this study.

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Figure legends:

Figure 1A-F: Cumulative incidence of postoperative outcomes during the 9-years follow up. All-cause mortality; Congestive heart failure; Kidney disease; Malnutrition; Psychiatric disorder; Alcohol abuse.

Figure 2A-F: Cumulative incidence of postoperative adverse events during the 9-years follow-up. Gastrointestinal (GI) surgery; Abdominal pain; Bowel obstruction; Gallstone and gallbladder disease; Wound complications; Plastic surgery

Table 1. Baseline characteristics

	GBP (n=5321)	Control (n=5321)	Standardized difference*
Sex			
Men	2098 (39.4%)	1926 (36.2%)	0.0471
Women	3223 (60.5%)	3395 (63.8%)	0.0471
Age	49.0 (9.5)	47.1 (11.5)	0.122
BMI	42.0 (5.7)	40.9 (7.3)	0.117
Income (SEK)	199.638 (139136; 261558)	168.380 (121840; 239368)	0.156
Marital status			
Single	1602 (30.1%)	2064 (38.8%)	0.130
Married	2518 (47.4%)	2227 (41.9%)	0.0781
Separated	1092 (20.5%)	881 (16.6%)	0.0723
Widowed	106 (2.0%)	147 (2.8%)	0.0358
Education level			
Compulsory school	1069 (20.1%)	1431 (26.9%)	0.114
University	3192 (60.0%)	2847 (53.5%)	0.0926
Upper secondary school	1037 (19.5%)	930 (17.5%)	0.0366
Missing data	23 (0.4%)	113 (2.1%)	0.107
Country of origin			
Sweden	4261 (80.1%)	4027 (75.7%)	0.075
Rest of Europe	514 (9.7%)	602 (11.3%)	0.0382
Rest of the world	546 (10.3%)	692 (13.0%)	0.0607
Cardiovascular			
Cardiovascular disease	273 (5.1%)	261 (4.9%)	0.00730
Acute myocardial infarction	173 (3.2%)	169 (3.2%)	0.00301
Coronary heart disease	395 (7.4%)	313 (5.9%)	0.0437
Congestive heart failure	140 (2.6%)	168 (3.2%)	0.0222
Atrial fibrillation	148 (2.8%)	149 (2.8%)	0.000807
Valvular heart disease	24 (0.4%)	27 (0.5%)	0.00577
Stroke	109 (2.0%)	103 (1.9%)	0.00571
Deep vein thrombosis/pulmonary embolism	71 (1.3%)	65 (1.2%)	0.00710
Diabetes-related			
Hyperglycemia	80 (1.5%)	130 (2.4%)	0.0478
Hypoglycemia (with or without coma)	57 (1.1%)	61 (1.2%)	0.00508

Numbers and proportions.

*Difference between sample means divided by standard deviation. Acceptable significance when standardized difference <0.1

Gastrointestinal			
Gastrointestinal surgery (not gastric bypass)	549 (10.3%)	644 (12.1%)	0.0400
Abdominal pain	386 (7.2%)	334 (6.3%)	0.0275
Gallstone, gallbladder disease and pancreatitis	419 (7.9%)	366 (6.9%)	0.0270
Gastrointestinal ulcer and reflux	86 (1.6%)	72 (1.4%)	0.0154
Hernia	204 (3.8%)	160 (3.0%)	0.0322
Bowel obstruction	18 (0.3%)	29 (0.6%)	0.0220
Gastrointestinal leakage	7 (0.1%)	17 (0.3%)	0.0280
Liver disease	16 (0.3%)	26 (0.5%)	0.0212
Surgical			
Plastic surgery	54 (1.0%)	33 (0.6%)	0.0310
Wound complications	192 (3.6%)	156 (2.9%)	0.0269
Bleeding	50 (0.9%)	32 (0.6%)	0.0273
Other			
Psychiatric disorders	318 (6.0%)	346 (6.5%)	0.0154
Alcohol abuse	94 (1.8%)	122 (2.3%)	0.0264
Cancer	111 (2.1%)	158 (3.0%)	0.0398
Malnutrition	21 (0.4%)	41 (0.8%)	0.0349
Kidney disease	56 (1.0%)	83 (1.6%)	0.0316
Pulmonary disease	128 (2.4%)	131 (2.5%)	0.00259
Anemia	55 (1.0%)	60 (1.1%)	0.00643
Amputation	10 (0.2%)	12 (0.2%)	0.00585
Dementia	1 (0.02%)	4 (0.08%)	0.0184

Table 2. Number of events and event rates during follow up

Outcome	GBP (n=5321)	Control (n=5321)	Hazard ratio [95% CI]	p-value
All-cause mortality	183 (72.90)	351 (142.06)	0.51 [0.43, 0.62]	<.0001
Cardiovascular				
Cardiovascular disease	108 (43.54)	150 (61.54)	0.66 [0.51, 0.85]	0.0014
Fatal cardiovascular disease	21 (8.38)	64 (25.94)	0.34 [0.20, 0.56]	<.0001
Acute myocardial infarction	51 (20.43)	85 (34.69)	0.55 [0.39, 0.79]	0.0010

Table 2. Number of events and event rates during follow up

Outcome	GBP (n=5321)	Control (n=5321)	Hazard ratio [95% CI]	p-value
Coronary heart disease	309 (128.66)	274 (114.28)	1.13 [0.95, 1.34]	0.156
Fatal coronary heart disease	28 (11.17)	77 (31.20)	0.35 [0.22, 0.54]	<.0001
Congestive heart failure	109 (43.94)	225 (93.05)	0.49 [0.39, 0.62]	<.0001
Atrial fibrillation	204 (83.64)	213 (88.16)	0.93 [0.76, 1.14]	0.486
Valvular heart disease	21 (8.39)	32 (13.00)	0.64 [0.36, 1.14]	0.131
Stroke	59 (23.69)	71 (28.94)	0.77 [0.54, 1.10]	0.158
Deep vein thrombosis/pulmonary embolism	56 (22.48)	59 (24.07)	1.01 [0.69, 1.48]	0.952
Diabetes-related				
Hypoglycemia (with or without coma)	43 (17.24)	46 (18.72)	1.04 [0.68, 1.60]	0.844
Hyperglycemia	23 (9.20)	89 (36.37)	0.33 [0.21, 0.53]	<.0001
Gastrointestinal				
Gastrointestinal surgery (not gastric bypass)	936 (422.59)	301 (125.76)	3.33 [2.91, 3.80]	<.0001
Abdominal pain	558 (239.25)	124 (50.94)	5.52 [4.51, 6.75]	<.0001
Gallstone, gallbladder disease and pancreatitis	312 (129.31)	125 (51.30)	2.49 [2.02, 3.08]	<.0001
Gastrointestinal ulcer and reflux	239 (98.58)	46 (18.73)	5.42 [3.91, 7.51]	<.0001
Hernia	235 (97.00)	86 (35.17)	2.75 [2.14, 3.54]	<.0001
Bowel obstruction	232 (95.29)	27 (10.97)	9.47 [6.31, 14.20]	<.0001
Gastrointestinal leakage	40 (16.05)	7 (2.84)	5.54 [2.46, 12.45]	<.0001
Liver disease	30 (12.00)	40 (16.26)	0.73 [0.45, 1.19]	0.205
Surgical				
Plastic surgery	380 (158.08)	22 (8.94)	19.85 [12.86, 30.67]	<.0001
Wound complications	290 (120.87)	87 (35.55)	3.45 [2.70, 4.42]	<.0001
Bleeding	172 (70.50)	26 (10.57)	6.87 [4.49, 10.52]	<.0001
Other				
Psychiatric disorder	317 (131.64)	268 (111.93)	1.33 [1.13, 1.58]	0.0008
Alcohol abuse	180 (73.10)	65 (26.52)	2.90 [2.16, 3.88]	<.0001
Cancer	153 (61.80)	188 (77.41)	0.78 [0.63, 0.97]	0.0257
Malnutrition	128 (51.69)	46 (18.72)	2.81 [1.98, 3.97]	<.0001
Kidney disease	105 (42.38)	187 (76.87)	0.58 [0.45, 0.75]	<.0001
Pulmonary complications	86 (34.66)	114 (46.64)	0.84 [0.63, 1.13]	0.249

Table 2. Number of events and event rates during follow up				
Outcome	**GBP (n=5321)**	**Control (n=5321)**	**Hazard ratio [95% CI]**	**p-value**
Anemia	84 (33.78)	46 (18.71)	1.92 [1.33, 2.76]	0.0005
Amputation	15 (5.99)	23 (9.33)	0.51 [0.26, 0.98]	0.0432
Dementia	4 (1.60)	12 (4.87)	0.46 [0.14, 1.57]	0.214

Event rates (%) per 10.000 person-years

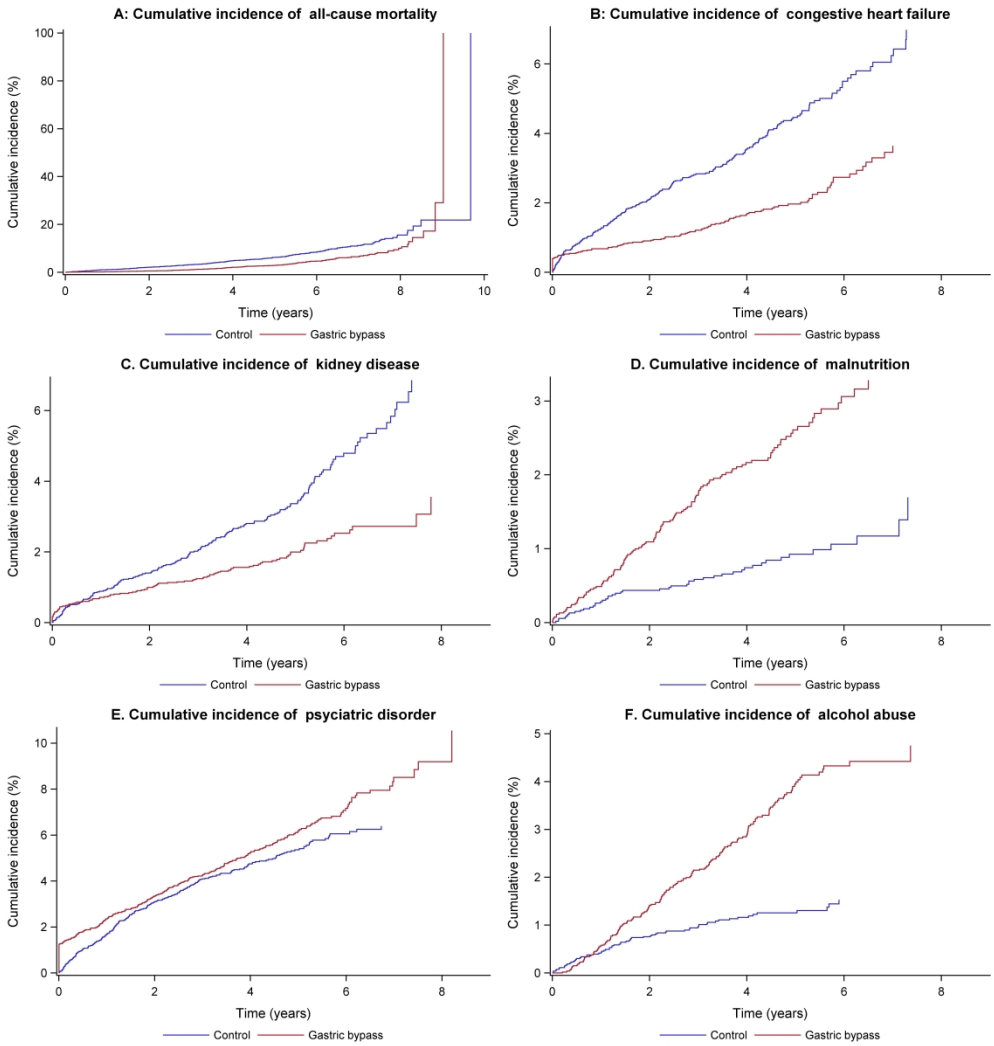


Figure 1A-F: Cumulative incidence of postoperative outcomes during the 9-years follow up. All-cause mortality; Congestive heart failure; Kidney disease; Malnutrition; Psychiatric disorder; Alcohol abuse.

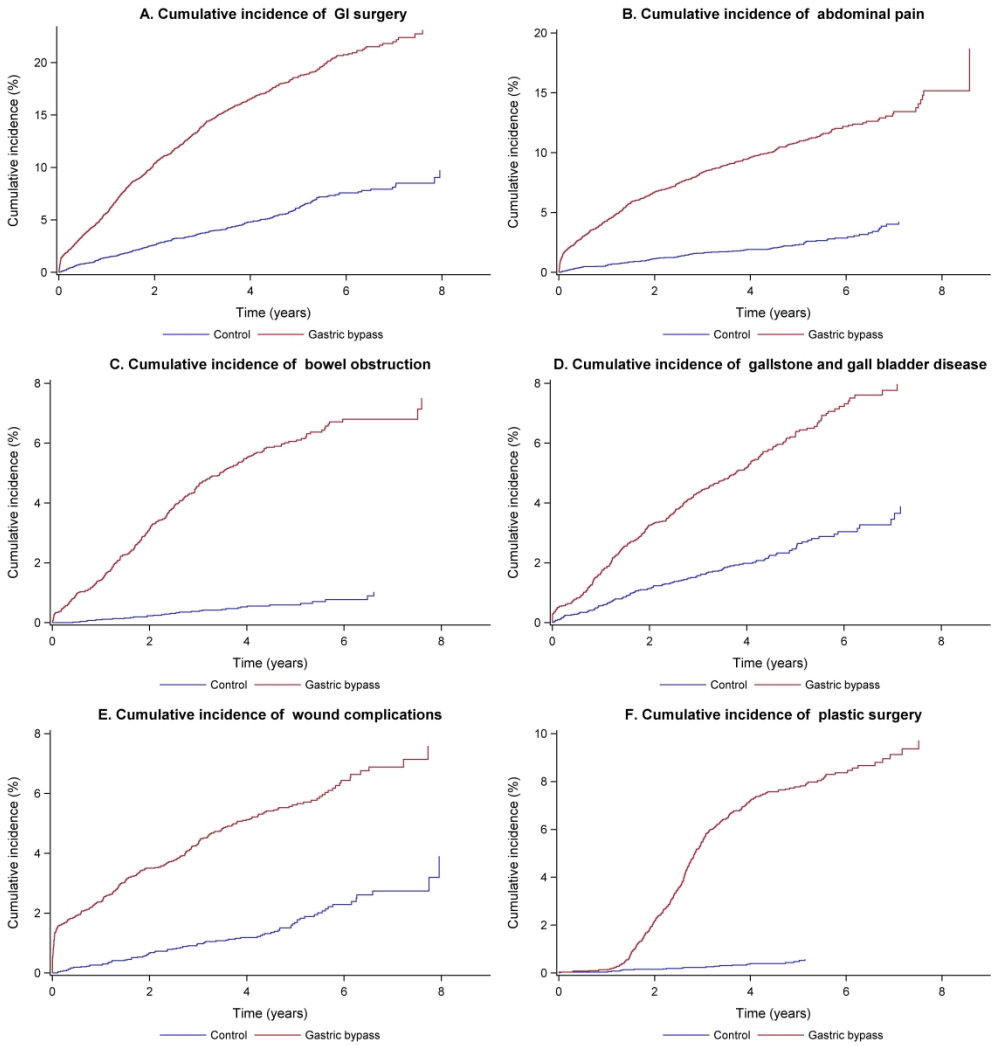


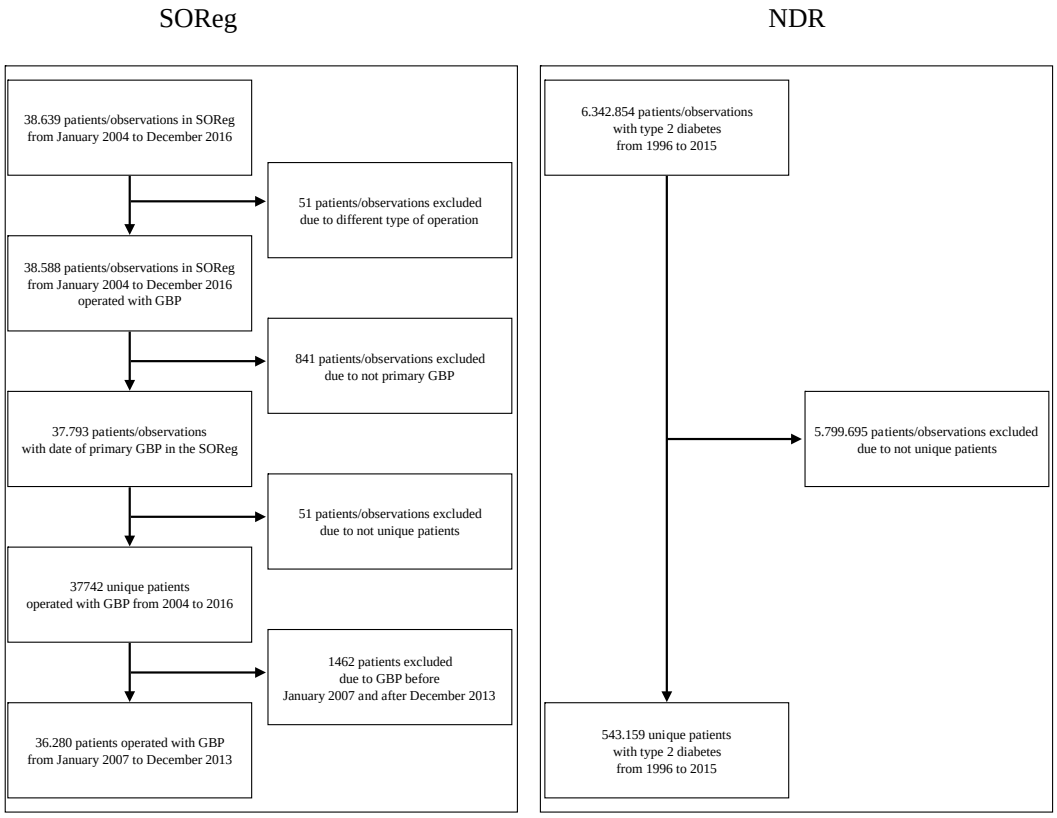
Figure 2A-F: Cumulative incidence of postoperative adverse events during the 9-years follow-up. Gastrointestinal (GI) surgery; Abdominal pain; Bowel obstruction; Gallstone and gallbladder disease; Wound complications; Plastic surgery

SUPPLEMENTARY MATERIAL

Table of contents

Flowchart

Selection of our data from Scandinavian Obesity Surgery Register (SOReg) before merging with data from the National Diabetes Registry (NDR).



Merging the two databases led to our study population of 5,321 patients in the SOReg who had T2DM and had undergone GBP, and 5,321 matched control patients in the NDR.

Methods – database linkages

This study is based on data from the NDR and SOReg. Both registers are linked to Statistics Sweden at the National Board of Health and Welfare, which also stores data in the Swedish Inpatient Register (1997-2015).

We filed an application with our data and personal identity numbers [SOReg (2007-2013) & NDR (1996-2015)] to the National Board of Health and Welfare, from which all personal identity numbers have been identified and replaced by serial numbers. The coded data from the National Board of Health and Welfare were subsequently forwarded to Statistics Sweden for linkage with the Inpatient Register and LISA Database, which provides socioeconomic data. The linked data were then returned to us for validation and analysis.

Table S1: Pre-index diagnoses and outcomes after GBP

Diagnoses before and after gastric bypass surgery (index date) until December 2015 according to ICD-10.

Diagnosis	ICD-10	Variable origin	Registration period
Acute Myocardial infarction	*I21*	Swedish Inpatient Register	2007-2015
Coronary heart disease	*I20-25*	Swedish Inpatient Register	2007-2015
Stroke	*I61-64*	Swedish Inpatient Register	2007-2015
Cardiovascular disease	*I21, I61-64*	Swedish Inpatient Register	2007-2015
Atrial fibrillation	*I48*	Swedish Inpatient Register	2007-2015
Heart failure	*I50*	Swedish Inpatient Register	2007-2015
Valvular heart disease	*I05-09, I34-37, Q22, Q23*	Swedish Inpatient Register	2007-2015
Liver disease	*K70-74*	Swedish Inpatient Register	2007-2015
Kidney disease	*V42A, V45B, V56A, V56W, Z940, Z491, Z492, Z992, N17-19, N99*	Swedish Inpatient Register	2007-2015
Hyperglycemia	*E100, E101, E110, E111, E120, E121, E130, E131, E140, E141, R739*	Swedish Inpatient Register	2007-2015
Hypoglycemia (with or without coma)	*E100, E106A, E110, E110C, E110X, E116A, E120, E130, E140, E159, E160, E161W, E162, R402*	Swedish Inpatient Register	2007-2015
Cancer	*C0-9*	Swedish Inpatient Register	2007-2015

Dementia	*G300, G301, G308, G309, G31, F00-03*	Swedish Inpatient Register	2007-2015
Psychiatric disorders	*F11-19, F20-29, F30-39, F50, F55, F40-F43, F60, F61, F68, F69, F99*	Swedish Inpatient Register	2007-2015
Alcohol abuse	*F10*	Swedish Inpatient Register	2007-2015
Anemia	*D508-9, D51.0,3,8, D520*	Swedish Inpatient Register	2007-2015
Malnutrition	*E15-16, E51.2, E42-44, E46, E50-64, G63.3-4, G62.9, K91.1-2, M81.3, M83.2*	Swedish Inpatient Register	2007-2015
Bleeding	*T81.0*	Swedish Inpatient Register	2007-2015
Deep vein thrombosis and pulmonary embolism	*I80.0-9, I26, I81*	Swedish Inpatient Register	2007-2015
Amputation	*NHQ09, 11-14, 16, 17, 99, NGQ09, 19, 99, NFQ19, 99*	Swedish Inpatient Register	2007-2015
Bowel obstruction	*K56, K45*	Swedish Inpatient Register	2007-2015
Gastrointestinal leakage	*T84.4, K65.0, K63.1*	Swedish Inpatient Register	2007-2015
Pulmonary complications	*J18.0-9, J69.0, J80, J98.1*	Swedish Inpatient Register	2007-2015
Wound complications	*T81.3-4, K43.0-9*	Swedish Inpatient Register	2007-2015
Gastrointestinal ulcer and reflux	*K21, K22.1-3, K25-26, K28*	Swedish Inpatient Register	2007-2015
Hernia	*K40-43*	Swedish Inpatient Register	2007-2015
Gallstone, gallbladder disease and pancreatitis	*K80-85*	Swedish Inpatient Register	2007-2015
Gastrointestinal surgery not	All the operative diagnoses with	Swedish Inpatient	2007-2015

GBP	"*J"* except for gastric operation	Register	
Plastic surgery	*QBE, QBJ, QCJ05, QDJ05, QAJ35*	Swedish Inpatient Register	2007-2015
Abdominal pain	*R10.1-4*	Swedish Inpatient Register	2007-2015
All-cause mortality	Everyone in the Cause of Death Register	Cause of Death Register	2007-2015
Fatal coronary heart disease	*I20-24* and entered in the Cause of Death Register	Swedish Inpatient Register & Cause of Death Register	2007-2015
Fatal cardiovascular disease	*I20-24,I61-64* and entered in the Cause of Death Register	Swedish Inpatient Register & Cause of Death Register	2007-2015

Table S2: Risk estimates for men and women (Cox proportional hazards regression)

Outcome	Men HR with 95% CI (n=4024)	Women HR with 95% CI (n=6618)	p-value
All-cause mortality	0.58 (0.45, 0.74)	0.46 (0.35, 0.60)	0.2091
Coronary heart disease	1.14 (0.90, 1.44)	1.12 (0.88, 1.42)	0.9011
Cardiovascular disease	0.63 (0.44, 0.92)	0.69 (0.49, 0.96)	0.7614
Fatal coronary heart disease	0.42 (0.24, 0.73)	0.25 (0.12, 0.54)	0.2853
Fatal cardiovascular disease	0.60 (0.32, 1.14)	0.13 (0.05, 0.36)	0.0118
Acute myocardial infarction	0.55 (0.32, 0.92)	0.56 (0.35, 0.90)	0.9522
Stroke	0.67 (0.32, 1.12)	0.88 (0.55, 1.41)	0.4429
Atrial fibrillation	1.13 (0.86, 1.47)	0.72 (0.53, 0.98)	0.0313
Heart failure	0.63 (0.46, 0.86)	0.35 (0.24, 0.51)	0.0201
Valvular heart disease	0.83 (0.38, 1.84)	0.49 (0.21, 1.13)	0.3645
Hyperglycemia	0.22 (0.09, 0.53)	0.40 (0.23, 0.69)	0.2624
Hypoglycemia with coma	0.79 (0.39, 1.63)	1.21 (0.71, 2.05)	0.3490
Dementia	0.73 (0.19, 2.86)	0.00 (.,.)	0.9991
Kidney disease	0.84 (0.28, 2.54)	0.37 (0.12, 1.13)	0.2995
Amputation	0.82 (0.36, 1.85)	0.16 (0.04, 0.72)	0.0613
Cancer	1.02 (0.69, 1.51)	0.69 (0.53, 0.90)	0.1068
Psychiatric disorder	1.02 (0.76, 1.37)	1.51 (1.23, 1.85)	0.0289
Alcohol abuse	2.87 (1.98, 4.15)	2.94 (1.85, 4.69)	0.9298
Liver diseases	0.53 (0.25, 1.13)	0.92 (0.49, 1.73)	0.2731
Anemia	1.96 (0.96, 4.01)	1.90 (1.24, 2.90)	0.9390

Outcome	Men HR with 95% CI (n=4024)	Women HR with 95% CI (n=6618)	p-value
Bleeding	9.74 (4.69, 20.22)	5.50 (3.26, 9.29)	0.2110
Deep vein thrombosis and pulmonary embolism	1.10 (0.59, 2.03)	0.96 (0.60, 1.55)	0.7455
Bowel obstruction	6.17 (3.33, 11.46)	12.10 (7.10, 20.64)	0.1035
Gastrointestinal leakage	5.28 (1.55, 18.01)	5.73 (1.96, 16.79)	0.9217
Malnutrition	2.72 (1.59, 4.67)	2.86 [1.83, 4.47]	0.8879
Pulmonary complications	0.96 (0.59, 1.56)	0.78 [0.54, 1.12]	0.4915
Wound complications	4.70 (2.79, 7.90)	3.12 [2.36, 4.13]	0.1743
Gastrointestinal ulcer and reflux	5.57 (3.49, 8.89)	5.28 (3.36, 8.31)	0.8719
Hernia	3.53 (2.19, 5.69)	2.47 (1.83, 3.33)	0.2136
Gallstone, gallbladder disease and pancreatitis	2.33 (1.59, 3.41)	2.56 (1.99, 3.30)	0.6810
Gastrointestinal surgery (not gastric bypass)	9.93 (8.35, 11.80)	7.13 (6.37, 7.98)	0.0015
Plastic surgery	16.96 (6.84, 42.07)	20.73 (12.67, 33.92)	0.7024
Abdominal pain	7.22 (4.64, 11.24)	5.12 (4.08, 6.41)	0.1703

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6,7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6, suppl
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8, suppl
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	suppl
		(c) Consider use of a flow diagram	suppl
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, 19
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8,9,19,21
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9,21
		(*b*) Report category boundaries when continuous variables were categorized	9,21
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	suppl
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11,12,13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Pros and cons of gastric bypass surgery in obese individuals with type 2 diabetes: nationwide, matched, observational cohort study

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Secondary Subject Heading:	Surgery
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TITLE PAGE

Complete title: Pros and cons of gastric bypass surgery in obese individuals with type 2 diabetes: nationwide, matched, observational cohort study

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ABSTRACT Word count: 300

Objectives: Long-term effects of gastric bypass (GBP) surgery have been presented in observational and randomized studies, but there are only limited data for obese persons with type 2 diabetes (T2DM) regarding postoperative complications.

Design: This is a nationwide observational study based on two quality registers in Sweden (National Diabetes Register (NDR) and Scandinavian Obesity Surgery Register (SOReg)) and other national databases.

Setting: After merging the data, we matched individuals with T2DM who had undergone GBP with those not surgically treated for obesity on propensity score, based on sex, age, BMI and calendar time. The risks of postoperative outcomes (rehospitalizations) were assessed using Cox regression models.

Participants: We identified 5,321 patients with T2DM in the SOReg and 5,321 matched controls in the NDR, aged 18-65 years, with BMI >27.5 kg/m² and followed for up to 9 years.

Primary and secondary outcome measures: We assessed risks for all-cause mortality and hospitalizations for cardiovascular disease, severe kidney disease, as well as for surgical and other medical conditions.

Results: The results agree with the previously suggested lower risks of all-cause mortality (49%) and cardiovascular disease (34%), and we also found positive effects for severe kidney disease but significantly increased risks (2 to 9-fold) of several short-term complications after GBP, such as abdominal pain and gastrointestinal conditions, frequently requiring surgical procedures, apart from reconstructive plastic surgery. Long-term, the risk of anemia was 92% higher, malnutrition developed approximately 3 times as often, psychiatric diagnoses were 33% more frequent and alcohol abuse was 3 times as great as in the control group.

Conclusions: This nationwide study confirms the benefits and describes the panorama of adverse events after bariatric surgery in obese persons with T2DM. Long-term postoperative monitoring and support, as better selection of patients by appropriate specialists in interdisciplinary settings, should be provided to optimize the outcomes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The major strength of our study is the unique and nationwide character of our population with type 2 diabetes that received gastric bypass operation.
- The high data reliability as well the external validity allow the generalizing of our results to similar developed countries using the same criteria and contraindications for bariatric surgery and quality of care.
- Our nonrandomized observational study may be limited by some minor differences between the matched groups on the propensity score.
- We tried to eliminate major confounders by careful matching between the two groups as well with an adjusted Cox regression model, however we cannot exclude underlying residual confounders.
- We studied effects and postoperative events after gastric bypass in in-patients (rehospitalizations) leaving unassessed a large proportion of out-patients visiting the primary care.

MAIN TEXT

Introduction

The most effective method for ensuring long-term weight reduction in obese individuals as well as beneficial effects on mortality, cardiovascular disease (CVD) and CV risk factors is bariatric surgery, Roux-en-Y gastric bypass (GBP) in particular (1, 2). These effects of GBP have also been shown in patients with type 2 diabetes (T2DM) in both observational (3-5) and randomized control trials (6-8) under different follow-up periods. However, it has also been demonstrated in cohorts with a low proportion of individuals with diabetes that GBP is associated with postoperative complications and readmission rates from 0.6% to 11.3% (9-12), as well as long-term adverse outcomes such as hypoglycemia (6), anemia, nutritional deficiencies (13), gallstones (14), depression (15), suicide and non-fatal self-harm (16) and alcohol problems (17).

Only few reports have addressed the long-term incidence of complications in obese patients with T2DM who have undergone bariatric surgery. The Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) study reported adverse events of GBP and sleeve gastrectomy compared to conventional medical therapy, but only in 142 individuals with T2DM randomized at a single center with follow-up period up to 5 years (6). Similarly, the Diabetes Surgery Study recently reported clinical effects and adverse events after GBP or lifestyle–medical management in 120 individuals after 5 years (18). Larger prospective studies such as Swedish Obese Subjects (SOS) study (1) and large American observational studies with broad samples (10, 19) have addressed postoperative outcomes and readmission rates of GBP or other types of bariatric surgery, but with only a small proportion of patients who have T2DM.

We recently conducted a nationwide observational study of individuals with T2DM who underwent GBP compared with matched individuals and reported beneficial effects on overall mortality and cardiovascular events (3), but we did not address short-term or long-term adverse effects. The objective of this observational cohort study is therefore to identify clinical benefits as well as a wide spectrum of early postoperative, as well as long-term, adverse effects of GBP for up to 9 years in individuals with T2DM compared to obese individuals who have not received surgical treatment.

Research Design and Methods

This study is based on two nationwide quality registers in Sweden: the National Diabetes Register (NDR) and the Scandinavian Obesity Surgery Register (SOReg), as well as linked data from the Swedish Inpatient Register, the Cause of Death Register and the Statistics Sweden. All these databases have previously been described and validated (20, 21). The NDR is a quality register tool that provides nearly full coverage (90% for T2DM and 95% for T1DM) of Swedes with diabetes since 1996. SOReg started in 2007 as a quality and research register. Since 2010, it has covered virtually all bariatric procedures in Sweden. All bariatric centers report to the register (surgical complications, postoperative reports and longitudinal effects).

Patient and Public Involvement

All individuals provided verbal informed consent before being included in the NDR and SOReg databases and that data could be used for research. They did not, however, provide consent for this specific study. Patients have the rights to deny being included in studies by the time of register. Furthermore, data and patients' personal identity numbers identified and replaced by serial numbers in the National Board of Health and Welfare, so patients had not direct

involvement to the design and results of the study. The regional ethical review board at the University of Gothenburg, Sweden, approved the study.

After merging the data of SOReg and NDR, we identified individuals with diabetes and obesity who had undergone primary GBP between January 1, 2007 and December 31, 2015 (see Supplementary material). We subsequently matched them with control patients in the NDR who had not undergone bariatric surgery. Propensity score matching (1:1) was performed on the basis of sex, age (18-75 years), body mass index (BMI) (>27.5 kg/m²) and calendar time.

We based our definition of T2DM on classical epidemiological criteria, i.e., treatment with diet, oral antihyperglycemic agents, insulin or different combinations, as well as patients who were ≥40 years of age at the time of diagnosis.

All clinical characteristics at baseline were obtained from the NDR and SOReg, socioeconomic status was taken from Statistics Sweden, and presurgical and postsurgical diagnoses were taken from the Swedish Inpatient Register (ICD-10) (Table S1, supplementary material), which are held by the National Board of Health and Welfare. The Inpatient Registry records all inpatient admissions since 1987. We studied admissions to the hospitals by including specific diagnoses for coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure and valvular heart disease, as well as acute and chronic diseases that were related to diabetes mellitus (hyperglycemia, hypoglycemia with coma, amputation, kidney, liver and pulmonary diseases, cancer, anemia, malnutrition, dementia, psychiatric disorders and alcohol abuse). We also report surgical history, such as hospitalization due to bleeding, gastrointestinal (GI) surgery and leakage, wound complications, GI ulcers and reflux disease, bowel obstruction, hernia, gall bladder disease and pancreatitis, as well previous plastic surgery.

Patients were followed up to 9 years or until the first admission to the hospital for specific diagnoses or group of diagnoses or death. Controls who were treated with GBP were censored on the date of such treatment.

Statistical analysis

One matched control was selected for each GBP patient using propensity scores for longitudinal exposure (22). The outcome of the propensity score matching was assessed only through descriptive statistics comparing the matched groups. Thus, controls were matched to GBP patients based on the estimated risk score from a Cox regression model with time-updated data, where exposure for GBP was the endpoint. The model contained covariates for sex, age and BMI. Controls were selected in chronological order.

Descriptive statistics are presented using means with standard deviation for age and BMI, median with quartiles for income and counts with percentages for all other variables. Incidence rates for each outcome were estimated using counts and person-years. Comparisons between GBP patients and controls used Cox regression, adjusted for sex, age, BMI and socioeconomic factors (income, marital status, education level and country of origin). No adjustments were made for multiple inferences. Thus, while p-values below 5% were considered statistically significant, the outcome of individual hypothesis tests should be interpreted with caution.

Results

We identified 5,321 patients in the SOReg who had T2DM and had undergone GBP (96.0% laparoscopic, 1.7% initially laparoscopic and converted to open surgery, and 2.3% primary open surgery), as well as 5,321 matched controls in the NDR (flowchart, supplementary material). Both groups were followed for up to 9 years (mean, 4.5 years). Table 1 shows the baseline

characteristics of both groups. There were some minor differences between the groups (standardized differences of more than 0·1): the GBP persons had a slightly higher mean age and BMI and were less likely to be single (marital status), with a greater mean income and higher educational level. The groups were well matched with respect to previous cardiovascular, gastrointestinal, psychiatric and surgical diseases (standardized differences less than 0.1).

Table 2 shows the number of events and incidence rates during the follow-up period. Event rates for all-cause mortality were 72.9 and 142.1 per 10.000 person-years in GBP and the control group respectively (HR 0.51, 95% CI 0.43-0.62; Figure 1A). Risks for cardiovascular or coronary heart disease, acute myocardial infarction and congestive heart failure (Figure 1B) were also lower after GBP.

Other benefits were observed after GBP. Hospitalization for hyperglycemia was less frequent, and the risks of kidney disease (Figure 1C), leg amputation and cancer were lower (Table 2). GBP individuals were, however, at greater risk for anemia (HR 1.92, 95% CI 1.33-2.76) and malnutrition (HR 2.81, 95% CI 1.98-3.97) (Figure 1D). The risks of hospitalization due to psychiatric disorders or alcohol abuse (Figure 1E-F) increased after GBP (73.1 and 26.5 per 10.000 person-years in GBP and the control group respectively, HR 1.33, 95% CI 1.13-1.58 and HR 2.90, 95% CI 2.16-3.88).

A number of adverse conditions, frequently necessitating additional gastrointestinal surgery, were also observed more often in the GBP group: abdominal pain, bowel obstruction, gallstones, gallbladder disease, pancreatitis, gastrointestinal ulcers, reflux, hernia, gastrointestinal leakage, wound complications and bleeding (Figure 2A-E). Subsequent reconstructive plastic surgery (Figure 2F) was also required frequently, while the risk for pulmonary complications, embolism, deep vein thrombosis or liver disease was slightly lower.

We analyzed results of GBP treatment in men and women using a Cox regression model adjusted for sex, age, BMI and socioeconomic factors (Table S2, supplementary material). The significant interactions we noted were risks for fatal CVD, atrial fibrillation, congestive heart failure and gastrointestinal surgery (higher in men after GBP, $p<0.05$), while women were at a higher risk (1.51, 95%CI 1.23-1.85) of being hospitalized due to a psychiatric disorder after GBP.

Discussion

This observational study compares outcomes after GBP (rehospitalizations) in individuals with obesity and TDM2 with a matched group of those who have not been surgically treated. We confirm the previously shown beneficial effects on all-cause mortality and cardiovascular morbidity in individuals with or without T2DM (1, 3), as well as presenting a panorama of short-term and long-term complications after GBP on a nationwide scale. Common reasons for postoperative hospital admissions were gastrointestinal conditions such as abdominal pain, gallstone/gallbladder disease, pancreatitis, gastrointestinal ulcer, leakage, reflux, hernia, bowel obstruction, psychiatric disorders and alcohol abuse.

Additional gastrointestinal surgery was performed in 17.6% of the GBP group, more than three times as much as in the control group. Gastrointestinal leakage, bleeding, abdominal pain and bowel obstruction are likely causes for these surgical interventions, as well as gallstone disease and cholecystitis, which are frequently observed after GBP and rapid weight loss (14, 23-25). Wanjura et al. recently showed that the incidence of cholecystectomy was substantially elevated before GBP and increased 6-36 months after surgery compared with the general population (24). Previous GBP doubled the risk of complications after cholecystectomy, almost quadrupled the risk of reoperation (24) and the simultaneous cholecystectomy increased the risk by increasing of

the operation time (25). It has been suggested that defective gallbladder emptying in conjunction with the production of crystallization-promoting compounds (mucin) can contribute to the development of cholesterol crystals and gallstones in obese subjects during weight reduction (23).

Some postoperative complications were common shortly after GBP (leakage, wound complications and ulcer/reflux), while others (hernia, bowel obstruction and gallstone) generally increased after 1-2 years. These findings were expected, although the incidence of ulcers and reflux disease soon after GBP may be exaggerated due to the endoscopies for dyspepsia and dysphoric symptoms. Hernias may well be undiagnosed preoperatively but detected during surgery and become symptomatic after weight loss when the associated fat disappears. The incidence of wound complications and gastrointestinal leakage shortly after GBP was comparable to other studies with short follow-up periods and a small percentage of patients with diabetes (26-28). There were no major differences between men and women in the risk for specific postoperative complications, apart from a slightly higher incidence of additional surgical procedures and cardiovascular risk (fatal CVD) in men, as previously suggested (11, 29).

There was a 42% lower relative risk of hospitalization due to severe kidney disease after GBP. A systematic review has previously suggested that weight loss is associated with reductions in proteinuria and microalbuminuria. A retrospective cohort study showed a higher mean estimated glomerular filtration rate (eGFR) in patients up to three years after bariatric surgery than those with moderately impaired renal function (CKD stages 3 and 4) who were referred for, but did not receive, surgery (30, 31). There has been no prospective study in patients with severe renal disease. Retrospective data are limited by study design and estimations of renal function. eGFR calculations depend on muscle mass and serum creatinine levels, both of which change after

weight loss independent of kidney function. Although the selection of patients eligible for bariatric surgery can contribute to the apparent beneficial effects on risk of severe kidney disease, these results should prompt new studies concerning the effects on renal function, as well as optimal patients for surgery to treat weight loss. Improved glycemic and blood pressure control after GBP (32, 33) could also contribute to the apparent effects of including changes in dose of antihypertensives, which are known to affect serum creatinine. We did not evaluate glycemic control in this study, but pronounced effects after bariatric surgery have been demonstrated repeatedly (6, 34, 35).

The anatomical and physiological consequences of GBP result in a higher risk of long-term deficiencies of several vitamins and minerals (36). The present study had no access to data from primary care, where follow-up should start 2 years after GBP, but malnutrition and anemia were twice as common. Poor compliance with vitamin and mineral supplements, as well as irregular follow-up, may very likely explain these results. A recent meta-analysis pointed to this potential problem in individuals without diabetes, suggesting that diabetes is not a risk factor per se (13). Adequate supplementation is paramount (37), since deficiencies after GBP tend to increase over time (13, 38).

A history of psychiatric disorders requiring hospitalization was not uncommon in either group of individuals with obesity in this study, and was 33% higher after GBP. Previous studies have shown that depression, which may improve in the first year following bariatric surgery, tends to progress (39) along with suicide and self-harm, particularly if they are preexisting conditions (15, 16). Thus, greater awareness is needed in order to identify vulnerable patients with a history of self-harm or depression who may need psychiatric services after GBP. Perhaps specific multidisciplinary teams should identify such patients and through treatment algorithms could

enhance the safety and efficacy pre and postoperatively (40). In agreement with previous studies (17, 41) we confirmed a higher event rate of alcohol-related problems that lead to hospitalization after GBP, which points to the importance of careful selection of patients who are offered surgery, as well as better follow-up of those with a history of alcohol-related risk behavior. The mechanisms of this well-known phenomenon are still unknown.

The indications for surgical treatment of obesity were presented by the National Institute of Health in 1991 (42) and have been repeatedly revised and expanded over the years. Severe and untreated psychopathology as well as active alcohol or substance abuse, or eating disorders are contraindications to bariatric surgery, although the decision to offer this treatment should always be individualized based on the stability of conditions and the assessment of multidisciplinary treatment teams (43). The need for more robust criteria and the possible application of scoring systems or algorithms that could facilitate the assessment of patients beyond BMI has been discussed (44).

A major strength of this study is its nationwide coverage of patients with obesity and type 2 diabetes, all of whom received recent Roux-en-Y gastric bypass surgery. The results are likely to be generalizable to similar developed countries using the same criteria and contraindications for bariatric surgery and quality of care. All linked databases are characterized by high participation rates and validation of medical data (21, 45).

Our study was nonrandomized and observational, but with carefully matched groups to maximize the size of the cohort as well as to reduce the influence of confounding factors. Minor differences in clinical characteristics may still influence our results, and we also did not include some variables (e.g. duration of diabetes, HbA1c, use of antidiabetic drugs) that potentially also could affect the results. Similarly, we did not exclude patients with multiple comorbidities before the

intervention, because we would have lost substantial data and they had all qualified for GBP. We also used Cox proportional hazards regression modelling, including baseline characteristics, to minimize the effects of confounding. Certainly, we cannot rule out residual confounding, unobserved factors that may be related to both exposure and outcome. However, the external validity is most likely high as our study includes virtually all GBP patients with type 2 diabetes in Sweden during the time period.

Another limitation is that we captured diagnoses during hospitalization, not outpatient care. Comorbidities and incidence of postoperative outcomes may be underestimates as a result, but the systematic flaw could not be avoided. Nevertheless, measurement errors may potentially arise because the patients who had received surgery were followed up more frequently than the control group. GBP was the only surgical procedure we studied (96% laparoscopic), given that sleeve gastrectomy and duodenal switch were not performed very often and follow-up data were too limited during the study period. We also did not address the importance of more specific surgical techniques.

Individuals with obesity and type 2 diabetes who have undergone GBP are generally at a reduced risk of all-cause mortality and cardiovascular morbidity, as well as severe kidney disease and cancer to a lesser extent. They also have, however, significantly higher risks of postoperative complications and adverse events both short-term and long-term, mostly abdominal pain and gastrointestinal conditions that frequently require additional surgical procedures, apart from reconstructive plastic surgery. Long-term consequences observed more often are anemia, malnutrition, psychiatric disorders and alcohol abuse. In order to maximize the benefit and minimize the risk of problems, long-term postoperative monitoring and support should be

provided. Better selection of patients for such treatment, performed by appropriate specialists in interdisciplinary settings, could probably also optimize outcomes.

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Competing of interest: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing statement: This is a registry study and therefore the data generated is not suitable for sharing beyond that contained within the report. Further information can be obtained from the corresponding author.

Ethical Approval: Ethics Review Board of the University of Gothenburg approved this study.

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Figure legends:

Figure 1A-F: Cumulative incidence of postoperative outcomes during the 9-years follow up. All-cause mortality; Congestive heart failure; Kidney disease; Malnutrition; Psychiatric disorder; Alcohol abuse.

Figure 2A-F: Cumulative incidence of postoperative adverse events during the 9-years follow-up. Gastrointestinal (GI) surgery; Abdominal pain; Bowel obstruction; Gallstone and gallbladder disease; Wound complications; Plastic surgery.

Table 1. Baseline characteristics

	GBP (n=5321)	Control (n=5321)	Standardized difference*
Sex			
Men	2098 (39.4%)	1926 (36.2%)	0.0471
Women	3223 (60.5%)	3395 (63.8%)	0.0471
Age	49.0 (9.5)	47.1 (11.5)	0.122
BMI	42.0 (5.7)	40.9 (7.3)	0.117
Income (SEK)	199.638 (139136; 261558)	168.380 (121840; 239368)	0.156
Marital status			
Single	1602 (30.1%)	2064 (38.8%)	0.130
Married	2518 (47.4%)	2227 (41.9%)	0.0781
Separated	1092 (20.5%)	881 (16.6%)	0.0723
Widowed	106 (2.0%)	147 (2.8%)	0.0358
Education level			
Compulsory school	1069 (20.1%)	1431 (26.9%)	0.114
University	3192 (60.0%)	2847 (53.5%)	0.0926
Upper secondary school	1037 (19.5%)	930 (17.5%)	0.0366
Missing data	23 (0.4%)	113 (2.1%)	0.107
Country of origin			
Sweden	4261 (80.1%)	4027 (75.7%)	0.075
Rest of Europe	514 (9.7%)	602 (11.3%)	0.0382
Rest of the world	546 (10.3%)	692 (13.0%)	0.0607
Cardiovascular			
Cardiovascular disease	273 (5.1%)	261 (4.9%)	0.00730
Acute myocardial infarction	173 (3.2%)	169 (3.2%)	0.00301
Coronary heart disease	395 (7.4%)	313 (5.9%)	0.0437
Congestive heart failure	140 (2.6%)	168 (3.2%)	0.0222
Atrial fibrillation	148 (2.8%)	149 (2.8%)	0.000807
Valvular heart disease	24 (0.4%)	27 (0.5%)	0.00577
Stroke	109 (2.0%)	103 (1.9%)	0.00571
Deep vein thrombosis/pulmonary embolism	71 (1.3%)	65 (1.2%)	0.00710
Diabetes-related			
Hyperglycemia	80 (1.5%)	130 (2.4%)	0.0478
Hypoglycemia (with or without coma)	57 (1.1%)	61 (1.2%)	0.00508

Numbers and proportions.

*Difference between sample means divided by standard deviation. Acceptable significance when standardized difference <0.1.

Gastrointestinal			
Gastrointestinal surgery (not gastric bypass)	549 (10.3%)	644 (12.1%)	0.0400
Abdominal pain	386 (7.2%)	334 (6.3%)	0.0275
Gallstone, gallbladder disease and pancreatitis	419 (7.9%)	366 (6.9%)	0.0270
Gastrointestinal ulcer and reflux	86 (1.6%)	72 (1.4%)	0.0154
Hernia	204 (3.8%)	160 (3.0%)	0.0322
Bowel obstruction	18 (0.3%)	29 (0.6%)	0.0220
Gastrointestinal leakage	7 (0.1%)	17 (0.3%)	0.0280
Liver disease	16 (0.3%)	26 (0.5%)	0.0212
Surgical			
Plastic surgery	54 (1.0%)	33 (0.6%)	0.0310
Wound complications	192 (3.6%)	156 (2.9%)	0.0269
Bleeding	50 (0.9%)	32 (0.6%)	0.0273
Other			
Psychiatric disorders	318 (6.0%)	346 (6.5%)	0.0154
Alcohol abuse	94 (1.8%)	122 (2.3%)	0.0264
Cancer	111 (2.1%)	158 (3.0%)	0.0398
Malnutrition	21 (0.4%)	41 (0.8%)	0.0349
Kidney disease	56 (1.0%)	83 (1.6%)	0.0316
Pulmonary disease	128 (2.4%)	131 (2.5%)	0.00259
Anemia	55 (1.0%)	60 (1.1%)	0.00643
Amputation	10 (0.2%)	12 (0.2%)	0.00585
Dementia	1 (0.02%)	4 (0.08%)	0.0184

Table 2. Number of events and event rates during follow up

Outcome	GBP (n=5321)	Control (n=5321)	Hazard ratio [95% CI]	p-value
All-cause mortality	183 (72.90)	351 (142.06)	0.51 [0.43, 0.62]	<.0001
Cardiovascular				
Cardiovascular disease	108 (43.54)	150 (61.54)	0.66 [0.51, 0.85]	0.0014
Fatal cardiovascular disease	21 (8.38)	64 (25.94)	0.34 [0.20, 0.56]	<.0001
Acute myocardial infarction	51 (20.43)	85 (34.69)	0.55 [0.39, 0.79]	0.0010

Table 2. Number of events and event rates during follow up

Outcome	GBP (n=5321)	Control (n=5321)	Hazard ratio [95% CI]	p-value
Coronary heart disease	309 (128.66)	274 (114.28)	1.13 [0.95, 1.34]	0.156
Fatal coronary heart disease	28 (11.17)	77 (31.20)	0.35 [0.22, 0.54]	<.0001
Congestive heart failure	109 (43.94)	225 (93.05)	0.49 [0.39, 0.62]	<.0001
Atrial fibrillation	204 (83.64)	213 (88.16)	0.93 [0.76, 1.14]	0.486
Valvular heart disease	21 (8.39)	32 (13.00)	0.64 [0.36, 1.14]	0.131
Stroke	59 (23.69)	71 (28.94)	0.77 [0.54, 1.10]	0.158
Deep vein thrombosis/pulmonary embolism	56 (22.48)	59 (24.07)	1.01 [0.69, 1.48]	0.952
Diabetes-related				
Hypoglycemia (with or without coma)	43 (17.24)	46 (18.72)	1.04 [0.68, 1.60]	0.844
Hyperglycemia	23 (9.20)	89 (36.37)	0.33 [0.21, 0.53]	<.0001
Gastrointestinal				
Gastrointestinal surgery (not gastric bypass)	936 (422.59)	301 (125.76)	3.33 [2.91, 3.80]	<.0001
Abdominal pain	558 (239.25)	124 (50.94)	5.52 [4.51, 6.75]	<.0001
Gallstone, gallbladder disease and pancreatitis	312 (129.31)	125 (51.30)	2.49 [2.02, 3.08]	<.0001
Gastrointestinal ulcer and reflux	239 (98.58)	46 (18.73)	5.42 [3.91, 7.51]	<.0001
Hernia	235 (97.00)	86 (35.17)	2.75 [2.14, 3.54]	<.0001
Bowel obstruction	232 (95.29)	27 (10.97)	9.47 [6.31, 14.20]	<.0001
Gastrointestinal leakage	40 (16.05)	7 (2.84)	5.54 [2.46, 12.45]	<.0001
Liver disease	30 (12.00)	40 (16.26)	0.73 [0.45, 1.19]	0.205
Surgical				
Plastic surgery	380 (158.08)	22 (8.94)	19.85 [12.86, 30.67]	<.0001
Wound complications	290 (120.87)	87 (35.55)	3.45 [2.70, 4.42]	<.0001
Bleeding	172 (70.50)	26 (10.57)	6.87 [4.49, 10.52]	<.0001
Other				
Psychiatric disorder	317 (131.64)	268 (111.93)	1.33 [1.13, 1.58]	0.0008
Alcohol abuse	180 (73.10)	65 (26.52)	2.90 [2.16, 3.88]	<.0001
Cancer	153 (61.80)	188 (77.41)	0.78 [0.63, 0.97]	0.0257
Malnutrition	128 (51.69)	46 (18.72)	2.81 [1.98, 3.97]	<.0001
Kidney disease	105 (42.38)	187 (76.87)	0.58 [0.45, 0.75]	<.0001
Pulmonary complications	86 (34.66)	114 (46.64)	0.84 [0.63, 1.13]	0.249

Table 2. Number of events and event rates during follow up				
Outcome	**GBP (n=5321)**	**Control (n=5321)**	**Hazard ratio [95% CI]**	**p-value**
Anemia	84 (33.78)	46 (18.71)	1.92 [1.33, 2.76]	0.0005
Amputation	15 (5.99)	23 (9.33)	0.51 [0.26, 0.98]	0.0432
Dementia	4 (1.60)	12 (4.87)	0.46 [0.14, 1.57]	0.214

Event rates (%) per 10.000 person-years.

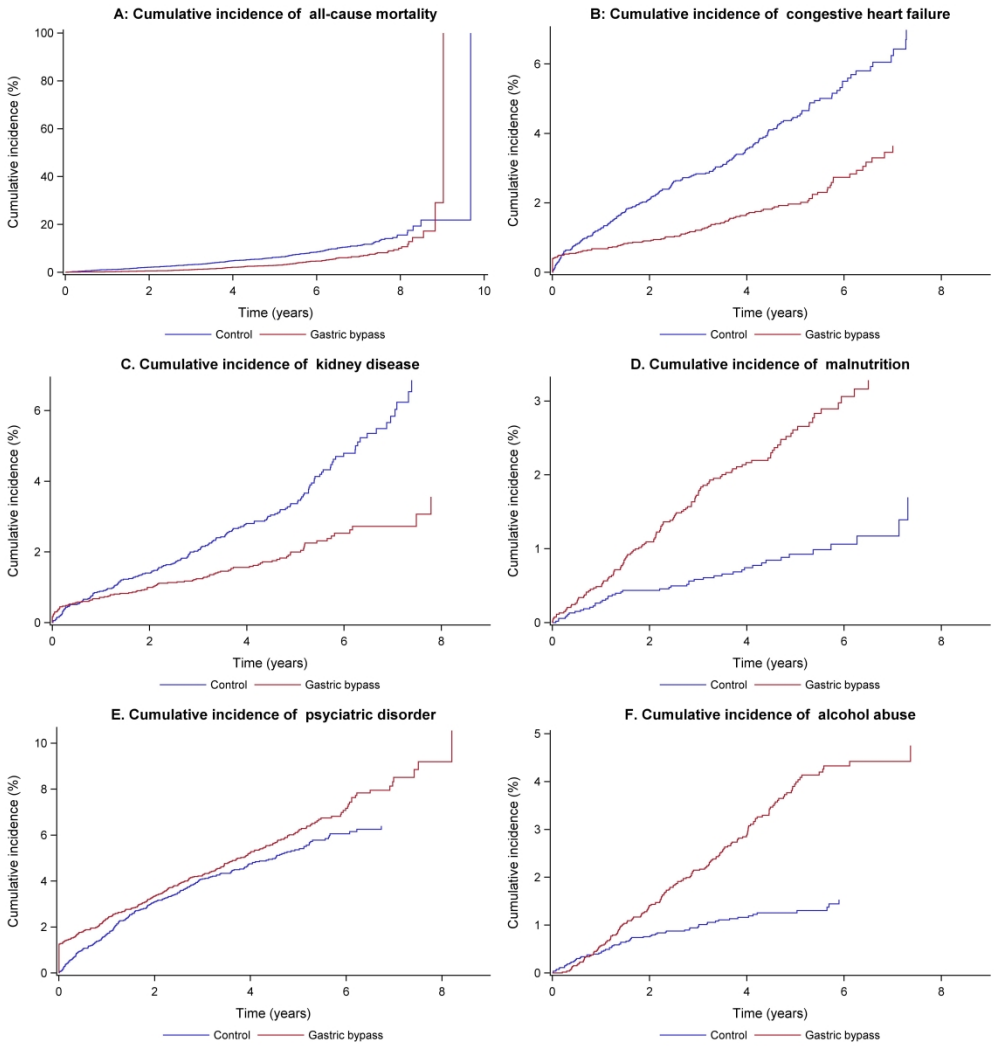


Figure 1A-F: Cumulative incidence of postoperative outcomes during the 9-years follow up. All-cause mortality; Congestive heart failure; Kidney disease; Malnutrition; Psychiatric disorder; Alcohol abuse.

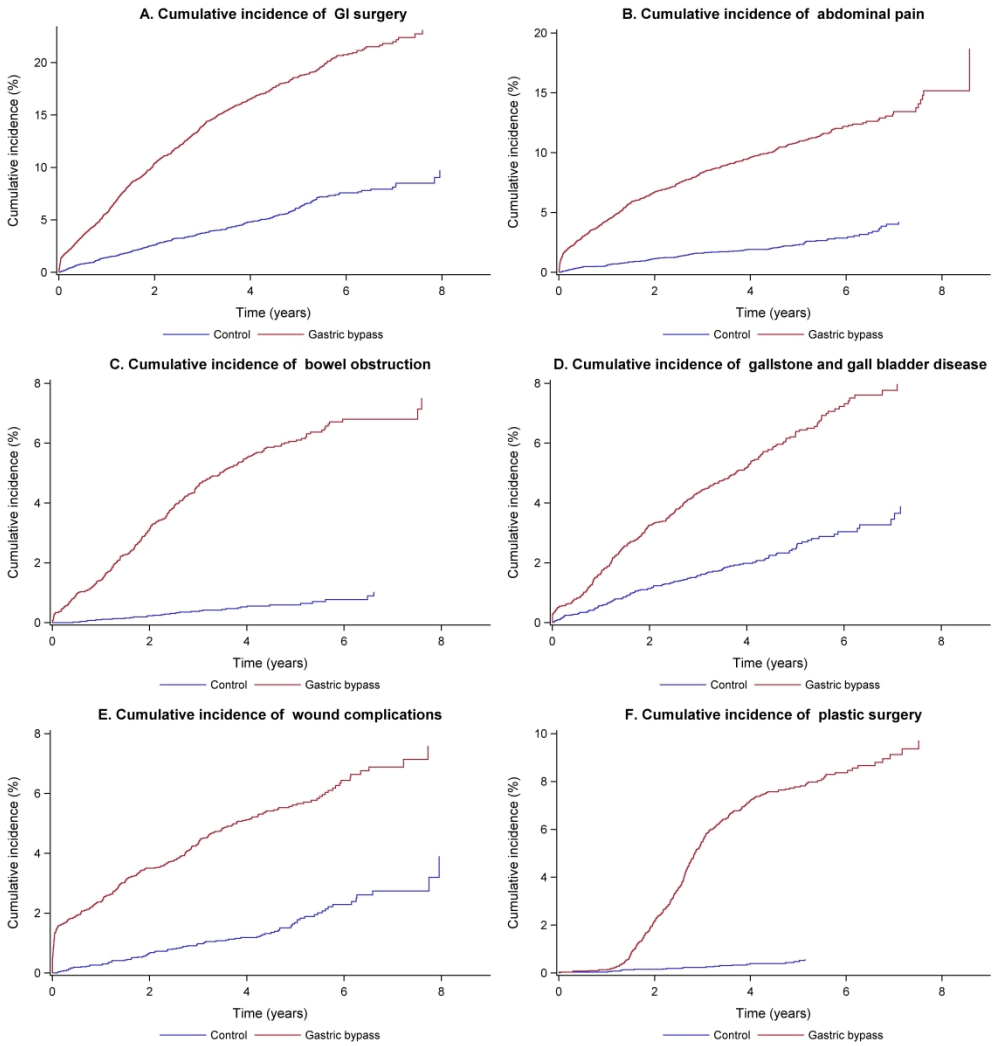


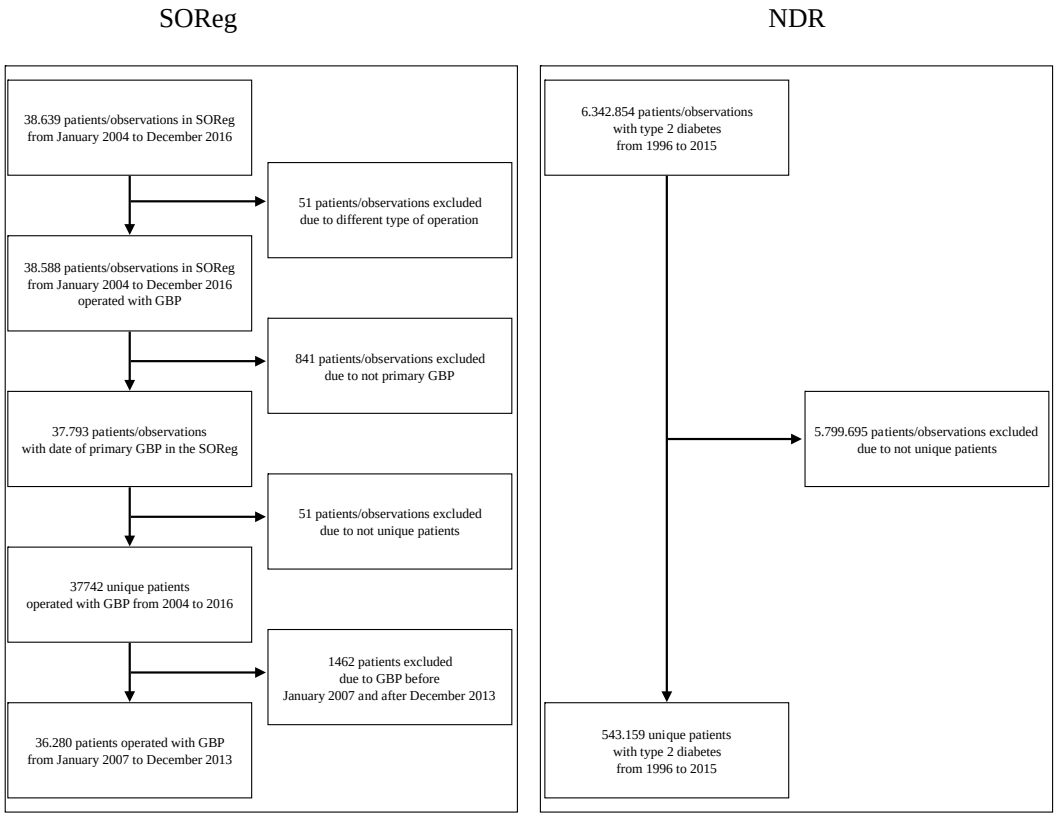
Figure 2A-F: Cumulative incidence of postoperative adverse events during the 9-years follow-up. Gastrointestinal (GI) surgery; Abdominal pain; Bowel obstruction; Gallstone and gallbladder disease; Wound complications; Plastic surgery

SUPPLEMENTARY MATERIAL

Table of contents

Flowchart

Selection of our data from Scandinavian Obesity Surgery Register (SOReg) before merging with data from the National Diabetes Registry (NDR).



Merging the two databases led to our study population of 5,321 patients in the SOReg who had T2DM and had undergone GBP, and 5,321 matched control patients in the NDR.

Methods – database linkages

This study is based on data from the NDR and SOReg. Both registers are linked to Statistics Sweden at the National Board of Health and Welfare, which also stores data in the Swedish Inpatient Register (1997-2015).

We filed an application with our data and personal identity numbers [SOReg (2007-2013) & NDR (1996-2015)] to the National Board of Health and Welfare, from which all personal identity numbers have been identified and replaced by serial numbers. The coded data from the National Board of Health and Welfare were subsequently forwarded to Statistics Sweden for linkage with the Inpatient Register and LISA Database, which provides socioeconomic data. The linked data were then returned to us for validation and analysis.

Table S1: Pre-index diagnoses and outcomes after GBP

Diagnoses before and after gastric bypass surgery (index date) until December 2015 according to ICD-10.

Diagnosis	ICD-10	Variable origin	Registration period
Acute Myocardial infarction	*I21*	Swedish Inpatient Register	2007-2015
Coronary heart disease	*I20-25*	Swedish Inpatient Register	2007-2015
Stroke	*I61-64*	Swedish Inpatient Register	2007-2015
Cardiovascular disease	*I21, I61-64*	Swedish Inpatient Register	2007-2015
Atrial fibrillation	*I48*	Swedish Inpatient Register	2007-2015
Heart failure	*I50*	Swedish Inpatient Register	2007-2015
Valvular heart disease	*I05-09, I34-37, Q22, Q23*	Swedish Inpatient Register	2007-2015
Liver disease	*K70-74*	Swedish Inpatient Register	2007-2015
Kidney disease	*V42A, V45B, V56A, V56W, Z940, Z491, Z492, Z992, N17-19, N99*	Swedish Inpatient Register	2007-2015
Hyperglycemia	*E100, E101, E110, E111, E120, E121, E130, E131, E140, E141, R739*	Swedish Inpatient Register	2007-2015
Hypoglycemia (with or without coma)	*E100, E106A, E110, E110C, E110X, E116A, E120, E130, E140, E159, E160, E161W, E162, R402*	Swedish Inpatient Register	2007-2015
Cancer	*C0-9*	Swedish Inpatient Register	2007-2015

Dementia	*G300, G301, G308, G309, G31, F00-03*	Swedish Inpatient Register	2007-2015
Psychiatric disorders	*F11-19, F20-29, F30-39, F50, F55, F40-F43, F60, F61, F68, F69, F99*	Swedish Inpatient Register	2007-2015
Alcohol abuse	*F10*	Swedish Inpatient Register	2007-2015
Anemia	*D508-9, D51.0,3,8, D520*	Swedish Inpatient Register	2007-2015
Malnutrition	*E15-16, E51.2, E42-44, E46, E50-64, G63.3-4, G62.9, K91.1-2, M81.3, M83.2*	Swedish Inpatient Register	2007-2015
Bleeding	*T81.0*	Swedish Inpatient Register	2007-2015
Deep vein thrombosis and pulmonary embolism	*I80.0-9, I26, I81*	Swedish Inpatient Register	2007-2015
Amputation	*NHQ09, 11-14, 16, 17, 99, NGQ09, 19, 99, NFQ19, 99*	Swedish Inpatient Register	2007-2015
Bowel obstruction	*K56, K45*	Swedish Inpatient Register	2007-2015
Gastrointestinal leakage	*T84.4, K65.0, K63.1*	Swedish Inpatient Register	2007-2015
Pulmonary complications	*J18.0-9, J69.0, J80, J98.1*	Swedish Inpatient Register	2007-2015
Wound complications	*T81.3-4, K43.0-9*	Swedish Inpatient Register	2007-2015
Gastrointestinal ulcer and reflux	*K21, K22.1-3, K25-26, K28*	Swedish Inpatient Register	2007-2015
Hernia	*K40-43*	Swedish Inpatient Register	2007-2015
Gallstone, gallbladder disease and pancreatitis	*K80-85*	Swedish Inpatient Register	2007-2015
Gastrointestinal surgery not	All the operative diagnoses with	Swedish Inpatient	2007-2015

GBP	"*J"* except for gastric operation	Register	
Plastic surgery	*QBE, QBJ, QCJ05, QDJ05, QAJ35*	Swedish Inpatient Register	2007-2015
Abdominal pain	*R10.1-4*	Swedish Inpatient Register	2007-2015
All-cause mortality	Everyone in the Cause of Death Register	Cause of Death Register	2007-2015
Fatal coronary heart disease	*I20-24* and entered in the Cause of Death Register	Swedish Inpatient Register & Cause of Death Register	2007-2015
Fatal cardiovascular disease	*I20-24,I61-64* and entered in the Cause of Death Register	Swedish Inpatient Register & Cause of Death Register	2007-2015

Table S2: Risk estimates for men and women (Cox proportional hazards regression)

Outcome	Men HR with 95% CI (n=4024)	Women HR with 95% CI (n=6618)	p-value
All-cause mortality	0.58 (0.45, 0.74)	0.46 (0.35, 0.60)	0.2091
Coronary heart disease	1.14 (0.90, 1.44)	1.12 (0.88, 1.42)	0.9011
Cardiovascular disease	0.63 (0.44, 0.92)	0.69 (0.49, 0.96)	0.7614
Fatal coronary heart disease	0.42 (0.24, 0.73)	0.25 (0.12, 0.54)	0.2853
Fatal cardiovascular disease	0.60 (0.32, 1.14)	0.13 (0.05, 0.36)	0.0118
Acute myocardial infarction	0.55 (0.32, 0.92)	0.56 (0.35, 0.90)	0.9522
Stroke	0.67 (0.32, 1.12)	0.88 (0.55, 1.41)	0.4429
Atrial fibrillation	1.13 (0.86, 1.47)	0.72 (0.53, 0.98)	0.0313
Heart failure	0.63 (0.46, 0.86)	0.35 (0.24, 0.51)	0.0201
Valvular heart disease	0.83 (0.38, 1.84)	0.49 (0.21, 1.13)	0.3645
Hyperglycemia	0.22 (0.09, 0.53)	0.40 (0.23, 0.69)	0.2624
Hypoglycemia with coma	0.79 (0.39, 1.63)	1.21 (0.71, 2.05)	0.3490
Dementia	0.73 (0.19, 2.86)	0.00 (.,.)	0.9991
Kidney disease	0.84 (0.28, 2.54)	0.37 (0.12, 1.13)	0.2995
Amputation	0.82 (0.36, 1.85)	0.16 (0.04, 0.72)	0.0613
Cancer	1.02 (0.69, 1.51)	0.69 (0.53, 0.90)	0.1068
Psychiatric disorder	1.02 (0.76, 1.37)	1.51 (1.23, 1.85)	0.0289
Alcohol abuse	2.87 (1.98, 4.15)	2.94 (1.85, 4.69)	0.9298
Liver diseases	0.53 (0.25, 1.13)	0.92 (0.49, 1.73)	0.2731
Anemia	1.96 (0.96, 4.01)	1.90 (1.24, 2.90)	0.9390

Outcome	Men HR with 95% CI (n=4024)	Women HR with 95% CI (n=6618)	p-value
Bleeding	9.74 (4.69, 20.22)	5.50 (3.26, 9.29)	0.2110
Deep vein thrombosis and pulmonary embolism	1.10 (0.59, 2.03)	0.96 (0.60, 1.55)	0.7455
Bowel obstruction	6.17 (3.33, 11.46)	12.10 (7.10, 20.64)	0.1035
Gastrointestinal leakage	5.28 (1.55, 18.01)	5.73 (1.96, 16.79)	0.9217
Malnutrition	2.72 (1.59, 4.67)	2.86 [1.83, 4.47]	0.8879
Pulmonary complications	0.96 (0.59, 1.56)	0.78 [0.54, 1.12]	0.4915
Wound complications	4.70 (2.79, 7.90)	3.12 [2.36, 4.13]	0.1743
Gastrointestinal ulcer and reflux	5.57 (3.49, 8.89)	5.28 (3.36, 8.31)	0.8719
Hernia	3.53 (2.19, 5.69)	2.47 (1.83, 3.33)	0.2136
Gallstone, gallbladder disease and pancreatitis	2.33 (1.59, 3.41)	2.56 (1.99, 3.30)	0.6810
Gastrointestinal surgery (not gastric bypass)	9.93 (8.35, 11.80)	7.13 (6.37, 7.98)	0.0015
Plastic surgery	16.96 (6.84, 42.07)	20.73 (12.67, 33.92)	0.7024
Abdominal pain	7.22 (4.64, 11.24)	5.12 (4.08, 6.41)	0.1703

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6,7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6, suppl
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8, suppl
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	suppl
		(c) Consider use of a flow diagram	suppl
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8,20,21
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8,9,20,21,22,23
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9,22,23
		(*b*) Report category boundaries when continuous variables were categorized	9,22,23
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	suppl
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11,12,13,14,15
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Pros and cons of gastric bypass surgery in individuals with obesity and type 2 diabetes: nationwide, matched, observational cohort study

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Secondary Subject Heading:	Surgery
Keywords:	DIABETES & ENDOCRINOLOGY, SURGERY, Adverse events < THERAPEUTICS

TITLE PAGE

Complete title: Pros and cons of gastric bypass surgery in individuals with obesity and type 2 diabetes: nationwide, matched, observational cohort study

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ABSTRACT Word count: 300

Objectives: Long-term effects of gastric bypass (GBP) surgery have been presented in observational and randomized studies, but there are only limited data for persons with obesity and type 2 diabetes (T2DM) regarding postoperative complications.

Design: This is a nationwide observational study based on two quality registers in Sweden (National Diabetes Register (NDR) and Scandinavian Obesity Surgery Register (SOReg)) and other national databases.

Setting: After merging the data, we matched individuals with T2DM who had undergone GBP with those not surgically treated for obesity on propensity score, based on sex, age, BMI and calendar time. The risks of postoperative outcomes (rehospitalizations) were assessed using Cox regression models.

Participants: We identified 5,321 patients with T2DM in the SOReg and 5,321 matched controls in the NDR, aged 18-65 years, with BMI >27.5 kg/m² and followed for up to 9 years.

Primary and secondary outcome measures: We assessed risks for all-cause mortality and hospitalizations for cardiovascular disease, severe kidney disease, along with surgical and other medical conditions.

Results: The results agree with the previously suggested lower risks of all-cause mortality (49%) and cardiovascular disease (34%), and we also found positive effects for severe kidney disease but significantly increased risks (2 to 9-fold) of several short-term complications after GBP, such as abdominal pain and gastrointestinal conditions, frequently requiring surgical procedures, apart from reconstructive plastic surgery. Long-term, the risk of anemia was 92% higher, malnutrition developed approximately 3 times as often, psychiatric diagnoses were 33% more frequent and alcohol abuse was 3 times as great as in the control group.

Conclusions: This nationwide study confirms the benefits and describes the panorama of adverse events after bariatric surgery in persons with obesity and T2DM. Long-term postoperative monitoring and support, as better selection of patients by appropriate specialists in interdisciplinary settings, should be provided to optimize the outcomes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The major strength of our study is the unique and nationwide character of our population with type 2 diabetes that received gastric bypass operation.
- The high data reliability as well the external validity allow the generalizing of our results to similar developed countries using the same criteria and contraindications for bariatric surgery and quality of care.
- Our nonrandomized observational study may be limited by some minor differences between the matched groups on the propensity score.
- We tried to eliminate major confounders by careful matching between the two groups as well with an adjusted Cox regression model, however we cannot exclude underlying residual confounders.
- We studied effects and postoperative events after gastric bypass in in-patients (rehospitalizations) leaving unassessed a large proportion of out-patients visiting the primary care.

MAIN TEXT

Introduction

The most effective method for ensuring long-term weight reduction in individuals with obesity as well as beneficial effects on mortality, cardiovascular disease (CVD) and CV risk factors is bariatric surgery, Roux-en-Y gastric bypass (GBP) in particular (1, 2). These effects of GBP have also been shown in patients with type 2 diabetes (T2DM) in both observational (3-5) and randomized control trials (6-8) under different follow-up periods. However, it has also been demonstrated in cohorts with a low proportion of individuals with diabetes that GBP is associated with postoperative complications and readmission rates from 0.6% to 11.3% (9-12), as well as long-term adverse outcomes such as hypoglycemia (6), anemia, nutritional deficiencies (13), gallstones (14), depression (15), suicide and non-fatal self-harm (16) and alcohol problems (17).

Only few reports have addressed the long-term incidence of complications in patients with obesity and T2DM who have undergone bariatric surgery. The Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) study reported adverse events of GBP and sleeve gastrectomy compared to conventional medical therapy, but only in 142 individuals with T2DM randomized at a single center with follow-up period up to 5 years (6). Similarly, the Diabetes Surgery Study recently reported clinical effects and adverse events after GBP or lifestyle–medical management in 120 individuals after 5 years (18). Larger prospective studies such as Swedish Obese Subjects (SOS) study (1) and large American observational studies with broad samples (10, 19) have addressed postoperative outcomes and

readmission rates of GBP or other types of bariatric surgery, but with only a small proportion of patients who have T2DM.

We recently conducted a nationwide observational study of individuals with T2DM who underwent GBP compared with matched individuals and reported beneficial effects on overall mortality and cardiovascular events (3), but we did not address short-term or long-term adverse effects. The objective of this observational cohort study is therefore to identify clinical benefits as well as a wide spectrum of early postoperative, as well as long-term, adverse effects of GBP for up to 9 years in individuals with T2DM compared to individuals with obesity who have not received surgical treatment.

Research Design and Methods

This study is based on two nationwide quality registers in Sweden: the National Diabetes Register (NDR) and the Scandinavian Obesity Surgery Register (SOReg), as well as linked data from the Swedish Inpatient Register, the Cause of Death Register and the Statistics Sweden. All these databases have previously been described and validated (20, 21). The NDR is a quality register tool that provides nearly full coverage (90% for T2DM and 95% for T1DM) of Swedes with diabetes since 1996. SOReg started in 2007 as a quality and research register. Since 2010, it has covered virtually all bariatric procedures in Sweden. All bariatric centers report to the register (surgical complications, postoperative reports and longitudinal effects). All individuals provided informed consent before being included in the NDR and SOReg registries. The regional ethical review board at the University of Gothenburg, Sweden, approved the study.

After merging the data of SOReg and NDR, we identified individuals with diabetes and obesity who had undergone primary GBP between January 1, 2007 and December 31, 2015 (see

Supplementary material). We subsequently matched them with control patients in the NDR who had not undergone bariatric surgery. Propensity score matching (1:1) was performed on the basis of sex, age (18-75 years), body mass index (BMI) (>27.5 kg/m²) and calendar time.

We based our definition of T2DM on classical epidemiological criteria, i.e., treatment with diet, oral antihyperglycemic agents, insulin or different combinations, as well as patients who were ≥40 years of age at the time of diagnosis.

All clinical characteristics at baseline were obtained from the NDR and SOReg, socioeconomic status was taken from Statistics Sweden, and presurgical and postsurgical diagnoses were taken from the Swedish Inpatient Register (ICD-10) (Table S1, supplementary material), which are held by the National Board of Health and Welfare. The Inpatient Registry records all inpatient admissions since 1987. We studied admissions to the hospitals by including specific diagnoses for coronary heart disease, acute myocardial infarction, stroke, atrial fibrillation, heart failure and valvular heart disease, as well as acute and chronic diseases that were related to diabetes mellitus (hyperglycemia, hypoglycemia with coma, amputation, kidney, liver and pulmonary diseases, cancer, anemia, malnutrition, dementia, psychiatric disorders and alcohol abuse). We also report surgical history, such as hospitalization due to bleeding, gastrointestinal (GI) surgery and leakage, wound complications, GI ulcers and reflux disease, bowel obstruction, hernia, gall bladder disease and pancreatitis, as well previous plastic surgery.

Patients were followed up to 9 years or until the first admission to the hospital for specific diagnoses or group of diagnoses or death. Controls who were treated with GBP were censored on the date of such treatment.

Statistical analysis

One matched control was selected for each GBP patient using propensity scores for longitudinal exposure (22). The outcome of the propensity score matching was assessed only through descriptive statistics comparing the matched groups. Thus, controls were matched to GBP patients based on the estimated risk score from a Cox regression model with time-updated data, where exposure for GBP was the endpoint. The model contained covariates for sex, age and BMI. Controls were selected in chronological order.

Descriptive statistics are presented using means with standard deviation for age and BMI, median with quartiles for income and counts with percentages for all other variables. Incidence rates for each outcome were estimated using counts and person-years. Comparisons between GBP patients and controls used Cox regression, adjusted for sex, age, BMI and socioeconomic factors (income, marital status, education level and country of origin). No adjustments were made for multiple inferences. Thus, while p-values below 5% were considered statistically significant, the outcome of individual hypothesis tests should be interpreted with caution.

Patient and Public Involvement Statement

The authors developed the research question and outcome measures. The patients and public were not involved in the design or conduct of the study. The results will be disseminated to study participants via media and health centres.

Results

We identified 5,321 patients in the SOReg who had T2DM and had undergone GBP (96.0% laparoscopic, 1.7% initially laparoscopic and converted to open surgery, and 2.3% primary open surgery), as well as 5,321 matched controls in the NDR (flowchart, supplementary material). Both groups were followed for up to 9 years (mean, 4.5 years). Table 1 shows the baseline

characteristics of both groups. There were some minor differences between the groups (standardized differences of more than 0·1): the GBP persons had a slightly higher mean age and BMI and were less likely to be single (marital status), with a greater mean income and higher educational level. The groups were well matched with respect to previous cardiovascular, gastrointestinal, psychiatric and surgical diseases (standardized differences less than 0.1).

Table 2 shows the number of events and incidence rates during the follow-up period. Event rates for all-cause mortality were 72.9 and 142.1 per 10.000 person-years in GBP and the control group respectively (HR 0.51, 95% CI 0.43-0.62; Figure 1A). Risks for cardiovascular or coronary heart disease, acute myocardial infarction and congestive heart failure (Figure 1B) were also lower after GBP.

Other benefits were observed after GBP. Hospitalization for hyperglycemia was less frequent, and the risks of kidney disease (Figure 1C), leg amputation and cancer were lower (Table 2). GBP individuals were, however, at greater risk for anemia (HR 1.92, 95% CI 1.33-2.76) and malnutrition (HR 2.81, 95% CI 1.98-3.97) (Figure 1D). The risks of hospitalization due to psychiatric disorders or alcohol abuse (Figure 1E-F) increased after GBP (73.1 and 26.5 per 10.000 person-years in GBP and the control group respectively, HR 1.33, 95% CI 1.13-1.58 and HR 2.90, 95% CI 2.16-3.88).

A number of adverse conditions, frequently necessitating additional gastrointestinal surgery, were also observed more often in the GBP group: abdominal pain, bowel obstruction, gallstones, gallbladder disease, pancreatitis, gastrointestinal ulcers, reflux, hernia, gastrointestinal leakage, wound complications and bleeding (Figure 2A-E). Subsequent reconstructive plastic surgery (Figure 2F) was also required frequently, while the risk for pulmonary complications, embolism, deep vein thrombosis or liver disease was slightly lower.

We analyzed results of GBP treatment in men and women using a Cox regression model adjusted for sex, age, BMI and socioeconomic factors (Table S2, supplementary material). The significant interactions we noted were risks for fatal CVD, atrial fibrillation, congestive heart failure and gastrointestinal surgery (higher in men after GBP, $p<0.05$), while women were at a higher risk (1.51, 95%CI 1.23-1.85) of being hospitalized due to a psychiatric disorder after GBP.

Discussion

This observational study compares outcomes after GBP (rehospitalizations) in individuals with obesity and TDM2 with a matched group of those who have not been surgically treated. We confirm the previously shown beneficial effects on all-cause mortality and cardiovascular morbidity in individuals with or without T2DM (1, 3), as well as presenting a panorama of short-term and long-term complications after GBP on a nationwide scale. Common reasons for postoperative hospital admissions were gastrointestinal conditions such as abdominal pain, gallstone/gallbladder disease, pancreatitis, gastrointestinal ulcer, leakage, reflux, hernia, bowel obstruction, psychiatric disorders and alcohol abuse.

Additional gastrointestinal surgery was performed in 17.6% of the GBP group, more than three times as much as in the control group. Gastrointestinal leakage, bleeding, abdominal pain and bowel obstruction are likely causes for these surgical interventions, as well as gallstone disease and cholecystitis, which are frequently observed after GBP and rapid weight loss (14, 23-25). Wanjura et al. recently showed that the incidence of cholecystectomy was substantially elevated before GBP and increased 6-36 months after surgery compared with the general population (24). Previous GBP doubled the risk of complications after cholecystectomy, almost quadrupled the risk of reoperation (24) and the simultaneous cholecystectomy increased the risk by increasing of

the operation time (25). It has been suggested that defective gallbladder emptying in conjunction with the production of crystallization-promoting compounds (mucin) can contribute to the development of cholesterol crystals and gallstones in subjects with obesity during weight reduction (23).

Some postoperative complications were common shortly after GBP (leakage, wound complications and ulcer/reflux), while others (hernia, bowel obstruction and gallstone) generally increased after 1-2 years. These findings were expected, although the incidence of ulcers and reflux disease soon after GBP may be exaggerated due to the endoscopies for dyspepsia and dysphoric symptoms. Hernias may well be undiagnosed preoperatively but detected during surgery and become symptomatic after weight loss when the associated fat disappears. The incidence of wound complications and gastrointestinal leakage shortly after GBP was comparable to other studies with short follow-up periods and a small percentage of patients with diabetes (26-28). There were no major differences between men and women in the risk for specific postoperative complications, apart from a slightly higher incidence of additional surgical procedures and cardiovascular risk (fatal CVD) in men, as previously suggested (11, 29).

There was a 42% lower relative risk of hospitalization due to severe kidney disease after GBP. A systematic review has previously suggested that weight loss is associated with reductions in proteinuria and microalbuminuria. A retrospective cohort study showed a higher mean estimated glomerular filtration rate (eGFR) in patients up to three years after bariatric surgery than those with moderately impaired renal function (CKD stages 3 and 4) who were referred for, but did not receive, surgery (30, 31). There has been no prospective study in patients with severe renal disease. Retrospective data are limited by study design and estimations of renal function. eGFR calculations depend on muscle mass and serum creatinine levels, both of which change after

weight loss independent of kidney function. Although the selection of patients eligible for bariatric surgery can contribute to the apparent beneficial effects on risk of severe kidney disease, these results should prompt new studies concerning the effects on renal function, as well as optimal patients for surgery to treat weight loss. Improved glycemic and blood pressure control after GBP (32, 33) could also contribute to the apparent effects of including changes in dose of antihypertensives, which are known to affect serum creatinine. We did not evaluate glycemic control in this study, but pronounced effects after bariatric surgery have been demonstrated repeatedly (6, 34, 35).

The anatomical and physiological consequences of GBP result in a higher risk of long-term deficiencies of several vitamins and minerals (36). The present study had no access to data from primary care, where follow-up should start 2 years after GBP, but malnutrition and anemia were twice as common. Poor compliance with vitamin and mineral supplements, as well as irregular follow-up, may very likely explain these results. A recent meta-analysis pointed to this potential problem in individuals without diabetes, suggesting that diabetes is not a risk factor per se (13). Adequate supplementation is paramount (37), since deficiencies after GBP tend to increase over time (13, 38).

A history of psychiatric disorders requiring hospitalization was not uncommon in either group of individuals with obesity in this study, and was 33% higher after GBP. Previous studies have shown that depression, which may improve in the first year following bariatric surgery, tends to progress (39) along with suicide and self-harm, particularly if they are preexisting conditions (15, 16). Thus, greater awareness is needed in order to identify vulnerable patients with a history of self-harm or depression who may need psychiatric services after GBP. Perhaps specific multidisciplinary teams should identify such patients and through treatment algorithms could

enhance the safety and efficacy pre and postoperatively (40). In agreement with previous studies (17, 41) we confirmed a higher event rate of alcohol-related problems that lead to hospitalization after GBP, which points to the importance of careful selection of patients who are offered surgery, as well as better follow-up of those with a history of alcohol-related risk behavior. The mechanisms of this well-known phenomenon are still unknown.

The indications for surgical treatment of obesity were presented by the National Institute of Health in 1991 (42) and have been repeatedly revised and expanded over the years. Severe and untreated psychopathology as well as active alcohol or substance abuse, or eating disorders are contraindications to bariatric surgery, although the decision to offer this treatment should always be individualized based on the stability of conditions and the assessment of multidisciplinary treatment teams (43). The need for more robust criteria and the possible application of scoring systems or algorithms that could facilitate the assessment of patients beyond BMI has been discussed (44).

A major strength of this study is its nationwide coverage of patients with obesity and type 2 diabetes, all of whom received recent Roux-en-Y gastric bypass surgery. The results are likely to be generalizable to similar developed countries using the same criteria and contraindications for bariatric surgery and quality of care. All linked databases are characterized by high participation rates and validation of medical data (21, 45).

Our study was nonrandomized and observational, but with carefully matched groups to maximize the size of the cohort as well as to reduce the influence of confounding factors. Minor differences in clinical characteristics may still influence our results, and we also did not include some variables (e.g. duration of diabetes, HbA1c, use of antidiabetic drugs) that potentially also could affect the results. Similarly, we did not exclude patients with multiple comorbidities before the

intervention, because we would have lost substantial data and they had all qualified for GBP. We also used Cox proportional hazards regression modelling, including baseline characteristics, to minimize the effects of confounding. Certainly, we cannot rule out residual confounding, unobserved factors that may be related to both exposure and outcome. However, the external validity is most likely high as our study includes virtually all GBP patients with type 2 diabetes in Sweden during the time period.

Another limitation is that we captured diagnoses during hospitalization, not outpatient care. Comorbidities and incidence of postoperative outcomes may be underestimates as a result, but the systematic flaw could not be avoided. Nevertheless, measurement errors may potentially arise because the patients who had received surgery were followed up more frequently than the control group. GBP was the only surgical procedure we studied (96% laparoscopic), given that sleeve gastrectomy and duodenal switch were not performed very often and follow-up data were too limited during the study period. We also did not address the importance of more specific surgical techniques.

Individuals with obesity and type 2 diabetes who have undergone GBP are generally at a reduced risk of all-cause mortality and cardiovascular morbidity, as well as severe kidney disease and cancer to a lesser extent. They also have, however, significantly higher risks of postoperative complications and adverse events both short-term and long-term, mostly abdominal pain and gastrointestinal conditions that frequently require additional surgical procedures, apart from reconstructive plastic surgery. Long-term consequences observed more often are anemia, malnutrition, psychiatric disorders and alcohol abuse. In order to maximize the benefit and minimize the risk of problems, long-term postoperative monitoring and support should be

provided. Better selection of patients for such treatment, performed by appropriate specialists in interdisciplinary settings, could probably also optimize outcomes.

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Data sharing statement: This is a registry study and therefore the data generated is not suitable for sharing beyond that contained within the report. Further information can be obtained from the corresponding author.

Ethical Approval: Ethics Review Board of the University of Gothenburg approved this study.

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Figure legends:

Figure 1A-F: Cumulative incidence of postoperative outcomes during the 9-years follow up. All-cause mortality; Congestive heart failure; Kidney disease; Malnutrition; Psychiatric disorder; Alcohol abuse.

Figure 2A-F: Cumulative incidence of postoperative adverse events during the 9-years follow-up. Gastrointestinal (GI) surgery; Abdominal pain; Bowel obstruction; Gallstone and gallbladder disease; Wound complications; Plastic surgery.

Table 1. Baseline characteristics			
	GBP (n=5321)	**Control (n=5321)**	**Standardized difference***
Sex			
Men	2098 (39.4%)	1926 (36.2%)	0.0471
Women	3223 (60.5%)	3395 (63.8%)	0.0471
Age	49.0 (9.5)	47.1 (11.5)	0.122
BMI	42.0 (5.7)	40.9 (7.3)	0.117
Income (SEK)	199.638 (139136; 261558)	168.380 (121840; 239368)	0.156
Marital status			
Single	1602 (30.1%)	2064 (38.8%)	0.130
Married	2518 (47.4%)	2227 (41.9%)	0.0781
Separated	1092 (20.5%)	881 (16.6%)	0.0723
Widowed	106 (2.0%)	147 (2.8%)	0.0358
Education level			
Compulsory school	1069 (20.1%)	1431 (26.9%)	0.114
University	3192 (60.0%)	2847 (53.5%)	0.0926
Upper secondary school	1037 (19.5%)	930 (17.5%)	0.0366
Missing data	23 (0.4%)	113 (2.1%)	0.107
Country of origin			
Sweden	4261 (80.1%)	4027 (75.7%)	0.075
Rest of Europe	514 (9.7%)	602 (11.3%)	0.0382
Rest of the world	546 (10.3%)	692 (13.0%)	0.0607
Cardiovascular			
Cardiovascular disease	273 (5.1%)	261 (4.9%)	0.00730
Acute myocardial infarction	173 (3.2%)	169 (3.2%)	0.00301
Coronary heart disease	395 (7.4%)	313 (5.9%)	0.0437
Congestive heart failure	140 (2.6%)	168 (3.2%)	0.0222

Atrial fibrillation	148 (2.8%)	149 (2.8%)	0.000807
Valvular heart disease	24 (0.4%)	27 (0.5%)	0.00577
Stroke	109 (2.0%)	103 (1.9%)	0.00571
Deep vein thrombosis/pulmonary embolism	71 (1.3%)	65 (1.2%)	0.00710
Diabetes-related			
Hyperglycemia	80 (1.5%)	130 (2.4%)	0.0478
Hypoglycemia (with or without coma)	57 (1.1%)	61 (1.2%)	0.00508
Gastrointestinal			
Gastrointestinal surgery (not gastric bypass)	549 (10.3%)	644 (12.1%)	0.0400
Abdominal pain	386 (7.2%)	334 (6.3%)	0.0275
Gallstone, gallbladder disease and pancreatitis	419 (7.9%)	366 (6.9%)	0.0270
Gastrointestinal ulcer and reflux	86 (1.6%)	72 (1.4%)	0.0154
Hernia	204 (3.8%)	160 (3.0%)	0.0322
Bowel obstruction	18 (0.3%)	29 (0.6%)	0.0220
Gastrointestinal leakage	7 (0.1%)	17 (0.3%)	0.0280
Liver disease	16 (0.3%)	26 (0.5%)	0.0212
Surgical			
Plastic surgery	54 (1.0%)	33 (0.6%)	0.0310
Wound complications	192 (3.6%)	156 (2.9%)	0.0269
Bleeding	50 (0.9%)	32 (0.6%)	0.0273
Other			
Psychiatric disorders	318 (6.0%)	346 (6.5%)	0.0154
Alcohol abuse	94 (1.8%)	122 (2.3%)	0.0264
Cancer	111 (2.1%)	158 (3.0%)	0.0398
Malnutrition	21 (0.4%)	41 (0.8%)	0.0349
Kidney disease	56 (1.0%)	83 (1.6%)	0.0316
Pulmonary disease	128 (2.4%)	131 (2.5%)	0.00259
Anemia	55 (1.0%)	60 (1.1%)	0.00643
Amputation	10 (0.2%)	12 (0.2%)	0.00585
Dementia	1 (0.02%)	4 (0.08%)	0.0184

Numbers and proportions.

*Difference between sample means divided by standard deviation. Acceptable significance when standardized difference <0.1.

Table 2. Number of events and event rates during follow up

Outcome	GBP (n=5321)	Control (n=5321)	Hazard ratio [95% CI]	p-value
All-cause mortality	183 (72.90)	351 (142.06)	0.51 [0.43, 0.62]	<.0001
Cardiovascular				
Cardiovascular disease	108 (43.54)	150 (61.54)	0.66 [0.51, 0.85]	0.0014
Fatal cardiovascular disease	21 (8.38)	64 (25.94)	0.34 [0.20, 0.56]	<.0001
Acute myocardial infarction	51 (20.43)	85 (34.69)	0.55 [0.39, 0.79]	0.0010
Coronary heart disease	309 (128.66)	274 (114.28)	1.13 [0.95, 1.34]	0.156
Fatal coronary heart disease	28 (11.17)	77 (31.20)	0.35 [0.22, 0.54]	<.0001
Congestive heart failure	109 (43.94)	225 (93.05)	0.49 [0.39, 0.62]	<.0001
Atrial fibrillation	204 (83.64)	213 (88.16)	0.93 [0.76, 1.14]	0.486
Valvular heart disease	21 (8.39)	32 (13.00)	0.64 [0.36, 1.14]	0.131
Stroke	59 (23.69)	71 (28.94)	0.77 [0.54, 1.10]	0.158
Deep vein thrombosis/pulmonary embolism	56 (22.48)	59 (24.07)	1.01 [0.69, 1.48]	0.952
Diabetes-related				
Hypoglycemia (with or without coma)	43 (17.24)	46 (18.72)	1.04 [0.68, 1.60]	0.844
Hyperglycemia	23 (9.20)	89 (36.37)	0.33 [0.21, 0.53]	<.0001
Gastrointestinal				
Gastrointestinal surgery (not gastric bypass)	936 (422.59)	301 (125.76)	3.33 [2.91, 3.80]	<.0001
Abdominal pain	558 (239.25)	124 (50.94)	5.52 [4.51, 6.75]	<.0001
Gallstone, gallbladder disease and pancreatitis	312 (129.31)	125 (51.30)	2.49 [2.02, 3.08]	<.0001
Gastrointestinal ulcer and reflux	239 (98.58)	46 (18.73)	5.42 [3.91, 7.51]	<.0001
Hernia	235 (97.00)	86 (35.17)	2.75 [2.14, 3.54]	<.0001
Bowel obstruction	232 (95.29)	27 (10.97)	9.47 [6.31, 14.20]	<.0001

Table 2. Number of events and event rates during follow up				
Outcome	**GBP (n=5321)**	**Control (n=5321)**	**Hazard ratio [95% CI]**	**p-value**
Gastrointestinal leakage	40 (16.05)	7 (2.84)	5.54 [2.46, 12.45]	<.0001
Liver disease	30 (12.00)	40 (16.26)	0.73 [0.45, 1.19]	0.205
Surgical				
Plastic surgery	380 (158.08)	22 (8.94)	19.85 [12.86, 30.67]	<.0001
Wound complications	290 (120.87)	87 (35.55)	3.45 [2.70, 4.42]	<.0001
Bleeding	172 (70.50)	26 (10.57)	6.87 [4.49, 10.52]	<.0001
Other				
Psychiatric disorder	317 (131.64)	268 (111.93)	1.33 [1.13, 1.58]	0.0008
Alcohol abuse	180 (73.10)	65 (26.52)	2.90 [2.16, 3.88]	<.0001
Cancer	153 (61.80)	188 (77.41)	0.78 [0.63, 0.97]	0.0257
Malnutrition	128 (51.69)	46 (18.72)	2.81 [1.98, 3.97]	<.0001
Kidney disease	105 (42.38)	187 (76.87)	0.58 [0.45, 0.75]	<.0001
Pulmonary complications	86 (34.66)	114 (46.64)	0.84 [0.63, 1.13]	0.249
Anemia	84 (33.78)	46 (18.71)	1.92 [1.33, 2.76]	0.0005
Amputation	15 (5.99)	23 (9.33)	0.51 [0.26, 0.98]	0.0432
Dementia	4 (1.60)	12 (4.87)	0.46 [0.14, 1.57]	0.214

Event rates (%) per 10.000 person-years.

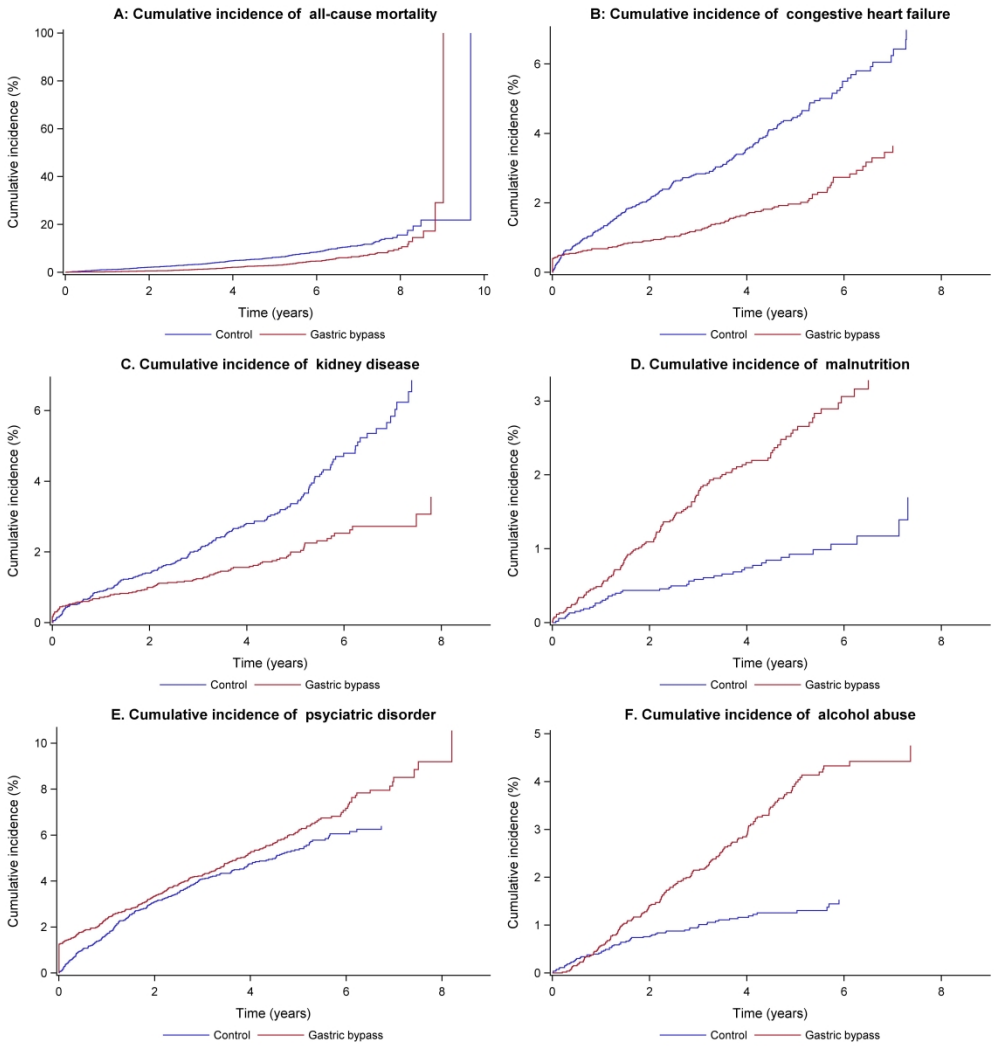

Figure 1A-F: Cumulative incidence of postoperative outcomes during the 9-years follow up. All-cause mortality; Congestive heart failure; Kidney disease; Malnutrition; Psychiatric disorder; Alcohol abuse.

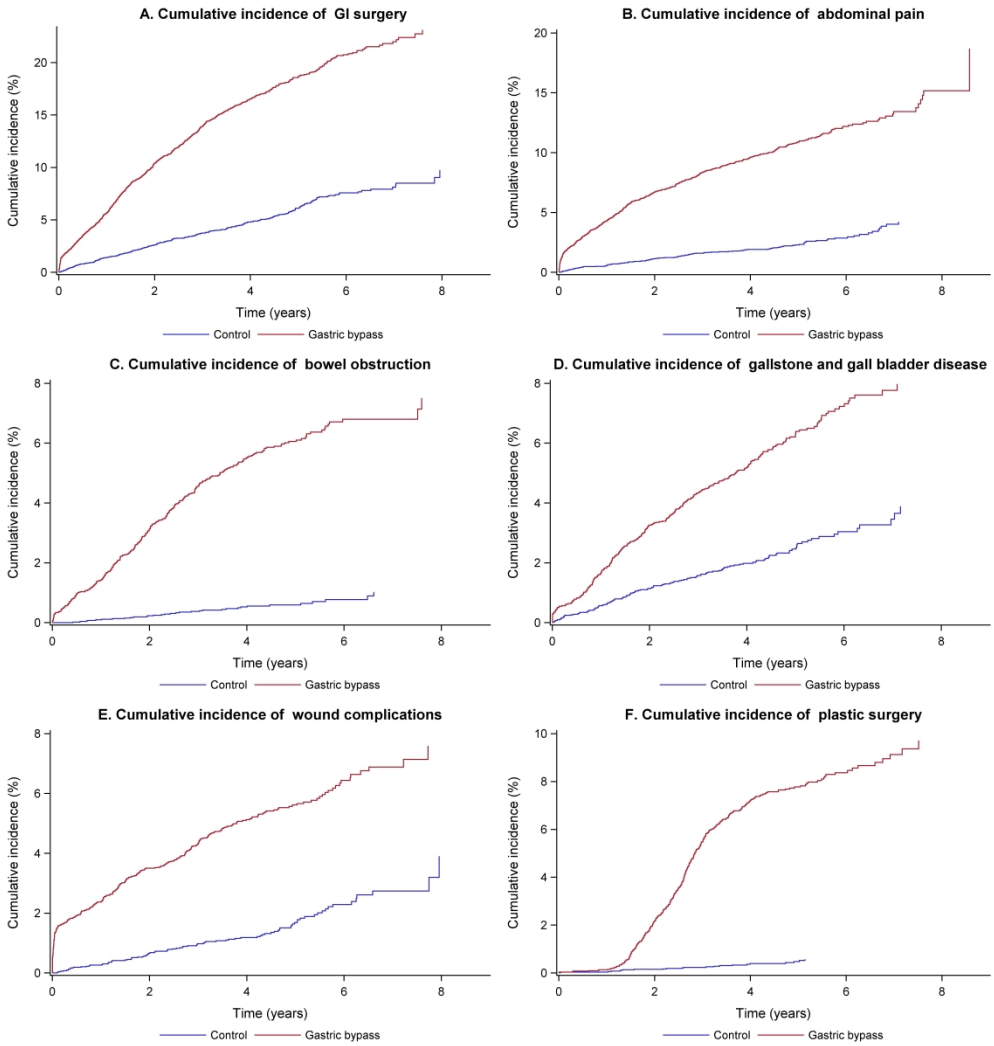

Figure 2A-F: Cumulative incidence of postoperative adverse events during the 9-years follow-up. Gastrointestinal (GI) surgery; Abdominal pain; Bowel obstruction; Gallstone and gallbladder disease; Wound complications; Plastic surgery

SUPPLEMENTARY MATERIAL

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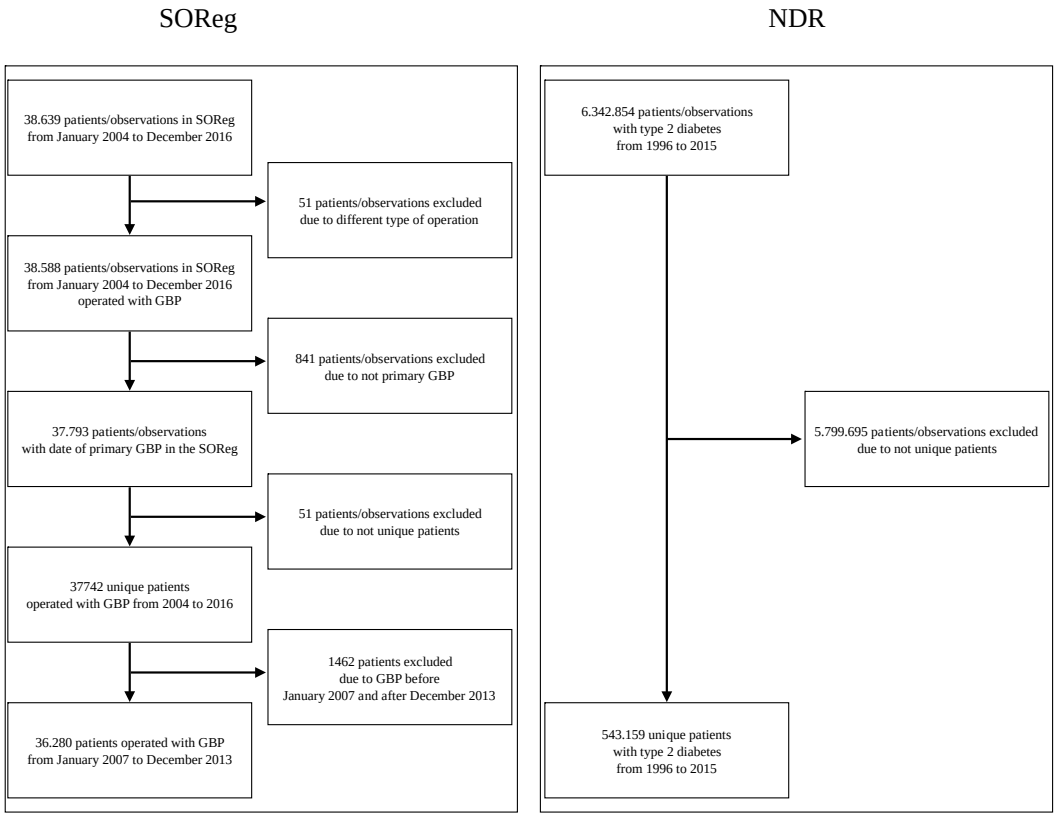
Flowchart

Selection of our data from Scandinavian Obesity Surgery Register (SOReg) before merging with data from the National Diabetes Registry (NDR).



Merging the two databases led to our study population of 5,321 patients in the SOReg who had T2DM and had undergone GBP, and 5,321 matched control patients in the NDR.

Methods – database linkages

This study is based on data from the NDR and SOReg. Both registers are linked to Statistics Sweden at the National Board of Health and Welfare, which also stores data in the Swedish Inpatient Register (1997-2015).

We filed an application with our data and personal identity numbers [SOReg (2007-2013) & NDR (1996-2015)] to the National Board of Health and Welfare, from which all personal identity numbers have been identified and replaced by serial numbers. The coded data from the National Board of Health and Welfare were subsequently forwarded to Statistics Sweden for linkage with the Inpatient Register and LISA Database, which provides socioeconomic data. The linked data were then returned to us for validation and analysis.

Table S1: Pre-index diagnoses and outcomes after GBP

Diagnoses before and after gastric bypass surgery (index date) until December 2015 according to ICD-10.

Diagnosis	ICD-10	Variable origin	Registration period
Acute Myocardial infarction	*I21*	Swedish Inpatient Register	2007-2015
Coronary heart disease	*I20-25*	Swedish Inpatient Register	2007-2015
Stroke	*I61-64*	Swedish Inpatient Register	2007-2015
Cardiovascular disease	*I21, I61-64*	Swedish Inpatient Register	2007-2015
Atrial fibrillation	*I48*	Swedish Inpatient Register	2007-2015
Heart failure	*I50*	Swedish Inpatient Register	2007-2015
Valvular heart disease	*I05-09, I34-37, Q22, Q23*	Swedish Inpatient Register	2007-2015
Liver disease	*K70-74*	Swedish Inpatient Register	2007-2015
Kidney disease	*V42A, V45B, V56A, V56W, Z940, Z491, Z492, Z992, N17-19, N99*	Swedish Inpatient Register	2007-2015
Hyperglycemia	*E100, E101, E110, E111, E120, E121, E130, E131, E140, E141, R739*	Swedish Inpatient Register	2007-2015
Hypoglycemia (with or without coma)	*E100, E106A, E110, E110C, E110X, E116A, E120, E130, E140, E159, E160, E161W, E162, R402*	Swedish Inpatient Register	2007-2015
Cancer	*C0-9*	Swedish Inpatient Register	2007-2015

Dementia	*G300, G301, G308, G309, G31, F00-03*	Swedish Inpatient Register	2007-2015
Psychiatric disorders	*F11-19, F20-29, F30-39, F50, F55, F40-F43, F60, F61, F68, F69, F99*	Swedish Inpatient Register	2007-2015
Alcohol abuse	*F10*	Swedish Inpatient Register	2007-2015
Anemia	*D508-9, D51.0,3,8, D520*	Swedish Inpatient Register	2007-2015
Malnutrition	*E15-16, E51.2, E42-44, E46, E50-64, G63.3-4, G62.9, K91.1-2, M81.3, M83.2*	Swedish Inpatient Register	2007-2015
Bleeding	*T81.0*	Swedish Inpatient Register	2007-2015
Deep vein thrombosis and pulmonary embolism	*I80.0-9, I26, I81*	Swedish Inpatient Register	2007-2015
Amputation	*NHQ09, 11-14, 16, 17, 99, NGQ09, 19, 99, NFQ19, 99*	Swedish Inpatient Register	2007-2015
Bowel obstruction	*K56, K45*	Swedish Inpatient Register	2007-2015
Gastrointestinal leakage	*T84.4, K65.0, K63.1*	Swedish Inpatient Register	2007-2015
Pulmonary complications	*J18.0-9, J69.0, J80, J98.1*	Swedish Inpatient Register	2007-2015
Wound complications	*T81.3-4, K43.0-9*	Swedish Inpatient Register	2007-2015
Gastrointestinal ulcer and reflux	*K21, K22.1-3, K25-26, K28*	Swedish Inpatient Register	2007-2015
Hernia	*K40-43*	Swedish Inpatient Register	2007-2015
Gallstone, gallbladder disease and pancreatitis	*K80-85*	Swedish Inpatient Register	2007-2015
Gastrointestinal surgery not	All the operative diagnoses with	Swedish Inpatient	2007-2015

GBP	"*J"* except for gastric operation	Register	
Plastic surgery	*QBE, QBJ, QCJ05, QDJ05, QAJ35*	Swedish Inpatient Register	2007-2015
Abdominal pain	*R10.1-4*	Swedish Inpatient Register	2007-2015
All-cause mortality	Everyone in the Cause of Death Register	Cause of Death Register	2007-2015
Fatal coronary heart disease	*I20-24* and entered in the Cause of Death Register	Swedish Inpatient Register & Cause of Death Register	2007-2015
Fatal cardiovascular disease	*I20-24,I61-64* and entered in the Cause of Death Register	Swedish Inpatient Register & Cause of Death Register	2007-2015

Table S2: Risk estimates for men and women (Cox proportional hazards regression)

Outcome	Men HR with 95% CI (n=4024)	Women HR with 95% CI (n=6618)	p-value
All-cause mortality	0.58 (0.45, 0.74)	0.46 (0.35, 0.60)	0.2091
Coronary heart disease	1.14 (0.90, 1.44)	1.12 (0.88, 1.42)	0.9011
Cardiovascular disease	0.63 (0.44, 0.92)	0.69 (0.49, 0.96)	0.7614
Fatal coronary heart disease	0.42 (0.24, 0.73)	0.25 (0.12, 0.54)	0.2853
Fatal cardiovascular disease	0.60 (0.32, 1.14)	0.13 (0.05, 0.36)	0.0118
Acute myocardial infarction	0.55 (0.32, 0.92)	0.56 (0.35, 0.90)	0.9522
Stroke	0.67 (0.32, 1.12)	0.88 (0.55, 1.41)	0.4429
Atrial fibrillation	1.13 (0.86, 1.47)	0.72 (0.53, 0.98)	0.0313
Heart failure	0.63 (0.46, 0.86)	0.35 (0.24, 0.51)	0.0201
Valvular heart disease	0.83 (0.38, 1.84)	0.49 (0.21, 1.13)	0.3645
Hyperglycemia	0.22 (0.09, 0.53)	0.40 (0.23, 0.69)	0.2624
Hypoglycemia with coma	0.79 (0.39, 1.63)	1.21 (0.71, 2.05)	0.3490
Dementia	0.73 (0.19, 2.86)	0.00 (.,.)	0.9991
Kidney disease	0.84 (0.28, 2.54)	0.37 (0.12, 1.13)	0.2995
Amputation	0.82 (0.36, 1.85)	0.16 (0.04, 0.72)	0.0613
Cancer	1.02 (0.69, 1.51)	0.69 (0.53, 0.90)	0.1068
Psychiatric disorder	1.02 (0.76, 1.37)	1.51 (1.23, 1.85)	0.0289
Alcohol abuse	2.87 (1.98, 4.15)	2.94 (1.85, 4.69)	0.9298
Liver diseases	0.53 (0.25, 1.13)	0.92 (0.49, 1.73)	0.2731
Anemia	1.96 (0.96, 4.01)	1.90 (1.24, 2.90)	0.9390

Outcome	Men HR with 95% CI (n=4024)	Women HR with 95% CI (n=6618)	p-value
Bleeding	9.74 (4.69, 20.22)	5.50 (3.26, 9.29)	0.2110
Deep vein thrombosis and pulmonary embolism	1.10 (0.59, 2.03)	0.96 (0.60, 1.55)	0.7455
Bowel obstruction	6.17 (3.33, 11.46)	12.10 (7.10, 20.64)	0.1035
Gastrointestinal leakage	5.28 (1.55, 18.01)	5.73 (1.96, 16.79)	0.9217
Malnutrition	2.72 (1.59, 4.67)	2.86 [1.83, 4.47]	0.8879
Pulmonary complications	0.96 (0.59, 1.56)	0.78 [0.54, 1.12]	0.4915
Wound complications	4.70 (2.79, 7.90)	3.12 [2.36, 4.13]	0.1743
Gastrointestinal ulcer and reflux	5.57 (3.49, 8.89)	5.28 (3.36, 8.31)	0.8719
Hernia	3.53 (2.19, 5.69)	2.47 (1.83, 3.33)	0.2136
Gallstone, gallbladder disease and pancreatitis	2.33 (1.59, 3.41)	2.56 (1.99, 3.30)	0.6810
Gastrointestinal surgery (not gastric bypass)	9.93 (8.35, 11.80)	7.13 (6.37, 7.98)	0.0015
Plastic surgery	16.96 (6.84, 42.07)	20.73 (12.67, 33.92)	0.7024
Abdominal pain	7.22 (4.64, 11.24)	5.12 (4.08, 6.41)	0.1703

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6,7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6, suppl
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8, suppl
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	suppl
		(c) Consider use of a flow diagram	suppl
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8,20,21
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8,9,20,21,22,23
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9,22,23
		(*b*) Report category boundaries when continuous variables were categorized	9,22,23
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	suppl
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11,12,13,14,15
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.