Impact of bariatric surgery on cardiovascular outcomes and mortality

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Title: A Population-Based Cohort Study Assessing The Impact of Bariatric Surgery On Cardiovascular Outcomes And Mortality

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Abstract

Background: Cohort studies have shown that bariatric surgery may reduce CVD incidence and mortality, but studies using real world data are limited. We conducted a population-based study examining the impact of bariatric surgery (BS) on incident cardiovascular disease (CVD), hypertension, atrial fibrillation and all-cause mortality.

Methods: A retrospective matched, controlled cohort study between 1/1/1990 and 31/1/2018 using The Health Improvement Network (THIN), primary care electronic database. Adults with a BMI ≥ 30 kg/m^2 who did not have gastric cancer were included in exposed group. Each exposed patient (had BS) was matched for age, sex, body mass index (BMI) & presence of type 2 diabetes (T2D) to 2 controls (not had BS).

Results: 5170 exposed and 9995 control participants were included. Mean (SD) age was 45.3 (10.5) years, 21.5% (n=3265) had T2D. The median follow-up was 3.9 years (IQR 1.8- 6.4).

BS was associated with a lower incident CVD (adjusted HR 0.80; 95%CI 0.62- 1.02, p=0.074), which was statistically significant in the gastric bypass group (0.53, 0.34- 0.81, p=0.003). BS was associated with significant reduction in all-cause mortality (0.70; 95%CI 0.55- 0.89, p=0.004), hypertension (0.41; 0.34- 0.50, p<0.001) and heart failure (0.57, 0.34- 0.96; p=0.033). Outcomes were similar in those with and without T2D (exposed vs control) except incident AF which was reduced in T2D cohort

Conclusions: BS was associated with a reduced risk of incident hypertension, CVD, and mortality in real-world data. Improvements in the provision of BS can help reduce the burden of obesity.

Introduction

Cardiovascular disease (CVD) is a leading cause of mortality worldwide (1-3). Obesity is a major risk factor for CVD and mortality and contributes to the pathogenesis of several CVD risk factors such as hypertension, hyperlipidaemia and type 2 diabetes (T2D) (4-6). Weight loss, via lifestyle intervention or bariatric surgery (BS), has been associated with significant improvements/remission of CVD risk factors (hypertension, hyperlipidaemia and T2D) as well as a reduction in CVD and mortality, although the impact on CVD and mortality is mainly from observational studies (7-10).

Several studies (including RCTs) have established that BS is associated with reduction in CVD risk factors (11-14) but the impact on CVD is limited to few observational studies (10, 15-17). In the UK, patients with a BMI ≥ 35 kg/m^2 and obesity-related complications, a BMI ≥40 kg/m^2 without obesity-related complications, or a BMI of 30-35 with recent onset T2D can be offered BS as per NICE guideline CG189 (18). Patients are usually followed up for 2 years post BS by the bariatric multidisciplinary team if they were treated in the National Health Service (NHS) and then discharged to primary care (18). A previous study from the United Kingdom National Bariatric Surgery Registry (NBSR) showed improvement/remission in obesity-related complications following BS (19), but the NBSR only include patients who had BS and hence there was no control group. In addition, the NBSR study did not report the impact on CVD or mortality (19). Hence, there is interest in real-world outcomes of BS in order to ascertain its place in the management paradigm of people with obesity

Our hypothesis was that BS is associated with a reduction in, CVD, all-cause mortality and hypertension. Hence, we conducted a population-based study with the primary aim to assess the impact of BS on incident combined CVD [ischaemic heart disease (IHD), heart failure (HF), cerebrovascular accident including stroke and transient ischaemic attack (CVA)] and all-cause mortality. Secondary aims included assessing the impact of BS on incident hypertension & atrial fibrillation (AF).

Methods

Study design and data source

We conducted a retrospective, matched, controlled cohort study utilising a dataset from The Health Improvement Network (THIN) database, from 1/1/1990 to 31/1/2018. THIN contains anonymised electronic records from 787 general practices. It includes longitudinal records of

15 million patients (3.1 million active patients) and covers around 6.2% of the UK population (20-22) and is representative of the UK general population in relation to age, sex, health conditions, major chronic illnesses, and mortality rates (23). THIN contains information on patient demographics, therapies, symptoms and medical diagnoses. In addition, THIN includes additional health data such as smoking and alcohol status, smoking, height, weight, death, and laboratory results and investigations results. Symptoms and diagnoses are recorded using Read codes (24). The THIN database has been previously used by our group and others to examine chronic non-communicable disease (such as diabetes, CVD, obesity and its related complications) and mortality (25-28).

Study Population

Primary care practices were eligible for inclusion in the study if they have been using the Vision electronic records system for at least 1 year, and had Acceptable Mortality Recording (an indicator of the practice data quality) for at last one year preceding study entry (29). In addition, study participants must have been registered with an eligible practice for at least one year before study entry to ensure adequate documentation of concomitant diseases and treatments.

The exposed cohort was defined as patients who had BS [gastric banding (GB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), duodenal switch (DS)] between 1/1/1990 and 31/1/2018. Every patient in the exposed cohort was matched to 2 controls (i.e. did not have BS) by age (± 2 years), sex and body mass index (BMI, ±2 kg/m^2) and presence of T2D. Patients were excluded from the study if they met any of the following criteria: had a BMI <30 kg/m^2, were aged > 75 years, had a record of gastric cancer before the index date (study entry date), had gastric balloon or endo-barrier or had revisional BS.

Follow-up

For patients in the exposed group, index date was defined as the first Read code documentation date of BS; the same index date was assigned to the corresponding matched controls to mitigate immortal time bias (30). Study participants were followed-up from the index date until the first record of any of the following: a) occurrence of the outcome of interest b) death c) study participant left the practice, d) the practice ceased contributing to THIN database.

Outcome measures

Incident composite CVD (IHD, HF, CVA) , all-cause mortality, incident hypertension & AF. We also examined the individual components of the composite CVD outcome separately

Statistical analysis

Baseline characteristics were summarised as mean (standard deviation) or median (interquartile range IQR) for continuous variables depending on data distribution and as proportions for categorical variable. We calculated crude and adjusted hazard ratios (HR) and 95% confidence intervals (CIs) for the occurrence (incident) of each outcome of interest in the exposed vs. control groups using Cox proportional hazards regression. Patients with the outcome of interest at baseline were excluded from the analysis; for example, when the outcome of interest was incident CVD, patients with baseline CVD were excluded. The proportional hazards assumption was checked using the Schoenfeld residuals test.

Covariates in the adjusted/multivariable model were selected based on biological plausibility; these included age, sex, BMI, smoking status, alcohol consumption, ethnicity, and social deprivation status (Townsend quantiles) (31, 32). BMI (in kg/m^2) was categorised as <35 kg/m^2, 35-40 kg/m^2 and > 40 kg/m^2. Smoking and alcohol intake were categorised as user, non-user and ex-user. Social deprivation status was represented by Townsend deprivation quintile which is based on material deprivation within a population (33) . Ethnicity was categorised as Caucasian, Afro-Caribbean, South Asian or mixed. Missing categories were used where values for BMI, smoking status, Townsend quintile, ethnicity were not recorded.

For composite CVD & AF outcomes, the HRs were adjusted for all above-mentioned covariates, and baseline hypertension and diabetes (model 1). For incident hypertension, the same covariates were included except for baseline hypertension. For mortality, an additional model was fitted adjusting for the same variables included in model 1 plus Charlson's co-morbidity index (model 2) (34).

Pre-planned subgroup analyses based on the type of BS and baseline T2D status were performed. Based on type of surgery, we analysed the outcome in participants undergoing each BS type and their corresponding controls. Multivariable analysis was not performed in DS subgroup due to small numbers. Based on T2D status, we analysed the outcomes in the participants with and without T2D. In the T2D subgroup analysis, diabetes duration was included in the regression model (model 3) along with all covariates included in model 1 (and model 2 in case of mortality).. A forest plot was used to graphically represent the impact of BS based onT2D status.

Percentage weight loss (%WL) was calculated as change in weight (post-surgical weight defined as the after the index date within 15 months - baseline weight) / baseline weight × 100. For control group who had no surgery, weight change was calculated using similar formula. Independent sample T-test was used to compare the %WL in exposed and the control group.

We used Nelson-Aalen plots (non-parametric estimator) to display the cumulative hazard function for each outcome over a 10-year period. A two-tailed p-value < 0.05 was considered statistically significant. All analyses were conducted using Stata version 15 (35).

Results

We identified 5170 participants who had BS over the study period (exposed) and 9995 matched controls (Figure 1). Figure 1 also show participant selection and the numbers in each surgical procedure and their matched control.

Baseline characteristics

Table 1 summarises the baseline demographics of exposed and matched control participants. The study population were mostly White European women and had class III obesity. There was a high prevalence of mental health disorders ranging from 24-46% in the study population, which might reflect the underlying psychological impact and drivers of obesity. Higher prevalence of OSA in the exposed vs. control cohort (11.1% vs 3.4%), which is likely to reflect the active screening for OSA in a population undergoing BS

Weight changes

4346 exposed (84% of the exposed) participants and 6957 control participants (69% of the control) had weight measurement at baseline and at least once following BS. The median follow-up for the weight measurement was 1 year (IQR 0.6-12 years)

The mean±SD %WL was 20.0±13.2% in exposed vs 0.8±9.5% in the control groups. All surgical procedures resulted in greater %WL compared to their matched control [GB (n=1610 vs. 2789): 12.8±11.8% vs 0.3±9.8%; SG (n=944 vs. 1338): 22±12.1% vs1.1±9.4%; RYGB (n=1764 vs. 2781): 26.1±11.8% vs 1.2±9.2%; DS (n=28 vs. 49): 23.4± 12.3% vs -0.1±7.0%(wt gain in DS control)].

Combined CVD:

The study included 4922 exposed and 9484 control participants after excluding participants with CVD at baseline (n=759) (Table 2). BS was associated with a reduction in hazard of composite CVD compared to the control group, though not statistically significant in the adjusted model [crude HR 0.78 (95%CI 0.61- 0.995, p=0.045); adjusted HR (aHR) 0.80 (95%CI 0.62-1.02, p=0.074)].

The RYGB cohort had a statistically significant reduction in incident composite CVD aHR 0.53, 95%CI 0.34 to 0.81, p=0.003) (Table 2).

Ischaemic Heart disease

After excluding the participants with diagnosis of IHD at baseline (n=485) we had 5013 exposed participants and 9667 control participants. There was no difference in incident IHD between the exposed vs. control cohorts (aHR 0.85, 95%CI 0.61- 1.19, p=0.349) (Table 2). There was favourable but statistically non-significant reduction in incident IHD in the RYGB group vs. control: aHR 0.57, 95% CI 0.32-1.03, p=0.061) (Table 2).

Heart failure

After excluding the participants with diagnosis of heart failure at baseline (n=119), 5127 exposed and 9919 control participants were included. There was a statistically significant reduction in incident HF in the exposed group compared to controls (aHR 0.57; 95% CI 0.34-0.96, p= 0.033). Examining the data based on the type of BS showed a statistically significant decrease in incident HF in the RYGB group (aHR 0.24, 95% CI 0.083- 0.68, p=0.007), but not in the GB and SG cohorts (Table 2).

Cerebrovascular accident

After excluding participants with a diagnosis of CVA at baseline (n=235), we had 5094 exposed participants and 9836 control participants. No association of BS and incident CVA was detected (aHR 0.98, 95% CI 0.66 1.45 p= 0.907). There was a non-statistically significant increase in incident CVA in the GB group vs. controls (aHR 1.67 95% CI 0.94-2.96, p=0.079) and no significant impact in SG or RYGB cohorts (Table 2).

All-cause Mortality

Over median follow-up period of 3.89 (1.77 to 6.4) years, 90 deaths in the exposed and 278 deaths in control groups were recorded (Table 3). Mortality was reduced in the exposed group vs. controls (aHR 0.70, 95%CI 0.55- 0.89, p=0.004). Further adjustment for Charlson's co-morbidity index (model 2) showed a similar result (aHR 0.70, 95%CI 0.55- 0.89), p=0.004) (Table 3). There was statistically significant mortality reduction in GB group (aHR of 0.54, 95% CI 0.35- 0.84, p= 0.007) and the RYGB group (aHR of 0.66, 95%CI 0.45- 0.97, p=0.033) (Table 3).

Incident Hypertension

After excluding the participants with hypertension at baseline (n=4547)), the study included 3567 and 7051 participants in the exposed and control groups respectively. BS was associated with significant reduction in incident hypertension compared to the control group (aHR 0.41; 95% CI 0.34- 0.50, p< 0.001) (Table 2). All bariatric procedures (except DS) were associated with statistically significant reduction in incident hypertension compared to matched controls (Table 2).

Atrial fibrillation

After excluding the participants with AF at baseline (n= 220), we included 5087 and 9858 participants in the exposed and control groups respectively (Table 2). There was no difference in incident AF between the exposed vs. control cohorts (aHR 0.93; 95%CI 0.68- 1.27, p=0.661) (Table 2). There was a non- statistically significant increase in incident AF in GB group vs. controls (aHR 1.21, 95% CI 0.77- 1.92, p=0.406) and a non-significant reduction in incident AF in the RYGB group vs. controls (aHR 0.65, 95% CI 0.38- 1.11, p=0.112) (Table 2).

The Nelson-Aalen cumulative hazard estimates for study outcomes

The cumulative hazard estimates for the study outcomes over 10 years period can be found in eFigure 1 in the online supplement. The figures show that the association between BS and the reduction in incident hypertension, CVD, heart failure and mortality started within the first 2 years following BS; with the impact on hypertension and heart failure becoming apparent within the first year following surgery.

T2D vs non T2D

We performed subgroup analyses in participants with and without T2D. We had 3265 participants (1176 exposed and 2089 controls) with T2D and 11900 without T2DM (3994 exposed and 7906 controls).

Pre- and post-weight were available for 1114 exposed and 1839 controls with T2D and 3232 exposed and 5118 controls without T2D. Over a median follow up period of 1-year (IQR 0.6- 1.1 years) the mean±SD %WL was 22.0±12.3% in exposed vs 1.62±6.69% in controls with

T2D. Similarly, over a median follow up of 1 year (IQR 0.6- 1.3 years), the mean±SD) %WL was 19.7 ±13.5% in exposed vs 0.6 ±10.3% in controls without T2D.

The relationship between BS and the outcomes examined was similar in those with and without T2DM except that BS was associated with lower hazard of AF in patients with T2DM (aHR 0.57, 95% CI 0.32- 1.00, p=0.053) ,but a higher hazard of AF in patients without T2DM (aHR 1.24, 95% CI 0.85- 1.81, p=0.271), and similarly for CVA (eTable 1 in the online Supplement and Figure 2).

The hazard of mortality was reduced in the surgical group compared to the control group in the cohorts with and without T2D (eTable 2 in the online Supplement).

Discussion

In this population-based study reflecting real-world data, we found that BS was associated with greater weight loss and reductions in the hazards of incident hypertension, CVD and all-cause mortality by 65%, 20% and 30% respectively compared to matched patients with obesity who did not have BS The study outcomes were largely similar in those with and without Type 2 diabetes.

Our findings are consistent with the Swedish Obese Subjects (SOS) study that found a lower incidence of CVD and mortality in patients who received BS compared to matched controls over a median follow up period of 14.7 years; however, unlike our study they also found reduction in incident AF (9, 10). This may be partially explained by the longer follow up in the SOS study. However, most of the procedures in the SOS were open surgery and >60% were vertical gastroplasty, which is also not performed nowadays. Furthermore, our data showed that the benefits of BS were evident even at shorter follow up duration (approx. 2 years) compared to SOS, in which the impact of BS on CVD started to become apparent approximately 6 years post-surgery (based on Kaplan-Meier graphs) (10).

Consistent with our findings, a systematic review including 8 controlled clinical studies (5 RYGB and 3 GB) with follow-up duration of 7.5 ±0.71 years showed evidence of mortality reduction (OR=0.55, 95% CI 0.49- 0.63) following BS (36). Our study also show that the mortality benefits started to occur relatively early post BS within the first two years. Similarly, the impact on heart failure, HTN and CVD also started early during the follow up within the first 2 years; which should be taken into consideration when assessing the cost effectiveness/savings of BS.

Consistent with the reduction in incident hypertension in our data, BS was also associated with significant reduction in the risk of heart failure vs the control group. A systematic review summarising the impact of BS using data from seven studies found a reduction in incident of HF in patients who had BS, similar to our study (37).

Our subgroup analysis based on the type of surgery showed a reduction in incident hypertension, irrespective of the type of intervention. This is not surprising considering the magnitude of weight loss observed in this study in all bariatric procedures given that previous studies showed even 5kg weight loss over 18 months reduced incident hypertension over 7 years follow-up (38). On the other hand, the observed reduction in incident combined CVD, IHD and HF was primarily evident in the RYGB group. The exact explanation for this difference between the bariatric procedure is not clear but could be due to multiple reasons. RYGB in our study resulted in greater %WL compared to GB and SG and hence could have contributed to the favourable outcomes observed in the RYGB group (39). In addition, unlike GB, RYGB results in increased GLP-1 secretion (40). Recent cardiovascular outcome studies in patients with Type 2 diabetes showed favourable impact on CVD in patients treated with GLP-1 receptor agonists (41).and hence GLP-1 might have contributed to the differential CVD impact observed in our study between the bariatric procedures.

Contrary to composite CVD, the reduction in mortality was mainly evident in the GB and RYGB groups but not in SG. The observed no effect on mortality in the SG group could be due to the smaller sample size in the SG group compared to the other 2 procedures.

In our study, the association between BS and CVD and hypertension were similar in patients with and without T2D, except that in patients with T2DM BS was associated with a non-significant reduction in the risk of AF and CVA compared to controls, while in patients without T2D there was a non-significant increased risk of AF and CVA following BS. The majority of previous studies analysing the impact of BS in populations with T2DM have focussed on weight loss and glycaemic control and had small sample size (42-45). A recent retrospective study from USA found lower risk of composite cardiovascular outcome in participants with diabetes undergoing BS (16). On analysing the outcomes separately, they found a reduction in coronary artery disease, but a non-significant difference in cerebrovascular disease as in our study (16). A meta-analysis including 5 cohort studies found a 48% reduction in macrovascular complications during a follow-up period ranging from 5 to 15 years, but no data were presented for individual components of macrovascular complications (46).

Our data showed the efficacy of BS in a real-world setting where patients are mostly followed up in primary care. It suggests that BS should be more widely utilised as a treatment option in patients with obesity (with and without T2D). Considering the favourable outcomes and the safety of the procedure reported from the NBSR (19), BS should be offered before patients develop long-term obesity-related complications. The focus of BS should shift from mere weight loss to metabolic, vascular and mortality benefits. The impact on quality of life is also important but not measured in this study.

Limitations and Strengths

Our findings should be interpreted within certain limitations. Given the observational nature of our study, residual biases cannot be ruled out. The THIN database is a validated primary care data source and had been used previously by our team and other researchers (25, 47, 48). However, as with all routinely collected data, there may be inconsistent or incomplete coding of conditions. We believe that recording will be good for CVD, stroke/TIA, AF, T2D and other chronic conditions in this study because these variables are part of the Quality and Outcomes Framework, a mandatory requirement for all primary care practices to document and monitor these conditions in the UK. BS is a hospital procedure and therefore accuracy relies on records being received by GPs and then recorded in patient notes by administrative staff. Nonetheless, our study provides robust data regarding the impact of BS in real world UK population. We used a well validated database which allowed us to include a large sample size with a well-matched control cohort and adjust for many variables. We also minimised immortal time bias by matching on the index date. Moreover, the large sample size allowed us to explore the relative effects of different bariatric procedures compared to previous studies that have included only one type of surgery. Our data included patients with and without diabetes and the outcomes were analysed separately in these groups.

Conclusion

In this real-world population-based cohort study, bariatric surgery was associated with reductions in incident CVD, mortality and hypertension. These benefits observed in both patients with and without type 2 diabetes. The non-significant increase in the risk of AF and CVA following gastric banding requires further studies. Considering our findings within the context of the low availability of BS in many countries, suggest that bariatric surgery should be utilised more often to reduce the burden of obesity on individuals and the health care system.

Ethics

Ethical approval for our project was granted from Scientific Review committee in January 2019, SRC Reference Number: 18THIN097

Acknowledgements

Author contributions:

AAT and KN had the original idea for the study. PS, AAT, and KN designed the study. KG undertook data extraction. PS designed and performed the analysis which was reviewed by AS. PS, AS, KN and AAT contributed to the data analysis and interpretation.PS wrote the first draft of the paper, which was revised and edited by NA, SB, KN and AAT.PS, AAT and KN affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. PS and KN had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Reference to prior publication of the study in abstract form, where applicable. - Parts of this study were presented as late poster submission at the ECO conference Glasgow 28th April-1st May

Table 1: Baseline characteristics of participants in the exposed and unexposed groups, <35= BMI in Exposed group range 30- 34.9 kg/m^2, & BMI in control group range from 28- 34.9 kg/m^2*

Demographics N (%)	Exposed N=5170	Unexposed N= 9995
Age Categories		
<40 years	1687 (32.6)	3192 (31.9)
41-60 years	3098 (59.9)	6040 (60.4)
>60 years	385 (7.5)	763 (7.6)
Mean (Standard Deviation)	45.2 (10.6)	45.3 (10.5)
Sex		
Male	1012 (19.6)	1890 (18.9)
Female	4158 (80.4)	8105 (81.1)
Body Mass Index Categories (BMI)		
<35*	493 (9.5)	1077 (10.8)
35- 39.9	950 (18.4)	1950 (19.5)
≥ 40	3634 (70.3)	6780 (67.8)
Missing	93 (1.8)	188 (1.9)
Smoker categories		
Non- Smoker	2866 (55.4)	5719 (57.2)
Smoker	700 (13.5)	1873 (18.7)
Ex- Smoker	1579 (30.5)	2319 (23.2)
Missing	25 (0.5)	84 (0.8)
Alcohol consumption Categories		
None- drinker	1196 (23.1)	2316 (23.2)
Current drinker	3266 (63.2)	6427 (64.3)
Ex-drinker	205 (4.0)	313 (3.1)
Missing	503 (9.7)	939 (9.4)
Ethnicity		
Caucasian	2154 (41.7)	3759 (37.6)
Black Afro-Caribbean	92 (1.8)	177 (1.8)
South Asian	77 (1.5)	124 (1.2)
Mixed Race	33 (0.6)	36 (0.4)
Other	32 (0.6)	33 (0.3)
Missing	2782 (53.8)	5866 (58.7)
Townsend		
1 – Least deprived	955 (18.5)	1454 (14.6)
2	860 (16.6)	1531 (15.3)
3	952 (18.4)	1845 (18/5)
4	961 (18.6)	2057 (20.6)
5 - Most deprived	672 (13.0)	1662 (16.6)
Missing	770 (14.9)	1446 (14.5)
Baseline Comorbidities		
Mental Health Conditions		
Anxiety	1469 (28.4)	2404 (24.1)
Depression	2381 (46.1)	3440 (34.4)
Cardiovascular Diseases		
Atrial Fibrillation	83 (1.6)	137 (1.4)
Heart Failure	43 (0.8)	76 (0.8)
Ischemic Heart Disease	157 (3.0)	328 (3.3)
Hypertension	1603 (31.0)	2944 (29.5)
Stroke/TIA	76 (1.5)	159 (1.6)
Diabetes Mellitus (DM)		
Type1 DM	17 (0.3)	47 (0.5)
Type2 DM	1176 (22.8	2089 (20.9)
Obstructive Sleep Apnoea	572 (11.1)	335 (3.4)

Table 2: The impact of bariatric surgery on study outcomes across all surgical procedures and for individual procedures.

		Hypertension		Atrial fibrillation		Combined Cardiovascular event	
		Exposed	Control	Exposed	Control	Exposed	Control
Population – Overall (All surgical procedures)		3567	7051	5087	9858	4922	9484
Outcome events, n(%)		118 (3.3)	567 (8.0)	59 (1.2)	130 (1.3)	87 (1.8)	230 (2.4)
Person-years		14297.2	28573.7	21011.7	43053.7	20242.2	41206.1
Crude Incidence Rate*		8.25	19.84	2.81	3.02	4.30	5.58
Follow-up years, Median(IQR)		3.5 (1.6- 6.0)	3.6 (1.6- 6.1)	3.6 (1.7- 6.1)	4.0 (1.8- 6.5)	3.6 (1.7- 6.1)	4.0 (1.8- 6.5)
HR ratio (95% CI), p value	**Unadjusted**	0.42 (0.34-0.51), <0.001		0.94 (0.69-1.28), 0.708		0.78 (0.61- 0.995), 0.045	
	Adjusted	0.41 (0.34- 0.5), <0.001		0.93 (0.68- 1.27), 0.661		0.80 (0.62- 1.02), 0.074	
Intervention – Gastric band		1470	2902	1946	3834	1883	3716
Outcome events, n(%)		72 (4.9)	278 (9.6)	31 (1.6)	51 (1.3)	45 (2.4)	92 (2.5)
Person-years		7439.7	14342.6	10274.7	20780.2	9954.9	20019.8
Crude Incidence Rate*		9.68	19.38	3.02	2.45	4.52	4.6
Follow-up years, Median(IQR)		4.9 (2.4- 7.4)	4.7 (2.2- 7.3)	5.1 (2.6- 7.6)	5.4 (2.6- 7.8)	5.2 (2.6- 7.6)	5.4 (2.6- 7.8)
HR ratio (95% CI), p value	**Unadjusted**	0.50 (0.39-0.65), <0.001		1.24 (0.80-1.94), 0.340		0.99 (0.69-1.41, 0.953)	
	Adjusted	0.50 (0.38-0.65), <0.001		1.21 (0.77-1.92), 0.406		1.07 (0.75-1.54), 0.708	
Intervention – Sleeve Gastrectomy		768	1512	1135	2162	1101	2064
Outcome events, n(%)		21 (2.7)	92 (6.1)	10 (0.9)	22 (1.0)	14 (1.3)	34 (1.7)
Person-years		2256.2	4538.8	3590.7	7075.4	3402.6	6706.9
Crude Incidence Rate*		9.31	20.27	2.785	3.11	4.12	5.07
Follow-up years, Median(IQR)		2.3 (1.0- 4.1)	2.3 (1.0- 4.4)	2.5 (1.2- 4.6)	2.5 (1.1- 4.8)	2.4 (1.1- 4.4)	2.5 (1.1- 4.8)
HR ratio (95% CI), p value	**Unadjusted**	0.45 (0.28- 0.73), 0.001		0.93 (0.44- 1.97), 0.852		0.83 (0.45- 1.55), 0.559	
	Adjusted	0.47 (0.29- 0.77), 0.002		0.98 (0.45- 2.16), 0.965		0.80 (0.42- 1.52), 0.494	
Intervention – Gastric Bypass		1305	2585	1971	3789	1903	3635
Outcome events, n(%)		24 (1.8)	194 (7.5)	18 (0.9)	57 (1.5)	27 (1.4)	104 (2.9)
Person-years		4538.5	9543.3	7049.8	14978.5	6787.3	14261.8
Crude Incidence Rate*		5.29	20.33	2.55	3.81	3.98	7.29
Follow-up years, Median(IQR)		3.1 (1.4- 5.1)	3.4 (1.5- 5.5)	3.2 (1.5- 5.3)	3.7 (1.7- 5.8)	3.2 (1.4- 5.2)	3.7 (1.7- 5.8)
HR ratio (95% CI), p value	**Unadjusted**	0.26 (0.17- 0.40), <0.001		0.68 (0 .40- 1.15), 0.149		0.55 (0.36- 0.85), 0.006	
	Adjusted	0.25 (0.16- 0.38), <0.001		0.65 (0.38- 1.11), 0.112		0.53 (0.34- 0.81), 0.003	
Intervention – Duodenal switch		24	52	35	73	35	69
Outcome events, n(%)		1 (4.2)	3 (5.8)	0	0	1 (2.86)	0
Person-years		62.7	148.9	96.5	219.5	97.34	217.53

*Rate per 1000 person years

HR= Hazard rate

Adjusted HR: Adjusted for age, sex, BMI, smoking status, alcohol consumption, Townsend deprivation quintile, ethnicity, baseline hypertension, T2DM

.

Cont..Table 2: The impact of bariatric surgery on separate cardiovascular events across all surgical procedures and in individual procedures

		Ischaemic Heart Disease		Heart Failure		Cerebrovascular Accident	
		Exposed	Control	Exposed	Control	Exposed	Control
Population – Overall		**5013**	**9667**	**5127**	**9919**	**5094**	**9836**
Outcome events, n(%)		49 (1.0)	123 (1.3)	19 (0.4)	72 (0.7)	37 (0.7)	83 (0.8)
Person-years		20681.4	42126.0	21281.1	43418.6	21102.1	43064.6
Crude Incidence Rate*		2.37	2.92	0.89	1.66	1.75	1.93
Follow-up years, Median(IQR)		3.6 (1.7- 6.1)	4.0 (1.8- 6.5)	3.6 (1.7- 6.2)	4 (1.8- 6.5)	3.6 (1.7- 6.1)	4 (1.8- 6.5)
HR ratio (95% CI), p value	**Unadjusted**	0.82 (0.59-1.14), 0.233		0.55 (0.33-0.90), 0.019		0.91 (0.62-1.35), 0.649	
	Adjusted	0.85 (0.61-1.19), 0.349		0.57 (0.34-0.96), 0.033		0.98 (0.66-1.45), 0.907	
Intervention – Gastric band		1912	3772	1954	3845	1943	3820
Outcome events, n(%)		25 (1.3)	54 (1.4)	9 (0.5)	23 (0.6)	21 (1.1)	29 (0.8)
Person-years		10139.5	20405	10402.9	20904.0	10308.8	20773.0
Crude Incidence Rate*		2.47	2.65	0.87	1.1	2.04	1.40
Follow-up years, Median(IQR)		5.2 (2.6- 7.6)	5.4 (2.6- 7.8)	5.2 (2.7- 7.6)	5.4 (2.7- 7.8)	5.2 (2.6- 7.6)	5.4 (2.7- 7.8)
HR ratio (95% CI), p value	**Unadjusted**	0.94 (0.59- 1.51), 0.800		0.79 (0.37-1.71), 0.553		1.46 (0.83-2.56), 0.186	
	Adjusted	1.02 (0.63- 1.65), 0.937		0.90 (0.41-1.99), 0.795		1.67 (0.94-2.96), 0.079	
Intervention – Sleeve Gastrectomy		1120	2111	1143	2177	1146	2157
Outcome events, n(%)		8 (0.7)	15 (0.7)	6 (0.5)	15 (0.7)	5 (0.4)	14 (0.7)
Person-years		3479.1	6863.8	3608.2	7129.8	3619.1	7067.4
Crude Incidence Rate*		2.3	2.19	1.66	2.10	1.38	1.98
Follow-up years, Median(IQR)		2.4 (1.1- 4.5)	2.5 (1.1- 4.8)	2.5 (1.2- 4.6)	2.5 (1.1- 4.8)	2.5 (1.2- 4.6)	2.5 (1.1- 4.8)
HR ratio (95% CI), p value	**Unadjusted**	1.06 (0.45-2.51), 0.887		0.81 (0.32-2.10), 0.669		0.71 (0.25-1.97), 0.509	
	Adjusted	1.05 (0.43-2.54), 0.920		0.91 (0.34-2.44), 0.854		0.68 (0.24-1.95), 0.470	
Intervention – Gastric Bypass		1946	3713	1993	3825	1969	3787
Outcome events, n(%)		15 (0.8)	54 (1.5)	4 (0.2)	34 (0.9)	11 (0.6)	40 (1.1)
Person-years		6965.5	14638.0	7164.8	15166.9	7069.2	15005.0
Crude Incidence Rate*		2.15	3.69	0.56	2.24	1.56	2.67
Follow-up years, Median(IQR)		3.2 (1.5- 5.3)	3.7 (1.7- 5.8)	3.2 (1.5- 5.2)	3.7 (1.7- 5.8)	3.2 (1.5- 5.2)	3.7 (1.7- 5.8)
HR ratio (95% CI), p value	**Unadjusted**	0.59 (0.33-1.05), 0.072		0.25 (0.09-0.72), 0.009		0.59 (0.30-1.15), 0.121	
	Adjusted	0.57 (0.32-1.03), 0.061		0.24 (0.08-0.68), 0.007		0.59 (0.3-1.16), 0.128	
Intervention – Duodenal switch		35	71	37	72	36	72
Outcome events, n(%)		1 (2.9)	0	0	0	0	0
Person-years		97.3	219.3	105.2	217.9	105.1	219.3

*Rate per 1000 person years

HR: Hazard rate

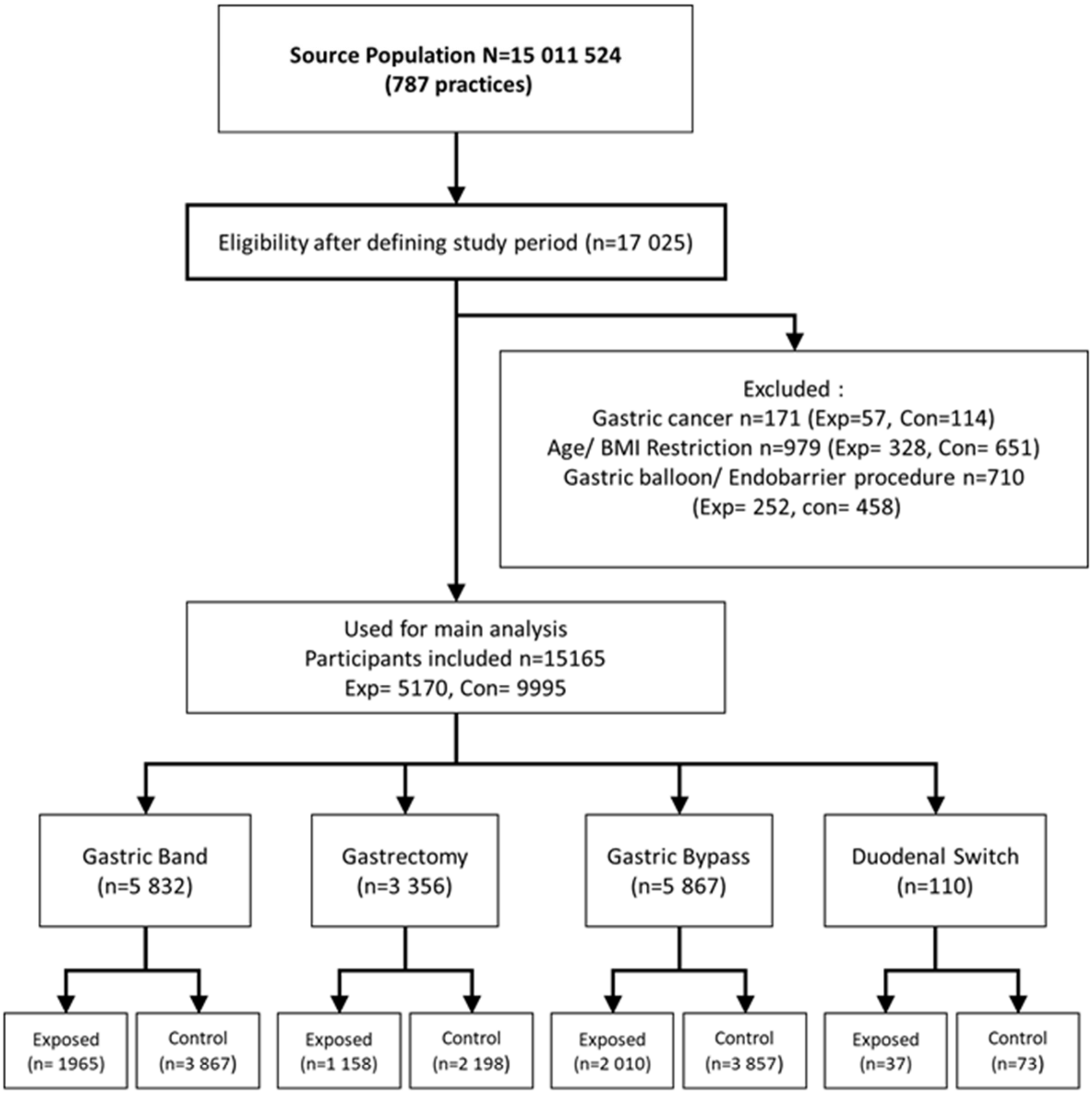
Adjusted HR(Model1): Adjusted for age, sex, BMI, smoking status, alcohol consumption, Townsend deprivation quintile, ethnicity, baseline hypertension, T2DM.

Table 3: The impact of bariatric surgery on mortality in all surgical procedures

Intervention		Overall		Gastric band		Sleeve Gastrectomy		Gastric Bypass	
		Exposed	Control	Exposed	Control	Exposed	Control	Exposed	Control
		5170	9995	1965	3867	1158	2198	2010	3857
Outcome events, n(%)		90 (1.7)	278 (2.8)	25 (1.3)	103 (2.7)	27 (2.3)	61 (2.8)	37 (1.8)	113 (2.9)
Person-years		21491.3	43863.6	10464.0	21086.9	3671.0	7216.0	7251.1	15341.2
Crude Incidence Rate*		4.19	6.34	2.39	4.88	7.36	8.45	5.10	7.37
Follow-up years, Median(IQR)		3.6 (1.7- 6.2)	4.0 (1.8- 6.5)	5.2 (2.7- 7.6)	5.5 (2.7- 7.8)	2.5 (1.2- 4.6)	2.6 (1.1- 4.8)	3.25 (1.49- 5.26)	3.76 (1.76- 5.86)
HR ratio (95% CI)	**Unadjusted**	0.67 (0.53- 0.85), 0.001		0.49 (0.32- 0.76), 0.001		0.89 (0.57- 1.40), 0.615		0.71 (0.49- 1.02), 0.067	
	Adjusted Model 1	0.70 (0.55- 0.89), 0.004		0.53 (0.34- 0.83), 0.005		0.97 (0.61- 1.55), 0.901		0.69 (0.47- 1.01), 0.055	
	Adjusted Model 2	0.70 (0.55- 0.89),0.004		0.54 (0.35- 0.84), 0.007		0.96 (0.60- 1.54), 0.874		0.66 (0.45- 0.97), 0.033	

*Rate per 1000 person years
HR = Hazard rate
Adjusted Model 1: Adjusted for age, sex, BMI, smoking status, alcohol consumption, Townsend deprivation quintile, ethnicity, baseline hypertension, T2DM.
Adjusted Model 2: Adjusted for age, sex, BMI, smoking status, alcohol consumption, Townsend deprivation quintile, ethnicity, baseline hypertension, Charlson comorbidity index.

Figure 1: Flowchart showing participant selection. Each exposed patient excluded was removed from the study along with their matching controls



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