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CLINICAL RESEARCH
Obesity and metabolic syndrome

Effect of bariatric surgery on long-term cardiovascular outcomes: a nationwide nested cohort study

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Aims This study aims to evaluate the long-term effect of bariatric surgery on cardiovascular outcomes of patients with obesity.

Methods and results A nested cohort study was carried out within the Clinical Practice Research Datalink. The study cohort included the 3701 patients on the database who had undergone bariatric surgery and 3701 age, gender, and body mass index-matched controls. The primary endpoint was the composite of fatal or non-fatal myocardial infarction and fatal or non-fatal ischaemic stroke. Secondary endpoints included fatal or non-fatal myocardial infarction alone, fatal or non-fatal ischaemic stroke alone, incident heart failure, and mortality. The median follow-up achieved was 11.2 years. Patients who had undergone bariatric surgery had a significantly lower occurrence of major adverse cardiovascular events [hazard ratio (HR) 0.410, 95% confidence interval (CI) 0.274–0.615; $P < 0.001$]. This was mainly driven by a reduction in myocardial infarction (HR 0.412, 95% CI 0.280–0.606; $P < 0.001$) and not in acute ischaemic stroke (HR 0.536, 95% CI 0.164–1.748; $P = 0.301$). A reduction was also observed in new diagnoses of heart failure (HR 0.403, 95% CI 0.181–0.897; $P = 0.026$) and mortality (HR 0.254, 95% CI 0.183–0.353; $P < 0.001$).

Conclusion The results of this large, nationwide cohort study support the association of bariatric surgery with lower long-term risk of major cardiovascular events and incident heart failure in patients with obesity.

Keywords Obesity • Bariatric surgery • Myocardial infarction • Ischaemic stroke

Introduction

Over the past 50 years, the global burden of obesity has grown exponentially.[1] Among the numerous effects of obesity on global health, the growing incidence of cardiovascular disease (CVD) is one of the most hazardous. The independent causal relationship between obesity and CVD has been previously well established.[2–4] Beyond this direct effect, metabolic changes associated with obesity, including hyperlipidaemia, insulin resistance, and hypertension (HTN), are independent major risk factors contributing to the development of CVD.[4]

Primary and secondary prevention measures for obesity-related disorders gravitate around the central paradigm of weight reduction. This principle is also employed for the primary prevention of cardiovascular disease.[5] However, current evidence on the efficacy of medical and dietary approaches to weight reduction on long-term

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improvement of cardiovascular outcomes remains conflicted. Overall, studies on pharmacological and lifestyle weight loss methods have thus far failed to demonstrate a clear and reliable clinical benefit.[6]

Strong evidence supports the role of bariatric surgery as a more reliable method of weight reduction than either pharmacological or lifestyle measures.[7–10] For this reason, its use has been steadily increasing in recent years,[11] though the proportion of eligible patients who undergo the procedure is still extremely low. Recently, a growing interest has developed in exploring its effectiveness not only on weight reduction but also on the reduction or improvement of obesity-related morbidities, such as HTN, diabetes, mortality, and cancer rates.[12–15] Considering the known beneficial effects of bariatric surgery on a number of risk factors for CVD, including HTN and diabetes, it is reasonable to hypothesize that bariatric surgery may be an effective means of improving long-term cardiovascular outcomes of patients with obesity.

The aim of this observational, retrospective nested cohort study carried out on a prospectively collected national patient database is to evaluate the effect of bariatric surgery on the long-term occurrence of major adverse cardiovascular events in patients with obesity.

Methods

Data for the study were extracted from the Clinical Practice Research Datalink (CPRD) database. The CPRD is a prospective, ongoing UK-based non-profit governmental research service funded by the National Institute for Health Research and the Department of Health. The CPRD data collection platform involves 674 General Practice surgeries in the UK, containing anonymized and coded healthcare records of over 11 million consenting patients dating from 1987 to the present. The design, implementation, and maintenance of this database have been previously described.

Scientific approval for the study was granted by the Regulatory Agency's Independent Scientific Advisory Committee; and ethical approval was granted by the Health Research Authority IRAS. Project ID: 203143. ISAC approval registration number: 16_140R2. Data access for the study was provided by the Big Data & Analytical Unit (BDAU) at the Institute of Global Health Innovation (IGHI) at Imperial College London.

Role of the funding source

Infrastructure support for this research was provided by the NIHR Imperial Biomedical Research Centre (BRC). The funding source had no involvement in the design, collection, analysis, or interpretation of data; or in the writing of the report.

Patient population

For this study, access was granted to healthcare records pertaining to patients who had a diagnosis of obesity or ≥30 kg/m^2 during follow-up. Patients were excluded if they had been lost to follow-up within 12 months of index date, other than due to a fatal event. Furthermore, patients were excluded if they were not eligible for bariatric surgery [body mass index (BMI) <35 kg/m^2] or had suffered a major adverse cardiovascular event before index date. Those with missing age, BMI, or gender data were also excluded due to inability to match. A nested cohort study design was implemented on the eligible population: the intervention group consisted of the 3701 eligible patients among these who had undergone bariatric surgery. The controls were 3701 age, gender, and baseline BMI-matched patients who had not undergone the surgery. The patient selection process is outlined in Supplementary material online, *Figure S1*. Data pertaining to all included patients were extracted from the database; age, gender, BMI, and the presence of clinical and treatment factors. These included HTN, hyperlipidaemia, diabetes mellitus (DM), cigarette smoking, alcohol use, cocaine use, exercise, Charlson comorbidity index, and use of medications, such as beta blockers (BB), calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACE-i) or angiotensin receptor blockers (ARBs), statins, aspirin, and hormone replacement therapy (HRT). Non-diagnostic variables (smoking, alcohol use, exercise, and cocaine use) were manually screened and selected by two co-authors; when in disagreement, the decision was settled by evaluation of a third author. Patients were considered smokers if they had indication of past or present smoking habit, including a direct quantification or referral or advice for smoking cessation. Alcohol use was considered in all patients who had indication of moderate or high alcohol intake, referral, or advice for alcohol use cessation, and the diagnosis of any alcohol-related morbidity (i.e. alcoholic hepatitis). Patients were considered to exercise if they had coded clinical information specifying mild, moderate, or intense regular exercise. Medication use was defined as medication use at any time and for any length during follow-up.

Endpoint definition

The primary endpoint was the composite of fatal or non-fatal myocardial infarction and fatal or non-fatal acute ischaemic stroke. Only ischaemic strokes were considered; intra-cerebral bleeds, traumatic bleeds, or subarachnoid haemorrhage were not considered as primary endpoints. The secondary endpoints considered were new occurrence of heart failure, and we also analysed the primary endpoint components individually: fatal or non-fatal myocardial infarction and fatal or non-fatal acute ischaemic stroke. All-cause mortality was also considered, as a safety outcome.

Further information regarding the CPRD-specific clinical codes used for endpoint definition in the study is provided in Supplementary material online, *Table S1–S3*, respectively for stroke, myocardial infarction, and heart failure.

Weight change and risk factor modification

The median weight for the two cohorts across follow-up time was compared by extracting the weight at index date and at every subsequent year of follow-up. When a patient had more than one weight reading during the year, the median value among these multiple readings was extracted. The closest weight to the index date, represented as weight at 'Time 0', was also recorded across both groups. Using these readings, the 'zero' weight and the median weight of the bariatric and control cohorts for each year of follow-up was then calculated for each year and graphically represented.

The rates of resolution of Type 2 diabetes during follow-up were assessed. This was defined as either a direct clinical code indicating diabetes resolution, or a last prescription for any hypoglycaemic or antidiabetic medication occurring >6 months before the end of follow-up. The time of diabetes resolution considered for statistical analysis was defined as either the time of entry of a clinical coded diagnosis or the time of last medication prescription; plus 6 months.

Statistical analysis

The data for the study were extracted, prepared, and analysed using the Statistical Package for Social Sciences, version 25 (SPSS Inc., New York, NY, USA).[9]

Baseline demographic, clinical, and treatment factors were compared across cohorts using Pearson's χ^2 test for categorical variables and Mann–Whitney *U* test for continuous data. Weight and BMI change across follow-up time, and rates of resolution of diabetes, were also compared across cohorts. This was done using Wilcoxon rank-sum test and

χ^2 test. The Mann–Whitney *U* test was chosen as the data were not normally distributed on Kolmogorov–Smirnov test.

Cox proportional hazards model was used to analyse time to event data adjusting for multiple covariates for both primary and secondary endpoints. Factors adjusted for in the Cox proportional hazards model include HTN, hyperlipidaemia, DM, smoking, alcohol use, cocaine use, exercise, and use of medications, such as BB, CCB, ACE-i or ARBs, statins, aspirin, and HRT. The interaction of gender, diabetes, and BMI category with bariatric surgery on the primary endpoint was tested using Cox proportional hazards model with interaction terms.

The interaction effects of predefined variables were tested using a Cox proportional hazards model with interaction terms. The cumulative event rates by bariatric surgery type were also assessed by means of a Kaplan–Meier analysis, and the relative rates across groups compared using a log-rank function.

The number of interventions needed to prevent a single cardiovascular event over 11.2 years [and therefore the number needed to treat (NNT)] was calculated as the reciprocal of the absolute risk reduction between the surgery and control cohorts. All *P*-values reported are two-sided; statistical significance was considered when $P < 0.05$.

Results

Baseline characteristics

A total of 7402 patients were included in the analysis; of which, 3701 had undergone bariatric surgery and 3701 had not. The average length of follow-up was 140.7 months (standard deviation = 79.9 months), equating to 86 603 person-years. The median age was 36 years across both cohorts; and the median BMI was 40.3 kg/m^2 in the bariatric surgery group, and 40.5 kg/m^2 in the group who had not undergone bariatric surgery.

The baseline clinical and treatment characteristics of patients subdivided by cohort are described in *Table 1*. Overall, risk factors for CVD were more prevalent among patients in the bariatric surgery group at baseline. These include HTN ($P = 0.014$) and use of hormone replacement therapy ($P = 0.007$). On the other hand, cocaine ($P = 0.012$) and beta-blocker use ($P = 0.037$) were less frequent in the bariatric surgery cohort. Charlson comorbidity index was similar across the two cohorts ($P = 0.071$), though a non-significant trend towards higher baseline morbidity in the bariatric surgery cohort was observed.

Primary endpoint

During follow-up, the primary endpoint of fatal or non-fatal myocardial infraction or ischaemic stroke occurred in 130 patients; 37 events occurred in patients that had undergone bariatric surgery, while 93 occurred in patients who had not [hazard ratio (HR) 0.410, 95% confidence interval (CI) 0.274–0.615; $P < 0.001$, NNT = 62]. The results of the analysis are outlined in *Table 2* and depicted in *Figure 1*. Twelve patients experienced more than one event: three in the bariatric surgery group and nine in the control group.

Myocardial infarction occurred less frequently in the bariatric surgery cohort (36 vs. 93; HR 0.412, 95% CI 0.280–0.606; $P < 0.001$, NNT = 64). Ischaemic stroke rates were similar across cohorts (13 vs. 4; HR 0.536, 95% CI 0.164–1.748; $P = 0.301$), as displayed in Supplementary material online, *Figures S2 and S3*.

Sixty-eight patients received a new diagnosis of heart failure during follow-up, of whom 22 belonged to the bariatric surgery group and 46 belonged to the control group (HR 0.403, 95% CI 0.181–0.897; $P = 0.026$, NNT = 153), as displayed in *Table 2* and *Figure 2A*. All-cause mortality was lower in the bariatric surgery cohort (45 vs. 182; HR 0.254, 95% CI 0.183–0.353; $P < 0.001$, NNT = 27), as displayed on *Table 2* and *Figure 2B*.

Secondary analysis

Patients in the bariatric surgery cohort experienced significantly more weight loss during follow-up compared with patients in the control group [median -4.22 kg (-19.3 to 8.0) vs. +6.00 kg (-2.9 to 16.7); *Z* -25.15; $P < 0.001$]. The median weight of patients across follow-up time is depicted in *Figure 3*. Among those with Type 2 diabetes at baseline, in the bariatric surgery cohort had significantly higher rates of resolution (371 vs. 107; HR 3.97, 95% CI 3.20–4.93; $P < 0.001$).

The number and proportion of all patients who underwent different bariatric surgery types and primary endpoint rates by surgery type are displayed in Supplementary material online, *Table S4*. The type of bariatric surgery was found not to significantly impact primary endpoint rates (log rank $P = 0.994$).

Interaction analysis

A total of 1803 patients in the study had diabetes; of these, 881 belonged to the control group and 922 to the bariatric surgery group. Diabetes did not significantly interact with bariatric surgery in the determination of primary endpoint (*P* for interaction = 0.529). Patients with diabetes who underwent bariatric surgery displayed an association with lower heart failure rates (HR 0.278; 95% CI 0.120–0.642, $P = 0.003$) whereas those with no diabetes did not (HR 0.780; 95% CI 0.362–1·681; $P = 0.527$). Though a trend was observed for this interaction, it did not fulfil statistical significance (*P* for interaction = 0.077).

Females made up a total of 79.8% of both the bariatric surgery cohort and the control cohort. Gender did not significantly interact with bariatric surgery for the primary endpoint (*P* for interaction = 0.148), and for heart failure (*P* for interaction = 0.622). Patients were equally split between bariatric surgery patients and control due to baseline matching. Body mass index category was found to not interact significantly for primary events (*P* for interaction $P = 0.682$) and for occurrence of incident heart failure (*P* for interaction = 0.263).

The results of the interaction analysis are displayed in *Figure 4* and *Table 3*.

Discussion

In this nationwide nested cohort study, bariatric surgery was associated with significantly lower incidence of major adverse cardiovascular events—defined as fatal and non-fatal myocardial infarction and stroke—and also lower rates of incident heart failure and mortality in a cohort of patients with obesity. These results were observed in spite of the presence of a greater number of classical risk factors typically used for the short-term risk prediction of cardiovascular events in the bariatric surgery group at baseline.

Table 1 Baseline demographic, clinical, and treatment characteristics of the patients by bariatric surgery status

Characteristics	No bariatric surgery (n = 3701)	Bariatric surgery (n = 3701)	P-value
Demographic			
Age (years), median (IQR)	36 (29–44)	36 (29–44)	
Male (%)	20.2%	20.2%	
BMI (kg/m^2), median (IQR)	40.3 (36.6–43.9)	40.5 (37.1–45.5)	
Index weight (kg), mean (SD)	109 (27)	125 (33)	
Clinical			
Hypertension, *n* (%)	1822 (49.2)	1928 (52.1)	0.014
Hyperlipidaemia, *n* (%)	39 (1.1)	50 (1.4)	0.241
Diabetes, *n* (%)	881 (23.9)	922 (25.0)	0.290
Smoking, *n* (%)	1354 (36.6)	1369 (37.0)	0.718
Alcohol, *n* (%)	792 (21.4)	758 (20.5)	0.331
Cocaine, *n* (%)	13 (0.4)	3 (0.1)	0.012
Exercise, *n* (%)	886 (23.9)	893 (24.1)	0.849
Charlson comorbidity index			P = 0.071
0	1695 (45.8)	1762 (47.6)	
1	1197 (32.3)	1177 (31.8)	
2	436 (11.8)	464 (12.5)	
3	211 (5.7)	177 (4.8)	
4	80 (2.2)	74 (2.0)	
5+	66 (1.7)	40 (1.1)	
Treatment			
Beta-blockers, *n* (%)	869 (23.5)	794 (21.5)	0.037
Calcium channel blockers, *n* (%)	760 (20.5)	765 (20.7)	0.886
Aspirin, *n* (%)	1185 (32.0)	1223 (33.0)	0.346
ACE inhibitor or ARB, *n* (%)	387 (10.5)	396 (10.7)	0.734
Statin, *n* (%)	1185 (32.0)	1223 (33.0)	0.346
Hormone replacement, *n* (%)	526 (14.2)	610 (16.5)	0.007

Acute cardiovascular events are one of the largest and most hazardous consequences of obesity. Despite the well-recognized causal relationship between obesity and CVD,[4] studies assessing the effect of lifestyle and medical weight reduction interventions have thus far yielded extremely conflicting results.

On the other hand, a small but growing pool of evidence assessing the impact of weight loss surgery on cardiovascular outcomes has begun to yield encouraging results. Randomized evidence supports the beneficial effect of bariatric surgery on a number of cardiovascular risk factors, including diabetes, HTN, and hyperlipidaemia.[16–18] However, no prospective randomized evidence is available to quantify the effect of bariatric surgery on long-term cardiovascular events so far. Nevertheless, a protective effect of weight loss surgery has been described in observational studies[13,19–22], including studies focussed on specific populations such as diabetics.[23–25] It has also been associated with better outcomes after myocardial infarction.[26] In the CPRD cohort specifically, Douglas *et al.*[18]; demonstrated higher weight loss alongside reductions in a number of obesity-related risk factors in bariatric surgery patients. To date, the Swedish Obese Study (SOS) remains the most comprehensive ongoing investigation. The results of our study, on a larger population of 7402 patients with no age restriction and a follow-up time of up to 38 years (average 11.2 years); are in line with findings of the SOS.[27]

In this study, the lower cardiovascular event rate observed in the bariatric surgery cohort occurred alongside higher rates of resolution of Type 2 diabetes and a greater degree of weight loss. Bariatric surgery patients tended towards greater weight at index time, though the variation was large; and lost significantly more weight during the study period and were thus lighter at the end of follow-up. This implies that the protective effect observed may be mediated by a substantial modification in cardiovascular risk factors. The protective effect indeed displayed a late and widening diversion of event curves that became most evident ~8 years after the surgery. This pattern of event curve diversion is analogous to that observed across other risk-factor modifying strategies, such as lipid-lowering therapies, which would be consistent with the known benefit of bariatric surgery on metabolic risk factor control.

Though this is one of the largest cohort studies on bariatric surgery patients thus far, there were unfortunately still not enough patients and event numbers to directly explore whether diabetes resolution may have mediated the reduction in cardiovascular events observed in the bariatric surgery cohort through a specific interaction analysis.

Table 2 Primary and secondary endpoints during follow-up

Events	No bariatric surgery (n = 3701)	Bariatric surgery (n = 3701)	HR	95% CI	P-value
Primary endpoint	93	37	0.410	0.274–0.615	**<0.001**
Fatal or non-fatal myocardial infarction	93	36	0.412	0.280–0.606	**<0.001**
Fatal or non-fatal ischaemic stroke	9	4	0.536	0.164–1.748	0.301
Secondary endpoints					
All-cause mortality	182	45	0.254	0.183–0.353	**<0.001**
Heart failure	46	22	0.403	0.181–0.897	**0.026**

Bold values indicate statistical significance.

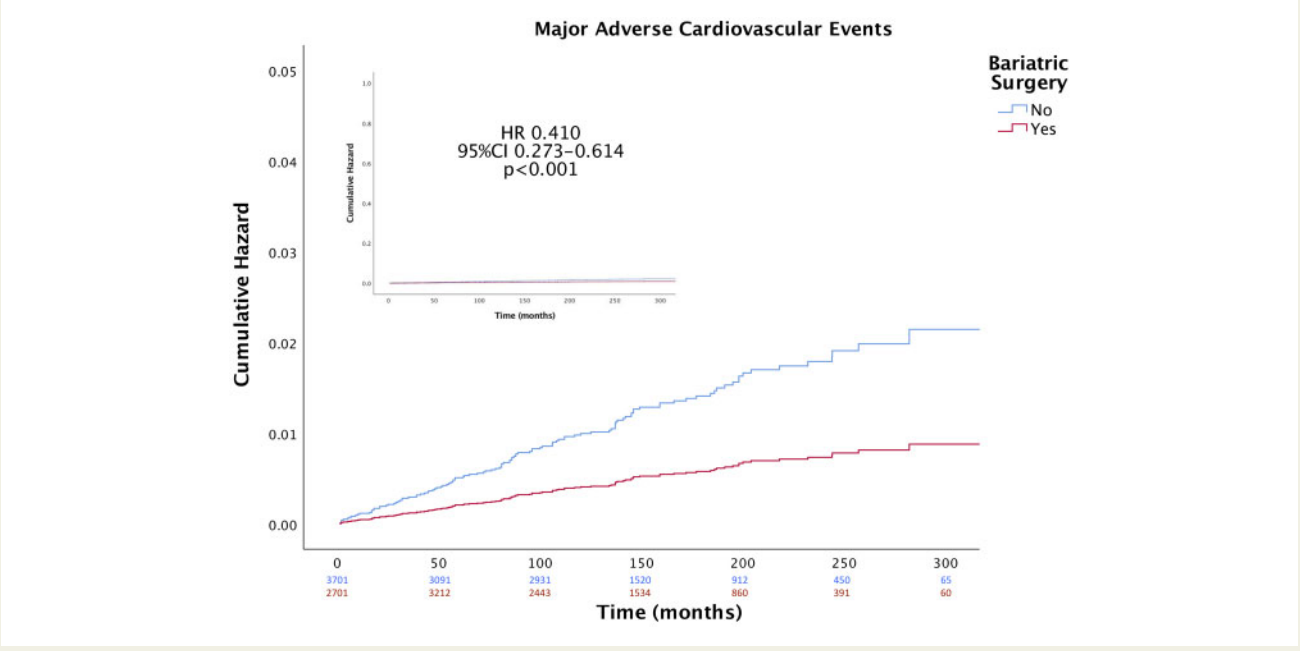


Figure 1 Cumulative incidence of adjusted primary endpoints (fatal or non-fatal myocardial infarction and fatal or non-fatal ischaemic stroke).

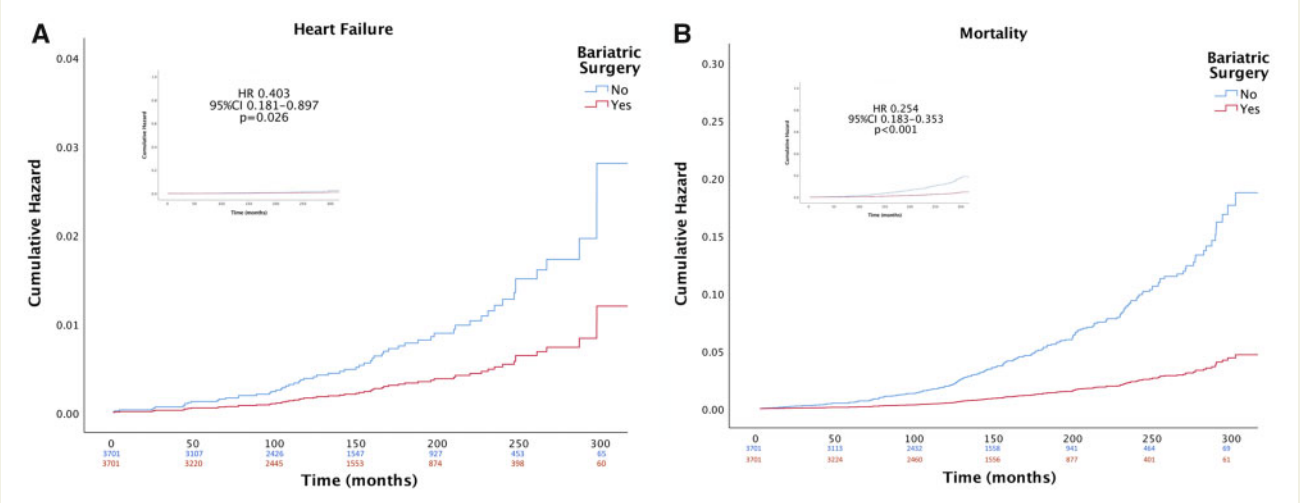


Figure 2 Cumulative incidence of secondary endpoints. (*A*) Incident heart failure. (*B*) All-cause mortality.

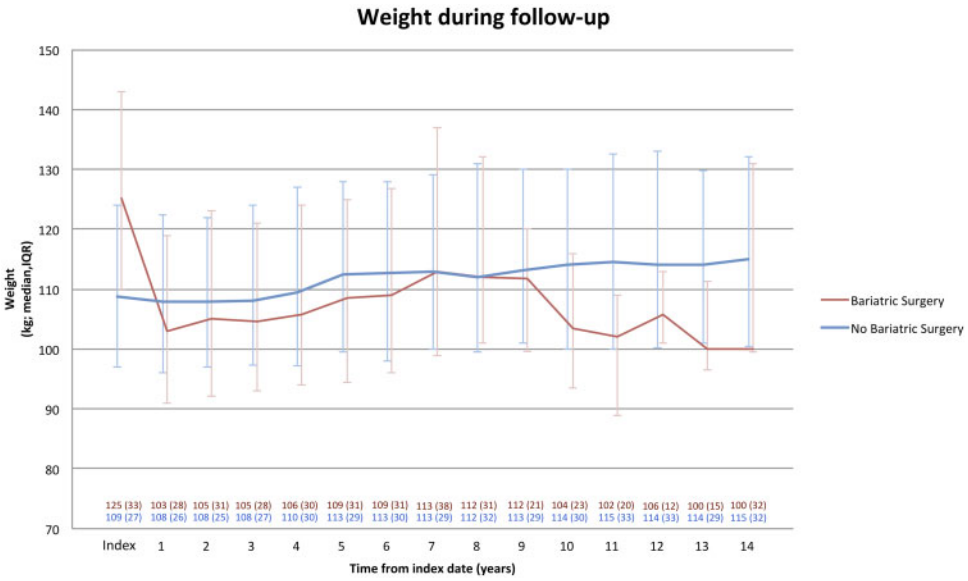


Figure 3 Median weight change by cohort during follow-up (median, interquartile range).

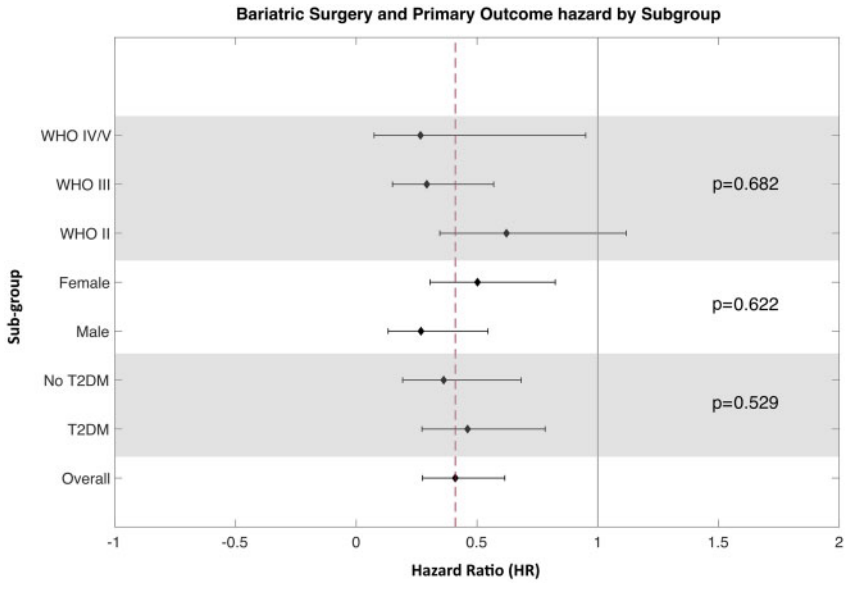


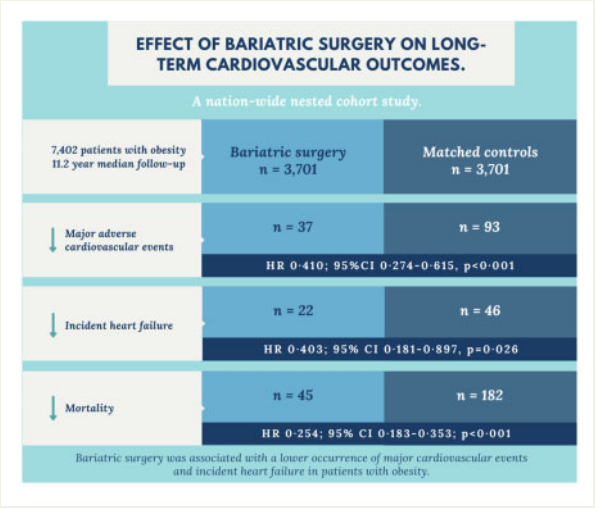
Figure 4 Interaction analysis for body mass index, gender and Type 2 diabetes mellitus: Cox proportional hazards model with interaction effects.

We did, however, find some evidence of potential interaction between diabetes and incident heart failure. This certainly calls for further investigation, especially in light of the higher rates of diabetes resolution in the bariatric surgery cohort compared with the controls.

The CPRD is an extremely rich database that has previously been shown to accurately represent the UK population in terms of age, sex, and ethnicity; the findings of this study are, therefore, generalizable to the population of the UK and most western countries of similar demographic profile. However, a limitation of the database lies in its potential for significant diagnostic variability. Misdiagnoses, erroneous entries, and variations in terminology may all impact the reliability of the data and may exert a non-negligible impact. Despite this, attempts to validate the diagnoses with linked secondary care records have thus far been successful[28]; though none have targeted the accuracy and completeness of major

Table 3 Subgroup analysis: primary and secondary event rates in subgroups during follow-up

Subgroup	Primary endpoint				Heart failure			
	HR	95% CI	*P*-value	*P*-value (interact)	HR	95% CI	*P*-value	*P*-value (interact)
Type 2 diabetes								
Yes (*n* = 1.803)	0.461	0.272–0.782	0.004	0.529	0.278	0.120–0·642	0.003	0.077
No (*n* = 5577)	0.362	0.192–0.683	0.002		0.780	0.362–1.681	0.527	
Gender								
Males (*n*=1414)	0.268	0.132–0.545	<0.001	0.148	0.541	0.232–1.262	0.155	0.622
Females (*n* = 5908)	0.502	0.306–0.824	0.006		0.403	0.194–0.836	0.015	
BMI category								
WHO II (BMI 35–40) (*n* = 3528)	0.622	0.346–1.118	0.112	0.682	0.671	0.2751–635	0.380	0.263
WHO III (BMI 40–50) (*n* = 3026)	0.292	0.150–0.569	<0.001		0.288	0.117–0·711	0.007	
WHO IV/V (BMI 50+) (*n* = 848)	0.266	0.074–0.950	0.041		1.325	0.3435–118	0.683	



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cardiovascular event records thus far. Furthermore, the lack of access to laboratory data prevented the ability to follow-up changes in inflammatory markers, glucose control, and lipid levels after bariatric surgery, and to cross-validate and enhance diagnoses (i.e. hyperlipidaemia) with corresponding laboratory data. The lack of access to causes of mortality is also an important limitation that prevents us from being able to assess specific cardiovascular mortality in the cohort.

Finally, of paramount importance is the potential limitation arising from unmeasured factors. This is a global limitation of all retrospective studies. Despite *post hoc* adjustment for covariates, a number of factors that are impossible to quantify from retrospective data (i.e. motivation levels, health-seeking behaviours, healthcare engagement) that are likely more prevalent among the bariatric surgery cohort, both as a selection bias and as a consequence of more intensive follow-up and screening engagement for the surgery, may have conceivably impacted the long-term outcomes, and have thus augmented the strength of the association shown in this study. Ideally, the findings of this study should thus be confirmed by a prospective randomized study.

In conclusion, the present study provides evidence of a potential protective effect of bariatric surgery on the long-term risk of acute cardiovascular events and incident heart failure in a large, nationwide comprehensive cohort of patients followed up for a median time of 11.2 years. With an NNT of 62 to prevent one cardiovascular event over only 11.2 years, the potential overall lifetime benefit that this study implies is large. Considering that currently <1% of eligible patients undergo bariatric surgery,[29] and considering the wealth of emerging evidence on its far-reaching benefits that range from mental health to cancer and cardiovascular risk, it is time to investigate, consider and amend the barriers creating this treatment gap in order to provide the best standard of care and optimize long-term outcomes of patients with obesity.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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